Organ on Chip in Development (ORCHID)

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Website: www.H2020-ORCHID.eu

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Contents

Executive Summary

This deliverable aims to describe and summarize all the communication and dissemination actions carried out in the frame of the ORCHID project. The main goal of this project was the identification of technical, regulatory and ethical issues not yet addressed to use them as the basis of a roadmap for Organ-on-Chip (OoC) technology considering the current state of the art of this technology as well as future needs and challenges.

The first part of this deliverable refers to the action plan approved (D6.1), as the basis for the activities in WP6. The main aim of this plan was to focus the dissemination activity on 3 segments of the European population: The public at large, industrial stakeholders and the scientific community. However, after some meetings and interviews with experts we identified additional relevant segments of the population potentially interested in OoC technology. Patients, clinicians and regulatory agents have also been included in our future dissemination plan.

The second part of this deliverable describes the actions carried out during the project. An assessment of the impact generated by the different types of actions in the different sectors previously mentioned has been performed. We conclude this part of the deliverable by identifying which actions have been the most successful to attract the attention of the different segments of the population.

Finally, the future strategic dissemination plan is briefly described. These future communication and dissemination actions will be carried out by the European Organ-on-Chip Society (EUROoCS). In the definition of the future strategic action plan all data obtained during ORCHID have been considered. Again, this novel action plan is dynamic and will be readjusted according to new inputs obtained during the next years.

As a conclusion, we worked actively to spread the OoC technology benefits and possibilities in all different segments of the population.

Introduction and Overview

The OoC technology has emerged as a very promising technology for the reduction of time and costs in the development of new drugs, as well as for the detection of new therapeutic targets of multiple diseases. The OoC technology combines knowledge coming from the microfluidic, cell biology and sensors fields, among others, to mimic in vitro the patho-physiological microenvironment of the cells in the most reliable way possible. This in vitro recreation allows cells to maintain their environmental stimuli just as they have them in vivo. During the last decade, the number of research groups involved in this technology has increased, as it can be appreciated in the significantly increased number of publications released during these years (Figure 1)[1]. However, in order to bridge the gap between the potential of OoCs and their worldwide acceptance the ORCHID (Organ-on-Chip In Development) project was envisioned, to build a cooperative ecosystem among different stakeholders to identify technical, ethical and regulatory issues not yet addressed and also to define in common future challenges and needs. All this information would be used to create a roadmap for OoC technology for the next years. Among the different work packages (WP) of the ORCHID project, one was related to the communication and dissemination of the results obtained (WP6). The main objective of this WP6 was to raise awareness about this technology among the different sectors of the population and to help in building the ecosystem for OoC technology. To achieve that goal, a dissemination plan was developed (deliverable 6.1) during the first months of the project. This dynamic action plan aimed to attract attention of 3 different segments of the European population: the scientific community, the industrial stakeholders and the public at large.

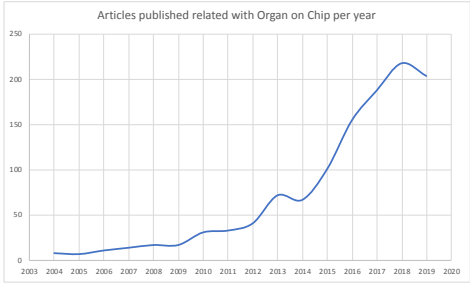


Figure 1: Number of papers published related with Organ on chip per year. Data obtained from pubmed.org

Scientific community

The scientists are key players in the implementation of the OoC technology because they can act as developers but also as end users.

The main dissemination objectives with respect to the scientific community were twofold:

- Promote the use of OoC technology among European researchers
- Increase the interest of the next generation younger researchers in the OoC field

To achieve these objectives, a series of dissemination actions were proposed that are described below:

Logo

A logo for ORCHID (Appendix 1) has been created that includes different organs (Brain, lungs and heart), in the form of an orchid, acronym of the project, that are connected to each other, simulating the human body. In addition, adjacent to the organs a microfluidic channel has been placed in the

[1] PUBMED search https://www.ncbi.nlm.nih.gov/pubmed with the tag ORGAN ON CHIP

letter "I" to symbolize the importance of the integration of technology and biology for OoC development. The selected colors are blue, violet and purple have been chosen because they can be associated with technology and health.

Website

The project website (https://h2020-orchid.eu has been conceived mainly as a site to disseminate the results of the ORCHID (Appendix 1). project. The website has several subsections that detail the project and its objectives, project participants, meetings related to this technology, news related to the project and a repository of the newsletter. In addition, the website has a restricted area for the ORCHID partners that serves as a common repository of internal documents.

Social media

As another communication channel for scientists social media networks of a more scientific nature such as Mendeley or LinkedIn were used. In the case of Mendeley, the results were not satisfactory (only 10 people in the first 6 months of the project). However, in the case of LinkedIn, it was possible to achieve the internally stated objective of contacting at least 100 people during the project period.

Scientific meetings and publications

A more classic strategy to approach researchers was through the presentation of ORCHID and its results at congresses / conferences / workshops and by publication of articles in scientific journals.

Industrial stakeholders

Within this community, several sectors were identified with different specific needs and expectations regarding the OoC technology. These include the end users (pharmaceutical, food, cosmetics and chemical industry) and the biotech/manufacturing industry developing and producing the OoC devices. As has been shown in other WP's of the ORCHID project a close collaboration between end users and developers is crucial to bridge the valley of death and overcome the challenges for implementation of the OoC models in practice. In this respect qualification and characterization, cost reduction and reproducibility, standardization and upscaling are very important issues to be addressed in the near future. Investors and business angels are also relevant players. They can promote the creation of new companies to guarantee competitiveness in the sector and promote R&D as a mechanism for differentiation between companies.

The main dissemination objectives related to the industrial sector were:

- Attract the attention of the main end users to align goals
- Promote the public-private collaboration

Different strategies were used to come into contact with the companies and investors. Among these were bilateral meetings and workshops, including the ORCHID Vision and Strategy workshop. This type of meetings were based on personal contacts between ORCHID partners and industrial representatives, facilitating productive and efficient conversations. However, also at international conferences numerous contacts were made with industrial partners, who were interested in the aims and progress of ORCHID. During these meetings, the flyer and brochures developed in the framework

of the project were used as dissemination tools to raise awareness about the developments in this field within Europe, and resume all the achievements accomplished during the project. In this way the ecosystem gradually was built further towards an active collaborating network of all relevant sectors, that is of great importance for the maturation and implementation of OoC technology in Europe.

Public at large

The last but not least sector approached was the European Community at large. Within this task, we aimed to make the general public familiar with Organ-on-Chip technology, and give information about future potential economic, social and ethical benefits. We focused initially on the general public and in a later phase of the project also on specific subgroups, including patient's associations, clinicians and also policy makers / regulatory agents subgroups. Dissemination was performed via the website and social media accounts specific for the project (twitter and youtube), mass media (tv, radio and newspapers) and by the presence at public scientific events like the European researcher's night or the Pint of Science.

Science and Technology

The Social media guide for EU funded R&I projects (1) mentions the importance to measure the impact of communication strategies by key performance indicators.

The key performance indicators for ORCHID are as follows:

- Nº of visitors to the project website (2000)
- Nº of followers in Twitter (500)
- Nº of follower in LinkedIn (100)
- Nº of researchers participating in the OoC conferences, organized by ORCHID partners during the project (at least 40% of PhD Students) (100)
- Nº of members of the Digital Platform (i.e. members of the European Organ-on-Chip Society EUROoCS; see D4.3 (100)

The main dissemination activities carried out in the ORCHID project are summarized in figure 2.

For a detailed overview of the dissemination activities see Appendix 5 (ORCHID Activities)

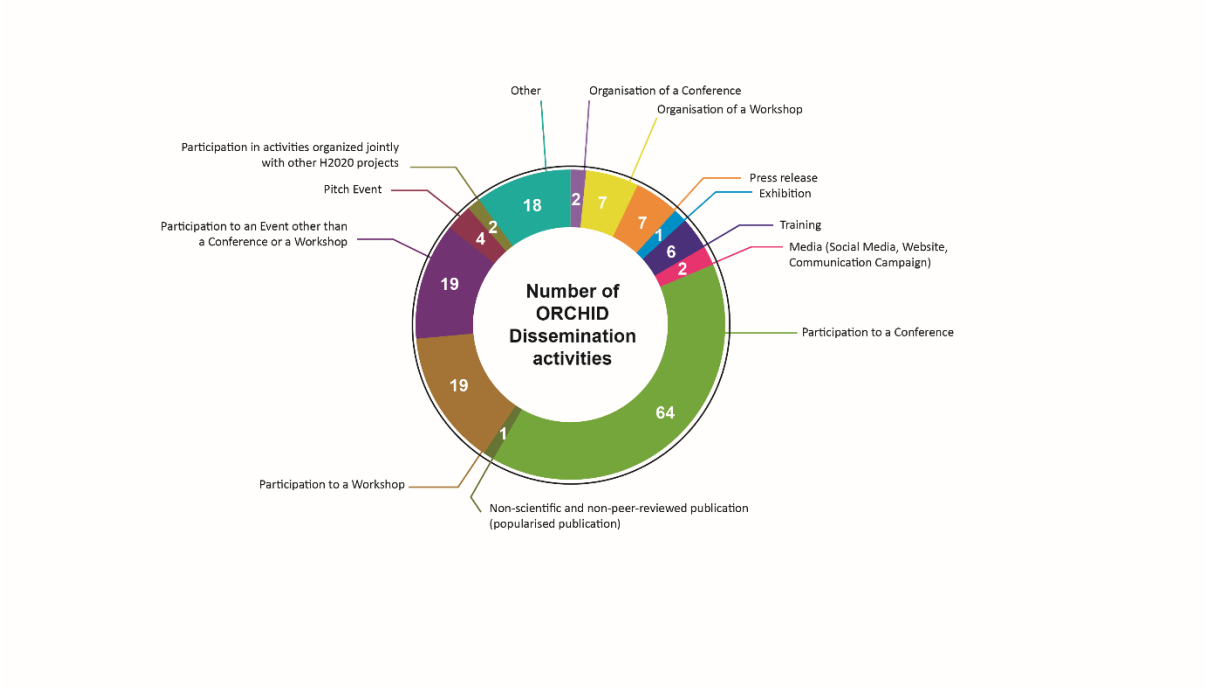


Figure 2: Graphic representation of the 152 dissemination activities carried out in the frame of the ORCHID project divided by categories

Website

The global account analysis report shows relevant data of visits and user behavior during the entire period from the launch of the ORCHID website until medio September 2019 (Appendix 1). In figure 3 an evolution in time can be observed with a clear growth in the number of visits in 2019. Throughout the project in total 3657 users with 16.870 visits to the different web pages were registered. The average duration of each session was2 minutes and 46 seconds, which indicates a certain interest in the content of the page. The decrease observed in the number of users in recent months might be due to a migration of users to the EUROoCS website.

Figure 3: Website number of visits since March 2018 till September 2019.

To make an analysis of the evolution in the number of visits to the website, we have taken two equal periods. The first is from April 19, 2018, until December 31, 2018, and the second from January 1, 2019, until September 14, 2019. As can be seen in Figure 4, there are more average visits in 2019, with an increase of 875%, in the second period (blue) compared with the first one (orange). The number of users doubled from 1241 in the first period to 2327 in the second. In r 2019 the number of sessions increased by 44%.

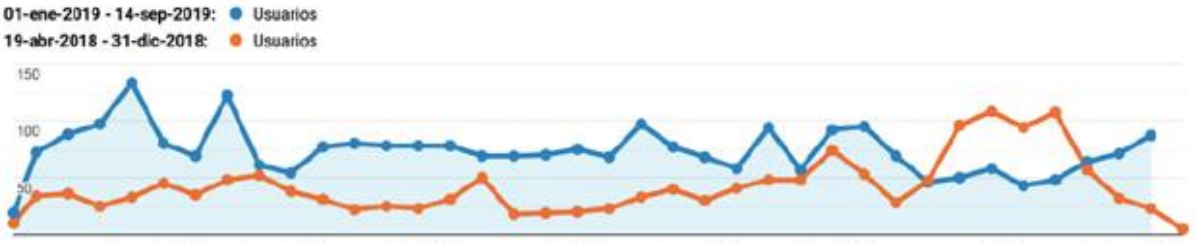


Figure 4: Website number of users since March 2018 till September 2019 divided in two periods. The first one from 10-Apr-2018 to 31-Dec-2018 in orange and the second one from 01-Jan-2019 to 14-Sep-2019 in blue.

If classified by country, the number of visits is headed by the United States with 20.9% of the visits, followed by Germany (10.5%), the Netherlands (8.1%), France (7.8%) and United Kingdom (6.9%). Analysis of the origin of the visits resulted in 45.9% coming from search engines (Google, Bing, etc.), 34.1% from a direct access, 14.8% from other websites and, finally, 5.2% from by social networks. A more detailed analysis can be found in appendix 3.

LinkedIn

The analysis carried out on the LinkedIn account of the project indicates that the objective set for this professional social network has been achieved: 110 contacts in a remarkable increasing progression in the last year of the project (Appendix 4). To better understand the profile of the contacts, an analysis of the sector to which they belong, their origin and gender was done. As summarized in Figure 5, 56% of contacts belong to the academic area. Of these, 42% are senior researchers and 14% are early-stage researchers. 29% of the contacts belong to the industrial sector and predominantly represent male CEOs of biotech companies

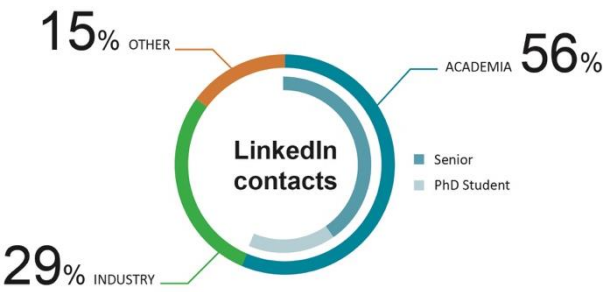


Figure 5: Analysis of the contacts in LinkedIn by sectors and experience in the academic sector

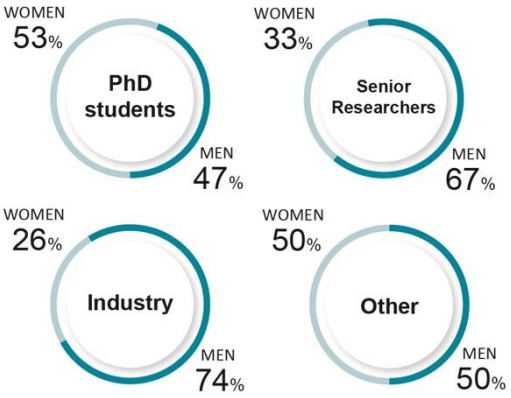


Figure 6: Gender analysis of the contacts in LinkedIn by gender and experience

Regarding gender aspects (figure 6), there is an equal gender distribution in the early-stage researchers segment. However, in the senior researchers and industry segment the number of men is almost tripled compared to that of women. Another relevant aspect analyzed (figure 7) is the origin by country of the contacts. Germany is in the lead with 15 connections, closely followed by the United States. Next in row are France and the Netherlands with 12 and 11 followers, respectively, followed by Spain and Switzerland with 9. The ORCHID project account attracted contacts from four different continents.

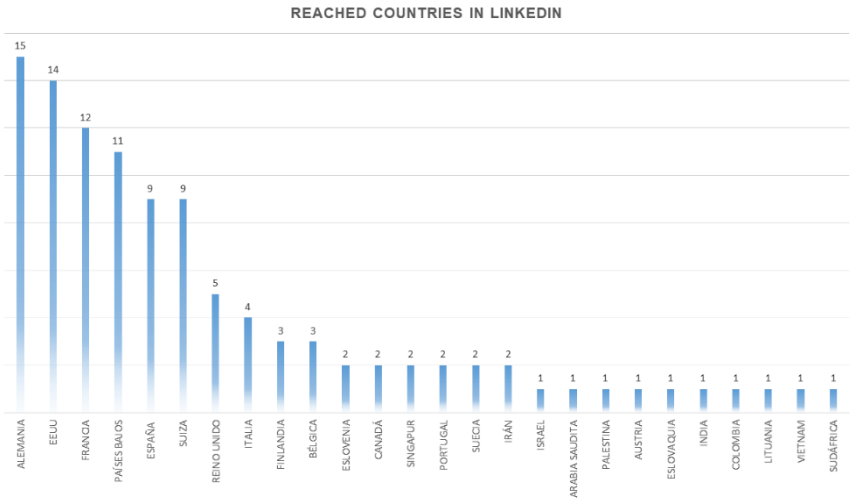


Figure 7: Origin by country distribution of the contacts

Papers in Scientific journals

Within the frame of this project, 4 papers have been published in scientific journals. The PDFs of these papers are included in appendix 5. Furthermore, 2 of them are the reports of the vision and strategy workshop organized by the ORCHID partners. They are also available as paper brochures in ORCHID layout. In the preprint repository the report of the ORCHID Vision had more than 900 views and more than 500 downloads. This data suggests that the results obtained in the ORCHID project are of great importance for the scientific community.

Congresses / conferences / workshops

The ORCHID project has been presented in more than 50 conferences. Moreover, ORCHID partners have (co-)organized 4 conferences in the project period (EUROoC 2018 in Stuttgart (Germany), IOOCS18 in Eindhoven (the Netherlands), Life On Chip conference 2019 in Leuven (Belgium) and EUROoCS 2019 in Graz (Austria) and 7 workshops. Among these workshops are the ORCHID Vision and Strategy workshop. As indicated before the reports of these workshops have been published in a scientific journal and are also available as paper brochures in ORCHID layout. The brochures are included in appendix 5. The other 5 workshops, most of them hands on training, were focused on young researchers in line with the objective to attract the attention of the early-stage researchers.

The EUROoC congress held in 2018 in Stuttgart (Germany) was attended by 120 participants, predominantly from the academic sector. The IOOCS18 conference in Eindhoven (the Netherlands) attracted over 180 participants, and the EUROoCS congress 2019 in Graz (Austria) was attended by 214 people, 30 of which came from the industrial sector. These data indicate that the number of conference attendees have almost doubled during the last year of the ORCHID project.

Moreover, at this moment (20th Sept 2019) there are 162 active EUROoCS members, which is significantly more compared to the 100 members of the Digital Platform that were set as an objective to be achieved in 2019.

Social media (twitter)

Analysis of the impact generated by the project account on the Twitter social network shows that 553 followers have been achieved per 20 September 2019 (Appendix 4). This number of followers exceeds the number of 500 that was defined as objective at the beginning of the project. During the last 12 months the number almost constantly increased at a rate of 25 new followers per month, except for January and March 2019 with36 and 38 new followers, respectively. In this social network, there is no gender difference in the followers, (49% being men and 51% women). Among the continents the European Union is leading with 51%, followed by the United States with 15%. The European countries are headed by the United Kingdom with 16%, followed by France, Spain, Germany, the Netherlands, and Italy, with percentages ranging from 8 to 5%. The main interest of our followers is "Science news" (96%), which is closely related to the main activity of ORCHID. During the first three months of 2019 there was much activity on, coinciding with the launch of the brochure of the ORCHID Vision workshop

and the publication of the ORCHID survey about training aspects. The highest number of visitors (110) was in April 2019, followed by March and May with 94 and 82 visits respectively. These results show that there is a gradually growing interest in the latest advances in the world of OoC technology.

Other dissemination actions

In addition to those mentioned above, another relevant number of actions have been carried, that appeared to be very useful but from which it is difficult to obtain quantitative data. ORCHID and EUROoCS have been presented during a meeting of the UK Organ-on-a-Chip Technologies Network, which has resulted in an increase of English EUROoCS members. In addition, EUROoCS and the European Society of Artificial Organs (ESAO) have organized a joint symposium at the annual ESAO congress in Hannover (Germany) in 2019 to exchange expertise and results and explore possible collaborations between these two different worlds. Initiatives to interact with other sectors of the population are starting to occur. The publication of an article in a local journal specific to the clinical sector had raised the interest of doctors to be educated in OoC technology. To a lesser extent meetings with politicians were held at different levels. ORCHID partners also participated in conferences of patient associations like the Spanish Association Against Cancer (AECC) to show them the new technologies that are being developed to fight cancer. In the two years of the ORCHID project the developments in the OoC field were presented in internationally recognized scientific dissemination events such as the pint of science and the European Researches night, but also on radio and television programs, and by giving talks in schools and institutes. In all these cases we experienced a great interest in OoC technology among the public at large

Figure 8 summarizes the number of persons reached per dissemination activity during the ORCHID project. For a more detailed schedule see Appendix 5 (ORCHID activities).

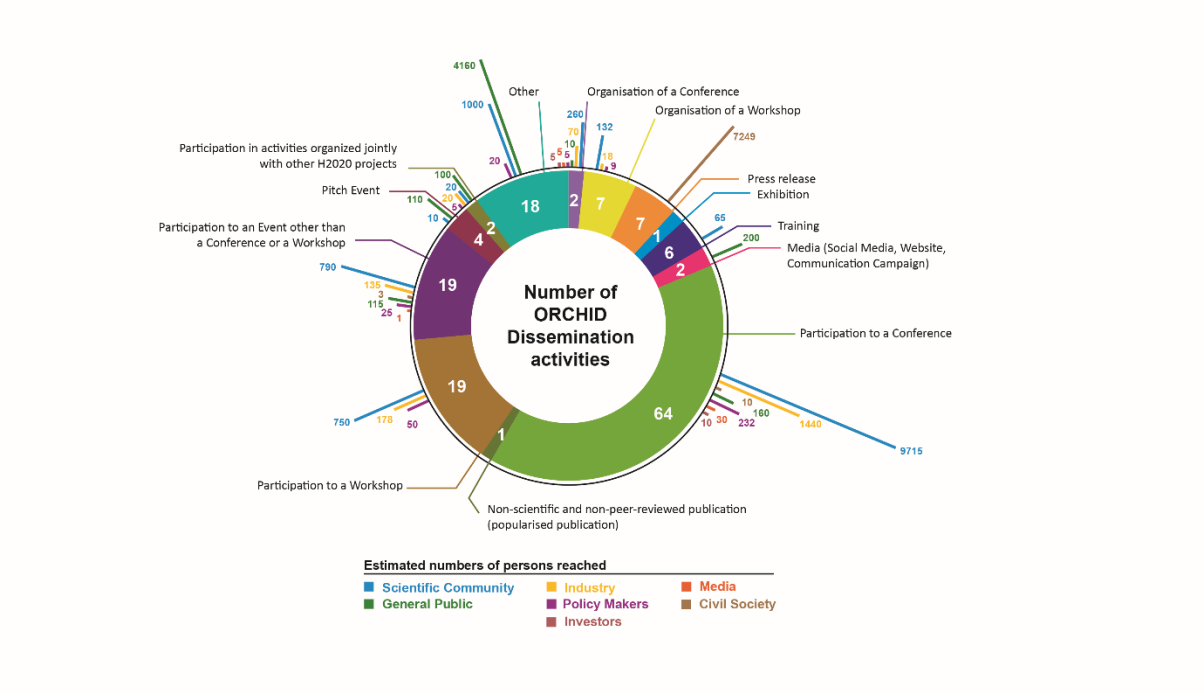


Figure 8: Graphic representation of the 152 dissemination activities carried out in the frame of the ORCHID project divided by categories with the estimated number of persons reached in each category.

Future actions:

After analyzing the data presented here and considering the suggestions received from the experts, there is general consensus that the dissemination and communication tasks should be continued by the European Organ-on-Chip Society (EUROoCS. To help with more local dissemination tasks, the formation of national organizations in different countries or regions of Europe is proposed. Below some of the main lines of action for the next 3-5 years are described.

One of the essential changes focuses on the more detailed segmentation of the group that we have considered the general public. In this segment, we can find groups that will have a high impact on the implementation of the roadmap of OoC technology. A critical group form the patients ; we must inform them about the state-of-the-art of OoC technology and the possible benefits of this technology for healthcare in developing new, faster, safer, and more precise treatments. Also, these patient groups can help to spread the word and generate social pressure to achieve the common goals.

Another important group are policymakers and regulatory agents who should be contacted at different levels (regional, national, and European). In the case of policymakers, there is a problem for long-term contacts since there is a particular political uncertainty in several countries of the union. Therefore, we propose contacts with policy officers at the highest level in the corresponding ministry or counseling to provide stable communication and connection with the different politicians on duty. In this process the national working groups and EUROoCS might play an important role as interlocutor at the national and European level. With the regulatory agents, a similar strategy will be followed going from the local-national to the European level. In this way, the same message will arrive in various

ways favoring the harmonization of regulatory standards in the different countries of the European Union.

Clinicians are another group that should be approached since they are the ones who finally will implement OoC technology in practice for their patients. A survey will be conducted among the clinicians that allows us to know the degree of knowledge that clinicians have about the OoC technology and what degree of utility they see in the short, medium and long term in their usual practice. This survey will consider the different services, experience, and position. Special attention will be paid to the survey at conferences of the different specialties, from where the survey can be submitted through specific clinical forums.

Conclusion

Deliverable 6.3 has been achieved in time.

- We have reached the most relevant key performance indicators related to the communication and dissemination of the ORCHID project.

- The number of EUROoCS new members is daily increasing demonstrating the rise in awareness about this novel technology in Europe.

- Social Media (Twitter and LinkedIn), brochures or reports, and bilateral meetings have been the most successful dissemination tools in the ORCHID project.

- The vision and strategic workshops organized by the ORCHID partners have been crucial to create an accurate diagnostic of the OoC status in Europe. Those one-day workshops with experts and relevant stakeholders are a very important tool in terms of dissemination.

- EUROoCS has become the reference for the newest developments in OoC and continues the activities that have been initiated by ORCHID.

- The Future communication and dissemination activities proposed in the roadmap will be performed by EUROoCS.

References

1. https://ec.europa.eu/research/participants/data/ref/h2020/other/grants_manual/amga/soc-med-guide_en.pdf

Appendix

Appendix 1: Logo and Website

Appendix 2: Flyers and brochures

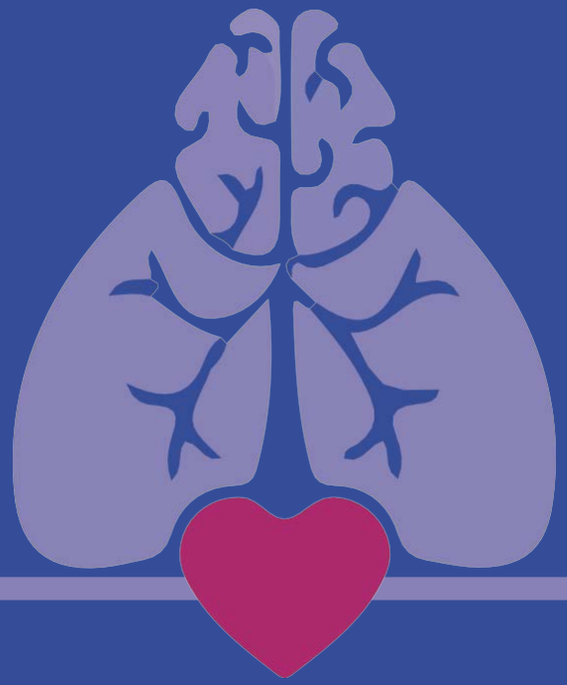
Appendix 3: Analytics report ORCHID website

Appendix 4: Analytics report Social media

Appendix 5: ORCHID papers and ORCHID activities

Appendix 6: Communication strategy

ORCHID
organ-on-chip in development



APPENDIX 1

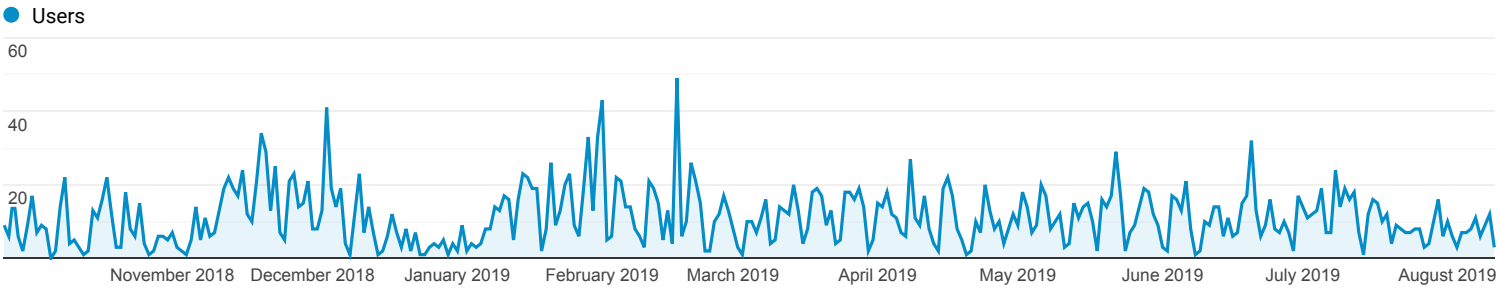
https://h2020-orchid.eu/

Audience Overview

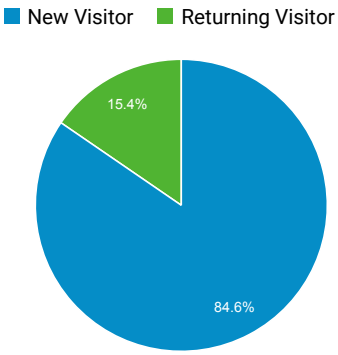
All Users
100.00% Users

Sep 26, 2018 - Aug 11, 2019

Overview



Users	2,713
New Users	2,676
Sessions	4,165
Number of Sessions per User	1.54
Pageviews	10,599
Pages / Session	2.54
Avg. Session Duration	00:02:27
Bounce Rate	64.03%



	Language	Users	% Users
1.	en-us	1,240	45.64%
2.	en-gb	229	8.43%
3.	fr-fr	158	5.82%
4.	de	132	4.86%
5.	de-de	125	4.60%
6.	es-es	124	4.56%
7.	nl-nl	118	4.34%
8.	it-it	87	3.20%
9.	fr	54	1.99%
10.	zh-cn	35	1.29%

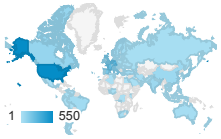
Location

All Users
100.00% Users

Sep 26, 2018 - Aug 11, 2019

Map Overlay

Summary



Country	Acquisition			Behavior			Conversions		
	Users	New Users	Sessions	Bounce Rate	Pages / Session	Avg. Session Duration	Goal Conversion Rate	Goal Completions	Goal Value
	2,713 % of Total: 100.00% (2,713)	**2,677** % of Total: 100.04% (2,676)	**4,165** % of Total: 100.00% (4,165)	**64.03%** Avg for View: 64.03% (0.00%)	**2.54** Avg for View: 2.54 (0.00%)	**00:02:27** Avg for View: 00:02:27 (0.00%)	**0.00%** Avg for View: 0.00% (0.00%)	**0** % of Total: 0.00% (0)	**€0.00** % of Total: 0.00% (€0.00)
1. United States	**550** (20.04%)	545 (20.36%)	587 (14.09%)	87.73%	1.36	00:00:25	0.00%	0 (0.00%)	€0.00 (0.00%)
2. Germany	**280** (10.20%)	274 (10.24%)	400 (9.60%)	59.00%	2.12	00:01:48	0.00%	0 (0.00%)	€0.00 (0.00%)
3. Netherlands	**247** (9.00%)	233 (8.70%)	593 (14.24%)	48.40%	4.55	00:04:50	0.00%	0 (0.00%)	€0.00 (0.00%)
4. France	**233** (8.49%)	222 (8.29%)	370 (8.88%)	61.62%	2.05	00:01:49	0.00%	0 (0.00%)	€0.00 (0.00%)
5. United Kingdom	**171** (6.23%)	169 (6.31%)	256 (6.15%)	69.14%	1.81	00:00:59	0.00%	0 (0.00%)	€0.00 (0.00%)
6. Spain	**159** (5.79%)	151 (5.64%)	537 (12.89%)	40.78%	4.72	00:06:29	0.00%	0 (0.00%)	€0.00 (0.00%)
7. Italy	**126** (4.59%)	127 (4.74%)	158 (3.79%)	67.09%	1.85	00:01:17	0.00%	0 (0.00%)	€0.00 (0.00%)
8. Ireland	**85** (3.10%)	82 (3.06%)	99 (2.38%)	83.84%	1.33	00:00:40	0.00%	0 (0.00%)	€0.00 (0.00%)
9. Belgium	**83** (3.02%)	80 (2.99%)	119 (2.86%)	63.03%	1.91	00:01:18	0.00%	0 (0.00%)	€0.00 (0.00%)
10. Switzerland	**73** (2.66%)	72 (2.69%)	113 (2.71%)	56.64%	2.27	00:01:27	0.00%	0 (0.00%)	€0.00 (0.00%)

Rows 1 - 10 of 80

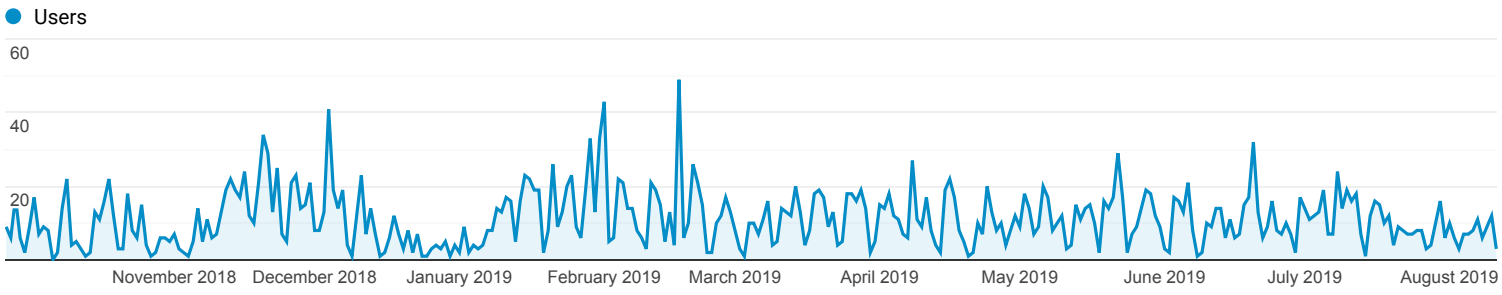
New vs Returning

All Users
100.00% Users

Sep 26, 2018 - Aug 11, 2019

Explorer

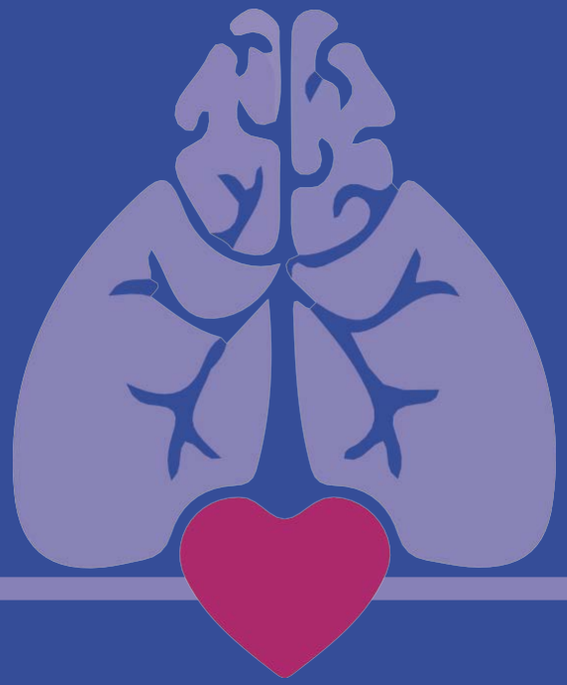
Summary



User Type	Acquisition			Behavior			Conversions		
	Users	New Users	Sessions	Bounce Rate	Pages / Session	Avg. Session Duration	Goal Conversion Rate	Goal Completions	Goal Value
	2,713 % of Total: 100.00% (2,713)	**2,677** % of Total: 100.04% (2,676)	**4,165** % of Total: 100.00% (4,165)	**64.03%** Avg for View: 64.03% (0.00%)	**2.54** Avg for View: 2.54 (0.00%)	**00:02:27** Avg for View: 00:02:27 (0.00%)	**0.00%** Avg for View: 0.00% (0.00%)	**0** % of Total: 0.00% (0)	**€0.00** % of Total: 0.00% (€0.00)
1. New Visitor	**2,674** **(84.57%)**	2,677 (100.00%)	2,677 (64.27%)	70.56%	1.79	00:01:14	0.00%	0 (0.00%)	€0.00 (0.00%)
2. Returning Visitor	**488** **(15.43%)**	0 (0.00%)	1,488 (35.73%)	52.28%	3.91	00:04:37	0.00%	0 (0.00%)	€0.00 (0.00%)

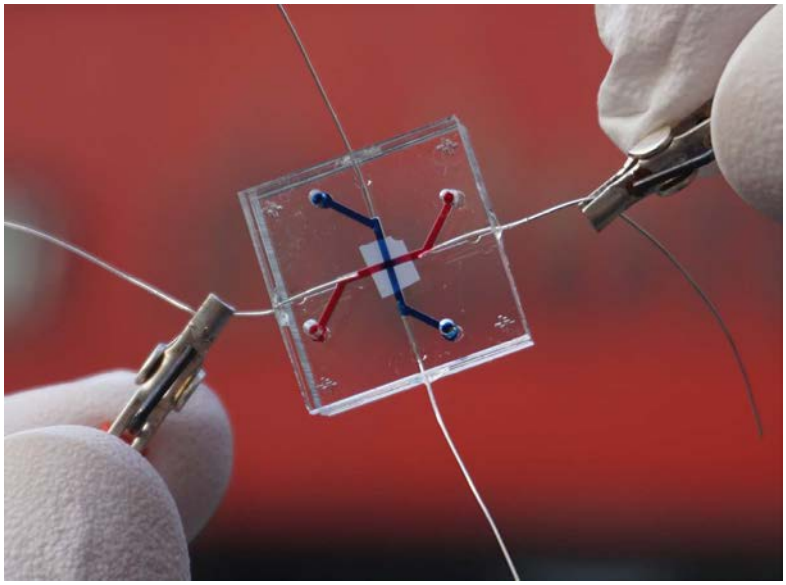
Rows 1 - 2 of 2

ORCHID
organ-on-chip in development



APPENDIX 2

ORCHID



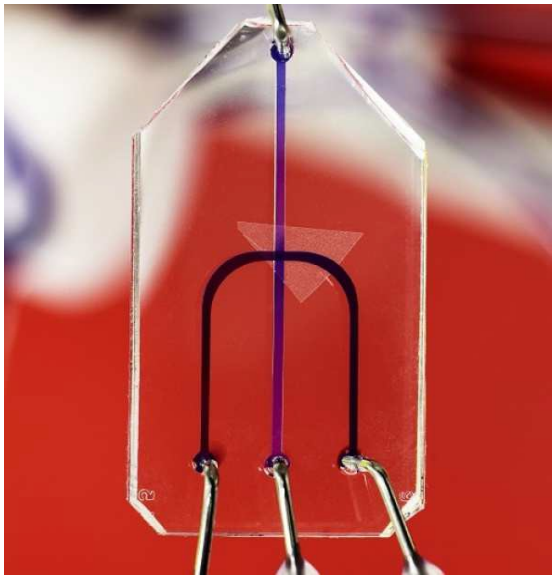
ORCHID
organ-on-chip in development

ORGAN ON CHIP IN DEVELOPMENT

The ORCHID project (Organ-on-Chip development) is an EU initiative, coordinated by Leiden University Medical Center and the Dutch Organ-on-Chip consortium hDMT in The Netherlands. The main goal of ORCHID is to create a roadmap for organ-on-chip technology and to build a network of all relevant stakeholders in this promising innovative field. In the ORCHID project that started on 1 October 2017 in total seven leading European research institutions are involved.

What is the Organ on Chip Technology?

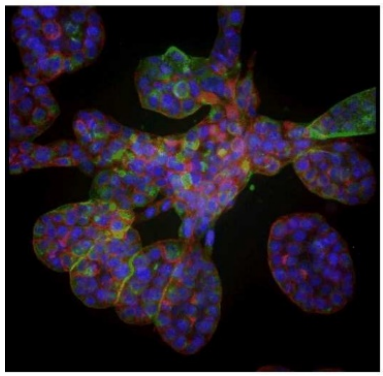
An organ-on-a-chip (OOC) is a microfluidic cell culture chip capable to resemble partial or totally the pathophysiological behaviour of entire organs or tissues. To achieve this goal, it is not only needed to place the different cell types in their proper location but also to mimic the chemical and mechanical stimuli inside the microfluidic chip. Fabrication technologies (Microfabrication, microelectronics and microfluidics) combined with advanced cell culture techniques will provide novel physiological and sophisticated in vitro models closer to the in vivo organ functions.

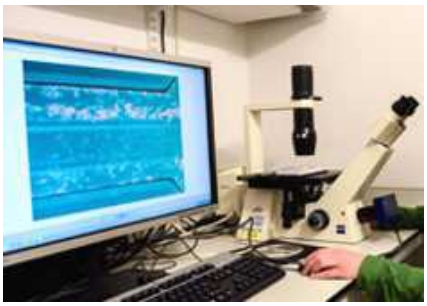


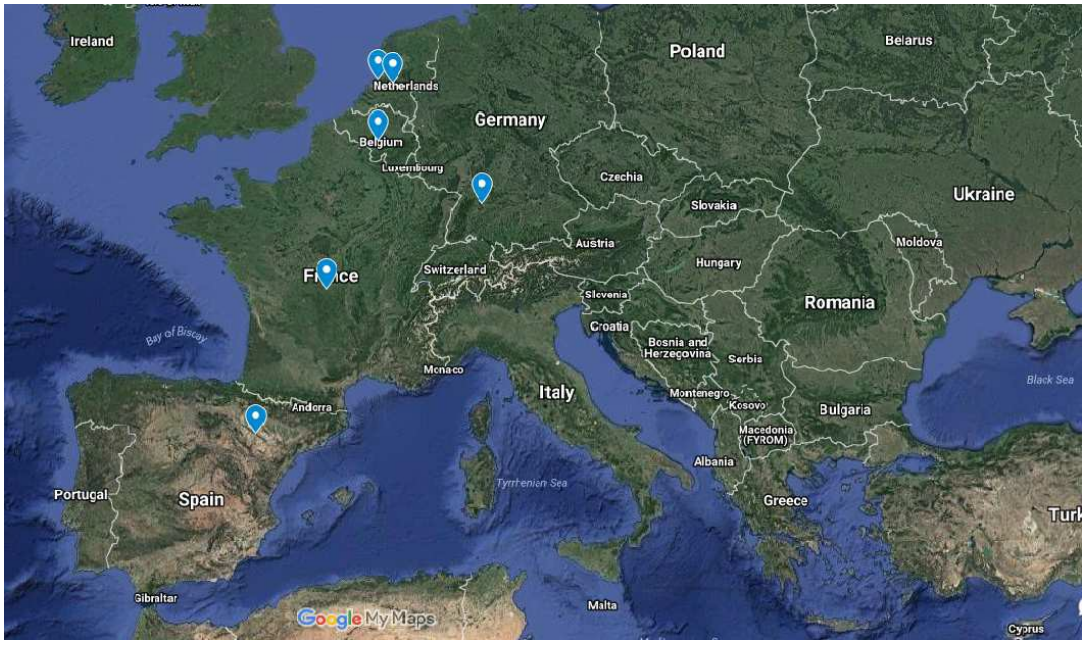
Organs-on-chips will radically change the way and the speed at which drugs can be implemented clinically, not only for general drug development but also for personalised drugs. This is not only key for making drug and cosmetic development test-animal free, but the accuracy and speed with which outcomes can be evaluated will surpass standard cell cultures and laboratory animals that presently capture human physiology and response on drugs imperfectly. Organ-on-chip technology is cutting-edge science, which goes beyond the frontiers of knowledge and requires multidisciplinary collaboration. hDMT, one of the partners of this consortium, has submitted a FET Flagship proposal for this technology with a broad support from European research centres and is actively working with other regenerative medicine proposals to settle a broad EU flagship. Partners are European leaders in their specialist area but their collaboration is essential to realize the potential of this emerging technology.

Summary

Organ-on-chip technology will revolutionize the healthcare domain by offering new and ground-breaking solutions to different industries and especially for regenerative medicine and medication. Organ-on-Chip In Development (ORCHID) will create a roadmap for organ-on-chip technology and the framework to build a network of relevant stakeholders. ORCHID will achieve this through 5 objectives: (i) evaluation of the technology (state of theart and unmet needs), (ii) identification of ethical issues, establishing standards and identifying measures for regulatory implementation, (iii) analysis of economic and societal impact, training and education, (iv) developing a roadmap which will guide the required R&D efforts and (v) raising awareness and building the ecosystem for organ-on-chip technology through a digital reference platform. ORCHID will have a broad impact: it will facilitate drug development, contribute significantly to reducing animal experiments and help in developing personalized medicine. ORCHID will achieve these goals by providing a framework to the main stakeholders, bringing together key players and raising awareness on organ-on-chip technology throughout Europe. The digital platform will gather all information on existing and new initiatives in the field. In this way ORCHID as a whole will secure and reinforce Europe's leadership on organ-on-chip. The consortium is composed of the main contributors to the field who are all very experienced and who will strongly collaborate with each other. Leiden University Medical Centrum (LUMC) will lead the consortium (Prof. dr. Christine Mummery is the Project Leader), the Institute for human Organ and Disease model (hDMT) and Delft University of Technology (TUD) will focus on the strategy and the roadmap, Fraunhofer IGB on impact assessment, CEA Leti on eco-system development and the digital platform, IMEC on the ethical aspects, regulation and standardization and the University of Zaragoza will lead dissemination. ORCHID will install an Advisory Board composed of complementary specialists in the field.







Objectives

The main goal of this project is to create a roadmap for organ-on-chip technology and to build a network of academia, research institutes, industry, and regulatory bodies to move organ-on-chip technology from promise in the laboratory into reality for the citizens of the Europe and the rest of the world.

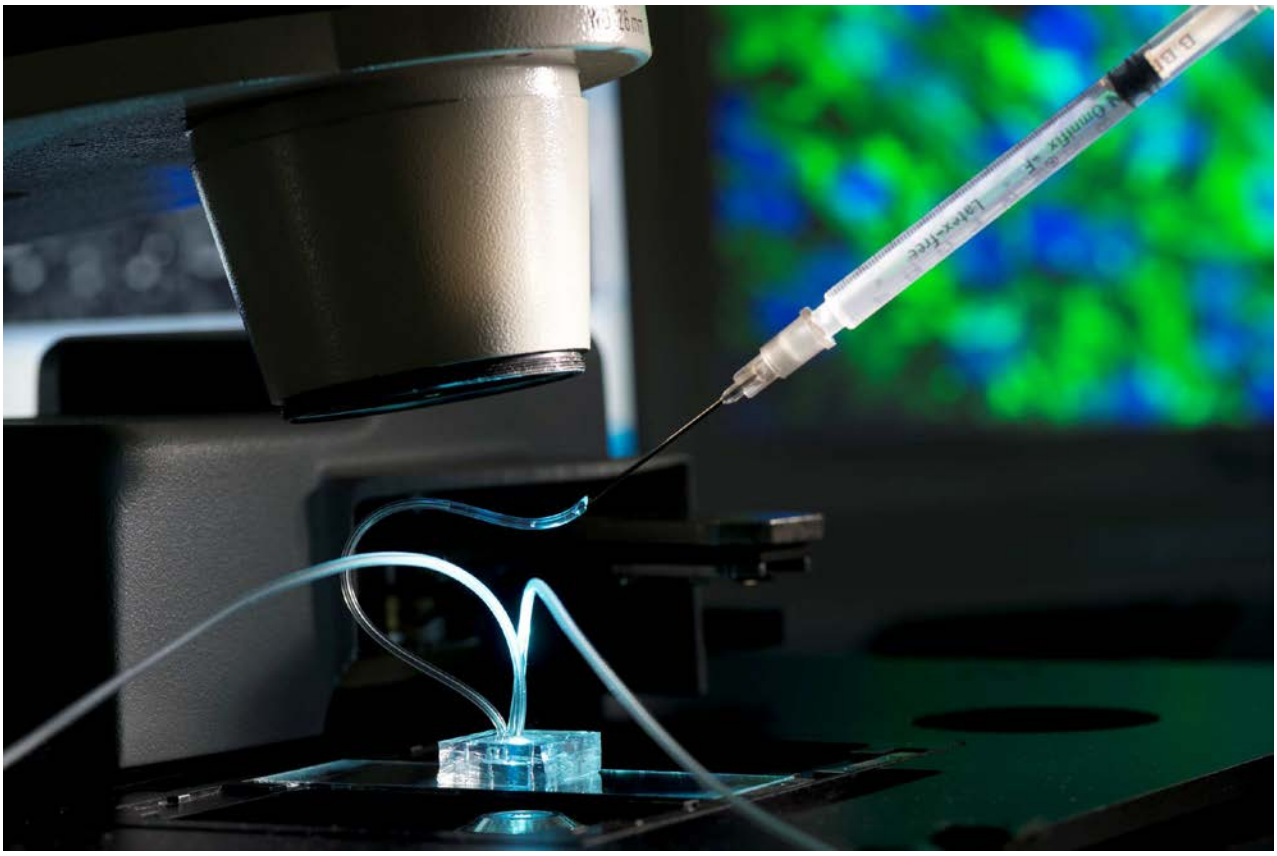
1: Assess the status of organ-on-chip technology in Europe

2: Identify ethical issues, drive standardization and take steps for regulatory take-off

3: Analyze the impact on economy, society, training and education

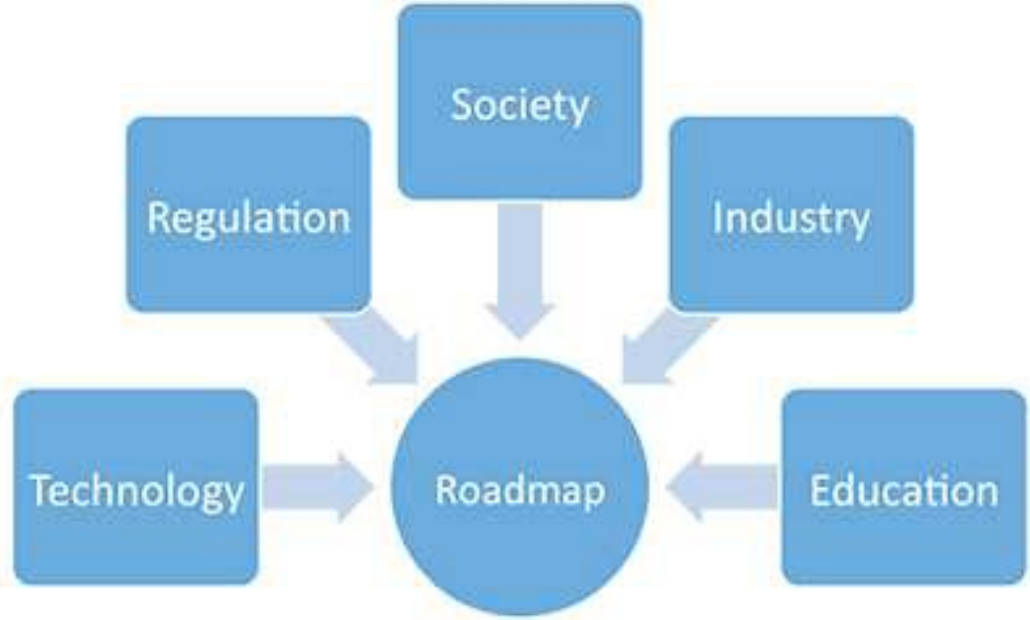
4: Establish the organ-on-chip technology roadmap

5: Raise awareness and build the ecosystem for organ-on-chip technology



Indicators

- The roadmap for organ-on-chip technology and its applications, based on the development status and the impact: technology v2.0, next areas to be explored, definition of the intermediate milestones and objectives, etc.
- Training, education and exchange research programs to promote the technology including relevant skills.
- Installation of a large international ORCHID advisory board to advise and raise awareness on the technology.
- Digital platform which will be the reference for all stakeholders.
- List of activities to raise awareness about organ-on-chip technology: events/workshops involving stakeholders, media publicity (social media/general media), publications. Recommendations to pave the way for innovation: facilitate market introduction, preparing the regulation and legislation for the organ-on-chip technology, solving ethical issues.



Partners

The consortium is composed by the following organizations:

LEIDEN UNIVERSITY MEDICAL CENTER

HUMAN ORGAN AND DISEASE MODEL TECHNOLOGIES

Fraunhofer IGB

1542 Universidad Zaragoza

imec

TU Delft

DE LA RECHERCHE À L'INDUSTRIE cea

CONTACT:

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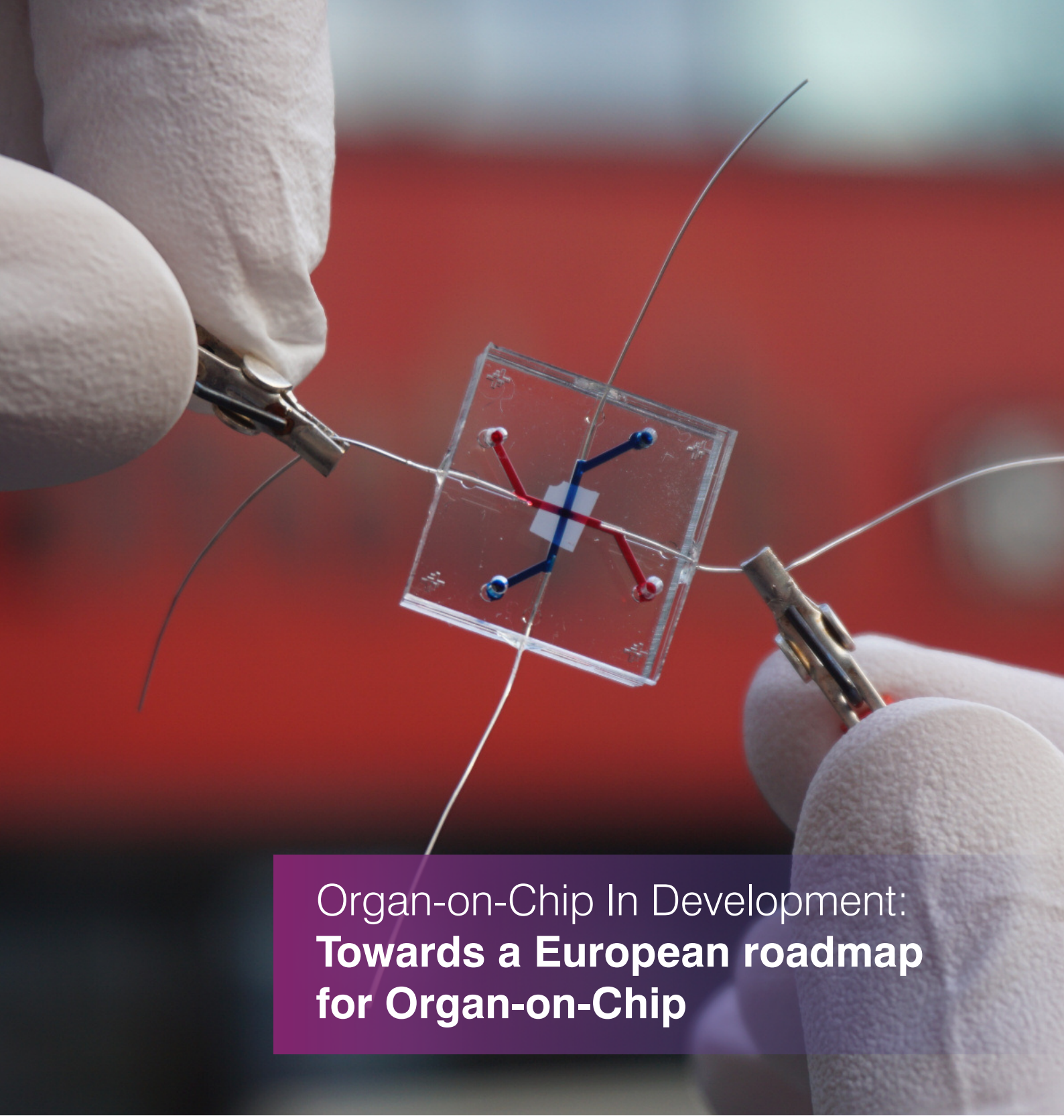

Organ-on-Chip In Development: **Towards a European roadmap for Organ-on-Chip**

ORCHID
organ-on-chip in development

LUMC · DMT Human Organ and Disease Model Technologies · Fraunhofer IGB · imec embracing a better life · cea · Universidad Zaragoza · TU Delft

Organ-on-Chip In Development: **Towards a European roadmap for Organ-on-Chip**

Massimo Mastrangeli*[1], Sylvie Millet*[2], Dries Braeken[3], Wolfgang Eberle[3], Luis Fernandez[4], Mart Graef[1], Xavier Gidrol[2], Nathalie Picollet-D'Hahan[2], Peter Loskill[5], Christine Mummery[6], Ignacio Ochoa[4], Mieke Schutte[7] and Janny van den Eijnden-van Raaij[7]

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*These authors contributed equally to this work.

Photo: Paul ter Braak/Marinke van der Helm; BIOS Lab on a Chip group, UTwente.
Device: Marinke van der Helm/Michaela Hällevall.

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Organ-on-Chip In Development: **Towards a European roadmap for Organ-on-Chip**

Abstract

This report surveys the current landscape in the research, development, applications and market opportunities for Organ-on-Chip (OoC) devices to establish the pillars of a European OoC ecosystem. Based on a bibliometric study, a market analysis, expert interviews, and panel discussions held at the ORCHID Vision Workshop (Stuttgart, 23 May 2018), this report outlines presently unmet needs, key challenges, barriers and perspectives of the field, and finally proposes recommendations towards the definition of a European roadmap that could render OoC systems (OoCs) realistic models of human (patho)physiology in the near future.

1. Introduction

The healthcare challenge

A critical problem in the development of effective disease treatments is the lack of adequate model systems to identify drug targets, screen toxicity, and predict clinical drug efficacy and the effects of active substances in humans. Traditional animal models or conventional cell cultures do not accurately mimic human physiology, and thus tend to fail to recapitulate diseases and to predict human responses to medical treatments. This is a major cause of late drug failures in clinical trials, expensiveness of new drugs, and lack of medication for some diseases. In addition, ethical questions raised by animal use increase the pressure to minimize animal experimentation. For these reasons, the pharmaceutical industry is looking for new ways to improve the drug development process and to identify effective and personalized treatments; biomedical researchers require better systems to model diseases for a better understanding of their mechanism and aetiology; and cosmetics, chemical, food and other industries are in need of physiologically relevant human models to test toxicological hazards and assess the risk of substances under increasingly stringent regulatory requirements.

Organ-on-Chip is a game-changing technology expected to offer solutions for these problems and meet the needs of different stakeholders. In spite of its allure, pharma is however cautious to invest in this new technology, presently awaiting evidence of its added cost-benefit value, and whether it could represent a feasible route to precision medicine and improved patient stratification. It is thus necessary to bridge the gap between the potential of OoCs and their worldwide acceptance. Defining the putative benefits of OoCs and how these can be proven and achieved is the preamble for an OoC roadmap, which is one of the aims of the ORCHID project.

ORCHID: Organ-on-Chip in Development

The Horizon 2020 FET-Open project *Organ-on-Chip In Development* (ORCHID) started in 2017 with the goal of creating a roadmap for OoC technology and of building a network of academic, research, industrial and regulatory institutions to move OoCs from laboratories into the reality of the citizens of Europe and the rest of the world. ORCHID is a collaboration between seven partners from six European countries, forming the ORCHID Consortium[1] (www.h2020-orchid.eu). ORCHID has an international Advisory Board, consisting of world-renown experts involved in the OoC field. As part of the project, these and other experts have been asked to share their view on the state-of-the-art, unmet needs, challenges and barriers of the field. The results of the expert interviews, together with the results of bibliographical, bibliometric and market analyses of the OoC technology, carried out within the ORCHID project (Appendix 1), formed the basis of the *ORCHID Vision Workshop*, held in Stuttgart on 23 May 2018. The goal of the workshop was to define the pillars of a European OoC roadmap, including the definition of desired and feasible goals for a concrete deployment of the OoC technology. This report summarizes the results, expert discussions, conclusions and recommendations that emerged from the workshop, which represented a considerable step forward in the establishment of a European OoC ecosystem: the birth of the European Organ-on-Chip Society and the Digital Platform 'Organ-on-Chip *For All*'.

[1] ORCHID partners are: Leiden University Medical Center (coordinator; The Netherlands), Institute for Human Organ and Disease Model Technologies (hDMT) and Delft University of Technology (Delft, The Netherlands), CEA (France), imec (Belgium), Fraunhofer Institute for Interfacial Engineering and Biotechnology (Fraunhofer IGB, Germany), and University of Zaragoza (Spain).

2. Organ-on-Chip definition and key features

According to the experts, and as confirmed during the ORCHID Vision Workshop, an OoC can be defined as "*a fit-for-purpose microfluidic device, containing living engineered organ substructures in a controlled microenvironment, that recapitulates one or more aspects of the organ's dynamics, functionality and (patho)physiological response* in vivo *under real-time monitoring".*

OoCs can be classified into two types with complementary goals and distinct complexity: (i) single-organ systems, emulating key functions of single tissues or organs, and (ii) multi-organ platforms, combining multiple OoCs to reproduce the systemic interaction and response of several organ models within a single system. Multi-OoCs link individual OoCs through microfluidic, preferably vascularized channels that mimic *in vivo* physiological coupling, and enforce cell-to-fluid volume ratios and flow distributions to create *in vitro* models of subsystems of the human body (Ronaldson-Bouchard & Vunjak-Novakovic, 2018). Further along this line, Human(-body)-on-Chip (HoC) systems are aiming to emulate whole organismal physiology by integrating many relevant single-organ models (Marx *et al.,* 2016).

As implied by these definitions, the OoC technology stands on converging advances in tissue engineering, semiconductor and polymer microfabrication, and human cell sourcing. The associated value chain emerging from our analyses (Appendix 2, Fig. 1) highlights the need of a multidisciplinary approach to implement OoCs, and of a facilitating dialogue between developers, both academic and industrial, and stakeholders such as clinicians, patients, regulators and different end-users. All these disciplines are represented in the ORCHID Consortium.

3. Methodology

The analytical methodology adopted in the ORCHID project is centred on experts' interviews supported by a documentary approach, relying on a bibliometric study combined with a market report to investigate the state-of-the-art and the unmet needs in the global OoC ecosystem (Appendix 1).

4. State-of-the-art

A worldwide growing field of research

As mentioned, the OoC field emerged from the convergence of microfluidics and tissue engineering research. Whereas in early 2000's patents and publications mainly focused on microfluidics and associated fabrication techniques, more recent advances in stem cell biology, combined with decades of fundamental biological studies in cell signalling and biomechanics, accelerated the development of OoCs. The ORCHID bibliometric approach reflected this increasing activity by evidencing a rise in both dedicated patents and publications with a compound annual growth rate (CAGR) of +46% over the last ten years (123 patents and publications in 2007, compared to at least 390 in 2017) (Appendix 2, Fig. 2a). Such continuous growth, driven by the huge market potential, was made possible by the concomitant diffusion of multidisciplinary approaches supported by an improved dialogue between developers such as biologists (cell culture, physiology), engineers (microfluidics, biosensing systems), material scientists (microenvironment, substrates), but also regulators, patients, clinicians and end users from both academia and industry. Originating from the USA, which pioneered the development of customized cellular microenvironments to capture the structural complexity of organs, this worldwide interest is rapidly engaging Europe, which has a strong track record in tissue engineering and microfluidics, and for which OoCs could represent a new growth opportunity (Appendix 2, Fig. 2b-c). The Asia-Pacific region (APAC) contributes also substantially to the field with both established players and newcomers, supported by an exponential growth in technological and biological research, especially in Korea, China and Japan.

OoCs hold great promises as avatars for native functional tissues

The very dynamic R&D activities have been translated into technological advances in both microfluidics and tissue engineering, providing OoCs with key added values towards a more accurate view of what happens in humans compared to other existing models (Appendix 2, Table 1). The OoC technology allows reconstitution of the microarchitecture of the organ supported by the design of a dedicated mechanical context matching the shape, surface pattern and stiffness of organ-specific microenvironments. The precise microfluidic flow control enables optimal oxygenation and nutrition that not only afford long-term viability of healthy tissues, but also an efficient circulation of immune system cells, antibodies, biochemical signalling molecules and metabolites, and the ability to collect tiny secretion volumes for analyses. Continuous perfusion and mechanical stress help to build dynamic tissue models, supposedly far more relevant than conventional static cell cultures, and enable the control of spatiotemporal chemical gradients and mechanical cues to study the influence of the microenvironment on the cells. Moreover, OoCs allow to precisely investigate specific tissue-tissue interfaces and biological events that cannot be monitored in animals or human patients. Their minute size, the control of the microenvironment, the facilitated optical access at high spatial resolution, and the integration of biosensors for real-time data collection bring OoCs large advantages over other models (Marx *et al*., 2016). The tightly monitored regulation of the cellular environment and homeostasis should facilitate long-term cell culture, possibly over months. In addition, the great diversity and range of complexity of OoCs offer the opportunity to optimize or even customize the design of targeted studies, paving the way to personalized medicine.

According to their expected benefits, the main applications of OoCs range from toxicity test to drug discovery, and target users from various fields, such as biomedical researchers, modelling diseases for improved understanding of their mechanisms and aetiology, and industrials from different profiles – pharmaceutics, biotechnology, cosmetics, chemistry and environment – especially interested in predicting efficacy and safety of compounds for humans. Some players are even going further, introducing in their scientific publications the more long-term potential of OoCs for regenerative tissues and medicine. Existing models and proposed applications are comprehensively reviewed in Marx *et al.* (2016), Zhang & Radisic (2017), Ronaldson-Bouchard & Vunjak-Novakovic (2018) and Zhang *et al.* (2018).

Nevertheless, OoCs still need scientific evidence of clinical correlation to physiological human behaviour. In particular, the metrics to be considered and their corresponding readouts largely remain to be defined. They are a prerequisite to demonstrate the relevance of the use of OoC compared to other traditional models, and to envision how they could influence the decision-making process.

The rapid development of OoC is driven by academics supplying multifaceted industrial companies

The OoC market gathers many players from different horizons, and evolves continuously due to rapid technological advances and the field's strong multidisciplinary attractiveness. The ORCHID bibliometric analysis identified at least 650 players (the top 30 are shown in Appendix 2, Fig. 3). Most of the well-known academic teams are concentrated within pioneering American hubs such as the Boston ecosystem (Wyss Institute, MIT, Harvard, Brigham Women Hospital) and the universities of California (Berkeley, UCLA, UCI, Stanford), New York (Cornell, Columbia) and Pennsylvania (Drexel, Pittsburgh). They tend to work especially on brain, lung and heart to address toxicological issues, but also on muscle, vasculature and bone marrow (*data not shown*). The Asia-Pacific region shows historical players like the University of Seoul (Korea), the Chinese Academy of Science (Beijing, China) and the University of Tokyo (Japan), leading chemical, physical and biological engineering approaches to emulate in particular brain, liver and lung tissues. The attractive market drives also the repositioning of key European players in microfluidics and cell culture, such as the Fraunhofer Institute (Germany), the University of Twente (The Netherlands), the CEA (France), the Technological University of Compiègne (part of the CNRS, France), and the Swiss Federal Institute of Technology (EPFL, Switzerland), which appear to focus their research on the modelling of brain, liver, kidney and skin for toxicological concerns (*data not shown*).

This academic ecosystem supplies industrials from various domains, which may coexist to play a dedicated role in the OoC value chain (Appendix 2, Figs. 4 and 5): *i.* pharmaceutical companies; *ii.* companies specialized in microfabrication, imaging and electronics/robotics; *iii.* lab-on-chip manufacturing companies; and *iv.* OoC companies (*i.e.* commercializing fully operational OoC). Indeed, the development of OoCs is supported since a few years by pharmaceutical companies (*e.g.* GSK, Roche, AstraZeneca) searching for alternative predictive models, especially for the lung, the liver, the digestive and the nervous systems. OoC manufacturing and peripheral instrumentation require the concomitant involvement of supplying companies specialized in microfabrication, imaging, electronics and robotics (*e.g.* Seiko, Philips, Carl Zeiss; Appendix 2, Fig. 5), in particular for OoC characterization and monitoring. Historical lab-on-chip manufacturing companies (*e.g.* Aline, Micronit, Microfluidic Chipshop, Minifab) consider OoCs as a promising growth opportunity. They are starting to partner with OoC companies and propose tailored approaches to support hardware development to scale up and standardize chip production.

OoC companies are mostly start-ups founded by ex-academic teams (*e.g.* Draper, CN Bio, TissUse, Emulate, Mimetas; Appendix 2, Fig. 5). According to the Yole market report, only 18 private OoC companies were found on the market in 2017. Among the most active companies, Draper, TissUse and Nortis are characterized by a multi-tissue R&D activity, whereas the others seem to prioritize single-tissue development. Very few of them are already in the production and commercialization phase, the others being engaged in an iterative process with end users to test different OoC solutions, *i.e.* manufacturing prototypes and producing small series in-house. For instance, Emulate formed various strategic partnerships with pharmaceutical industries (Roche, Takeda Pharmaceuticals, Merck, Janssen) to improve its solutions, but also with the Food and Drug Administration (FDA) to evaluate and qualify the use of its technology for toxicology testing. The latest collaborative partnership, led with AstraZeneca's Innovative Medicines and Early Development Unit (IMED), aims to integrate Emulates' OoCs within the IMED drug safety laboratories and to co-locate Emulate's scientists within AstraZeneca's labs to accelerate the development of OoCs[2]. In addition to its successful collaboration with AstraZeneca on a comprehensive type 2 diabetes-on-a-chip model, TissUse recently announced a cooperative agreement with Roche to develop applications for its multi-OoC platform in drug R&D. The aim of this three years project is to establish *in vitro* assays for the assessment of lineage-specific hematopoietic toxicity and the evaluation of pharmacokinetics of therapeutic antibodies[3]. OoC companies need both external partners and high financial investments to go through the prototyping phase and to scale up the production. Impressive growth is also possible by a switch towards the small-scale stage, as shown by Mimetas which is mass-producing its OrganoPlate® after only 3 years of existence, and is supplying nearly all major pharmaceutical companies.

The current market positioning of OoC companies is tightly associated with the type of devices developed and their level of maturity. Three different business models can be distinguished: *i.* ready-for-culture microfluidic devices (chips and/or plates); *ii.* fully operational OoCs, including the microfluidic device and cell culture integration; and/or *iii.* a full-service offering to perform in-house tests requested by end users. Companies may switch between these business models; and according to the Yole's report, the large majority of OoC companies are even not sure whether they should sell the devices or offer testing services. Starting with a service-based business model may help to build strong relationships with customers, whereas getting direct input and better understanding of customers' needs enables the joint development of effective OoC platforms. From an end-user point of view, the service-based offer could be of great value for early stage screening, when there is a large amount of compounds to be tested, especially in terms of logistic organization. It is mostly more convenient to ship a drug or a chemical compound than cell cultures. To understand a complex biological interaction, though, some customers, particularly pharmaceutical, may be more interested in buying the OoC to do their experiments in-house.

Whatever the business model of choice, the OoC companies know that minimizing the operational complexity is crucial for commercialization and market penetration. They need to entertain tight relationships with academia to ensure a continuous technological sourcing and to remain competitive.

[2] Press release on Emulate Inc. website: https://emulatebio.com/press/emulate-atrazeneca-partner/
[3] Press release on TissUse Gmbh website: https://www.tissuse.com/en/news/press-releases/

Public and private investments are required to move OoC from bench to bedside

Both public and private sources have substantially funded OoC start-ups and research groups during the last few years. For instance, USA's National Center for Advancing Translational Sciences (NCATS), in conjunction with the National Institutes of Health (NIH) Common Fund, has invested $70 million over a 5-year period to launch the Microphysiological Systems or Organs-on-Chips Program (2012). The aim of this program, part of a coordinated effort between the NIH, the Defense Advanced Research Projects Agency (DARPA) and the Food and Drug Administration (FDA), was to accelerate the development of human OoC that *"will improve the reliability to identify human drug toxicities and predict the potential efficacy of a drug in a human population prior to use of the drug in late-stage clinical studies"* (NCATS website).

In the meantime, private investors have gained confidence in OoC technology. In particular, 2018 was a prolific year in fundraising, with $36M and $20.5M secured by Emulate and Mimetas respectively. According to the Yole market report, the most efficient company in fundraising is Emulate with 4 rounds in 4 years for a total of $93M. Other US companies have also raised several millions of dollars, such as H*μ*rel Corporation ($9.2M in 2013), Nortis (more than $8M in total, with a first round of $2.65M in 2014), and Tara Biosystems (fundraisings in 2014, 2016 and 2017, for a total of $11.75M) (Yole market report, 2017; Tara Biosystems website). In Europe, 2 companies have also succeeded to raise funds: Mimetas (The Netherlands) with a total of $27.65M (3 rounds in 2014, 2015 and 2018), and TissUse (Germany) with $4.6M in 2015. The Netherlands have funded a national OoC initiative (NOCI) with €18.8M for 10 years; a H2020 ITN project on OoC (EUROoC), coordinated by Fraunhofer IGB was recently granted with 3.94M for 4 years. Globally, American companies are way ahead with regard to fundraising: the US government is willing to support the OoC field, especially through the DARPA and the NIH, and lately the NASA and CASIS, with an investment of more than $200M over the past 5 years.

Market forecasts: potential development from an emerging market towards an exponential growth

The Yole market report estimates the combined sales of OoC devices and services at no more than $7,5M in 2016, with the potential to undergo an impressive growth and become a multi-billion dollar market in the mid- to long-term, in view of the fact that OoCs could help the industry to save billions of dollars every year, especially by bridging the translational gap between preclinical and clinical studies required for the drug development process. As already indicated, very few players are currently in the production and commercialization phase; and while pharmaceutical and cosmetics companies are engaged in an iterative process to test different OoC solutions, they are conservative and might need time to widely adopt the technology. This overall context led Yole Développement to detail both a realistic and optimistic scenario, in which the market could grow at a CAGR from 2017-2022 of 38% to 57% to reach $60M to $117M, respectively in 2022 (Appendix 2, Fig. 6; for further market data, see the Yole report, 2017).

In the optimistic scenario, based on the companies' forecasted revenues (Appendix 2, Fig. 6a), the Yole report considers that if all conditions are met, *i.e.* industrial adoption is speeding up, OoC companies are able to overcome technical challenges and to upscale production, a production of 858k units will be reached in 2022, corresponding to an overall market of $117M. The service-based market is expected to remain much smaller than the device-sales market, and may not be sustainable

in the long-term.

In the realistic scenario (Appendix 2, Fig. 6b), the Yole report forecasts that the majority of OoC developers will face issues when the demand will grow. Especially, it considers that scaling up the production will likely slow down the growth of OoC companies during the period 2018-2021. Most of them will have to switch from PDMS prototyping and small-series to large-scale production in other materials (glass, polymer injection moulding), requiring redesign steps that will be very expensive for the relatively small companies involved. In this scenario, the OoC market will grow from $7,5M in 2016 to $59,7M in 2022 because only few companies have already managed to scale up their production. The revenue fraction deriving from services is higher than for the optimistic scenario because OoC companies will focus on customized services to offset losses due to the costs for production upscaling.

5. Challenges

Unmet needs

Evidence of added value

A notable unmet need that emerged from the experts' interviews is data-supported evidence of actual advantages of the OoC technology compared to existing conventional models or well-established approaches to tissue engineering. Particularly, while the superiority of 3D over 2D cell cultures for *e.g.* phenotypic expression is attested in recent scientific literature, the advantages deriving from the inclusion of dynamic perfusion and *in situ* stimulation in OoCs arguably need more substantial support.

OoCs can pave the way to personalized medicine and de-risking drug development

The failure of preclinical cell cultures and animal models to reliably predict drug efficacy and safety at the human clinical trial stage ends up wasting billions of dollars each year and slows down the development of medical treatments. Whereas spending on drug development increased over the past 20 years, the number of drugs approved annually declined (Zhang & Radisic, 2017). Many compounds with high potential health benefit are eliminated early in development due to the poor predictability of preclinical models. Drugs could even be withdrawn shortly after entering the market, mainly because of cardiac, liver and kidney toxicities. Late-stage failures cause catastrophic losses while significantly driving up cumulative costs and patient risk. Positioning OoCs as powerful predictive tools for preclinical screening might represent the ideal solution for the pharmaceutical industry to eliminate ineffective drug candidates as early as possible and curb the costs of drug development (Zhang & Radisic, 2017).

As expected, the OoC application most cited in scientific literature and in the ORCHID experts' interviews lies in the pharmaceutical drug development process, including safety assessment and efficacy testing. The main idea shared by all players is that OoCs may enable more rapid, accurate, cost-effective and clinically relevant testing of drugs. According to a recent scenario-based cost analysis conducted in the context of the ORCHID project, experts expect a positive budget impact, reaching a reduction up to

26% in the total R&D costs for drug development (Franzen *et al.*, 2018). While all cost drivers may be impacted, savings would mostly be achieved by improving the success rates. The R&D phases in which experts expect the most benefits are lead optimization and preclinical phases.

Data from animal studies are often poorly indicative of the human situation, since animal preclinical models have limitations in mimicking the complex processes specifically occurring within the human body (Marx *et al.*, 2016). OoC models may potentially bridge this translational gap by fostering the implementation of 3Rs, *i.e*. Reduction, Refinement, and Replacement of animal testing. However, all interviewed experts agreed that OoCs are currently far away from replacing all animal models, and should be used mostly as a complementary approach to animal testing. Specifically, and as evidenced in the ORCHID impact analysis (Franzen *et al.*, 2018), high-throughput plate-based microphysiological systems may find use in target identification, lead selection and lead optimization at assay scale; chip-based, low-to-medium throughput devices may find most fitting use in pre-clinical, single-organ toxicity or efficacy tests; and multi-organ systems may target the replacement of animal models for toxicity screening, and phase I / phase II clinical testing in patients – which is being prefigured as (pre)clinical-trials-on-chip.

Replacing (pre)clinical human trials and advancing towards the implementation of personalized medicine are the grand unmet needs targeted by multi-OoC and Human-(body-)on-Chip (HoC) systems. OoCs pave the way to personalized medicine approaches by enabling the use of patient-specific, primary and stem cells to capture important differences due to genetic diversity, origin, gender or age. For instance, OoCs can enable the development of *in vitro* clinical trials for patient populations unfit for standard clinical trial designs (*i.e.* rare and/or paediatric diseases) or to develop drug regimens that are optimized for specific patient biology (Ronaldson-Bouchard & Vunjak-Novakovic, 2018). Along this path, OoCs may represent models not only capable of capturing prior organ(ismal) knowledge and recapitulating known physiological responses, but also, and even more importantly, unique tools for unprecedented investigations and new discoveries for the further advancement of physiology and medical science.

OoCs can benefit toxicology testing

The interviewed experts share the opinion that industries developing cosmetic, chemical and agro-food consumer products can find a huge potential in OoCs regarding toxicological hazard and risk assessment of substances for the study of *e.g.* metabolism, effect of toxicants including nanomaterials, collective responses and allergies (see also Zhang and Radisic, 2017). Regulatory requirements for chemicals and cosmetics do not accept any significant hazard potential of substances used for humans. Moreover, there is rising interest in alternative models allowing skin sensitization assessment and systemic toxicity testing for regulatory use, because animal testing has been banned in 2013 for cosmetic and fragrance products marketed in Europe. China is meanwhile changing regulations about animal testing for cosmetics, has approved in 2016 a first non-animal tested cosmetics, and is pushing the authorities for reducing animal use; and the USA have included a ban on animal testing in their 2007 roadmap for all industries, including pharmaceutical, chemical and cosmetics industry (Yole market report, 2017). The chemical industry is also actively working on such strategies, especially on *in vitro* skin sensitization testing, to avoid unnecessary reassessment of chemicals due to the Registration, Evaluation, Authorization and Restrictions of Chemicals (REACH) regulation (Marx *et al.*, 2016). Nevertheless, more formal validation efforts will be needed prior to full industrial adoption of OoCs in chemical and cosmetics industries.

Though not mentioned by any ORCHID interviewee, the tobacco industry could represent another

OoC targeted segment in the near future due to the high pressure to increase the safety of this industry's product portfolio (Marx *et al*., 2016). Ethical considerations lead the tobacco industry to develop new approaches and tools to assess smoke-related adverse effects on the human respiratory system, primarily airways and alveoli. OoCs could represent ideal tools to investigate the onset of lung diseases, such as the smoking-induced chronic obstructive pulmonary disease and its malignant transformation.

The future of OoCs lies in automation, relevance and integration of complexity

Automation and ease of use

Present OoCs are typically complicated pieces of engineering, whereby the microfluidic chip hosting the cell co-cultures is connected to external control and supply peripherals. For this reason, ease of use of the systems and increased automation in setting up cell cultures and keeping them viable throughout study times are commonly perceived unmet needs in laboratory practice. The ideal OoCs would be simple devices displaying user-friendly interfaces that facilitate the work of users with even limited training on *e.g.* cell cultures and instrumentation. These devices should be easily transferrable from developers to end users and from lab to lab by means of standardized guidelines concerning biomarkers and endpoints.

Improving the relevance of single OoCs

Among the many different tissue types that can be currently emulated (Marx *et al.*, 2016), the outcome of the experts' interviews and of the ORCHID bibliometric analysis shows a strong preference for ADME pathways (Absorption, Distribution, Metabolism, Excretion) including metabolic (liver, kidney) and digestive organs, along with cardiac tissue, lung and the central nervous systems coupled to a blood-brain barrier. Organ-specific needs to be met include, among others: for the liver, the development of models making use of iPSC-derived hepatocytes; for the heart, efficient maturation protocols for iPSC-derived cardiomyocytes to avoid expression of immature phenotypes; for skin, establishing methods to derive all skin cells from iPSCs, including *e.g.* dermal papilla cells needed for hair generation. OoC devices can perfuse vessels, thereby including the vitally important flow of a blood surrogate to feed nutrients and remove excretion products through vasculature, and the accompanying shear stress. The experts emphasized that, while immunogenicity testing of drug candidates in animals is obsolete, immune and endocrine systems are missing components required to improve the physiological relevance of OoCs. Different academic players are indeed developing bone marrow-on-chip to integrate aspects of immunocompetence in OoC-based drug safety and efficacy testing (Marx *et al.*, 2016). As described above, the skin is also a main target of OoC research. Moreover, predictive models for gametogenesis and testicular toxicity, an infrequent but severe cause of arrest of drug development, and for other specific toxicities for which no satisfactory pre-clinical model exists are presumed to be valuable as a niche market for OoCs.

The ORCHID bibliometric analysis highlights a very high interest in OoCs as cancer modelling systems, which could help to better understand tumour progression (Appendix 2, Fig. 7). The exponential growth of publications dedicated to OoC cancer models may correlate with the fact that OoCs are the only systems to model tumour cell intravasation into a surrogate blood stream or immune cell extravasation into the tumour by combining human micro-perfused 3D tumour models with human vasculature (Marx *et al.*, 2016). Such strong interest is also supported by epidemiology data and the

high market potential for cancer treatments. The expert interviews also indicated that, from a patient perspective, stringent medical unmet needs are represented by ways to improve the treatment of diseases – such as *e.g.* cancer, dementia, kidney and rare diseases – for which there is currently no treatment, insufficient treatment, or only treatments which are too expensive.

Integrating more complexity within multi-OoCs

As mentioned, the development of multi-OoCs is envisioned in the perspective of recapitulating the complexity of the human physiology at organism level, which is lost in moving away from animal models. An eminent example of a multi-OoC is the Evatar system, which couples Fallopian tubes, uterus, cervix and liver made from human tissues with ovaries from mouse tissue to recapitulate 28-day female hormonal cycles (Xiao *et al.*, 2017).

The original claim of a forthcoming full HoC-type system appears to be presently more realistically modulated by a technical assessment of the formidable difficulties facing its achievement. The latter include: (1) the onset and maintenance of self-contained homeostasis; (2) the inclusion of the influence of missing organs, particularly the hormone background (*e.g.* gender and reproductive hormones) and immunocompetent cells; and (3) the identification of (alternative solutions to) a single perfusion medium shared by the multiple cell types comprised within the system. Other challenges for multi-OoC and HoC systems lie in scaling the relative volumes of the individual OoCs (Wikswo *et al.*, 2014), the interconnection topology, and perfusion rates approximating physiological flow configurations (Ronaldson-Bouchard & Vunjak-Novakovic, 2018). Organs involved in the ADME are considered the basis of a HoC, since they are responsible for significant homeostatic effects and are foreseen in comprehensive organ models for compound testing, for instance in skin and lung models to evaluate compound concentration in urine and blood. Modelling of ADME is considered central also because drug distribution is a main cause of unwanted drug side effects – a global leading cause of death. To this purpose, efforts should focus on combining a set of organs which can match the critical functions needed for drug study with a functional endothelium serving as selective barrier for transport of drugs and bioactive factors (Ronaldson-Bouchard & Vunjak-Novakovic, 2018).

Technical challenges

Structural materials: alternatives to PDMS?

Polydimethylsiloxane (PDMS) supplanted glass and ceramic as the most commonly used substrate material for the fabrication of OoCs. The very wide adoption of this type of silicone ensues from a convenient combination of advantages, such as biocompatibility and oxygen permeation (crucial for cell viability), optical transparency (suiting real-time optical inspection), softness (which supports mechanical actuation), wide availability, and general ease of processing (no strict need for specific cleanroom facilities) – including deposition by casting and spin-coating, functionalisation, metallisation, and patterning by soft lithography and moulding (Zhang *et al.*, 2018). The almost-unanimously remarked disadvantage of PDMS – though common to most polymers, including the plastics of interconnecting tubes – lies in its lipophilicity and ensuing unselective absorption of hydrophobic drugs, particularly of small molecular weight (van Meer *et al.*, 2017). Unselective absorption complicates the localization of target compounds in the devices and, in absence of models predicting drug absorption rates in substrates, can drastically affect the interpretation of analytical results. Moreover, drug absorption directly affects the choice of the method used to deliver drugs to OoCs. Drug delivery in

OoCs should generally replicate the physiological application in humans, *e.g.* direct exposure to cells, inhalation, skin absorption, oral delivery, or intravascular delivery by perfusion in vessels. The limitations of PDMS may be tolerated during device prototyping and characterization, but may hinder future large-scale integration. Unselective compound absorption in PDMS is being faced mainly by (1) the search for application-specific formulations of PDMS or alternative polymers, most of which – based on *e.g.* polycarbonate, polystyrene, Styrene Ethylene Butylene Styrene (SEBS), polyimide, polyurethane, hydrogels – represent intellectual property covered by patents; or (2) the coating of polymer surfaces with layers of endothelial cells, providing a barrier to drug absorption into the substrate.

Optimal cell sourcing and shared culture media

Access to abundant, good quality human cell sources represents an essential technical aspect of OoCs. Multiple cell sources are currently available, and each cell type presents advantages and issues. The highest clinical relevance for humans is guaranteed by the use in OoC models of adult primary cells obtained directly from patients. However, genetic variance between individuals may be present when the cells cannot be obtained from the same donor; and these cells cannot be obtained in large quantities from all tissues, *e.g.* from the brain and the heart. Adult stem cells on the contrary are obtained from almost all endodermal organs, *e.g.* the organs of the gastro-intestinal tract and the lungs, and they can be genetically modified and grown in culture in large quantities; but they are not available for all tissues. Pluripotent stem cells (PSCs), derived from reprogramming of adult somatic cells (human induced PSCs, hiPSCs in short) can give rise to almost all types of cells in the human body, and can be obtained from any individual. On the other hand, they are phenotypically immature, similar to foetal cells; hence it is a challenge to develop culture conditions for the maturation of such cells, and to use them to model diseases occurring after birth. Spheroids and organoids derived from human biopsies are also being envisioned as sources of pre-organized, higher-order cell tissues to be included in OoCs.

While the dynamic microenvironment of OoCs, mimicking the human physiology, can support cell differentiation and maturation better than static cell culture conditions, the co-presence of multiple cell types in the same microphysiological device sharing a common conditioning medium may be an issue. According to the ORCHID experts, a solution for the formulation of a single perfusion medium may come from a strict biochemical approach, rather than from simple media mixing; and whereas media such as high concentration glucose are standard, many application-specific media are proprietary. Serum, widely used at the beginning of the century, is currently disfavoured, and ethical issues are implied with foetal serum particularly. Blood is being used for media as well, and should be on the roadmap in spite of increasing constraints on its usage. Finally, whereas the choice of cell types is generally dependent on the target organs and applications, a related challenge concerns the appropriate representation of the diversity inherent in the human population in terms of *e.g.* gender, origin and age.

Long-term viability and multimodal real-time characterization can revolutionize cell cultures and analysis

With typical sizes in the order of few millimetres, OoCs afford a distinct advantage in terms of non-invasive organ monitoring and tissue investigation compared to the actual inspection of human

patients. The small volumes of tissues and culture media confined within the closed, controlled environment of the devices limit the dilution of xenobiotics and metabolites. Small chip volumes additionally help preserving sterile culture conditions, though they are also responsible for reduced throughput. A related advantage concerns the extended viability of the cells in OoC models, enabled by continuous microfluidic nutrient feeding and removal of waste products. Required model viability is considered by the interviewed experts to be sensibly dependent on the application and specific question at hand: it can range from a few hours to a few days (*e.g.* 3 to 8 days) for repeated dose/exposure and acute toxicity testing; up to a few weeks for safety and efficacy testing (*e.g.* 28 days for systemic testing, in accord with the Organisation for Economic Co-operation and Development (OECD)'s guidelines for animal tests); and up to several months for chronic toxicity testing or disease course modelling, in analogy with phase II clinical trials. Tissue viability is supposed to extend indefinitely in the presence of self-contained homeostasis, particularly when sustained by vascularized interconnections among several organ modules.

Online characterization of organ- or tissue-specific phenotypes, readouts and endpoints in OoCs – *e.g.* vascular contraction, cell migration, genetic reporters, metabolic pathways – is largely dominated by optical and fluorescence microscopy, expected to remain prevalent also in the future. A challenge for assay imaging systems is translation into high-throughput industrial settings. Incubators are commonly used to host OoCs and regulate cell culture parameters, such as temperature and CO_2 levels. Composition of perfusion media, fluid flow rates and gas pressure for pneumatic actuation of flexible membranes are mostly controlled by external, partly automated equipment. Connection of fluidic peripherals to chip or plate devices typically involves silicone tubes, which may cause bubble formation and non-selective drug absorption. Proper utilization of devices and peripherals typically requires specific training of users and is expected to be regulated by standardized guidelines. Including such peripherals as integral components of actual, self-contained OoC devices is a standing challenge.

According to the ORCHID experts, OoCs should be consumables whereby real-time sensor readout and system control are simultaneous and aligned. The experts recognized that real-time monitoring of bioreactions in OoCs may revolutionize *in vivo* studies by increasing the throughput of analyses, and acknowledged the current existence of a gap between hardware development and the needed absolute quantification of biological response, partly because the physical, chemical or electrical responses to bioreactions in OoCs are not fully understood. Therefore, the integration of bio-compatible electrical, chemical or physical sensors and actuators is highly sought after and widely investigated. For instance, trans-epithelial electrical resistance (TEER) is being measured for real-time readout of tissue barrier functions (Henry *et al.* 2017); and micro-impedance tomography is used to quantify the deflection of membranes induced by breathing motion (Mermoud *et al.*, 2018).

Qualification for contexts of use should be preferred to validation

A form of *validation* of OoC systems is critical for their acceptance in industrial and clinical settings. The OECD defines validation as "the process by which the reliability and relevance of a particular approach, method, process or assessment, is established for a defined purpose". However, validation per se is not considered by experts an appropriate nor meaningful concept, because it implies the existence of an accepted standard to be used to confirm or measure validity. In fact, neither animal models nor human clinical effects can be univocally used as golden standard for validity. Besides, a universal approach to validation is probably unrealistic, and a harmonisation across contexts and cultures would take too long, if possible at all. The attention should instead concentrate first on specific

and well-defined *contexts of use*, before eventually extracting elements common to multiple contexts. This was the general outcome of a recent series of workshops devoted to this important topic – held both in the US by the FDA and in Europe by the European Medicines Agency (EMA)'s Safety Working Party – and it was confirmed in the ORCHID Vision Workshop. The complementary recommendation is to focus on the *qualification* or *characterization* of the devices, rather than on the validation in the broadest sense. For the purpose of drug development, the typical practice is recommended, which involves, given a well-defined and specific context of use, a comparison between data obtained from OoCs and corresponding data derived from conventional drug development models (*e.g.*, animal models, cell suspensions). This will instruct the assessment of whether the OoC response corresponds to the expected response and/or can be used as reliable predictor for the human response.

More generally, it is desired and expected that the OoCs reproduce salient functions and physiology of human organs to predict *in vivo* human response. To achieve or reinforce such qualification practice, a challenge consists in establishing an extended and shared database describing the effects of a standard set of benchmarking compounds (*e.g.* paracetamol, beta blockers). This would represent per se an important step towards standardization. There exist initiatives – by *e.g.* the NIH in the US, and the Crack it! European program – aiming to establish a public database to collect readout data in a very specific and platform-independent format, useful for both pharmaceutical companies and regulatory agencies. The ORCHID experts suggested that such initiatives may inform an open platform shared by partners in pre-competitive settings, tapping crowdsourcing approaches to *e.g.* data analysis and device testing, and crowdfunding to share costs. They may be inspired by examples of shared technology planning and development, such as the former International Technology Roadmap for Semiconductors (ITRS) and the International Roadmap for Devices and Systems (IRDS)[4].

The current scenario is nonetheless fragmented, as most pharmaceutical companies intend qualification as an internal recognition process that does not need to be translatable to other companies, let alone the whole sector. Accordingly, OoCs need only comply with company-specific qualification protocols using company-specific test sets of compounds, established or under development. Though such compounds are typically proprietary and not easily accessible to academic research groups, the IQ Consortium, a not-for-profit organization of pharmaceutical and biotechnology companies, is compiling a list of reference compounds, that might be shared for qualification purposes.

Standardization: when is the right time?

Standardization of OoC devices includes reproducibility and robustness of results both within a single lab and across different labs; uniformity or compatibility of cell or tissue types and sources; and compatibility among chips or modules fabricated by different developers upon interconnection into a multi-organ system. Standardization is desirable from an industrial and regulatory point of view, though not well aligned with the current stage of academic and commercial development of the devices. The exponential growth of the number of publications on OoCs, whose dynamics is even superior to that which accompanied the development of the Human Genome Project, testifies to the continuous introduction, at least in the academic domain, of novel or ever updated OoC models which contemplate variations in the substrate technology and/or in cell sources and types. The interviewed experts mostly share the opinion that such wide exploration of solutions is welcome and typical of early stages of technology development. To bring the most benefit to the field, it should currently not be hindered, at least in academic research, by the strict imposition of standards or constraints deriving from intellectual

[4] https://irds.ieee.org/

property, even though this would defy the perceived interest of pharmaceutical companies and industrial end users. Additionally, it would be premature and counterproductive to converge towards robustly qualified or standardized manufacturing processes prior to gathering substantial evidence and characterization of the capacity of OoC models to host the intended target biology and recapitulate the *in vivo* human physiology and response of interest. Standardization of OoC devices and readouts may appear at some later stage, as in the case of other technologies, due to the convergence towards solutions generally considered most convenient or optimal, issues related to intellectual property, reorganization of companies, market conditions and end-user demands. Finally, standardization may alter the landscape of players in the field by constraining the number of players that can afford to comply with both its financial and engineering aspects.

6. Barriers and perspectives

From industrial hesitance towards acceptance

OoC developers expect a large market to take off in the next 2-3 years. This optimism is supported by major recent technical breakthroughs (Zhang *et al.* 2018), which make OoCs a credible option to provide a variety of end users with more predictive testing models. Once OoC models are available, demand is expected to increase and smoothen the road to applications. On the other hand, focusing on lesser applications may provide an additional point of market entry for OoCs.

Nevertheless, a more realistic view of the situation shows that there are heavy barriers to be crossed. Industry is still testing OoCs in comparison with alternatives (*e.g.*, 3D cell cultures, spheroids, tumoroids, organoids) to determine the models most suited for their needs. Evidence-based convenience of the models is required to induce industrials, especially pharmaceutical, to integrate OoCs into near-future routine processes. Although OoCs may be more relevant and accurate than animal models or cell cultures, they are still expensive and need costly redesign to suit mass production. In addition, compatibility problems may occur due to the current lack of standardization (*e.g.*, different shapes, interfaces, sizes, tissue types and quality, ways of use); and it may take years before OoCs are accepted by regulatory agencies. Hence a pragmatic attitude prevails in the industrial context – which, as for any available alternative, evaluates OoCs either on a fit-for-purpose or on a cost-per-data point benefit they may afford. Accordingly, the new technology may be accepted if it provides simpler or cheaper alternatives to established models while reproducing the same results, or if it affords models for which no alternatives currently exist. An example of the latter is provided by a joint work of the Wyss Institute with Janssen to model the toxicity of a monoclonal antibody therapeutic which caused death in patients due to pulmonary embolism in Phase I clinical trials: Janssen had not observed any toxicity in preclinical animal models, whereas the Wyss Institute's OoC could replicate the thrombotic behaviour (Barrile *et al.*, 2018).

According to the Yole market report, in the most likely scenario OoCs will be increasingly adopted by the industry, due to their significant advantages over existing solutions in terms of *e.g.* predictivity, cost saving, alternative to animal testing. Newcomers, mostly spin-off from academia, will appear in the OoC developers' market, but in the meantime some companies will fail. It would not be surprising to see biotech companies and instrument developers, who are providing tools to the pharmaceutical industry, acquiring OoC developers, because of the good synergies between these organizations.

Early dialogue to ease regulatory hurdles

Regulatory aspects can represent another significant barrier towards the broader adoption of OoCs. There is a generic and non-OoC specific need to speed up regulatory validation processes. Examples of prior technologies attest to a resistance in the adoption and regulation of new medical options. The decisions of regulatory authorities on the efficacy of novel treatments can have significant repercussions in delaying the acceptance and implementation of those treatments, in making the treatment costs liable to reimbursements to patients, and generally on the societal costs of healthcare. In addition, the costs of the certification procedure, involving an extensive series of tests, may escape the possibilities of academic research groups. This conversely should incentivize the involvement of companies and funding agencies in the development of OoCs as well as in early dialogue with regulatory authorities to ensure effective and transparent communication and to avoid procedural obstacles at later stages of development. Industrial acceptance typically precedes and pushes regulation (Marx *et al.,* 2016). Still there may be a catch in the transfer of the device development process from initial developers to companies: the developers may be in immediate need for funding to advance or characterize their models to a degree sufficient to attract the interest of the companies, whereas the companies may hesitate to provide funding until the developers have demonstrated that their models fit their specific purposes or that they can overcome the companies' fear to be the first to introduce a new model on the market that later might eventually reveal ineffective in humans, or not compliant to future regulations.

Keeping expectations realistic

The industry and government agencies have placed huge expectations on a few developers of OoC technology, in particular academic centres like the Wyss Institute and the MIT as well as companies such as Emulate Inc. and CN Bio. These developers were repeatedly awarded funding for several tens of millions of dollars, and are the most visible in the field. The Yole market report suggests that the success of these well-funded organizations might be critical for the future of the OoC area. Some industry players believe these organizations cannot fail, whereas some think the gap between prototyping and mass commercialization is too significant. The consequence of a potential failure of such field pioneers would be devastating for the OoC field: besides the high visibility of the failure (media coverage, top-rank universities), a loss of confidence from both industry and investors would disrupt many small companies.

The interviewed experts echoed similar concerns, and expressed almost unanimously the need to keep realistically optimistic about the OoC technology. They generally expect OoC to become a key technology in the coming years, yet prescribe to remain very cautious in stating the promises and the potential of the OoC technology to media and general public to avoid the pitfalls of hype psychology. While the experts do not agree whether the OoC technology is currently the object of a hype, the Human Genome Project, stem cells for regenerative medicine, microarray technology, proteomics and gene therapy represent significant examples of initiatives or technologies that may risk to fail to deliver to the high expectations they raised at the outset.

A further analogy with these precedents is represented by the size of funding considered necessary to achieve the field's purported goals, expectedly in the order of hundreds of millions to billions of dollars. A large fraction of the costs concerns the translation of proof-of-concept devices from laboratories to market entry, and the tests prescribed for regulatory approval. OoC-related companies are expected to drive such advances, eventually in partnership with governmental agencies,

and they find themselves in a critical position in this respect. Attracting investors and considerable funding is critical to gather the multidisciplinary technical expertise and build the layered infrastructure that can support the development of prototypes into mass-fabrication to meet the industrial demands of quality control and reproducibility. To achieve this, the companies need to rely on advertising, which is susceptible to involve overstatements. The latter may raise premature or unmatched societal expectations about a technology, which conversely is generally considered to be still in an early development stage.

A common perception of the interviewed experts is that the lay public easily grasps the core concept of the OoC technology, and tends to get quickly excited about the potential to decrease or even replace animal testing. However, *organ-on-chip* as technology-defining name may deceit the public to associate it with artificial organ prostheses, organ replacement, regenerative medicine if not with science fiction technology. The public may not understand how the OoC technology actually works and what its limitations are, unless by browsing specialized journals. On the other hand, the more popular media may tend to cover sensational stories and thus feed the false impression that the technology is already achieving all the advertised promises. An antidote to such perceived distortions may be a synergistic outreach activity by key players and stakeholders based on careful communication of recent achievements and ongoing developments that could inform about actual trends and realistic perspectives.

Collaboration and education must be encouraged early on

The interviewed experts remarked the strong need for integrative programs, collaborative projects, consortia and international funding strategies for the development of OoC technology and applications. Lack of international coordination may be caused by the heterogeneity of the global legislative, regulatory, financial and ethical scenario. Coordination efforts should be supported by a widespread outreach activity, targeting all levels of audience, and by an improved dialogue between regulators, industries, clinicians and patient groups since the early stages of development. In this respect, a digital platform is now being developed within ORCHID to bring together players (*e.g.* researchers, laboratories, companies, patient associations, regulators) and to create a community in the OoC field. The platform will evolve over time through the addition of publications, collaborative projects and additional information supplied by the members who will progressively become part of it.

Finally, besides topical and field-specific workshops and conferences, incubators of talents are elicited as prime accelerators for the progress of the technology. This should be the pivotal role of institutes, inspired by analogous initiatives of successful information technology companies, where diverse experts could freely interact to traverse linguistic and departmental boundaries and dispose of ample resources to develop new ideas and conduct multi-disciplinary research.

7. Summary and recommendations

The synergistic convergence of microfabrication technologies and tissue engineering renders OoCs promising tools for the realistic modelling of human physiology and pathology. The aim of an OoC is not to replicate a whole living organ, rather to sustain a minimal functional (sub)unit of an organ or tissue that can controllably recapitulate salient aspects of human physiology. For this purpose, as argued in this report, the main and desired features of an OoC can be divided into three categories:

Tissue architecture
- Integrated long-term cell culture in defined spatial organizations
- Tissue-tissue interfaces/cell-cell contacts/cellular heterogeneity
- Miniaturization

Conditions
- Controlled microenvironment (topology, biochemistry, physics)
- Controlled dynamics (fluid flow, electro-mechanical stimuli)
- Continuous automated perfusion
- Real-time monitoring of multiple physical, bio- and electro-chemical parameters
- Automated reproducible multi-sample analysis, comparable or compatible with R&D robotics
- Large-scale manufacturability

Functions
- Physio- and pathological relevance
- Recapitulation of organ structure and function
- Recapitulation of dynamic mechano-biological properties and stimuli response of organs

In view of this, the ORCHID Vision Workshop elicited the following recommendations, summarized in Fig. 8 of Appendix 2, to foster further progress in this rapidly establishing field:

Characterization, qualification and standardization

1 *Do not aim for the whole human: start mimicking single organs first.*
2 *Demonstrate the benefits and prove with data the added value of OoCs compared to other models.*
3 *Only consider standardization of OoCs once there is substantial evidence for OoC platforms to recapitulate the* in vivo *human physiology and response of interest.*
4 *Develop guidelines for standardized qualification, characterization and monitoring of OoCs, and describe their value on a fit-for-purpose or cost-per-data point scenario.*
5 *Create a list of reference compounds for specific organs to qualify OoCs for a specific context of use, and share the data through a public database.*

Technology

6 *Integrate real-time, bio-compatible electrical, chemical or physical sensing and analysis, and define and measure the salient parameters that can be predictive.*
7 *Address the issue of unselective compound absorption in OoC substrate materials.*
8 *Minimize operational complexity: develop OoC automation and enhance ease of use for speeding up assays, reproducibility and robustness, and ease the transfer from developer to end user.*
9 *Integrate OoC and computational (open source) models, starting with pharmacokinetics.*

Biology

10 *Define strategies to tackle issues on cell-to-cell variation, maturation and stability of cells.*
11 *Standardize the culture medium and explore the use of blood in single perfusion of multi-OoC.*
12 *Include immune and endocrine system components in OoC to improve physiological relevance.*
13 *Include gender, origin and age-related aspects in OoCs for representation of human diversity.*

Applications

14 *Define the type of throughput required for the application of OoCs*.
15 *Address personalized medicine (*you-on-a-chip*), clinical trials-on-chip and environmental toxicological assays as highest priority applications*.
16 *Involve the food industry to raise their interest for OoC applications.*
17 *Focus on toxicities or diseases for which no satisfactory pre-clinical models and treatment exist as a niche market for OoCs.*
18 *Combine a set of organs involved in ADME pathways that can match the critical functions needed for compound testing and studying transport of drugs and bioactive factors*

Dissemination, communication and collaboration

19 *Keep expectations about the technology realistic when communicating with media and the public.*
20 *Develop a synergistic outreach based on careful communication of achievements and new developments by developers and stakeholders.*
21 *Involve patients, clinicians, companies and regulatory authorities early in the development of OoCs to ensure effective dialogue and avoid procedural obstacles for implementation.*
22 *Attract investors and funding agencies to support the development of prototypes into mass fabrication to meet the industrial demands of quality and reproducibility.*
23 *Build the network, and realize integrative programs, collaborative projects, consortia, a digital platform and international funding strategies for the development of OoC technology.*
24 *Foster next generation researchers: organize exchanges among institutes, trainings, workshops and conferences to nurture talents as prime accelerators for the progress of OoC technology.*

Acknowledgements

The authors would like to thank Aurore Puech (CEA, France) for assistance in the bibliometric analysis, Berend van Meer (Leiden University Medical Center, the Netherlands), and Ioanna Zergioti (National Technical University of Athens, Greece) for notetaking during the ORCHID Vision Workshop, Nora Franzen (University of Twente, the Netherlands) for previewing early results of the impact study of ORCHID WP3 at the Vision Workshop, and all 17 interviewees and other experts that took part in the Workshop. This work was funded by the European Union's Horizon 2020 Research and Innovation program under grant agreement No 766884.

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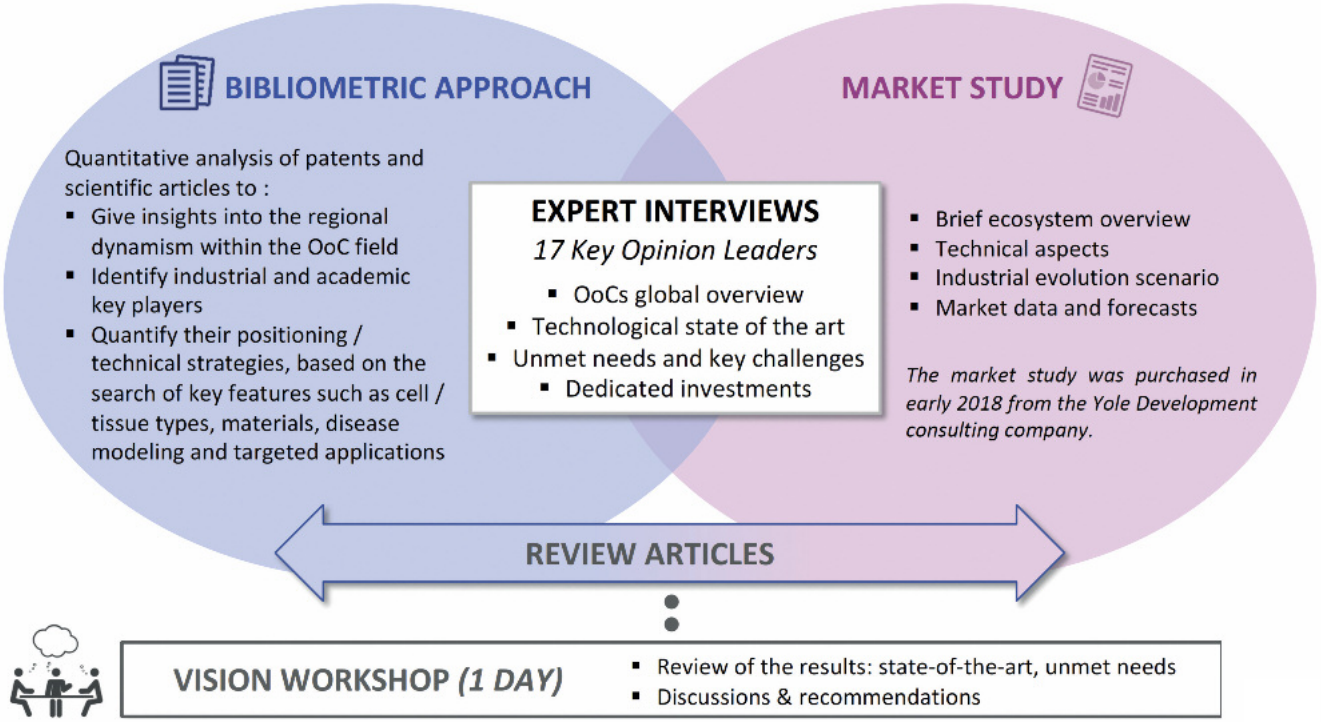
Appendix 1:
Methodology

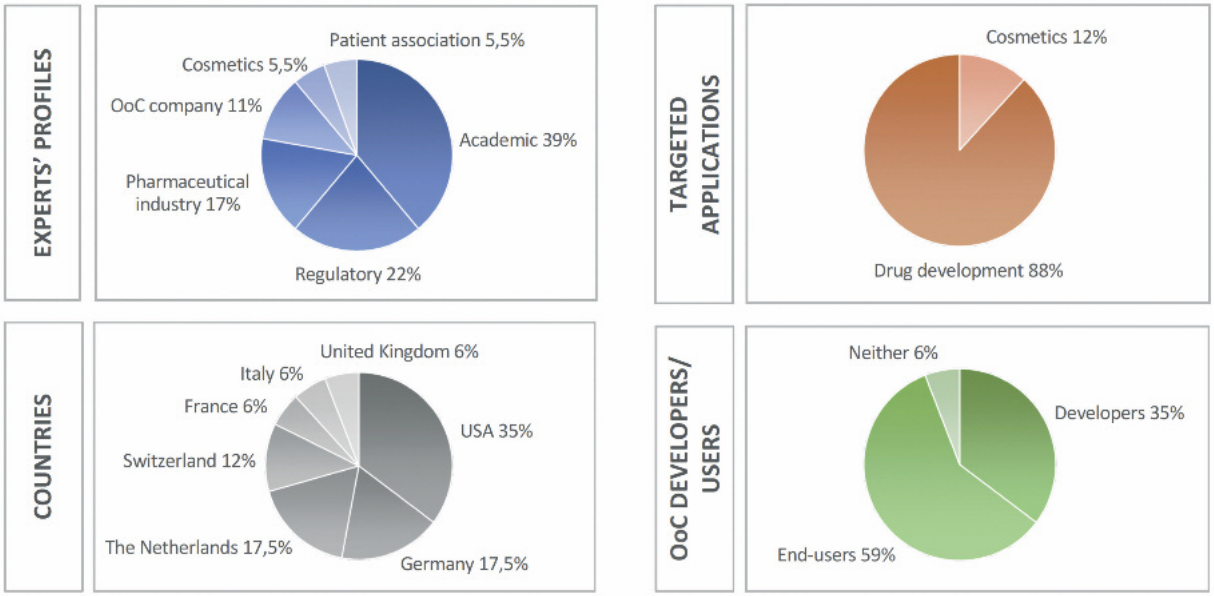
METHODOLOGY OVERVIEW

The present study draws on (1) expert interviews, and (2) a documentary approach, combining bibliometric and market analyses. The study was reviewed and discussed by a committee of experts during a 1-day workshop on May 23, 2018.

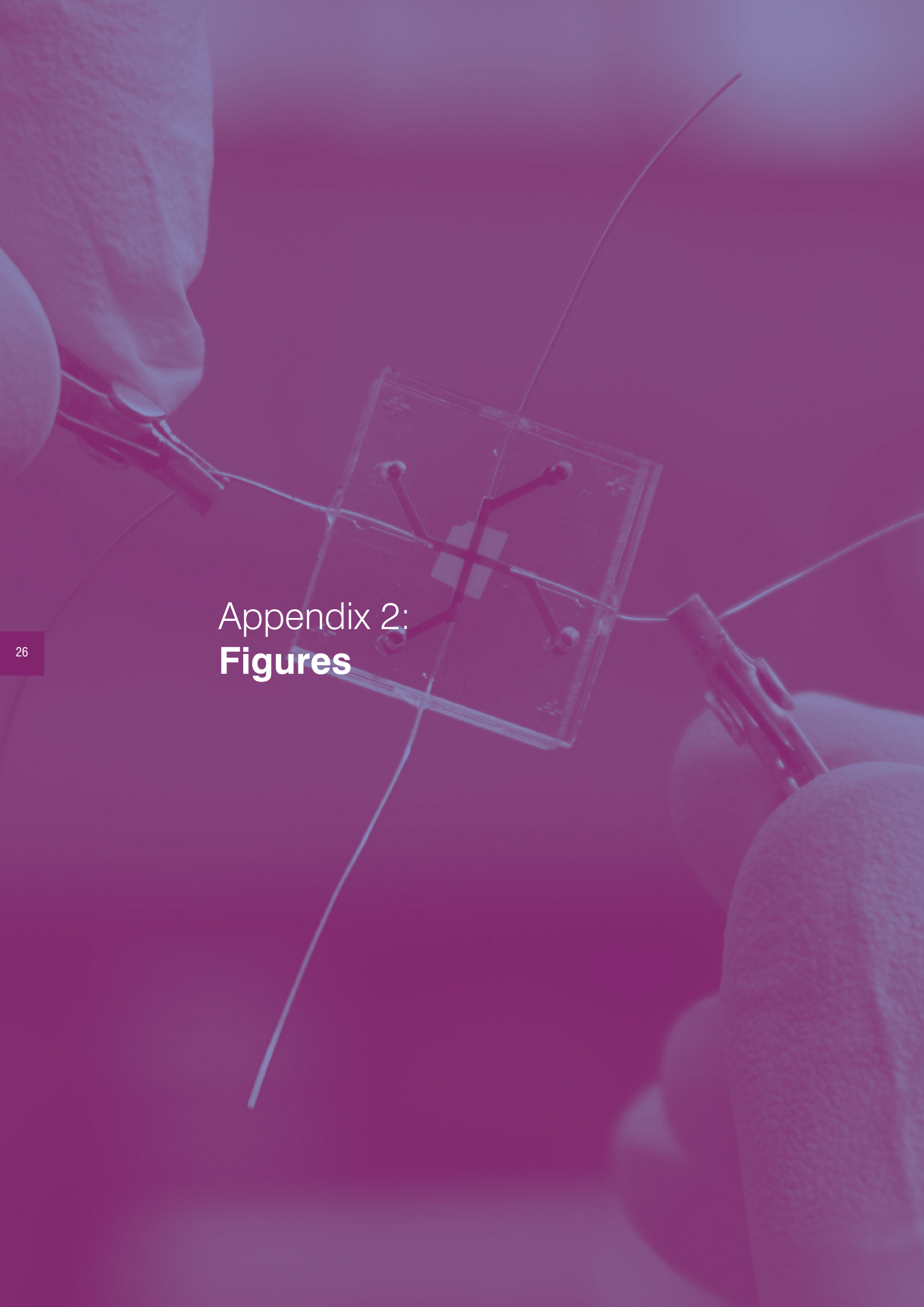


EXPERTS' INTERVIEWS

To support the state-of-the-art analysis, 17 interviews with key opinion leaders in the OoC field were conducted over a 4 months period, from January until April 2018.

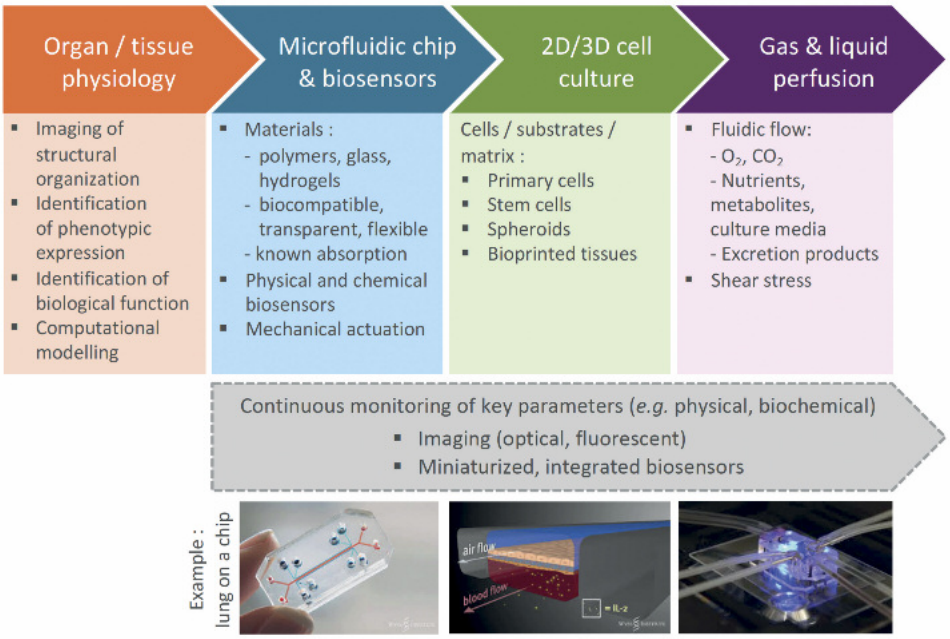


NB : a bias is observed regarding the applications targeted by the interviewees, since they mostly develop/use OoCs in the drug development process. Other clinicians and experts from food industries and cosmetics were also contacted, but they did not answer to our inquiry within the period dedicated to the interviews.



Appendix 2:
Figures

Figure 1: Simplified synopsis of the OoC value chain.

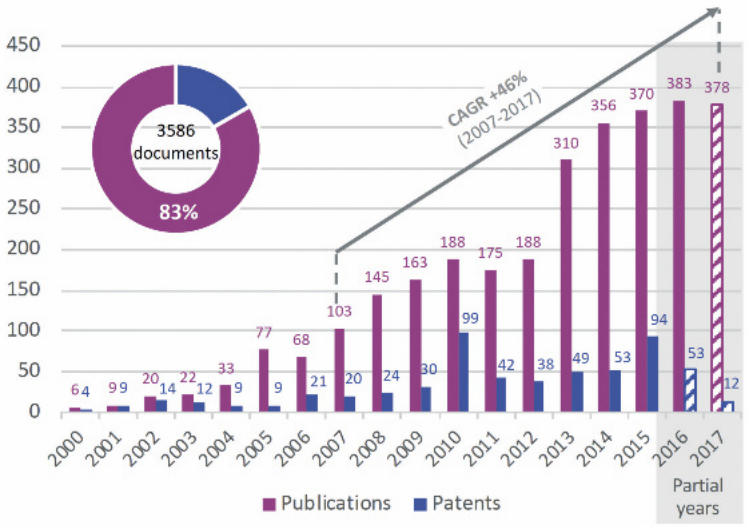


Creating an OoC requires the identification of the physiological function or complex interface to be modeled, in order to design the minimal biological unit by using dedicated materials, concomitantly with continuously perfused chambers inhabited by appropriate living cells cultured in environmental matrixes. The microfluidic chip fabrication part could include the integration of specific and miniaturized biosensors to monitor in real-time key parameters supporting the control of the OoC, its characterization and helping to evaluate its performance. The continuous real-time monitoring of biomarkers and endpoints is an identified global trend, most commonly implemented by imaging. The integration of miniaturized biosensors is an identified technical challenge.

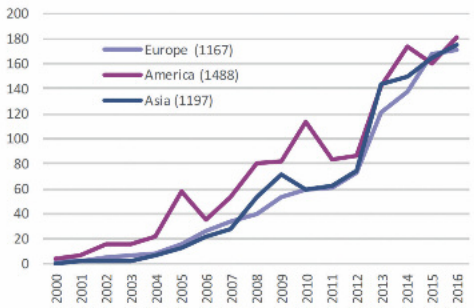
Photos: Wyss Institute at Harvard University

Figure 2: Rise in OoCs patents and scientific publications since 2000s.

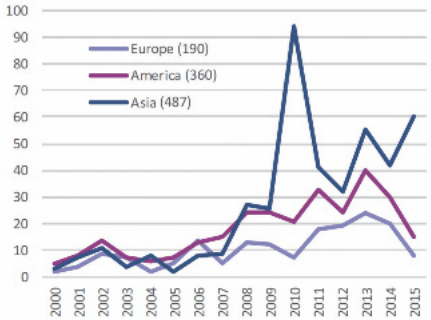
a. Temporal evolution of OoC-related patents and scientific publications over the 2000-2017 period



b. Temporal evolution of the number of publications per region



c. Temporal evolution of the number of patents per region



a. The bibliometric analysis of published patents and publications conducted by the ORCHID consortium led to an imported database including 3586 documents, mostly publications (83% *versus* 17% of patents). The 592 identified patents include granted (38.9%), pending (25.8%) and fallen or revoked (35.3%) patents. Year 2015: latest complete year for patents (18 months are needed to publish the patent application). Year 2016: latest complete year for publications (documents were imported in November 2017). CAGR: Compound Annual Growth Rate.

b & **c**. Three major geographical regions are considered: America, Asia-Pacific and Europe, regrouping the overall identified countries.

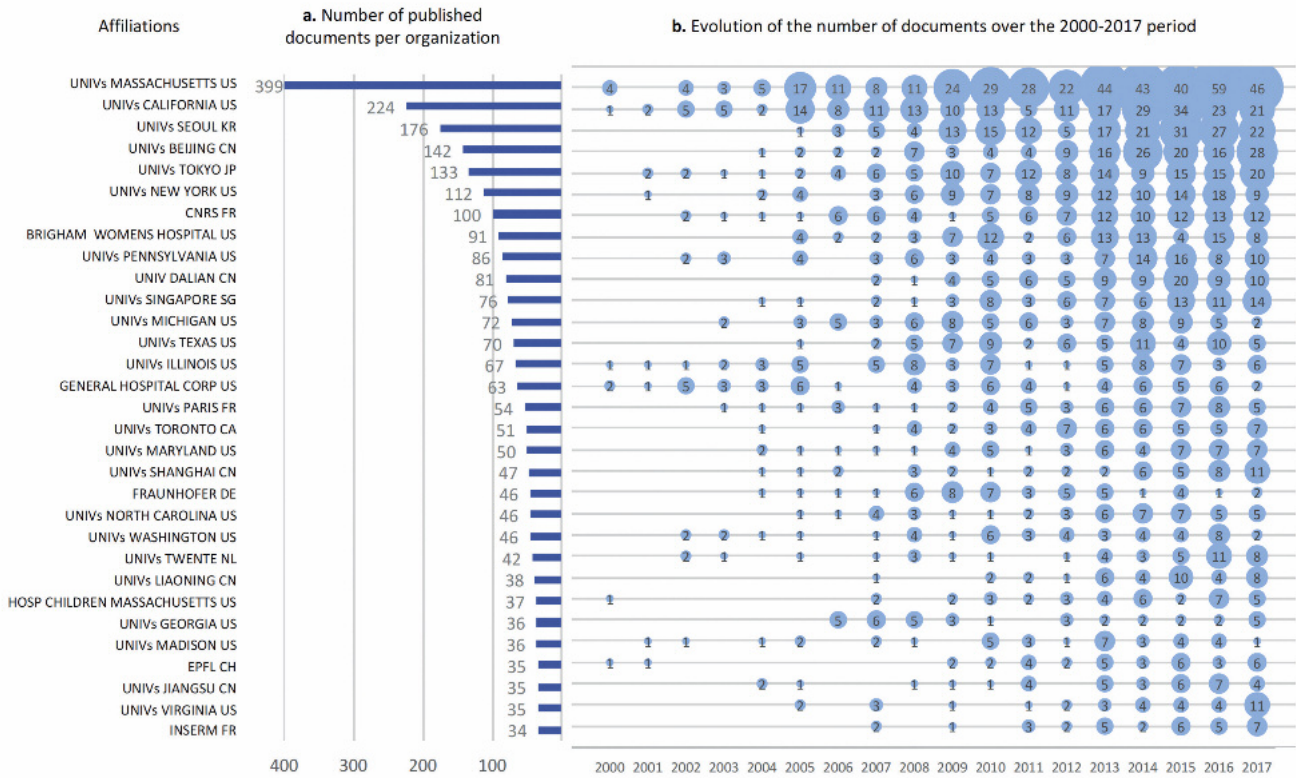
Table 1: Expected benefits of OoC systems compared to conventional biological models.

OoC specifications		2D cell culture	3D organoids	Single OoC models	Multi-OoC models	Animal models	Human biology
Cell sources	Human cells						
Cellular interaction	Co-culture						
	Integration of immunocompetency						
	Vascularization for nutrition, oxygenation, biochemical signaling molecules and metabolites						
Tissue architecture	3D tissue structure						
	Non-rigid biological environment						
	Controlled microenvironment						
Other physiological components	Emulation of exchanges between different organs						
	Tissue barriers						
	Mechanical / shear stress						
	Cell viability / long-term experiments						
Perfusion systems and control strategies	Perfusion, precise and reproducible dynamic flow						
Real-time monitoring	integration of biosensors for real-time data collection at a microscale level or below						
Toxicology and efficacy testing	Comprehensive chemical exposure						
	High-throughput						
	Low cost						
Ethics	Free of ethical concerns						

Key OoC specifications compared to existing traditional biological models as well as human biology from both a physiological and clinical point of view. *Red boxes*: not feasible; *green boxes*: already technically available or envisioned in the near future.

Source : Adapted from the Yole report, Yole Développement | Organs-on-chips market report © 2017 | www.yole.fr |

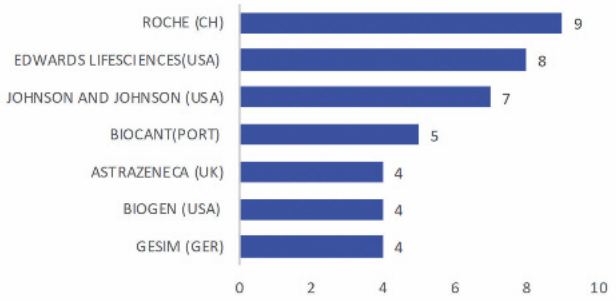
Figure 3: TOP 30 academic players.



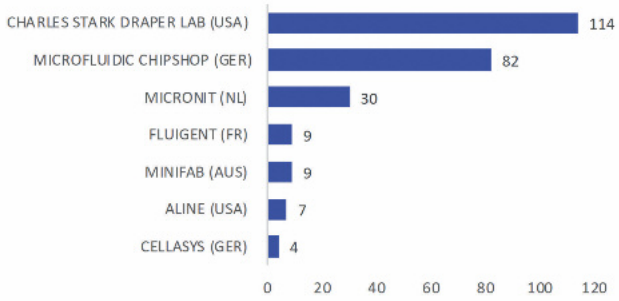
Out of 650 identified academic players, the graphs show an overview of the top 30, who published more than 34 documents over the 2000-2017 period (a), and their related evolution over time (b). a: blue bars – number of patents and publications. b: the size of the circles are directly proportional to the number of identified documents published each year.

Figure 4: Key industrial players' profiles.

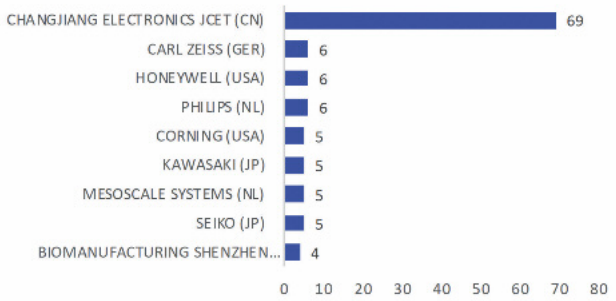
a. Pharmaceutical companies



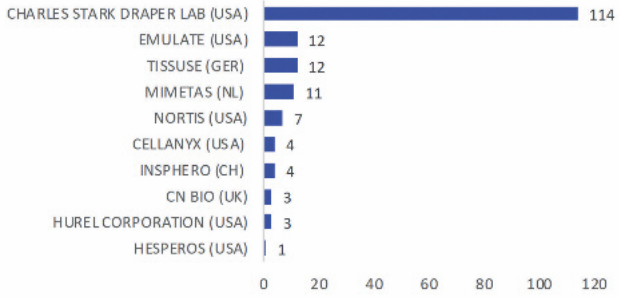
c. Lab-on-Chip manufacturing companies



b. Microfabrication, imaging, electronics/robotics companies



d. Organ-on-Chip companies

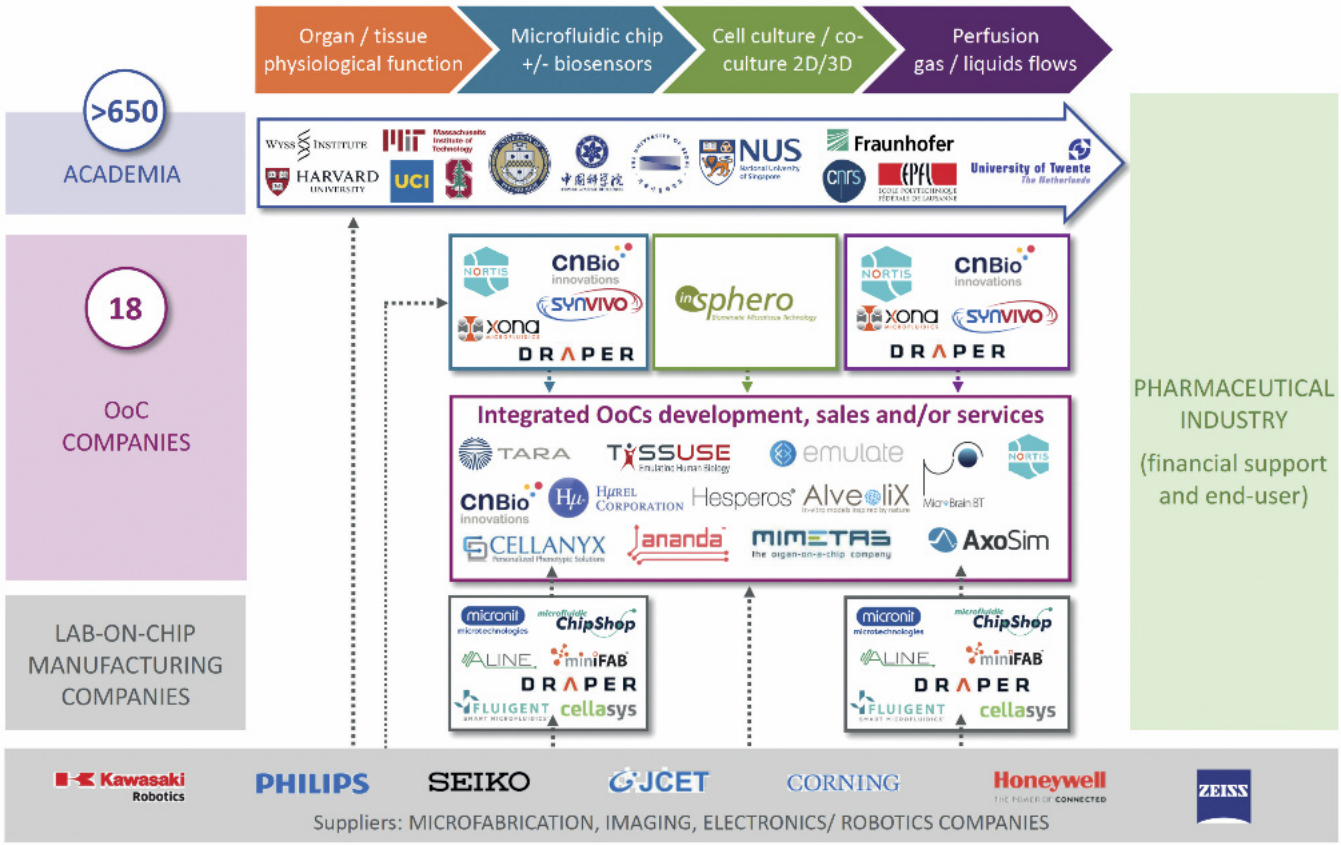


e. Other OoC companies identified in the Yole market report or in the bibliography

Other OoC companies	▪ Alveolix (CH) ▪ Ananda Devices (CA) ▪ Axosim (USA) ▪ 4Design Biosciences (USA)	▪ MicroBrain Biotech (FR) ▪ Synvivo (USA) ▪ TARA Biosystems (USA) ▪ Xona Microfluidics (USA)

a to d. The histograms show an overview of the first 30 industrial players, who published more than 3 documents over the 2000-2017 period. The American Draper company shows various activities, including both lab-on-chip and OoC manufacturing.
e. Some OoC companies were not identified by the bibliometric analysis but found in the Yole market report or in the bibliography.

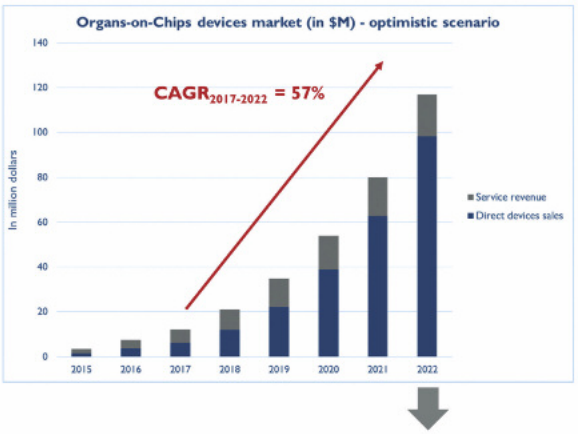
Figure 5: OoC players' positioning along the value chain



For each profile, only the top players are shown. The figures represent the number of academic players (blue circle) and OoC companies (purple circle) identified *via* the bibliometric approach. Academics and OoC companies show a dedicated expertise for the development of fully operational OoCs, whereas the other industrials are supporting their development technological expertise, financing and/or partnerships.

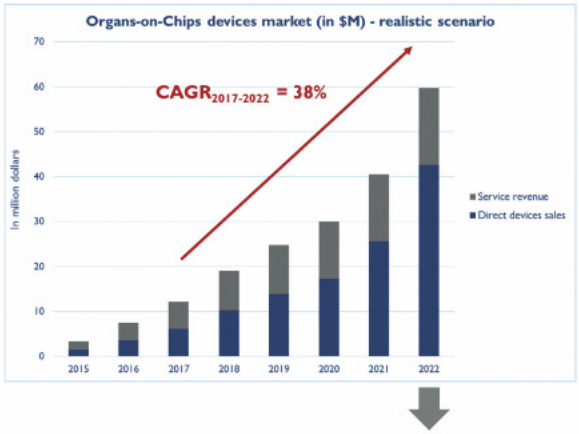
Figure 6: OoC devices market forecasts over the 2017-2022 period.

a. OoC devices market - optimistic scenario



production of 858k units in 2022
overall market of $117M

b. OoC devices market - realistic scenario



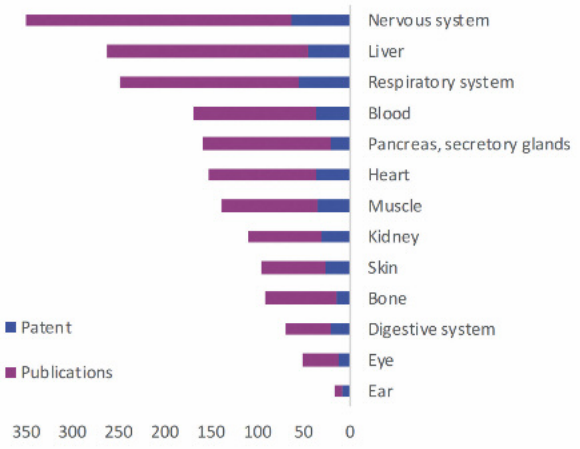
production of 310k units in 2022
overall market of $59,7M

a. The optimistic and b. the realistic scenario proposed by the Yole market report. The estimated revenues are shown in million dollars and split in direct devices sales (ready-for-culture devices and fully operational OoC; blue bars) and full service sales (tests performed in-house; grey bars). CAGR: Compound Annual Growth Rate.

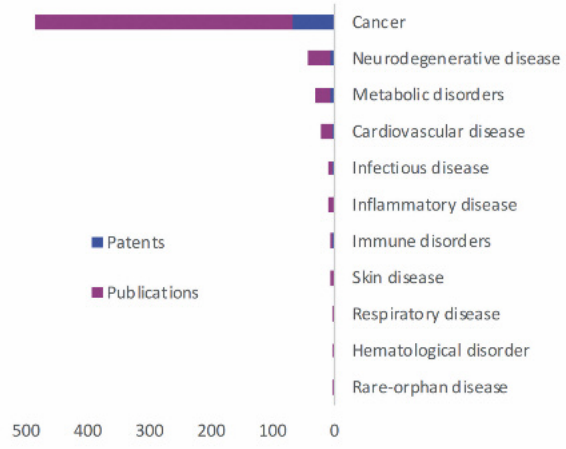
Source : Yole Développement|Organs-on-chips market report © 2017| www.yole.fr|

Figure 7: Pathophysiological models and tissue types' global trends.

a. Number of patents and publications per tissue type

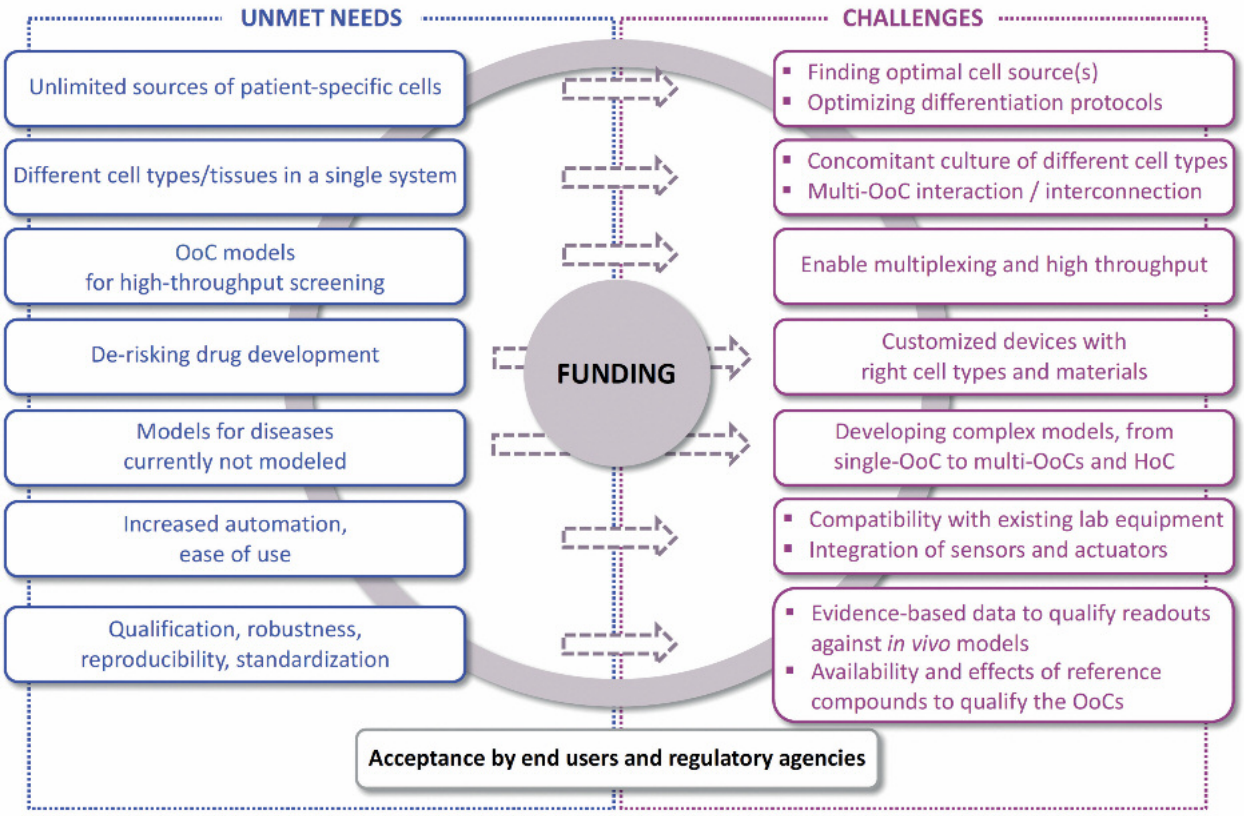


b. Number of patents and publications per pathophysiological model



The imported database of patents and scientific publications was segmented with regards to emulated tissue types (a) and pathophysiological models (b), on a worldwide perspective. Both panels: blue bars - number of patents; purple bars: number of scientific publications.

Figure 8: Key unmet needs and challenges for OoC development.



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ORGAN ON CHIP IN DEVELOPMENT

The ORCHID project (Organ-on-Chip development) is an EU initiative, coordinated by Leiden University Medical Center and the Dutch Organ-on-Chip consortium hDMT in The Netherlands. The main goal of ORCHID is to create a roadmap for Organ-on-Chip technology and to build a network of all relevant stakeholders in this promising innovative field. In the ORCHID project that started on 1 October 2017 in total seven leading European research institutions are involved.

More information: **https://h2020-orchid.eu**

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 766884

Organ-on-Chip In Development:
Building blocks for a European Organ-on-Chip roadmap

ORCHID
organ-on-chip in development

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Organ-on-Chip In Development: **Building blocks for a European Organ-on-Chip roadmap**

Massimo Mastrangeli[1], Sylvie Millet[2], Christine Mummery[3], Peter Loskill[4], Dries Braeken[5], Wolfgang Eberle[5], Madalena Cipriano[4], Luis Fernandez[6], Mart Graef[1], Xavier Gidrol[2], Nathalie Picollet-D'hahan[2], Berend van Meer[3], Ignacio Ochoa[6], Mieke Schutte[7] and Janny van den Eijnden-van Raaij[7]

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Photo: Paul ter Braak/Marinke van der Helm; BIOS Lab on a Chip group, UTwente.
Device: Marinke van der Helm/Michaela Hällevall.

Table of contents

Organ-on-Chip In Development: **Building blocks for a European Organ-on-Chip roadmap**

Abstract

This report summarizes the outcome of the Organ-on-Chip (OoC) ORCHID Strategy workshop (Leiden, the Netherlands, 17 January 2019) intended to establish a European OoC roadmap through expert discussions, conclusions and recommendations. The workshop identified six specific building blocks for the OoC roadmap: (1) application, (2) specification, (3) qualification, (4) standardization, (5) production and upscaling, and (6) adoption. Complementary aspects relating to ethics and communication were also addressed. Priorities, methods and targets for the roadmap were proposed for each building block. General consensus was reached on the potential contribution of the newly founded European Organ-on-Chip Society (EUROoCS), which could facilitate deployment of each block. EUROoCS would ideally initiate and catalyze dialogue between OoC developers, end users and regulators. The dialogue should address qualification, open technology platforms, standardization and implementation of OoC technology, as well as ethical aspects of human tissue mimics, training the next generation of OoC researchers, dissemination and communication.

1. Introduction

1.1 The current landscape of Organ-on-Chip technology

Born at the confluence of tissue engineering and microfluidics, Organ-on-Chip (OoC) technology is widely postulated as a promising approach to better model systems for healthcare research. OoC models aim to recapitulate aspects of human physiology and pathology for use in drug discovery, efficacy and toxicology testing, and personalized (or precision) medicine, with the goal to improve upon existing bioassays and provide insights into the mechanisms underlying the development and progression of diseases. In addition, OoCs are considered as relevant to reduce the need, cost and ethical burden of animal studies.

Though the OoC field is still in its infancy, several showcases of OoC models have already provided insight into disease aetiology and supported identification of drug target pathways. These showcases include detection of thrombotic risk in Vessels-on-Chip (Barrile *et al*, 2018), discovery of targets for metastases in Cancer-on-Chip (Song *et al*., 2018), test for kidney toxicity in Kidney-on-Chip (Vormann *et al*., 2018), drug effects on neurons and Glia cells-on-Chip (Wevers *et al*., 2016), prediction of toxicity of nanoparticles in Lung-on-Chip (Zhang *et al*., 2018) and drug discovery in a disease model for amyotrophic lateral sclerosis (Osaki *et al*., 2018). These and multiple other examples are at the stage of validation/qualification, which in general means that compounds and drugs already demonstrated as toxic or effective in treating disease in animals or patients show similar effects in OoC models. This is expected to encourage OoC adoption by industry, acceptance by regulatory bodies and further development as animal alternatives. However, this outcome is still pending growth in confidence on OoC predictivity and utility.

A comprehensive survey of the current OoC landscape in research, development, applications and market opportunities was recently carried out by the Horizon 2020 FET-Open project *Organ-on-Chip In Development* (ORCHID[1]). The goal of ORCHID is to create a roadmap for OoC technology, identify potential roadblocks and corresponding solutions, raise awareness and build ecosystems conducive to wide implementation and use of OoCs in science, R&D and regulatory guidelines in Europe and elsewhere. ORCHID recently published a report (Mastrangeli *et al*., 2019) based on a bibliometric study, market analysis, interviews and panel discussions with 31 experts in a Vision workshop (*ORCHID Vision workshop,* Stuttgart, Germany, 23 May 2018). The report described current unmet needs (including evidence of added value, methods for automation and robustness), key challenges (structural materials, cell sourcing and culture media, long-term cell viability, real-time characterization, increasing complexity, qualification), barriers and perspectives (industrial acceptance, appropriate and timely dialogue among players) of this technology, as well as recommendations for defining a European OoC roadmap. The present document builds on this preliminary assessment and identifies potential solutions.

1.2 The future strategy for Organ-on-Chip technology

Following up on the ORCHID Vision workshop, the *ORCHID Strategy workshop* was held in Leiden on 17 January 2019. 32 experts from academia, innovation hubs, pharmaceutical and cosmetic

[1] ORCHID partners are: Leiden University Medical Center (coordinator; The Netherlands), Institute for Human Organ and Disease Model Technologies (hDMT) and Delft University of Technology (Delft, The Netherlands), CEA (France), imec (Belgium), Fraunhofer Institute for Interfacial Engineering and Biotechnology (Fraunhofer IGB, Germany), and University of Zaragoza (Spain).

industry, patient organizations, ethics schools, biotech companies and regulatory agencies attended. They represented OoC developers, end users and regulators in Europe. The aim of the workshop was to sketch an OoC landscape for future development of the technology by defining concrete goals and milestones that would form the roadmap strategy for moving forward. During two brainstorm sessions, expert groups focused on four application domains: personalized medicine, drug efficacy, drug toxicity and disease mechanisms. The groups addressed domain-specific issues from the perspective of both developers and end users/regulators.

This report summarizes the expert discussions, conclusions and recommendations that emerged from the ORCHID Strategy workshop. Six building blocks of the OoC roadmap were identified: (1) application, (2) specification, (3) qualification, (4) standardization, (5) production and upscaling, and (6) adoption. These are discussed individually in depth in Section 4. Potential ethical issues were also considered, as well as training of the next generation OoC researchers and dissemination and communication of the technology. These issues are addressed in the following Sections 2 and 3, which set the context for the core building blocks. We take as given the prominent role that the existing OoC community will play in this endeavor.

2. The European Organ-on-Chip Society (EUROoCS[2])

2.1 The role of EUROoCS in community building

As articulated in the Strategy workshop and detailed below, collaboration between all stakeholders is key to further acceptance, development and implementation of OoC technology. In Europe, an OoC network of more than 28 partners in 17 countries has recently been formed. Many countries, including the United Kingdom, Scandinavia, Belgium and Israel, have drawn inspiration from the Dutch OoC consortium hDMT[3] and are starting to link OoC players in their own countries in similar ways. This paves the way for a European Center of Excellence on human OoC by creating strong research collaborations throughout Europe and beyond. The European Organ-on-Chip Society (EUROoCS), an outcome of ORCHID, aims to facilitate and stimulate further growth of OoC networks.

EUROoCS was launched during the International OoC Symposium (IOOCS18) at the Eindhoven University of Technology in the Netherlands on 8 November 2018. Its purpose is to encourage and develop OoC research, and provide opportunities for sharing and advancing knowledge and expertise in this field towards a better health for all (Fig. 1). Membership is open to individual researchers and others with an interest in OoC technology worldwide. Benefits include access to the digital OoC platform, where members can present their expertise and research projects, interact with others in the OoC field, and find new collaborators and tailored information (see Section 3.3). EUROoCS will stimulate and provide a platform for dialogue and interaction between all parties involved in the implementation of the OoC roadmap strategy. This is captured in the EUROoCS logo, which symbolizes both technology and community building in Europe and beyond (Fig. 1).

[2] www.euroocs.eu
[3] www.hdmt.technology

Figure 1: The facilitating role of the European Organ-on-Chip Society (EUROoCS) in the context of the proposed OoC roadmap.

3. General aspects of an Organ-on-Chip roadmap

3.1 Ethics

An ethics roadmap was regarded as important for identifying emerging ethical issues and addressing them in a timely way as the technology progresses. Such a roadmap is a sensible way to balance short-term issues related to the use of human cells, donor procedures, ownership and present work in the laboratory with longer-term discussions about future 'Human-on-Chip' models that would include but not be limited to Brain-on-Chip, Reproduction system-on-Chip and the right to know/not to know regarding unexpected phenotypes revealed by chip technology.

Communication to the public warrants care

The ethics roadmap will help the discussion of ethical and societal issues with the general public, as well as the conversation on possible future societal impacts and controversies. To avoid misunderstanding, communication about OoC technology should carefully consider language used and how it is understood by the public and different stakeholder groups. The workshop participants noted a discrepancy between expansive ambitions (*e.g.* 'Human-on-Chip') and actual work in the laboratory (technical innovation). Discussions overly focusing on the ambitions may create unjustified expectations and ensuing disappointment (also known as *the hype cycle*), or lead to controversy over issues not related to the research actually undertaken. Cautious language use is all the more essential with regards to patients potentially waiting for these technological developments to become healthcare reality. The expert group therefore recommended to carefully plan a fine-tuned dissemination strategy that might also manage eventual associated risks.

Privacy and ownership issues ask for clear management

There is a strong awareness of bioethics issues among researchers, and experience on how to manage them properly. However, privacy and informed consent procedures may have to be revisited to address issues related to personalized medicine, especially if rare diseases with only few patients are targeted.

In addition, standardization of technology platforms raise issues related to the ownership of results. There is an underlying dilemma between the ambition to contribute to societal goals (*e.g.* new therapies, replacement, reduction, and refinement (3Rs) of animal testing) and the need for economic viability of the solutions. Though there is no best solution, these questions should be addressed further.

Interdisciplinary research and global dialogue raise awareness

OoC research requires interdisciplinary collaboration between physicists, biologists, engineers, chemists and researchers from other disciplines. Researchers active across disciplines may be incorrectly presumed to have correspondingly adequate skills, whereas different laboratories often require different or specific training. Care therefore must be taken so that all personnel is offered appropriate trainings, including regarding safety (see next Subsection).

Another dilemma to be addressed relates to the organization of collaborative research communities on complex high-tech platforms and ensuing requirements for data sharing. By lowering the entry point threshold, new entrants may bring in new innovative ideas, though they may also be less aware of safety issues.

The European OoC strategy explicitly addresses ethical issues; however, this may not *per se* prevent the emergence of new products or systems in other parts of the world which conflict with European values. Therefore, a role for EUROoCS might be to engage in a global dialogue on ethical issues and common understanding of how these can be addressed.

3.2 Training

Tailored training programmes for next generation OoC professionals

The multidisciplinary character of the OoC technology raises challenges for developing appropriate training programmes, as it requires experts with a broad skillset covering various aspects of bioengineering, cell biology, materials science and other disciplines. Specialized training and expertise is of utmost importance for anyone involved in the development and utilization of OoC systems as well as in the assessment of the systems and results they yield. The recommended training programmes will prepare scientists and technicians for new types of employment that will arise but also provide industry and academia with professionals able to keep up with innovation in the field. Training programmes will thus need to cover a wide range of topics – including not just biomaterials, microfabrication and manufacturing technologies and microfluidic principles, but also cell culture, stem cell technology, biobanking, data management and protection, monitoring and analysis (molecular biology/omics, sensors, imaging), pharmacology and toxicology principles, pharmacokinetics/pharmacodynamics (PK/PD) modelling, quality assurance, science communication, regulatory affairs, ethics. Each of these have differing degrees of relevance depending on end-user or developer requirements. Specifically tailored training programmes will be necessary for scientists in academia and industry, for decision-makers (regulators, grant evaluators or peer reviewers), as well as for technicians and research clinicians.

The level of complexity and depth of the training could range from introductory knowledge (awareness) and basic competence (theoretical or practical skills) to deep knowledge (theoretical and practical skills). The programmes might be implemented at various stages of education (bachelor-, master-, doctorate studies or postdoctoral training) and could include either specific postgraduate courses (1 to 2 years), seminars/courses integrated in a broader training programme (1 semester), or only individual training sessions (theoretical or practical). Besides specific training programmes, focussed seminars/courses/workshops on aspects of OoC could be incorporated into traditional educational programmes such as engineering (mechanic, materials, chemical), bioengineering (biotechnology, biomedical), physics, chemistry, biochemistry/biology, medicine, and pharmacology/toxicology. Input into curriculum development will be essential.

In the process of European roadmap development for OoC, comprehensive stakeholder consultation is currently taking place to assess training needs and skillset requirements and provide recommendations for specific training programmes[4].

3.3 Dissemination and communication

The EUROoCS digital platform as a market place: *Organ-on-Chip for all*

A dissemination and communication strategy for OoC research and activities is essential if the EU scientific knowledge base is to be implemented optimally and to foster innovation, economic growth and jobs. EUROoCS, its support website, including a digital platform for members, and its annual conference can contribute to forming a central coordination point, ensuring good visibility for European

Figure 2: The EUROoCS website/digital platform as a "market place" for all.

[4] *Questionnaire for stakeholders: Training needs of the next generation of researchers and technicians in Organ-on-a-Chip*, available at: https://ec.europa.eu/eusurvey/runner/Orchid_Questionnaire_Training_needs_Organ-on-a-chip (accessed: March 29, 2019).

research teams that will promote their leadership in the OoC field. The EUROoCS platform will gather information centrally and promote OoC implementation, development and community building at European and international levels (Organ-on-Chip *For All,* Fig. 2). EUROoCS board and members will ensure that sector-specific boundaries and language barriers are crossed to facilitate effective dialogue and collaboration between the scientific community, regulators, industry, clinicians and patient groups from the earliest stages of development, and catalyze OoC adoption by end-users. Working together as a community and becoming visible through the EUROoCS website/digital platform could also help establish standards in the field that would provide industry with confidence regarding implementation. As a standardization catalyst, the EUROoCS digital platform will also collect expert insights from different stakeholder groups to provide an indirect roadmap through building guidelines for OoC implementation.

The EUROoCS website was conceived by ORCHID members and validated by a test group of selected OoC experts to provide key information efficiently. The majority of tabs (library, latest news and recent events, announcements of trainings, workshops, OoC timeline, reports and reviews) are available with a free subscription to allow the users better understanding of OoC and keep them informed about new scientific and technological developments. It is regularly updated by members and will continue beyond the lifetime of ORCHID through EUROoCS. Specific links to general brochures are included in the website. Moreover, the website was designed to be inviting for students looking for jobs, funding opportunities and informative newsletters, and accessing social networks whereby EUROoCS will host different groups interested in OoC technology. Information on key publications, patents and discoveries will thus be distributed to the dissemination target groups besides being acces-sible directly from the website. The EUROoCS website will evolve over time through the continuing addition of publications, latest news, event announcements, collaborative projects and member-supplied content. Finally, by giving the opportunity to industry for exposure of their technology and being attractive for investors and funding agencies to support the development of prototypes, the EUROoCS website will also contribute to increase innovation and competitiveness for European health-related industries and services.

The ORCHID expert community unanimously perceived the EUROoCS digital platform as a means to build a network, realize integrative programs and collaborative projects or consortia, and find new academic/industrial partners or individuals involved in regulation and patient associations. In this respect, a reserved area, accessible to EUROoCS members, provides expert contacts, project descriptions and mapping. This detailed information as well as the opportunity to debate specific topics through a discussion forum aim at encouraging membership and joining the community. This member-restricted area of the digital platform is expected to be a market place for OoC-stakeholders, with individuals from a wide range of backgrounds benefitting from availability of OoC ideas and expertise, initiating specific working groups or discussing updated topics on OoC.

Building dedicated communication tools to continuously raise awareness

Having established a communication strategy, it is important to determine whether the expected impact is actually achieved. To this end, online dissemination tools (*e.g,* website, newsletters, social media) will be regularly monitored and some key performance indicators (number of visitors, downloads/open clicks, statistics on the impact of the newsletter, number of articles viewed, user feedback on the newsletter's content) will be periodically checked for quantitative and qualitative evaluation (Fig. 3). Qualitative evaluation will also be conducted on the basis of questionnaires following special events. Finally, the impact, strengths and weaknesses of the dissemination strategy on target groups will be examined regularly as well as the quality of communication on OoC.

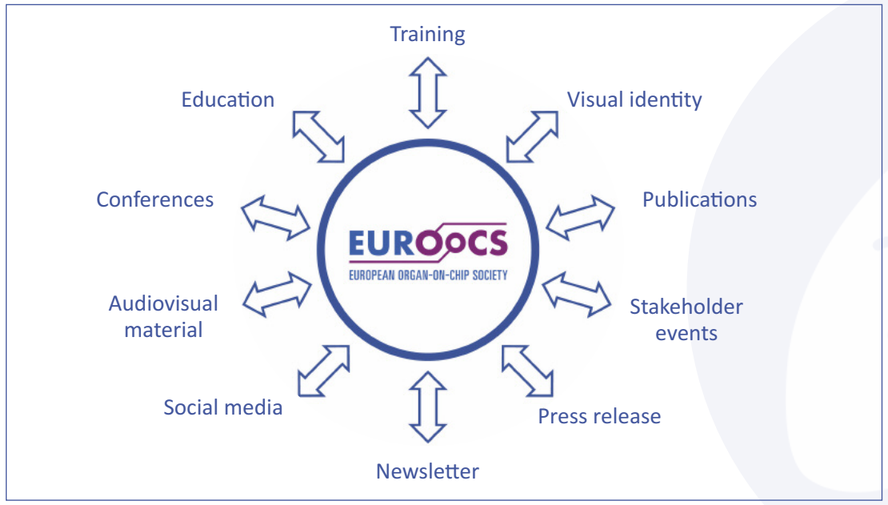

Figure 3: Tools of dissemination.

Participating in conferences and organizing training and dedicated workshops on OoC will raise awareness of the community and capture young researcher attention on OoC activities. This is essential if full potential of OoC is to be realized. To that end, EUROoCS members are being encouraged to establish connections with press, media, politicians, general public and schools, to act as focal points for local dissemination of information, to use connections to other academics working in related domains at local and international levels, and to generate active social media content to introduce European citizens to OoC technology as a concept. A visual identity of OoC in Europe was developed to ensure consistency and higher visibility of the OoC field. Communication tools (*e.g.* social media, brochures, newsletters, press releases) will be adjusted to the type of information and to the specific targeted group. Establishing a proper platform for critical dialogue and dissemination, monitoring interest and acceptance at every level are essential features of the roadmap that will determine rate of progress and ultimate outcome beyond promise.

4. Specific building blocks of the Organ-on-Chip roadmap

4.1 Application

Priority for disease mechanisms, drug efficacy and toxicity, and personalized (or precision) medicine

An important domain to which OoCs can contribute is the drug screening and development process[5], which ranges from fundamental research to personalized medicine and targets users such as biomedical researchers, (research) hospitals and pharmaceutical industries. According to the consulted OoC experts, there are four main contexts of use:

- improving understanding of human disease mechanisms and etiology;
- predicting drug efficacy in humans;
- predicting drug toxicity in humans;
- paving the way to personalized (or precision) medicine.

The associated priority (patho)physiological areas are driven by the need for new therapeutics discovery, including emerging drug modalities (*e.g.* large molecules/biologicals like monoclonal antibodies, antibody-drug conjugates, protein therapeutics), especially for diseases for which there are little or no effective drugs available, due to poor knowledge of pathophysiological mechanisms in humans combined with a paucity of predictive disease models (see Table 1). Among the most cited public health priorities are cancer, neurodegenerative conditions like Alzheimer's disease, cardio/metabolic disorders, autoimmune diseases, fibrosis and rare diseases, such as hemophilia and metabolic syndromes. Each requires its own panel of cell/tissue models that may include single- to multi-OoCs. Primary or stem cell-derived cells and tissues can be a first approach of choice, but in some cases cells will not respond to drugs or reveal disease mechanisms as expected outside a 3D environment or without biophysical stress/flow. For toxicity testing and safety assessment, there may be a strong preference for OoCs mimicking ADME pathways (Absorption, Distribution, Metabolism, Excretion) including metabolic organs (liver, kidney) and barrier/digestive systems (blood-brain barrier and gut for physiological absorption) and the presence of the immune component of the disease. OoCs can be also personalized with patient samples to mimic key aspects of a (patho)physiological state, including specific disease-related parameters. By capturing a higher level of physiological complexity from particular individuals, OoCs are predicted to be of value as companion diagnostic tools to differentiate patients that are "responders" from "non-responders" to medication, to refine doses for individual patients (exposure-response relationships by PK/PD modeling), to define combination therapies and personalized drug delivery, or evaluate disease progression, and predict specific adverse events (patients at risk) thereby tailoring treatment strategies to improve the benefit-risk ratio. OoCs might also contribute to patient pre-stratification for clinical trials, leading to protocol optimization and supporting clinical decision-making processes. As importantly, patients often become tolerant to drugs which are then no longer effective. Identification of "back-up" drugs that have similar effects to the original in the OoC model but via a different pathway can offer an alternative in the clinic which is then highly relevant to treatment benefit. In the future, the implementation of health-related data in OoCs (lifestyle, epigenetics) may lead to even more predictive personalized devices, to position OoCs as physical avatars for individuals or groups of individuals (*e.g.* from different ethnic backgrounds, gender, age).

CONTEXT OF USE	DISEASE AREA	KEY TISSUE MODEL	END-USER
Diseases' mechanisms	Cancer	Tumor models	Biomedical researchers Clinicians Pharmaceutical industry
	Neurodegenerative diseases	Brain, BBB, neurons, retina	
	Cardiometabolic disorders	Heart, lung, liver, pancreas, vessels, adipose	
	Autoimmune diseases	Immune system, gut, pancreas, neurons, skin …	
	Fibrosis	Connective tissues, lung, liver, kidney	
Drug efficacy	Cancer	All types	Industries: pharmaceutical, cosmetics Biomedical researchers
	Neurodegenerative diseases	Brain, BBB, neurons	
	Cardiometabolic disorders	Heart, lung, liver, pancreas, vessels	
	Autoimmune diseases	Immune system, gut	
	Fibrosis	Connective tissues, lung, liver, kidney	
Drug toxicity	All types	ADME pathway (liver, kidney), barrier systems (gut, lung, BBB), heart, brain Immune system	Industries: pharmaceutical, cosmetics Biomedical researchers
Personalized medicine: ▪ **patients' stratification** (adverse effects, dynamics/ resistance, identification of vulnerable population) ▪ **Companion diagnostic** (responders, disease progression)	Cancer	All types	Pharmaceutical industry Hospitals/clinicians
	Rare diseases	All types	
	Systemic diseases	Multi-organs	
	Autoimmune diseases	Immune system, gut	

Table 1: Overview of the applications and associated models discussed during the ORCHID Strategy workshop. ADME: Absorption, Distribution, Metabolism, Excretion; BBB: Blood Brain Barrier..

[5] Other relevant applications include toxicity screening of compounds for cosmetic and chemical industries and for environmental agencies, and counter-measures against chemical and biological warfare – for a comprehensive overview, see the ORCHID Vision workshop report (Mastrangeli *et al.* 2019).

4.2 Specification

Customizable platforms for fit-for-purpose modular OoCs

It was generally agreed that OoCs should be conceived and proposed as robust tools tailored to fit a purpose by the end users. End users should accordingly be provided with flexible solutions ranging from ready-for-use devices to open customizable platforms. Existing ready-to-use OoCs offer a certain level of customization, which can be further extended towards models of increasing complexity via acquired laboratory experience and with customizable platforms. In this respect, the group and collective discussions of the Strategy workshop highlighted the following technical and functional recommendations for the development of OoC models:

a ***Modularity.*** It is unlikely that a single OoC device would be able to satisfy the requirements to serve all conceivable functions or applications within the reach of the OoC technology. For instance, and even though certain molecular pathways are repeatedly defective in multiple diseases (*e.g.* SMAD, WNT signalling), a comprehensive list of disease mechanisms is hardly feasible. Besides, the requirements may be mutually incompatible, and a single device may easily turn out to be

overwhelmingly complex, economically non-convenient and ultimately not effective for potential end users. Instead, a reductionist, flexible integration approach is suggested whereby OoC devices are assembled over platforms out of sets of basic and standardized modules according to user needs. Standardized interfaces and well-defined assembly of modules are essential for the success of such modular approach. Both technical and biological modules are considered:

1. *Technical modules*: mechanical actuators and stimuli (forces, stresses, strains), electrical stimuli, perfusion (microfluidics, pumps, valves), reporter systems and sensors (for *e.g.* oxygen, carbon dioxide, pH, glucose, metabolites, flow rates, impedance);
2. *Biological modules ('functions')*: 3D scaffolds, cell-cell interactions, neuron/neurite outgrowth, barrier mechanisms, vascularization, air/liquid interface.

The modular composition of OoCs within standard platforms shortcuts the issue of defining *a priori* the end use of the devices, leaving it open instead and suitable to a variety of different users and applications. This approach is envisioned to afford or be compatible with:

- simplicity and ease of use;
- possibility to stack levels of complexity in 4 dimensions (space + time);
- customization and user-defined fit-for-purpose;
- standardization of modules (see also Section 4.4).

b ***Increased throughput/scalability,*** to reduce cost-per-data point and extend the range of OoC use in pre-clinical screening. Required throughput depends on applications, research questions and drug development stage (Probst *et al*., 2018; see also Section 4.5).

c ***Automation*** to limit errors and improve reproducibility, repeatability and cost-effectiveness.

d ***Multi-parametric assays*** to benefit from various data points in a single test system, thereby improving efficiency and limiting heterogeneity. The selected parameters should provide sufficient data to support study conclusions allow regulatory acceptance, and they should be linked to clinical expectations to prove the added value of the technology.

e ***Use of genetically & phenotypically characterized human cells*** to mimic human (patho)physiology, with eventual dedicated benchmarking (not based on animal use).

f ***Sustain long-term measurements*** to evaluate (chronic effects of) compounds, perceived as preferred or complementary to short kinetic and metabolic measurements.

g Generic and standardized ***open technology platforms***, both in hardware and software, for full public availability and compatibility across platforms (see Section 4.4).

Modular as well as flexible ready-to-use OoCs align with the belief that the ultimate purpose of the devices may only emerge from the end users themselves once the devices are in their hands.

4.3 Qualification

Qualification processes for context of use need independent testing centers

The Vision workshop highlighted the need to focus on the qualification or characterization of the OoCs rather than on the validation *per se*. The latter was considered by most experts neither an appropriate nor a meaningful concept for highly complex models such as OoCs, because it implies the existence of an accepted standard or reference to measure validity. The Strategy workshop confirmed that while regulatory acceptance is beneficial for the commercialization of OoC devices, this acceptance should not hinder the development process. Indeed, regulatory agencies should be considered as key players involved in the early stages of OoC development, along with end users, in order to better understand the potential of the technology and its applications. Industry needs confidence in the robustness of the data retrieved through the devices, whereas regulators typically require a case-by-case analysis. Therefore, while considered necessary, the qualification of a device does not necessarily prelude to its regulatory acceptance nor to user adoption.

For drug screening and development, OoCs should recapitulate human tissue physiology but also disease-related parameters to be used as predictive models for assessing safety and efficacy of promising therapies that are preferably better than current cell and animal models. The characterization and qualification of such devices should be based on a generic study design including the following key aspects:

i. Defining the context of use and its associated outcomes, to select the most relevant OoC model;

ii. Challenging OoC systems with reference compounds insofar as they are classified regarding context of use and specific parameters. This aspect will help determining the biological relevance of the devices and will allow qualification of their performance. It will by definition rely on known outcomes of animal experiments and preferably their discrepancies with clinical/patient data or safety/feasibility in phase I trials on healthy human individuals.

iii. Implementing quality control assays ensuring the functional characterization of cell cultures to fit with human (patho)physiological responses but also expressed in the form of material qualification (drug-biomaterial interaction), manufacturability and availability of devices.

iv. Evaluating effectiveness of OoC compared to current *in vivo* profiles, through the analysis of the corresponding data derived from conventional drug development models, and correlation with clinical data or manifestations.

v. Performing intra- and inter-laboratory assays (ring trials) to assess the reproducibility and accuracy of OoC devices as well as monitoring technological performances (stability and robustness).

These last aspects should be considered as iterative approaches, supported by ongoing pharmaceutical projects to bring added value, aiming at investigating the correlation between OoCs and *in vivo* data, if relevant, and to make the critical link with the clinical expectations. Ideally, all qualification studies should be performed by a third party, as proposed by the testing center initiatives in the US funded by NCATS, to ensure an independent analytical characterization (Fig. 4).

Towards a centralized database to share information and promote OoC development

To achieve optimal results from the qualification studies, a key challenge is establishing an evolutive database clustering all available data on a reference set of the most appropriate compounds and biomarkers, together with the results on the performance and accuracy of the specific OoC systems under test and the context of use for the target tissue(s). The aim of this centralized and publicly accessible database would be to provide the scientific community with in-depth information (including raw data and negative results) on well-characterized pharmacological and toxic compounds to demonstrate *in vivo*-like responses in OoC devices and to go beyond a simple and linear annotation of the compounds' effects. Providing relative data from reference compounds/biomarkers and allowing the community to use it wisely (including stakeholders and regulators) may help both developers and end users to challenge OoC systems and may influence the decision-making process.

However, the quest for qualification of OoC devices entails abundant human data sets being available as well as multi-parameter readouts without bias (achievable via proper automated statistical data analysis). In addition, a relevant list of test compounds/biomarkers is not readily available or in the making at best, thanks to several independent initiatives (*e.g.* the NIH in the US and the Crack it! European program). Beyond having a list of compounds upon which the outcome and mechanisms of action are agreed, the compounds may not necessarily be available to academic research groups since they are proprietary or may no longer be synthesized. A solution would be to work closely with structures like the IQ Consortium[6], a not-for-profit organization of pharmaceutical and biotechnology companies, which is compiling a list of reference compounds that might be shared for qualification purposes. NCATS is also currently working with well-known pharmaceutical companies like AstraZeneca, GSK, Pfizer, Roche or Sanofi, and has for that purpose already established a material transfer agreement to ensure that compounds/biomarkers provided for the characterization are cleared for inclusion in academic work (Ewart *et al*., 2017). Alternatively, medicinal chemists may be contacted to synthesize specific compounds or variants of those.

EUROoCs may play a catalyzing role in collecting the information with the necessary infrastructure, data management and statistical capabilities to ensure an extended dissemination among the OoC community and beyond (Fig. 4). Vice versa, this publicly accessible database could also be a promising tool to promote OoCs' adoption supported by early engagement of academic, industrial and regulatory players. Finally, the coordination of a EUROoCS-supported database with other international existing ones should reinforce multi-partner task forces and contribute to international harmonization.

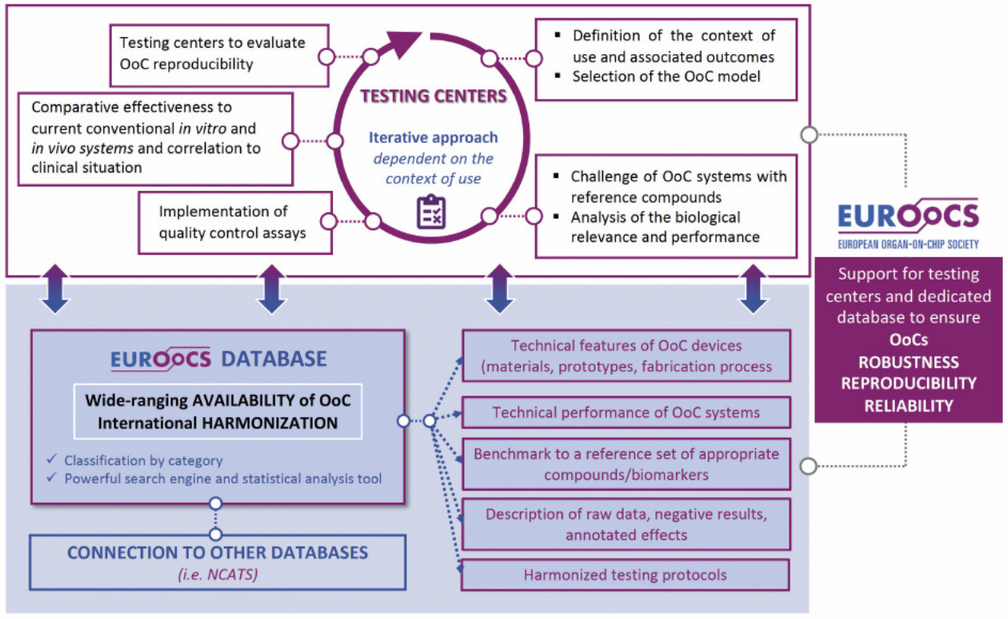

Figure 4: Synopsis of OoCs qualification processes and interfacing with a centralized database.

4.4 Standardization

A task for the OoC community that should be internationally harmonized

Standardization is an overloaded concept with multiple interpretations across different sectors and markets. Standardization of OoCs is very challenging since OoC is inherently interdisciplinary. In recent history, technological standards have usually arisen either from dominant commercial players or from collective entities such as regulatory authorities or roadmaps jointly established among field competitors. While the former appear to be the current case in US, where several larger groups are trying to define OoC standards, standardization emerging from a collective dialogue among developers and end users and from ensuing cross-constraints is ultimately expected to prevail. Successful examples of standardizations in electronics (*e.g.* data communication protocols, interfaces, and peripheral cross-compatibility) can be capitalized as important learning experiences. In particular, lack of standardization for Lab-on-Chip approaches may be responsible for the problems it currently encounters in getting into the market.

Also to avoid this risk, OoC standardization should be addressed very early in development to enhance the prospect of being competitive with alternatives. On the other hand, standardization cannot be promoted by most of the current stakeholders, as these are mostly small (biotech or start-up) companies without sufficient finance to support a standardization strategy. OoC standardization is therefore considered a task for the OoC community. The role of the community is in fact central, because the purpose of standards is foremost to enable the OoC community itself to work together towards developing prototypes. Community-driven standardization may also ensure that standardization addresses sufficiently common issues, benefitting a set of users and thus becoming a means to accelerate innovation. EUROoCS can play an important role in bringing developers, stakeholders, regulators and end users together into a community, as well as in serving as a collective expert group to advise on OoC standards, protocols, methods and guidelines, similarly to prior experiences in *e.g.* stem cell research and toxicology, whereby protocols were defined by panels of experts.

Different standardization layers should be identified

Layers of standardization can be envisioned, ranging across multiple levels of abstraction and user experience. They include: materials, dimensions, cell input and content, perfusion media, flow rates, interconnections and interfaces, optical access, platforms, cross-compatibility among modules, back-compatibility with existing substrate standards (*e.g.* multi-well plates, microscope slides, multi-electrode arrays) and laboratory instrumentation, cell sources and lines, cell phenotypic and genotypic characterization and protocols for cell differentiation, cell handling, use of devices and quality control. Additional layers should be further considered. Standards for commercialization could eventually emerge from research prototypes, though this should not be the primary aim of the community. Commercial standardization should be internationally harmonized, avoiding competing groups particularly between US and Europe.

Towards standardization: open technology platforms for OoC

One way experts recommended to encourage the OoC community to converge towards standardization was the realization of open technology platforms. These can be seen as shared technology platforms to gather knowledge and expertise into a centralized database, in which potential users could contribute by developing and sharing building blocks of modular systems to enable customized solutions for specific applications. The open technology platform concept is in line with the modular approach suggested for the development of OoCs. It will stimulate further innovation, rather than restrain it. These platforms would reduce barriers to expensive manufacturing of devices, because they could generate the production volumes needed for sustained technology development. The freedom to develop demonstrators in parallel may moreover lead to quick learning cycles and broad uptake of the successful innovations in the community. However, the implementation of an open technology platform rises crucial questions concerning the co-existence of, on the one hand, open interfaces, open standards, and the freedom to exploit together open source content with, on the other, patenting and licensing of intellectual property as sources of commercial drive and market penetration. These and similar issues related to the co-existence of private profit and public availability are well-known from prior standardization attempts in other fields, and they represent evidently an important aspect of the proposed roadmap that needs to be resolved.

Further information on the benefits and pitfalls of standardization in the field of OoC devices and systems is described in the *ORCHID whitepaper on standardization*. The whitepaper was written by ORCHID partners in the context of the ORCHID project in addition to the Strategy workshop, and is provided here in Appendix. The whitepaper in particular identifies ongoing standardization efforts which address certain aspects of technology and operational processes in the OoC field.

4.5 Production and upscaling

Industrialization requires choices in early development of OoC devices

OoC production perspectives will be determined by the type and scale of use of OoCs – whether for *e.g.* drug screening or replacement of animal tests or personalized medicine – such that a 96-well plate format or similar may need to be developed for applications requiring high throughput, whereas in other cases a 2-well plate or single-chip format may be sufficient if examining efficacy for example. Clear and standard guidelines for quality control of technology and biology should be introduced in all cases to get and maintain robustness. The type of use will also determine the allocation of resources. In this respect, drug development prioritizes rate of success and time-to-market, and hence time saving rather than cost saving.

It is important to remark that upscaling of OoCs inherently involves both technological and biological components. This respectively implies mass production of chips or microfluidic devices and generation of large batches of differentiated cells that are quality controlled prior to use in OoCs. As demonstrated by the success of microelectronics, high volume production of chips typically coincides with decreased manufacturing costs and variability and leads to highly reproducible devices. However, there is a caveat here. On the one hand, device-level reproducibility would be required especially in early stage OoC development and qualification (see Section 4.3) since the inherently variable biology introduces another potential layer of variability and cannot otherwise be properly assessed. On the other hand, setting up mass production of devices requires large investments which are not likely for non-qualified devices. Solving this issue might require specific, public-private funding calls.

Depending on applications (see Table 1), at least three different upscaling strategies could be envisioned:

1. *Drug efficacy and toxicity* in pharmaceutical industry. In this case the SBS well-plate format will likely be the preferred and target format, with highly characterized, robust and reproducible OoC enabling relative comparison of hundreds of drugs (Probst *et al*., 2018);
2. *Personalized medicine*, possibly in a hospital setting or dedicated SMEs. This will entail robust and reproducible OoCs with (patient-derived or genetically modified disease bearing) cells, and upscaling to test tens (*i.e.*, 10 to 50) of potential drugs and find the right concentration of the right drug for specific patients or disease states;
3. In the longer term, *clinical trials*. To date, there are no clinical trials on *e.g.* children, pregnant women, or on specific or unique ethnic groups. OoC could enable better representation of human phenotypic diversity in clinical trials. The upscaling requirement to perform Clinical-Trial-on-Chip in CRO's will be dependent on the trial.

An industrial-level fabrication volume puts manufacturing constraints on the design, dimension and structural materials of the devices. These choices should be considered as early as possible in device development along with back-compatibility with established laboratory tools and cross-compatibility among platforms. At the same time, the use of standard cell lines might not match such extended device request, though standard cell handling protocols could still be helpful, and banks hosting cells for different population subgroups might need to be established.

4.6 Adoption

Adoption of OoC technology requires well-documented showcases

The OoC technology may be accepted and thus adopted if it provides simpler, cheaper and relevant alternatives to established models (even those based on multi-cell type cultures) while reproducing at least the same results supported by convincing and reliable metrics, or if it affords models for which no alternatives currently exist (such as rare diseases in which microfluidics is required to reveal the phenotype; see Mastrangeli *et al*, 2019). OoC adoption implies the satisfaction of many other conditions including ease of use, back-compatibility with established laboratory processes, cross-laboratory reliability, together with a supporting and organized user's community (Fig. 5).

In this respect, experts deemed the identification and stratification of end users, stakeholders and sectors as critical. It should be part of a primary action conducted by dedicated methodologies and teams, and a prerequisite to organize a global community centered around open technology and allowing smooth transfer of expertise among disciplines and domains (*e.g.* including regulatory bodies). To build confidence in the value of OoCs and facilitate engagement of all players, structuring of (a) neutral organization(s) capable of testing and qualifying devices has been proposed, in line with OECD guidance. The adoption process will emerge from collective end users of OoC and will rely on the data obtained with OoC included in a regulatory approval and perceived by regulatory bodies as complementary data to standard benchmark. The applicability of these guidelines to rapidly developing technologies like OoCs remains a key challenge. A convincing way to circumvent these issues would be to encourage multi-partner task forces to conduct showcases capable of fostering end user adoption. Such showcases may be represented by case studies, such as the CRACK it! challenges, even non-optimized or finalized, involving end users along with regulators and developers to start and sustain a fruitful and timely dialogue. As pointed out by the regulatory experts, the final decision will be up to developers since today there are no restrictions or requirements from regulatory bodies for the use of specific cells.

Finally, community organization and subsequent adoption of OoCs by end users will need sustained dialogue and collaboration to move across the limitations of sector-specific cultures and languages: EUROoCS is expected to play a leading and catalyzing role in that respect.

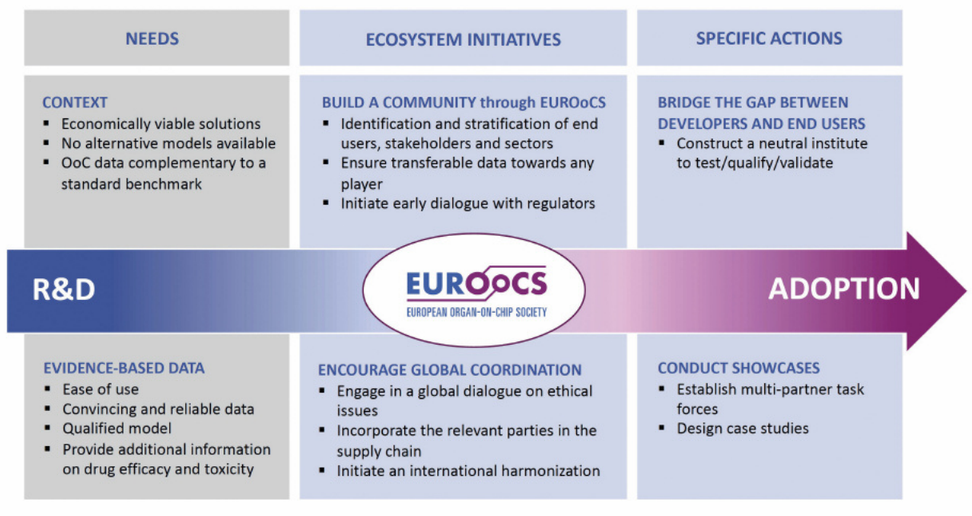

Figure 5: Overview of the context needs, initiatives and specific actions to promote OoCs adoption.

5. Discussion and recommendations

The ORCHID Strategy workshop converged on the proposition of the roadmap for OoC development represented in Fig. 6. The roadmap emphasizes a dual path, involving proprietary ready-to-use devices and open technology platforms, running in parallel and interacting along the way. OoCs are expected to serve three major markets: 1) Industry (mainly pharma, cosmetics and chemicals), 2) hospitals, and 3) academic research. Industry and hospitals might mostly require ready-to-use devices, whereas the latter would strongly benefit from open technology platforms. As described in the previous Sections, to move forward from the current status to applications of OoCs, the roadmap is envisioned as making use of a set of main building blocks. Some building blocks are specific to the present state of the art, whereas others correspond to common development stages for which prior experience in collateral roadmaps can be capitalized. Along with the concept of the OoC roadmap, the experts agreed on the catalyzing role that EUROoCS could and should play in the deployment and actualization of each building block.

It should be noted that the entries in Table 1 are not exhaustive but rather priority lists. This holds in particular for known disease mechanisms, for which a complete list is hardly conceivable, and for OoC applications, whereby the long-term list may even turn out to be different from the one proposed depending on the future needs of actual end users and how their drugs discovery priorities change. Whereas the application domains were chosen mainly to guide the discussions, the roadmap and its building blocks are expected to apply irrespective of the directed versus emergent nature of the final applications.

Alongside flexible ready-to-use devices, the modular approach to OoCs based on customizable platforms was recommended as a solution to enable both user-defined and specific fit-for-purpose applications and at the same time align or facilitate qualification, standardization and large-scale production of OoCs. Device qualification, *per se* not corresponding to device adoption or regulation, should pass through independent testing centers, preferably established in Europe following the US lead. A single worldwide database, eventually emerging from the harmonization and interconnection of local databases, would be ideal to collect and share all related data, following the example of shared compounds lists by *e.g.* the IQ consortium. Standardization should address multiple levels of OoC technology and should start from forming task forces of expert groups and learning from existing standards (see Appendix). It is worth emphasizing once again the advantages of open technology platforms, along with the need to manage the coexistence of, at times, divergent needs related to intellectual property and technology sharing. Successful handling of these aspects additionally highlights the key role of a wide, open and interconnected OoC community, not least for its role in innovation. In this respect, while supporting the roadmap the experts at the same time acknowledged the possible dualism and coexistence of a more directed and linear approach to OoC development, as indeed embodied in a roadmap, and of an emergent and more non-linear approach building upon crowdsourcing and user-generated targets and solutions. Both approaches have earlier examples in recent history, and can certainly interact for mutual benefit. Irrespectively, it is clear that to achieve the long-term goals of globally improved healthcare and personalized medicine envisaged, OoCs will need to be suitable for large-scale production, an aspect that should involve the choice of biological and synthetic materials and of manufacturing technologies from early stages of development. Along this line, compatibility of the devices with established laboratory practice and standards as well as successful showcases of complete OoC platforms and applications should favor OoC penetration and speed up worldwide adoption.

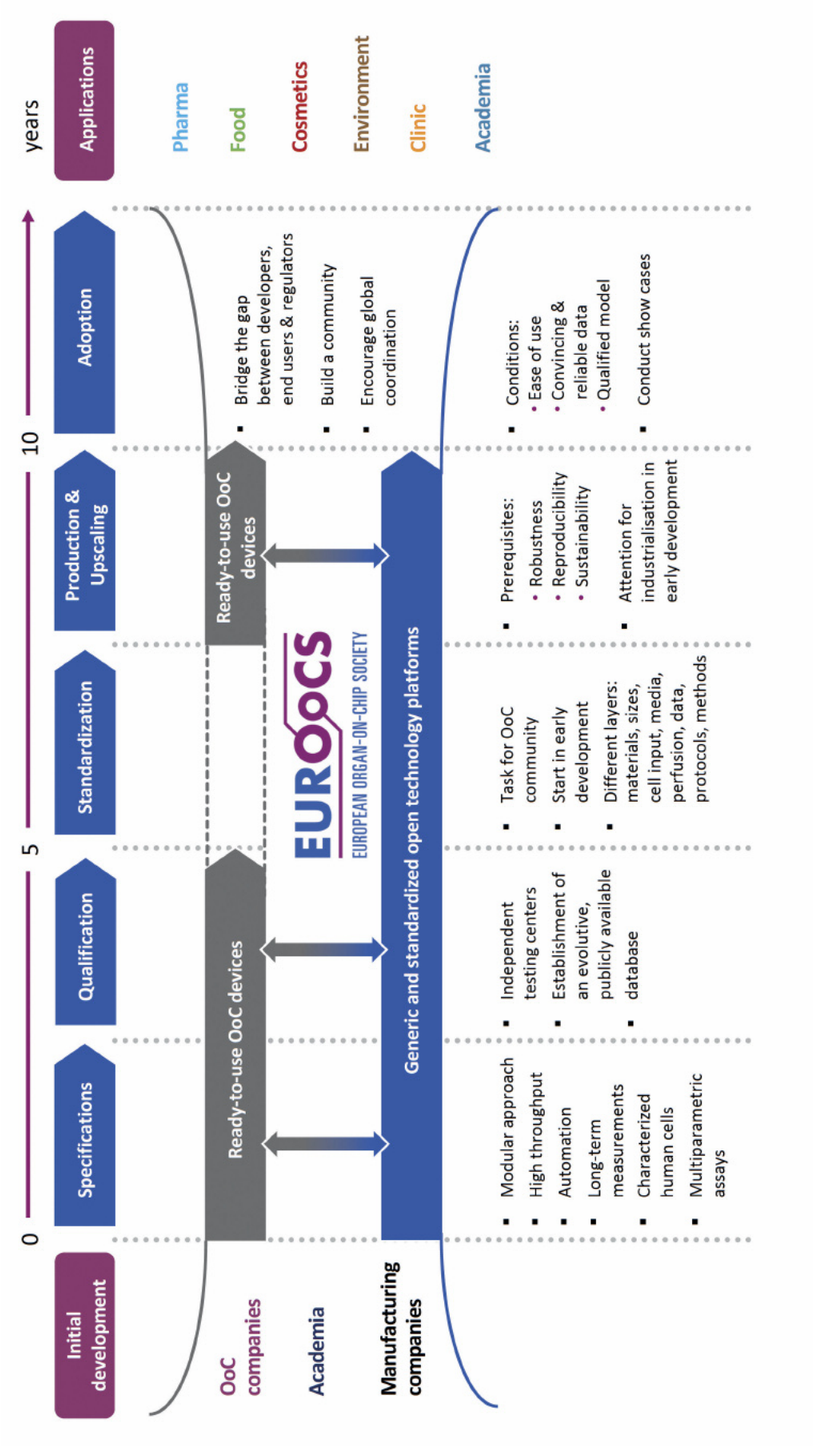

Figure 6. The ORCHID roadmap for OoC development.

Finally, the roadmap that this report has introduced – and of which the final structure will be released in October 2019 – necessarily addresses related ethical questions, cautiously optimistic communicational strategies, and information of laypeople as well as in-depth training and education of the next generation of experts. For all of the above tasks, EUROoCS, supported by its digital platform, publications and recurrent meetings, should be ready to play a central role.

Recommendations

1. Focus on selected pathophysiological areas in the context of OoC models for disease mechanisms, drug efficacy and toxicity, and personalized medicine: cancer, neurodegenerative diseases, cardio-metabolic disorders, autoimmune diseases, fibrosis and rare diseases.
2. Provide end users with customizable platforms for fit-for-purpose OoC models.
3. Explore a modular approach for the OoC models, with technical and biological modules that can be assembled within standard open technology platforms.
4. Converge towards standardization of components, methods and data via collective dialogue among experts, facilitated by EUROoCS, and starting very early in the development.
5. Establish independent testing centers for the qualification and characterization of OoC models for a specific context of use.
6. Develop a publicly accessible evolutive database, supported by EUROoCS, that clusters all available data from reference compounds and OoC test data, and interfaces with other databases to contribute to international harmonization.
7. Resolve issues related to the co-existence of private profit and public availability of technology in the OoC field.
8. Address upscaling requirements and constraints on design, dimension and structural materials as early as possible in device development to make the right choices for industrial-level fabrication.
9. Encourage multi-partner task forces to come up with well-documented showcases, based on case studies, to stimulate adoption of the OoC technology. EUROoCs should catalyze this process.
10. Engage as EUROoCS in a global dialogue on ethical issues, and address them timely as the technology progresses.
11. Develop tailored training programs for the next generation OoC researchers.
12. Build the OoC community further and bridge the gap between end users, developers and regulators with the support of EUROoCS.
13. Stimulate information, communication and interaction via the digital platform and targeted meetings of EUROoCS and measure the impact on OoC ecosystem development.
14. Plan a careful dissemination strategy for the general public based on realistic expectations and ambitions.

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Appendix:
White paper on Standardization

Executive Summary

Standardization is a method to provide guidance in a particular industry. It has a persistent and often ambiguous influence on innovation. Standardization efforts are very different for industries in different stages of development. The Organ-on-Chip (OoC) community can find a basis for standardization in standards already developed in areas of individual components such as sensors, microfluidics and cell cultures. This document aims to introduce the theoretical framework of the process of standardization, its functionality, and a current and future view of standardization efforts related or of importance to the OoC field

Introduction and Overview

Standardization is the process of developing and implementing specifications based on the consensus of the views of firms, users, interest groups and governments. This process then ensures an optimum degree of order of the rules, guidelines or specifications. In this document, the definition and impact of standardization are introduced, the functions of standardization, and the methodologies to create new standards. Finally, the benefits and pitfalls of standardization in the field of OoC devices and systems are discussed. Further, already running standardization efforts are identified which address certain aspects of technology and operational processes in the OoC field.

1. Definition and impact of standardization on innovation

Standardization is the process of developing and implementing specifications based on the consensus of the views of firms, users, interest groups and governments (Sherif, 2001; Xie, Hall, McCarthy, Skitmore, & Shen, 2016). The resulting standards are intended to promote compatibility, interoperability and quality. Standards can be developed by standard development organizations, such as the International Organization for Standardization (ISO), or independently by companies who have a dominant position in the market (Utterback & Suarez, 1993). The economic cost of inadequate or non-existing standardization in a particular industry can be very high. For example, in the automobile industry in the US, about US$ 1 billion per year is lost due to interoperability problems associated with sharing product and engineering data (Tassey, Brunnermeier, & Martin, 1999).

To understand the functional aspects of technology standards, it is helpful to consider the differences between the supply and demand side. On the supply side, a technology standard represents the synthesis of proven concepts on the design logics to organize the hierarchy and functional parameters of a particular type of product (Narayanan & Chen, 2012; Tassey, 2000; Tushman & Anderson, 1986). On the demand side, it reflects the desire for a consumer or user for agreement on a uniform technological format that allows for integration and interchangeability across multiple end products (Axelrod, Mitchell, Thomas, Bennett, & Bruderer, 1995). Thus, a technology standard represents the collective choice resulting from a balance between utility, technical possibilities and the cost structure of manufacturers on the one hand, and constraints of political, social and economic institutions on the other (Garud, Jain, & Kumaraswamy, 2002; Hargadon & Sutton, 1997; Narayanan & Chen, 2012; Tassey, 2000).

Standards played an important role in the industrial revolution as they allowed companies to achieve economies of scale and enabled markets to execute transactions in an equitable and efficient manner (Tassey, 2000). The traditional economic function of standards can restrict the product choice in exchange for the cost advantages of scale, but more advanced standards can, on the contrary, facilitate product variety and thus choice.

Although there is a large group of researchers that claims that standardization has a significant positive and accelerating effect on innovation (Hashem & Tann, 2007; Rysman & Simcoe, 2005), there are also other reports claiming that it constrains innovation by hampering creativity and delaying commercialization of inventions (Hamel, 2006; Hill & Rothaermel, 2003). As standardization affects both innovation and technology diffusion, the concern of R&D policy should be the evolutionary path by which a new technology becomes standardized. Standardization can indeed increase efficiency within a technology life cycle, but it can also prolong existing life cycles to an excessive degree by inhibiting investment in technological innovation that creates the next cycle (Tassey, 2000). In the following Section, we will elaborate on the functioning of standards, and how to develop them.

2. Standards functions and development methodology

2.1 Functions of standardization

Some of the basic functions of standards can be categorized in 4 groups: *quality/reliability, information standards, compatibility/interoperability, and variety reduction*. A standard that specifies a minimum level of performance often provides the point of departure for competition, which benefits the user or consumer eventually. By reducing the transaction cost between buyer and seller drastically, a range of measurement and test method standards provides information in advanced industries. For R&D processes, an efficient way of working can be obtained by standardizing the scientific and engineering data, and by using standardized equipment calibration techniques. Besides this, real-time monitoring and control of certain processes can eliminate wasted material and increase product mix flexibility (Tassey, 2000).

Standards specify properties that a product must have in order to work with complementary products within a product or service system. Compatibility or interoperability is typically manifested in the form of a standardized interface between components of a larger system. Most commonly, interface standards provide ‘open’ systems that allows proprietary component designs to coexist. So, they enable innovation at the component level by being competitively neutral with respect to design. Competitors can innovate on either side of the interface leaving the consumer with a choice to select particular components to optimize the system. Standards do limit a product to a certain range or number of characteristics such as size or quality levels. The 4th function is thus the reduction of variety to attain economies of scale. This is achieved by most standards, but not only by treating particular physical dimensions of a product, but also data formats and combined physical and functional attributes.

Standardization is not an all-or-nothing proposition; it typically proceeds in an evolutionary manner. Its patterns are determined by the pace of the technology development and changes in market structure. Government can play an important role in establishing and demonstrating a backbone

infrastructure, which in turn promotes private-sector R&D investment in standards to enable effective use of this infrastructure. Innovation in certain markets can be heavily impacted by regulatory instruments. Although regulation often comes with increased costs or restriction in freedom of action, well designed regulation may guide or even force firms to invest in innovative activities (Porter & Linde, 1995). Regulation stems primarily from a top-down approach, while formal standards are typically the result of a market-driven process, or differently put, self-regulation vs. direct governmental regulation. Moreover, regulation is mandatory, while the adoption of formal standards is voluntary. According to Blind *et al.*, in uncertain markets, the effects of formal standards and regulation in relation to regulatory capture do not differ substantially from each other (Blind & Mangelsdorf, 2016). In uncertain markets, regulators have less access to information than the standard setters, causing an information asymmetry.asymmetry.

2.2 Development of standards

ISO is an independent, non-governmental organization with members being the standard organizations of the 162 member countries. It is around since 1926 and is the largest developer of international standards, with over 20,000 standards been set up. Other technology standard organizations are the Institute of Electrical and Electronics (IEEE), Internet Engineering Task Force (IETF), and 3rd Generation Partnership Project (3GPP). Like a symphony, it takes a lot of people working together to develop a new standard. The role of the standard development organization is to conduct this process, while the orchestra is made up of independent technical experts[7]. These experts form then a technical committee that is responsible for a specific subject area. They begin the process by developing a draft that meets a specific market need. This is then shared for commenting and further discussion.

The voting process in the technical committee is key to achieve consensus on the standard development. If no agreement is reached, the draft will be modified further, and voted on again. In the experience of ISO, developing a standard typically takes about 3 years. Figure 1 shows the main stages in the process of ISO.

The key principles in standard development can be summarized in the following 4 items:

1. **ISO standards respond to a need in the market**
   The request to develop a new standard always comes from industry or other stakeholders. In the process, a member of the stakeholder group contacts the national member of ISO, who then contacts ISO.
2. **ISO standards are based on global expert opinion**
   ISO standards are developed by groups of experts from all over the world as part of larger groups called technical committees. These experts negotiate all aspects of the standard, including its scope, key definitions and content.
3. **ISO standards are developed through a multi-stakeholder process**
   The technical committees are made up of experts from the relevant industry but also from consumer associations, academia, NGOs and government.
4. **ISO standards are based on a consensus**
   Developing ISO standards is a consensus-based task. Comments from all stakeholders are considered.

[7] Available at: ISO (accessed: March 19, 2019). https://www.iso.org/home.html

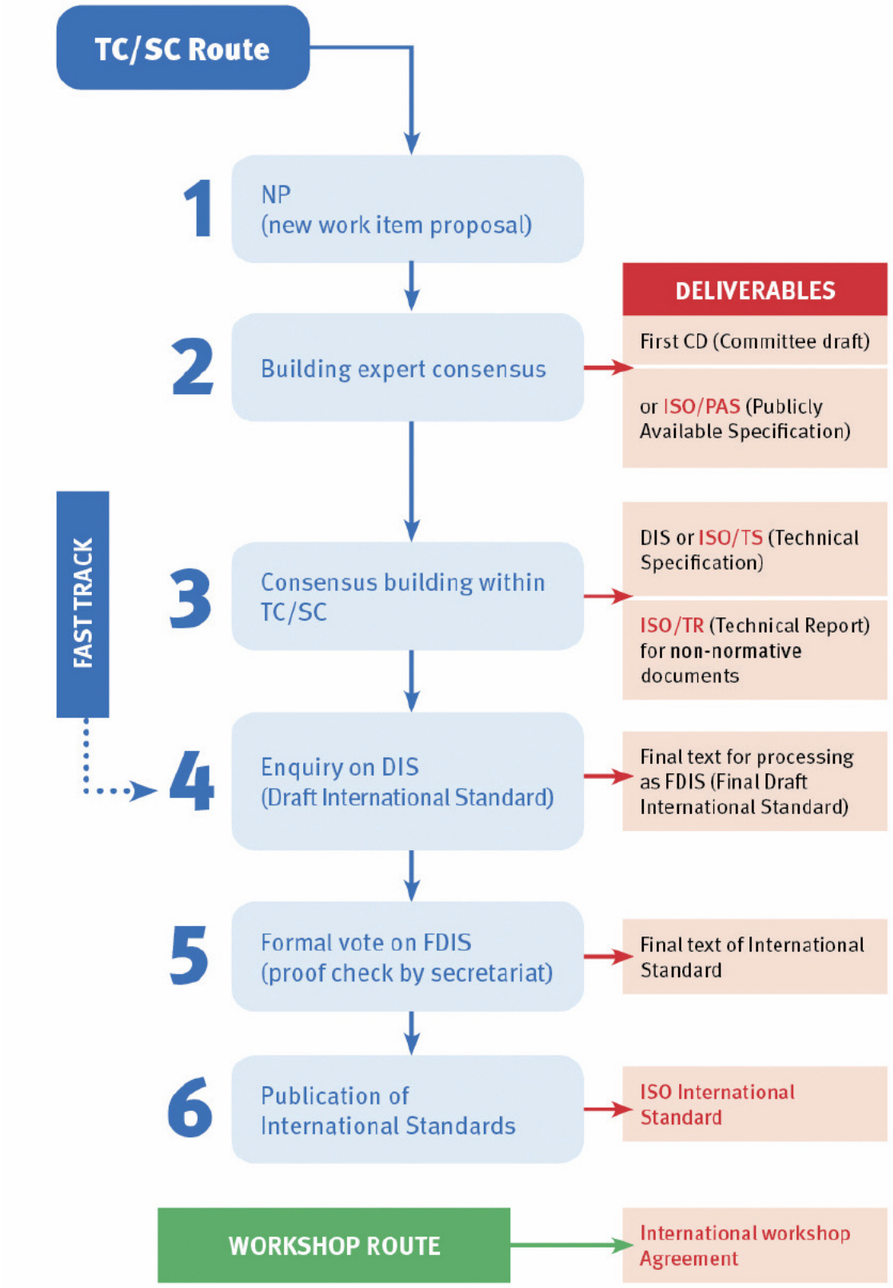

Figure A1. ISO standards development process.
(TC): a Technical Committee, which develops standards in a certain sector or industry
(SC): a Subcommittee, which addresses a specialized area within a TC

In the electronics industry, the Semiconductor Equipment and Materials International (SEMI) is an organization that provides industry stewardship and engages its members to advance the interests of the global electronics supply chain. SEMI has a standards program which is also one of their key services for the benefit of the worldwide semiconductor, photovoltaic LED, MEMS and flat panel display industries. The program started over 40 years ago in North America but was expanded in 1985 to include worldwide programs. It operates as a neutral forum for the exchange of information among suppliers and users resulting in the production of timely and technically accurate specifications and other standards of economic importance to the industry. Over 5,000 technologists representing both device manufacturers and equipment and materials suppliers participate in the program.

The SEMI standards program provides a framework and procedures for industry experts to meet, discuss, and develop essential standards and guidelines. Once the need for a standard has been identified with appropriate input from the user community, a task force is assembled to carry out the development effort. The result of this process is a draft document, which is then reworked until consensus is reached. The consensus is then reported regionally to obtain comments from other members. When that stage finishes, the worldwide balloting process is initiated to search for global consensus.

The new standard is then communicated to the industry and users are advised to cite and utilize them, although the use is entirely voluntary. Management of the program is provided by industry volunteers serving on administrative Regional Standard Committees in North America, Europe, and Japan. The international Standards Committee has the overall responsibility for the conduct of the program. It establishes the regulations governing the program procedures and maintains relationships with other standard-setting organizations worldwide[8].

3. Standardization for Lab-on-Chip and Organ-on-Chip devices.

3.1 Debate and ongoing efforts

As Lab-on-Chip (LoC) technology matures, there is a growing debate about standardization. As previously discussed, there are advantages and disadvantages of standardization and their impact on innovation. This has led to different views on whether standards need to be developed for microfluidic devices (Klapperich, 2009; Van Heeren, 2012; Zengerle, 2007). Microfluidic technology is the heart of a LoC device, and also forms a crucial aspect of OoC devices.

One of the key points that hamper standardization efforts is the lack of vocabulary for microfluidics. Before reaching a standard for a product, testing standards have to be developed. Testing standards enable an objective comparison between the data sheets of competing products, independently of any specified technical requirement for the product. A variety of testing standards have been suggested already[9,10] based on the current need for methods to measure *e.g.* the internal dimensions of microfluidic devices, solution temperature, electroosmotic mobility, zeta potential and autofluorescence (Stavis, 2012).

[8] Available at: SEMI (accessed: March 19, 2019). http://www1.semi.org/en/Standards/P_000787
[9] iNEMI Technology Roadmap, MEMS Technology Working Chapter 2011.
[10] SEMI International Standards, Technical Committee Charter, Charter of Global MEMS/NEMS Committee.

One of the key features under discussion is the standardization of interconnects, connections made to/from microfluidic devices (Fredrickson & Fan, 2004). One of the remaining issues to be solved is what aspects of interconnects should and can be standardized. A possible solution is to make a strong link between microfluidic interconnects with existing standards already found in laboratory equipment such as (mini)Luer connections to microscope slides or microtiter plates (Harink, Le Gac, Barata, Van Blitterswijk, & Habibovic, 2014; Van Heeren, 2012). Still, following that trajectory might lead to increasing costs. The effort of attempting to publish document standards has led to the creation of a working group in ISO, CEN/TC 332 (WG 7 micro process engineering), and subsequently the publication of a document entitled *"Micro process engineering – vocabulary" (ISO 10991 2009)*. Additionally, there is a DIN (Deutsches Institut für Normung) standardization group on characterization for microreactors.

Ongoing efforts exist between stakeholders from the Microfluidics Consortium[11] and consortium partners of an EU project called MFmanufacturing[12], some national groups and SEMI. A questionnaire was sent around, and responders consisted of small-medium enterprises (SMEs) for about 50% and research laboratories (a quarter). The rest of the responders consisted of large enterprises and other research organizations. The discussion has identified several implementations of connectors in microfluidic devices and it was found that, for example, connectors should be easy to plug, be removable and reusable. Another outcome identified the need to have the microfluidic connector be easily combined with other connectors such as electrical and optical. Further, because of the growing trend of miniaturization, smaller components and thus smaller pitch spacing dimensions are needed. The MFmanufacturing project defined a specific standard pitch spacing based on a 0.75mm grid using multiples of 0.75. Another outcome of discussions among stakeholders identified the need for edge connectors and reliability (van Heeren, Tantra, & Salomon, 2015). From the need of reliability arises in turn the need to develop suitable testing schemes. A common testing strategy can also speed up the process of testing and limit duplication efforts, eventually leading to harmonization on activity on a global scale.

In a simplified view, adding of cell cultures to microfluidic Lab-on-Chip devices has led to the development of Organ-on-Chip systems. Indeed, with the advent of human stem cell-based cell cultures, study and testing of human physiology and pathophysiology in a dish has become reality. A key challenge, though, is the quality control and lack of standards in cell culture in terms of *e.g.* protocols and reference cell lines. Besides the cells themselves, *in vitro* culture conditions also need standardization: culture medium, medium conditions, frequency of replenishment. Operations linked to cell culture include cell culture handling and maintenance, antibiotics use, and are also of great importance in the process of standardization.

The International Society for Stem Cell Research (ISSCR) has historically developed guidelines that address the international diversity of cultural, political, legal, and ethical perspectives related to stem cell research and its translation to medicine. The guidelines were updated in 2016 to encompass a broad and expansive scope of research and clinical endeavor, imposing rigor on all stages of the research, addressing the costs of regenerative medicine products, and highlighting the need for accurate and effective public communication[13]. However, standardization is implemented to a very limited degree so far, especially in the field of induced pluripotent stem (iPS) cells, which is strongly linked to the OoC technology.

[11] Available at: Microfluidics Consortium (accessed: March 19, 2019). www.microfluidicsinfo.com
[12] Available at: Mf-manufacturing (accessed: March 19, 2019). http://mf-manufacturing.eu/
[13] ISSCR Guidelines for Stem Cell Research and Clinical Translation.http://www.isscr.org/docs/default-source/all-isscr-guidelines/guidelines-2016/isscr-guidelines-for-stem-cell-research-and-clinical-translationd67119731dff6ddbb37cff0000940c19.pdf?sfvrsn=4

3.2 Steps towards harmonization

For LoC devices, and more in particular microfluidic chips, a first step towards harmonization is the development of a generic classification system which is independent of the application. One potential way to do this is by classifying microfluidic devices according to certain similarities, for example according to the temperature and pressure under which they have to operate. A recent example of a path towards standardization of microfluidics was presented by Dekker *et al.*, where a modular toolbox of microfluidic components was demonstrated, and which standardization effort was backed up by the MFmanufacturing consortium (Dekker *et al*., 2018). A combination of microfluidic building blocks (MFBB) and fluidic circuit boards (FCB) designed and fabricated according to guidelines which have been documented in an ISO workshop agreement[14]. Interoperability is key to make this concept work. Therefore, the outside dimensions are standardized according to a grid. A library of CAD based designs is available for any designer to develop specific devices with unique physical dimensions, while decoupling this from the functional design. This approach is very similar to methods used in the electronics industry.

In the field of cell culture-based systems, harmonization was found by a group of stakeholders seeking a set of specialized standards to ensure quality in cell culture-based systems and tools. The recently approved OECD Guidance Document on Good In Vitro Method Practices (GIVIMP)[15], coordinated by the European Commission Joint Research Centre's EU Reference Laboratory for alternatives to animal testing (EURL ECVAM), provides a framework of technical and quality practices to help ensure that the overall development and implementation of in vitro methods is of scientific integrity and of the highest quality possible. While the guidance is intended for all OECD member states and encompasses a wide range of audiences including method developers, validation bodies and end users, its greatest impact may be in regions where *in vitro* methods are just beginning to take root. GIVIMP tackles the following key aspects related to in vitro work: (1) Roles and responsibilities, (2) Quality considerations, (3) Facilities (4) Apparatus, material and reagents, (5) Test systems, (6) Test and reference/control items, (7) Standard operating procedures (SOPs), (8) Performance of the method, (9) Reporting of results, (10) Storage and retention of records and materials. The document identified quality requirements for equipment, material and reagents (*e.g.* cell line authentication, cell purity, stability and functional integrity, testing for microbial contaminations, use of serum, alternatives to the use of animal sourced serum, antibiotics, special media, certificate of analysis, stability and traceability). Within GIVIMP, there are relevant annexes such as the Good Cell Culture Practice (GCCP), established to reduce the risk of generating erroneous data as well as worker health issues and legal liabilities (Coecke *et al*., 2005), the Good Cell Culture Practice for stem cells and stem-cell-derived models (Pamies *et al*, 2017), and mentions to standardization and accreditation bodies as well as to Good Laboratory Practice (GLP).

[14] IWA 23, Interoperability of Microfluidic Devices – Guidelines for Pitch Spacing Dimensions and Initial Device Classification, 2016
[15] *Guidance Document on Good In Vitro Method Practices (GIVIMP)*, OECD Series on Testing and Assessment, No. 286, OECD Publishing, Paris. Available at: https://doi.org/10.1787/20777876 (accessed: March 27, 2019). https://www.oecd-ilibrary.org/environment/oecd-series-on-testing-and-assessment_20777876

3.3 Standardization for the OoC field

The OoC field is a young but fast developing field. The industry today is consisting mainly of start-ups and many developments are still in a research phase. However, individual technology and biology components and operational processes of the OoC systems have been around much longer, and standardization efforts can be found (see above; microfluidics). The challenge for the OoC field will be integrating these components and adapt existing standards to the more complex nature of the OoC technology. Ongoing harmonization in the field of microfluidics and cell culture, and existing standards in the electronics industry can represent a strong base for guidelines in the OoC field[7,8]. Moreover, efforts initiated by regulatory stakeholders, industry and academic labs by a need for novel regulation, such as novel ICH (E14, S7B) guidelines for cardiotoxicity as presented by the CIPA initiative[16], can possibly overcome the challenges that are related to an immature and uncertain market (see above), and drive standardization in the field.

The electronics industry follows strict roadmaps in terms of technology nodes, packaging, handling, etc. OoC systems can benefit from these standardization efforts by adopting those standards (see IEEE, SEMI) for the development of new sensor/actuator technology. Currently, there is a myriad of sensor implementations, few of which are based on standardized fabrication flows. Interaction with stakeholders or technical experts in the SEMI organization represents an opportunity for OoC developers to seek harmonization.

Regarding standardization of cell cultures and operations related to them, OoC systems can build readily on efforts already developed by the toxicology and stem cell research community, and which are embedded in the OECD guidance document GIVIMP, GCCP documentation and ISSCR guidelines[7]. Specific guidelines related to OoC systems are already described in the GCCP document, and challenges for the OoC field are defined as: (1) the lack of detailed understanding of some human organs and tissues, (2) complexity of protocols, (3) expensive technologies, (4) requirement of precise cellular manipulation, (5) reproducibility of the systems. Further, there are also training/education guidelines described in the GCCP document: iPSC differentiation protocols, co-culture of differentiated cells, the use of microfluidics in combination with cells are the main challenges (Pamies & Hartung, 2017).

In analogy to many existing overarching organizations in different fields of research and development driving standardization efforts, the newly founded European Organ-on-Chip Society (EUROoCS)[17] can play a role in mediating and facilitating standards in the field of OoC by bringing together stakeholders of industry, regulators, academia, clinicians and patient organizations. Thereby it will be important to keep its actions open to the international OoC community and search for international harmonization of guidelines.

To move OoC technology towards standardization, the OoC community (stakeholders, national and international societies) needs to get organized to reach a common goal. Regular meetings between Key Opinion Leaders (KOL) from industry, regulatory bodies, academia, clinics, and patient organizations should be organized to discuss standardization in detail. This working group can then disseminate the outcome of the meetings, *i.e.* report on the discussion points and if possible, formulate guidelines.

Standardization can be a step towards open technology platforms, as criteria defined in the guidelines can result in common design environments and building blocks (cfr. Microfluidics). As described above in the theoretical framework and from learnings of other industries (such as the

[16] CIPA. https://cipaproject.org/
[17] EUROoCS press release, available at: EUROoCS (accessed: March 19, 2019). https://h2020-orchid.eu/european-organ-on-chip-society-launched/

automobile), the earlier efforts are taken up for standardization, the easier implementation will be. Further, this would also translate in a more efficient spending of available development costs, and thus have a distinct influence on the level of maturity of the field.

Within EUROoCS, a standardization workgroup/committee, consisting of KOL's of different stakeholder groups, can take up the role to drive standardization effort. The committee could meet on a regular basis to identify standardization needs and could invite relevant stakeholders from academics, industry or regulatory bodies to aid the process.

Conclusion

Standardization in relatively new industries can be driven by government, a changing regulatory landscape or a dominant player. The young OoC field is defined by several small companies and a growing academic crowd. Pharmaceutical industry as end users and regulatory bodies are closely involved in several initiatives. OoC technologies, however, can build upon established standardization efforts related to its subcomponents such as microfluidics and stem cell technology. Finally, a leading role in terms of standardization could be taken up by the EUROoCS consortium, considering international initiatives, so that guidelines are harmonized on a global scale.

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Leids Universitair Medisch Centrum

DMT HUMAN ORGAN AND DISEASE MODEL TECHNOLOGIES

Fraunhofer IGB

1542 Universidad Zaragoza

cea FROM RESEARCH TO INDUSTRY

imec embracing a better life

TU Delft Delft University of Technology

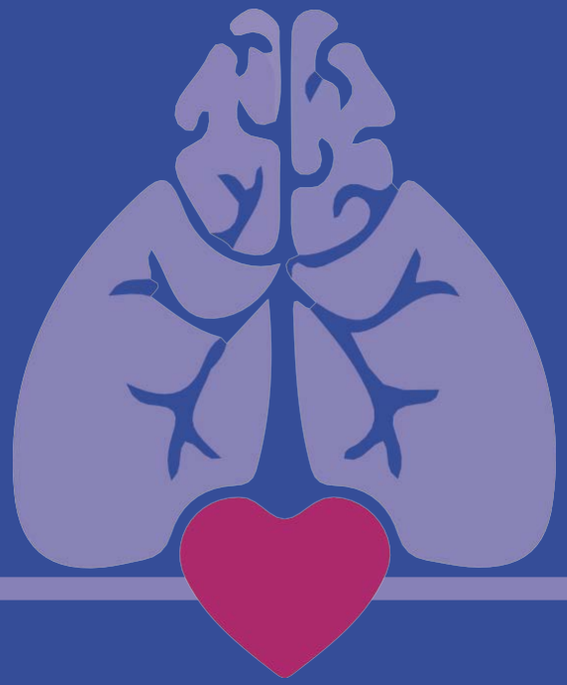
ORGAN ON CHIP IN DEVELOPMENT

The ORCHID project (Organ-on-Chip development) is an EU initiative, coordinated by Leiden University Medical Center and the Dutch Organ-on-Chip consortium hDMT in The Netherlands. The main goal of ORCHID is to create a roadmap for Organ-on-Chip technology and to build a network of all relevant stakeholders in this promising innovative field. In the ORCHID project that started on 1 October 2017 in total seven leading European research institutions are involved.

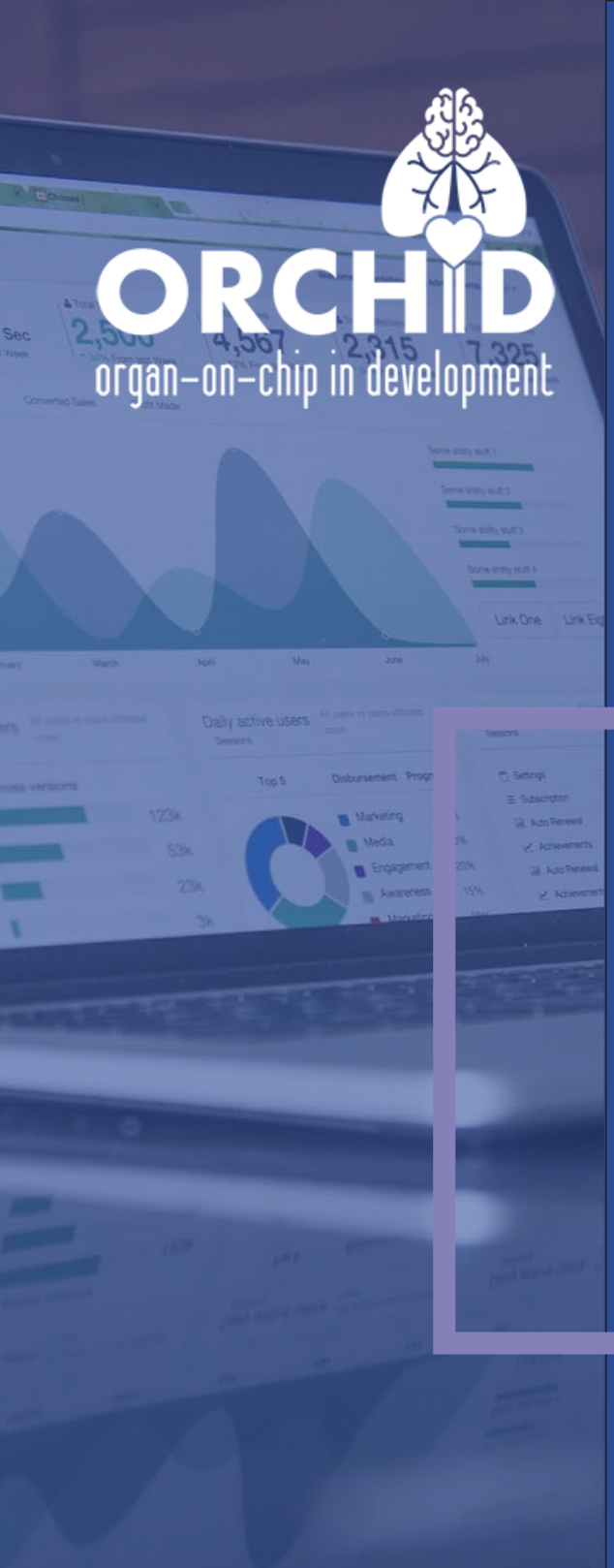
More information: **https://h2020-orchid.eu**

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 766884

ORCHID
organ-on-chip in development



APPENDIX 3



ORCHID

organ-on-chip in development

ANALYTICS REPORT

Global view

The global analysis inform of the account shows some relevant data about the visits and the users' behaviour and preferences. This analysis has been performed since the first publication (February 2018) until today)

3657

TOTAL USERS

16827

PAGES' VISITS

2'46''

MEDIA SESSION TIME

61,58%

BOUNCE RATE

Analysing its evolution over time, a clear increase in the number of visits is observed

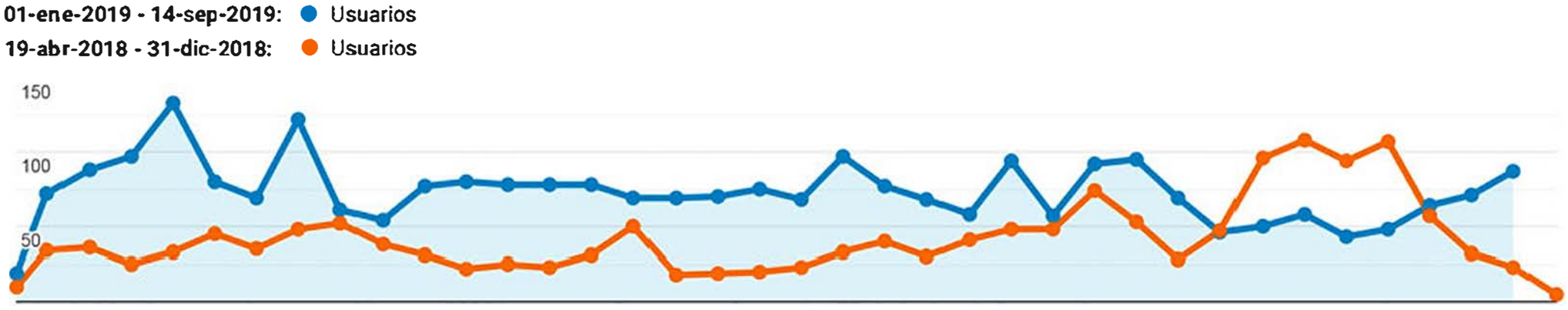

Usuarios
400
200
marzo d…
junio de 2018
septiembre de 2018
diciembre de 2018
marzo de 2019
junio de 2019
septie…

January 1, 2019
September 15, 2019

We will take, from now on, as a period to analyze the period
between January 1, 2019 and on September 15, 2019.
As a comparative reference, we will use the immediately preceding interval,
with the same number of days, which will begin on April 19, 2018 and end on December 31, 2018.

+87,51% **23727**

T
he first graph (graph n°2) represents the number of users who have accessed the web.
During the periods studied, there has been an increase of 87.51%. 2327 users accessed the web in that time
versus the 1241 users in the former section



Usuarios

87,51 %

2.327 frente a 1.241

Usuarios nuevos

86,77 %

2.273 frente a 1.217

Sesiones

44,05 %

3.293 frente a 2.286

Visits by country

20,95%

USA

10,48%

GERMANY

8,09%

NETHERLANDS

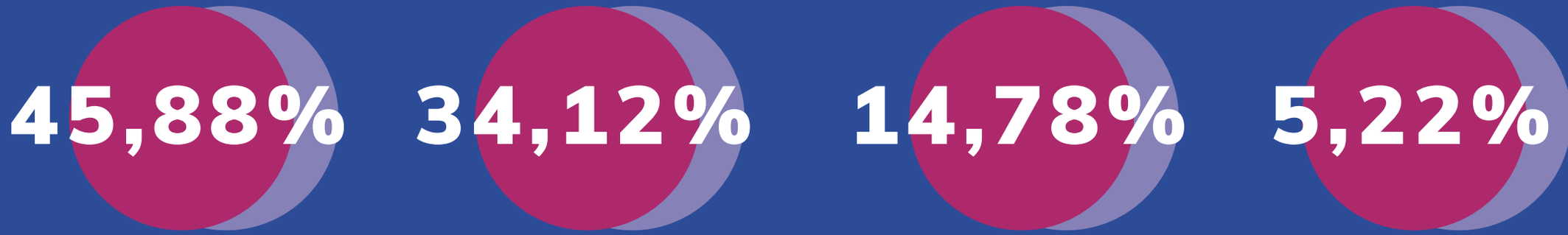
6,94%

UNITED KINGDOM

If we make a classification by countries, we see in graph n°4 the first five countries according to their visits, having first of all the United States with 20.95% of visits, f
ollowed by Germany (10.48%), Netherlands (8.09%), France (7.75%) and United Kingdom (6.94%)

País	Adquisición		
	Usuarios	Usuarios nuevos	Sesiones
	87,51 % ↑ 2.327 frente a 1.241	**86,70 %** ↑ 2.274 frente a 1.218	**44,05 %** ↑ 3.293 frente a 2.286
1. United States			
01-ene-2019 - 14-sep-20...	**492** (20,95 %)	489 (21,50 %)	524 (15,91 %)
19-abr-2018 - 31-dic-2018	**187** (14,83 %)	185 (15,19 %)	207 (9,06 %)
% de cambios	**163,10 %**	**164,32 %**	**153,14 %**
2. Germany			
01-ene-2019 - 14-sep-20...	**246** (10,48 %)	239 (10,51 %)	347 (10,54 %)
19-abr-2018 - 31-dic-2018	**121** (9,60 %)	118 (9,69 %)	159 (6,96 %)
% de cambios	**103,31 %**	**102,54 %**	**118,24 %**
3. Netherlands			
01-ene-2019 - 14-sep-20...	**190** (8,09 %)	175 (7,70 %)	377 (11,45 %)
19-abr-2018 - 31-dic-2018	**130** (10,31 %)	122 (10,02 %)	462 (20,21 %)
% de cambios	**46,15 %**	**43,44 %**	**-18,40 %**
4. France			
01-ene-2019 - 14-sep-20...	**182** (7,75 %)	175 (7,70 %)	287 (8,72 %)
19-abr-2018 - 31-dic-2018	**134** (10,63 %)	129 (10,59 %)	253 (11,07 %)
% de cambios	**35,82 %**	**35,66 %**	**13,44 %**
5. United Kingdom			
01-ene-2019 - 14-sep-20...	**163** (6,94 %)	159 (6,99 %)	250 (7,59 %)
19-abr-2018 - 31-dic-2018	**52** (4,12 %)	52 (4,27 %)	75 (3,28 %)
% de cambios	**213,46 %**	**205,77 %**	**233,33 %**

Visits' origin



The graph n°5 displays the origin of the visits: 45.88% come from search engines (Google, Bing, etc.), 34.12% from a direct access, 14.78% from or after webs and, finally, 5.22% of visits are provided by social media

Default Channel Grouping	Adquisición		
	Usuarios	Usuarios nuevos	Sesiones
	87,51 % ↑ 2.327 frente a 1.241	**86,70 %** ↑ 2.274 frente a 1.218	**44,05 %** ↑ 3.293 frente a 2.286
1. Organic Search			
01-ene-2019 - 14-sep-20...	**1.124** (45,88 %)	1.043 (45,87 %)	1.565 (47,53 %)
19-abr-2018 - 31-dic-2018	**586** (45,04 %)	551 (45,24 %)	963 (42,13 %)
% de cambios	**91,81 %**	**89,29 %**	**62,51 %**
2. Direct			
01-ene-2019 - 14-sep-20...	**836** (34,12 %)	827 (36,37 %)	998 (30,31 %)
19-abr-2018 - 31-dic-2018	**352** (27,06 %)	345 (28,33 %)	584 (25,55 %)
% de cambios	**137,50 %**	**139,71 %**	**70,89 %**
3. Referral			
01-ene-2019 - 14-sep-20...	**362** (14,78 %)	295 (12,97 %)	565 (17,16 %)
19-abr-2018 - 31-dic-2018	**311** (23,90 %)	277 (22,74 %)	659 (28,83 %)
% de cambios	**16,40 %**	**6,50 %**	**-14,26 %**
4. Social			
01-ene-2019 - 14-sep-20...	**128** (5,22 %)	109 (4,79 %)	165 (5,01 %)
19-abr-2018 - 31-dic-2018	**52** (4,00 %)	45 (3,69 %)	80 (3,50 %)
% de cambios	**146,15 %**	**142,22 %**	**106,25 %**

Most visit pages

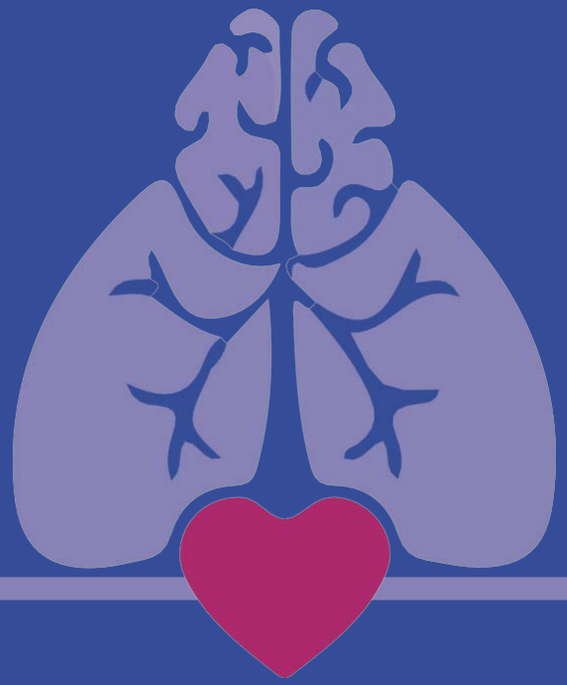
The graph n°6 and n°7 displays the

10 PAGES MOST VISITED

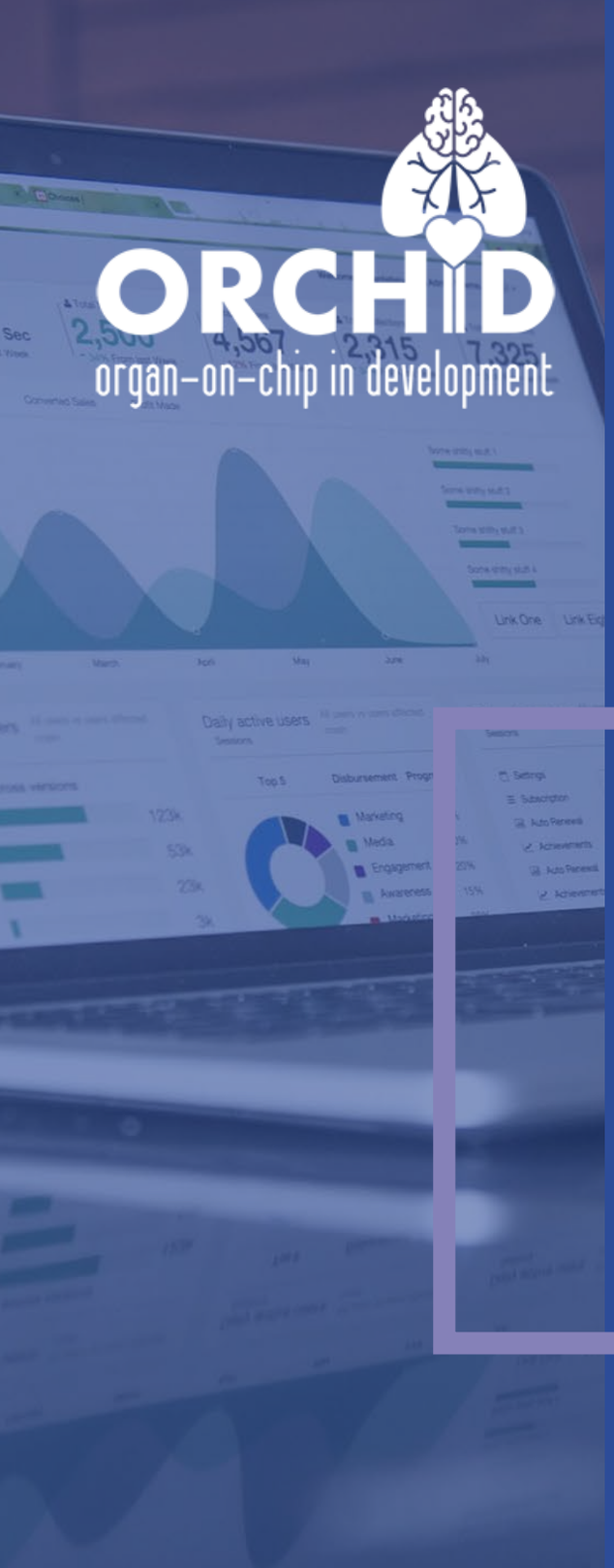
Página	Número de visitas a páginas	Número de páginas vistas únicas	Promedio de tiempo en la página
	31,66 % ▼ 6.484 frente a 9.488	**1,95 %** ▲ 5.065 frente a 4.968	**15,56 %** ▲ 00:01:38 frente a 00:01:24
1. /			
01-ene-2019 - 14-sep-2019	**3.124** (48,18 %)	2.316 (45,73 %)	00:01:58
19-abr-2018 - 31-dic-2018	**3.260** (34,36 %)	1.945 (39,15 %)	00:01:44
% de cambios	**-4,17 %**	**19,07 %**	**14,15 %**
2. /orchid-news/			
01-ene-2019 - 14-sep-2019	**571** (8,81 %)	415 (8,19 %)	00:01:16
19-abr-2018 - 31-dic-2018	**52** (0,55 %)	33 (0,66 %)	00:01:39
% de cambios	**998,08 %**	**1.157,58 %**	**-23,14 %**
3. /advisory-board/			
01-ene-2019 - 14-sep-2019	**338** (5,21 %)	296 (5,84 %)	00:01:06
19-abr-2018 - 31-dic-2018	**238** (2,51 %)	199 (4,01 %)	00:00:58
% de cambios	**42,02 %**	**48,74 %**	**14,84 %**
4. /meetings-2/			
01-ene-2019 - 14-sep-2019	**321** (4,95 %)	231 (4,56 %)	00:01:22
19-abr-2018 - 31-dic-2018	**907** (9,56 %)	409 (8,23 %)	00:01:14
% de cambios	**-64,61 %**	**-43,52 %**	**10,65 %**
5. /european-organ-on-chip-society-launched/			
01-ene-2019 - 14-sep-2019	**311** (4,80 %)	276 (5,45 %)	00:01:39
19-abr-2018 - 31-dic-2018	**113** (1,19 %)	84 (1,69 %)	00:02:35
% de cambios	**175,22 %**	**228,57 %**	**-36,24 %**

Página	Número de visitas a páginas	Número de páginas vistas únicas	Promedio de tiempo en la página
	31,66 % ▼ 6.484 frente a 9.488	**1,95 %** ▲ 5.065 frente a 4.968	**15,56 %** ▲ 00:01:38 frente a 00:01:24
6. /orchid-interim-roadmap-report/			
01-ene-2019 - 14-sep-2019	**309** (4,77 %)	289 (5,71 %)	00:04:17
19-abr-2018 - 31-dic-2018	**1** (0,01 %)	1 (0,02 %)	00:00:00
% de cambios	**30.800,00 %**	**28.800,00 %**	**∞ %**
7. /newsletter/			
01-ene-2019 - 14-sep-2019	**249** (3,84 %)	216 (4,26 %)	00:01:01
19-abr-2018 - 31-dic-2018	**350** (3,69 %)	159 (3,20 %)	00:01:26
% de cambios	**-28,86 %**	**35,85 %**	**-29,65 %**
8. /past-meetings/			
01-ene-2019 - 14-sep-2019	**196** (3,02 %)	160 (3,16 %)	00:01:15
19-abr-2018 - 31-dic-2018	**546** (5,75 %)	215 (4,33 %)	00:01:27
% de cambios	**-64,10 %**	**-25,58 %**	**-14,12 %**
9. /other-meetings/			
01-ene-2019 - 14-sep-2019	**148** (2,28 %)	132 (2,61 %)	00:00:22
19-abr-2018 - 31-dic-2018	**199** (2,10 %)	128 (2,58 %)	00:00:53
% de cambios	**-25,63 %**	**3,12 %**	**-58,84 %**
10. /partner-login/			
01-ene-2019 - 14-sep-2019	**141** (2,17 %)	84 (1,66 %)	00:01:08
19-abr-2018 - 31-dic-2018	**247** (2,60 %)	120 (2,42 %)	00:01:10
% de cambios	**-42,91 %**	**-30,00 %**	**-2,30 %**

ORCHID
organ-on-chip in development



APPENDIX 4



LINKEDIN REPORT

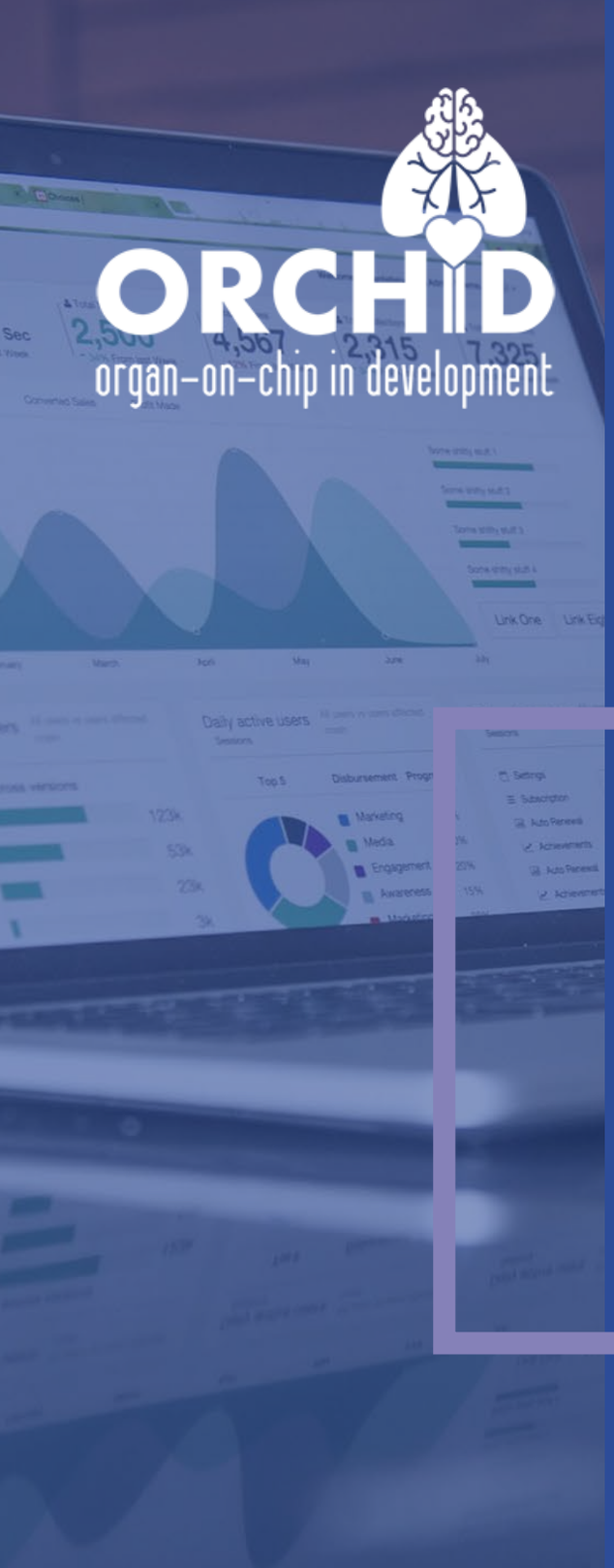
GLOBAL VIEW

A global analysis of the account verifies that a proper interaction has been reached throughout this whole period.
110 contacts and 115 followers have been achieved with a total number of 28 posts.

110
CONTACTS

115
FOLLOWERS

28
POSTS



ORCHID

organ-on-chip in development

TWITTER REPORT

JANUARY - SEPTEMBER 2019

GLOBAL VIEW

A global review performed on this account shows a constant growth.During the current course, the number of followers has increased in 194reaching a total of 553.
The number of followers is five times greater than the number of followed accounts

TOTAL NUMBER OF FOLLOWERS

AUDIENCE

A global review performed on this account shows a constant growth.

During the current course,the number of followers has increased in 194 reaching a total of 553.

The number of followers is five times greater than the number of followed accounts

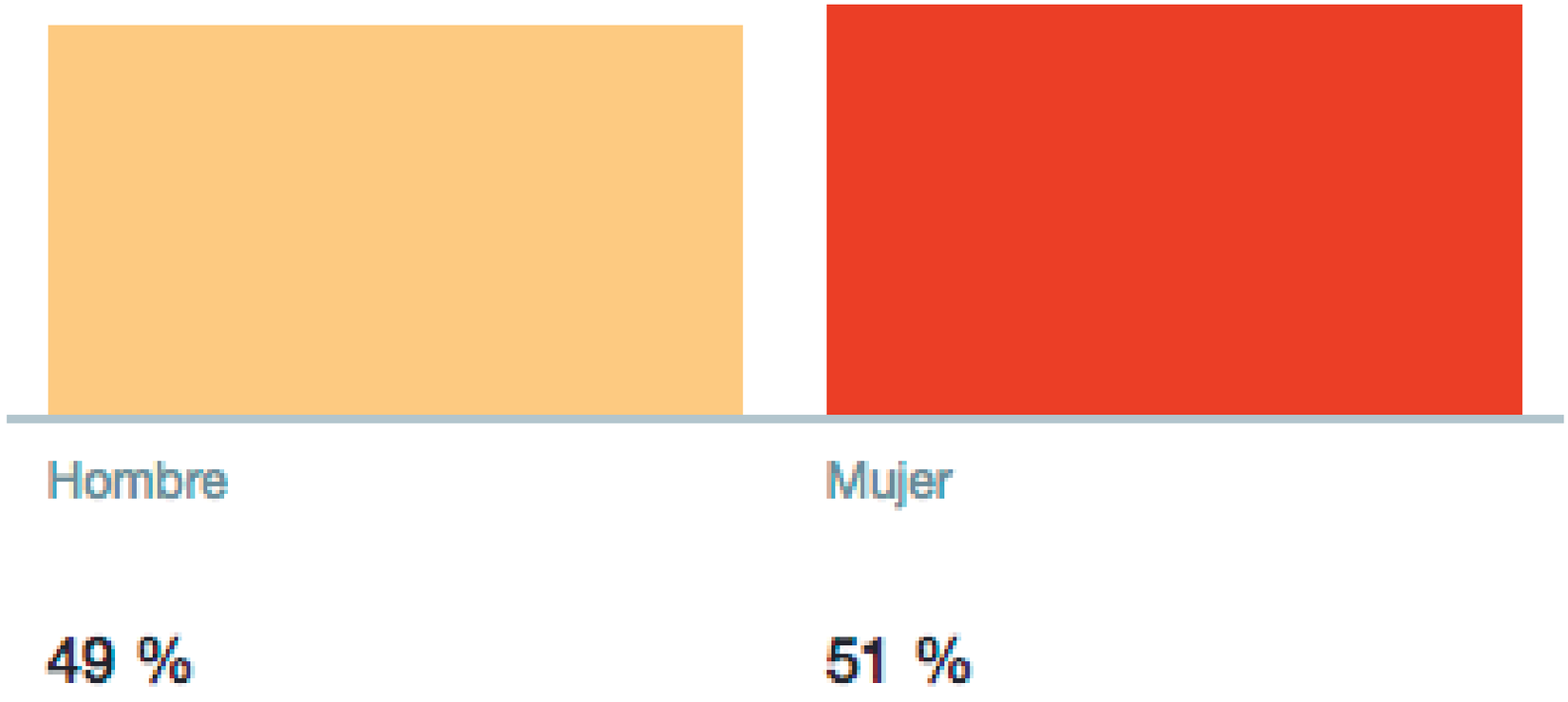
49%

MEN

51%

WOMEN

Sex



Visits by country

The following graph shows the classification by countries of the received visits.
The first one is the United Kingdom, which is accountable of 16% of the visits;
followed by the United States (15%).
51% of the visits came from different countries of the European Union.

País

Nombre de país	% de la audiencia
Reino Unido	16 %
Estados Unidos	15 %
Francia	9 %
España	8 %
Alemania	5 %
Países Bajos	5 %
Italia	5 %
Canadá	4 %
India	3 %
Turquía	3 %

Región

Estado o región	% de la audiencia
England, GB	14 %
Greater London, GB	6 %
California, US	4 %
Ontario, CA	3 %
New York, US	2 %
Barcelona, ES	2 %
East England, GB	2 %
Cataluña / Catalonia, ES	2 %
Massachusetts, US	2 %
Rhône-Alpes, FR	1 %

Interests

SCIENCE

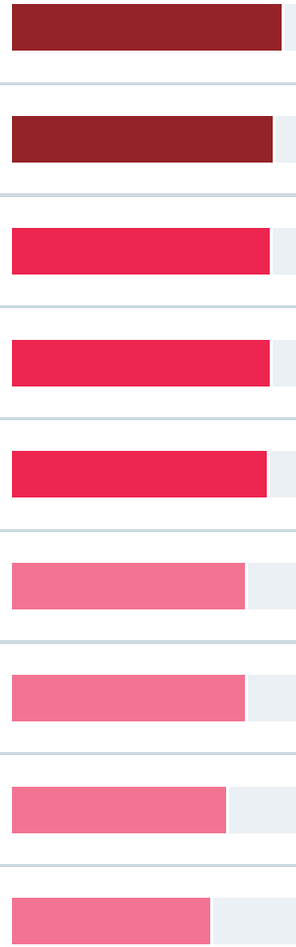
SPACE AND ASTRONOMY

CLIMATE

TECHNOLOGY

In this graph, the principal interests are identified. The main ones are “Science news” and “Space and Astronomy”, immediately followed by “Climate” and “Technology”.
All of them are closely related to the main activity of Orchid.

Noticias de ciencia	96 %
Espacio y astronomía	93 %
Clima	92 %
Tecnología	91 %
Noticias de tecnología	90 %
Noticias deportivas	83 %
Festivales de música y conciertos	83 %
Política	76 %
Noticias sobre educación e información general	70 %



INTERACTION DATA

During the first months of 2019 a great interaction was achieved. Specifically, the january-march period was really profitable

+58%

IMPRESSIONS

more than 58% of impressions achieved from January to September came from this period.

94

RETWEETS

the total number of retweets is 94. January is the most noteworthy month with 51 of them.

36,7%

CLICKS

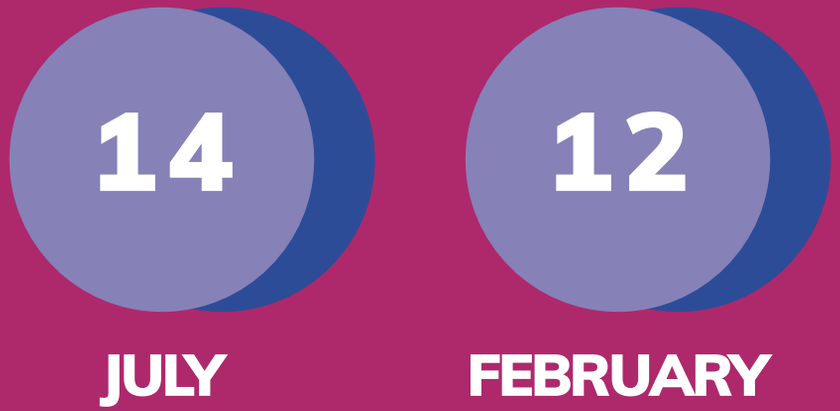
During this period, we found the two months with more clicks on links: January and March with 36.7% and 27.35% respectively of total clicks to this day.

209

LIKES

ffom January to March, we achieved 209 likes. Again, January was the best month, with 104 likes, practically half of the total.

NUMBER OF VISITS



MENTIONS AND ANSWERS

It should also be noted that April was the month with the highest number of visits to the account, with 110, followed by March and May with 94 and 82 visits respectively.
In regard to mentions and answers, two months stand out above the rest: July, with 14, and February, with 12.

	IMPRESIONES	VISITAS	NUEVOS SEGUIDOORES	TASA INTERACCIÓN	CLICS EN EL ENLACE	RT	ME GUSTA	RESPUESTAS Y MENCIONES
ENERO	16300	10	36	2,1	82	51	104	2
FEBRERO	9107	13	21	1,6	21		48	12
MARZO	9352	94	38	2,0	61	25	57	4
ABRIL	6439	110	28	3,2	29	5	17	4
MAYO	5747	82	14	0,7	9	2	11	8
JUNIO	5455	40	22	3,3	16	3	14	4
JULIO	4641	71	28	6,2	5	3	8	14
AGOSTO	1765	21	7	0,3	0	0	1	2
SEPTIEMRE	706	10	0	0		0	1	0
	59432	451	194	223		107	261	20

Followers evolution

+36

JANUARY

+38

MARCH

The evolution during these months has been constant and growing, since they present an average of 25 new followers per month.
January and March have greater growth in terms of followers;
they have obtained 36 and 38 new followers, respectively.

DISTINGUISHED TWEETS

It should be noted that all these posts have a common feature:
they look for a direct interaction with our audience.
An audience interested in the latest advances in the world of technology.

196

INTERACTIONS

The Tweet with the highest number of interaction was one published on January 11th in which the project was presented.

6791

IMPRESSIONS

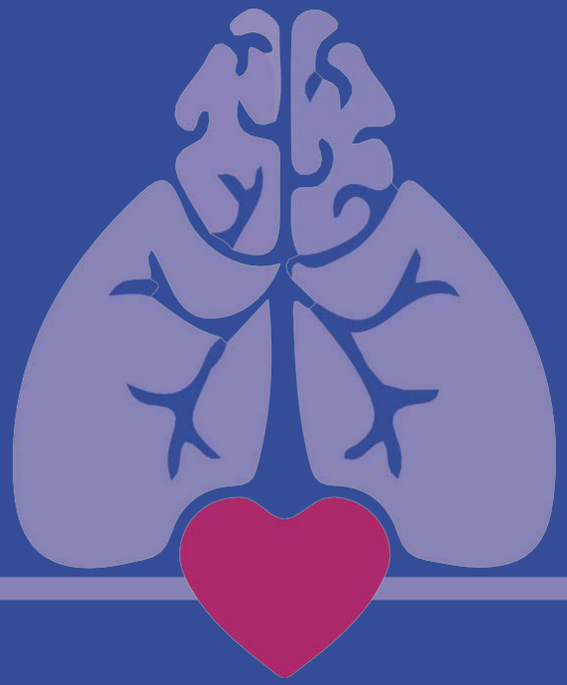
The Tweet with the highest number of impressions, published on January 29, reached a total numberof 6791 interactions. In it tweet, the user was redirected to an Orchid survey about the “organ on chip roadmap” inviting they to help us with their opinions.

JANUARY - MARCH DISTINGUISHED TWEETS

Organonchip @organonchip · 29 ene. Dear colleagues, Could you help us to develop the **@organonchip** roadmap ???Please answer the next online survey about **#Training** needs for the next generation of researchers and technicians. ec.europa.eu/eusurvey/runne… Please disseminate it also among your colleagues Thanks !!!!! Ver la Actividad del Tweet	6.791	145	2,1 % Promocionar
Organonchip @organonchip · 11 ene. We are very proud to present our first interim roadmap report entitled: 'Organ-on-Chip in Development: Towards a European roadmap for Organ-on-Chip' This report outlines presently unmet needs, key challenges, barriers and perspectives of the field. h2020-orchid.eu/orchid-interim… pic.twitter.com/iKuKDGCTMT Ver la Actividad del Tweet	5.292	196	3,7 % Promocionar

JULY - SEPTEMBER
DISTINGUISHED TWEETS

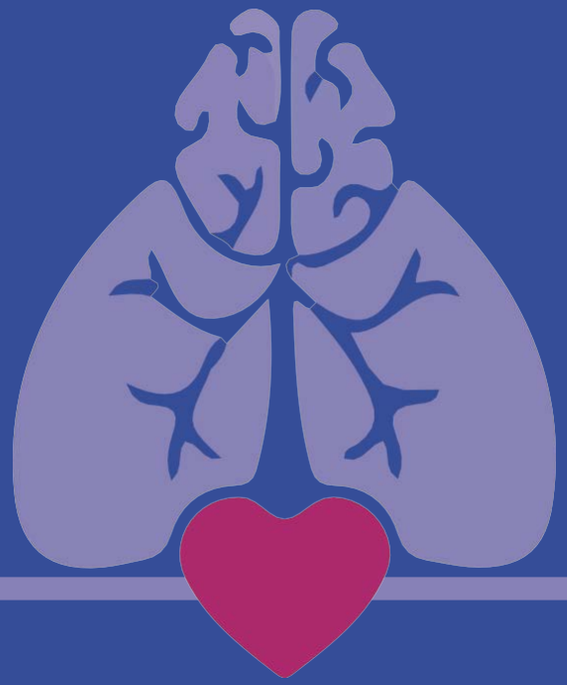
ORCHID
organ-on-chip in development



APPENDIX 5

ORCHID

organ-on-chip in development



ORCHID PAPERS

ORCHID Publications

"This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 766884".

Nr	Type of publication	Title	Authors	DOI	Publisher	Year of publication	Open Access	Peer-Reviewed Y/N	Partner
1	Article in Journal	Impact of organ-on-a-chip technology on pharmaceutical R&D costs	Nora Franzen, Wim H.van Harten, Valesca P.Retèl, Peter Loskill, A.J.M.van den Eijnden-van Raaij, Maarten J.Ijzerman	10.1016/j.drudis.2019.06.003	Drug Discovery Today	2019	Yes - Gold	Y	P3 - Fraunhofer
2	Article in Journal	Organ-on-Chip In Development:Towards a roadmap for Organs-on-Chip	M. Mastrangeli , S. Millets , J. van den Eijnden-van Raaij	10.20944/preprints201903.0031.v1	Preprints	2019	Yes - Gold	N	P2 - hDMT & P7 - TUD
3	Article in Journal	Building blocks for a European Organ-on-Chip roadmap	Mastrangeli, M., Millet, S., Mummery, C., Loskill, P., Braeken, D., Eberle, W., Cipriano, M., Fernandez, L., Graef, M., Gidrol, X., Picollet-D'Hahan, N., van Meer, B., Ochoa, I., Schutte, M. and van den Eijnden-van Raaij, J.	10.14573/altex.1905221	ALTEX - Alternatives to Animal Experimentation	2019	Yes - Gold	N	ALL
4	Article in Journal	Organ-on-Chip in Development: Toward a roadmap for organs-on-chip	M. Mastrangeli, S. Millet, the ORCHID partners, J. van den Eijnden-van Raaij	10.14573/altex.1908271	ALTEX - Alternatives to Animal Experimentation	2019	Yes - Gold	Y	ALL

feature

Impact of organ-on-a-chip technology on pharmaceutical R&D costs

Nora Franzen[1,2], Wim H. van Harten[1,2], Valesca P. Retèl[1,2], Peter Loskill[3,4], Janny van den Eijnden-van Raaij[5] and Maarten IJzerman[2,6], m.j.ijzerman@utwente.nl

Healthcare systems are faced with the challenge of providing innovative treatments, while shouldering high drug costs that pharmaceutical companies justify by the high costs of R&D. An emergent technology that could transform R&D efficiency is organ-on-a-chip. The technology bridges the gap between preclinical testing and human trials through better predictive models, significantly impacting R&D costs. Here, we present an expert survey on the future role of organ-on-a-chip in drug discovery and its potential quantitative impact. We find that the technology has the potential to reduce R&D costs significantly, driven by changes in direct costs, success rates and the length of the R&D process. Finally, we discuss regulatory challenges to efficiency improvements.

Introduction

Healthcare systems are faced with the challenge of providing access to innovative and lifesaving treatments while shouldering the cost of expensive medicines. Pharmaceutical companies often justify high drug prices by the costs of pharmaceutical R&D. The actual R&D costs, however, are unknown to the public and highly disputed [1,2]. Because there is no direct relationship between costs and pricing [3,4], transparency in aspects of both processes contributes to the debate on acceptable prices [5]. Additionally, R&D requires a large amount of externally financed capital, which restricts the market entry of biotechnology companies [6]. The cost of R&D, therefore, burdens society by limiting innovation and ostensibly keeping drug prices high. R&D cost and efficiency data are sparse but relevant for all stakeholders.

Industry and academia are constantly seeking to increase the efficiency of pharmaceutical R&D by improving the ratio between investment (input) and new drugs (output). The main drivers of costs are success rates, development time (cycle time) and the direct costs per R&D project (costs-per-project) [7,8]. These cost drivers differ significantly between R&D phases [8]. For instance, 60–75% of all projects that succeed in non-human phases with lower costs-per-project fail in the more expensive Phase II, and 20–30% fail in Phase III [8,9]. About 50% of these failures are caused by insufficient drug efficacy and 15–25% by safety concerns [10,11]. Clinical phase failure is thus considered a major driver of R&D costs [8,12] and better predictive models are needed. A prominent example is the epacadostat/Keytruda® combination – in April 2018 the biotechnology company Incyte announced the failure of its Phase III combinational study in patients with unresectable or metastatic melanomas [13]. Previous studies had shown promising results and other major players were also invested in trials. After the announcement of failure, not only did Incyte's stock price fall by 23% within one day [14] but Roche and Bristol-Myers Squibb also discontinued their trials. This example shows the consequences of late failure and the need for better predictive models.

An emergent technology that might play a transformative part in pharmaceutical R&D is organ-on-a-chip. An organ-on-a-chip is a microfluidic platform creating controlled microenvironments with vasculature-like perfusion, in which human multicellular structures mimicking the physiological architecture and function of human tissues and organs are integrated [15,16]. The technology has been

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developed to substitute *in vitro* and animal models, which often inaccurately model human physiology [17,18]. Organ-on-a-chip technology is thus thought to improve drug discovery by reducing the gap between preclinical testing and human trials [19,20]. Despite the potential for R&D efficiency, the majority of research so far is directed toward the biophysical potential of organ-on-a-chip, leaving its financial impact unclear. Although several research groups have performed studies showing its actual potential in drug research [21–23] and made strong assumptions about a possible impact, no quantitative study has been published. The objective of this study is to explore the quantitative impact of organ-on-a-chip on the efficiency of pharmaceutical R&D. We surveyed experts to evaluate the technology's impact on R&D cost in relationship to the three main efficiency drivers (costs-per-project, success rate and cycle time), per R&D phase, within a timescale of 5 years.

Estimating the costs of R&D

Establishing an appropriate comparator is a challenge in the impact evaluation of any new technology in the pharmaceutical R&D process. We assessed the expected impact of organ-on-a-chip in comparison to the current costs of R&D per new drug. Cost estimates were derived from literature, because actual cost data are not publicly available. Cost estimates per new drug vary widely and range from US$330[†] [24], US $660[†] [2], US$2060 [8] to US$2760[†] [1]. Methodology and data sources are often nontransparent and differ in choices like time horizon and the approach to account for failures [2,25]. The true costs of R&D are hence unknown. To account for this uncertainty, we assessed only a relative change and applied this result to a cost range of US$660–US$2760 per new drug using two mostly cited estimates. We chose the model of Paul *et al.* [8] as a primary comparator to assess the relative change because it demonstrates methodological transparency, and granularly breaks down cost drivers per R&D phase.

To estimate the costs of a drug launch, Paul *et al.* [8] defined eight phases of R&D (from 'target-to-hit' to 'submission to launch'), and modeled costs per phase along the three most important independent cost drivers: cost-per-project, success rate, cycle time. Cost-per-project refers to the direct costs of a project, for example the costs of running a lab. Success rate describes the numbers of projects needed for one launch and is used to account for the costs of failed projects. Finally, cycle time is used as a time reference for the duration of each phase and the total process. Because the R&D process is lengthy, time is used to estimate the capitalized costs of the investment. All variables are analyzed on a per project basis, for example per single drug candidate. Together, values for each cost driver and phase are used to calculate the overall costs of R&D per new drug [8].

Using this granular model structured the discussion on application and impact with experts. Fifteen experts were surveyed to quantitatively estimate the change in cost drivers per R&D phase. These data were used to rebuild the model of Paul *et al.* and calculate a total change in R&D costs. We also surveyed the underlying uncertainty of estimates and fitted beta distributions to the elicited data. All experts were in leading R&D positions with practical experience with the organ-on-a-chip. They belonged to the stakeholder categories innovative pharmaceutical ($n = 7$), biotechnology ($n = 3$), academia ($n = 3$), organ-on-a-chip developer ($n = 1$) and regulator ($n = 1$). Detailed explanations of the model are presented in supplementary files (see supplementary material S1 online).

Total impact on R&D costs

We sought to fill a gap in the knowledge surrounding organ-on-a-chip by determining its impact on pharmaceutical R&D costs after promising results appeared in several studies regarding its biophysical potential [21–23]. Overall, the surveyed exerts confirmed the significant potential impact of organ-on-a-chip on the total costs of R&D over a modeled timescale of 5 years. With an average total R&D cost reduction of 10–26%, the experts estimated a positive (cost saving) impact of the technology. Experts estimated that the impact of organ-on-a-chip on R&D could range between −32% (reduction) to +3% (increase). Figure 1 shows the combined probability density function of the elicited beta distribution including the 95th confidence interval. Fifty percent of the distribution values fall between −26% and −10% change of total R&D cost reduction, and 80% of the distribution values lie between −30% and −4%. The combined probability distribution of all experts on total R&D costs consisted of the following limits: lower limit −32%; Q1 −26%; median −19%; Q3 −10%; upper limit +3%. The corresponding beta-distribution was defined with parameters $\alpha = 0.9643751$ and $\beta = 1.360814$ standard errors of the elicited limits and percentiles ranged from 1.5% for lower limit and 0.8% for Q3. Applying cost reductions of 10–26% to estimates of total R&D costs, absolute cost savings in an average scenario range from US$66–169 million [2] to US$276–706 million [1]. Further information on a scenario analysis can be found in the supplementary information (see supplementary material S3 online).

Impact per cost driver and R&D phase

The experts reported the most impact in the preclinical phase where 73% of experts identified a change in cost-per-project, 80% in success rate and 40% in cycle time. Lead optimization was the second-most impacted phase (53% cost-per-project, 47% success rate and 67% cycle time). The biggest impact was reported in the cost-per-project in the preclinical phase (Q1 −21%), cycle time in lead optimization (Q1 −19%) and success rate in Phase II (Q3 +17%) (Fig. 2).

We analyzed how the isolated cost drivers impact the cost reduction (Fig. 3). Here, baseline costs were applied to two drivers to examine the total cost change attributable to the third variable. Success rate was the biggest driver of efficiency change (lower limit −22%; Q1 −26%; median −13%; Q3 −10%; upper limit 0%), followed by the costs-per-project (lower limit −14%; Q1 0%; median −4%; Q3 −9% upper limit +5%). The smallest reduction, but the highest level of certainty, was seen in the cycle time (lower limit −5%; Q1 −2%; median −3%; Q3 −5%; upper limit −1%). Additionally, we conducted a series of additional analyses, including two granular cost driver analyses, sensitivity analyses and scenario analyses, which we present in the supplementary information (see supplementary material S3 online).

Connecting impact estimates and areas of application

With 73% of experts believing in an impact on the cost-per-project, and 80% in an impact on the success rates, the preclinical phase showed the highest applicability, followed by the lead optimization phase. Because organ-on-a-chip is thought to substitute animal models and 2D cell culture assays, this confirms the areas of technical application that have been discussed [15,18,19]. As organ-on-a-chip increases the predictability in early R&D phases, success rates increase because only projects with a better chance of success will be selected. Hence, fewer projects at early stages are needed to achieve a launch of a new drug. The large impact on the cost-per-project of the preclinical phase (Q1 −21%) and the cycle time of the lead optimi-

[†] Converted to 2018 US$ million.

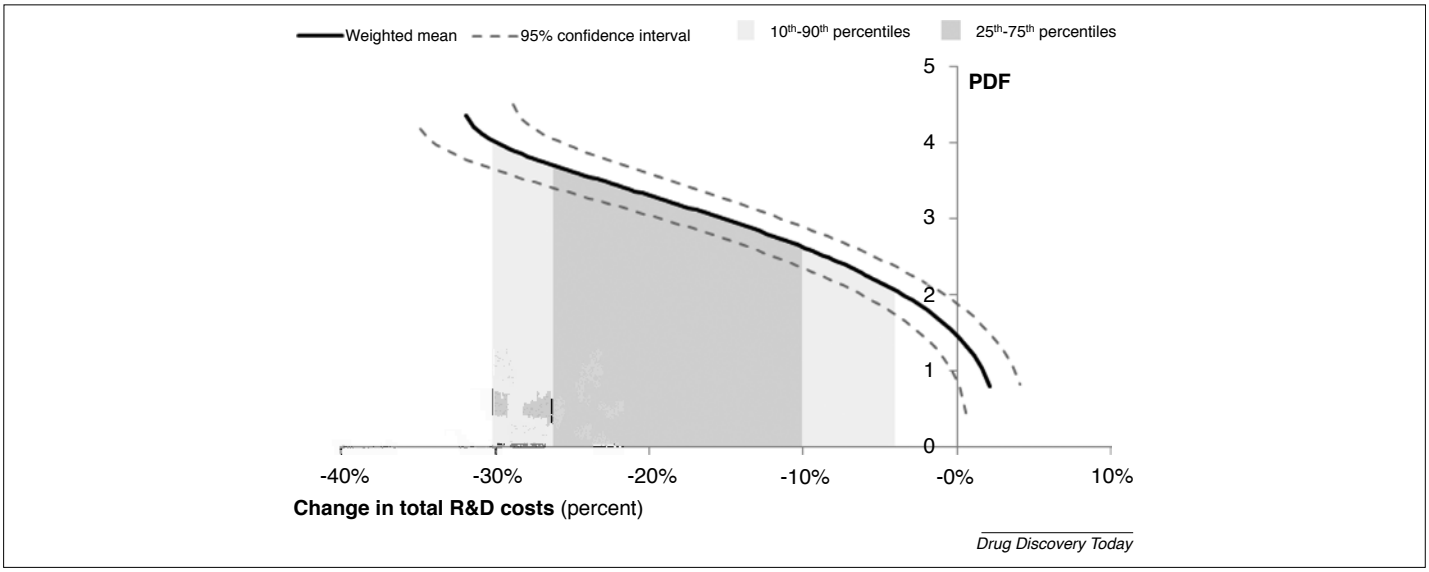

FIGURE 1

Relative likelihood of organ-on-a-chip-induced change in total R&D costs: probability density function (PDF) of the beta distribution. Analysis of the relative likelihood of the change in total R&D costs owing to organ-on-a-chip in 5 years. The probability density function (y axis) is plotted as a function of the from the experts' survey probable change in total R&D costs (x axis). The dashed lines represent the 95th confidence interval of all values. The shaded area represents the area under the curve: 50% of all values show a reduction in total R&D costs of 10–26% (dark gray). Eighty percent of the values show a reduction in total R&D costs of 4–30% (light gray).

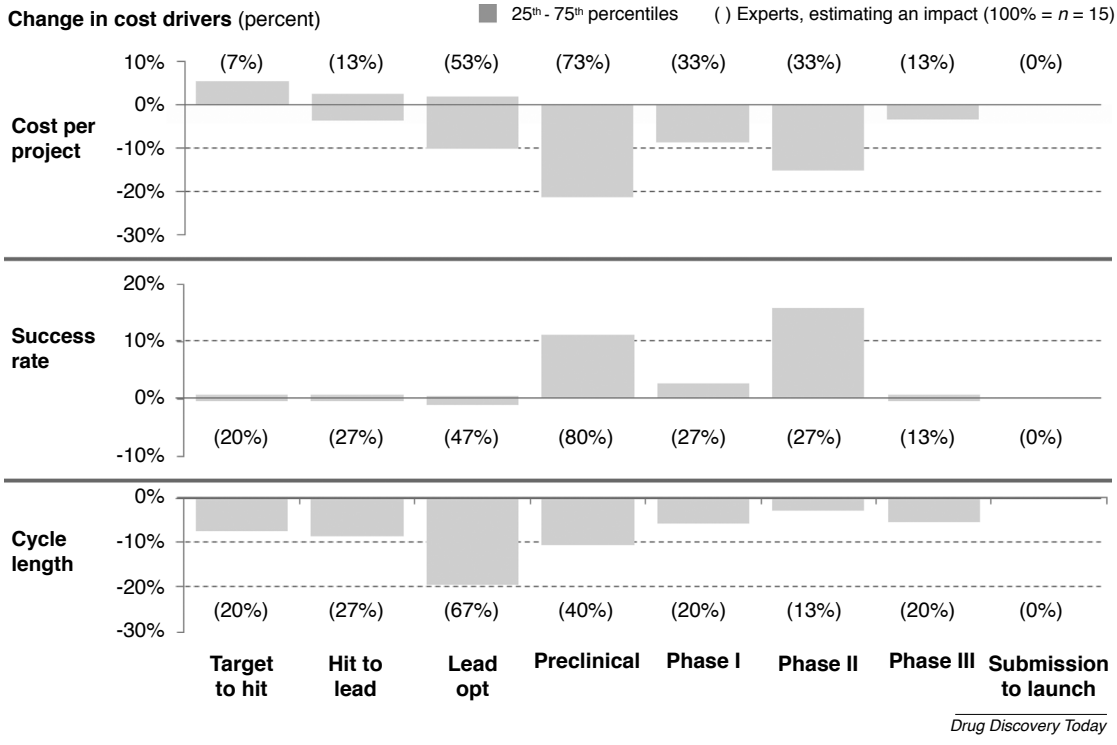

FIGURE 2

Impact of organ-on-a-chip on cost drivers per R&D phase. Analysis of the change in cost drivers per R&D phase owing to organ-on-a-chip in 5 years. Experts (n = 15) were allowed to choose a maximum of three phases per cost driver, in which they estimated organ-on-a-chip to have the most impact. The percentage of experts that believe in a change is shown in brackets. The level of relative change in cost drivers (percent) per R&D phase is represented by the bars.

zation phase (Q1 −19%) are also a result of better predictability. The experts believed that the technology will help to make quicker and more-precise decisions during these stages. We also reported an effect on the success rates (Q3 −17%) and cost-per-project (Q1 −15%) of Phase II. Our results showed, however, disagreement among experts whether and to what degree the technology will increase predictability in clinical phases within 5 years. Only 13–33% of experts (depending on the cost driver) expected an impact in Phase I–III. From these experts, the

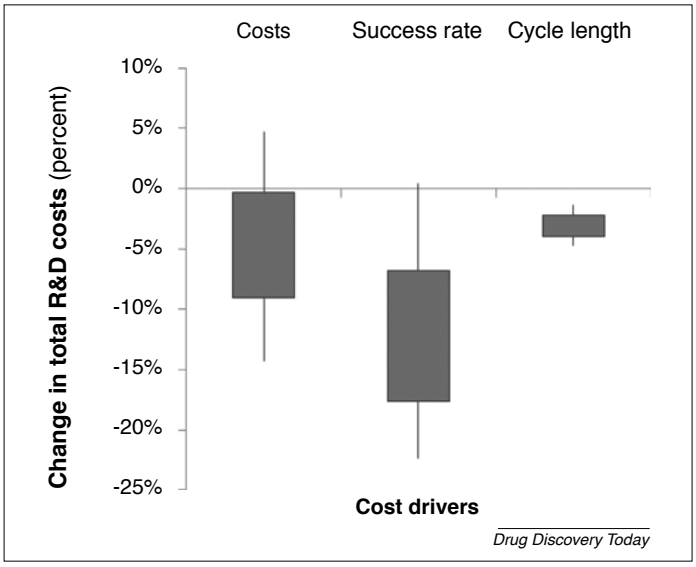

FIGURE 3

Cost driver analysis. Analysis of the impact of the cost drivers on a change in total R&D costs. The vertical lines show the range of possible values and represent the minimum and maximum values. The gray columns represent the interquartile range of the results (n = 15).

majority reported an effect in Phase II, suggesting that the technology's advantages are mainly in terms of efficacy and not safety. Experts discussed that a better understanding of the target population could lead to easier, more-targeted patient recruitment. One expert remarked that, if organ-on-chip was capable of identifying appropriate biomarkers, it would be the 'Holy Grail' of biotechnology.

Looking at the importance of the different cost drivers, our results showed a significant 10–26% reduction potential in total R&D costs, mostly driven by improvements in success rates (Q1 +12%; Q3 +38%) and the cost-per-project (Q1 −1%; Q3 −9%). The high impact of the changed success rates shows the high influence of the indirect costs of failure. In our model and that of Paul *et al.* [8], the success rate of Phase II was the most important efficiency driver [8]. However, as previously discussed, there is disagreement between experts as to whether organ-on-a-chip will fulfill this potential within 5 years. The importance of other drivers of R&D costs differs between our results and the model of Paul *et al.* [8] – success rates in the preclinical phase and the cost-per-project in Phase II are less important in the latter model (rank 12 and 8) and are thus a result of a large change rather than the sensitivity of the model. The success rate in Phase III was ranked second place in terms of sensitivity by Paul *et al.* [8] but did not drive the impact of organ-on-a-chip in our analysis.

Changes in the R&D environment

Organ-on-a-chip could considerably change the existing R&D framework. At the current technological stage, changes are driven by developers and pharmaceutical companies. With better predictive tools, the industry is likely to move toward a model where a proof-of-concept is sought at a much earlier phase. This potentially reduces financial risks and capital requirements of pharmaceutical companies. Next to uncertainties originating from the study design (see supplementary material S5 online), there are technical uncertainties that reflect this initial change within pharmaceutical companies. The extent to which organ-on-a-chip can evolve in terms of predictability and applicability to the human biophysiology is yet to be seen. Challenges of automation, parallelization, standardization and ease of use remain, which are crucial for the adoption in an industrial setting [26–28]. Additionally, technical requirements and adoption speed will evolve differently for therapeutic areas and mechanisms-of-action of the diseases [29]. These concerns are driving the current technical discussions among experts.

Another driver of uncertainty is how regulation will adapt to technological changes. This process will determine whether organ-on-a-chip will be a mere addition to existing R&D procedures or a substitute to conventional protocols, triggering a fundamental change in the R&D. There is uncertainty as to how a highly regulated environment such as the pharmaceutical R&D process could change the status quo of *in vitro* protocols and animal models that, although with limitations of their own, are very well defined. Surveyed regulators stressed this challenge and emphasized the importance of meaningful data provision from industry.

Skepticism that technology can reduce R&D costs

Overall, the modeled cost reduction of 10–26% in the average scenario is substantial and leads to savings of up to US$169 million [2] and US$706 million [1] per new drug reaching the market. Although our results showed a clear trend, the actual magnitude of impact can only be an estimate. Because all of our experts are either already using or highly interested in organ-on-a-chip, our results are more likely to reflect a positive view on the technology's potential. Experts who are currently not working with the new technology are likely to have a more critical perspective, as is common in the diffusion of innovations. There is, for example, a general skepticism toward the idea that technology can actually reduce costs in R&D. According to Eroom's law, R&D becomes slower and more expensive as a function of time, independent of technological progress [30]. Often the expected results, as anticipated by innovators and early adopters, take much longer to materialize when meeting the skepticism of the 'late majority and laggards'. If organ-on-a-chip increases R&D turnover, improves drugs and/or reduces the usage of animal models, the technology clearly produces social benefits. In addition, because public investments play an important part this can also trigger a public discussion if potential efficiency improvements have to be openly monitored and passed along to society in terms of lower drug prices.

Concluding remarks

With organ-on-a-chip systems evolving from a theoretical concept to an actual alternative in drug discovery and development, decision makers are challenged to determine their commercial viability. Based on the expert's input we estimated a reduction of 10–26% in R&D costs per new drug, and thus a positive cost impact. Although the discussion regarding organ-on-a-chip is currently still very technical, it is crucial that decision makers consider the challenge of adapting the regulatory environment to keep pace with the technology's maturation. More research is necessary to analyze regulatory challenges as well as actual insight in the exact cost impact. A public discussion is also needed to establish the importance of social returns, specifically in the form of lower drug prices.

Acknowledgments

We are grateful to the 17 experts for their willingness and time to give interviews for the impact study. The authors would like to thank Massimo Mastrangeli (TU Delft, The Netherlands) and Sylvie Millet (CEA, Grenoble, France) for their support in defining the experts for the interviews; and Adele Tufford for her help with the review of the manuscript. Finally, we would like to express our sincere gratitude for the support of the ORCHID consortium to this research. This project has received funding from the EU's Horizon 2020 research and innovation program under grant agreement no. 766884.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.drudis.2019.06.003.

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Organ-on-Chip In Development: Towards a roadmap for Organs-on-Chip

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Abstract

Organ-on-Chip is a game-changing technology born from the convergence of tissue engineering and microfluidic technology. Organ-on-Chip devices (OoCs) are expected to offer effective solutions to persisting problems in drug development and personalized disease treatments. This opinion paper surveys the current landscape in research, development, application and market opportunities for OoCs to help establishing a global and multi-stakeholder OoC ecosystem. Based on a bibliometric study, a market analysis, expert interviews, and panel discussions held at the *ORCHID Vision Workshop* (Stuttgart, 23 May 2018), we outline presently unmet needs, key challenges, barriers and perspectives of the field, and finally propose recommendations towards the definition of a comprehensive roadmap that could render OoCs realistic models of human (patho)physiology in the near future.

1. Introduction: the healthcare challenge and the Organ-on-Chip roadmap

A critical problem in the development of effective disease treatments is the lack of adequate model systems to identify drug targets, screen toxicity, and predict clinical drug efficacy and the effects of active substances in humans [1]. Traditional animal models [2] or conventional cell cultures [3] often do not accurately mimic human physiology, and thus tend to poorly recapitulate human disease pathophysiology or accurately predict *in vivo* responses to medical treatments. This is a major cause of late drug failures in clinical trials, expensiveness of new drugs, and lack of medication for some diseases [1]. In addition, translational issues [2] and ethical questions raised by animal use increase the pressure to minimize animal experimentation. For these reasons, the pharmaceutical industry is looking for new ways to improve the drug development process [4], drug toxicity assessment [5], and to identify effective and personalized treatments; biomedical researchers require better systems to model diseases for a better understanding of their mechanism and aetiology; and cosmetics, chemical, food and other industries are in need of physiologically relevant human models to test toxicological hazards and assess the risk of substances under increasingly stringent regulatory requirements [1].

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Organ-on-Chip (OoC) is a game-changing technology expected to offer effective solutions for these problems [6] and meet the needs of different stakeholders [7]. In spite of its allure [8], pharma has thus far remained cautious to invest in this new technology, presently awaiting evidence of its added cost-benefit value, and whether it could represent a feasible route to precision medicine and improved patient stratification. It is thus necessary to bridge the gap between the potential of OoC systems (OoCs) and their worldwide acceptance. Defining the putative benefits of OoCs and how these can be proven and achieved is the preamble for an OoC roadmap – which was one of the aims of the ORCHID project.

The Horizon 2020 FET-Open project *Organ-on-Chip In Development* (ORCHID) started in 2017 with the goal of creating a roadmap for OoC technology and of building a network of academic, research, industrial and regulatory institutions to move OoCs from laboratories into the reality of the citizens of Europe and the rest of the world. The ORCHID Consortium is a collaboration between 7 partner organisations from 6 European countries*, and engages an international advisory board of world-renown experts involved in the OoC field (www.h2020-orchid.eu). As part of the project, these and other experts have been asked to share their view on the state-of-the-art, unmet needs, challenges and barriers of the field. The results of the expert interviews†, together with the results of bibliographical, bibliometric and market analyses of the OoC technology carried out within the ORCHID project (see the Appendix for a description of the analytical methodology), formed the basis of the *ORCHID Vision Workshop*, held in Stuttgart on 23 May 2018. The goal of the workshop was to define the pillars of a European OoC roadmap, including the definition of desired and feasible goals for a concrete deployment of the OoC technology.

This paper outlines the state-of-the-art, results, expert discussions, conclusions and recommendations that emerged from the ORCHID's analyses and workshop, in the perspective of fostering the establishment of a thriving global OoC ecosystem.

2. Organ-on-Chip: Definition, key features and value chain

According to the interviewed experts, and as confirmed during the ORCHID workshop, an OoC can be defined as "*a fit-for-purpose microfluidic device, containing living engineered organ substructures in a controlled microenvironment, that recapitulates one or more aspects of the organ's dynamics, functionality and (patho)physiological response* in vivo *under real-time monitoring"*.

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† Refer to the section A.2 of Appendix for the full list of interviewees and experts that contributed to the ORCHID.

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OoCs can be classified into two types with complementary goals and distinct complexity: (i) *single-organ systems*, emulating key functions of single tissues or organs, and (ii) *multi-organ platforms*, combining multiple OoCs to reproduce the systemic interaction and response of several organ models within a single system. Multi-OoCs link individual OoCs through microfluidic, preferably vascularized channels that mimic *in vivo* physiological coupling, and enforce cell-to-fluid volume ratios and flow distributions to create *in vitro* models of subsystems of the human body [9]. Further along this line, Human(-body)-on-Chip (HoC) systems are aiming to emulate whole organismal physiology by integrating many relevant single-organ models [1].

As implied by these definitions, the OoC technology stands on converging advances in tissue engineering, semiconductor and polymer microfabrication, and human cell sourcing. The associated value chain emerging from the ORCHID analyses (Fig. 1) highlights the need of a multidisciplinary approach to implement OoCs, and of a facilitating dialogue between developers, both academic and industrial, and stakeholders such as clinicians, patients, regulators and different end-users. All these disciplines are represented in the ORCHID Consortium.

3. State-of-the-art

A worldwide growing field of research

The OoC field emerged from the convergence of microfluidics and tissue engineering research. Whereas in early 2000's patents and publications mainly focused on microfluidics and associated fabrication techniques, more recent advances in stem cell biology, combined with decades of fundamental biological studies in cell signalling and biomechanics, accelerated the development of OoCs. The ORCHID bibliometric approach reflected this increasing activity by evidencing a rise in both dedicated patents and publications with a compound annual growth rate (CAGR) of +46% over the last ten years (123 patents and publications in 2007, compared to at least 390 in 2017) (Fig. 2a). Such continuous growth, driven by the huge market potential, was made possible by the concomitant diffusion of multidisciplinary approaches supported by an improved dialogue between developers such as biologists (cell culture, physiology), engineers (microfluidics, biosensing systems), material scientists (microenvironment, substrates), but also regulators, patients, clinicians and end users from both academia and industry. Originating from the USA, which pioneered the development of customized cellular microenvironments to capture the structural complexity of organs, this worldwide interest is rapidly engaging Europe, which has a strong track record in tissue engineering and microfluidics, and for which OoCs could represent a new growth opportunity (Fig. 2b-c). The Asia-Pacific region (APAC) contributes also substantially to the field with both established players and newcomers, supported by an exponential growth in technological and biological research, especially in Korea, China and Japan.

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OoCs hold great promises as avatars for native functional tissues

Very dynamic R&D activities have been translated into technological advances in both microfluidics and tissue engineering, providing OoCs with key added values towards a more accurate view of what happens in humans compared to other existing models (Fig. 3). OoC technology allows reconstitution of the microarchitecture of the organ supported by the design of a dedicated mechanical context matching the shape, surface pattern and stiffness of organ-specific microenvironments. Precise microfluidic flow control enables optimal oxygenation and nutrition that not only afford long-term viability of healthy tissues, but also an efficient circulation of immune system cells, antibodies, biochemical signalling molecules and metabolites, and the ability to collect tiny secretion volumes for analyses. Continuous perfusion and mechanical stress help to build dynamic tissue models, supposedly far more relevant than conventional static cell cultures, and enable the control of spatiotemporal chemical gradients and mechanical cues to study the influence of the microenvironment on the cells. Moreover, OoCs allow the precise investigation of specific tissue-tissue interfaces and biological events that cannot be monitored in animals or human patients. Their minute size, the control of the microenvironment, the facilitated optical access at high spatial resolution, and the integration of biosensors for real-time data collection bring OoCs large advantages over other models [1]. The tightly monitored regulation of the cellular environment and homeostasis should facilitate long-term cell culture, possibly over months. In addition, the great diversity and range of complexity of OoCs offer the opportunity to optimize or even customize the design of targeted studies, paving the way to personalized medicine.

According to their expected benefits, the main applications of OoCs range from toxicity test to drug discovery, and target users from various fields, such as biomedical researchers, modelling diseases for improved understanding of their mechanisms and aetiology, and industrials from different profiles – pharmaceutics, biotechnology, cosmetics, chemistry and environment – especially interested in predicting efficacy and safety of compounds for humans. Some players are even going further, introducing in their scientific publications the more long-term potential of OoCs for regenerative tissues and medicine. Existing models and proposed applications are comprehensively reviewed in [1, 8-10].

Nevertheless, OoCs still need scientific evidence of clinical correlation to physiological human behaviour. In particular, the metrics to be considered and their corresponding readouts largely remain to be defined. They are a prerequisite to demonstrate the relevance of the use of OoC compared to other traditional models, and to envision how they could influence the decision-making process.

The rapid development of OoC is driven by academics supplying multifaceted industrial companies

The OoC market gathers many players from different horizons, and evolves continuously due to rapid technological advances and the field's strong multidisciplinary attractiveness. The ORCHID bibliometric analysis identified at least 650 players (the top 30 are shown in Fig. 4). Most of the well-known academic

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teams are concentrated within pioneering American hubs such as the ecosystema of Boston (Wyss Institute, MIT, Harvard, Brigham Women Hospital) and California (Berkeley, UCLA, UCI, Stanford), and the universities of New York (Cornell, Columbia) and Pennsylvania (Drexel, Pittsburgh). They tend to work especially on brain, lung and heart to address toxicological issues, but also on muscle, vasculature and bone marrow. The APAC region shows historical players like the University of Seoul (Korea), the Chinese Academy of Science (Beijing, China) and the University of Tokyo (Japan), leading chemical, physical and biological engineering approaches to emulate in particular brain, liver and lung tissues. The attractive market drives also the repositioning of key European players in microfluidics and cell culture, such as the Fraunhofer Institute (Germany), the University of Twente (The Netherlands), the CEA (France), the Technological University of Compiègne (part of the CNRS, France), Jena University (Germany), and the Swiss Federal Institute of Technology (EPFL, Switzerland), which appear to focus their research on the modelling of brain, liver, kidney and skin for toxicological concerns.

This academic ecosystem supplies industrials from various domains, which may coexist to play a dedicated role in the OoC value chain (Figs. 5 and 6): *i.* pharmaceutical companies; *ii.* companies specialized in microfabrication, imaging and electronics/robotics; *iii.* lab-on-chip manufacturing companies; and *iv.* OoC companies (*i.e.* commercializing fully operational OoC). Indeed, the development of OoCs has been supported over the past several years by pharmaceutical companies (*e.g.* GSK, Roche, AstraZeneca) searching for alternative predictive models, especially for the lung, the liver, the digestive and the nervous systems. OoC manufacturing and peripheral instrumentation require the concomitant involvement of supplying companies specialized in microfabrication, imaging, electronics and robotics (*e.g.* Seiko, Philips, Carl Zeiss; Fig. 6), in particular for OoC characterization and monitoring. Historical lab-on-chip manufacturing companies (*e.g.* Aline, Micronit, Microfluidic Chipshop, Minifab) consider OoCs as a promising growth opportunity. They are starting to partner with OoC companies and propose tailored approaches to support hardware development to scale up and standardize chip production.

OoC companies are mostly start-ups founded by ex-academic teams (*e.g.* Draper, CN Bio, TissUse, Emulate, Mimetas; Fig. 6) [8]. According to the Yole market report, only 18 private OoC companies were found on the market in 2017 [11]. Among the most active companies, TissUse and Nortis are characterized by a multi-tissue R&D activity, whereas the others seem to prioritize single-tissue development. Very few of them are already in the production and commercialization phase, the others being engaged in an iterative process with end users to test different OoC solutions, *i.e.* manufacturing prototypes and producing small series in-house. For instance, Emulate formed various strategic partnerships with pharmaceutical industries (Roche, Takeda Pharmaceuticals, Merck, Janssen) to improve its solutions, but also with the Food and Drug Administration (FDA) to evaluate and qualify the use of its technology for toxicology testing. The latest collaborative partnership, led with AstraZeneca's Innovative Medicines and Early Development Unit

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(IMED), aims to integrate Emulates' OoCs within the IMED drug safety laboratories and to co-locate Emulate's scientists within AstraZeneca's labs to accelerate the development of OoCs[‡]. In addition to its successful collaboration with AstraZeneca on a comprehensive type 2 diabetes-on-a-chip model, TissUse recently announced a cooperative agreement with Roche to develop applications for its multi-OoC platform in drug R&D. The aim of this three-year project is to establish *in vitro* assays for the assessment of lineage-specific hematopoietic toxicity and the evaluation of pharmacokinetics of therapeutic antibodies[§]. OoC companies need both external partners and high financial investments to go through the prototyping phase and to scale up the production. Impressive growth is also possible by a switch towards the small-scale stage, as shown by Mimetas which is mass-producing its OrganoPlate® after only 3 years of existence, and is supplying nearly all major pharmaceutical companies.

The current market positioning of OoC companies is tightly associated with the type of devices developed and their level of maturity. Three different business models can be distinguished: *i.* ready-for-culture microfluidic devices (chips and/or plates); *ii.* fully operational OoCs, including the microfluidic device and cell culture integration; and/or *iii.* a full-service offering to perform in-house tests requested by end users. Companies may switch between these business models; and according to the Yole market report, the large majority of OoC companies are even not sure whether they should sell the devices or offer testing services [11]. Starting with a service-based business model may help to build strong relationships with customers, whereas getting direct input and better understanding of customers' needs enables the joint development of effective OoC platforms. From an end-user point of view, the service-based offer could be of great value for early stage screening, when there is a large amount of compounds to be tested, especially in terms of logistic organization. It is mostly more convenient to ship a drug or a chemical compound than cell cultures. To understand a complex biological interaction, though, some customers, particularly pharmaceutical, may be more interested in buying the OoC to do their experiments in-house.

Whatever the business model of choice, the OoC companies know that minimizing the operational complexity is crucial for commercialization and market penetration. They need to entertain tight relationships with academia to ensure a continuous technological sourcing and to remain competitive.

Public and private investments are required to move OoC from bench to bedside

Both public and private sources have substantially funded OoC start-ups and research groups during the last few years. For instance, USA's National Center for Advancing Translational Sciences (NCATS), in conjunction with the National Institutes of Health (NIH) Common Fund, has invested $70M over a 5-year period to launch the Microphysiological Systems or Organs-on-Chips Program (2012) [12]. The aim of this

[‡] Emulate Inc., available at https://emulatebio.com/collaborations/ (accessed: February 25th, 2019)
[§] TissUse Gmbh, available at https://www.tissuse.com/en/news/press-releases/ (accessed: February 25th, 2019)

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program, part of a coordinated effort between the NIH, the Defense Advanced Research Projects Agency (DARPA) and the FDA, was to accelerate the development of human OoCs that "*will improve the reliability to identify human drug toxicities and predict the potential efficacy of a drug in a human population prior to use of the drug in late-stage clinical studies"* (NCATS website).

In the meantime, private investors have gained confidence in OoC technology. In particular, 2018 was a prolific year in fundraising, with $36M and $20.5M secured by Emulate and Mimetas respectively. According to the Yole market report, the most efficient company in fundraising is Emulate with 4 rounds in 4 years for a total of $93M [11]. Other US companies have also raised several millions of dollars, such as Hμrel Corporation ($9.2M in 2013), Nortis (more than $8M in total, with a first round of $2.65M in 2014), and Tara Biosystems (fundraisings in 2014, 2016 and 2017, for a total of $11.75M; source: Tara Biosystems website). In Europe, 2 companies have also succeeded to raise funds: Mimetas (The Netherlands) with a total of $27.65M (3 rounds in 2014, 2015 and 2018), and TissUse (Germany) with $4.6M in 2015. The Netherlands have funded a national OoC initiative (NOCI) with €18.8M for 10 years; a H2020 Innovative Training Network project on OoC (EUROoC), coordinated by Fraunhofer IGB, was recently granted with €3.94M for 4 years. Globally, American companies are way ahead with regard to fundraising: the US government is willing to support the OoC field, especially through the DARPA and the NIH, and lately the NASA and CASIS, with an investment of more than $200M over the past 5 years.

Market forecasts: Potential development from an emerging market towards an exponential growth

The Yole market report estimates the combined sales of OoC devices and services at no more than $7,5M in 2016, with the potential to undergo an impressive growth and become a multi-billion dollar market in the mid- to long-term, in view of the fact that OoCs help the industry to save billions of dollars every year, especially by bridging the translational gap between preclinical and clinical studies required for the drug development process [11]. As already indicated, very few players are currently in the production and commercialization phase; and while pharmaceutical and cosmetics companies are engaged in an iterative process to test different OoC solutions, they are conservative and might need time to widely adopt the technology. This overall context led Yole Développement to detail both a realistic and optimistic scenario, in which the market could grow at a CAGR from 2017-2022 of 38% to 57% to reach $60M to $117M, respectively in 2022 (Fig. 7; for further market data, see [11]).

In the optimistic scenario, based on the companies' forecasted revenues (Fig. 7a), the Yole report considers that if all conditions are met, *i.e.* industrial adoption is speeding up, OoC companies are able to overcome technical challenges and to upscale production, production of 858k units will be reached in 2022, corresponding to an overall market of $117M [11]. The service-based market is expected to remain much smaller than the device-sales market, and may not be sustainable on the long-term.

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In the realistic scenario (Fig. 7b), the Yole report forecasts that the majority of OoC developers will face issues when the demand will grow [11]. Especially, it considers that scaling up the production will likely slow down the growth of OoC companies during the period 2018-2021. Most of them will have to switch from PDMS prototyping and small-series to large-scale production in other materials (glass, polymer injection moulding), requiring redesign steps that will be very expensive for the relatively small companies involved. In this scenario, the OoC market will grow from $7,5M in 2016 to $59,7M in 2022 because only few companies have already managed to scale up their production. The revenue fraction deriving from services is higher than for the optimistic scenario because OoC companies will focus on customized services to offset losses due to the costs for production upscaling.

4. Challenges

Unmet needs

Evidence of added value

A notable unmet need that emerged from the experts' interviews is data-supported evidence of actual advantages of the OoC technology compared to existing conventional models or well-established approaches to tissue engineering. Particularly, while the superiority of 3D over 2D cell cultures for *e.g.* phenotypic expression is attested in recent scientific literature [13], the advantages deriving from the inclusion of dynamic perfusion and *in situ* stimulation in OoCs arguably need more substantial support.

Organs-on-Chip can pave the way to personalized medicine and de-risking drug development

The failure of preclinical cell cultures and animal models to reliably predict drug efficacy and safety at the human clinical trial stage ends up wasting billions of dollars each year and slows down the development of medical treatments. Whereas spending on drug development increased over the past 20 years, the number of drugs approved annually declined [8]. Many compounds with high potential health benefit are eliminated early in development due to the poor predictability of preclinical models. Drugs could even be withdrawn shortly after entering the market, mainly because of cardiac, liver and kidney toxicities. Late-stage failures cause catastrophic losses while significantly driving up cumulative costs and patient risk. Positioning OoCs as powerful predictive tools for preclinical screening might represent the ideal solution for the pharmaceutical industry to eliminate ineffective drug candidates as early as possible and curb the costs of drug development [8].

As expected, the OoC application most cited in scientific literature and in the ORCHID experts' interviews lies in the pharmaceutical drug development process, including safety assessment and efficacy testing. The main idea shared by all players is that OoCs may enable more rapid, accurate, cost-effective and clinically relevant testing of drugs. According to a recent scenario-based cost analysis conducted in the

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context of the ORCHID project, experts expect a positive budget impact, reaching a reduction up to 26% in the total R&D costs for drug development [14]. While all cost drivers may be impacted, savings would mostly be achieved by improving the success rates. The R&D phases in which experts expect the most benefits are lead optimization and preclinical phases.

Data from animal studies are often poorly indicative of the human situation [2, 15], since animal preclinical models have limitations in mimicking the complex processes specifically occurring within the human body [1]. OoC models may potentially bridge this translational gap by fostering the implementation of 3Rs, *i.e.* Reduction, Refinement, and Replacement of animal testing. However, all interviewed experts agreed that OoCs are currently far away from replacing all animal models, and should be used mostly as a complementary approach to animal testing. Specifically, and as evidenced in the ORCHID impact analysis [14], high-throughput plate-based microphysiological systems may find use in target identification, lead selection and lead optimization at assay scale; chip-based, low-to-medium throughput devices may find most fitting use in pre-clinical, single-organ toxicity or efficacy tests; and multi-organ systems may target the replacement of animal models for toxicity screening, and phase I / phase II clinical testing in patients – which is being prefigured as (pre)clinical-trials-on-chip.

Replacing (pre)clinical human trials and advancing towards the implementation of personalized medicine are the grand unmet needs targeted by multi-OoC and HoC systems. OoCs pave the way to personalized medicine approaches by enabling the use of patient-specific, primary and stem cells to capture important differences due to genetic diversity, origin, gender or age. For instance, OoCs can enable the development of *in vitro* clinical trials for patient populations unfit for standard clinical trial designs (*i.e.* rare and/or paediatric diseases) or to develop drug regimens that are optimized for specific patient biology [9]. Along this path, OoCs may represent models not only capable of capturing prior organ(ismal) knowledge and recapitulating known physiological responses, but also, and even more importantly, unique tools for unprecedented investigations and new discoveries for the further advancement of physiology and medical science.

OoC can benefit toxicology testing

The interviewed experts share the opinion that industries developing cosmetic, chemical and agro-food consumer products can find a huge potential in OoCs regarding toxicological hazard and risk assessment of substances for the study of *e.g.* metabolism, effect of toxicants including nanomaterials, collective responses and allergies (see also [8]). Regulatory requirements for chemicals and cosmetics do not accept any significant hazard potential of substances used for humans. Moreover, there is rising interest in alternative models allowing skin sensitization assessment and systemic toxicity testing for regulatory use, because animal testing has been banned in 2013 for cosmetic and fragrance products marketed in Europe. China is

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meanwhile changing regulations about animal testing for cosmetics, has approved in 2016 a first non-animal tested cosmetics, and is pushing the authorities for reducing animal use; and the USA has included a ban on animal testing in their 2007 roadmap for all industries, including pharmaceutical, chemical and cosmetics industry [11]. The chemical industry is also actively working on such strategies, especially on *in vitro* skin sensitization testing, to avoid unnecessary reassessment of chemicals due to the Registration, Evaluation, Authorization and Restrictions of Chemicals (REACH) regulation [1]. Nevertheless, more formal validation efforts will be needed prior to full industrial adoption of OoCs in chemical and cosmetics industries.

Though not mentioned by any ORCHID interviewee, the tobacco industry could represent another OoC targeted segment in the near future due to the high pressure to increase the safety of this industry's product portfolio [1]. Ethical considerations lead the tobacco industry to develop new approaches and tools to assess smoke-related adverse effects on the human respiratory system, primarily airways and alveoli. OoCs could represent ideal tools to investigate the onset of lung diseases, such as the smoking-induced chronic obstructive pulmonary disease and its malignant transformation.

The future of OoCs lies in automation, robustness and integration of complexity

Automation and ease of use

Present OoCs are typically complicated pieces of engineering, whereby the microfluidic chip hosting the cell co-cultures is connected to external control and supply peripherals. For this reason, ease of use of the systems and increased automation in setting up cell cultures and keeping them viable throughout study times are commonly perceived unmet needs in laboratory practice. The ideal OoCs would be simple devices displaying user-friendly interfaces that facilitate the work of users with even limited training on *e.g.* cell cultures and instrumentation. These devices should be easily transferrable from developers to end users by means of standardized guidelines concerning biomarkers and endpoints.

Improving single OoCs

Among the many different tissue types that can be currently emulated [1], the outcome of the experts' interviews and of the ORCHID bibliometric analysis shows a strong preference for ADME pathways (Absorption, Distribution, Metabolism, Excretion) including metabolic (liver, kidney) and digestive organs [16], along with cardiac tissue, lung and the central nervous systems coupled to a blood-brain barrier [17]. Organ-specific needs to be met include, among others: for the liver, the development of models making use of iPSC-derived hepatocytes; for the heart, efficient maturation protocols for iPSC-derived cardiomyocytes to avoid expression of immature phenotypes; for skin, establishing methods to derive all skin cells from iPSCs, including *e.g.* dermal papilla cells needed for hair generation. OoC devices can perfuse vessels, thereby including the vitally important flow of a blood surrogate to feed nutrients and remove excretion products

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through vasculature, and the accompanying shear stress. The experts emphasized that, while immunogenicity testing of drug candidates in animals is obsolete, immune and endocrine systems are missing components required to improve the physiological relevance of OoCs [18]. Different academic players are indeed developing bone marrow-on-chip to integrate aspects of immunocompetence in OoC-based drug safety and efficacy testing [1]. Moreover, predictive models for gametogenesis and testicular toxicity, an infrequent but severe cause of arrest of drug development, and for other specific toxicities for which no satisfactory preclinical model exists are presumed to be valuable as a niche market for OoCs.

The ORCHID bibliometric analysis highlights a very high interest in OoCs as cancer modelling systems, which could help to better understand tumour progression (Fig. 8). The exponential growth of publications dedicated to OoC cancer models may correlate with the fact that OoCs are the only systems to model tumour cell intravasation into a surrogate blood stream or immune cell extravasation into the tumour by combining human micro-perfused 3D tumour models with human vasculature [1]. Such strong interest is also supported by epidemiology data and the high market potential for cancer treatments.

The expert interviews also indicated that, from a patient perspective, stringent medical unmet needs are represented by ways to improve the treatment of diseases – such as *e.g.* cancer, dementia, kidney and rare diseases – for which there is currently no treatment, insufficient treatment [19], or only treatments which are too expensive.

Integrating more complexity within multi-OoCs.

As mentioned, the development of multi-organ OoCs is envisioned in the perspective of recapitulating the complexity of the human physiology at organism level, which is lost in moving away from animal models. A recent eminent example of a multi-OoC is the Evatar system, which couples Fallopian tubes, uterus, cervix and liver made from human tissues with ovaries from mouse tissue to recapitulate 28-day female hormonal cycles [20].

The original claim of a forthcoming full HoC system appears to be presently more realistically modulated by a technical assessment of the formidable difficulties facing its achievement. The latter include: (1) the onset and maintenance of self-contained homeostasis; (2) the inclusion of the influence of missing organs, particularly the hormone background (*e.g.* gender and reproductive hormones) and immunocompetent cells; and (3) the identification of (alternative solutions to) a single perfusion medium shared by the multiple cell types comprised within the system. Other challenges for multi-OoC and HoC systems lie in scaling the relative volumes of the individual OoCs [21], the interconnection topology, and perfusion rates approximating physiological flow configurations [9]. Organs involved in the ADME are considered the basis of a HoC, since they are responsible for significant homeostatic effects and are foreseen in comprehensive organ models for compound testing, for instance in skin and lung models to evaluate compound concentration in urine

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and blood. Modelling of ADME is considered central also because drug distribution is a main cause of unwanted drug side effects – a global leading cause of death. To this purpose, efforts should focus on combining a set of organs which can match the critical functions needed for drug study with a functional endothelium serving as selective barrier for transport of drugs and bioactive factors [9].

Technical challenges

Structural materials: alternatives to PDMS?

Polydimethylsiloxane (PDMS) supplanted glass and ceramic as the most commonly used substrate material for the fabrication of OoCs. The very wide adoption of this type of silicone ensues from a convenient combination of advantages, such as biocompatibility and oxygen permeation (crucial for cell viability), optical transparency (suiting real-time optical inspection), softness (which supports mechanical actuation), wide availability, and general ease of processing (no strict need for specific cleanroom facilities) – including deposition by casting and spin-coating, functionalisation, metallisation, and patterning by soft lithography and moulding [10]. The almost-unanimously remarked disadvantage of PDMS – though common to most polymers, including the plastics of interconnecting tubes – lies in its lipophilicity and ensuing unselective absorption of hydrophobic drugs, particularly of small molecular weight [22]. Unselective absorption complicates the localization of target compounds in the devices and, in absence of models predicting drug absorption rates in substrates, can drastically affect the interpretation of analytical results. Moreover, drug absorption directly affects the choice of the method used to deliver drugs to OoCs. Drug delivery in OoCs should generally replicate the physiological application in humans, *e.g.* direct exposure to cells, inhalation, skin absorption, oral delivery, or intravascular delivery by perfusion in vessels. The limitations of PDMS may be tolerated during device prototyping and characterisation, but may hinder future large-scale integration. Unselective compound absorption in PDMS is being faced mainly by (1) the search for application-specific formulations of PDMS or alternative polymers, most of which – based on *e.g.* polycarbonate, polystyrene, Styrene Ethylene Butylene Styrene (SEBS), polyimide, polyurethane, hydrogels – represent intellectual property covered by patents; or (2) the coating of polymer surfaces with layers of endothelial cells, providing a barrier to drug absorption into the substrate.

Optimal cell sourcing and shared culture media

Access to abundant, good quality human cell sources represents an essential technical aspect of OoCs. Multiple cell sources are currently available, and each cell type presents advantages and issues. The highest clinical relevance for humans is guaranteed by the use in OoC models of adult primary cells obtained directly from patients. However, genetic variance between individuals may be present when the cells cannot be obtained from the same donor; and these cells cannot be obtained in large quantities from all tissues, *e.g.* from the brain and the heart. Adult stem cells on the contrary are obtained from almost all endodermal

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organs, *e.g.* the organs of the gastro-intestinal tract and the lungs, and they can be genetically modified and grown in culture in large quantities; but they are not available for all tissues. Pluripotent stem cells (PSCs), derived from reprogramming of adult somatic cells (human induced PSCs, hiPSCs in short) can give rise to almost all types of cells in the human body, and can be obtained from any individual [23]. On the other hand, they are phenotypically immature, similar to foetal cells; hence it is a challenge to develop culture conditions for the maturation of such cells, and to use them to model diseases occurring after birth [24]. Spheroids and organoids [25] derived from human biopsies and pluripotent stem cells are also being envisioned as sources of pre-organized, higher-order cell tissues to be included in OoCs [26].

While the dynamic microenvironment of OoCs, mimicking the human physiology, can support cell differentiation and maturation better than static cell culture conditions, the co-presence of multiple cell types in the same microphysiological device sharing a common conditioning medium may be an issue. According to the ORCHID experts, a solution for the formulation of a single perfusion medium may come from a strict biochemical approach, rather than from simple media mixing; and whereas media such as high concentration glucose are standard, many application-specific media are proprietary. Serum, widely used at the beginning of the century, is currently disfavoured, and ethical issues are implied with foetal serum particularly. Blood is being used for media as well, and should be on the roadmap in spite of increasing constraints on its usage. Finally, whereas the choice of cell types is generally dependent on the target organs and applications, a related challenge concerns the appropriate representation of the diversity inherent in the human population in terms of *e.g.* gender, origin and age.

Long-term viability and multimodal real-time characterisation can revolutionize cell cultures and analysis

With typical sizes on the order of a few millimetres, OoCs afford a distinct advantage in terms of non-invasive organ monitoring and tissue investigation compared to the actual inspection of human patients. The small volumes of tissues and culture media confined within the closed, controlled environment of the devices limit the dilution of xenobiotics and metabolites. Small chip volumes additionally help preserving sterile culture conditions, though they are also responsible for reduced throughput. A related advantage concerns the extended viability of the cells in OoC models, enabled by continuous microfluidic nutrient feeding and removal of waste products. Required model viability is considered by the interviewed experts to be sensibly dependent on the application and specific question at hand: it can range from a few hours to a few days (*e.g.,* 3 to 8 days) for repeated dose/exposure and acute toxicity testing; up to a few weeks for safety and efficacy testing (*e.g.*, 28 days for systemic testing, in accord with the Organisation for Economic Co-operation and Development (OECD)'s guidelines for animal tests) [16]; and up to several months for chronic toxicity testing or disease course modelling, in analogy with phase II clinical trials. Tissue viability

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is supposed to extend indefinitely in the presence of self-contained homeostasis, particularly when sustained by vascularized interconnections among several organ modules.

Online characterisation of organ- or tissue-specific phenotypes, readouts and endpoints in OoCs – *e.g.* vascular contraction, cell migration, genetic reporters, metabolic pathways – is largely dominated by optical and fluorescence microscopy, expected to remain prevalent also in the future. A challenge for assay imaging systems is translation into high-throughput industrial settings. Incubators are commonly used to host OoCs and regulate cell culture parameters, such as temperature and CO_2 levels. Composition of perfusion media, fluid flow rates and gas pressure for pneumatic actuation of flexible membranes are mostly controlled by external, partly automated equipment. Connection of fluidic peripherals to chip or plate devices typically involves silicone tubes, which may cause bubble formation and non-selective drug absorption. Proper utilization of devices and peripherals typically requires specific training of users and is expected to be regulated by standardized guidelines. Including such peripherals as integral components of actual, self-contained OoC devices is a standing challenge. According to the ORCHID experts, OoCs should be consumables whereby real-time sensor readout and system control are simultaneous and aligned. The experts recognized that real-time monitoring of bioreactions in OoCs may revolutionize *in vivo* studies by increasing the throughput of analyses, and acknowledged the current existence of a gap between hardware development and the needed absolute quantification of biological response, partly because the physical, chemical or electrical responses to bioreactions in OoCs are not fully understood. Therefore, the integration of biocompatible electrical, chemical or physical sensors and actuators is highly sought after and widely investigated [26]. For instance, trans-epithelial electrical resistance (TEER) is being measured for real-time readout of tissue barrier functions [27]; and micro-impedance tomography is used to quantify the deflection of membranes induced by breathing motion [28].

Qualification for contexts of use should be preferred to validation

Some form of validation of OoC systems is critical for their broader acceptance and uptake in industrial and clinical settings, particularly in relation to supporting decision-making in a regulatory context. In the Guidance Document 34, the OECD defines *validation* as "the process by which the reliability and relevance of a particular approach, method, process or assessment is established for a defined purpose". Although this definition is in principle applicable to OoC devices used for a particular purpose, the context of OECD guidance typically relate to the validation of methods intended to form the basis of internationally recognised test guidelines that can be used in any of the 36 OECD member countries, implemented within a Good Laboratory Practice (GLP) quality system (as exemplified in *e.g.* the OECD's Guidance Document on Good *In Vitro* Method Practices (GIVIMP)), and satisfying the conditions of Mutual Acceptance of Data (MAD) between jurisdictions and regulatory agencies. Therefore the validation processes foreseen in this context may be more appropriate for highly standardised and widely applicable methods, and probably

unsuitable for emerging OoC devices in the near future. Moreover, validation per se is not considered by some experts an appropriate nor meaningful concept, because it implies the existence of an accepted standard to be used to confirm or measure validity. In fact, neither animal models nor human clinical effects can be univocally used as golden standard for validity. Besides, a universal approach to validation is probably unrealistic, and a harmonisation across contexts and cultures is expected to take too long, if possible at all.

Considering that the application of OoC devices in the short/medium term is most likely to be in the pharmaceutical sector, and will primarily target specific and well-defined contexts of use, focus should be on the qualification of devices, rather than on the validation in the broader sense. *Context of use* refers here to a clearly articulated description delineating the manner and purpose of use of a tool, while *qualification* is understood as arriving at a conclusion that the results of an assessment using a model or assay can be relied on to have a specific interpretation and application in product development and regulatory decision-making. Aiming for qualification of OoC devices was in fact the approach proposed in a recent series of workshops devoted to this important topic – held both in the US by the FDA and in Europe by the European Medicines Agency (EMA)'s Safety Working Party – and it was confirmed in the ORCHID workshop. The typical qualification process applied to OoC devices would foresee a comparison between OoC data and corresponding data derived from conventional preclinical drug development models (*e.g.*, animal models, cell suspensions) or human clinical data if available. If feasible and appropriate, this will inform the assessment of whether the OoC response corresponds to the expected behaviour, and thus can be used as a reliable predictor of human response.

More generally, it is desired and expected that OoCs reproduce salient physiological features and functional aspects of organs which recapitulate the human condition and responses to exogenous stimuli such as drug molecules. A challenge in qualification practice is therefore the establishment of relevant sets of reference or benchmarking compounds with well-known and properly documented pharmacological action and *in vivo* effects (*e.g.* paracetamol, beta blockers). Initiatives exist – such as led by the NIH in the USA, or the SEURAT-1 program[**] funded by the European Union – which aim to establish a public database to collect readout data in a very specific and platform-independent format, useful for both pharmaceutical companies and regulatory agencies. The ORCHID experts suggested that such initiatives may inform an open platform shared by partners in pre-competitive settings, tapping crowdsourcing approaches to *e.g.* data analysis and device testing, and crowdfunding to share costs. They may be inspired by examples of shared technology planning and development, such as the former International Technology Roadmap for Semiconductors (ITRS) and the International Roadmap for Devices and Systems (IRDS)[††].

[**] Available at: http://www.seurat-1.eu/ (accessed: February 25th, 2019)
[††] Available at: https://irds.ieee.org/ (accessed: February 25th, 2019)

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The current scenario is nonetheless fragmented, as most pharmaceutical companies intend qualification as an internal recognition process that does not need to be translatable to other companies, let alone the whole sector. Accordingly, OoCs need only comply with company-specific qualification protocols using company-specific test sets of compounds, established or under development. Though such compounds are typically proprietary and not easily accessible to academic research groups, the IQ Consortium, a not-for-profit organization of pharmaceutical and biotechnology companies[‡‡], is compiling a list of reference compounds, that might be shared for qualification purposes.

Standardization: when is the right time?

Standardization of OoC devices will likely contribute to ensuring reproducibility and robustness of results both within a single lab and across different labs; uniformity or compatibility of cell or tissue types and sources; and compatibility among chips or modules fabricated by different developers upon interconnection into a multi-organ system. Moreover, standardization will aid in the practical incorporation of OoC-based studies into analysis workflows and the utilization of results within decision-making contexts. Thus a move towards standardization is desirable from an industrial as well as from a regulatory point of view. This objective is however not compatible with the current, early stage of academic and commercial development of the majority of devices. The exponential growth of the number of publications on OoCs, whose dynamics is even superior to that which accompanied the development of the Human Genome Project, testifies to the continuous introduction, at least in the academic domain, of novel or ever updated OoC models which contemplate variations in the substrate technology and/or in cell sources and types. The interviewed experts mostly share the opinion that such wide exploration of solutions is welcome and typical of early stages of technology development. To bring the most benefit to the field, it should currently not be hindered, at least in academic research, by the strict imposition of standards or constraints deriving from intellectual property, even though this would defy the perceived interest of pharmaceutical companies and industrial end users. Additionally, it would be premature and counterproductive to converge towards robustly qualified or standardized manufacturing processes prior to gathering substantial evidence and characterization of the capacity of OoC models to host the intended target biology and recapitulate the *in vivo* human physiology and response of interest. Standardization of OoC devices and readouts may appear at some later stage, as in the case of other technologies, due to the convergence towards solutions generally considered most convenient or optimal, issues related to intellectual property, reorganization of companies, market conditions and end-user demands. Finally, standardization may alter the landscape of players in the field by constraining the numbers that can afford to comply with both its financial and engineering aspects.

‡‡ Available at: https://iqconsortium.org/ (accessed: February 25th, 2019)

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5. Barriers and perspectives

From industrial hesitance towards acceptance

OoC developers expect a large market to take off in the next 2-3 years. This optimism is supported by major recent technical breakthroughs [10], which make OoCs a credible option to provide a variety of end users with more predictive testing models. Once OoC models are available, demand is expected to increase and smoothen the road to applications. On the other hand, focusing on lesser applications may provide an additional point of market entry for OoCs.

Nevertheless, a more realistic view of the situation shows that there are heavy barriers to be crossed. Industry is still testing OoCs in comparison with alternatives (*e.g.*, 3D cell cultures, spheroids, tumoroids, organoids) to determine the models most suited for their needs. Evidence-based convenience of the models is required to induce industrials, especially pharmaceutical, to integrate OoCs into near-future routine processes. Although OoCs may be more relevant and accurate than animal models or cell cultures, they are still expensive and need costly redesign to suit mass production. In addition, compatibility problems may occur due to the current lack of standardization (*e.g.*, different shapes, interfaces, sizes, tissue types and quality, ways of use); and it may take years before OoCs are accepted by regulatory agencies. Hence a pragmatic attitude prevails in the industrial context – which, as for any available alternative, evaluates OoCs either on a fit-for-purpose or on a cost-per-data point benefit they may afford. Accordingly, the new technology may be accepted if it provides simpler or cheaper alternatives to established models while reproducing the same results, or if it affords models for which no alternatives currently exist. An example of the latter is provided by a joint work of the Wyss Institute with Janssen to model the toxicity of a monoclonal antibody therapeutic which caused death in patients due to pulmonary embolism in Phase I clinical trials: Janssen had not observed any toxicity in preclinical animal models, whereas the Wyss Institute's OoC could replicate the thrombotic behaviour [29].

According to the Yole market report, in the most likely scenario OoCs will be increasingly adopted by the industry, due to their significant advantages over existing solutions in terms of *e.g.* predictivity, cost saving, alternative to animal testing [11]. Newcomers, mostly spin-off from academia, will appear in the OoC developers market, but in the meantime some companies will fail. It would not be surprising to see biotech companies and instrument developers, who are providing tools to the pharmaceutical industry, acquiring OoC developers, because of the good synergies between these organizations.

Early dialogue to ease regulatory hurdles

Regulatory aspects can represent another significant barrier towards the broader adoption of OoCs. There is a generic and non-OoC specific need to speed up regulatory validation processes. Examples of prior technologies attest to a resistance in the adoption and regulation of new medical options. The decisions

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of regulatory authorities on the efficacy of novel treatments can have significant repercussions in delaying the acceptance and implementation of those treatments, in making the treatment costs liable to reimbursements to patients, and generally on the societal costs of healthcare. In addition, the costs of the certification procedure, involving an extensive series of tests, may escape the possibilities of academic research groups. This conversely should incentivize the involvement of companies and funding agencies in the development of OoCs as well as in early dialogue with regulatory authorities to ensure effective and transparent communication and to avoid procedural obstacles at later stages of development. Industrial acceptance typically precedes and pushes regulation [1]. Still, there may be a catch in the transfer of the device development process from initial developers to companies. On one hand, the developers may be in immediate need for funding to advance or characterize their models to a degree sufficient to attract the interest of the companies. On the other hand, the companies may hesitate to provide funding until the developers have demonstrated that their models fit their specific purposes or that they can overcome the companies' fear to be the first to introduce a new model on the market – a model that later might eventually reveal ineffective in humans, or not compliant to future regulations.

Keeping expectations realistic

Industry and government agencies have placed huge expectations on a few developers of OoC technology, in particular academic centres like the Wyss Institute and the MIT as well as companies such as Emulate Inc. and CN Bio. These developers were repeatedly awarded funding for several tens of millions of dollars, and are the most visible in the field. The Yole market report suggests that the success of these well-funded organizations might be critical for the future of the OoC area [11]. Some industry players believe these organizations cannot fail, whereas some think the gap between prototyping and mass commercialization is too significant. The consequence of a potential failure of such field pioneers would be devastating for the OoC field: besides the high visibility of the failure (media coverage, top-rank universities), a loss of confidence from both industry and investors would disrupt many small companies.

The interviewed experts echoed similar concerns, and expressed almost unanimously the need to keep realistically optimistic about the OoC technology. They generally expect OoC to become a key technology in the coming years, yet prescribe to remain very cautious in stating the promises and the potential of the OoC technology to media and general public to avoid the pitfalls of hype psychology. While the experts do not agree whether the OoC technology is currently the object of a hype, the Human Genome Project, stem cells for regenerative medicine, microarray technology, proteomics and gene therapy represent significant examples of programs, initiatives or technologies that may risk to fail to deliver to the high expectations they raised at the outset.

A further analogy with these precedents is represented by the size of funding considered necessary to achieve the field's purported goals, expectedly in the order of hundreds of millions to billions of dollars. A

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large fraction of the costs concerns the translation of proof-of-concept devices from laboratories to market entry, and the tests prescribed for regulatory approval. OoC-related companies are expected to drive such advances, eventually in partnership with governmental agencies, and they find themselves in a critical position in this respect. Attracting investors and considerable funding is critical to gather the multidisciplinary technical expertise and build the layered infrastructure that can support the development of prototypes into mass-fabrication to meet the industrial demands of quality control and reproducibility. To achieve this, the companies need to rely on advertising, which is susceptible to involve overstatements. The latter may raise premature or unmatched societal expectations about a technology, which conversely is generally considered to be still in an early development stage.

A common perception of the interviewed experts is that the lay public easily grasps the core concept of OoC technology, and tends to get quickly excited about the potential to decrease or even replace animal testing. However, *Organ-on-Chip* as technology-defining name may confuse the public by association with other technologies such as artificial organ prostheses, organ replacement or regenerative medicine. The public may not understand how OoC technology actually works and what its limitations are, unless browsing specialized journals. On the other hand, the more popular media may tend to cover sensational stories and thus feed the false impression that the technology is already achieving all the advertised promises. An antidote to such perceived distortions may be a synergistic outreach activity by key players and stakeholders based on careful communication of recent achievements and ongoing developments that could inform about actual trends and realistic perspectives.

Collaboration and education must be encouraged early on

The interviewed experts remarked the strong need for integrative programs, collaborative projects, consortia and international funding strategies for the development of OoC technology and applications. Lack of international coordination may be caused by the heterogeneity of the global legislative, regulatory, financial and ethical scenario. Coordination efforts should be supported by a widespread outreach activity, targeting all levels of audience, and by an improved dialogue between regulators, industries, clinicians and patient groups since the early stages of development. In this respect, a digital platform is now being developed within the ORCHID to bring together players (*e.g.*, researchers, laboratories, companies, patient associations, regulators) and to create a community in the OoC field. The platform will evolve over time through the addition of publications, collaborative projects and additional information supplied by the members who will progressively become part of it.

Finally, besides topical and field-specific workshops and conferences, incubators of talents are elicited as prime accelerators for the progress of the technology. This should be the pivotal role of institutes, inspired by analogous initiatives of successful information technology companies, where diverse experts could

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freely interact to traverse linguistic and departmental boundaries and leverage ample resources to develop new ideas and conduct multi-disciplinary research.

6. Summary and recommendations

The synergistic convergence of microfabrication technologies and tissue engineering renders OoCs as promising tools for the realistic modelling of human physiology and pathology. The aim of an OoC is not to replicate a whole living organ, but rather to sustain a minimal functional (sub)unit of an organ or tissue that can controllably recapitulate salient aspects of human physiology. For this purpose, as argued in this paper, the main and desired features of an OoC can be divided into three categories:

(1) Tissue architecture

- Integrated long-term cell culture in defined spatial organizations
- Tissue-tissue interfaces/cell-cell contacts/cellular heterogeneity
- Miniaturization

(2) Conditions

- Controlled microenvironment (topology, biochemistry, physics)
- Controlled dynamics (fluid flow, electro-mechanical stimuli)
- Continuous automated perfusion
- Real-time monitoring of multiple physical, bio- and electro-chemical parameters
- Automated reproducible multi-sample analysis, comparable with R&D robotics
- Large-scale manufacturability

(3) Functions

- Physio- and pathological relevance
- Recapitulation of organ structure and function
- Recapitulation of dynamic mechano-biological properties and stimuli response of organs

In view of this and of the unmet needs and challenges, the ORCHID elicited the following recommendations (summarised in Fig. 9) to foster further progress in this rapidly establishing field:

Characterization, qualification and standardization

1. *Do not aim for the whole human: start mimicking single organs first.*
2. *Demonstrate the benefits and prove with reliable data OoCs' added value compared to other models.*
3. *Describe the value of OoCs on a fit-for-purpose or cost-per-data point scenario.*
4. *Develop guidelines for qualification of OoCs through a collaborative process involving developers, end-users and regulatory bodies.*

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5. *Create a list of reference compounds and related annotations for specific organ effects to qualify OoCs for a specific context of use, and share the data through a public database.*
6. *Compare OoC's tissue architectures and cellular phenotypes with* in vivo *tissue histology or histopathology using existing technologies.*
7. *Only consider standardization of OoCs once there is substantial evidence for OoC platforms to recapitulate the* in vivo *human physiology and response of interest.*

Technology

8. *Integrate real-time, bio-compatible electrical, chemical or physical sensing and analysis, and define and measure the salient parameters that can be predictive.*
9. *Address the issue of unselective compound absorption in OoC substrate materials.*
10. *Minimize operational complexity: develop automation for speeding up OoC assays, and improve ease of use to enhance reproducibility, robustness, and ease of transfer from developer to end user.*
11. *Integrate OoC and computational (open source) models, starting with pharmacokinetics.*

Biology

12. *Define strategies to tackle issues on cell-to-cell variation, maturation and stability of cells.*
13. *Standardize the culture medium and explore the use of blood in single perfusion of multi-OoC.*
14. *Include immune and endocrine system components in OoC to improve physiological relevance.*
15. *Include gender-, origin- and age-related aspects in OoCs for representation of human diversity.*

Applications

16. *Define the type of throughput required for the application of OoCs.*
17. *Address personalized medicine (*you-on-a-chip*), clinical trials-on-chip and environmental toxicological assays as highest priority applications.*
18. *Involve the food industry to raise their interest for OoC applications.*
19. *Focus on toxicities or diseases for which no satisfactory pre-clinical models and treatment exist as a niche market for OoCs.*
20. *Combine a set of organs involved in ADME pathways (Absorption, Distribution, Metabolism, Excretion) that can match the critical functions needed for compound testing and studying transport of drugs and bioactive factors.*

Dissemination, communication and collaboration

21. *Keep expectations about the technology realistic when communicating with media and the public.*
22. *Develop a synergistic outreach based on careful communication of achievements and new developments by developers and stakeholders.*

23. *Involve patients, clinicians, companies and regulatory authorities early in the development of OoCs to ensure effective dialogue and avoid procedural obstacles for implementation.*
24. *Attract investors and funding agencies to support the development of prototypes into mass fabrication to meet the industrial demands of quality and reproducibility.*
25. *Build the network, and realize integrative programs, collaborative projects, consortia, a digital platform and international funding strategies for the development of OoC technology.*
26. *Foster next generation researchers: organize exchanges among institutes, trainings, workshops and conferences to nurture talents as prime accelerators for the progress of OoC technology.*

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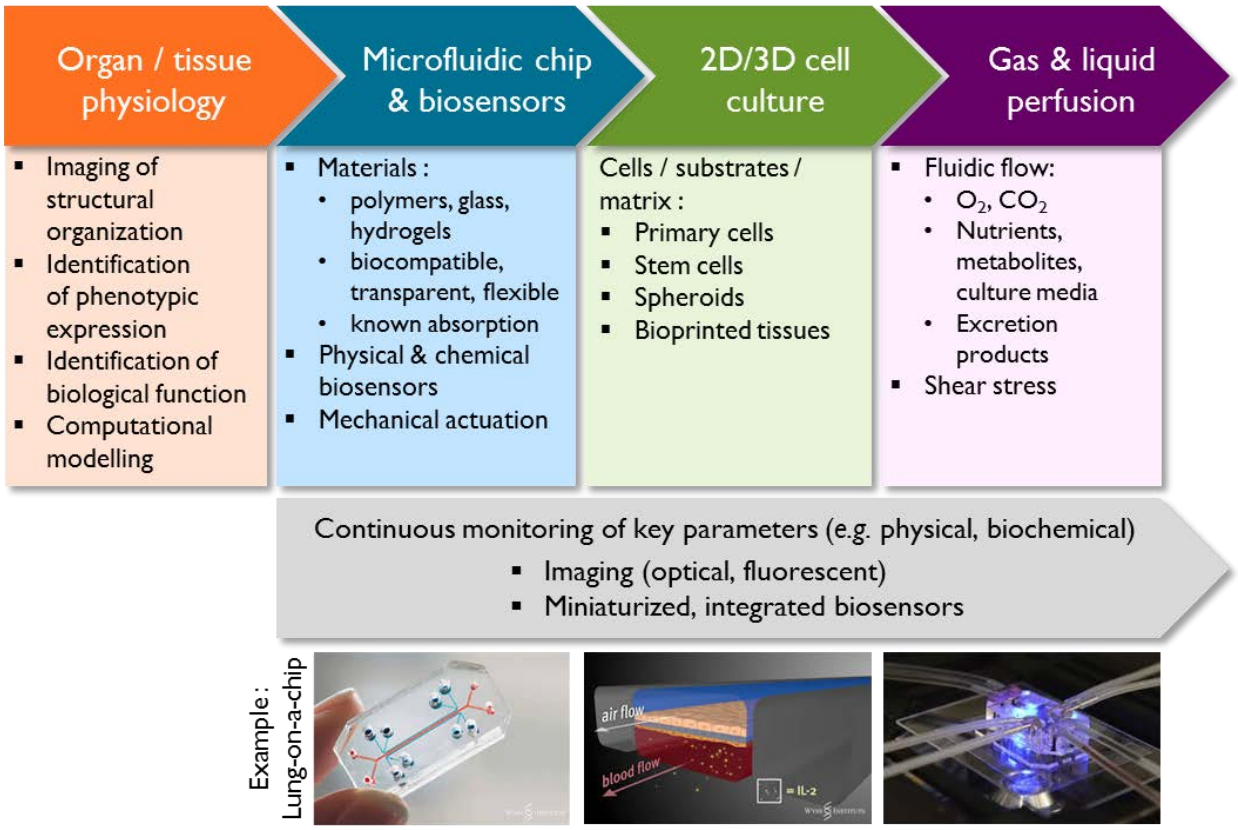

Figure 1. Simplified synopsis of the OoC value chain, according to the ORCHID analyses (pictures: courtesy of the Wyss Institute at Harvard University).

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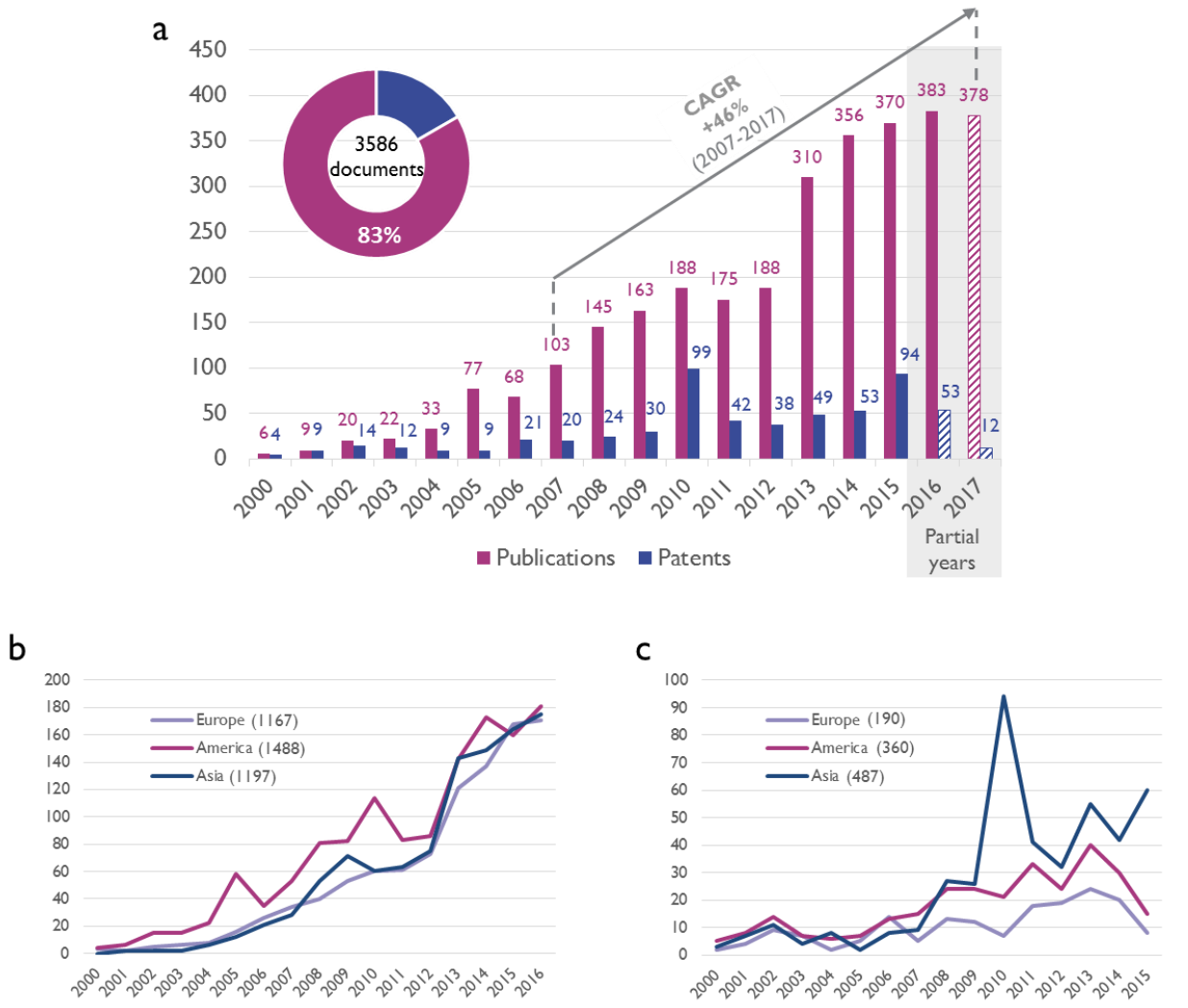

Figure 2. The ORCHID bibliographic analysis. **a)** Temporal evolution of the number of OoC-related patents and scientific publications over the 2000-2017 period. The imported database includes 3586 documents, mostly publications (83% *versus* 17% of patents). The 592 identified patents include granted (38.9%), pending (25.8%) and fallen or revoked (35.3%) patents. Year 2015: latest complete year for patents (18 months are needed to publish the patent application). Year 2016: latest complete year for publications (documents were imported in November 2017). CAGR: Compound Annual Growth Rate. **b)** Temporal evolution of the number of publications per region. **c)** Temporal evolution of the number of patents per region.

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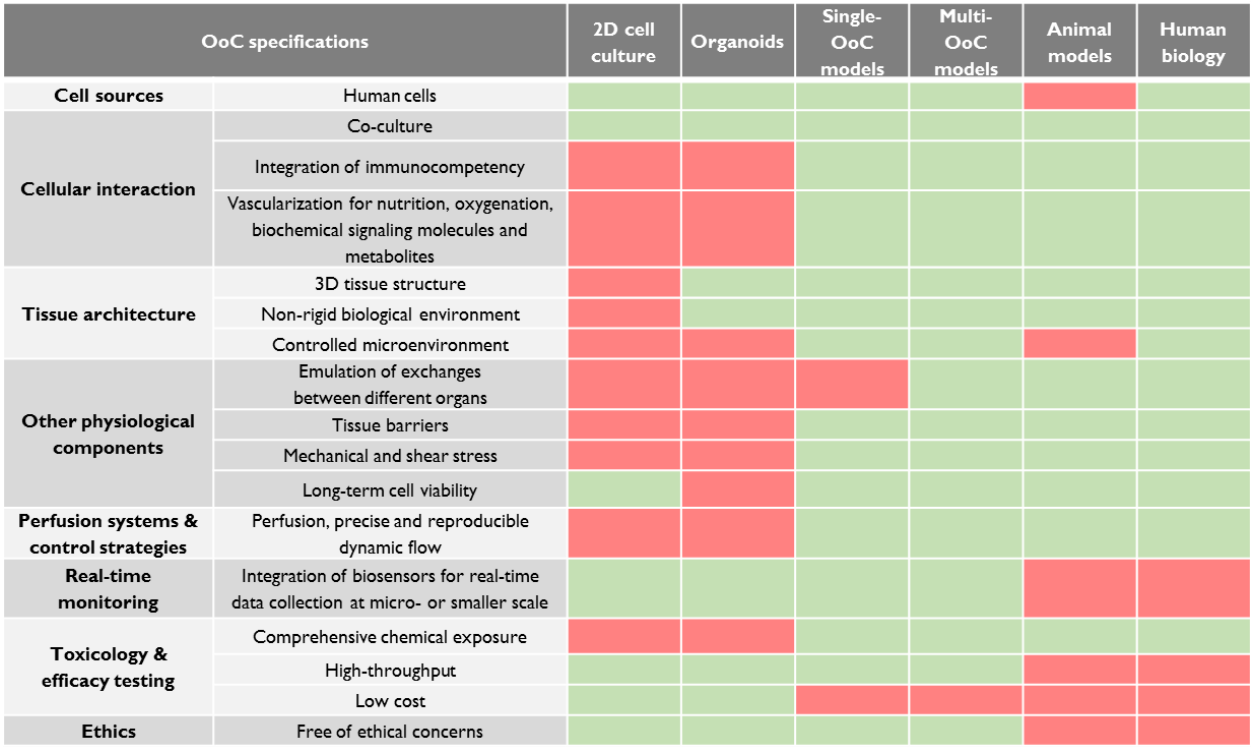

Figure 3. Comparison of key specifications and features across available biological models. *Red boxes*: not feasible; *green boxes*: already technically available, or envisioned in the near future.

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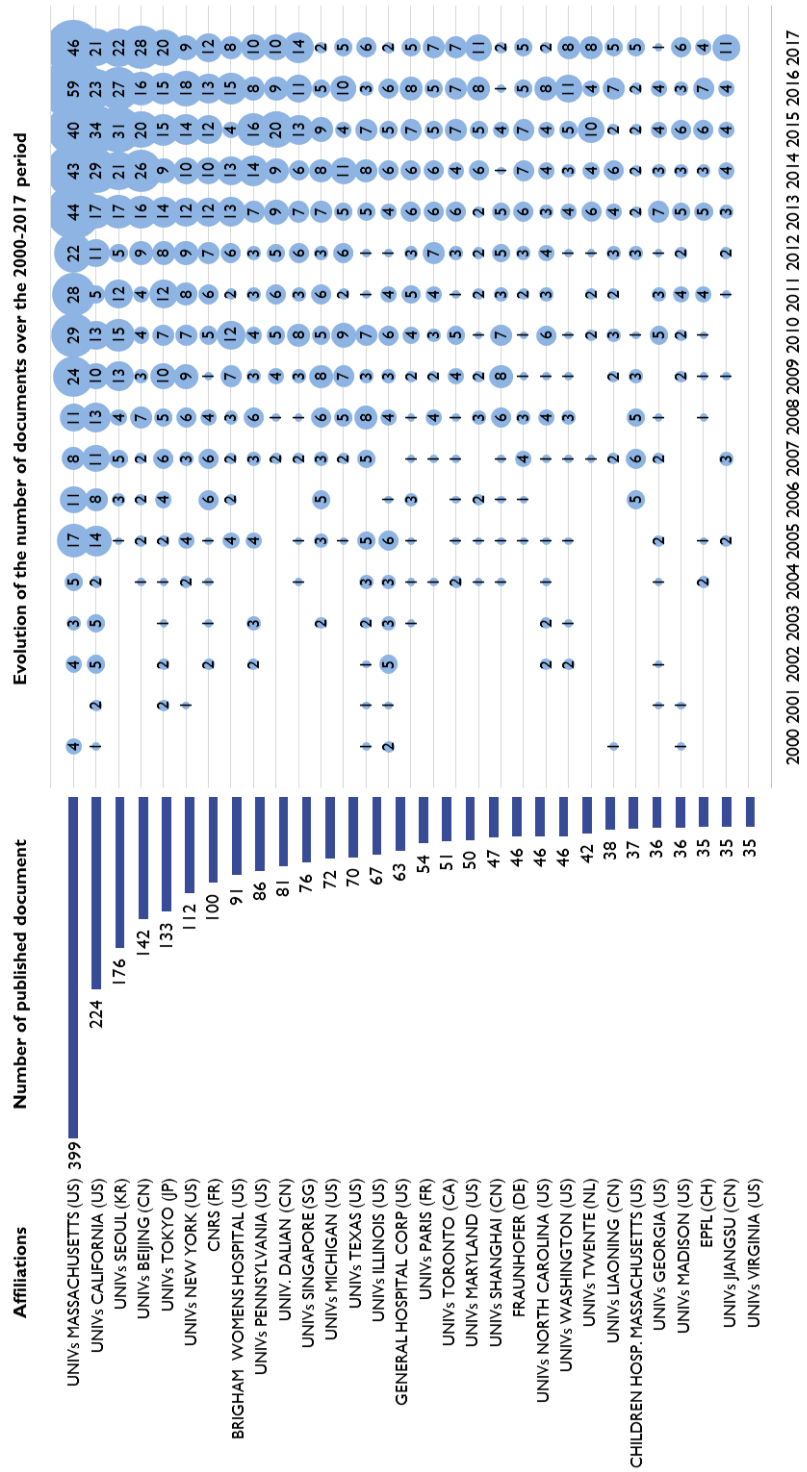

Figure 4. The top 30 academic players in the OoC field according to the ORCHID bibliographic analysis. These, out of 650 identified academic players, published more than 34 documents over the 2000-2017 period. *Blue bars*: number of patents and publications. The size of the circles is directly proportional to the number of identified documents published each year.

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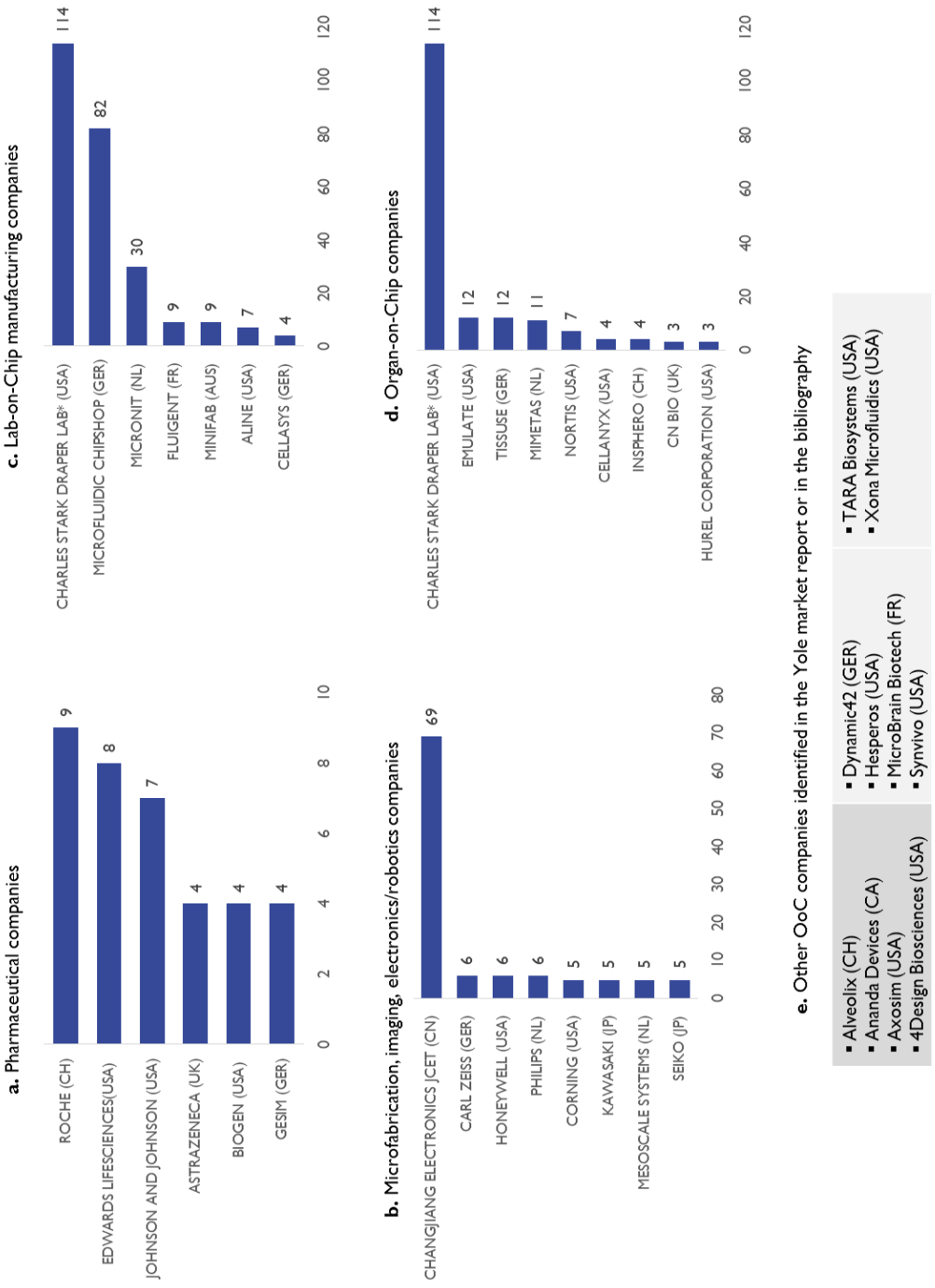

Figure 5. Overview of the top 30 industrial players in the OoC field, which published more than 2 documents over the 2000-2017 period. (Note: Charles Draper Lab is a non-profit and non-stockholding organization with a strong R&D activity. For this reason, it is listed here among companies.)

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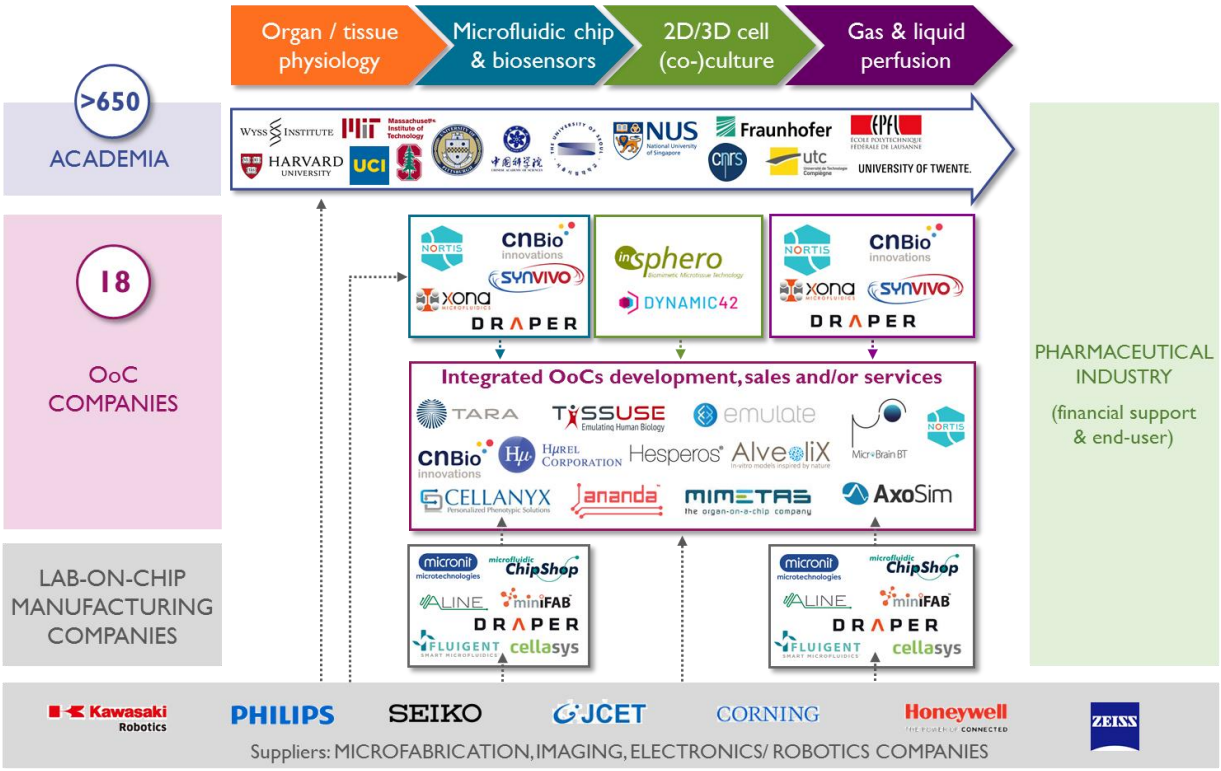

Figure 6. OoC players' positioning along the value chain (see Fig. 1). The figures represent the number of academic players (blue circle) and OoC companies (purple circle) identified *via* the bibliometric approach. Academics and OoC companies show a dedicated expertise for the development of fully operational OoCs, whereas the other industrials are supporting their development technological expertise, financing and/or partnerships. For each profile, only the top players are shown.

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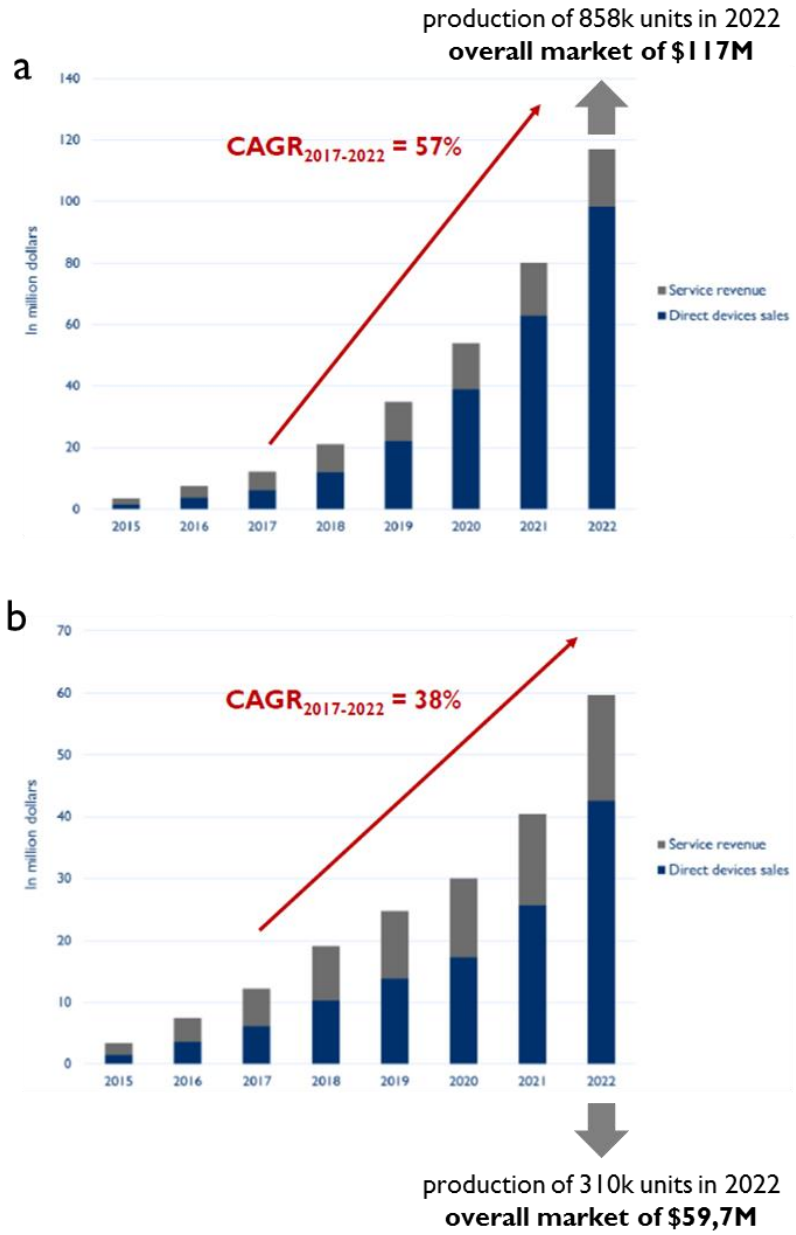

Figure 7. The optimistic (a) and realistic (b) OoC market scenario proposed by the Yole market report [11]. The estimated revenues are in million dollars and split between direct devices sales (ready-for-culture devices and fully operational OoC; blue bars) and full service sales (tests performed in-house; grey bars). CAGR: Compound Annual Growth Rate.

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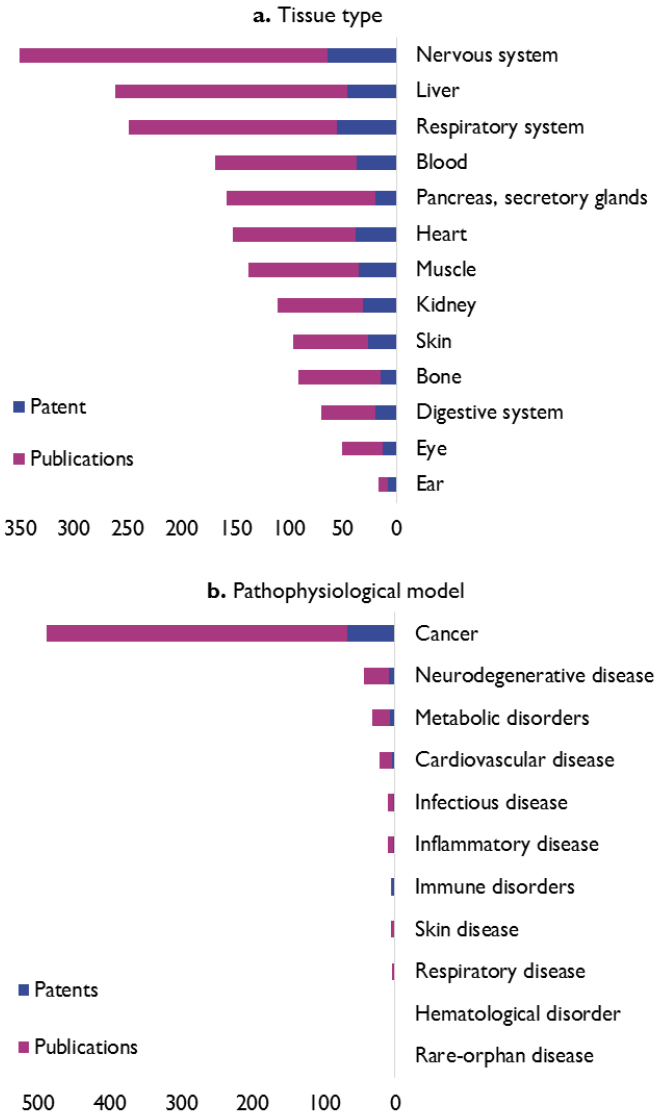

Figure 8. Global trends in pathophysiological models and tissue types. The imported database of patents and scientific publications was segmented with regards to emulated tissue types (a) and pathophysiological models (b) on a worldwide scale.

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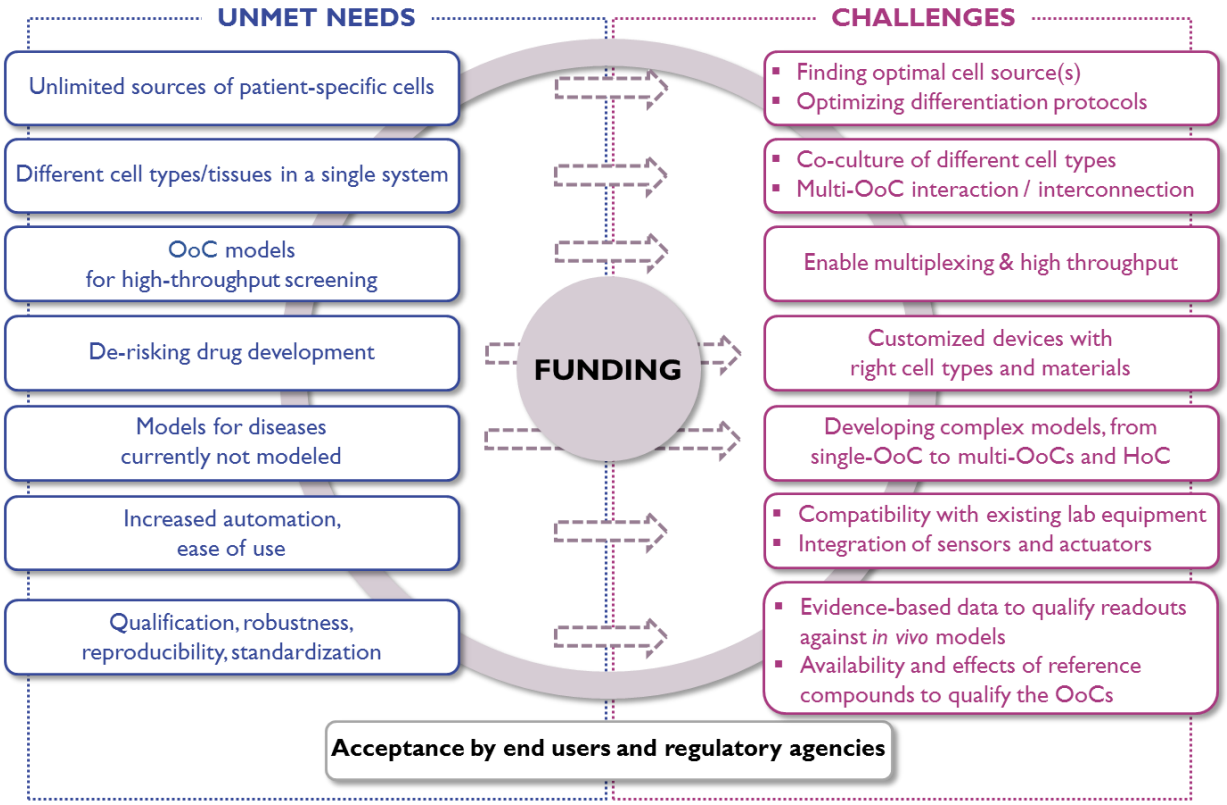

Figure 9. Key unmet needs and challenges for OoC development.

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Appendix: Methodology overview

The studies presented in this paper draw on (1) a documentary approach, combining both a bibliometric and a market analysis, and (2) interviews with field experts, with the aim of assessing the existing and perspective OoC landscape. The methodology and results of the studies were reviewed and discussed by a committee of experts during the *ORCHID Vision Workshop*, held on May 23, 2018 in Stuttgart (DE).

The methodology is summarized in the Fig. A1 and detailed in the following sections.

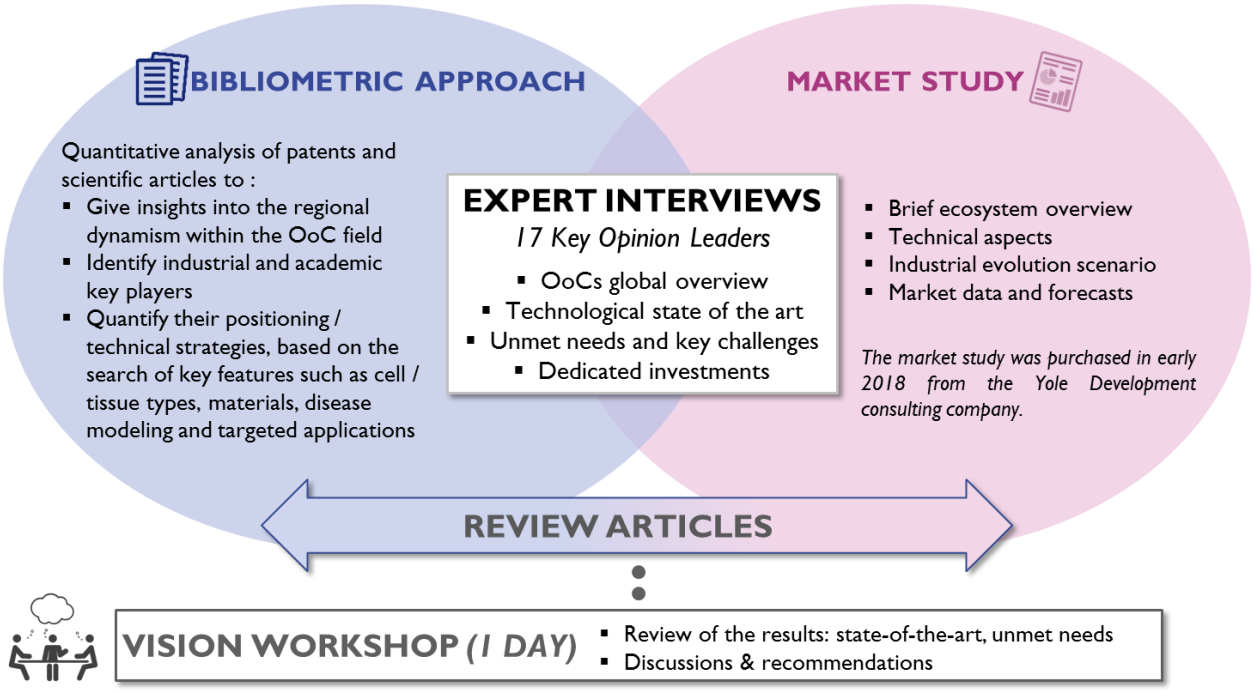

Figure A1. The methodology of the ORCHID OoC analyses presented in this paper.

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A1. Documentary approach

A.1.1 Bibliometric study

A bibliometric study is a quantitative analysis of scientific and technical information in a given area to provide a global overview of the associated ecosystem. The ORCHID bibliometric study was meant to give insights into the OoC's regional R&D dynamism, to identify the key players, and to quantify their positioning and technical strategies. The study was based on the search and classification of key features – including cell/tissue types, materials, disease modeling and targeted applications – in peer-reviewed articles and patents.

The bibliometric study followed a five key steps methodology: a. the definition of the keywords; b. the validation of the associated corpus of documents; and c. its associated segmentation, followed by d. a semi-manual normalization of the affiliations and e. the final analysis.

a. The keywords definition is related to the technological scope specified through discussions with experts in the OoC field. The keyword definition led to the implementation of six search strategies characterized by a complex combination of keywords with Boolean operators which were used to build a dedicated corpus of documents: Organ on chip / Specific terms (artificial organs, organoids, spheroids, 3D cultures, etc.) / Human tissues & cells / 3D bioprinting / Microsystems / OoC Companies.
b. The associated relevant documents were collected from the specific databases *Orbit* (patents) and *Scopus* (scientific articles) over the 2000-2017 period. An additional expert's validation of the imported documents was required to ensure that the extracted documents were reasonably exhaustive and relevant.
c. A customized segmentation of the documents was used to sort articles and patents within the database. The four main identified segments were in turn divided into sub-segments to facilitate the analysis:
    1. Human cell technologies: *i.* environment substrate & scaffolds; *ii.* tissue types; *iii.* cell types.
    2. Chip technologies: *i.* material; *ii.* microsystem.
    3. Monitoring & analysis technologies (sensors, imaging, computational modelling, TEER, OoC characterization)
    4. Market: *i.* applications; *ii*. targeted areas (pharmaceutical, cosmetics, chemical & environment).
d. The normalization of the identified organizations' affiliations was required to perform
e. an efficient quantitative analysis of the collected documents. This was performed using the Intellixir statistical analysis tool (Questel).

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This overall process enabled us to extract a database of 3497 relevant documents for further analysis.

Nevertheless, such bibliometric approach has limitations:

i. it inherently provides a screenshot of the OoC ecosystem at the time of the documents' extraction from the databases (namely, November 2017). Patents and scientific articles published since that date were not included within the analysis;

ii. the search strategies were limited to the title, abstract or keywords of the documents, so that some documents might have been excluded or overseen although potentially relevant;

iii. the approach gives mainly quantitative information. Such information helps to identify key players as well as key used technologies on the basis of the number of patents and scientific articles found; on the other hand, the quantitative aspect of such approach may assign poor visibility to recent organizations with limited track record, despite the eventual quality of their contributions to the field.

A.1.2 Market analysis

Since market reports are already available from consulting firms, a customized market report dedicated to OoCs was purchased in early 2018 from Yole Développement [11]. This report, published early 2017, provided the ORCHID consortium with market data and forecasts as well as a focus on OoC's technological aspects and challenges.

Yole Développement's methodology for building market forecasts is, reportedly, to lay out a model where all the data from product shipments, average selling price of the devices, and player market share, are aggregated and processed with detailed assumptions. Data were collected from several sources, including primary data from direct interviews and visits with key players, direct contact and surveys with equipment & materials suppliers, and comparisons across publicly-available secondary data. A market tracker on the OoC field was implemented to update the market information presented in the report on a regular basis. As a result, the report presents synthetic market metrics intrinsic to the OoC specific industry. The main advantage of this approach is the delivery of homogeneous data, ranging from unit shipments and system sales to player market share.

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A2. The ORCHID partners: interviewees and other contributors

17 interviews with recognized experts and key opinion leaders in the OoC field were conducted within the ORCHID WP2 over a 4 months period, namely from January until April 2018, to support the state-of-the-art analysis described in the previous sections. A list of about 50 questions, spanning all aspects of the field mentioned in the main text, formed the base of the interviews. Each expert was interviewed once, and the duration of each interview was set to about 1 hour.

The expert selection process proceeded through 1) the identification of eminent expert profiles with different backgrounds (academic, industrial, clinicians, patients, regulatory), and 2) a subsequent prioritization within the candidate set, which ensured a relatively consistent profile distribution (Fig. A2).

The experts that participated in the interviews are[§§] (in alphabetical order): Sofia Batista Leite (EC-JRC, Italy), Anthony Bahinski[1,3] (GlaxoSmithKline, USA), Lorna Ewart[1,3] (IMED Biotech Unit Drug Safety and Metabolism, AstraZeneca, UK), Suzanne Fitzpatrick (FDA, USA), Marie Fortin (Jazz Pharmaceuticals, USA), Olivier Guenat[1] (University of Bern & AlveoliX AG, Switzerland), Donald E. Ingber (Wyss Institute at Harvard University, USA), Jochen Kuehnl[1] (Beiersdorf AG, Germany), Cecile Legallais (CNRS, France), Uwe Marx[3] (TissUse GmbH, Germany), Alexander Mosig (Universitaetsklinikum Jena & Dynamic42 GmbH, Germany), Christine Mummery[1,2] (Leiden University Medical Center, the Netherlands), Kevin Parker (Harvard University, USA), Adrian Roth (Hoffmann-La Roche, Switzerland), Cees Smit[3] (EGAN, the Netherlands), Danilo Tagle (NIH, USA), Jan Willem van der Laan[1] (MEB, the Netherlands).

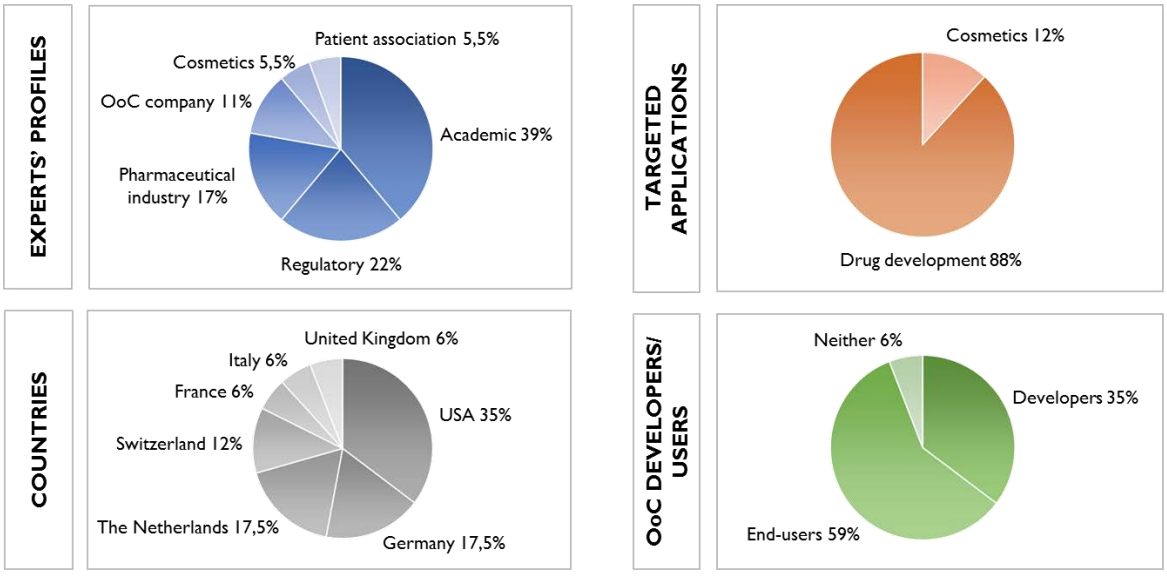

Figure A2. Profile of the 17 interviewed experts.

[§§] In the reminder, the following description applies: [1] Participant of the ORCHID Vision Workshop, [2] ORCHID partner, [3] Member of the ORCHID Advisory Board.

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Within the profile distribution of the interviewed experts (Fig. A2), a bias is observed regarding the applications targeted by the interviewees, since they mostly develop or use OoCs in the drug development process. Other clinicians and experts from food industries and cosmetics were also contacted, but they did not answer to our inquiry within the period dedicated to the interviews.

In addition to experts' interviews, a short survey composed by a selection of the interview's questions was submitted to 9 experts within the ORCHID consortium to additionally benefit also from their technical expertise and point of view.

The other experts involved in the ORCHID were (in alphabetical order): Dries Braeken[1,2] (imec, Belgium), Wolfgang Eberle[1,2] (imec, Belgium), Thomas Eschenhagen[3] (University Medical Center Hamburg, Germany), Luis Fernandez[2] (University of Zaragoza, Spain), Lino Ferreira[1,3] (Biocant & University of Coimbra, Portugal), Xavier Gidrol[1,2] (CEA, France), Mart Graef[1,2] (TU Delft, the Netherlands), Anna Herland[1], (KTH & Karolinska Institutet, Sweden), Reyk Horland[1] (TissUse GmbH, Germany), Steven Kushner (Erasmus MC, the Netherlands), Shannon Layland[1] (Fraunhofer IGB, Germany), Peter Loskill[1,2] (Fraunhofer IGB, Germany), John Martens (Erasmus MC, the Netherlands), Torsten Mayr[1,3] (University of Graz, Austria), Ignacio Ochoa[1,2] (University of Zaragoza, Spain), Nathalie Picollet-d'Hahan[1,2] (CEA, France), Mieke Schutte[1,2] (hDMT, the Netherlands), Jens Schwamborn[1,3] (University of Luxembourg, Luxembourg), Pietro Siciliano[1,3] (IMM, Italy), Maria Tenje[1,3] (Uppsala University, Sweden), Andries van der Meer (University of Twente, the Netherlands), Anja van de Stolpe (Philips Research (Philips Group Innovation) & Clinical Advisory Board hDMT, the Netherlands), Jacqueline van Engelen[1,3] (RIVM, the Netherlands), Maurice Whelan[1] (EC-JRC, Italy), Ioanna Zergioti[1,3] (NTUA, Greece).

Workshop Report

Building Blocks for a European Organ-on-Chip Roadmap

doi:10.14573/altex.1905221

1 Introduction

This paper summarizes the outcome of the Organ-on-Chip (OoC) ORCHID Strategy workshop (Leiden, The Netherlands, January 17, 2019) intended to establish a European OoC roadmap through expert discussions, conclusions, and recommendations. The workshop identified six specific building blocks for the OoC roadmap: (1) application, (2) specification, (3) qualification, (4) standardization, (5) production and upscaling, and (6) adoption. Complementary aspects relating to ethics and communication were also addressed. Priorities, methods and targets for the roadmap were proposed for each building block. General consensus was reached on the potential contribution of the newly founded European Organ-on-Chip Society (EUROoCS), which could facilitate deployment of each block. EUROoCS would ideally initiate and catalyze dialogue between OoC developers, end users and regulators. The dialogue should address qualification, open technology platforms, standardization and implementation of OoC technology, as well as ethical aspects of human tissue mimics, training the next generation of OoC researchers, dissemination and communication.

1.1 The current landscape of Organ-on-Chip technology

Born at the confluence of tissue engineering and microfluidics, OoC technology is widely postulated as a promising approach to better model systems for healthcare research. OoC models aim to recapitulate aspects of human physiology and pathology for use in drug discovery, efficacy and toxicology testing, and personalized (or precision) medicine, with the goal to improve upon existing bioassays and provide insights into the mechanisms underlying the development and progression of diseases. In addition, OoCs are considered relevant to reduce the need, cost, and ethical burden of animal studies.

Though the OoC field is still in its infancy, several showcases of OoC models have already provided insight into disease etiology and supported identification of drug target pathways. These showcases include detection of thrombotic risk in vessels-on-chip (Barrile et al., 2018), discovery of targets for metastases in cancer-on-chip (Song et al., 2018), a test for kidney toxicity in kidney-on-chip (Vormann et al., 2018), drug effects on neurons and glia cells-on-chip (Wevers et al., 2016), prediction of toxicity of nanoparticles in lung-on-chip (Zhang et al., 2018), and drug discovery in a disease model for amyotrophic lateral sclerosis (Osaki et al., 2018). These and multiple other examples are at the stage of validation/qualification, which in general means that compounds and drugs already demonstrated as toxic or effective in treating disease in animals or patients show similar effects in OoC models. This is expected to encourage OoC adoption by industry, acceptance by regulatory bodies, and further development as animal alternatives. However, this outcome is still pending growth in confidence on OoC predictivity and utility.

A comprehensive survey of the current OoC landscape in research, development, applications, and market opportunities was recently carried out by the Horizon 2020 FET-Open project *Organ-on-Chip In Development* (ORCHID[1]). The goal of ORCHID is to create a roadmap for OoC technology, identify potential roadblocks and corresponding solutions, raise awareness and build ecosystems conducive to wide implementation and use of OoCs in science, R&D, and regulatory guidelines in Europe and elsewhere. ORCHID recently published a report (Mastrangeli et al., 2019) based on a bibliometric study, market analysis, interviews, and panel discussions with 31 experts at the ORCHID Vision workshop (Stuttgart, Germany, May 23, 2018). The report described current unmet needs (including evidence of added value, methods for automation and robustness), key challenges (structural materials, cell sourcing and culture media, long-term cell viability, real-time characterization, increasing complexity, qualification), barriers and perspectives (industrial acceptance, appropriate and timely dialogue among players) of this technology, as well as recommendations for defining a European OoC roadmap. The present document builds on this preliminary assessment and identifies potential solutions.

1.2 The future strategy for Organ-on-Chip technology

Following up on the ORCHID Vision workshop, the ORCHID Strategy workshop was held in Leiden on January 17, 2019. 32 experts (see Appendix B)[2] from academia, innovation hubs, pharmaceutical and cosmetic industry, patient organizations, ethics schools, biotech companies, and regulatory agencies attended. They represented OoC developers, end users, and regulators in Europe. The aim of the workshop was to sketch an OoC landscape for future development of the technology by defining concrete goals and milestones that would form the roadmap strategy for moving forward. During two brainstorm sessions, expert groups focused on four application domains: personalized medicine, drug efficac , drug toxicity, and disease mechanisms. The groups addressed domain-specific issues from the perspective of both developers and end users/regulators.

[1] ORCHID partners are: Leiden University Medical Center (coordinator; The Netherlands), Institute for Human Organ and Disease Model Technologies (hDMT) and Delft University of Technology (Delft, The Netherlands), CEA (France), imec (Belgium), Fraunhofer Institute for Interfacial Engineering and Biotechnology (Fraunhofer IGB, Germany), and University of Zaragoza (Spain).

[2] doi:10.14573/altex.1905221s

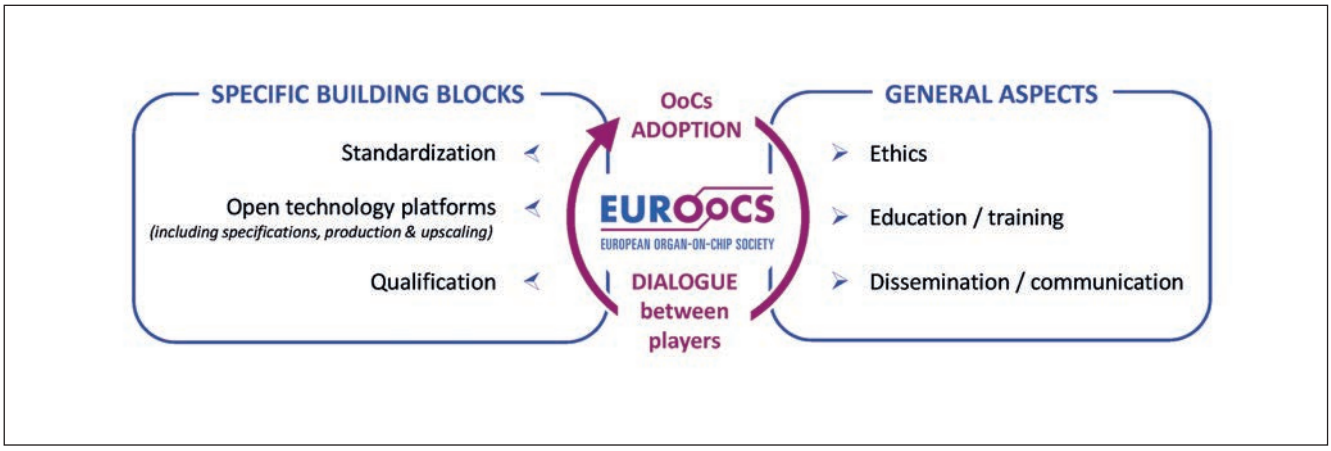

Fig. 1: The facilitating role of the European Organ-on-Chip Society (EUROoCS) in the context of the proposed OoC roadmap

This report summarizes the expert discussions, conclusions, and recommendations that emerged from the ORCHID Strategy workshop. Six building blocks of the OoC roadmap were identified: (1) application, (2) specification, (3) qualification, (4) standardization, (5) production and upscaling, and (6) adoption. These are discussed individually in depth in Section 4. Potential ethical issues were also considered, as well as training of the next generation of OoC researchers, and dissemination and communication of the technology. These issues are addressed in Sections 2 and 3, which set the context for the core building blocks. We take as given the prominent role that the existing OoC community will play in this endeavor.

2 The European Organ-on-Chip Society (EUROoCS[3])

2.1 The role of EUROoCS in community building

As articulated at the ORCHID Strategy workshop and detailed below, collaboration between all stakeholders is key to further acceptance, development and implementation of OoC technology. In Europe, an OoC network of more than 28 partners in 17 countries has recently been formed. Many countries, including the United Kingdom, Scandinavia, Belgium, and Israel, have drawn inspiration from the Dutch OoC consortium hDMT[4] and are starting to link OoC players in their own countries in similar ways. This paves the way for a European Center of Excellence on human OoC by creating strong research collaborations throughout Europe and beyond. The European Organ-on-Chip Society (EUROoCS), an outcome of ORCHID, aims to facilitate and stimulate further growth of OoC networks.

EUROoCS was launched during the International OoC Symposium (IOOCS18) at the Eindhoven University of Technology in the Netherlands on 8 November 2018. Its purpose is to encourage and develop OoC research, and provide opportunities for sharing and advancing knowledge and expertise in this field towards a better health for all (Fig. 1). Membership is open to individual researchers and others with an interest in OoC technology worldwide. Benefits include access to the digital OoC platform, where members can present their expertise and research projects, interact with others in the OoC field, and find new collaborators and tailored information (see Section 3.3). EUROoCS will stimulate and provide a platform for dialogue and interaction between all parties involved in the implementation of the OoC roadmap strategy. This is captured in the EUROoCS logo, which symbolizes both technology and community building in Europe and beyond (Fig. 1).

3 General aspects of an Organ-on-Chip roadmap

3.1 Ethics

An ethics roadmap was regarded as important to identify emerging ethical issues and address them in a timely way as the technology progresses. Such a roadmap is a sensible way to balance short-term issues related to the use of human cells, donor procedures, ownership, and present work in the laboratory with longer-term discussions about future "human-on-chip" models that would include but not be limited to brain-on-chip, reproduction system-on-chip, and the right to know/not to know regarding unexpected phenotypes revealed by chip technology.

Communication to the public warrants care

The ethics roadmap will help the discussion of ethical and societal issues with the general public, as well as the conversation on possible future societal impacts and controversies. To avoid misunderstanding, communication about OoC technology should carefully consider the language used and how it is understood by the public and different stakeholder groups. The workshop participants noted a discrepancy between expansive ambitions (e.g., "human-on-chip") and actual work in the laboratory (technical innovation). Discussions overly focusing on the ambitions may create unjustified expectations and ensuing disappointment (also

[3] https://www.euroocs.eu

[4] https://www.hdmt.technology

known as the hype cycle), or lead to controversy over issues not related to the research actually undertaken. Cautious language use is all the more important with regards to patients potentially waiting for these technological developments to become healthcare reality. The expert group therefore recommended to carefully plan a fine-tuned dissemination strategy that might also manage possible associated risks.

Privacy and ownership issues ask for clear management
There is a strong awareness of bioethics issues among researchers, and experience on how to manage them properly. However, privacy and informed consent procedures may have to be revisited to address issues related to personalized medicine, especially if rare diseases are targeted.

In addition, standardization of technology platforms raises issues related to the ownership of results. There is an underlying dilemma between the ambition to contribute to societal goals (e.g., new therapies, replacement, reduction, and refinement (3Rs) of animal testing) and the need for economic viability of the solutions. Though there is no best solution, these questions should be addressed further.

Interdisciplinary research and global dialogue raise awareness
OoC research requires interdisciplinary collaboration between physicists, biologists, engineers, chemists, and researchers from other disciplines. Researchers who are active across disciplines may be incorrectly presumed to have correspondingly adequate skills, whereas different laboratories often require specific training. Therefore, care must be taken so that personnel are offered appropriate training, including regarding safety (see next subsection).

Another dilemma to be addressed relates to the organization of collaborative research communities on complex high-tech platforms and ensuing requirements for data sharing. By lowering the entry point threshold, new entrants may bring in innovative ideas, though they may also be less aware of safety issues.

The European OoC strategy explicitly addresses ethical issues; however, this may not *per se* prevent the emergence of new products or systems in other parts of the world that conflict with European values. Therefore, a role for EUROoCS might be to engage in a global dialogue on ethical issues and develop a common understanding of how these can be addressed.

3.2 Training

Tailored training programs for next generation OoC professionals
The multidisciplinary character of the OoC technology raises challenges to develop appropriate training programs, as working in this field requires experts with a broad skillset covering various aspects of bioengineering, cell biology, materials science, and other disciplines. Specialized training and expertise is of utmost importance for anyone involved in the development and utilization of OoC systems as well as in the assessment of the systems and results they yield. The recommended training programs shall prepare scientists and technicians for new types of employment that will arise, but also provide industry and academia with professionals who are able to keep up with innovation in the field. Training programs will thus need to cover a wide range of topics including biomaterials, microfabrication and manufacturing technologies, and microfluidic principles, but also cell culture, stem cell technology, biobanking, data management and protection, monitoring and analysis (molecular biology/omics, sensors, imaging), pharmacology and toxicology principles, pharmacokinetics/pharmacodynamics (PK/PD) modelling, quality assurance, science communication, regulatory affairs and ethics. Each of these have differing degrees of relevance depending on end-user or developer requirements. Tailored training programs will be necessary for scientists in academia and industry, for decision-makers (regulators, grant evaluators or peer reviewers), as well as for technicians and research clinicians.

The level of complexity and depth of the training could range from introductory knowledge (awareness) and basic competence (theoretical or practical skills) to deep knowledge (theoretical and practical skills). The programs could be implemented at various stages of education (bachelor-, master-, doctorate studies, or post-doctoral training) and could include either specific postgraduate courses (1 to 2 years), seminars/courses integrated in a broader training program (1 semester), or only individual training sessions (theoretical or practical). Besides specific training programs, focused seminars/courses/workshops on aspects of OoC could be incorporated into traditional educational programs such as engineering (mechanic, materials, chemical), bioengineering (biotechnology, biomedical), physics, chemistry, biochemistry/biology, medicine, and pharmacology/toxicology. Input into curriculum development will be essential.

In the process of European roadmap development for OoC, comprehensive stakeholder consultation is currently taking place to assess training needs and skillset requirements and to provide recommendations for specific training programs[5].

3.3 Dissemination and communication

The EUROoCS digital platform as a market place: Organ-on-Chip for all
A dissemination and communication strategy for OoC research and activities is essential if the EU scientific knowledge base is to be implemented optimally and to foster innovation, economic growth, and jobs. EUROoCS, its support website, including a digital platform for members, and its annual conference can contribute to forming a central coordination point, ensuring good visibility for European research teams that will promote their leadership in the OoC field. The EUROoCS platform will gather information centrally and promote OoC implementation, development and community building at European and international levels (Fig. 2).

EUROoCS board and members will ensure that sector-specific boundaries and language barriers are crossed to facilitate effective dialogue and collaboration between the scientific community, regulators, industry, clinicians, and patient groups from the earliest stages of development, and to catalyze OoC adoption by

[5] Questionnaire for stakeholders: Training needs of the next generation of researchers and technicians in Organ-on-a-Chip, available at: https://ec.europa.eu/eusurvey/runner/Orchid_Questionnaire_Training_needs_Organ-on-a-chip (accessed 29.09.2019).

Fig. 2: The EUROoCS website/digital platform as a "market place" for all

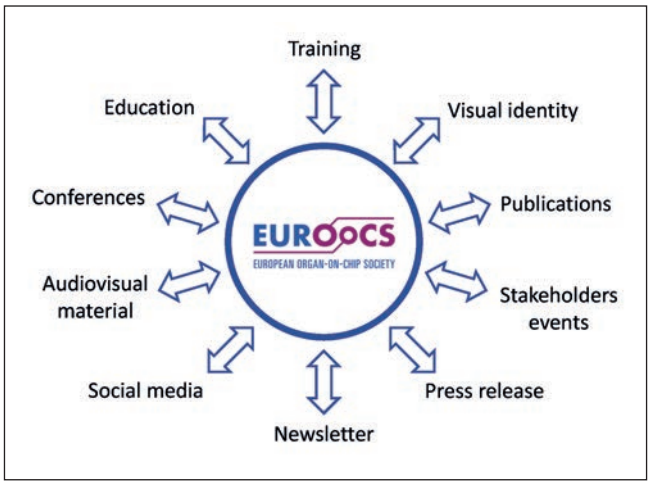

Fig. 3: Tools of dissemination

end-users. Working together as a community and becoming visible through the EUROoCS website/digital platform could also help establish standards in the field that would provide industry with confidence regarding implementation. As a standardization catalyst, the EUROoCS digital platform will also collect expert insights from different stakeholder groups to provide an indirect roadmap through building guidelines for OoC implementation.

The EUROoCS website[3] was conceived by ORCHID members and validated by a test group of selected OoC experts to provide key information efficientl . The majority of tabs (library, latest news and recent events, announcements of trainings, workshops, OoC timeline, reports and reviews) are available with a free subscription to allow the users to gain a better understanding of OoC and keep them informed about new scientific and technological developments. It is updated regularly by members and will continue beyond the lifetime of ORCHID through EUROoCS. Specific links to general brochures are included in the website. Moreover, the website was designed to be inviting for students looking for jobs, funding opportunities and informative newsletters, and accessing social networks, whereby EUROoCS will host different groups interested in OoC technology. Information on key publications, patents, and discoveries will thus be distributed to the dissemination target groups besides being accessible directly from the website. The EUROoCS website will evolve over time through the continuing addition of publications, latest news, event announcements, collaborative projects, and member-supplied content. Finally, by providing the opportunity to industry for exposure of their technology and by being attractive for investors and funding agencies to support the development of prototypes, the EUROoCS website will also contribute to increase innovation and competitiveness for European health-related industries and services.

The ORCHID expert community unanimously perceived the EUROoCS digital platform as a means to build a network, realize integrative programs and collaborative projects or consortia, and to find new academic/industrial partners or individuals involved in regulation or patient associations. In this respect, a reserved area, accessible to EUROoCS members, provides expert contacts, project descriptions, and mapping. This detailed information as well as the opportunity to debate specific topics through a discussion forum aim at encouraging membership and joining the community. This member-restricted area of the digital platform is expected to be a market place for OoC-stakeholders, with individuals from a wide range of backgrounds benefitting from the availability of OoC ideas and expertise, initiating specific working groups, or discussing current topics on OoC.

Building dedicated communication tools to continuously raise awareness

Having established a communication strategy, it is important to determine whether the expected impact is actually achieved. To this end, online dissemination tools (e.g., website, newsletters, social media) will be regularly monitored and some key performance indicators (number of visitors, downloads/open clicks, statistics on the impact of the newsletter, number of articles viewed, user feedback on the newsletter's content) will be periodically checked for quantitative and qualitative evaluation (Fig. 3). Qualitative evaluation will also be conducted on the basis of questionnaires following special events. Finally, the impact, strengths, and weaknesses of the dissemination strategy on target groups will be examined regularly as well as the quality of communication on OoC.

Participating in conferences and organizing training and dedicated workshops on OoC will raise awareness of the community and capture young researcher attention on OoC activities. This is essential if the full potential of OoC is to be realized. To that end, EUROoCS members are being encouraged to establish connections with press, media, politicians, general public, and schools, to act as focal points for local dissemination of information, to use connections to other academics working in related domains at local and international levels, and to generate active social media content to introduce European citizens to OoC technology as a concept. A visual identity of OoC in Europe was developed to ensure consistency and higher visibility of the OoC field. Commu-

Tab. 1: Overview of the applications and associated models discussed during the ORCHID Strategy workshop
ADME, absorption, distribution, metabolism, excretion; BBB, blood brain barrier

Context of use	Disease area	Key tissue model	End user
Disease mechanisms	Cancer	Tumor models	Biomedical researchers Clinicians Pharmaceutical industry
	Neurodegenerative diseases	Brain, BBB, neurons, retina	
	Cardiometabolic disorders	Heart, lung, liver, pancreas, vessels, adipose	
	Autoimmune diseases	Immune system, gut, pancreas, neurons, skin	
	Fibrosis	Connective tissues, lung, liver, kidney	
Drug efficacy	Cancer	All types	Industry: pharmaceutical, cosmetics Biomedical researchers
	Neurodegenerative diseases	Brain, BBB, neurons	
	Cardiometabolic disorders	Heart, lung, liver, pancreas, vessels	
	Autoimmune diseases	Immune system, gut	
	Fibrosis	Connective tissues, lung, liver, kidney	
Drug toxicity	All types	ADME pathway (liver, kidney), barrier systems (gut, lung, BBB), heart, brain, immune system	Industry: pharmaceutical, cosmetics Biomedical researchers
Personalized medicine: – Patient stratification (adverse effects, dynamics/resistance, identification of vulnerable population) – Companion diagnostics (responders, disease progression)	Cancer	All types	Pharmaceutical industry Hospitals/clinicians
	Rare diseases	All types	
	Systemic diseases	Multi-organs	
	Autoimmune diseases	Immune system, gut	

nication tools (e.g., social media, brochures, newsletters, press releases) will be adjusted to the type of information and to the specific targeted group. Establishing a proper platform for critical dialogue and dissemination, monitoring interest, and acceptance at every level are essential features of the roadmap that will determine rate of progress and ultimate outcome beyond promise.

4 Specific building blocks of the Organ-on-Chip roadmap

4.1 Application

Priority for disease mechanisms, drug efficacy and toxicity, and personalized (or precision) medicine

An important domain to which OoCs can contribute is the drug screening and development process[6], which ranges from fundamental research to personalized medicine and targets users such as biomedical researchers, (research) hospitals, and pharmaceutical industries. According to the consulted OoC experts, there are four main contexts of use:

- improving understanding of human disease mechanisms and etiology;
- predicting drug efficacy in humans;
- predicting drug toxicity in humans;
- paving the way to personalized (or precision) medicine.

The associated priority (patho)physiological areas are driven by the need for new therapeutics discovery, including emerging drug modalities (e.g., large molecules/biologicals like monoclonal antibodies, antibody-drug conjugates, protein therapeutics), especially for diseases for which few or no effective drugs are available due to poor knowledge of pathophysiological mechanisms in humans combined with a paucity of predictive disease models (see Tab. 1). Among the most cited public health priorities are cancer, neurodegenerative conditions like Alzheimer's disease, cardio/metabolic disorders, autoimmune diseases, fibrosis, and rare diseases, such as hemophilia and metabolic syndromes. Each requires its own panel of cell/tissue models that may include single- to multi-OoCs. Primary or stem cell-derived cells and tissues can be a first approach of choice, but in some cases cells will not respond to drugs or reveal disease mechanisms as expected

[6] Other relevant applications include toxicity screening of compounds for cosmetic and chemical industries and for environmental agencies, and countermeasures against chemical and biological warfare – for a comprehensive overview, see the ORCHID Vision workshop report (Mastrangeli et al., 2019).

outside a 3D environment or without biophysical stress/flo . For toxicity testing and safety assessment, there may be a strong preference for OoCs mimicking ADME pathways (absorption, distribution, metabolism, excretion) including metabolic organs (liver, kidney), barrier/digestive systems (blood-brain barrier and gut for physiological absorption), and the presence of the immune component of the disease.

OoCs also can be personalized with patient samples to mimic key aspects of a (patho)physiological state, including specific disease-related parameters. By capturing a higher level of physiological complexity from particular individuals, OoCs are predicted to be of value as companion diagnostic tools to differentiate patients that are "responders" from "non-responders" to medication, to refine doses for individual patients (exposure-response relationships by PK/PD modeling), to define combination therapies and personalized drug delivery, or evaluate disease progression, and to predict specific adverse events (patients at risk), thereby tailoring treatment strategies to improve the benefit-risk ratio. OoCs might also contribute to patient pre-stratification for clinical trials, leading to protocol optimization and supporting clinical decision-making processes. As importantly, patients often become tolerant to drugs which are then no longer effective. Identification of "back-up" drugs that have similar effects to the original but via a different pathway in the OoC model can offer an alternative in the clinic, which is then highly relevant to treatment benefit. In the future, the implementation of health-related data in OoCs (lifestyle, epigenetics) may lead to even more predictive personalized devices and to position OoCs as physical avatars for individuals or groups of individuals (e.g., of different ethnic backgrounds, gender, age).

4.2 Specification

Customizable platforms for fit-fo -purpose modular OoCs

It was generally agreed that OoCs should be conceived and proposed as robust tools tailored to fit a purpose by the end users. End users should accordingly be provided with flexible solutions ranging from ready-for-use devices to open customizable platforms. Existing ready-to-use OoCs offer a certain level of customization, which can be further extended towards models of increasing complexity via acquired laboratory experience and with customizable platforms. In this respect, the group and collective discussions of the ORCHID Strategy workshop highlighted the following technical and functional recommendations for the development of OoC models:

a) *Modularity*. It is unlikely that a single OoC device would be able to satisfy the requirements to serve all conceivable functions or applications within the reach of the OoC technology. For instance, and even though certain molecular pathways are repeatedly defective in multiple diseases (e.g., SMAD, WNT signaling), a comprehensive list of disease mechanisms is hardly feasible. Besides, the requirements may be mutually incompatible, and a single device may easily turn out to be overwhelmingly complex, economically non-viable, and ultimately not effective for potential end users. Instead, a reductionist, flexible integration approach is suggested whereby OoC devices are assembled over platforms out of sets of basic and standardized modules according to user needs. Standardized interfaces and well-defined assembly of modules are essential for the success of such a modular approach. Both technical and biological modules are considered:
   1. *Technical modules:* mechanical actuators and stimuli (forces, stresses, strains), electrical stimuli, perfusion (microfluidics, pumps, valves), reporter systems and sensors (for, e.g., oxygen, carbon dioxide, pH, glucose, metabolites, flow rates, impedance);
   2. *Biological modules ("functions"):* 3D scaffolds, cell-cell interactions, neuron/neurite outgrowth, barrier mechanisms, vascularization, air/liquid interface.

   The modular composition of OoCs within standard platforms shortcuts the issue of defining the end use of the devices *a priori*, instead leaving it open and suitable to a variety of different users and applications. This approach is envisioned to afford or be compatible with:
   − simplicity and ease of use;
   − possibility to stack levels of complexity in 4 dimensions (space + time);
   − customization and user-defined fit-fo -purpose;
   − standardization of modules (see also Section 4.4).
b) *Increased throughput/scalability* to reduce cost-per-data point and extend the range of OoC use in pre-clinical screening. Required throughput depends on applications, research questions, and drug development stage (Probst et al., 2018; see also Section 4.5).
c) *Automation* to limit errors and improve reproducibility, repeatability, and cost-effectiveness.
d) *Multi-parametric assays* to benefit from various data points in a single test system, thereby improving efficiency and limiting heterogeneity. The selected parameters should provide sufficient data to support study conclusions, allow regulatory acceptance, and they should be linked to clinical expectations to prove the added value of the technology.
e) *Use of genetically & phenotypically characterized human cells* to mimic human (patho)physiology, with eventual dedicated benchmarking (not based on animal use).
f) Sustain *long-term measurements* to evaluate (chronic effects of) compounds, perceived as preferred or complementary to short kinetic and metabolic measurements.
g) Generic and standardized *open technology platforms*, both in hardware and software, for full public availability and compatibility across platforms (see Section 4.4).

Modular as well as flexible, ready-to-use OoCs align with the belief that the ultimate purpose of the devices may only emerge from the end users themselves once the devices are in their hands.

4.3 Qualification

Qualification processes for context of use need independent testing centers

The ORCHID Vision workshop highlighted the need to focus on the qualification or characterization of the OoCs rather than on their validation *per se*. The latter was considered by most experts neither an appropriate nor a meaningful concept for highly complex models such as OoCs, because it implies the existence of an accepted standard or reference to measure validity. The ORCHID Strategy workshop confirmed that while regulatory acceptance

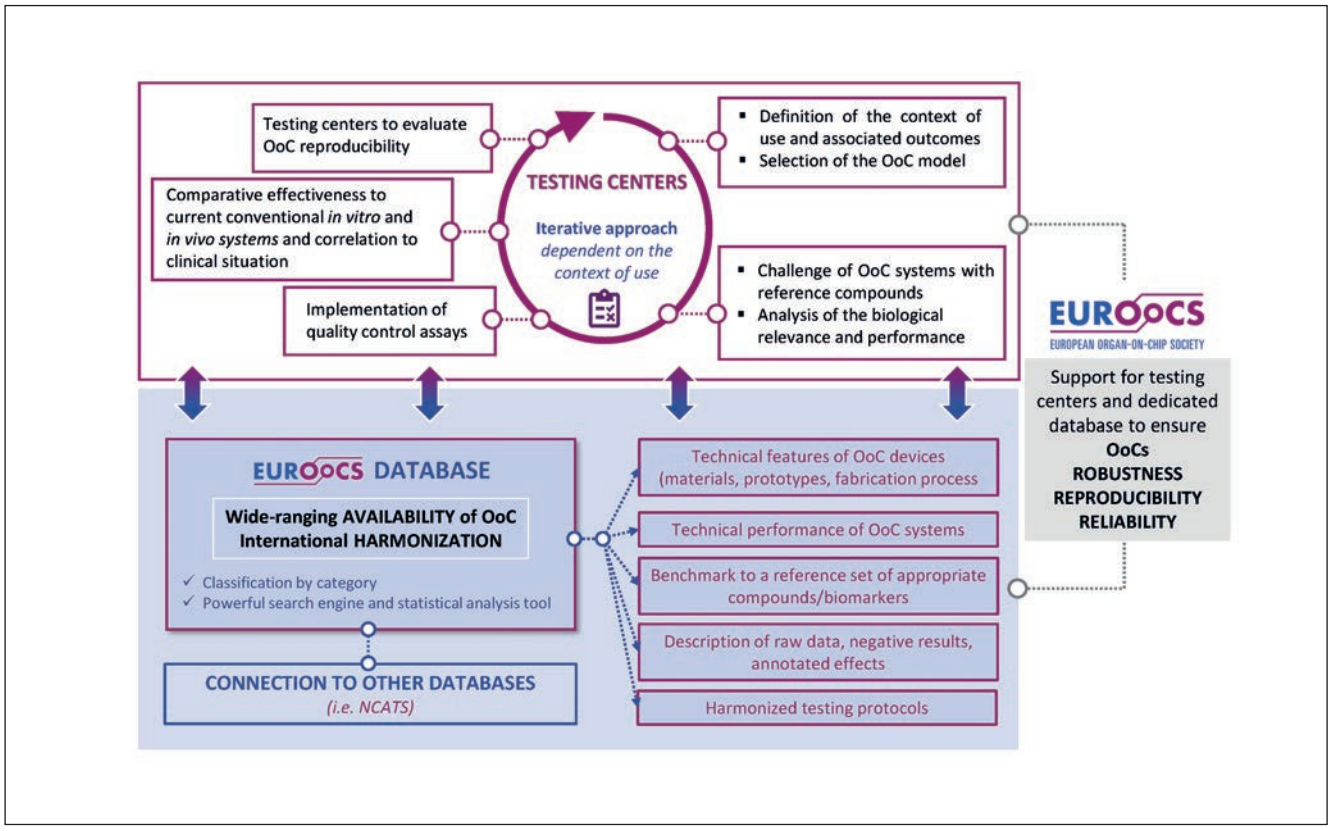

Fig. 4: Synopsis of OoC qualification processes and interfacing with a centralized database

is beneficial for the commercialization of OoC devices, this acceptance should not hinder the development process. Indeed, regulatory agencies should be considered key players, involved in the early stages of OoC development along with end users, in order to better understand the potential of the technology and its applications. Industry needs confidence in the robustness of the data retrieved through the devices, whereas regulators typically require a case-by-case analysis. Therefore, while considered necessary, the qualification of a device does not necessarily prelude to its regulatory acceptance nor to user adoption.

For drug screening and development, OoCs should recapitulate human tissue physiology but also disease-related parameters to be used as predictive models for assessing safety and efficacy of promising therapies that are preferably better than current cell and animal models. The characterization and qualification of such devices should be based on a generic study design including the following key aspects:

a) Defining the context of use and its associated outcomes to select the most relevant OoC model;
b) Challenging OoC systems with reference compounds insofar as they are classified regarding context of use and specific parameters. This aspect will help determine the biological relevance of the devices and will allow qualification of their performance. It will by definition rely on known outcomes of animal experiments and preferably their discrepancies with clinical/patient data or safety/feasibility in phase I trials on healthy human individuals.
c) Implementing quality control assays ensuring the functional characterization of cell cultures to fit with human (patho)physiological responses but also expressed in the form of material qualification (drug-biomaterial interaction), manufacturability, and availability of devices.
d) Evaluating effectiveness of OoC compared to current *in vivo* profiles, through the analysis of the corresponding data derived from conventional drug development models, and correlation with clinical data or manifestations.
e) Performing intra- and inter-laboratory assays (ring trials) to assess the reproducibility and accuracy of OoC devices as well as monitoring technological performances (stability and robustness).

These last aspects should be considered as iterative approaches, supported by ongoing pharmaceutical projects to bring added value, aiming at investigating the correlation between OoCs and *in vivo* data, if relevant, and to establish the critical link to clinical expectations. Ideally, all qualification studies should be performed by a third party, as proposed by the testing center initiatives in the US funded by NCATS, to ensure an independent analytical characterization (Fig. 4).

Towards a centralized database information sharing and promoting OoC development

To achieve optimal results from the qualification studies, a key challenge is to establish an evolutive database, clustering all available data on a reference set of the most appropriate com-

pounds and biomarkers, together with the results on the performance and accuracy of the specific OoC systems under test and the context of use for the target tissue(s). The aim of this centralized and publicly accessible database would be to provide the scientific community with in-depth information (including raw data and negative results) on well-characterized pharmacological and toxic compounds to demonstrate *in vivo*-like responses in OoC devices and to go beyond a simple and linear annotation of the compounds' effects. Providing relative data from reference compounds/biomarkers and allowing the community (including stakeholders and regulators) to use it wisely, may help both developers and end users to challenge OoC systems and may influence the decision-making process.

However, the quest for qualification of OoC devices entails abundant human data sets being available as well as multi-parameter readouts without bias (achievable via proper automated statistical data analysis). In addition, a relevant list of test compounds/biomarkers is not readily available but may be in the making thanks to several independent initiatives (e.g., the NIH in the US and the Crack it! Program in the UK). Beyond having a list of compounds for which the outcome and mechanisms of action are agreed, the compounds may not necessarily be available to academic research groups since they may be proprietary or may no longer be synthesized. A solution would be to work closely with structures like the IQ Consortium[7], a not-for-profit organization of pharmaceutical and biotechnology companies, which is compiling a list of reference compounds that may be shared for qualification purposes. NCATS is also currently working with well-known pharmaceutical companies like AstraZeneca, GSK, Pfize , Roche and Sanofi, and has for that purpose already established a material transfer agreement to ensure that compounds/biomarkers provided for characterization are cleared for inclusion in academic work (Ewart et al., 2017). Alternatively, medicinal chemists may be contacted to synthesize specific compounds or variants of those.

EUROoCs may play a catalyzing role in collecting the information with the necessary infrastructure, data management and statistical capabilities to ensure an extended dissemination among the OoC community and beyond (Fig. 4). This publicly accessible database could also be a promising tool to promote OoC adoption supported by early engagement of academic, industrial, and regulatory players. Finally, the coordination of a EUROoCS-supported database with other international existing ones should reinforce multi-partner task forces and contribute to international harmonization.

4.4 Standardization

A task for the OoC community that should be internationally harmonized

Standardization is an overloaded concept with multiple interpretations across different sectors and markets. Standardization of OoCs is very challenging since OoC technology is inherently interdisciplinary. In recent history, technological standards have usually arisen either from dominant commercial players or from collective entities such as regulatory authorities or roadmaps jointly established among field competitors. While the former appear to be the current case in the US, where several larger groups are trying to define OoC standards, standardization emerging from a collective dialogue among developers and end users and from ensuing cross-constraints is ultimately expected to prevail. Successful examples of standardizations in electronics (e.g., data communication protocols, interfaces, and peripheral cross-compatibility) can be capitalized as important learning experiences. In particular, lack of standardization for lab-on-chip approaches may be the reason for the problems that technology currently has in getting into the market.

To avoid this risk, OoC standardization should be addressed very early in development to enhance the prospect of being competitive with its alternatives. On the other hand, standardization cannot be promoted by most of the current stakeholders, as these are mostly small (biotech or start-up) companies without sufficient financial flexibility to support a standardization strategy. OoC standardization is therefore considered a task for the OoC community. The role of the community is in fact central, because the purpose of standards is foremost to enable the OoC community to cooperate towards developing prototypes. Community-driven standardization may also ensure that standardization addresses sufficiently common issues, benefitting a large set of users and thus becoming a means to accelerate innovation. EUROoCS can play an important role in bringing developers, stakeholders, regulators, and end users together into a community, as well as in serving as a collective expert group to advise on OoC standards, protocols, methods, and guidelines, similarly to prior experiences in, e.g., stem cell research and toxicology, whereby protocols were defined by panels of experts.

Different standardization layers should be identifie

Layers of standardization can be envisioned, ranging across multiple levels of abstraction and user experience. They include: materials, dimensions, cell input and content, perfusion media, flow rates, interconnections and interfaces, optical access, platforms, cross-compatibility among modules, back-compatibility with existing substrate standards (e.g., multi-well plates, microscope slides, multi-electrode arrays) and laboratory instrumentation, cell sources and lines, cell phenotypic and genotypic characterization and protocols for cell differentiation, cell handling, use of devices, and quality control. Additional layers should be further considered. Standards for commercialization could eventually emerge from research prototypes, though this should not be the primary aim of the community. Commercial standardization should be internationally harmonized, avoiding competing groups particularly between the US and Europe.

Towards standardization: open technology platforms for OoC

One approach that experts recommended to encourage the OoC community to converge towards standardization was the realization of open technology platforms. These can be seen as shared technology platforms created to gather knowledge and expertise into a centralized database, in which potential users could contribute by developing and sharing building blocks of modular sys-

[7] https://iqconsortium.org/

tems to enable customized solutions for specific applications. The open technology platform concept is in line with the modular approach suggested for the development of OoCs. It will stimulate further innovation rather than restrain it. These platforms would reduce barriers to expensive manufacturing of devices, because they could generate the production volumes needed for sustained technology development. The freedom to develop demonstrators in parallel may, moreover, lead to quick learning cycles and broad uptake of successful innovations in the community. However, the implementation of an open technology platform raises crucial questions concerning the co-existence of, on the one hand, open interfaces, open standards, and the freedom to exploit open source content together with, on the other, patenting and licensing of intellectual property as sources of commercial drive and market penetration. These and similar issues related to the co-existence of private profit and public availability are well-known from prior standardization attempts in other fields, and they evidently represent an important aspect of the proposed roadmap that needs to be resolved.

Further information on the benefits and pitfalls of standardization in the field of OoC devices and systems is described in the *ORCHID whitepaper on standardization*. The whitepaper was written by ORCHID partners in the context of the ORCHID project in addition to the Strategy workshop, and is provided in Appendix A[2]. The whitepaper in particular identifies ongoing standardization efforts which address certain aspects of technology and operational processes in the OoC field.

4.5 Production and upscaling

Industrialization requires choices in early development of OoC devices

OoC production perspectives will be determined by the type and scale of use of OoCs – whether for, e.g., drug screening or replacement of animal tests or personalized medicine – such that a 96-well plate format or similar may need to be developed for applications requiring high throughput, whereas in other cases a 2-well plate or single-chip format may be sufficient if examining, for example, efficac . Clear and standard guidelines for quality control of technology and biology should be introduced in all cases to ensure and maintain robustness. The type of use will also determine the allocation of resources. In this respect, drug development prioritizes rate of success and time-to-market, and hence time-saving rather than cost-saving.

It is important to remark that upscaling of OoCs inherently involves both technological and biological components. This respectively implies mass production of chips or microfluidic devices and generation of large batches of differentiated cells that are quality-controlled prior to use in OoCs. As demonstrated by the success of microelectronics, high volume production of chips typically coincides with decreased manufacturing costs and variability and leads to highly reproducible devices. However, there is a caveat here. On the one hand, device-level reproducibility would be required, especially in early stage OoC development and qualification (see Section 4.3), since the inherently variable biology introduces another potential layer of variability and cannot otherwise be properly assessed. On the other hand, setting up mass production of devices requires large investments, which are not likely for non-qualified devices. Solving this issue might require specific, public-private funding calls.

Depending on applications (see Tab. 1), at least three different upscaling strategies could be envisioned:

1) *Drug efficacy and toxicity* in pharmaceutical industry. In this case, the SBS well-plate format will likely be the preferred and target format, with highly characterized, robust, and reproducible OoC enabling relative comparison of hundreds of drugs (Probst et al., 2018);
2) *Personalized medicine*, possibly in a hospital setting or dedicated SMEs. This will entail robust and reproducible OoCs with (patient-derived or genetically-modified) disease bearing cells, and upscaling to test tens (i.e., 10 to 50) of potential drugs and find the right concentration of the right drug for specific patients or disease states;
3) In the longer term, *clinical trials*. To date, there are no clinical trials on, e.g., children, pregnant women, or specific or unique ethnic groups. OoC could enable a better representation of human phenotypic diversity in clinical trials. The upscaling requirement to perform clinical-trials-on-chip by contract research organizations will be dependent on the trial.

An industrial-level fabrication volume puts manufacturing constraints on the design, dimension and structural materials of the devices. These choices should be considered as early as possible in device development along with back-compatibility with established laboratory tools and cross-compatibility among platforms. At the same time, the use of standard cell lines might not match such extended device requests, though standard cell handling protocols could still be helpful, and banks hosting cells for different population subgroups might need to be established.

4.6 Adoption

Adoption of OoC technology requires well-documented showcases

The OoC technology may be accepted and thus adopted if it provides simpler, cheaper, and more relevant alternatives to established models (even those based on multi-cell type cultures) while reproducing at least the same results supported by convincing and reliable metrics, or if it affords models for which no alternative approaches currently exist (such as rare diseases in which microfluidics is required to reveal the phenotype; see Mastrangeli et al., 2019). In addition, OoC adoption implies the satisfaction of many other conditions, including ease of use, back-compatibility with established laboratory processes, cross-laboratory reliability, along with a supporting and organized user's community (Fig. 5).

In this respect, experts deemed the identification and stratific - tion of end users, stakeholders, and sectors as critical. It should be part of a primary action conducted by dedicated methodologies and teams, and a prerequisite to organize a global community centered around open technology and allowing a smooth transfer of expertise among disciplines and domains (e.g., including regulatory bodies). To build confidence in the value of OoCs and facilitate engagement of all players, structuring of (a) neutral organization(s) capable of testing and qualifying devices has been proposed, in line with OECD guidance. The adoption process will emerge from collective end users of OoCs and will rely on

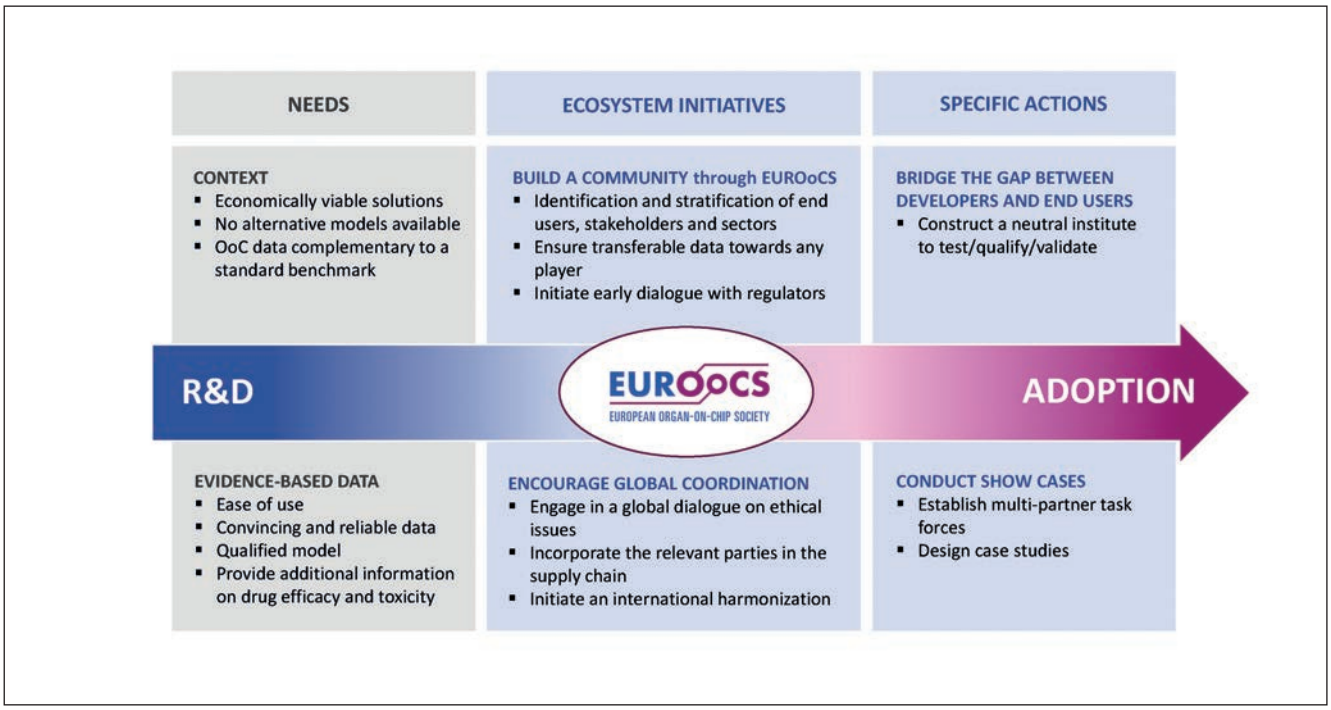

Fig. 5: Overview of the context needs, initiatives and specific actions to promote OoC adoption

the data obtained with OoCs included in a regulatory approval and perceived by regulatory bodies as complementary data to the standard benchmark. The applicability of these guidelines to rapidly developing technologies like OoCs remains a key challenge. A convincing way to circumvent these issues would be to encourage multi-partner task forces to conduct showcases capable of fostering end user adoption. Such showcases may be represented by case studies, such as the Crack it! challenges, could be non-optimized or finalized, and should involve end users along with regulators and developers to start and sustain a fruitful and timely dialogue. As pointed out by the regulatory experts, the final decision will be up to developers, since currently there are no restrictions or requirements from regulatory bodies for the use of specific cells.

Finally, community organization and subsequent adoption of OoCs by end users will need sustained dialogue and collaboration to move across the limitations of sector-specific cultures and languages: EUROoCS is expected to play a leading and catalyzing role in that respect.

5 Discussion and recommendations

The ORCHID Strategy workshop converged on the proposition of the roadmap for OoC development represented in Figure 6. The roadmap emphasizes a dual path, involving proprietary, ready-to-use devices and open technology platforms running in parallel and interacting along the way. OoCs are expected to serve three major markets: 1) industry (mainly pharma, cosmetics, and chemicals), 2) hospitals, and 3) academic research. Industry and hospitals might mostly require ready-to-use devices, whereas the latter would strongly benefit from open technology platforms. As described in the previous sections, to move forward from the current status to applications of OoCs, the roadmap is envisioned as making use of a set of main building blocks. Some building blocks are specific to the present state of the art, whereas others correspond to common development stages for which prior experience in collateral roadmaps can be capitalized. Along with the concept of the OoC roadmap, the experts agreed on the catalyzing role that EUROoCS could and should play in the deployment and actualization of each building block.

It should be noted that the entries in Table 1 are not exhaustive but are rather priority lists. This holds in particular for known disease mechanisms, for which a complete list is hardly conceivable, and for OoC applications, whereby the long-term list may even turn out to be different from the one proposed, depending on the future needs of actual end users and how their drug discovery priorities change. Whereas the application domains were chosen mainly to guide the discussions, the roadmap and its building blocks are expected to apply, irrespective of the directed *versus* emergent nature of the final applications.

Alongside flexible, ready-to-use devices, the modular approach to OoCs based on customizable platforms was recommended as a solution to enable both user-defined and specific fit-fo -purpose applications and at the same time to align or facilitate qualific - tion, standardization, and large-scale production of OoCs. Device qualification, *per se* not corresponding to device adoption or regulation, should pass through independent testing centers, preferably established in Europe following the US lead. A single, worldwide database, eventually emerging from the harmonization and interconnection of local databases, would be ideal to collect and share all related data, following the example of shared compound

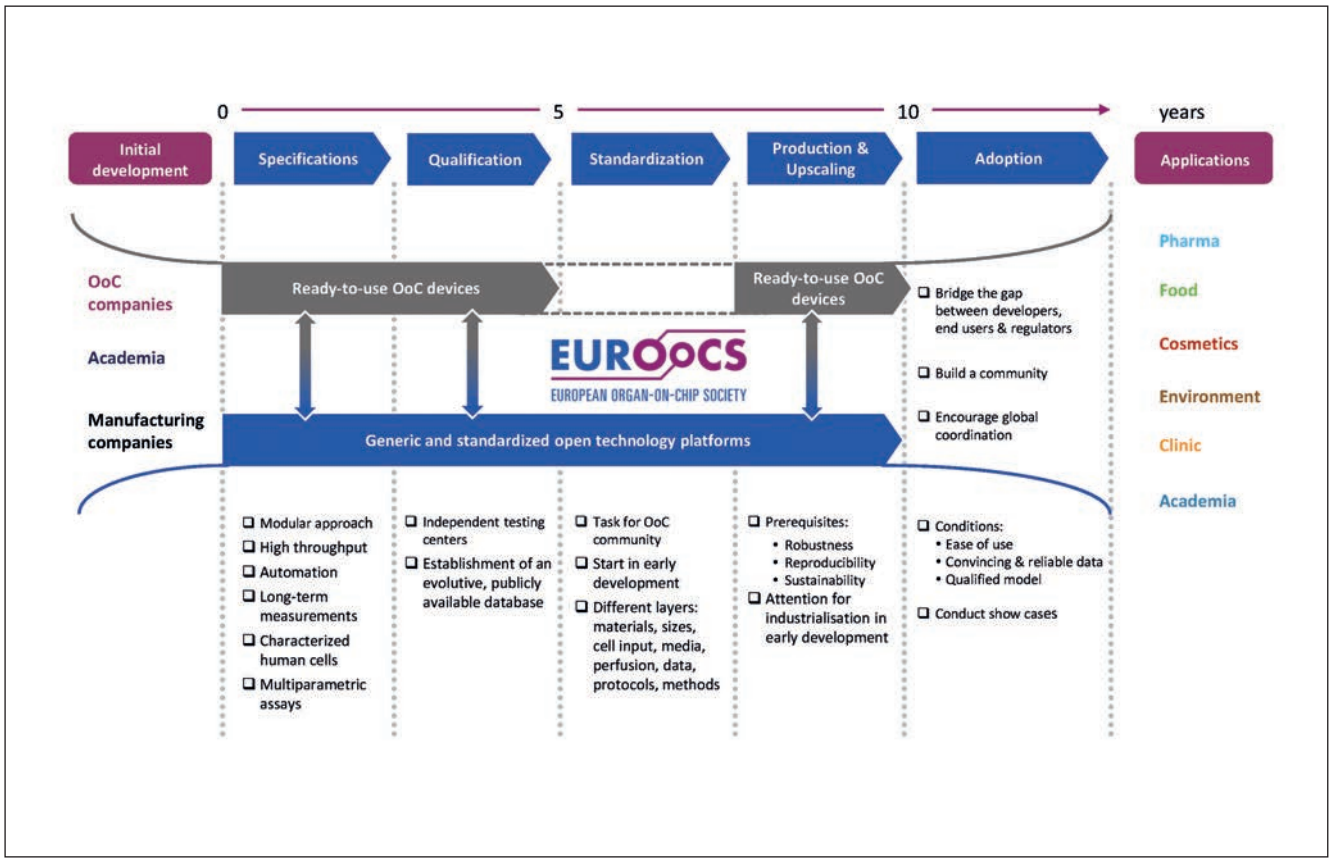

Fig. 6: The ORCHID roadmap for OoC development

lists of, e.g., the IQ consortium. Standardization should address multiple levels of OoC technology and should start by forming task forces of expert groups and learning from existing standards (see Appendix A2). It is worth emphasizing once again the advantages of open technology platforms, along with the need to manage the coexistence of, at times, divergent needs related to intellectual property and technology sharing. Successful handling of these aspects additionally highlights the key role of a large, open, and interconnected OoC community, not least for its role in innovation. In this respect, while supporting the roadmap, the experts at the workshop at the same time acknowledged the possible dualism and coexistence of a more directed and linear approach to OoC development, as indeed embodied in a roadmap, and of an emergent and more non-linear approach building upon crowdsourcing and user-generated targets and solutions. Both approaches have earlier examples in recent history, and can certainly interact for mutual benefit. Irrespectively, it is clear that to achieve the envisaged long-term goals of globally improved healthcare and personalized medicine, OoCs will need to be suitable for large-scale production, an aspect that should consider the choice of biological and synthetic materials and of manufacturing technologies from early stages of development. Along this line, compatibility of the devices with established laboratory practice and standards as well as successful showcases of complete OoC platforms and applications should favor OoC penetration and speed up worldwide adoption.

Finally, the roadmap that this report has introduced – and of which the final structure will be released in October 2019 – necessarily addresses related ethical questions, cautiously optimistic communicational strategies, and information of laypeople as well as in-depth training and education of the next generation of experts. For all of the above tasks, EUROoCS, supported by its digital platform, publications, and regular meetings, should be ready to play a central role.

Recommendations

1. Focus on selected pathophysiological areas in the context of OoC models for disease mechanisms, drug efficacy and toxicity, and personalized medicine: cancer, neurodegenerative diseases, cardio-metabolic disorders, autoimmune diseases, fibrosis, and rare diseases.
2. Provide end users with customizable platforms for fit for-purpose OoC models.
3. Explore a modular approach for the OoC models, with technical and biological modules that can be assembled within standard open technology platforms.
4. Converge towards standardization of components, methods, and data via collective dialogue among experts, facilitated by EUROoCS, and starting very early in the development.

5. Establish independent testing centers for the qualific - tion and characterization of OoC models for a specific context of use.
6. Develop a publicly accessible evolutive database, supported by EUROoCS, that clusters all available data from reference compounds and OoC test data, and interfaces with other databases to contribute to international harmonization.
7. Resolve issues related to the co-existence of private profit and public availability of technology in the OoC field
8. Address upscaling requirements and constraints on design, dimension, and structural materials as early as possible in device development to make the right choices for industrial-level fabrication.
9. Encourage multi-partner task forces to come up with well-documented showcases, based on case studies, to stimulate adoption of the OoC technology. EUROoCs should catalyze this process.
10. Engage as EUROoCS in a global dialogue on ethical issues, and address them in a timely manner as the technology progresses.
11. Develop tailored training programs for the next generation OoC researchers.
12. Build the OoC community further and bridge the gap between end users, developers, and regulators with the support of EUROoCS.
13. Stimulate information, communication, and interaction via the digital platform and targeted meetings of EUROoCS and measure the impact on OoC ecosystem development.
14. Plan a careful dissemination strategy for the general public based on realistic expectations and ambitions.

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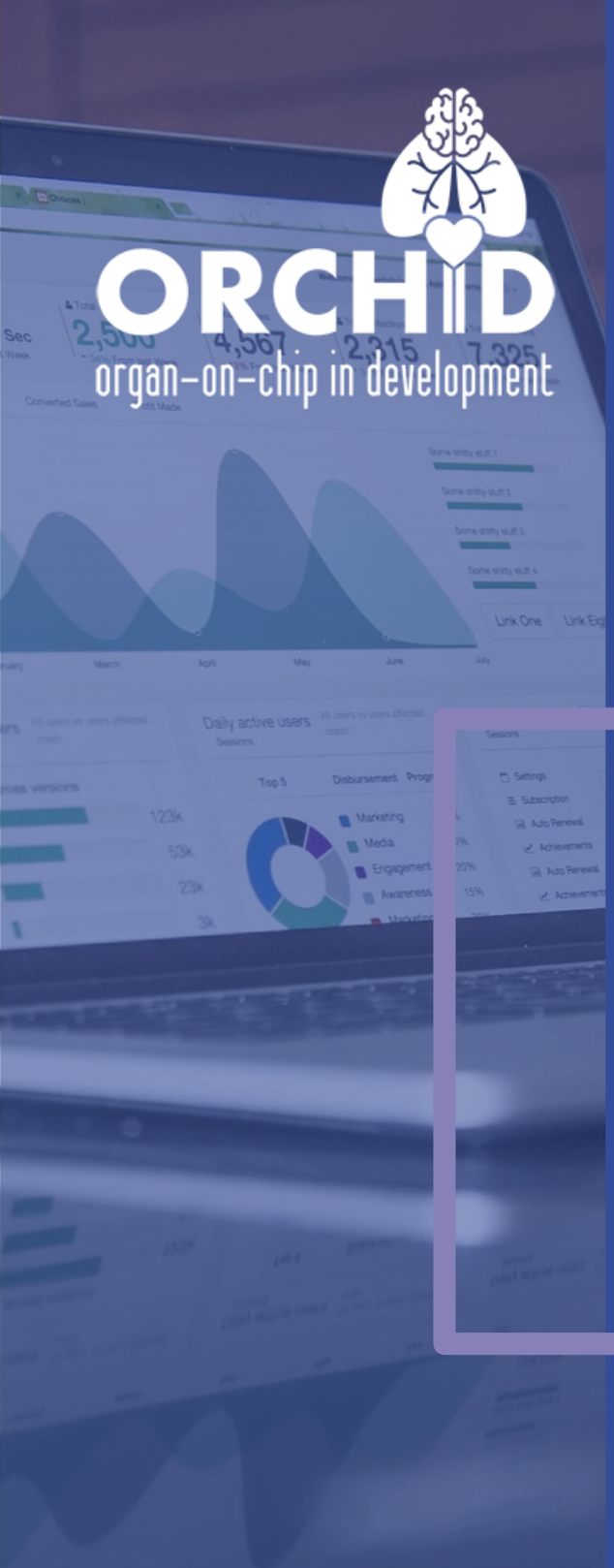

ORCHID ACTIVITIES

ORCHID Dissemination activities

#	Partner	date yy-mm-dd	end date yy-mm-dd	category as called in ECAS	Explaination	Estimated numbers of persons reached								
						Scientific	Industry	Civil Society	General Public	Policy Makers	Media	Investors	Customers	Other
1	P2 - hDMT	05-10-2017	05-10-2017	Participation to a Workshop	Oral presentation at first EMA workshop on non-animal approaches in support of medicinal product development: challenges and opportunities for use of micro-physiological systems, London (UK). https://www.ema.europa.eu/en/events/first-ema-workshop-non-animal-approaches-support-medicinal-product-development-challenges	50								
2	P1 - LUMC	05-10-2017	05-10-2017	Participation to a Workshop	Oral presentation "MicroPhysiological Systems"- EMA London UK	50								
3	P6 - UNIZAR	05-10-2017	07-10-2017	Participation to a Conference	Presentation at 3rd Serbian Association For Cancer Research Congress, Belgrade (Serbia)	100	5			2				
4	P6 - UNIZAR	09-10-2017	11-10-2017	Participation to a Conference	Oral presentation Defence is the Best Attack: Immuno-Oncology Breakthroughs	200	10							
5	P1 - LUMC	28-10-2017		Participation to a Conference	National HHTpatient day - Doorn, the Netherlands – lecture				100					
6	P5 - IMEC	30-10-2017	30-10-2017	Press release	Imec has joined ORCHID, a European initiative that will establish a European infrastructure to enable coordinated development, production and implementation of Organs-on-Chips by a consortium of academic and private partners.									
7	P6 - UNIZAR	30-10-2017	30-10-2017	Press release	Investigadores de la Universidad de Zaragoza forman parte de un proyecto europeo para el desarrollo de modelos de investigación que nos acerquen a la medicina personalizada y a la farmacología de seguridad, Zaragoza (Spain)									
8	P4 - CEA	30-10-2017	30-10-2017	Press release	Organ-on-chip technology will revolutionize healthcare, especially in regenerative medicine and medication. It is already providing new drug research platforms, while offering alternatives to conventional animal testing, and will soon deliver applications in personalized medicine and safety pharmacology. Grenoble (France)									
9	P3 - Fraunhofer	30-10-2017	30-10-2017	Press release	Fraunhofer IGB joins international consortium to advance organ-on-a-chip technology in Europe, Sttugart (Germany)									
10	P1 - LUMC	30-10-2017	30-10-2017	Press release	Dutch-researchers-lead-consortium-on-organ-on-chip-development-in-europe, Leiden (the Netherlands)									
11	P2 - hDMT	30-10-2017	30-10-2017	Press release	Dutch-researchers-lead-consortium-on-organ-on-chip-development-in-europe, Eindhoven (the Netherlands)									
12	P1 - LUMC	02-11-2017	03-11-2017	Participation to a Conference	"Scalability of iPSC Technology for future drug discovery & therapy", EBiSC Conference, Berlin, Germany - keynote lecture. https://www.ebisc.org/documentation/videos.php	60								
13	P6 - UNIZAR	03-11-2017	03-11-2017	Participation to an Event other than a Conference or a Workshop	Conference for PhD students of the University of Navarra, Pamplona (Spain)	15								
14	P6 - UNIZAR	10-11-2017	10-11-2017	Organisation of a Workshop	Hands-on training for the IMIBIC researchers in collaboration with the company BEONCHIP, Cordoba (Spain)	10								

15	P1 - LUMC	11-11-2017	14-11-2017	Participation to a Conference	"Cardiomyocytes from human pluripotent stem cells in modelling disease and heart repair", Cell Press LabLinks event on Stem Cells in Disease Modeling and Therapeutics, Tokyo, japan - keynote lecture. http://info.cell.com/lablinks-2017-stem-cells-in-disease-modeling-and-therapeutics	150								
16	P2 - hDMT	14-11-2017	15-11-2017	Participation to a Conference	Presentation at Design of Medical Devices Europe Conference, Eindhoven (The Netherlands)	60	40							
17	P6 - UNIZAR	21-11-2017	21-11-2017	Participation to an Event other than a Conference or a Workshop	Presentation at Seminar: Cell and Molecular Biology Master of the University of Zaragoza, Zaragoza (Spain)	5			25					
18	P1 - LUMC	22-11-2017		Participation to a Conference	"Bio Art & Science", AKI & DesignLab workshop and a symposium, Utwente, Enschede the Netherlands - prentation and leading discussion. https://www.utwente.nl/en/events/!/2017/11/229409/science-frictions	25								
19	P6 - UNIZAR	23-11-2017	23-11-2017	Participation in activities organized jointly with other H2020 projects	Presentation at ERA CAREER DAY (Zaragoza) in the frame of the EUESCADA project, Zaragoza (Spain). http://eventos.unizar.es/11161/section/8247/era-career-day.-oportunidades-profesionales-en-la-carrera-investigadora-del-siglo-xxi.html	20	5		100	5				
20	P1 - LUMC	24-11-2017		Other	"Stem cells and treating Parkinson's disease", Parkinson TV, Nijmegen, the Netherlands - presentation. http://www.parkinsontv.nl/	1000			1000					
21	P6 - UNIZAR	24-11-2017	24-11-2017	Participation to an Event other than a Conference or a Workshop	Dissemination to the general public "Science in the bars", Zaragoza (Spain)	20			40		1			
22	P4 - CEA	02-12-2017	06-12-2017	Participation to a Conference	Oral presentation at IEEE International Electron Devices Meeting (IEDM), San Francisco (USA). https://ieee-iedm.org/2017/									
23	P3 - Fraunhofer	12-12-2017	12-12-2017	Participation to a Conference	Presentation at the International MicroNanoConference, Amsterdam, The Netherlands	100	20							
24	P6 - UNIZAR	16-01-2018	16-01-2018	Participation to a Workshop	Presentation at 1st Workshop on NanoOncology, Zaragoza (Spain)	30								
25	P4 - CEA	19-01-2018		Exhibition	Grenoble 2018 Les midis Minatech « les organes sur puces ; une brève histoire de l'avenir des biopuces » http://midis-minatec.inviteo.fr/index.php?onglet=1&embedded=1									
26	P6 - UNIZAR	22-01-2018	22-01-2018	Other	Visit of the IES "El Salvador" to our lab, Zaragoza (Spain)				40					
27	P3 - Fraunhofer	24-01-2018	24-01-2018	Participation to a Conference	Presentation at the 3D Cell Models Congress (Berlin, Germany).https://3dcellmodelscongress.com/events/3d-cell-models-congress#agenda	20	10			5				
28	P3 - Fraunhofer	15-02-2018	15-02-2018	Participation to a Conference	Presentation at the Oslo Life Science 2018 congress (Norway)	50	20		50		5			
29	P2 - hDMT	26-02-2018	26-02-2018	Participation to a Conference	Visit JRC Ispra. Ispra (Italy). https://ec.europa.eu/jrc/en/about/jrc-site/ispra					50				
30	P6 - UNIZAR	17-03-2018	17-03-2018	Participation to a Workshop	Presentation at Tumor Immunology and Cancer Immunotherapy Course, Zaragoza (Spain)	25								
31	P1 - LUMC	17-03-2018		Participation to a Conference	"Pharmacology Futures 2018", Royal society of Edinburgh meeting, Edingburgh UK – presentation.https://www.rse.org.uk/event/itmat-in-edinburgh-pharmacology-futures-2018/	100								
32	P3 - Fraunhofer	19-03-2018	19-03-2018	Participation to a Conference	Presentation at the ENDO 2018 congress (US).https://www.endocrine.org/endo-2018	250	20			10				

33	P1 - LUMC	25-03-2018	30-03-2018	Participation to a Conference	"A Decade of Progress and Beyond", 2018 Keystone Symposia on iPSCs, Olympic valley, US – presentation.https://www.keystonesymposia.org/index.cfm?e=Web.Meeting.Summary&meetingid=1533&subTab=summary	220								
34	P1 - LUMC	27-03-2018	30-03-2018	Participation to a Conference	"The Stem Cell Niche - Development and Disease" conference", Stem Cell meeting, Copenhagen, Denmark - chair session and presentation.http://cph-bioscience.com/en/events/stem-cell-niche-2018	200								
35	P3 - Fraunhofer	28-03-2018	28-03-2018	Participation to a Conference	Presentation at the Keystone meeting iPSCs: A Decade of Progress and Beyond,Olympic Valley, California (USA).https://www.keystonesymposia.org/index.cfm?e=Web.Meeting.Summary&meetingid=1533&subTab=summary	200	10			10				
36	P1 - LUMC	09-04-2018	13-04-2018	Participation to a Conference	"Organs- and Tissues-on-Chips", Keystone Symposia, Big Sky, Montana, US – presentation.https://www.keystonesymposia.org/index.cfm?e=Web.Meeting.Summary&meetingid=1514&subTab=summary	250								
37	P3 - Fraunhofer	12-04-2018	12-04-2018	Participation to a Conference	Presentation at the Keystone meeting Organs- and Tissues-on-Chips, Big Sky, Montana (USA) - *Fraunhofer IGB/hDMT*	200	10			10				
38	P7 - TUD	20-04-2018		Participation to a Conference	Kick-off Strategic Governing group Digital Health & Patient-Centric Evidence Generation, IMI joint undertaking, Paris, invited speaker 20-04-2018	40								
39	P6 - UNIZAR	03-05-2018	03-05-2018	Other	Visit of the primary school "CEP Miraflores" during their research week, Zaragoza (Spain)				75					
40	P6 - UNIZAR	15-05-2018	15-05-2018	Pitch Event	Presentation at Pint of Science, Zaragoza (Spain).https://pintofscience.es/event/erase-una-vez-el-cuerpo-humano	10			50					
41	P1 - LUMC	17-05-2018	17-05-2018	Participation to a Conference	Human pluripotent stem cell models for future drug discovery and disease modelling. British Farmacological Society, invited speake, Christimne Mummery									
42	P2 – hDMT	23-05-2018	23-05-2018	Organisation of a Workshop	Presentations and discussions at ORCHID Vision Workshop, Stuttgart (Germany).https://h2020-orchid.eu/orchid-vision-workshop-in-stuttgar/									
43	P2 - hDMT	24-05-2018	25-05-2018	Participation to a Conference	Presentation and poster at EUROoC conference, Stuttgart (Germany).https://cbmsociety.org/conferences/eurooc/	120								
44	P1 - LUMC	27-05-2018	31-05-2018	Participation to a Conference	"The Stem Cell Niche - Development and Disease" conference", Stem Cell meeting, Copenhagen, Denmark - chair session and presentation.http://cph-bioscience.com/en/events/stem-cell-niche-2018	200								
45	P2 - hDMT	28-05-2018	30-05-2018	Participation to a Conference	Presentations at ETPN conference 2018, Berlin (Germany)	50								
46	P6 - UNIZAR	29-05-2018	29-05-2018	Other	Visit of the IES "Bajo Aragón" to our lab, Zaragoza (Spain)				45					
47	P1 - LUMC	04-06-2018	05-06-2018	Participation to a Conference	"Cardiovascular derivatives of human pluripotent stem cells: challenges in next generation disease modelling", Stanford Cardiovascular Institute meeting, Stanford University, US - invited speaker. http://med.stanford.edu/cvi/mission/frontiers-in-cv-science.html	200								
48	P3 - Fraunhofer	05-06-2018	05-06-2018	Participation to a Conference	Oral presentation at Selectbio Organ-on-a-Chip & Tissue-on-a-Chip EUROPE 2018, Rotterdam (The Netherlands).https://selectbiosciences.com/conferences/Agenda.aspx?conf=OOACEU2018	70	70			10				
49	P2 - hDMT	05-06-2018	05-06-2018	Participation to a Conference	Presentation at PDA Europe Conference on ATMP's, Amsterdam.https://www.hdmt.technology/event/8114/PDA-Europe-Conference-on-Advanced-Therapy-Medicinal-Products-ATMPs-	30				5				
50	P3 - Fraunhofer	06-06-2018	06-06-2018	Participation to a Conference	Oral presentation at DECHEMA 3D Cell Culture, Freiburg (Germany).https://dechema.de/en/3DCC2018_Programme.html	80	30			5				

51	P1 - LUMC	06-06-2018		Participation to an Event other than a Conference or a Workshop	"Cardiovascular diseases and drugs: human pluripotent stem cell models moving forward", Distinguished Speaker Seminar Series, Los Angeles - invited speaker.https://keck.usc.edu/events/27591/usc-stem-cell-seminar-christine-mummery-leiden-university-the-netherlands	150								
52	P6 - UNIZAR	07-06-2018	07-06-2018	Participation to a Conference	Presentation at SINO-SPAIN Biomedical and Pharmaceutical Conference, Zaragoza (Spain)	120	70							
53	P2 - hDMT	07-06-2018	07-06-2018	Participation to an Event other than a Conference or a Workshop	Presentation at UMCG Kick-off meeting, Groningen, the Netherlands	100								
54	P1 - LUMC	07-06-2018	08-06-2018	Participation to an Event other than a Conference or a Workshop	"Complex multicellular cardiovascular disease models based on pluripotent stem cells", University of Minnesota meeting, Minneaplois, US - invited speaker	100								
55	P4 - CEA	11-06-2018	11-06-2018	Other	Webinar 2018 Cell Press 3D Cell Culture Systems for Personalized Medicine.https://www.workcast.com/register?cpak=5643272354603939&referrer=web inprogress									
56	P1 - LUMC	18-06-2018	24-06-2018	Participation to a Conference	"Cardiac microtissues from hPSC in modelling cardiovascular disease", ISSCR annual meeting 2018, Melbourne AUS – presentation.https://www.eventscribe.com/2018/ISSCR/biography.asp?h=Browse%20By%20Speakers&bcfo=P|G|PO|IS|FS	3000								
57	P2 - hDMT	19-06-2018	19-06-2018	Participation to an Event other than a Conference or a Workshop	Presentation at Strategic meeting public-private partnerships (Topsector LSH), Utrecht (the Netherlands)	20	10			10				
58	P2 - hDMT	25-06-2018	25-06-2018	Participation to an Event other than a Conference or a Workshop	Informative meeting members Lower Chamber and Health Holland, Utrecht (the Netherlands)					5				
59	P6 - UNIZAR	26-06-2018	26-06-2018	Participation to an Event other than a Conference or a Workshop	Presentation at Seminar: Instituto Regional de Investigación Científica Aplicada (IRICA), Cuidad Real (Spain)	50								
60	P4 - CEA	27-06-2018	28-06-2018	Organisation of a Workshop	Bordeaux 2018 2nd Workshop « BioFabrication & Cancer » Human 3D models & Biological Avatars in Oncology. http://www.canceropole-gso.org/download/fichiers/3999/BioFabrication-2018-PGM.pdf									
61	P2 - hDMT	28-06-2018	28-06-2018	Participation to an Event other than a Conference or a Workshop	Presentation at Health EU meeting, Lausanne (Switzerland), *Fraunhofer IGB/ hDMT/ LUMC*	80	20							
62	P6 - UNIZAR	02-07-2018	02-07-2018	Press release	Press release: Newspaper of the official Aragon College of Medicine, Zaragoza (Spain)			7249						
63	P7 - TUD	03-07-2018	14-07-2018	Participation to a Conference	MARSS conference Nagoya, 3-14 July 2018.https://www.ieee-ras.org/component/rseventspro/event/1325-marss-2018-call-for-papers-deadline?Itemid=101	200								

64	P2 – hDMT	05-07-2018	06-07-2018	Participation to an Event other than a Conference or a Workshop	Presentation and discussions at Eye-on-chip meeting, Enschede (the Netherlands).https://www.utwente.nl/en/events/!/2018/7/446467/eye-on-a-chip-workshop	30	5	3						
65	P6 - UNIZAR	20-07-2018	24-07-2018	Participation in activities organized jointly with other H2020 projects	Presentation and discussions at the meeting with Elvesys, Blackhole lab and Eden Microfluidics,Paris (France)		15							
66	P1 - LUMC	28-08-2018	29-08-2018	Participation to a Conference	"Cardiac microtissues in modelling disease and drug responses", Minerva Conference, Helsinki, Finland – presentation	150								
67	P2 - hDMT	09-04-2018	09-04-2018	Participation to a Conference	Presentation of a poster about ORCHID Keystone meeting	200								
68	P3 - Fraunhofer	05-09-2018	05-09-2018	Participation to a Conference	Presentation at the TERMIS conference, Kyoto, Japan.https://www.termis.org/wc2018/index.php	400	100			10	10	5		
69	P2 – hDMT	07-09-2018	07-09-2018	Participation to a Workshop	Discussion in workshop: UK Organ-on-Chip network launch, London (UK).https://www.sems.qmul.ac.uk/news/4863/organ-on-a-chip-network-launch-a-great-success	50	15							
70	P6 - UNIZAR	09-09-2018	12-09-2018	Participation to a Conference	Presentation at Good bye Flat Biology EACR conference, Berlin (Germany).https://www.eacr.org/user_uploads/files/GFB18%20A5%20Programme%20Book%20ONLINE.pdf	200								
71	P3 - Fraunhofer	24-09-2018	24-09-2018	Participation to a Conference	21st European Congress on Alternatives to Animal Testing, Linz. https://eusaat-congress.eu/images/2018/PDF/Abstractbook_Linz_2018_EUSAAT_2018_e_version.pdf	50	30	10		20	5			
72	P6 - UNIZAR	27-09-2018	27-09-2018	Participation to a Workshop	Congress for medicine students									
73	P6 - UNIZAR	28-09-2018	28-09-2018	Other	Presentation and Hands-on for children, Dissemination to the general public “European Researchers´Night”, Zaragoza (Spain). https://i3a.unizar.es/es/noticia/2018/09/27/el-i3a-se-sumo-un-ano-mas-la-noche-de-los-investigadores				3000					
74	P2 - hDMT	02-10-2018	02-10-2018	Participation to a Workshop	Workshop Dutch TechCenter for Life Sciences (Netherlands)					20				
75	P6 - UNIZAR	04-10-2018	05-10-2018	Participation to a Conference	Therapy optimization in glioblastoma: An integrative human data-based approach using mathematical models. TOG meeting									
76	P4 - CEA	12-10-2018	12-10-2018	Participation to a Conference	Presentation MIFOBIO 2018. http://imabio-cnrs.fr/mifobio/programme-de-mifobio-2018/	500	100							
77	P2 - hDMT	15-10-2018	18-10-2018	Participation to a Conference	MNBS workshop, Thessaloniki Greece, invited speaker, 18-10-2018. https://www.smart-systems-integration.org/event/eposs-general-assembly-annual-forum-2018-and-mnbs-2018	30				20				
78	P6 - UNIZAR	15-10-2018	05-12-2018	Training	Master Course in Molecular and Cellular Biology									
79	P4 - CEA	17-10-2018	17-10-2018	Organisation of a Workshop	INSERM WORKSHOP : THEORY Phase . https://www.inserm.fr/sites/default/files/media/entity_documents/Inserm_programme_AteliersInserm_2018.pdf	75	10							
80	P6 - UNIZAR	24-10-2018	26-10-2018	Participation to an Event other than a Conference or a Workshop	Meeting in Bordeaux with the Rector of the University of Zaragoza ond the rest of the delegation to encourage collaboration between universities (Subsequent contact with Maria Urdaci)									

81	P4 - CEA	25-10-2018	25-10-2018	Organisation of a Workshop	INSERM WORKSHOP : PRACTICAL Phase .https://www.inserm.fr/sites/default/files/media/entity_documents/Inserm_programme_AteliersInserm_2018.pdf		1							
82	P6 - UNIZAR	30-10-2018	30-10-2018	Other	Presentation at the "Futurnanotech TERMINATOR", Zaragoza (Spain)									
83	P2 - hDMT	31/10/2018	31/10/2018	Participation to a Conference	MF-10 microfluidics conference Eindhoven (Netherlands)		50							
84	P4 - CEA	05-11-2018	05-11-2018	Participation to a Workshop	ECOPA Workshop . https://www.ecopa.eu/wp-content/uploads/2019/05/ecopa_symposium_2018.pdf	90	30							
85	P2 - hDMT	08-11-2018	09-11-2018	Organisation of a Conference	International Organ-on-Chip symposium. https://www.ioocs18.com/home	160	20							
86	P7 - TUD	10-11-2018	10-11-2018	Participation to a Conference	Microelectronic Circuit Centre Ireland annual 2018 Forum, invited presentation Health.E lighthouse, including ORCHID, Cork (Ireland) invited speaker. https://www.mcci.ie/mcci-annual-forum-2018/		70							
87	P3 - Fraunhofer	13-11-2018	13-11-2018	Participation to a Workshop	Interfakultäre Biomedizinische Forschungseinrichtung, Universität Heidelberg	50								
88	P2 - hDMT	14/11/2018	14/11/2018	Participation to an Event other than a Conference or a Workshop	Kick-off meeting Organ-on-Chip Nijmegen University Medical Center (Netherlands)	60								
89	P6 - UNIZAR	16-11-2018	16-11-2018	Other	Visit of the Elementasl School del Salvador, Zaragoza (Spain)									
90	P4 - CEA	26-11-2018	28-11-2018	Participation to a Workshop	INSERM Workshop 249. http://ateliers249-inserm.evenium-site.com/site/atelier-de-l-inserm249;jsessionid=MZpjFJUsEgbT5PMFg8L5Rau1.gl3	40	10							
91	P3 - Fraunhofer	27-11-2018	29-11-2018	Participation to a Conference	World Preclinical Congress Europe, Lissabon.https://www.worldpreclinicaleurope.com/ https://www.worldpreclinicaleurope.com/Organ-on-a-Chip	20	40			10				
92	P3 - Fraunhofer	28-11-2018	28-11-2018	Participation to a Conference	ATDG 2018, Edinburgh	50				5				
93	P2 - hDMT	10-12-2018	10-12-2018	Participation to a Workshop	EUROoC workshop Stuttgart (Germany)	20	3							
94	P2 - hDMT	11-12-2018	12-12-2018	Participation to a Conference	International MicroNano conference Amsterdam (Netherlands). https://www.hdmt.technology/event/7854/International-Micro-Nano-Conference	150	200							
95	P2 - hDMT	11-12-2018	11-12-2018	Other	Policy meeting Topsector Life Science and Health Utrecht (Netherlands)					20				
96	P3 - Fraunhofer	14-12-2018	14-12-2018	Participation to a Workshop	Roche pRed Symposium, Basel	20	100							
97	P6 - UNIZAR	08-01-2019	08-01-2019	Training	Talk during Master course in Medicine									
98	P6 - UNIZAR	11-01-2019	11-01-2019	Other	Meeting with AITIIP Technological Center in Zaragoza									
99	P4 - CEA	15-01-2019		Training	Licence Pro Biotechnologie "méthodes et systèmes en bioanalyses" 2h	25								
100	P6 - UNIZAR	17-01-2019	04-04-2019	Participation to a Workshop	Presentation at Tumor Immunology and Cancer Immunotherapy Course, Zaragoza (Spain)									
101	P2 - hDMT	17-01-2019	17-01-2019	Organisation of a Workshop	ORCHID Strategy workshop	22	5			3				
102	ALL	17-01-2019	17-01-2019	Participation to a Workshop	ORCHID Strategy Meeting									
103	P2 - hDMT	01-02-2019	01-02-2019	Participation to an Event other than a Conference or a Workshop	hDMT Consortium meeting	85								

104	P6 - UNIZAR	08-02-2019	08-02-2019	Other	Meetings with Menarini Group Spain, Pharmaceutical Laboratory									
105	P1 - LUMC	13-02-2019		Social Media	Science in Holten: Organ on chip in advancing biomedicine for general public (in Dutch, to encourage students/parents to STEM, explaining to general public on ORCHID/OoC).http://holtenscience.nl/lezingen-en-sprekers-stamceltechnologie/				200					
106	P6 - UNIZAR	13-02-2019	14-02-2019	Participation to a Conference	Open Innovation Area. Transfirere 2020. Subsequent contact with Repsol and Inveniam group									
107	P1 - LUMC	15-02-2019	15-02-2019	Non-scientific and non-peer-reviewed publication (popularised publication)	The lecture that included Organs-on-Chip examples from ORCHID was reported in the local newspaper “Holten Extra” on Feb 15th 2019									
108	P6 - UNIZAR	15-02-2019	15-02-2019	Other	Visit of the Elemental School Sagrado Corazón de Jesús, Zaragoza (Spain)									
109	P2 - hDMT	21-02-2019	21-02-2019	Participation to a Conference	Life-on-Chip Leuven (Belgium). https://lifeonchip.b2match.io/	100	50		10	5	5	5		
110	P5 - IMEC	21-02-2019	22-02-2019	Organisation of a Conference	Life On Chip conference: the road from idea to reality, Leuven BE. https://www.flanders.bio/en/what-we-do/flandersbio-events/2019/february/life-on-chip-the-road-from-idea-to-reality/	100	50		10	5	5	5		
111	P6 - UNIZAR	26-02-2019	26-02-2019	Other	Meeting the Minister of Science, Innovation and Universities participated at the 'Heraldo Breakfasts' https://www.heraldo.es/noticias/aragon/2019/02/26/pedro-duque-deja-la-puerta-abierta-a-repetir-como-ministro-de-ciencia-1300044.html									
112	P6 - UNIZAR	27-02-2019	27-02-2019	Other	Talk during the meeting CANCER RESEARCH in ARAGÓN									
113	P6 - UNIZAR	14-03-2019	14-03-2019	Training	Course in Tumor Immunology and Cancer Immunotherapy. https://www.iisaragon.es/evento/curso-de-inmunologia-tumoral-e-inmunoterapia-del-cancer-3/	15								
114	P6 - UNIZAR	27-03-2019	27-03-2019	Participation to a Conference	Conference "Cancer research in Aragon". Spanish Association Against Cancer (AECC) and IIS Aragón									
115	P3 - Fraunhofer	08-03-2019	17-03-2019	Participation to a Conference	Konferenz SOT, Baltimore, USA. https://www.toxicology.org/pubs/docs/Prog/2019Program.pdf	100	30			20	5			
116	P2 - hDMT	26-03-2019	26-03-2019	Participation to an Event other than a Conference or a Workshop	Meeting Dutch government to Leiden University Medical Center and hDMT Leiden (Netherlands)					10				
117	P4 - CEA	29-03-2019	29-03-2019	Participation to a Conference	Human 3D models in oncology: from organoids to organ-on-chip. https://cancercellchip2.sciencesconf.org/data/pages/Final_Program_Cancer_Cells_on_Chip_2019_DEF_26mars2019.pdf	120	15							
118	P4 - CEA	01-04-2019		Other	Application Note in FLUIGENT Website : https://www.fluigent.com/applications/microencapsulated-organoids/									
119	P6 - UNIZAR	04-04-2019	04-04-2019	Pitch Event	Science in the bars. Drink and Pool ASBAR									
120	P3 - Fraunhofer	08-04-2019	11-04-2019	Participation to a Conference	EMBO Konferenz , Spanien. http://meetings.embo.org/event/19-whole-cell-modelling	30								
121	P2 - hDMT	08-04-2019	08-04-2019	Participation to a Workshop	Queen Mary networking event London (UK)	120								
122	P2 - hDMT	16-04-2019	16-04-2019	Participation to an Event other than a Conference or a Workshop	Panasonic Health Care Europe meeting Rotterdam (Netherlands)		100							

123	P2 - hDMT	18-04-2019	18-04-2019	Participation to a Workshop	Building Blocks of Life meeting Amersfoort (Netherlands)	50								
124	P6 - UNIZAR	15-05-2019	15-05-2019	Other	Visit of Minister Pedro Duque to the Research Institutes https://i3a.unizar.es/es/noticia/2019/05/15/visita-del-ministro-pedro-duque-los-institutos-de-investigacion									
125	P3 - Fraunhofer	16-05-2019	17-05-2019	Participation to a Conference	Joint Ontario-on-a-Chip and TOeP Symposium. http://torontomicrofluidics.ca/ooac/program/	50	20			10				
126	P5 - IMEC	20-05-2019	20-05-2019	Participation to an Event other than a Conference or a Workshop	Pint of science presentation, Brussels, BE				50					
127	P3 - Fraunhofer	21-05-2019	24-05-2019	Participation to a Conference	JRC Summer School on Non-Animal Approaches in Science. https://ec.europa.eu/jrc/en/science-update/jrc-summer-school-non-animal-approaches	80	10			20				
128	P6 - UNIZAR	22-05-2019	22-05-2019	Pitch Event	Pint of Science https://pintofscience.es/event/el-guapo-el-bueno-y-el-bicho. https://pintofscience.es/event/el-guapo-el-bueno-y-el-bicho									
129	P1 - LUMC	05-06-2019	06-06-2019	Training	Course for PhD students (engineers/biologists) of deriving stem cell derivatives for OoC use									
130	P4 - CEA	22-05-2019	16-05-2019	Participation to a Conference	Grenoble Minatech 3R policy. http://mut2019.insight-outside.fr/	100	20							
131	P4 - CEA	13-06-2019	13-06-2019	Pitch Event	Pint of science https://pintofscience.fr/event/Substitut%20d%E2%80%99organes%20et%20m%C3%A9decine%20du%20futur				60					
132	P4 - CEA	13-06-2019	14-06-2019	Participation to a Conference	Conference STCM. https://www.afssi.fr/event/congres-fondateur-stcm-2019/	70	10							
133	P2 - hDMT	17-06-2019	17-06-2019	Participation to an Event other than a Conference or a Workshop	Biology-inspired MPS to advance Medicines for Patients Benefit Berlin (Germany). https://www.biologie.uni-konstanz.de/typo3temp/secure_downloads/102096/0/6c45b056a293f0fd532cb82f823a45f9e81f39c8/Agenda_Biology-inspired_MPS_to_advance_Medicines_for_Patients_Benefit__17.06.2019_v7.pdf	75								
134	P7 - TUD	17-06-2019	18-06-2019	Participation to a Conference	ORCHID was part of the HEALTH.E exhibit at the ECSEL JU Symposium in Bucharest. https://www.earto.eu/ecsel-ju-symposium-on-17-18-june-2019-in-bucharest/									
135	P2 - hDMT	18-06-2019	20-06-2019	Participation to a Workshop	CAAT Think tank Microphysiological Systems Workshop Berlin (Germany). https://www.hdmt.technology/event/10980/CAAT-Europe-Information-Day-on-Biology-inspired-Microphysiological-Systems	15	10			10				
136	P3 - Fraunhofer	18-06-2019	19-06-2019	Participation to a Conference	Organ-on-a-Chip & Tissue-on-a-Chip Europe 2019. http://selectbiosciences.com/pastConferences/pastconferenceID.aspx?conf=OOACEU2019	40	40							
137	P5 - IMEC	18-06-2019	19-06-2019	Participation to a Conference	SelectBio OoC conference talk, Rotterdam, NL. http://selectbiosciences.com/pastConferences/pastconferenceID.aspx?conf=OOACEU2019	100	20			5				
138	P3 - Fraunhofer	18-06-2019	20-06-2019	Participation to a Workshop	CAAT-Europe think tank on "Biology-Inspired MPS". https://www.biologie.uni-konstanz.de/en/leist/caat-europe/activities/workshops/2019/	15	10			10				
139	P7 - TUD	01-07-2019	01-07-2019	Other	ORCHID roadmap is one of the guiding elements in the CSA HELoS, which is supporting the HEALTH.E Lighthouse Initiative.									
140	P2 - hDMT	02-07-2019	03-07-2019	Participation to a Conference	EUROoCS conference Graz (Austria). http://www.analytchem.tugraz.at/eurooc/?page_id=880	180	30							
141	P5 - IMEC	02-07-2019	03-07-2019	Participation to a Conference	3 posters and 1 oral presentation at the EUROoCS conference in Graz, AU. http://www.analytchem.tugraz.at/eurooc/?page_id=880	200	20							

142	P4 - CEA	26-08-2019	27-08-2019	Participation to a Conference	TERMIS 3D Bioprinting, Nantes, France. http://sites.altilab.com/files/CONGRES/2019/TERMIS2019.pdf	200	20							
143	P2 - hDMT	04-09-2019	04-09-2019	Participation to a Conference	Symposium EUROoCS at ESAO congress Hannover (Germany). https://www.esao2019.org/ https://www.imp.uni-hannover.de/fileadmin/imp/pdf/Program_Book_Final.pdf	350								
144	P1 - LUMC	15-09-2019		Communication Campaign (e.g. Radio, TV)	Dutch TV programme "Clockhouse" for children (8-14 years) on OoC/body on chip									
145	P2 - hDMT	23-09-2019	23-09-2019	Organisation of a Workshop	Final meeting ORCHID project Leiden (Netherlands)	25	2			6				
146	P6 - UNIZAR	23-09-2019	25-09-2019	Participation to a Conference	7th edition of the European Congress of Life Sciences Eurobiotech in Krakow, Poland https://www.eurobiotech.krakow.pl/gb/									
147	P6 - UNIZAR	27-09-2019	27-09-2019	Participation to an Event other than a Conference or a Workshop	Presentation , Dissemination to the general public “European Researchers´Night”, Zaragoza (Spain)									
148	P4 - CEA	01-10-2019		Training	Master II ISM Ingenieries pour la santé et le médicament "Biotherapies". 3D Cell culture on Chip (2h). http://formations.univ-grenoble-alpes.fr/en/catalog/master-s-degree-XB/sciences-technologies-and-health-STS/master-in-health-engineering-program-program1-master-ingenierie-de-la-sante-en/science-and-management-of-biotechnologies-cell-and-gene-therapy-tissue-engineering-2nd-year-subprogram-subprogram-parcours-sciences-et-management-des-biotechnologies-therapie-cellulaire-genique-et-ingenierie-tissulaire-en.html	25								
149	P2 - hDMT	22-10-2019	23-10-2019	Participation to a Workshop	MNBS workshop Smart bioeectronic and wearable systems Brussels (Belgium). https://www.smart-systems-integration.org/event/smart-bioelectronic-and-wearable-systems-ec-workshop	125				10				
150	P2 - hDMT	10-12-2019	11-12-2019	Participation to a Conference	International Micronano Conference Utrecht (The Netherlands). https://www.micronanoconference.org/	150	250							
151	P7 - TUD	31-05-2020	04-06-2020	Participation to a Conference	Talk during the workshop 'applications of micro-nanorobotics ' held during the IEEE ICRA 2020 conference									
152	P6 - UNIZAR			Other	Bilateral contacts with National Politicians (Ignacio Urquizu) and Visit of Minister of Science, Innovation and Universities at our lab									
						12942	1861	7262	4855	346	36	15	0	0

On the next pages, the number in the upper right corner corresponds to the # of dissemination activity (first column of the table)

imec

Imec partners in European initiative to develop Organs-on-Chip

Call to unite stakeholders and experts

Scroll

academic and private partners. In total six leading European research institutions are involved.

The aim is to accelerate the societal and economic impact of Organ-on-Chip technology through coordinated action. Organs-on-Chips combine human mini-organs with microelectronics, microfluidics and nanosensors. This technology is already providing new platforms for drug discovery but is poised to deliver applications in personalized medicine and safety pharmacology, and offers alternatives to conventional animal testing. Over the next two years, the EU will invest 0.5 million Euros in the ORgan-on-CHip In Development (ORCHID) project.

ORCHID will facilitate dialogue and documentation towards accelerating the development of prototypes of Organs-on-Chips, validated cell systems that mimic diseased or healthy human tissue, and implementation of this technology by a broad group of potential users in science, health care and industry.

ORCHID will build an infrastructure for scientists, policy makers, funders and end-users to join the decision-making processes that will direct future European developments in Organ-on-Chip applications. An essential contribution of ORCHID will be the establishment of a digital platform enabling knowledge sharing between researchers and representatives of private corporations including insurance companies, pharmaceutical and biotech companies, food industry, health foundations and patient organizations.

The ORCHID platform will provide overviews and updates of current and new Organ-on-Chip initiatives so that users can track progress easily, consult developers directly and identify gaps in present knowledge, limiting implementation. ORCHID will also address ethical and regulatory issues, particularly concerning personalized information, economic and societal impact, training of researchers, and the design of an R&D 'roadmap'.

The consortium is composed of the following organizations:

2. Organ-on-Chip consortium hDMT (the Netherlands): strategy and the roadmap

contact: Janny van den Eijnden van Raaij, PhD, Managing director

3. Fraunhofer IGB (Germany): impact assessment, training, education

contact: Peter Loskill, PhD, Attract Group Manager Organ-on-a-Chip, Department of Cell and Tissue Engineering

4. CEA (France): eco-system development and the digital platform

contact: Adrienne Pervès PhD, Deputy Head of Department-LETI-Technologies for biology and health & Nathalie Picollet D'Hahan, PhD, Deputy Head Biomics Laboratory.

5. imec (Belgium): ethical aspects, regulation and standardization

contact: Wolfgang Eberle, PhD, Funded Program Manager Smart Health and NERF Coordinator EIT Health

6. University of Zaragoza (Spain): dissemination

contact: Luis Fernandez, PhD, Professor at the Dept. of Mechanical Engineering, microfluidic leader of the Applied Mechanics and Bioengineering group

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 766884

Organs-on-Chips and hDMT

The Organ-on-Chip consortium hDMT (www.hdmt.technology) is a pre-competitive,

Redacción Lunes, 30 de octubre de 2017

PROYECTO EUROPEO ORCHID: TECNOLOGÍA PARA IMITAR EL TEJIDO HUMANO EN EL LABORATORIO

Investigadores de la Universidad de Zaragoza forman parte de un proyecto europeo para el desarrollo de modelos de investigación que nos acerquen a la medicina personalizada y a la farmacología de seguridad

Noticia clasificada en: Innovación

Junto a instituciones y centros de investigación de otros cuatro países europeos crearán mejoras tecnológicas que permitirán imitar mejor el tejido humano en el laboratorio, acortando el coste y el tiempo de desarrollo de nuevos fármacos.

La Universidad de Zaragoza es el socio español del proyecto europeo ORCHID (Organ-On-Chip In Development). Los científicos del Instituto de Investigación en Ingeniería de Aragón (I3A), Luis Fernández e Iñaki Ochoa, van a trabajar en este proyecto cuyo objetivo es acelerar el impacto social y económico de la tecnología conocida como Organ-on-Chip. Esta tecnología basada en el uso de plataformas microfluídicas está ya facilitando el descubrimiento de fármacos, pero que puede dar un paso más con aplicaciones en **medicina personalizada y farmacología de seguridad** y que, además, ofrece alternativas a las pruebas convencionales en animales.
El proyecto, que se llevará a cabo durante dos años, está liderado por el Centro Médico de la Universidad de Leiden y el consorcio holandés Organ-on-Chip hDMT. La Universidad de Zaragoza es una de las instituciones de este proyecto en el que participan entidades y centros de investigación de otros cuatro países, Alemania, Bélgica, Francia y Holanda. El consorcio cuenta con el respaldo económico de la Unión Europea, que ha destinado para ello medio millón de euros.

Los integrantes de Organ-on-CHip In Development (ORCHID) trabajarán para facilitar y acelerar el **desarrollo de prototipos, sistemas celulares** validados que imitan el **tejido humano enfermo o sano** y la implantación de esta tecnología por un amplio grupo de usuarios potenciales en **ciencias, cuidado de la salud e industria.**

Asimismo, está prevista la **construcción de una infraestructura** para que los científicos, los responsables de las políticas, los financiadores y los usuarios finales se unan a los procesos de toma de decisiones que orientarán los futuros desarrollos europeos en las aplicaciones Organ-on-Chip. Entre sus acciones destaca el establecimiento de una **plataforma digital** que permita el intercambio de conocimientos entre investigadores y representantes de corporaciones privadas, incluidas las

SECTOR TEXTIL
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Entrevistas

ENTREVISTA A CRISTINA SÁNCHEZ
Cristina Sánchez: "Las energéticas trabajan en temas medioambientales de una manera muy innovadora

Cristina Sánchez García, subdirectora de la Red Española del Pacto Mundial de Naciones Unidas asistió al 6º Congreso Internacional de RS en Aragón como ponente.

COLUMNAS DE OPINIÓN

Ana Belen Hernandez Sanche
POLITÓLOGA Y TÉCNICO EN MARKETING Y COMERCIO EXTERIOR
LA EVOLUCION DE LA MUJER EN LA ESFERA PUBLICO POLITICA

Juan José Pontaque
Industrializar Aragón
OBJETIVO CREAR EMPLEO. LA FORMACIÓN PROFESIONAL Y LA FP DUAL

Alberto Joven
Asesor Laboral Seiko Asesores S.L.

compañías de seguros, las empresas farmacéuticas y biotecnológicas, la industria alimentaria, las fundaciones de salud y las organizaciones de pacientes.

Esta plataforma proporcionará una visión general y actualizaciones para que los usuarios puedan rastrear el progreso fácilmente, consultar a los desarrolladores directamente e identificar las lagunas en el conocimiento actual, que limita la implementación. También abordará **cuestiones éticas y regulatorias**, particularmente en lo que respecta a la información personalizada, el impacto económico y social, la capacitación de investigadores y el diseño de una "hoja de ruta" de I + D.

Enlaces automáticos por temática

ARAID acudirá a China a unas de las ferias internacionales más importantes en biomedicina

El I3A, 15 AÑOS INVESTIGANDO

Aula Magna del Edificio Paraninfo de la Universidad de Zaragoza

Concedidos los premios de la cátedra BSH-UZ a la Innovación en su XI Edición

Una investigadora ARAID consigue una ayuda para un proyecto de investigación de la Asociación Española contra el Cáncer

Casi 500 investigadores, 35 grupos de investigación y más de 100 líneas de trabajo al servicio de la sociedad

6 de cada 10 corredores españoles sufren problemas de salud, aumentando los casos de muerte súbita

Economía y la Universidad de Zaragoza renuevan su acuerdo para formar en prevención de riesgos laborales

Campus Iberus presente en los "Open Days 2017" de Bruselas

Las universidades de Zaragoza y Pau analizan en Jaca y Formigal las posibilidades del "turismo sostenible" transfronterizo en los Pirineos

MALDITA INCERTIDUMBRE

Antonio Morlanes
Presidente de Aragonex
Fronteras contra el egoismo

Joaquín Moreno
Alcalde de Utrillas
Es hora de que la España vacía se oiga

AGENDA

« **Marzo 2019** »

Lun	Mar	Mié	Jue	Vie	Sáb	Dom
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

EVENTOS DE AGENDA

Lunes, 11 de marzo de 2019
Cámara de Comercio: Una jornada analiza en Cámara Zaragoza los retos de 'La restauración del siglo XXI'

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CEOE: Medidas de seguridad en la empresa a la luz del RGPD

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9ª Edicion de Menuda Feria

Jueves, 21 de marzo de 2019
#desayunoARAME con Magdalena Lasala Pérez

Jueves, 21 de marzo de 2019
Cámara de Zaragoza: Mujer y Economía

Investigadores de la Universidad de Zaragoza forman parte de un proyecto europeo para el desarrollo de modelos de investigación que nos acerquen a la medicina personalizada y a la farmacología de seguridad

30/10/2017 - SD

Puntos clave

- Junto a instituciones y centros de investigación de otros cuatro países europeos crearán mejoras tecnológicas que permitirán imitar mejor el tejido humano en el laboratorio, acortando el coste y el tiempo de desarrollo de nuevos fármacos
- Entre las acciones a llevar a cabo destaca la creación de una plataforma digital para el intercambio de conocimientos entre investigadores y corporaciones privadas

La Universidad de Zaragoza es el socio español del proyecto europeo ORCHID (Organ-On-Chip In Development). Los científicos del Instituto de Investigación en Ingeniería de Aragón (I3A), Luis Fernández e Iñaki Ochoa, van a trabajar en este proyecto cuyo objetivo es acelerar el impacto social y

económico de la tecnología conocida como Organ-on-Chip. Esta tecnología basada en el uso de plataformas microfluídicas está ya facilitando el descubrimiento de fármacos (/-/medicamentos-home), pero que puede dar un paso más con aplicaciones en **medicina personalizada y farmacología de seguridad** y que, además, ofrece alternativas a las pruebas convencionales en animales.

El proyecto, que se llevará a cabo durante dos años, está liderado por el Centro Médico de la Universidad de Leiden y el consorcio holandés Organ-on-Chip hDMT. La Universidad de Zaragoza es una de las instituciones de este proyecto en el que participan entidades y centros de investigación de otros cuatro países, Alemania, Bélgica, Francia y Holanda. El consorcio cuenta con el respaldo económico de la Unión Europea, que ha destinado para ello medio millón de euros.

Los integrantes de Organ-on-CHip In Development (ORCHID) trabajarán para facilitar y acelerar el **desarrollo de prototipos, sistemas celulares** validados que imitan el **tejido humano enfermo o sano** y la implantación de esta tecnología por un amplio grupo de usuarios potenciales en **ciencias, cuidado de la salud e industria.**

Asimismo, está prevista la **construcción de una infraestructura** para que los científicos, los responsables de las políticas, los financiadores y los usuarios finales se unan a los procesos de toma de decisiones que orientarán los futuros desarrollos europeos en las aplicaciones Organ-on-Chip. Entre sus acciones destaca el establecimiento de una **plataforma digital** que permita el intercambio de conocimientos entre investigadores y representantes de corporaciones privadas, incluidas las compañías de seguros, las empresas farmacéuticas y biotecnológicas, la industria alimentaria, las fundaciones de salud y las organizaciones de pacientes.

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MENÚ

Investigadores de la UZ participan en un proyecto europeo para desarrollar modelos hacia la medicina personalizada

Categoría: Universidad Autor: Redacción AU 30 OCTUBRE, 2017

La Universidad de Zaragoza es el socio español del proyecto europeo Orchid (Organ-On-Chip In Development). Los científicos del Instituto de Investigación en Ingeniería de Aragón (I3A), Luis Fernández e Iñaki Ochoa, van a trabajar en este proyecto cuyo objetivo es acelerar el impacto social y económico de la tecnología conocida como Organ-on-Chip. Esta tecnología, basada en el uso de plataformas microfluídicas, está ya facilitando el descubrimiento de fármacos, pero puede dar un paso más con aplicaciones en medicina personalizada y farmacología de seguridad y, además, ofrece alternativas a las pruebas convencionales en animales.

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Proyecto europeo ORCHID: tecnología para imitar el tejido humano en el laboratorio

Investigadores de la Universidad de Zaragoza forman parte de un proyecto europeo para el desarrollo de modelos de investigación que nos acerquen a la medicina personalizada y a la farmacología de seguridad

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Notas de prensa ANIS

La contaminación ambiental nos acorta la vida 9 meses en España (/actualidad/notas-de-prensa-anis/4178-la-contaminación-ambiental-nos-acorta-la-vida-9-meses-en-españa)

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Un informe pone de manifiesto los desafíos actuales del paciente de cáncer

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Este proyecto ha recibido fondos del Programa Horizon 2020 (investigación e innovación) de la Unión Europea bajo el acuerdo Num. 766884. Más información (http://cordis.europa.eu/project/rcn/211282_es.html)

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ORIVA entrega sus I Premios de Comunicación (/actualidad/notas-de-prensa-anis/4013-oriva-entrega-sus-i-premios-de-comunicación) **18-01-2019**
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Asociación Nacional de Informadores de la Salud

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El Blog de Zoe
INFORMACIÓN DE SALUD, SINÓNIMO DE VIDA

30/10/2017

Proyecto europeo ORCHID, investigando en tecnología para imitar el tejido humano en el laboratorio

Investigadores de la Universidad de Zaragoza forman parte de esta iniciativa para el desarrollo de modelos de investigación que nos acerquen a la medicina personalizada y a la farmacología de seguridad

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- El programa formativo Focuss saca 108 cursos y bate récords con la convocatoria más numerosa de su historia
- El cribado de cáncer de cérvix en España tiene deficiencias e inequidades en su cobertura
- Enfermedades raras, más investigación y mayor sensibilidad social

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Este proyecto ha recibido fondos del Programa Horizon 2020 (investigación e innovación) de la Unión Europea bajo el acuerdo Num. 766884. **Más información**

ETIQUETAS: investigación, i3aunizar, tecnología, tejidos,

Investigación y Ciencia

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Published on 29 November 2017

Leti and BIG working on tomorrow’s Organ-on-chip technology

As part of an EU initiative, Leti and our institute will establish infrastructure for coordinating ORgan-on-Chip development, production and implementation.

Organ-on-chip technology will revolutionize healthcare, especially in regenerative medicine and medication. It is already providing new drug research platforms, while offering alternatives to conventional animal testing, and will soon deliver applications in personalized medicine and safety pharmacology.

Over the next two years, the European Union will finance the ORgan-on-CHip In Development (ORCHID) [1] project, led by Leiden University Medical Center and Dutch organ-on-chip consortium hDMT, to the tune of 0.5 M€.
ORCHID has five objectives:
• Assessing state-of-the-art technology and unfulfilled needs;
• Identifying ethical issues, preparing standards and measures for regulatory implementation;
• Analyzing economic and social impact, training and education;
• Developing a R&D roadmap and;
• Raising awareness and building an organ-on-chip technology ecosystem *via* a digital reference platform.

ORCHID will have a broad impact in facilitating drug development, curtailing animal experiments and promoting personalized medicine. It will achieve these goals by offering key players a common framework and by raising awareness of organ-to-chip technology. This platform will concentrate data on existing and new initiatives, enabling ORCHID to secure and reinforce Europe's leadership.

The consortium of principal contributors to the field includes leader Leiden University Centrum, the Institute for Human Organ and Disease Model Technology focusing for strategy, Frauenhofer IGB for impact assessment, training and education, **Leti for eco-system development, our institute (BIG) for digital knowledge sharing platform creation**, IMEC for ethical issues, regulation and standardization and the University of Zaragoza, which manages knowledge dissemination.

REFERENCES

[1] *This project has received funding from the European Union’s Horizon 2020 research and innovation programme under a grant agreement (No 766884)*

Keywords : organ-on-chip

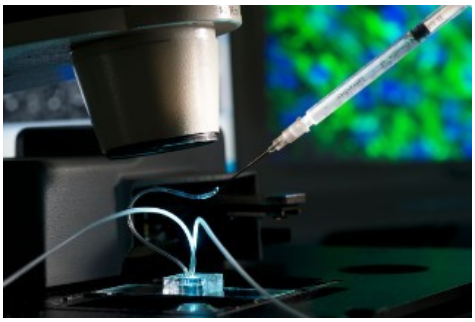
Fraunhofer MATERIALS

Press release

Fraunhofer IGB joins international consortium to advance organ-on-a-chip technology in Europe

press release Fraunhofer IGB / 2.11.2017

The consortium led by Leiden University Medical Center and the Dutch hDMT (human Disease Model Technologies) has been assigned by the EU with the task to create a roadmap for the future development of organ-on-chip technology. Its aim is to establish a European infrastructure to enable coordinated development, production and implementation of organ-on-a-chip systems. The consortium is funded by the EU FET-Open Program and brings together six leading European research institutions, including the Fraunhofer-Institute for Interfacial Engineering and Biotechnology IGB in Stuttgart, Germany.



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Microphysiological Organ-on-a-chip system.

The consortium's aim is to accelerate the societal and economic impact of organ-on-a-chip technology through coordinated action. Organs-on-chips combine human mini-organs with microelectronics, microfluidics and nanosensors. This technology is already providing new platforms for drug discovery but is poised to deliver applications in personalized medicine and safety pharmacology, and offers alternatives to conventional animal testing. Over the next two years, the EU will invest 0.5 million Euros in the ORgan-on-CHip In Development (ORCHID) project.

ORCHID will facilitate dialogue and documentation towards accelerating the development of prototypes of organs-on-chips, validated cell systems that mimic diseased or healthy human tissue, and implementation of this technology by a broad group of potential users in science, health care and industry.

Within the consortium, the Fraunhofer IGB will focus on the economic and educational aspects of the ORCHID project. Dr. Peter Loskill, head of the institute's research group on organ-on-a-chip systems, and his team will evaluate which skills are essential for the development and application of organ-on-a-chip technology. On this basis, it is possible to identify specific training contents for the further education of researchers, developers, and users. A further task of Dr. Loskill and his team will be the assessment of suitable business models for the commercialization of organ-on-a-chip systems, taking advantage of the extensive economic expertise of the Fraunhofer IGB as an application-oriented research institute.

Ultimately, ORCHID will build an infrastructure for scientists, policy makers, funders and end-users to join the decision-making processes that will direct future European developments in organ-on-a-chip applications. An essential contribution of ORCHID will be the establishment of a digital platform enabling knowledge sharing between researchers and representatives of private corporations including insurance companies, pharmaceutical and biotech companies, food industry, health foundations and patient organizations.

The ORCHID platform will provide overviews and updates of current and new organ-on-a-chip initiatives so that users can track progress easily, consult developers directly and identify gaps in present knowledge, limiting implementation. ORCHID will

also address ethical and regulatory issues, particularly concerning personalized information, economic and societal impact, training of researchers, and the design of an R&D roadmap.

The consortium is composed of the following organizations:

Leiden University Medical Center, the Netherlands; coordinator contact: Christine Mummery, PhD, Professor of Developmental Biology, Chair Dept. of Anatomy

Organ-on-Chip consortium hDMT, the Netherlands; strategy and the roadmap contact: Janny van den Eijnden van Raaij, PhD, Managing director

Fraunhofer IGB, Germany; Peter Loskill, PhD, Attract Group Manager Organ-on-a-chip, Department of Cell and Tissue Engineering

CEA LETI, France; eco-system development and the digital platform contact: Adrienne Pervès PhD, Deputy Head of Department-LETI-Technologies for biology and health

Imec, Belgium; ethical aspects, regulation and standardization contact: Wolfgang Eberle, PhD, Funded Program Manager Smart Health and NERF Coordinator EIT Health

University of Zaragoza, Spain; dissemination contact: Luis Fernandez, PhD, Professor Mechanical Engineering, Dept. of Applied Mechanics and Bioengineering

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 766884.

For further information please subscribe to the ORCHID newsletter:

www.hdmt.technology/orchid

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-> Website Fraunhofer IGB

Online in Internet; URL: https://www.materials.fraunhofer.de/en/press/igb---fraunhofer-igb-joins-international-consortium-to-advance-o.html

Date: 10.5.2019 14:59

Leiden University Medical Center

Dutch researchers lead consortium on Organ-on-Chip development in Europe

30 October 2017 • *PRESSRELEASE*

Leiden University Medical Center (LUMC) and the Dutch Organ-on-Chip consortium hDMT are now leading an EU initiative that will establish a European infrastructure to enable coordinated development, production and implementation of Organs-on-Chips by a consortium of academic and private partners. In total six leading European research institutions are involved.

The aim is to accelerate the societal and economic impact of Organ-on-Chip technology through coordinated action. Organs-on-Chips combine human mini-organs with microelectronics, microfluidics and nanosensors. This technology is already providing new platforms for drug discovery but is poised to deliver applications in personalized medicine and safety pharmacology, and offers alternatives to conventional animal testing. Over the next two years, the EU will invest 0.5 million Euros in the ORgan-on-CHip In Development (ORCHID) project.

ORCHID will facilitate dialogue and documentation towards accelerating the development of prototypes of Organs-on-Chips, validated cell systems that mimic diseased or healthy human tissue, and implementation of this technology by a broad group of potential users in science, health care and industry.

Infrastructure

ORCHID will build an infrastructure for scientists, policy makers, funders and end-users to join the decision-making processes that will direct future European developments in Organ-on-Chip applications. An essential contribution of ORCHID will be the establishment of a digital platform enabling knowledge sharing between researchers and representatives of private corporations including insurance companies, pharmaceutical and biotech companies, food industry, health foundations and patient organizations.

Roadmap

The ORCHID platform will provide overviews and updates of current and new Organ-on-Chip initiatives so that users can track progress easily, consult developers directly and identify gaps in present knowledge, limiting implementation. ORCHID will also address ethical and regulatory issues, particularly concerning personalized information, economic and societal impact, training of researchers, and the design of an R&D 'roadmap'.

Participating organizations

The consortium is composed of the following organizations:

1. Leiden University Medical Center (The Netherlands): coordinator
   contact: Christine Mummery, PhD, Professor of Developmental Biology, Chair Dept. of Anatomy
2. Organ-on-Chip consortium hDMT (The Netherlands): strategy and the roadmap
   contact: Janny van den Eijnden van Raaij, PhD, Managing director
3. Fraunhofer IGB (Germany): impact assessment, training, education
   contact: Peter Loskill, PhD, Attract Group Manager Organ-on-a-Chip, Department of Cell and Tissue Engineering

4. CEA (France): eco-system development and the digital platform
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6. University of Zaragoza (Spain): dissemination
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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 766884

Organs-on-Chips and hDMT

The Organ-on-Chip consortium hDMT is a pre-competitive, non-profit, technological research institute with renowned scientists from 14 Dutch organizations (academic research centers, research institutes, University Medical Centers, and biotech companies). In this consortium the hDMT researchers collaborate, share and integrate their knowledge, expertise and research facilities in technology, biology, physics, chemistry, pharmacology and medicine to develop Organs-on-Chips using human stem cells. hDMT aims to disseminate Organ-on-Chip models and research data through open access publication and valorization.

> Stay informed on the latest news of the Leiden University Medical Center, and sign up for our biweekly newsletter or subscribe to our LUMC Magazine.

Leids Universitair Medisch Centrum

Nederlandse onderzoekers leiden Europees organen-op-chips-consortium in Europa

30 oktober 2017 • *PERSBERICHT*

Het Leids Universitair Medisch Centrum (LUMC) en het Nederlandse orgaan-op-chip-consortium hDMT zijn de trekkers van een EU-project dat een Europese infrastructuur op gaat zetten voor het gezamenlijk ontwikkelen, produceren en implementeren van organen-op-chips door wetenschap en bedrijfsleven. Aan het project doen in totaal zes toonaangevende Europese onderzoeksinstellingen mee.

Het doel is om gezamenlijk deze technologie zo snel mogelijk een zo groot mogelijke maatschappelijke en economische impact te geven. Organen-op-chips zijn combinaties van menselijke mini-orgaantjes met onder andere microelektronica, microfluidica en nanosensors. Ze zijn belangrijk voor het ontwikkelen van veilige nieuwe medicijnen, het toepassen van personalized medicine en het verminderen van proefdiergebruik. De EU investeert de komende twee jaar een half miljoen Euro in het ORgan-on-CHip In Development (ORCHID) project.

ORCHID faciliteert dialoog en documentatie en versnelt daarmee het ontwikkelen van prototypes van organen-op-chips, gevalideerde celsystemen die ziek of gezond menselijk weefsel nabootsen, alsook hun implementatie en beschikbaarheid voor een brede groep potentiële gebruikers in de wetenschap, de gezondheidszorg en de industrie.

Digitaal platform voor kennisuitwisseling

ORCHID bouwt een infrastructuur waarin wetenschappers, beleidsmakers, financiers en eindgebruikers kunnen meedenken en meedoen bij het bepalen van de koers van de toekomstige Europese ontwikkelingen op het gebied van organen-op-chips. Een essentieel onderdeel van het project is een digitaal platform voor kennisuitwisseling en samenwerking tussen onderzoekers, bedrijfsleven en maatschappelijke organisaties, zoals verzekeraars, farmaceutische en biotechnologische bedrijven, voedingsindustrie, gezondheidsfondsen en patiëntenverenigingen.

Stappenplan

Het ORCHID-platform zal de stand van zaken met betrekking tot nieuwe en bestaande organen-op-chips-initiatieven publiceren, zodat gebruikers de vooruitgang makkelijk kunnen bijhouden, direct contact op kunnen nemen met ontwikkelaars en de hiaten in de huidige kennis kunnen identificeren die implementatie nog in de weg staan. Daarnaast zal ORCHID de ethische en regulatoire aspecten van deze nieuwe technologie adresseren, met name wat betreft persoonlijke informatie, de economische en maatschappelijke impact, de training van onderzoekers en het opzetten van een stappenplan ('roadmap') voor de R&D van de toekomst.

Deelnemende organisaties

ORCHID wordt gerund door de volgende 6 organisaties:

1. Leids Universitair Medisch Centrum (LUMC): coördinator
   contactpersoon: Prof. Christine Mummery, PhD, Professor of Developmental Biology, Chair Dept. of Anatomy

2. Orgaan-op-chip-consortium hDMT: ontwikkeling van strategie en roadmap
   contactpersoon: Janny van den Eijnden van Raaij, PhD, Managing director
3. Fraunhofer IGB (Duitsland): impact assessment, training, education
   contactpersoon: Peter Loskill, PhD, Attract Group Manager Organ-on-a-Chip, Department of Cell and Tissue Engineering
4. CEA (Frankrijk): ontwikkeling van ecosysteem en digitaal platform
   contactpersoon: Adrienne Pervès, PhD, Deputy Head of Department-LETI-Technologies for biology and health & Nathalie Picollet D'Hahan, PhD, Deputy Head Biomics Laboratory
5. imec (België): ethische aspecten, regulering en standaardisatie
   contactpersoon: Wolfgang Eberle, PhD, Funded Program Manager Smart Health and NERF Coordinator EIT Health
6. University of Zaragoza (Spanje): kennisverspreiding (disseminatie)
   contactpersoon: Luis Fernandez, PhD, Professor at the Dept. of Mechanical Engineering, microfluidic leader of the Applied Mechanics and Bioengineering group

Dit project wordt gefinancierd vanuit het Horizon 2020 onderzoek- en innovatie programma van de Europese Unie (subsidieovereenkomst nr 766884).

Organen-op-chips en hDMT

Het orgaan-op-chip consortium hDMT is een pre-competitief, non-profit, technologisch R&D-instituut, met toonaangevende wetenschappers vanuit 14 Nederlandse organisaties (academische onderzoekscentra, onderzoeksinstituten, UMC's en biotechbedrijven). Binnen dit consortium werken de hDMT-onderzoekers samen en delen en integreren hun kennis, expertise en onderzoeksfaciliteiten in de techniek, biologie, natuurkunde, scheikunde, farmacologie en geneeskunde om organen-op-chips te ontwikkelen met behulp van menselijke stamcellen. hDMT streeft ernaar om de ontwikkelde organen-op-chips-modellen en onderzoeksgegevens via open access-publicatie en valorisatie toegankelijk te maken.

> Wilt u op de hoogte blijven van de laatste ontwikkelingen bij het LUMC?
> Abonneer u dan op onze tweewekelijkse nieuwsbrief of neem een abonnement op het LUMC Magazine.

NEWS

ICT&health
Transforming Healthcare Through Technology

Dit artikel staat op icthealth.nl.

Link: https://www.ictandhealth.com/news/eu-funded-orchid-establishes-infrastructure-for-organs-on-a-chip-rd

EU funded ORCHID establishes infrastructure for organs-on-a-chip R&D

Belgian digital research and innovation hub imec has joined ORCHID, a European initiative that will establish a European infrastructure to enable coordinated development, production and implementation of Organs-on-Chips by a consortium of academic and private partners. In total six leading European research institutions are involved. The project is headed by Dutch university hospital LUMC and Organ-on-Chip consortium hDMT.

The aim is to accelerate the societal and economic impact of Organ-on-Chip technology through coordinated action. Organs-on-Chips combine human mini-organs with microelectronics, microfluidics and nanosensors. This technology is already providing new platforms for drug discovery but is poised to deliver applications in personalized medicine and safety pharmacology, and offers alternatives to conventional animal testing.

Main objective ORCHID project

Over the next two years, the EU will invest 0.5 million Euros in the ORgan-on-CHip In Development (ORCHID) project. The project has received funding from the European Union's Horizon 2020 research and innovation programme. It has three main objectives:

- ORCHID will facilitate dialogue and documentation towards accelerating the development of prototypes of Organs-on-Chips, validated cell systems that mimic diseased or healthy human tissue, and implementation of this technology by a broad group of potential users in science, health care and industry.
- ORCHID will build an infrastructure for scientists, policy makers, funders and end-users to join the decision-making processes that will direct future European developments in Organ-on-Chip applications. An essential contribution of ORCHID will be the establishment of a digital platform enabling knowledge sharing between researchers and representatives of private corporations including insurance companies, pharmaceutical and biotech companies, food industry, health foundations and patient organizations.
- The ORCHID platform will provide overviews and updates of current and new Organ-on-Chip initiatives so that users can track progress easily, consult developers directly and identify gaps in present knowledge, limiting implementation. ORCHID will also address ethical and regulatory issues, particularly concerning personalized information, economic and societal impact, training of researchers, and the design of an R&D 'roadmap'.

The consortium co-operating within ORCHID is composed of the following organizations:

- Leiden University Medical Center (the Netherlands): coordinator
- Organ-on-Chip consortium hDMT (the Netherlands): strategy and the roadmap
- Fraunhofer IGB (Germany): impact assessment, training, education
- CEA (France): eco-system development and the digital platform

- imec (Belgium): ethical aspects, regulation and standardization
- University of Zaragoza (Spain): dissemination

Organs-on-Chips and hDMT

The Organ-on-Chip consortium hDMT (www.hdmt.technology) is a pre-competitive, non-profit, technological research institute with renowned scientists from 14 Dutch organizations (academic research centers, research institutes, University Medical Centers, and biotech companies). In this consortium the hDMT researchers collaborate, share and integrate their knowledge, expertise and research facilities in technology, biology, physics, chemistry, pharmacology and medicine to develop Organs-on-Chips using human stem cells. hDMT aims to disseminate Organ-on-Chip models and research data through open access publication and valorization.

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NEWS

Dutch researchers lead consortium on Organ-on-Chip development in Europe

Monday, 30 October 2017

Call to unite stakeholders and experts

Leiden University Medical Center and the Dutch Organ-on-Chip consortium hDMT are now leading an EU initiative that will establish a European infrastructure to enable coordinated development, production and implementation of Organs-on-Chips by a consortium of academic and private partners. In total six leading European research institutions are involved.

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contact: Luis Fernandez, PhD, Professor at the Dept. of Mechanical Engineering, microfluidic leader of the Applied Mechanics and Bioengineering group

ORCHID kick-off meeting in Leiden (the Netherlands) on 19 October 2017

Standing (from left to right): Luis Fernandez (University of Zaragoza, Spain), Mart Graef (hDMT/TU Delft, the Netherlands)
Mieke Schutte (hDMT, the Netherlands), Christine Mummery (LUMC, the Netherlands), Janny van den Eijnden-van Raaij (hDMT, the Netherlands), Ellen Thomassen (LUMC, the Netherlands), Remco den Dulk (CEA, France), Dennis Doorakkers (LUMC, the Netherlands), Peter Loskill (Fraunhofer IGB, Germany).
Sitting (from left to right): Ignacio Ochoa (University of Zaragoza, Spain), Nathalie Picollet D'Hahan (CEA, France), Massimo Mastrangeli (hDMT/ TU Delft, The Netherlands), Dries Braeken (imec, Belgium)

Sign up for the ORCHID newsletter

For questions about the ORCHID project you can contact prof. Christine Mummery (LUMC) or dr. Janny van den Eijnden - van Raaij (hDMT)

Back to the news overview

ORCHID：ORgan-on-CHip In Development

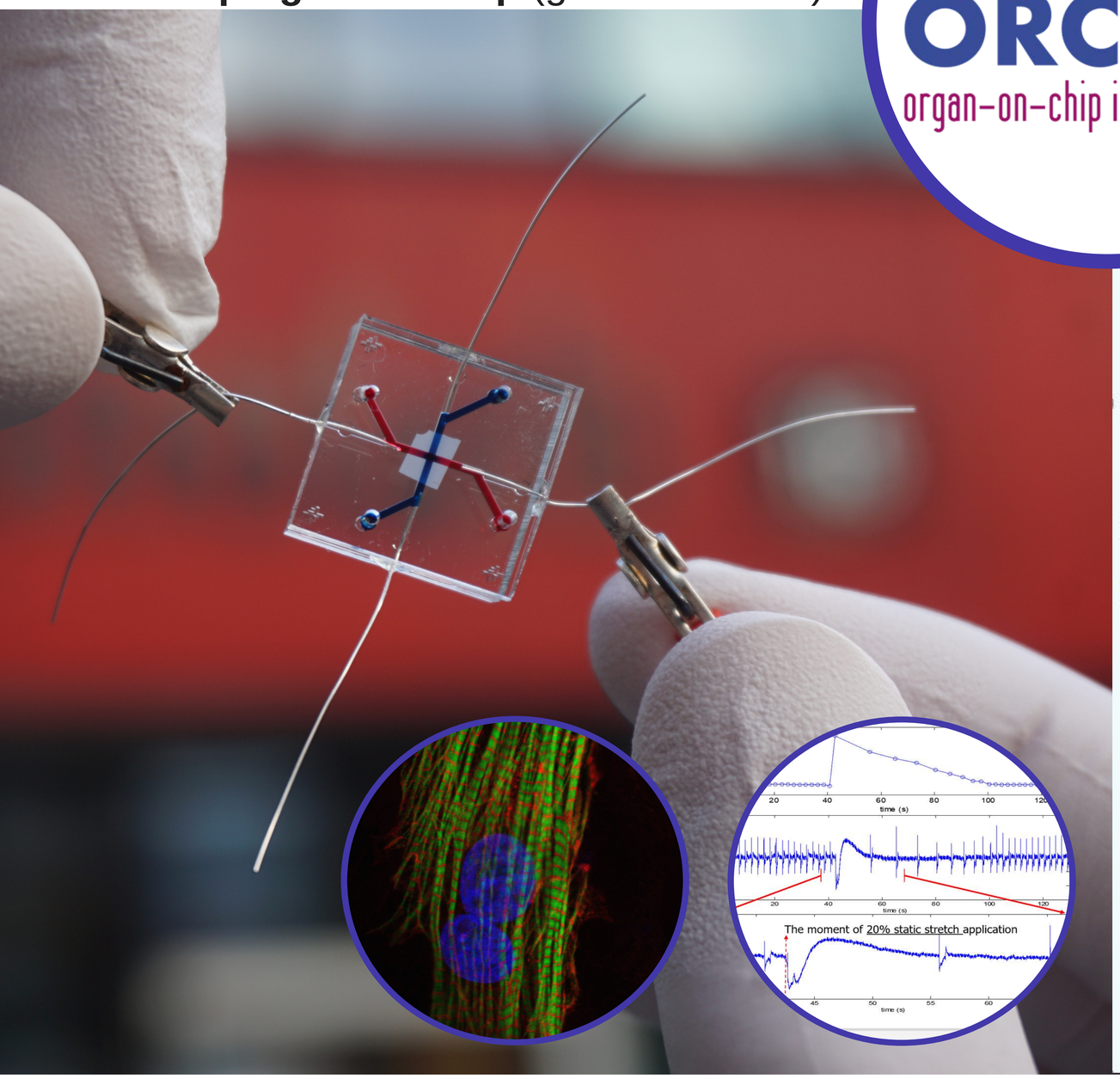
Janny van den Eijnden-van Raaij (1) and Christine Mummery (2)
(1)hDMT; (2)Leiden University Medical Center, the Netherlands

Goals

- **Create a roadmap** for Organ-on-Chip technology
- **Build a network** (academia, industry, regulatory bodies, patient organizations)
- **Raise awareness** by dissemination and communication

Objectives

- **Evaluation of the technology and unmet needs**
- **Identification of ethical issues**, **establishing standards and identifying measures for regulatory implementation**
- **Raising awareness** and **building the ecosystem** (digital reference platform for Organ-on-Chip)
- **Analysis of economic and societal impact, training and education**
- **Developing a roadmap** (guide for R&D)



ORCHID
organ-on-chip in development

ORCHID Research Consortium

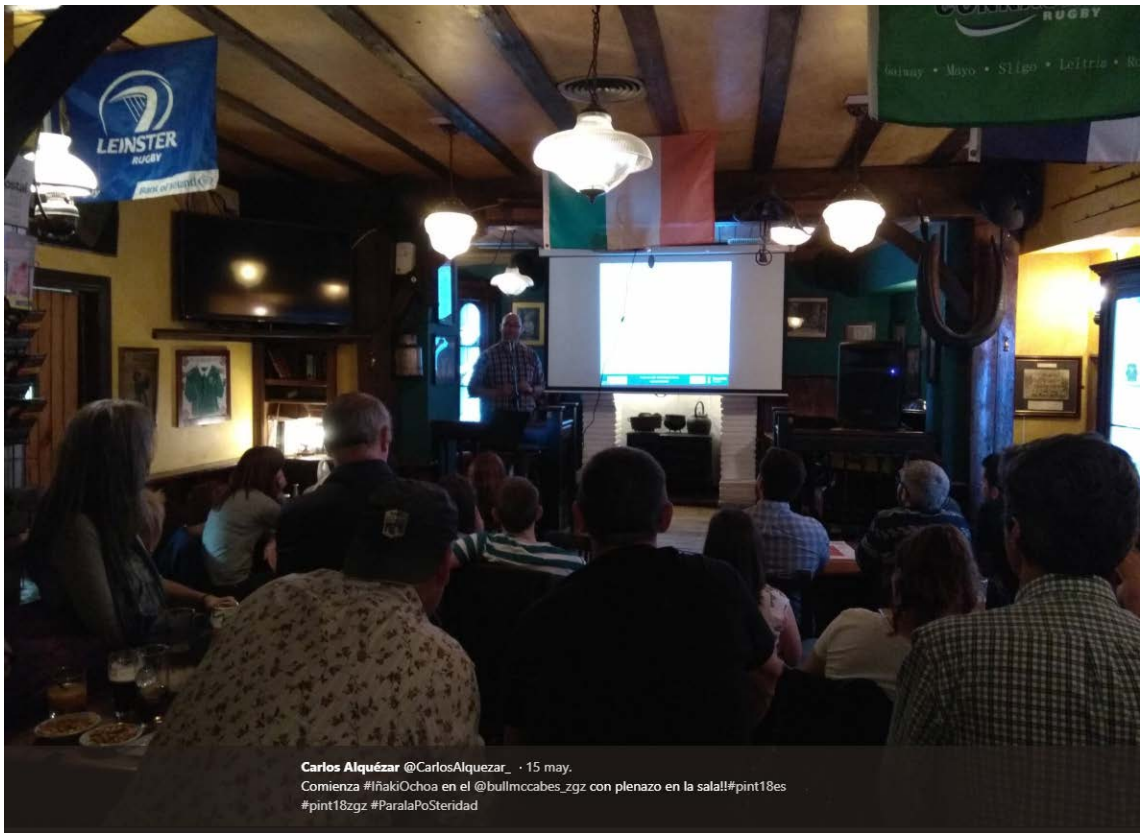
hDMT consortium

Related

Meet and join us!

www.h2020-orchid.eu
www.hdmt.technology
www.noci-organ-on-chip.nl
www.health-eu.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 766884.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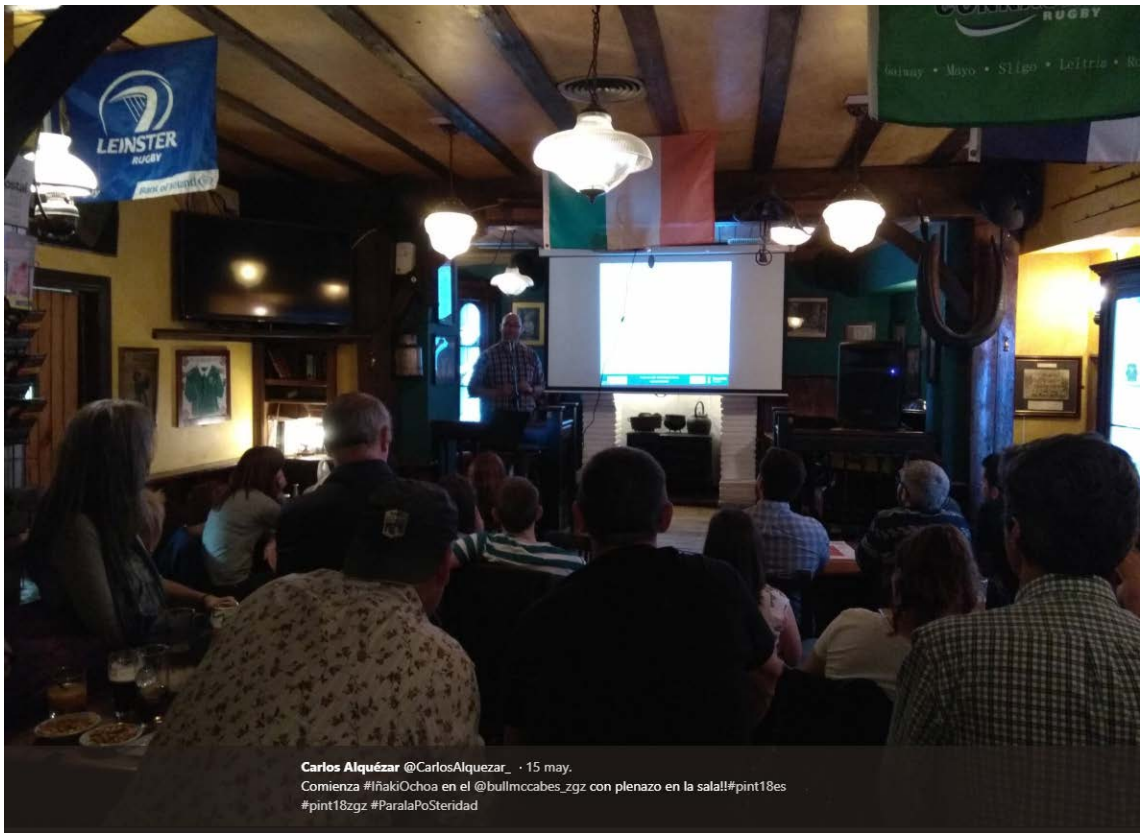
Carlos Alquézar @CarlosAlquezar_ · 15 may.
Comienza #IñakiOchoa en el @bullmccabes_zgz con plenazo en la sala!!#pint18es
#pint18zgz #ParalaPoSteridad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‘ZARAGOZA VALLEY’ CON LA SALUD

*La tecnología y el desarrollo no sólo se fragua en las laderas californianas, **Zaragoza también tiene su particular Silicon Valley**. En esta nueva sección de la revista Aragón Médico iremos mostrando los asombrosos descubrimientos que se desarrollan en la capital aragonesa y cómo éstos pueden ayudar a la profesión médica a mejorar la calidad de vida del paciente. La ciencia en Zaragoza trabaja en temas como las células madre para crear un corazón, en la digitalización de las muestras patológicas, en la creación de tejidos artificiales…. Abrimos esta sección con un reportaje sobre los chips microfluídicos y cómo éstos pueden ayudar a entender el comportamiento de las células, facilitando así el descubrimiento de fármacos más eficaces contra los tumores cancerígenos.*

“Utilizamos la microtecnología para que las células actúen en el laboratorio como si estuviesen en el cuerpo humano”

El grupo de investigación de Mecánica Aplicada y Bioingeniería (AMB), del Instituto de Investigación en Ingeniería de Aragón-I3A, ideó hace ocho años una línea de trabajo que se centra en crear dispositivos de plástico capaces de imitar el entorno que tiene la célula cuando está dentro del cuerpo humano.

Son chips microfluídicos para cultivos celulares que, como nos explica **Ignacio Ochoa**, coordinador del proyecto junto a **Luis Fernández**, “nos permiten generar estructuras, cámaras y canales, a la escala de la célula. Con esta tecnología se puede reproducir la disposición de las células, tal y como están en el organismo”. Es decir, “utilizamos la microtecnología para que las células actúen en el laboratorio como si estuviesen en el cuerpo humano”.

Además, continúa, “se puede aprovechar el pequeño tamaño de las cámaras y canales de estos chips -en el orden de magnitud de las micras- para emplear células específicas de cada paciente”. Un avance que, subraya Ignacio Ochoa, “nos acerca a la medicina personalizada, reto prioritario en la salud del siglo XXI”.

> Los chips microfluídicos para cultivo celular, también conocido como Organ on Chip, son una tecnología que se está desarrollando en el Instituto de Investigación en Ingeniería de Aragón-I3A y que permite simular in vitro la organización de las células en los tejidos humanos.

> La utilización de estos dispositivos, con células de cada paciente, permitirá hacer ensayos de fármacos personalizados y reducirá, en un futuro, el uso de animales de experimentación.

En definitiva, gracias a este ‘recipiente’, señala Ochoa, “podemos reproducir la respuesta que tienen las células frente a los fármacos” y, “nos da posibilidades de encontrar tratamientos más eficaces”.

De hecho, uno de los principales logros que han conseguido a lo largo de este tiempo es “ser capaces de detectar un punto débil del glioblastoma”. Un importante paso para poder encontrar un fármaco que combata este tipo de tumor que en la actualidad es de los más comunes y letales.

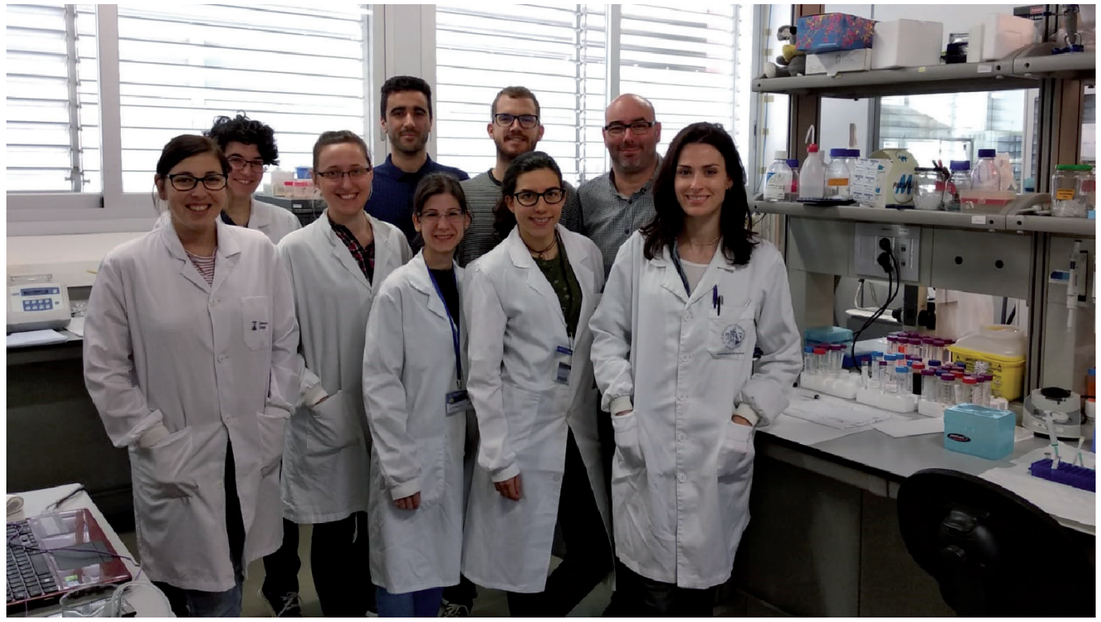
De una estructura bidimensional a una tridimensional

Antes de que llegase esta tecnología, en el laboratorio solo se utilizaba la placa de petri, pero “este tipo de recipiente es bidimensional y los seres humanos somos estructuras tridimensionales altamente organizadas”, indica el coordinador del proyecto. Es por ello que “en muchas ocasiones, los resultados positivos que se obtenían en el laboratorio no se correspondían con la eficacia en la práctica clínica”.

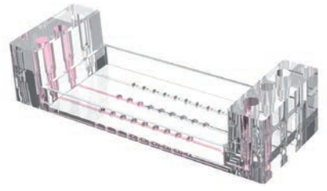
Por ejemplo, explica Ignacio Ochoa, “sucedía que, utilizando la placa petri, podíamos obtener resultados que indicaban que un fármaco destinado a combatir tumores cerebrales mataba el 70% de las células cancerígenas”. Sin embargo, “cuando ese tratamiento se aplicaba en ensayos clínicos con personas, el resultado era más discreto y solo se ganaban unas semanas más de vida”.

Por otro lado, para simular entornos complejos, “se siguen empleando modelos animales que tratan de compensar la simplicidad de los modelos anteriores”. Sin embargo, con este tipo de práctica tampoco se obtiene resultados certeros ya que “como es obvio, hay diferencias significativas en algunos aspectos entre roedores y humanos, lo que dificulta todavía más los estudios de ciertas enfermedades”.

Ahora gracias al diseño interno 3D de los chip microfluídicos, que permite que las células tengan estimulaciones mecánicas y químicas y sensación de estar dentro de un ser vivo, concluye, “tenemos datos reales y sabemos de antemano cuál va a ser el resultado real en el paciente”.



Los miembros de la línea de microfluídica del grupo de investigación de Mecánica Aplicada y Bioingeniería (AMB).

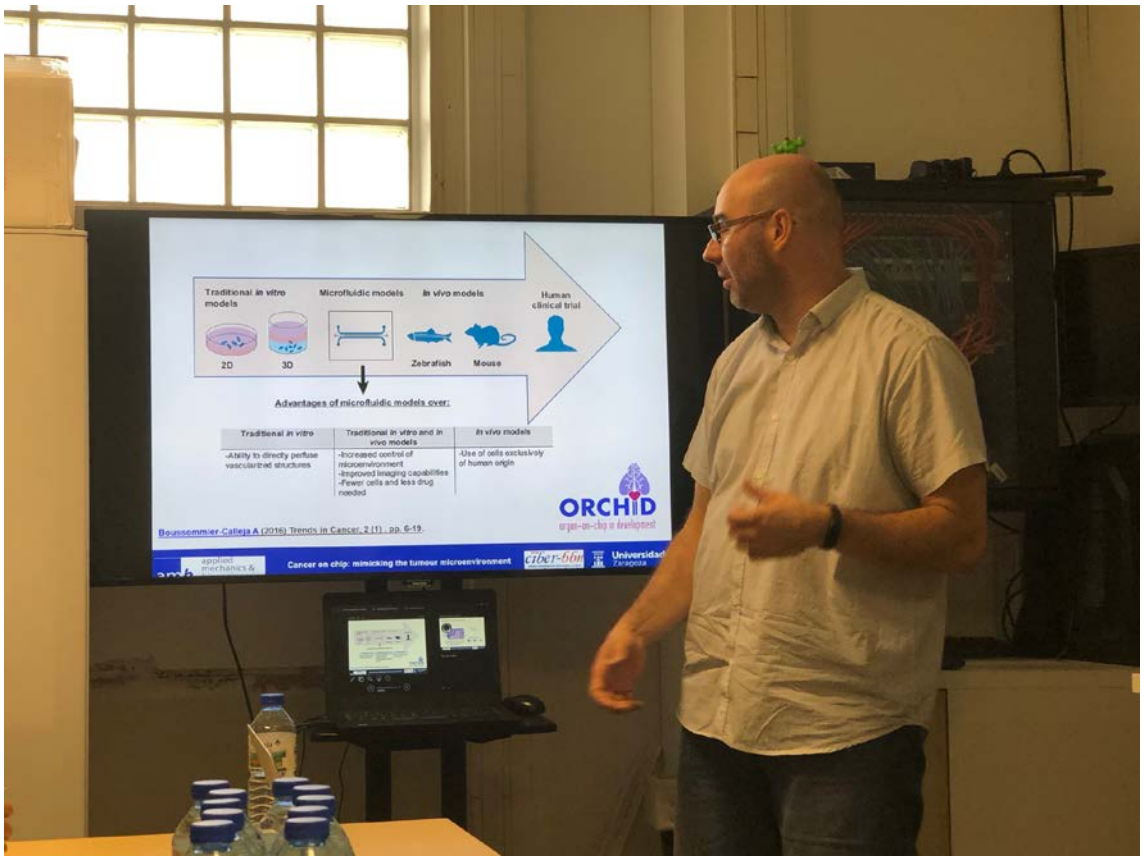


En la actualidad el uso de estos chips es exclusivo de la empresa aragonesa Beonchip. Precisamente, su directora de I+D y cofundadora, Rosa Monge, formaba parte del grupo de investigación de Mecánica Aplicada y Bioingeniería del I3A cuando nació la idea.

Tecnología Organs-on-Chips

Los chips microfluídicos forman parte de la tecnología conocida como Organs-on-Chips. En Aragón, existe un consorcio de grupos de investigación que trabaja actualmente en ella y está liderado por la línea de microfluídica del grupo de Mecánica Aplicada y Bioingeniería AMB del Instituto de Investigación en Ingeniería de Aragón. El consorcio cuenta también con la colaboración de otros grupos de la Universidad de Zaragoza y otras entidades como el Instituto de Investigación Sanitaria de Aragón (IIS Aragón) y el Servicio Aragonés de Salud (SALUD).

El grupo de AMB también participa en el proyecto europeo Organ-on-CHip In Development (ORCHID) lo que le va a permitir ir un paso allá en sus investigaciones, asimismo, trabajan ya para facilitar y acelerar el desarrollo de prototipos y sistemas celulares validados que imitan el tejido humano enfermo o sano.


Traditional in vitro models
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Advantages of microfluidic models over:
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Traditional in vitro and in vivo models
In vivo models
-Ability to directly perfuse vascularized structures
-Increased control of microenvironment
-Improved imaging capabilities
-Fewer cells and less drug needed
-Use of cells exclusively of human origin
Boussommier-Calleja A (2016) Trends in Cancer, 2 (1) , pp. 6-19.
ORCHID
Cancer on chip: mimicking the tumour microenvironment
ciber-bbn

Activated allogeneic human primary NK cells efficiently kill colorectal cancer cells in 3D spheroid cultures.

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0. Abstract

Haploidentical Natural Killer (NK) cells have been shown as an effective treatment of haematological malignancies with poor prognosis. In contrast, solid carcinomas are characterised by a 3D architecture that provide specific surviving advantages and resistance against chemo- and radiotherapy. We have recently developed a protocol to activate ex vivo human primary NK cells using B lymphoblastic cell lines, which generates NK cells able to overcome chemoresistance in haematological cancer cells. Here we have analysed the activity of these allogeneic NK cells against colorectal (CRC) human cell lines growing in 3D spheroid culture.

1.Material and Methods

2) Dot-Plot of a representative spheroid control showing the percentage of viable cells after 4 days (Ann-V^-/AAD^-) (A). PS exposure on plasma membrane (annexin-V) and membrane permeabilization (7AAD) were analysed by flow cytometry. (B) CRC spheroid area evolution in control group shows tumour progression in absence of treatment along the study time course. Monocellular suspensions from 2D or 3D cultures were analysed by flow cytometry for the expression of HLA-ABC (C) and ICAM-1 (D). Bar charts represent the Mean Fluorescence Intensity in 2D (white) and 3D (black) conditions for HLA-ABC and ICAM-1. Insets in the figure show histograms of a representative determination. The dotted line corresponds to isotype control, the black line to 2D conditions and the grey line to 3D conditions. Data in the graphics are represented as the mean±SEM of at least 5 independent experiments. *p<0.05, **p<0.01, ***p<0.001 statistically significance was analysed by Wilcoxon test.

3.1) NK cells were enriched by MACS whether A) from fresh PBMCs or B) after a 5 day incubation with R69-LCLs. Subsequently they were incubated with HCT116 cells seeded in monolayers (circles) or spheroids (squares) at low (up to 3:1) or high (9:1) e:t ratios. PS exposure on plasma membrane (annexin-V) and membrane permeabilization (7AAD) were analysed by flow cytometry. Results are presented as mean +/ SEM of at least 3 independent donors.

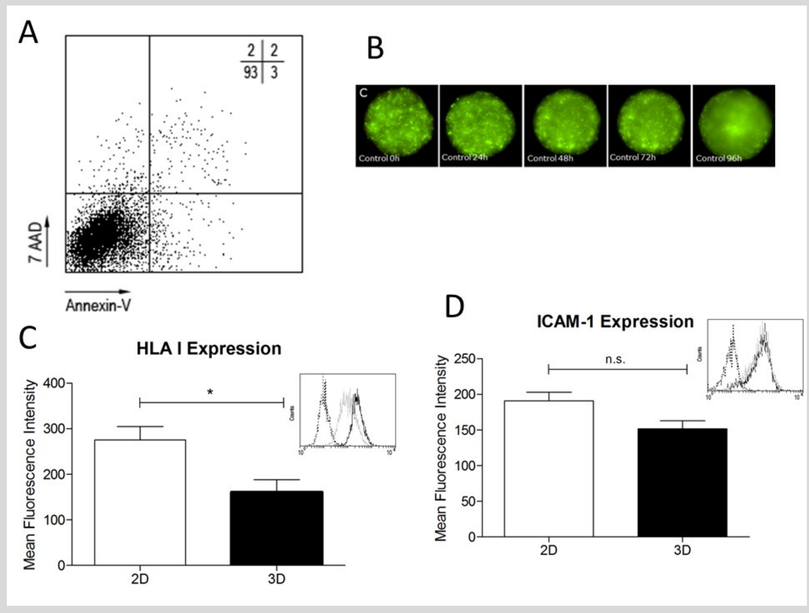
3.2) (A, B and C) Fluorescent images of HCT116 cells (green) and NK cells (red) in a high e:t ratio during 96 hours treatment. Area evolution of CRC spheroids after treatment with nNK (A), activated NK cells (B), and control group with no NK presence (C). (D, E). One of the at least three experiments performed with 3 different donors in which relative spheroid area was measured. (D) Naïve NK cells were able to reduce partially the tumour size but after 72h, spheroids star to grow and no clear effect after 96h. (E) Activated NK cells at high e:t ratio are able to diminish drastically CRC spheroids size until almost complete elimination of GFP signal expressed by CRC cells.

4) (A, B, C and D) Fluorescent images of HCT116 cells (green) and NK cells (red) in different e:t ratio after 96 hours of co-culture. (E, F and G) Relative area progression of the spheroids after treatment with different e:t ratio of activated NK cells from 3 different donors. (B and E) correspond to a 3:1 ratio of activated NK cells, (C and F) shows results obtained from the treatment of NK cells at a 6:1 ratio. (D and G) describe the 9:1 ratio activated aNK cell cytotoxic response.

5) GFP-HCT-116 cells were embedded in a 1.2 mg/ml collagen hydrogel within the central microchamber. After collagen hydrogel polymerization, eFluor670-labelled NK cells were perfused through one of the lateral microchannels. A time lapse movie was performed.

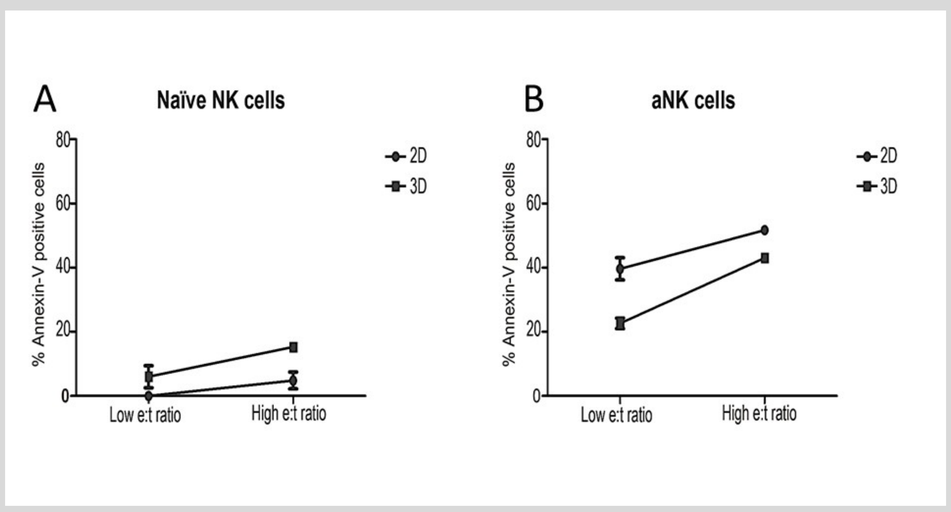
6) Time lapse of the central planes of an CRC spheroids (green) obtained by confocal microscopy during the aNK (red) in vitro co-culture at 3:1 e:t ratio. After 24h in co-culture, aNK cells are able to infiltrate the tumor spheroid. This infiltration is observed till the 4th day in which NK cells tends to migrate towards the periphery.

2. Spheroid characterization



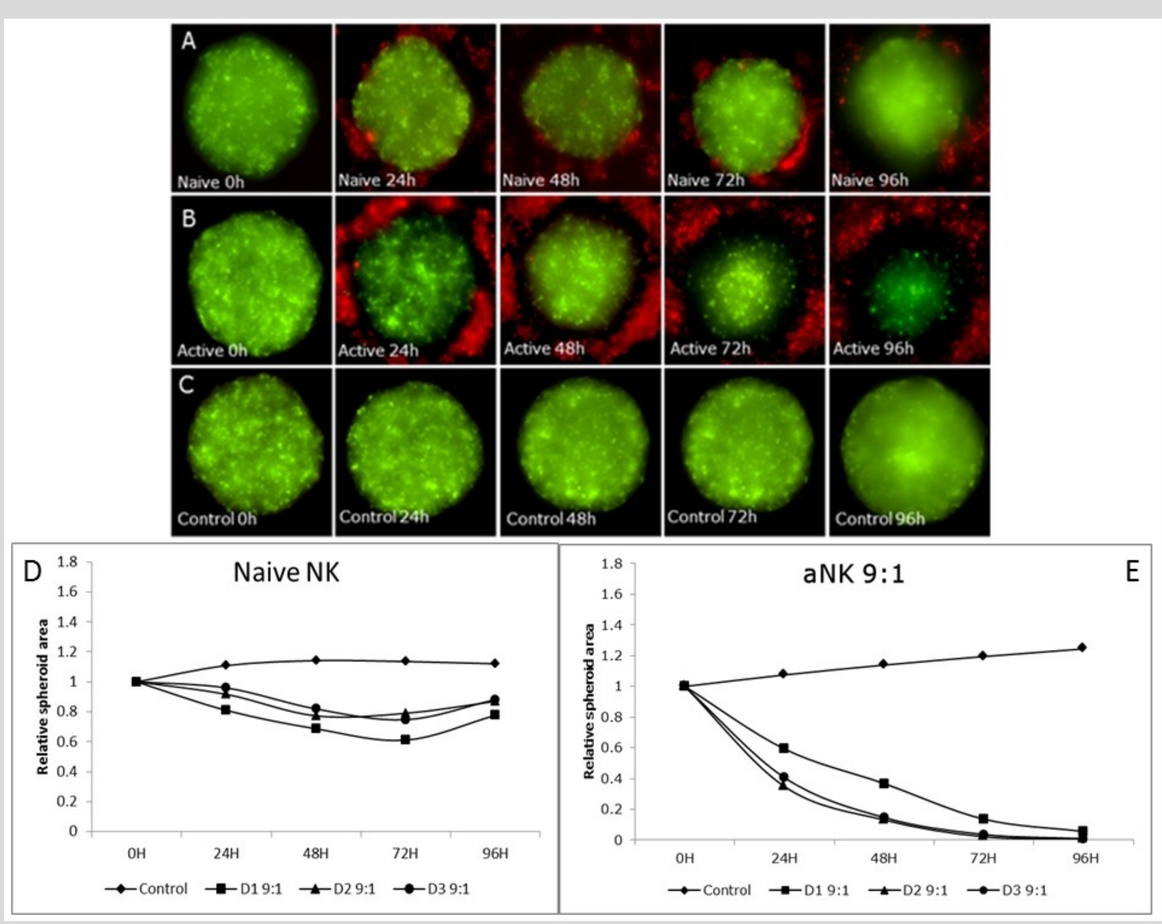
Colorectal cancer cells cultured as 3D spheroids downregulate MHC-I while maintaining high levels of ICAM-1 expression

3. NK Killing



3.1) Naïve and activated NK cells are able to kill colorectal tumour cells in 3D and 2D cultures

3.2) Cytotoxic effect of NK R69-LCL activated cells on HCT116 spheroid compared with naïve NK cells at high e:t ratio.



4. NK density effect

The e:t Ratio determines the the cytotoxic effect of activated NK cells.

5. Video

https://www.nature.com/articles/srep36086#supplementary-information

6. NK invasion

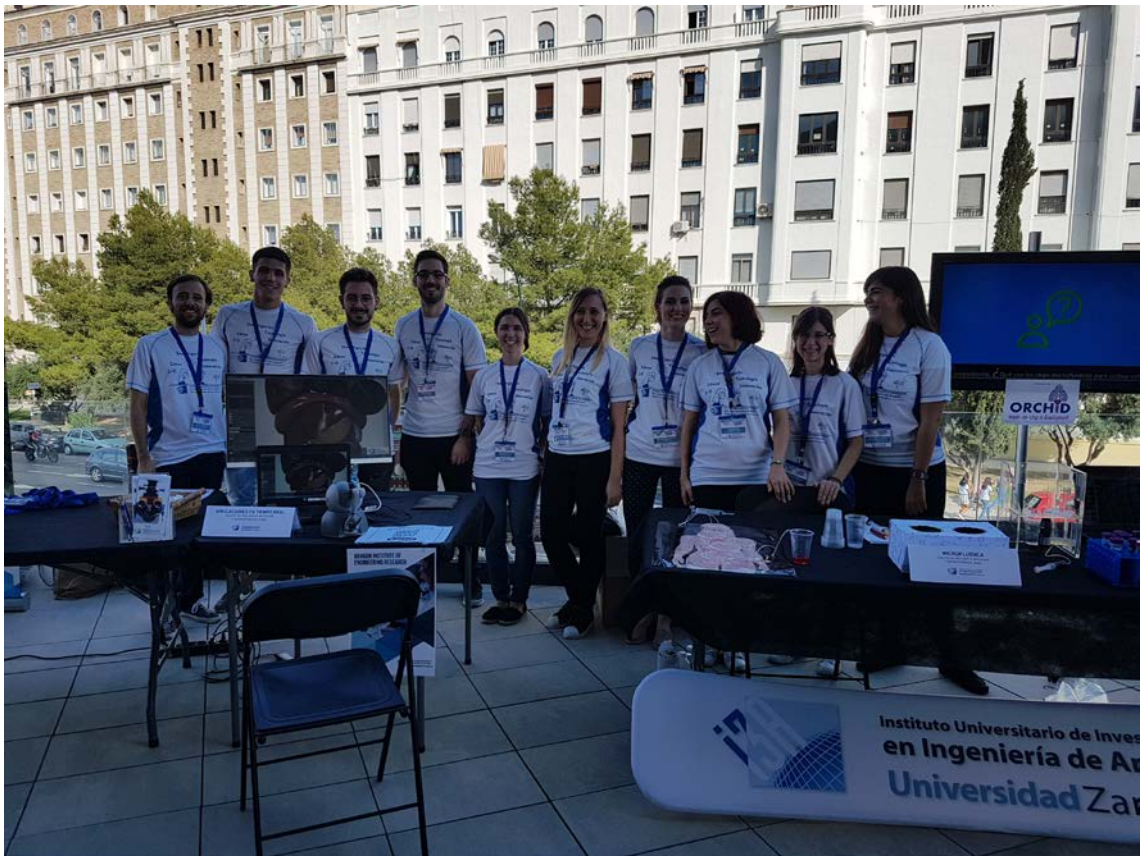
Activated NK cells infiltrate the tumor spheroid at low e:t ratios.

Acknowlegments

Studentships have been provided by Aragon government (DGA) and the Spanish government. S. Olivan financial support was provided by CIBER-BBN. This work has been supported by the national research program of Spain, (projects DPI2015-65401-C3-1-R and BIO2016-79092-R) and the EU H2020 ORCHID Project Nº 766884

Conclusions:

1) Activated NK cells efficiently killed colorectal tumour cell spheroids. 2) Low NK cell density favours cell infiltration, meanwhile higher densities promote tumoral cell death.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en Ingeniería de Ar
Universidad Zar

- Inserm workshops 2018 -

249 Multidimensional imaging and quantitative analysis of cell dynamic's: focus on traffic and cell migration

Date limite d'inscription : 6 avril 2018

Organisateurs : Lydia DANGLOT (Institut de Psychiatrie et Neurosciences de Paris), Franck DEBARBIEUX (Institut de Neurosciences de la Timone, Marseille), Alexandre DUFOUR (Institut Pasteur, Paris)

●●● **Phase I* 20-22 juin 2018, Bordeaux**
●●● **Phase II* Octobre 2018, Paris et Marseille**

250 Intracellular dynamics of molecules: analysis and models

Date limite d'inscription : 6 avril 2018

Organisateurs : Hugues BERRY (INRIA, Villeurbanne), Cyril FAVARD (IRIM, Montpellier), Jean-Baptiste MASSON (Institut Pasteur, Paris)

●●● **Phase I* 25-27 juin 2018, Bordeaux**
●●● **Phase II* 26-29 novembre 2018, Lyon**

251 Non coding RNA: from detection to function

Date limite d'inscription : 1er juin 2018

Organisateurs : Sébastien PFEFFER (IBMC-CNRS UPR 9002 - Université de Strasbourg), Claire ROUGEULLE (UMR 7216 - Université Paris Diderot, Paris)

●●● **Phase I* 24-26 septembre 2018, Bordeaux**
●●● **Phase II* 6-8 novembre 2018, Paris**

252 DNA/RNA nanoengineering: biological and biomedical applications

Date limite d'inscription : 29 juin 2018

Organisateurs : Gaëtan BELLOT (Inserm U1191, Montpellier), André ESTEVEZ-TORRES (UMR 8237-Laboratoire Jean Perrin, Paris), Didier GASPARUTTO (CEA, Grenoble)

●●● **Phase I* 26-28 septembre 2018, Bordeaux**
●●● **Phase II* Octobre 2018, Montpellier**

253 Organ-on-chip: understanding and mimicking living organisms for better treatment

Date limite d'inscription : 29 juin 2018

Organisateurs : Nathalie PICOLLET D'HAHAN (CEA-BGE-Biomics, Grenoble), Donald K. MARTIN (TIMC-IMAG, UGA, Grenoble), Christophe MARQUETTE (ICBMS-Université Lyon1-CNRS, Villeurbanne)

●●● **Phase I* 15-17 octobre 2018, Bordeaux**
●●● **Phase II* 22-25 octobre 2018, Lyon et Grenoble**

254 Principles and Methods of Population Health Intervention Research

Date limite d'inscription : 29 juin 2018

Organisateurs : François ALLA (Inserm UMR 1219 - Université de Bordeaux), Bruno GIRAUDEAU (Inserm UMR 1246, Tours)

●●● **Phase I* 17-19 octobre 2018, Bordeaux**
●●● **Phase II* 24-25 octobre 2018, Bordeaux et Tours**

PLACES LIMITÉES à 80 participants par atelier (Phase I)

Information and registration :
Pôle des Ateliers de l'Inserm
101 Rue de Tolbiac
75654 Paris Cedex 13
Tel : +33 (0) 1 44 23 62 04 or 62 03
Fax +33 (0) 1 44 23 62 93
ateliers@inserm.fr

Objectifs

*** Phase I : théorique**

- **Faire le point** sur les questions et les méthodes émergentes en biologie ou en biomédecine.
- **Diffuser** rapidement des techniques de pointe.

*** Phase II : pratique**

- **Faire acquérir une maîtrise technique** effective par une formation pratique sur mesure.

Inserm
La science pour la santé
From science to health

Rédaction : Ateliers (DRH-BFSSR) - Réalisation : Julie Arqué (DRH-MO) - Mise à jour : Audrey Peloni (DRH-MOM) - Impression : service des affaires générales, Administration du Siège - Février 2018

FUTURNANOTECH
"Terminator"

Fnac Plaza España.
Martes, 30 de octubre, 19 h.

Proyección de fragmentos de la película para la charla sobre la visión de la Nanotecnología en la narrativa actual.

Intervienen: Dr. Iñaki Ochoa (investigador del I3A), Alfredo Moreno (crítico cinematográfico y novelista) y Jerusalén Jaime.

Instituto Universitario de Investigación
en Nanociencia de Aragón
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1542

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AVATAR

HUMAN ORGAN AND DISEASE MODEL TECHNOLOGIES

TU/e Technische Universiteit Eindhoven University of Technology
Where innovation starts

noci Netherlands Organ on Chip Initiative

INTERNATIONAL ORGAN-ON-CHIP SYMPOSIUM 2018

IOOCS18

SAVE THE DATE !

EINDHOVEN, THE NETHERLANDS

NOVEMBER 8-9, 2018

Save the date for IOOCS18!
Researchers from different disciplines, organisations and countries will share their knowledge, expertise and plans. There will be opportunities for establishing new collaborations to tackle the many challenges and meet the needs of this exciting and innovative field, and to further extend and strengthen the existing network. IOOCS18 is a unique opportunity for young scientists to meet international leaders in the field of organ-on-chip technology and to interact with them during a 'Meet-the-Experts' lunch.

Symposium Format
IOOCS18 will have the same format as the previous IOOCS symposia in Twente (the Netherlands) and Lausanne (Switzerland):

- a two-day (lunch-to-lunch) meeting
- meet-the-experts lunch
- interactive poster session
- plenary sessions only
- plenty of time for interaction, networking, exchanging results and new developments.

Abstracts and registration
Submitted abstracts will be selected either for an oral presentation or for the interactive poster session. Information about registration and abstract submission will follow soon.

Organising committee IOOCS18
Scientific programme
Jaap den Toonder (chair)
Albert van den Berg
Ronald Dekker
Janny van den Eijnden-van Raaij
Christine Mummery
Mieke Schutte
Cees Storm

Logistics
Inge Haest

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Building blocks for a European Organ-on-Chip roadmap

The role of the European Organ-on-Chip Society (EUROoCS)

Massimo Mastrangeli[1], Sylvie Millet[2], Christine Mummery[3], Peter Loskill[4], Dries Braeken[5], Wolfgang Eberle[5], Madalena Cipriano[4], Luis Fernandez[6], Mart Graef[1], Xavier Gidrol[2], Nathalie Picollet-D'hahan[2], Berend van Meer[3], Ignacio Ochoa[6], Mieke Schutte[7] and Janny van den Eijnden-van Raaij[7]

[1] Delft University of Technology (Delft, the Netherlands); [2] CEA (Grenoble, France); [3] Leiden University Medical Center (Leiden, the Netherlands); [4] Fraunhofer IGB (Stuttgart, Germany); [5] imec (Leuven, Belgium); [6] University of Zaragoza (Zaragoza, Spain); [7] hDMT (Eindhoven, the Netherlands)

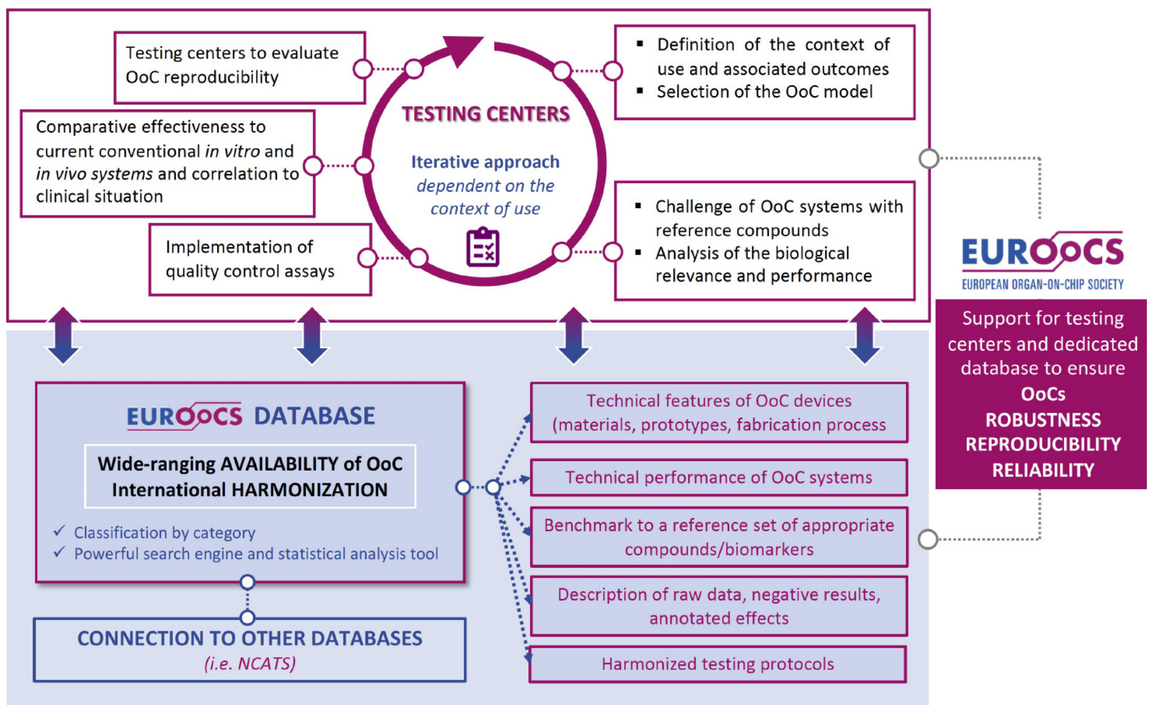
EUROOCS EUROPEAN ORGAN-ON-CHIP SOCIETY

ORCHID organ-on-chip in development

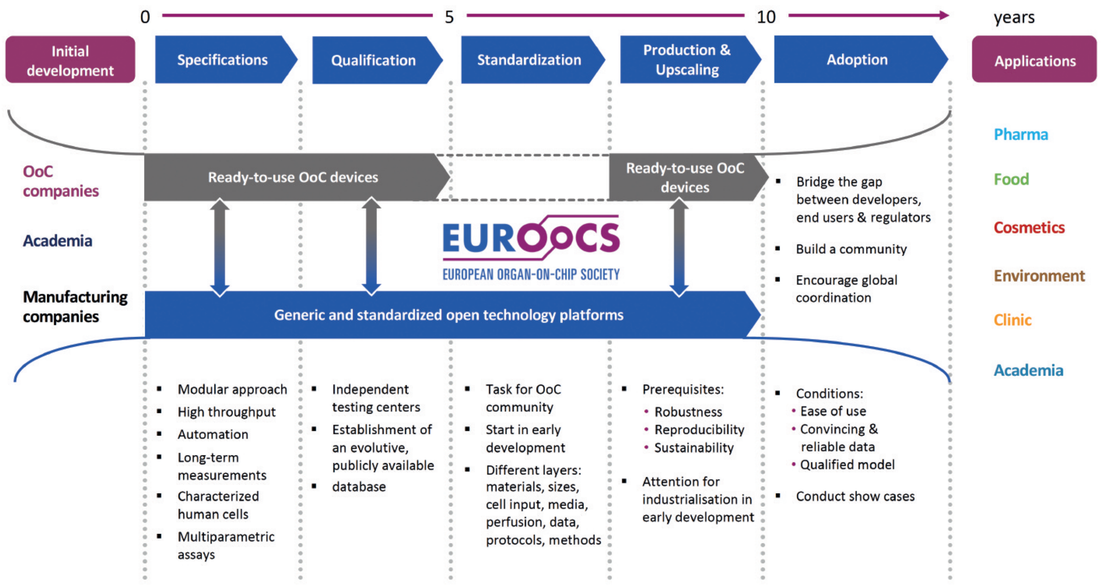
Community building

Dissemination & communication

Qualification process & database



The ORCHID roadmap for OoC development



Membership

JOIN EUROOCS

EUROOCS EUROPEAN ORGAN-ON-CHIP SOCIETY

The European Organ-on-Chip Society (EUROoCS) is an independent, not-for-profit organization established to encourage and develop Organ-on-Chip research, and to provide opportunities to share and advance knowledge and expertise in the field towards better health for all.

For who?

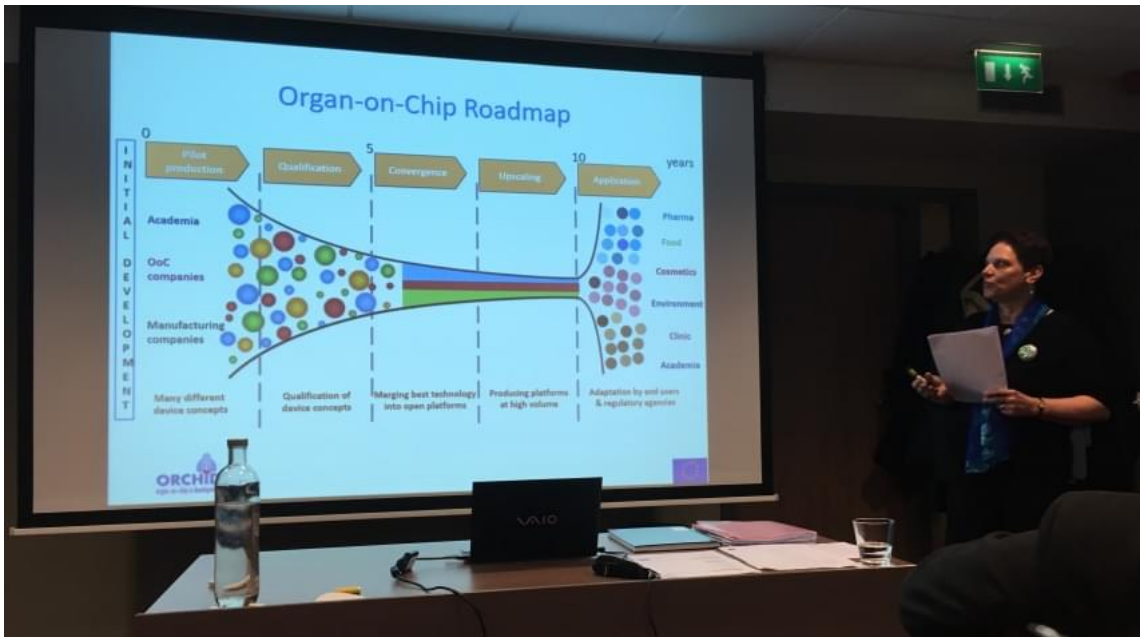
The European Organ-on-Chip Society brings together a broad audience including the general public and institutions (government, health foundations, charities), the academic research community (universities, research Institutes), the pharmaceutical industry, other industries (cosmetics, chemical, environmental toxicity and food industries), hospitals, medical centers and medical practitioners, patients associations, policy makers and testing centers.

www.euroocs.eu

This work was funded by the European Union's Horizon 2020 Research and Innovation program under grant agreement No. 766884.

101 ALL PARTNERS

101 hDMT



#102 All partners


Innovation
into value
ORCHID
Open

Roadmap and Society for Organ-on-Chip in Europe

#121

from hDMT via ORCHID to EUROoCS

#121

Janny van den Eijnden-van Raaij (1) and Christine Mummery (2)
(1) hDMT; (2) Leiden University Medical Center, the Netherlands

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Community building
dialogue

Dissemination & communication
awareness

Membership
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The European Organ-on-Chip Society (EUROoCS) is an independent, not-for-profit organization established to encourage and develop Organ-on-Chip research, and to provide opportunities to share and advance knowledge and expertise in the field towards better health for all.

EUROoCS[1] was launched on 8 November 2018 during the 3rd International Organ-on-Chip Symposium (IOOCS18) at the University of Technology in Eindhoven, the Netherlands.

[1]EUROoCS is one outcome of the Horizon 2020 project ORCHID (Organ-on-Chip In Development), that aims to create a roadmap for Organ-on-Chip technology and to build a network of stakeholders.

Membership
Membership is open to individual researchers worldwide and others with an interest in Organ-on-Chip technology. Benefits include access to the digital Organ-on-Chip platform (with forum, research projects, experts' profiles and more), discounted registration for the annual conference and up-to-date information on advances and activities in the field.

Active members
Active membership is open to researchers in the Organ-on-Chip field. For this membership researchers must have a professional qualification (PhD, MD, MSc or equivalents in experience). Membership entitles voting at the members' meetings. Fees: € 40,- per year.

Student members
Student membership is open to students enrolled in a graduate program leading to an advanced degree (PhD, MD, MSc or BSc). Upon receipt of an advanced degree a student member is eligible for active membership. Membership entitles voting at the members' meetings. Fees: € 20,- per year.

Affiliate members
Affiliate membership is open to individual representatives of industry, regulatory agencies and others with an interest in Organ-on-Chip technology who do not qualify for active or student membership. Affiliated members are not entitled to vote at the members meetings. Fees € 40,- per year.

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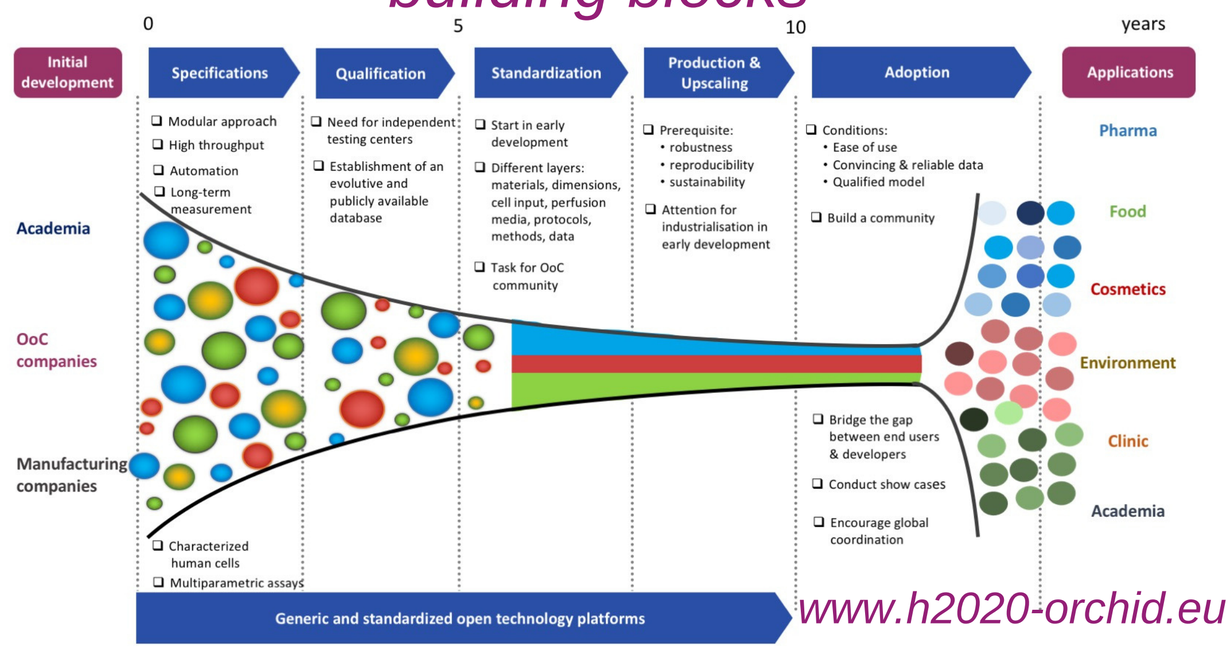
annual **EUROoCS conference 2019**
Registration is open now!

ORCHID
organ-on-chip in development

Roadmap
building blocks

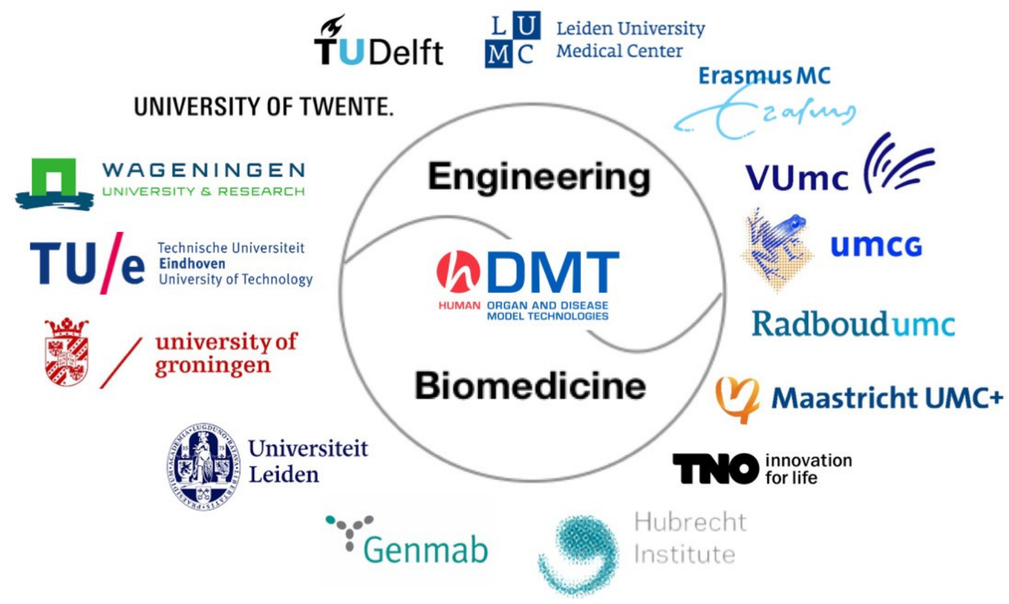


www.h2020-orchid.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 766884

Dutch Organ-on-Chip Consortium
www.hdmt.technology

Organ-on-chip Consortium
Bottom-up initiative since 2015



*h*DMT's dream

Imagine:
organ-on-chip models
that mimic any part of the human body,
to study human sickness and health,
for personalized disease treatment
or even prevention
available and affordable for everyone.

#160

ORCHID

organ-on-chip in development

BUILD THE ECOSYSTEM FOR ORGAN-ON-CHIP TECHNOLOGY

IDENTIFY ETHICAL ISSUES AND DRIVE STANDARDIZATION

ANALYSE THE IMPACT ON ECONOMY, SOCIETY, TRAINING AND EDUCATION

ROADMAP FOR ORGAN-ON-CHIP TECHNOLOGY

The Horizon 2020 FET-Open project Organ-on-Chip In Development (ORCHID) started in 2017 with the goal of creating a roadmap for OoC technology and of building a network of academic, research, industrial, regulatory institutions and others to move OoCs from laboratories into the reality of the citizens of Europe and the rest of the world. ORCHID is a collaboration between seven partners from five European countries, forming the ORCHID Consortium.

LUMC · DMT Human Organ and Disease Model Technologies · Fraunhofer IIS · imec · CEA · Universidad Zaragoza 1542 · TU Delft

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 766884

#140

EUROoCS

EUROPEAN ORGAN-ON-CHIP SOCIETY

CONFERENCE 2019

Graz, Austria, 2-3 July 2019

eurooc2019.eu

Organising Commitee

Torsten Mayr, Graz University of Technology, Austria (Chairman)
Maria Tenje, Uppsala University, Sweden
Peter Loskill, Fraunhofer IGB/ University of Tübingen, Germany
Alexander Mosig, Jena University Hospital, Germany
Christine Mummery, Leiden University Medical Center/ University of Twente, The Netherlands
Janny van den Eijnden - van Raaij, hDMT, The Netherlands
Irene Dalfen, Graz University of Technology, Austria

Organising Institutions

Institute of Analytical Chemistry and Food Chemistry

EUROoCS - The European Organ-on-Chip Society

Photographing and Video Recording Policy

Please note that it is not allowed to take photos or record videos in the sessions and poster presentations!

IMPRESSUM
Graz University of Technology
Institute of Analytical Chemistry and Foodchemistry
Stremayrgasse 9/II
8010 Graz, Austria
www.analytchem.tugraz.at

The cover picture was provided by Sergey M. Borisov.

EUROoCS
EUROPEAN ORGAN-ON-CHIP SOCIETY

Become part of an expanding network of experts

Help to move emerging Organ-on-Chip technology forward

We believe in the power of collaboration. Scientists, industry and regulators meeting to build future Organ-on-Chip platforms together

Stay tuned and join the Organ-on-Chip Society

We welcome everyone with a genuine interest in this field

Member benefits

- enjoy discounted registration fee for the Annual Conference
- have exclusive access to the digital platform and forum
- share latest results and news
- find and connect with experts in the field
- receive regular updates on latest developments through our newsletter

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The European Organ-on-Chip Society is an independent, not-for-profit organization established to encourage and develop Organ-on-Chip research and provide opportunities to share and advance knowledge and expertise in the field towards better health for all.
www.euroocs.eu

JOIN **EUROoCS** TODAY

ORCHID (Organ-on-Chip In Development): Achievements and Future Perspectives
Final Meeting Leiden (The Netherlands), 23 September 2019.
Johannes Vermeer room (5th floor), Fletcher Hotel Leiden - Bargelaan 180 - 2333 CW LEIDEN – NL
The hotel is located in the Level Building next to Leiden Central Station and Leiden University Medical Center (LUMC).

8.30-9.00	*Arrival and registration*
9.00-9.15	**Welcome and introduction** Chair: Christine Mummery (LUMC, the Netherlands)
9.15-9.45	**Organ-on-Chip Technology: State-of-the-Art** Christine Mummery (LUMC, the Netherlands) ***Integrating Organ-on-Chip and Computational Modelling for Translational Pharmacology Applications*** Christian Maass (Certara Berlin, Germany) (via telco)
9.45-10.15	**Building Blocks of the Organ-on-Chip Roadmap** *Role of the European Organ-on-Chip Society (EUROoCS)* Janny van den Eijnden-van Raaij (hDMT, the Netherlands)
10.15-10.45	*Coffee break*
10.45-11.15	**Unmet Needs, Key Challenges and Market Perspectives** Massimo Mastrangeli (TU Delft, the Netherlands) Sylvie Millet (CEA, France)
11.15-11.45	**Standardization, Regulation and Ethics** Dries Braeken/Wolfgang Eberle (imec, Belgium)
11.45-12.45	*Lunch*
12.45-13.15	**Economic Impact and Training** Madalena Cipriano/Peter Loskill (Fraunhofer IGB, Germany)
13.15-13.45	**Digital Platform and Community Building** Nathalie Picollet-d'Hahan/Xavier Gidrol (CEA, France)
13.45-14.15	**Awareness and Communication** Luis Fernandez/Ignacio Ochoa (Univ of Zaragoza, Spain)
14.15-15.15	**Future Perspectives** Discussion about opportunities to bridge the Valley of Death Mart Graef (TU Delft, the Netherlands)
15.15	*Closure and drinks*

List of Participants

ORCHID Partners

1. Dries Braeken (imec, Belgium)
2. Madalena Cipriano (Fraunhofer IGB, Germany)
3. Remco den Dulk (CEA, France)
4. Wolfgang Eberle (imec, Belgium)
5. Janny van den Eijnden-van Raaij (hDMT, the Netherlands)
6. Luis Fernandez (Univ. Zaragoza, Spain)
7. Astrid van de Graaf (hDMT, the Netherlands)
8. Mart Graef (TUD, the Netherlands)
9. Massimo Mastrangeli (TUD, the Netherlands)
10. Christine Mummery (LUMC, the Netherlands)
11. Nathalie Picollet-d'Hahan (CEA, France)
12. Mieke Schutte (hDMT, the Netherlands)
13. Ellen Thomassen (LUMC, the Netherlands)

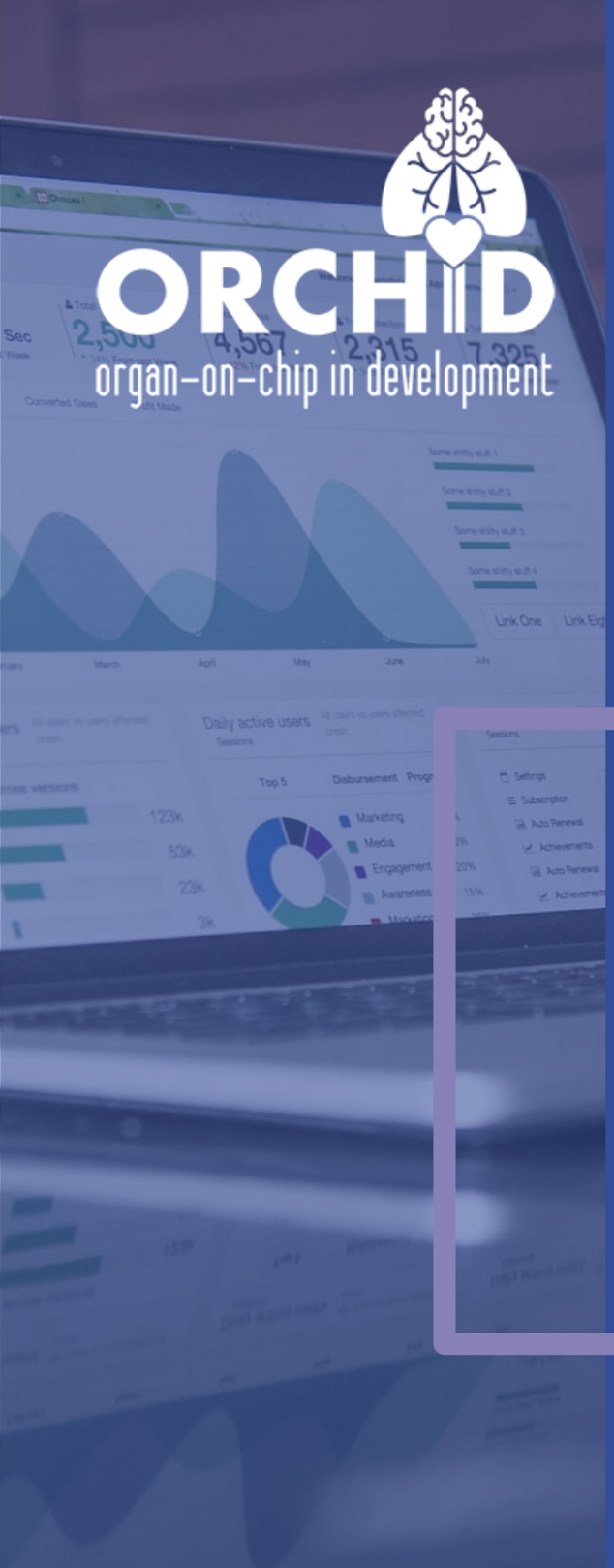
ORCHID Advisory Board

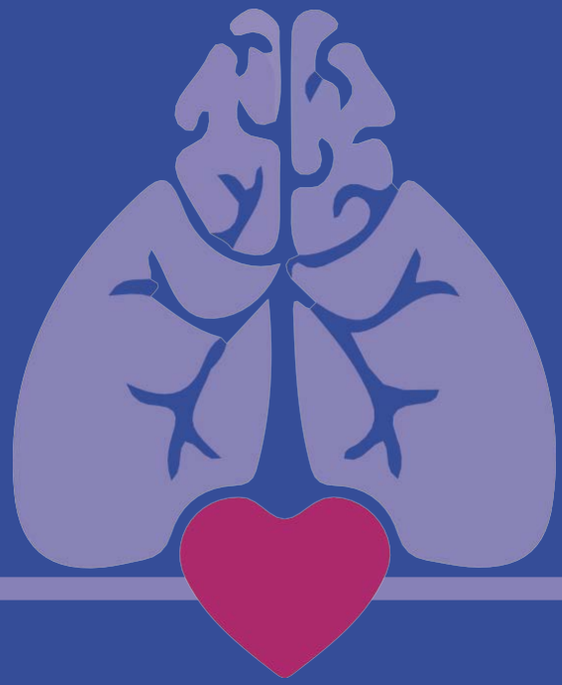
14. Tony Bahinski (GSK, USA)
15. Jacqueline van Engelen (RIVM, the Netherlands)
16. Lorna Ewart (United Kingdom)
17. Torsten Mayr (Univ. of Graz, Austria)
18. Jens Schwamborn (Univ. Luxembourg, Luxembourg)
19. Pietro Siciliano (IMM-CNR, Italy)
20. Ioanna Zergioti (Nat. Tech. Univ of Athens, Greece)

Other Stakeholders

21. Sonja Beken (Federal agency for medicines and health products, Belgium)
22. Ngoc Berris-Pham (Transition Animal-free Innovation, the Netherlands)
23. Peter-Paul van Benthem (Federation Medical Specialists, the Netherlands)
24. Patrick Boisseau (MedTech, CEA, France)
25. Milton Bonelli (EMA, the Netherlands)
26. Lissa Boxy (Innovation Quarter the Hague, the Netherlands)
27. Sandra Coecke (ECVAM, Italy)
28. Patrick Courtney (Association Consortium Standardization in Lab Automation, SiLA, Switzerland)
29. Raquel Fernandez-Horcajada (European Commission, Belgium)
30. Reyk Horland (Tissuse Berlin, Germany)
31. Stefan Krauss (Institute of Basic Medical Sciences, Univ of Oslo, Norway)
32. Niels van Leeuwen (Dutch Enterprise Agency, the Netherlands)
33. Andreas Lymberis (DG Connect, European Commission, Belgium)
34. Christian Maass (Certara Berlin, Germany) (via telco)
35. Terry McCann (TJM Consultancy, United Kingdom)
36. Amélie Moreau (Servier/EFPIA, France)
37. Cor Oosterwijk (VSOP, the Netherlands)
38. Debby Weijers (Dutch Society for the Replacement of Animal Testing (dsRAT), the Netherlands)
39. Rosário Zincke Dos Reis (Alzheimer Portugal, Portugal)

ORCHID
organ-on-chip in development





APPENDIX 6

2019

Communication Strategy

Plan for achieving our communication objectives

ORCHID project

University of Zaragoza – AMB Group

Index

Mission / Impact

01

What is our mission?

Organ-on-Chip (OoC) technology will revolutionize the healthcare domain by offering new and ground-breaking solutions to different industries and especially for regenerative medicine and medication.

Organ-on-Chip In Development (ORCHID) will create a roadmap for Organ-on-Chip technology and the framework to build a network of relevant stakeholders.

Organ-on-Chip technology will revolutionize the healthcare domain by offering new and ground-breaking solutions to different industries and especially for regenerative medicine and medication.

What do we want to achieve?

It is important to make society aware of the potential of OoC, but also of the steps that are still necessary and being taken to mature this technology further and improve its implementation in Europe.

Targets

02

- GENERAL PUBLIC
- POLITICIANS
- SCIENTISTS
- PATIENTS
- REGULATORY AGENTS
- CLINICIANS
- COMPANIES

General Public

Who are they?

*All **citizens** of an **EU country**.*

What is the message?

Let people see the benefits and possibilities of OoC technology to improve the quality of life for European citizens and that OoCs may one day replace animal testing.
Objective is to accelerate the social and economic impact of OoC.

General Public

HOW TO REACH THEM

- *Prepare an explanatory, illustrative document, such as a brochure, summarizing the definition and impact of OoC.*
- *Draw up a list with European scientific dissemination organizations (give examples), student associations.*
- *Contact a scientific dissemination organization, student association to periodically present OoC material at schools, institutes.*
- *Prepare a video explaining the OoC technology and the advantages and deliver it to the organization in charge of the dissemination.*
- *Present OoC at events and conferences (Pint of Science; talks in schools)*
- *Prepare a script with possible questions and answers to advertise on radio and TV (select the most relevant radio channels; invite people to ask questions via the radio)*
- *Prepare an explanatory document about OoC technology to publish in popular dissemination Journals and newspapers.*
- *Communicate about OoC via social networks (Twitter, Linkedin)*

General Public

FOLLOW UP INITIATIVES

- *Continue the previous activities using updated information about OoC technological developments and results achieved*
- *Compile a report every two years for publication in the most influential newspapers in European countries about the most significant advances in the OoC field*

Patients

Who are they?

Associations of patients of different pathologies at European level.

What is the message?

Let the patient see the benefits and possibilities of OoC technology to improve the quality of life.
Innovative technology helping to bring safe new drugs faster to every individual patient.

Patients

HOW TO REACH THEM

- *An explanatory, illustrative document should be prepared, with specific information for the patients.*
- *Draw up a list of 20 most important patient associations in Europe.*
- *Contact the president of the patient association for an interview.*
- *Give a presentation about the technology (personally) and the roadmap of ORCHID focusing on their needs.*

Patients

FOLLOW UP INITIATIVES

- *Invite a patient's association each year to take part in a round table at the EUROoCS congress to explain their problems and / or needs.*
- *Maintain regular contact through newsletters or events.*
- *Each year select new patient associations to contact with in order to obtain feedback on OoC´s application priorities.*

Companies

Who are they?

Pharmaceutical companies that want to develop and validate new medicines and CRO´s.
Food companies (testing food additives/supplements)
Chemical industry (testing chemical compounds)

What is the message?

Let them know and understand the OoC concept, its advantages and the economic-temporal impact using OoC technology. Getting a new drug from an idea in the chemistry lab to market takes many years and billions of euros.
OoCs have the potential to completely transform that system.

COMPANIES

HOW TO REACH THEM

- *Participate in conferences setting up the stand and publish the OoC technology.*
- *Draw up a list of 50 most important Pharmaceutical companies in Europe, try to contact by phone with the 10 most relevant and try to make a presentation of OoC technology. Send an email to the following 20 of the list with information and link to subscribe to the newsletter.*

Companies

FOLLOW UP INITIATIVES

- *Invite companies to take part in the EUROoCS round table together with patients, researchers and clinicians.*
- *Invite them to become members of EUROoCS.*
- *Periodically interact with pharmaceutical companies through various channels (matchmaking events)*
- *Organize specific annual meetings within EUROoCS events with end users to identify their needs and to define ways to increase collaboration.*

Scientists

Who are they?

Scientists with a research activity related to OoC and researchers in areas where this technology is not evident but can have an impact.

What is the message?

Let them know the advances in the field of OoC technology in Europe and what OoC can do to improve their research.

Scientists

HOW TO REACH THEM

- *Choose 3 areas in which OoC can have impact: Food, Biomedicine and Bioengineering*
- *Select key researchers to write a review in each of these areas.*
- *Participate with a stand at scientific events organized by these sectors.*
- *Select journals in different areas and publish articles on the advancement of OoC technology.*
- *Promote the creation of national OoC groups of researchers by country to be able to work more efficiently at a local level.*
- *Social media (Linkedin).*

Scientists

FOLLOW UP INITIATIVES

- *Organize an annual EUROoCS meeting to exchange the newest developments, stimulate new collaborations and align strategies and actions.*
- *Invite research organizations to the EUROoCS round table.*
- *Record EUROoCS round table and conference sessions for uploading onto a specific Youtube channel and on the EUROoCS website.*
- *Draw up an OoC journal managed by EUROoCS to centralize information related to this area of knowledge.*

Clinicians

Who are they?

Medical staff.

What is the message?

Let them know the OoC concept and the implications for the clinic and at the same time get information about their needs.

Clinicians

HOW TO REACH THEM

- *Approach them in medical conferences, setting up a stand.*
- *Draw up a list with the most relevant Health Research Institutes in Europe .*
- *Select the 10 most relevant and try to make a personal interview with the key responsible.*
- *Prepare an explanatory, illustrative document, such as a brochure (specific for clinicians), explaining OoC technology and its benefits and disseminate it among the next 20 Institutes.*
- *Invite medical associations to the EUROoCS round table and request space in their congresses to demonstrate the OoC technology.*
- *Organize outreach sessions in hospitals for resident doctors and medical students (3 per year).*

Clinicians

FOLLOW UP INITIATIVES

Involve clinicians in round tables and conferences.
Develop courses on OoC technology and include them in the curriculum of medical students.
Bridge the gap between clinicians and technicians by specifying clinical needs and technical possibilities

Regulatory Agencies

Who are they?

Independent government commission established by legislative act in order to set standards in a specific field of activity.

What is the message?

Let them see the advances in the field of OoC, the benefits and possibilities of this technology to improve the quality of life for European citizens, and to reduce or in the end replace animal testing.

Regulatory Agencies

HOW TO REACH THEM

- *Continuing the dialogue with regulators by organizing face to face meetings.*
- *Invite them to EUROoCS round table discussions and ask for their advice how to get OoC into the regulatory line.*

Regulatory Agents

FOLLOW UP INITIATIVES

Establish annual visits to report on progress

Politicians

Who are they?

Politicians are people who are politically active, especially in party politics. Positions range from local offices to executive, legislative, and judicial offices of regional and national governments.

What is the message?

Let them learn about OoC technology, the benefits and possibilities of this technology to improve the quality of life of European citizens, and the sustainability of the healthcare system.
Let them realize that OoC might reduce and in the end replace animal testing.
Objective is to accelerate the societal and economic impact.
Enhance funding for this technology, influence call topics.

Politicians

HOW TO REACH THEM

- *Detect at European level the political cabinet related to the development of drugs or animal experimentation in order to present the technology OoC.*
- *Present the ORCHID roadmap and guide to politicians.*

Politicians

FOLLOW UP INITIATIVES

Establish annual visits to report on progress

03

Last Considerations

European funding for further professionalization of EUROoCS