Mastrangeli et al.:
Organ-on-Chip in Development: Towards a Roadmap for Organs-on-Chip

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 prospective 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 Figure S1 and detailed in the following sections.

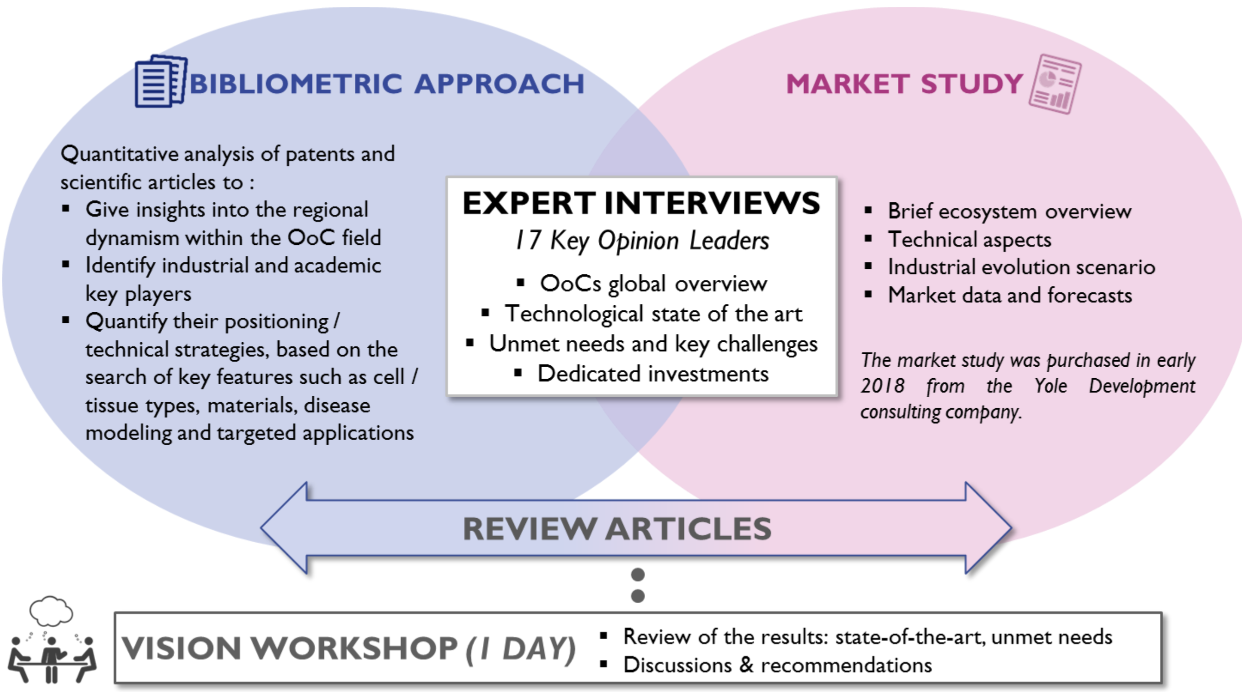

Fig. S1: The methodology of the ORCHID OoC analyses presented in this paper

doi:10.14573/altex.1908271s

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 OoC's regional R&D dynamism, to identify 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-step 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 ensured 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).

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 (Roussel et al., 2018). 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 reportedly consists in laying 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 (Fig. S2). Data was 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.

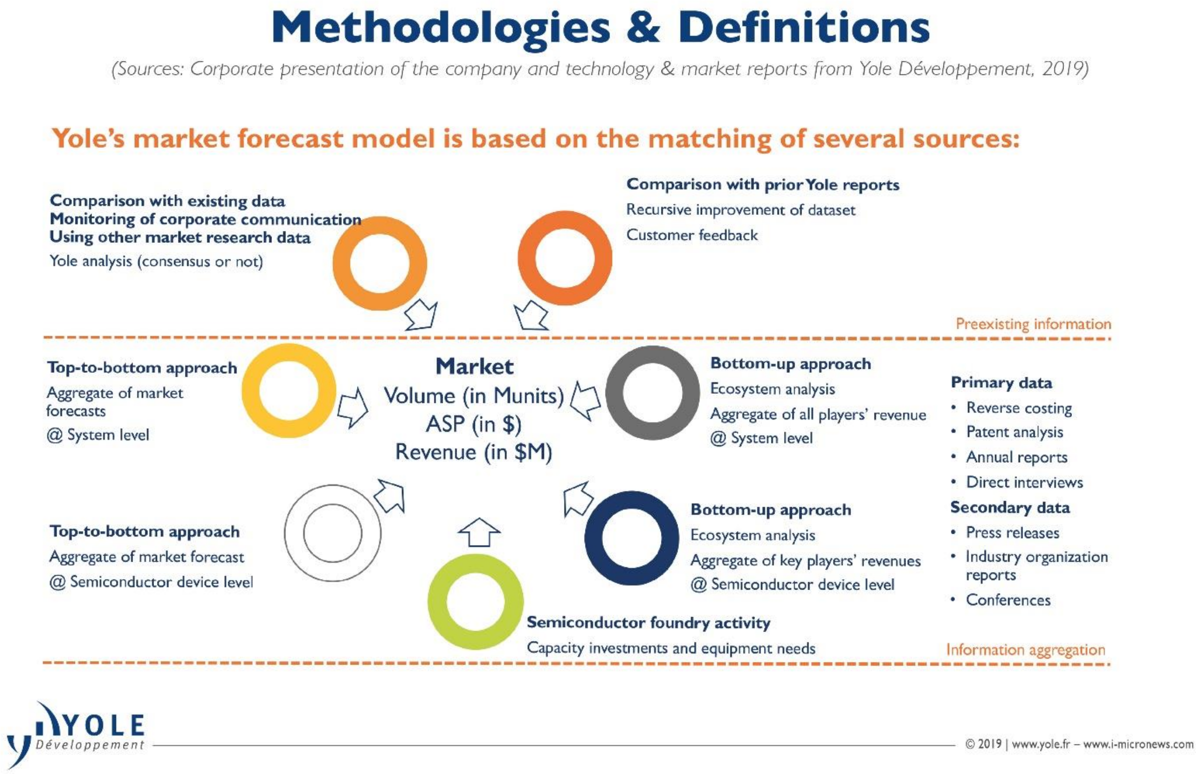

Fig. S2: Overview of Yole Développement methodology for the OoC market report
(reproduced with permission from Roussel et al., 2017).

In the making of Yole's OoC report, 30 entities were interviewed, including:

- 12 start-up companies developing OoC devices and models, including the 2017 market leaders.
- 12 microfluidic device contract manufacturers ("microfluidic foundries") which prototype and will, in the future, mass-produce the microfluidic chips at the core of OoC devices. These players have a good overview of the evolution of the needs of OoC developers and of the quantity of devices produced.
- 6 other players including key opinion leaders in universities strongly involved in OoC research and development, along with end-users of OoC such as pharmaceutical and cosmetics companies, which have a good understanding of how OoC devices are used and how the demand will evolve, depending on technology developments.

Yole's market forecasts were built by aggregating data shared by all these players (volume in units at device level and system level, average selling price in US dollars, growth rate) concerning past, current and future years. Information was gathered among players at different levels of the supply chain, which limits the bias induced when interviewing only one type of player having similar interests and point of view.

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-month 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. S3).

The experts who 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).

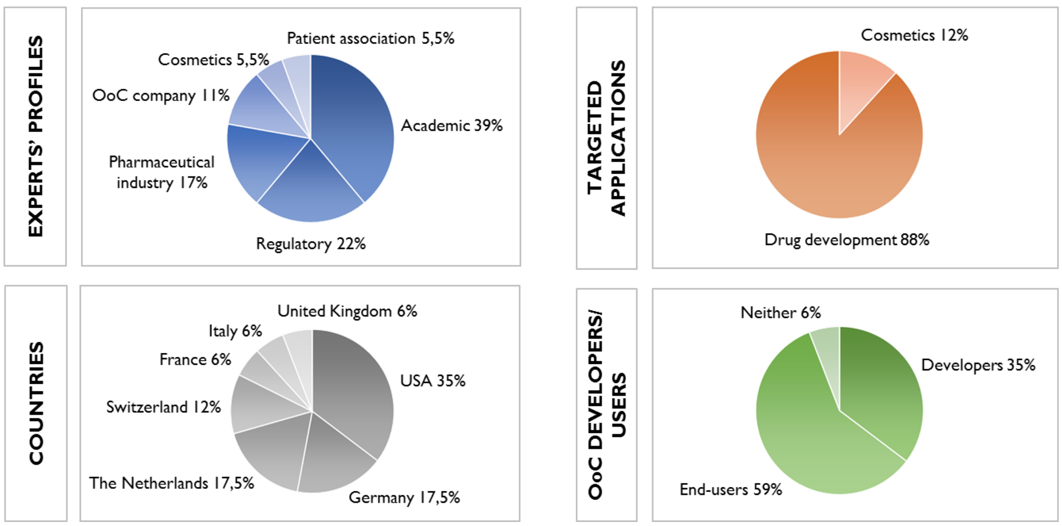

Fig. S3: Profile of the 17 experts interviewed by ORCHID

Within the profile distribution of the interviewed experts (Fig. S3), 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 our inquiry within the period dedicated to the interviews.

In addition to experts' interviews, a short survey composed of a selection of the interview 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).

[1] Participant of the ORCHID Vision Workshop, [2] ORCHID partner, [3] Member of the ORCHID Advisory Board.