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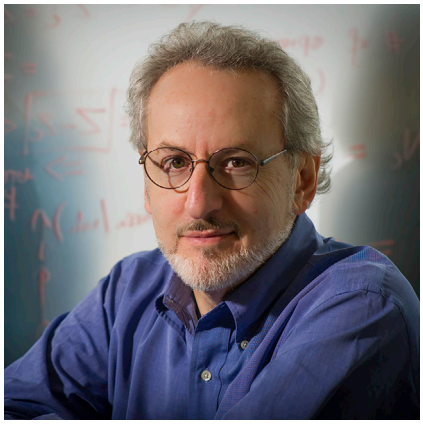
Interview of Don Ingber with Albert van den Berg and Andries van der Meer (University of Twente, the Netherlands, and EUROoCs board members)

Don Ingber is the founding director of the Wyss Institute for Biologically Inspired Engineering at Harvard. His work has led to major advances in mechanobiology, cell structure, tumor angiogenesis, tissue engineering, systems biology, nanobiotechnology, and translational medicine. He is probably most famous for his development of organs-on-chips upon which he founded the company Emulate.

Could you provide a brief historical perspective of how you came to see the importance of biophysics in cell culture?

I started pursuing my hypothesis that mechanical forces are as important as chemicals and genes in cell biology in the mid-1970s when I had my "Aha moment" about cells controlling their shape and mechanics using tensegrity structures in an art class. This was at the same time that I was taking undergraduate courses in development biology where I first saw movies showing how living cells organize into tissues and how embryos form. This led me to read articles and books by early developmental biologists in the late 1800s and early 1900s who essentially described all of biology and development in terms of mechanics (the physics of their day) because biochemistry and genetics did not exist yet. I majored in molecular biophysics and biochemistry as an undergrad where I was learning that the shape and mechanics of molecules governs their function, and so it seemed pretty obvious to me that this must apply to cells as well if it applied to molecules and embryos. Then I saw Judah Folkman's 1978 paper in *Nature* entitled "Role of Cell Shape in Growth Control," which both convinced me that mechanical forces are important in biology and led me to do a postdoctoral fellowship in Folkman's lab. From there, there was no turning back.



Donald E. Ingber

Donald E. Ingber is the founding director of the Wyss Institute for Biologically Inspired Engineering at Harvard University; the Judah Folkman Professor of Vascular Biology in the Harvard Medical School & Vascular Biology Program at Boston Children's Hospital; and a professor of bioengineering in the John A. Paulson School of Engineering and Applied Sciences in the Wyss Institute at Harvard.

Do you have any insights from your active role in building a research community in the US (and in Europe) on what your main lessons ("do"s and "don't"s) would be to stimulate growth in the field?

Organs-on-chips (OoC) and microphysiological systems (MPSs) are the result of crossing boundaries between disciplines and trying to solve problems rather than making small iterative advances in a single narrow scientific field. Thus, it is critical to create organizational structures and incentives for scientists and engineers from different disciplines to collaborate, learn each other's languages (and quirks), and confront big problems head on. This is what we did at the Wyss Institute and it has been incredibly impactful. However, we added another layer of crossing disciplines, which was to recruit scientists and engineers who had industrial experience in product development and entrepreneurial experience, and to blend them into the mix. This proved to be extremely valuable given the focus of this field on trying to solve specific problems and meeting the needs of users in commercial areas (e.g., pharma, biotech, cosmetics, etc.) and academia in order to help patients.

Do you see differences between the US and Europe in the approach of collaboration versus competition in the field?

Our scientific funding systems are different, much like our political and economic systems, so I can't say that I am fully familiar with the European approach. However, from what I have seen at a high level in regards to OoC funding, I would say that Europe is building a wonderful bottom-up approach where interest from the scientists in the trenches is garnering the interest and support of governments and funding agencies. In the US, DARPA kickstarted this effort, with early FDA support, and then NIH has been trying to support it

from the top down. This is great, and it has attracted the attention of bioengineers, but I am not sure that this has been successful in attracting the attention of the hard-core biologists and clinicians who will be the end users. I also see bigger and broader collaborative efforts across multiple institutions in Europe than in the US, but I suspect this could be based more on the independent entrepreneurial style of American scientists.

Do you have any views on the next steps in creating mutual benefit between the communities of stem cell researchers and OoC technology developers?

Clearly one of the biggest challenges in OoC is cell sourcing: we need to be able to access high-quality, human (and animal) cells that can produce the same results in repeated experiments carried out by different groups with the same experimental systems around the world. We also need patient-specific cell sources to pursue challenges in personalized medicine. We need to see greater collaboration between expert teams in these fields and between leading companies in these areas. What you are doing in the Netherlands is great in this regard.

Technically, do you think OoC will move toward a more integrated ("system-on-a-chip") approach or a more "hybrid" approach with different technologies being linked?

We are definitely going to see more and more sensors integrated directly into chips, but to keep them inexpensive and simplify manufacturing, I expect that there will be an even greater focus on developing "in-line" or easy connected analytical systems to provide faster, cheaper, and higher throughput readouts of multiple biological functions (e.g., numerous cytokines, hormones, growth factors, etc.) as well as trans-epithelial electrical resistance (TEER), oxygen levels, etc.

In your opinion, in which field will we see the most widespread adoption and application of OoC? Drug development? Clinical (personalized medicine)? Biomedical research?

I see great value for OoC in all fields, but I see the uptake of the technology leading with biomedical research and drug development (both toxicology and drug discovery) at present. Personalized medicine will soon follow but likely at a slower pace. Once there is a major success in drug development (e.g., using OoC data in a successful drug regulatory package for FDA approval), mechanistic discovery (e.g., uncovering a new disease mechanism or drug target that is proven to have clinical value), or personalized medicine (e.g., expediting clinical trials in patients with a rare genetic disorder), the entire game will change.

Are there emerging application domains for OoC?

Testing potential toxicities of cosmetics, industrial chemicals, radiation exposures, and environmental toxins represent other areas that are beginning to be explored. But the biggest and most unique value for microfluidic OoC I see today is the microbiome, which for the first time can be co-cultured in direct contact with living tissues in an organ-relevant context for days *in vitro*. One other area that will be exciting to explore is modeling young versus old, male versus female, and different genetic subpopulations on chips in terms of responses to both drugs and environmental stimuli given the current limitations we face in addressing these issues in human clinical trials.

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