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How human are our models?

Human-based in vitro models, such as organoids and organs-on-chips, may have the potential to replace certain animal models in preclinical research. But how much 'human' is needed in these models?

Animal models are not only routinely used in biomedical research to investigate fundamental mechanisms but are also at the heart of many preclinical testing protocols for drugs, medical devices or tissue repair and replacement therapies. However, given the high number of drugs that fail in clinical trials, despite passing preclinical testing in animals, the relevance of small animal models in preclinical research has been questioned. Notwithstanding the ethical concerns of exploiting hundreds of thousands of animals, sometimes engineered with questionable disease models that poorly resemble human conditions (even though statistical power remains poor in many animal studies — but that is another story).

So, what are the alternatives? The truth is, for a long time, there was no real alternative to animal models. 2D cell culture, in particular with patient-derived cells, can provide some basic insight into cellular responses to treatments or certain conditions; however, cell responses greatly differ between 2D models and 3D dynamic tissues in a living body. Moreover, the interplay between the many different cell types in our body and their microenvironment cannot be recapitulated in a petri dish. The obvious path is thus to go into 3D and to include more players — and this is where bioengineering comes in.

A variety of bioengineered human-relevant disease models with high clinical mimicry are currently being developed, including organoids, microphysiological systems, organs-on-chips and 3D-printed platforms, which may even be combined to mimic the interactions of multiple tissues. Importantly, they allow real-time readout and imaging, which remains challenging in animal models. Furthermore, many initial limitations of these platforms, such as the lack of vascularization and immune system involvement, are being increasingly addressed.

Various organ-on-chip platforms are now also commercially available, providing a substantial level of robustness and usability. However, such models may lack the complexity needed for their use as a predictive platform. By contrast, self-made systems may be less robust and standardized, but allow the design of customized, complex models, required for human disease modelling. For example, models can be engineered for different pathophysiologies of a given organ, such as, pulmonary fibrosis[1] and pulmonary oedema[2].

Encouragingly, as Sarah Hedtrich and colleagues write in this issue, several clinical trials are exploring patient-derived cancer organoids for the guidance of treatment decisions, and human-relevant in vitro models are finding their way into preclinical drug screening[3]. In addition, the recent FDA Modernization Act 2.0, which has broadened the scope of accepted cell-based models in preclinical testing, may further accelerate the development and adaption of such models.

However, there is no in vitro model (yet) that can replace an entire human, and it may be a lot to ask a researcher working on a specific disease to first develop the appropriate organoid or organ-on-chip. One could argue though that it may take about the same time to develop a disease-specific animal model (and learn how to work with it) as a human-relevant in vitro model of the same disease.

A survey among scientists[4] that do not use organ-on-chip platforms revealed that the lack of ready-to-use-systems and production facilities as well as high entry barriers and costs are the main reasons for not employing these platforms. Moreover, looking at the complexity of some of the most promising new bioengineered treatment modalities, such as immunotherapies, nanomaterial-based vaccines and brain-machine interfaces, animal models may, for now, be indispensable, for example, to investigate complex multi-organ adaptive immune responses or neurological mechanisms.

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Thus, the question remains how 'human' the model has to be and what it takes to get over the activation barrier of routinely using these models in biomedical research? It may all come down to whether you know what your response or mechanism is. You can then start simple and mimic the response with high fidelity, adding greater complexity as needed[5]. And even if you do not know the mechanism, human-based in vitro models may provide the more accurate testing ground. A prime example is the identification of Zika virus tropism towards neural progenitor cells in brain organoids[6], which could not be revealed in rodents, as they lack the additional cortical layer of human brains that contains radial glial cells. Ultimately, the goal should be to reach maximal clinical mimicry, which may be achieved by an in vitro model, the appropriate animal model, or a combination thereof.

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