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Commentary

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Tissue-Engineered Disease Models

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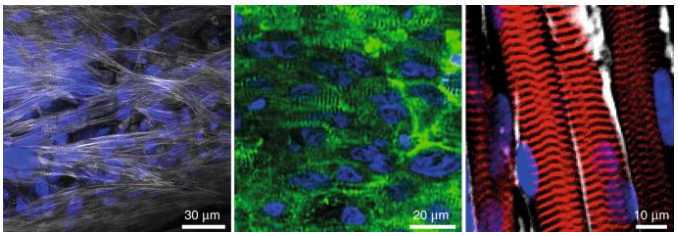
Description

Small-animal models are a cornerstone of biomedical research. Genetic, phenotypic and physiological differences between animals and humans can often be large enough that biomedical results based on animal models are insufficiently representative of the disease in humans. And if the condition is highly dependent on the genetic or epigenetic make-up of the individual, or on their immune status or characteristics of their microbiome, even genetically engineered animal models can fail to recapitulate critical biological aspects of the patient's diseased cells and their microenvironment, their diseased tissue or organs, or their physiology.



Organoids can more faithfully recapitulate the biology of specific tissue and can be used for longer periods, yet they lack proper vasculature and immune cells; and as with animal models, they do not offer the simplicity and controllability of minimalist *in vitro* systems, such as transwell inserts. Yet it is possible to engineer increasingly sophisticated models of human tissues and organs that permit the study of the effects of specific molecular factors, cell types. Such engineered tissue models and microphysiological systems incorporating them (such as tissues on chips) can complement animal models because the engineered models offer a higher degree of controllability, repeatability and reproducibility. Although, compared to organoids and *ex vivo* tissues, engineered *in vitro* tissues can be too simplistic, they can benefit from the increased modularity, flexibility and scale-up advantages of microfabrication methods.

In this issue, four Articles provide examples of such tissue-engineered models. Kevin Kit Parker and colleagues made scale models of the human left heart ventricle (250 times smaller by volume) by pull-spinning nanofibres made of polycaprolactone and gelatin onto a rotating ellipsoidal collector and then seeding the casted nanofibrous scaffold with cardiomyocytes derived from human induced pluripotent stem cells. Also, the model ventricles can be interrogated using catheters, and used to study arrhythmia caused by structural defects (in the case of the model vesicles, punched holes).

The engineered tissues, which recapitulated the synergistic effects of the genetic defect and environmental stresses (*via* the tissue's mechanical resistance to contraction), allowed the authors to conclude that the genetic deficiency and external stresses synergistically lead to contractile deficits characteristic of the cardiomyopathies. By making cylindrically shaped tissues made of adult rat myogenic cells in a hydrogel of fibrinogen and matrigel, Nenad Bursac and colleagues show that the incorporation of macrophages derived and when the tissues where implanted in mice through a dorsal-skinfold window chamber. Implantable, engineered tissues can also address a few limitations of mouse models in the study of cancer metastasis in humans, such as the inability to recapitulate the role of the immune system and to manipulate properties of the pre-metastatic niche, as well as impracticalities in the detection of metastatic recurrence, which is driven by dormant disseminated tumour cells. In this respect, Jungwoo Lee and collaborators studied how disseminated tumour cells that are dormant can become active, the main cause of metastatic relapse and of mortality for most cancers. The team created a humanized tissue-engineered model of a pre-metastatic niche in mice, *via* the subdermal implantation of microfabricated porous hydrogel scaffolds coated with collagen and pre-seeded with human bone-marrow stromal cells.

As exemplified by these four advances, it is the relative biological simplicity and controllability of tissue-engineered models that makes it possible, or easier, to unveil individual and combined contributions of the genetics, microstructure, architecture, biological make-up and mechanical properties of the tissue microenvironment to human disease.. Yet at present it is still largely unclear how similar engineered tissues and native tissues are, and whether the former can faithfully and robustly recapitulate the hallmarks of most human diseases. Although for most preclinical studies, small animals need to stick around; further scientific and technological developments should increasingly replace, reduce or refine their use in research.

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