‘HEARTS IN A DISH’ HELP UNDERSTAND CARDIAC DISORDERS

2D AND 3D MODELS OF HUMAN HEARTS IN CULTURE DISHES are shedding light on inherited diseases and advancing the search for personalized therapies.

‘Beating heart in a dish’ techniques are helping cardiovascular researcher, Christopher Toepfer, get to the crux of diseases such as hypertrophic cardiomyopathy (HCM), which leads to a gradual thickening of the heart muscle. Over time, this inherited disorder increases the risk of serious problems including atrial fibrillation and heart failure. A team led by Toepfer, who is director of the Oxford Organoid Hub at the University of Oxford, in the United Kingdom, has identified several disease mechanisms for HCM. Toepfer outlines the vital role of multidisciplinary teams in cardiovascular science, the extraordinary world of motor proteins, and gives an insight into life in his lab.

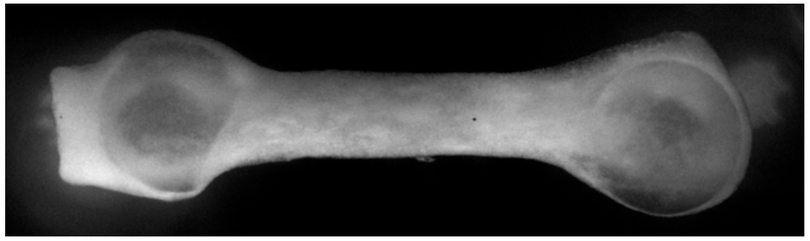
What inspired you to work in this field?
Encouraged by my family and love of nature, I’ve always been keen on the sciences. But it was during my undergrad at Imperial College London that I became fascinated by muscle physiology. I worked summers in a biophysics lab studying the regulation of muscle contraction. The heart is an elegant, life-giving pump, but its cells do not regenerate, and it has to continue functioning well throughout our entire lives. How does it do that?

I was hooked by the interdisciplinary nature of cardiovascular study combining physics, chemistry and biology to understand how our hearts beat correctly. I thoroughly enjoy working closely with my team and our collaborators to piece together the puzzles that help explain inherited heart diseases.

What lies behind hypertrophic cardiomyopathy?
Myosin proteins are the molecular motors of muscle tissues that power every heartbeat. Their relaxation between beats is equally crucial in maintaining healthy, efficient heart function. In the relaxed state, the heart ‘refuels’ on oxygen and energy. The two myosin conformational states — the super relaxed state (SRX) and the disordered relaxed state (DRX) — can be disrupted by mutations in genes that regulate myosin function[1]. These variants can cause the myosin to be too active, resulting in irregular rhythm (atrial fibrillation) and increased energy consumption. If myosins remain ‘on’ instead of relaxing fully, the heart becomes overworked, rather like a bodybuilder’s muscle. The tissues thicken and stiffen. We’ve identified individual gene variants that can cause HCM[2,3], but the disease can be fuelled by multiple variants in many patients. This is why research into genetic causes remains crucial.



Christopher Toepfer
Director of the Oxford Organoid Hub at the University of Oxford

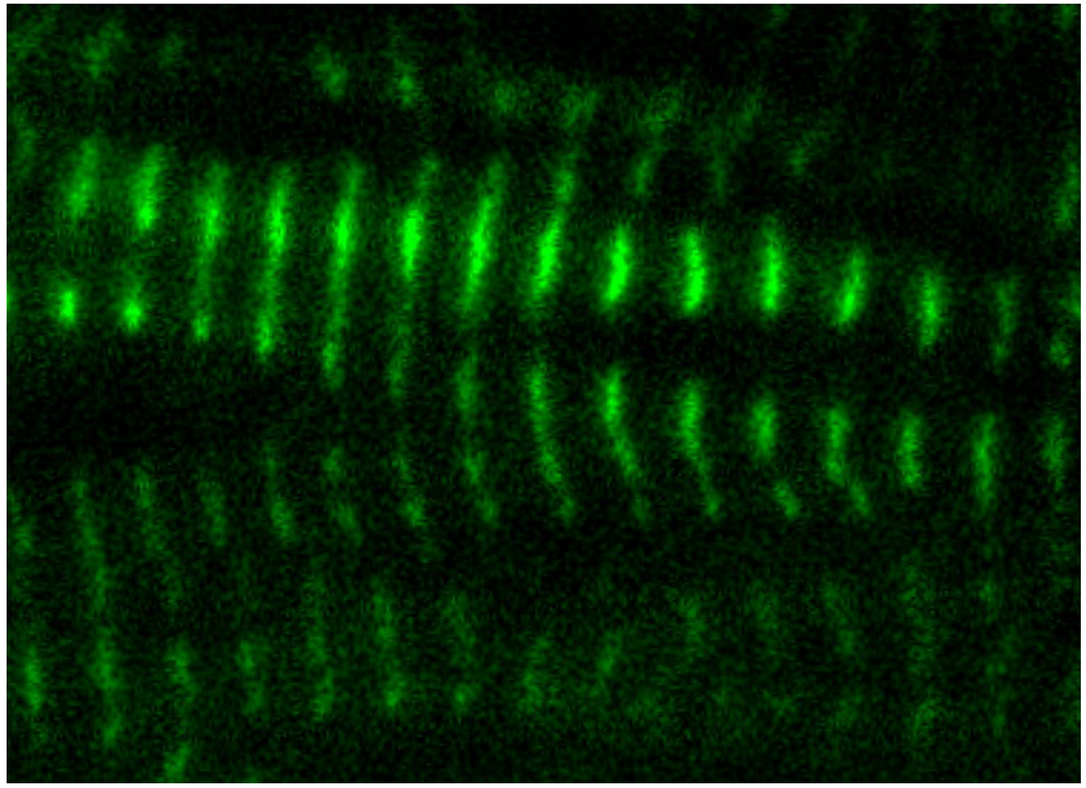


▲ Engineered heart tissue held between two rods, which allows measurement of force across the tissue.

Christopher Toepfer

What techniques do you use to study inherited heart disease?
We create 2D and 3D ‘beating hearts in a dish’; in other words, we grow living heart cells (cardiomyocytes) and tissues in culture dishes and use these to test different theories. 2D monolayers of cells help us examine individual contractions in sarcomeres (heart muscle filaments). More complex 3D organoids allow us to track the progression of diseases over time. We can also generate miniature heart tissues and observe how much force and power they produce under different stresses.

How do you make these models, and use them to identify new treatments?
We source heart cells either by asking patients for blood samples from which we derive stem cell lines that match their specific phenotype, or we use CRISPR-Cas9 genetic engineering to introduce specific variants to cell cultures. This allows us to identify causative mutations, and understand how they cause the resulting disease phenotypes, which allows us to identify potential drug targets. Interestingly, myosin SRX–DRX states are promising drug targets[4], not just for cardiomyopathies, but potentially also for other muscle-related disorders.



Christopher Toepfer

▲ Fluorescence microscopy image of 2D stem cell-derived cardiomyocytes, showing heart muscle filaments (sarcomeres) in green.

Has a setback ever led to a breakthrough in your organoid work?
Much of what we do involves solving methodological hurdles as a team. In every step, there’s trial and error to find optimal ways to examine diseases, and some errors have unexpected outcomes. For example, one of us accidentally uses the wrong matrix to grow cells, but then those cells flourish in that matrix allowing us to more quickly examine cells and disease.

We collaborate across disciplines to solve problems related to organoid development, and we’ve developed valuable tools to help us scale up production of 3D systems cost-effectively. Developments such as building human hearts in a dish with functioning vascular networks could allow us to one day replace entire hearts, generated from patients’ own stem cells, which would reduce rates of organ rejection.

What have patients taught you about the importance of your work?
Being involved in conversations with patients and their advocates brings home to me the lasting impact one can have as a researcher. We’re also broadening our lab research into other conditions that have cardiac complications, like the neurodegenerative disorder, Friedreich’s ataxia (FRDA). 60% of these patients die of a cardiac complication[5], yet the cardiac aspect of the disease is poorly understood. We’ve been working on FRDA for three years now, and the patients are highly motivated to work with us to find answers, which is hugely empowering. ■

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