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Miniature Hearts: Cardiac Organoids With an Immune System

The development of novel therapeutics offer great hope for the fight against widespread diseases such as cancer, but they can impair the cardiovascular system, so development often fails early on. Researchers from the Fraunhofer Institute for Toxicology and Experimental Medicine ITEM and Hannover Medical School have developed a complex cardiac organoid model that can be used to study the potential cardiotoxicity of new medications. Their miniature heart even has an immune system of its own.

Cardiotoxicity is the phenomenon that describes a medication's harmful effects on the heart, which can lead to cardiac arrhythmias, cardiomyopathy or other cardiovascular side effects. It is one of the main reasons that drugs fail during their development for clinical use or get withdrawn from the market after their initial approval. One crucial issue is that cardiotoxic effects cannot be predicted adequately in preclinical models. Due to the complexity required, conventional cell cultures cannot be used to sufficiently study and simulate the potential cardiotoxicity of new medications, including cutting-edge immune and cell therapies. To address this issue, researchers from Fraunhofer ITEM and Hannover Medical School (MHH), with the involvement of the Fraunhofer Institute for Cell Therapy and Immunology IZI and the Fraunhofer Institute for Silicate Research ISC, have developed a novel cardiac organoid model with its own immune system. This model system due to its multicellularity and complexity can recapitulate the human heart in its (patho-)physiological propertries closer to in vivo then conventional test platforms. This means the human cardiac organoid can be used to model cardiotoxicity, an essential area of research for the development and testing of new drugs. "Our model can essentially be used to test the cardiotoxicity of any medication," says Prof. Dr. Christian Bär, a research group leader at Fraunhofer ITEM. "That's a huge advantage, since many drugs make it to the late phases of preclinical development but fail there because of their cardiotoxic side effects, so they never end up being approved. Our cardiac organoid can save a lot of time and money."

Functional miniature hearts with a spontaneous heartbeat

The functional organoids — miniature hearts smaller than a pinhead — comprise heart muscle cells (cardiomyocytes), cardiac fibroblasts (connective tissue cells), and endothelial cells (vascular cells), all of which are derived from human induced stem cells (hiPSCs), as well as mesenchymal stem cells. HiPSCs are very similar to embryonic stem cells, but they are generated by reprogramming adult cells collected from the connective tissue or blood of adult donors. "We differentiate induced pluripotent stem cells into cardiac muscle cells, fibroblasts and endothelial cells. Then we mix them with mesenchymal stem cells in a certain ratio and pipette the cell mix into an agarose mold that we place inside a Petri dish," explains Elisa Mohr, a research scientist at Hannover Medical School and Fraunhofer ITEM. In the process, these individual cells assemble and self-organize into a functional spheric organoid structure of about 200 µm which spontaneously starts to beat similar lika a tiny heart. A single organoid is made up of about 2,000 cells. Electrostimulation can also be applied to induce the miniature heart to contract, in much the same way a cardiac pacemaker works.

Versatile organoid for many kinds of heart disease

These organoids offer many different ways to study the potential cardiotoxicity of new drugs, from high-resolution analysis of beating behavior to traditional histology and state-of-the-art gene expression analyses at the individual cell level. Beyond cardiotoxicity, the human cardiac organoids also allow researchers to model a wide range of various cardiovascular diseases, such as myocardial infarction (heart attack), arrhythmias, and cardiac hypertrophy, which occurs when the heart muscle thickens abnormally. “We can utilize this cardiac organoid as a test platform for the human heart,” Bär says. Due to the possibility of cultivating the organoids over a period of at least 30 days, experiments with chronic test setups are feasable. This includes studies of novel drug classes such as RNA therapies.

With their disease modeling approaches, the team of researchers has been able to prove that medication can influence contractility in the cardiac organoids. Here, the team of Prof. Bär generated organoids that composed diseased cardiomyocytes which were differentiated from a patient-specific hiPSC line, the patient suffered from hypertrophic cardiomyopathy. “With our organoid platform, we were able to show that mavacamten, a recently approved treatment for patients suffering from hypertrophic cardiomyopathy, improved the contractile performance of the cardiac organoids without displaying cardiotoxic effects,” Mohr says.

The research team is currently working to equip the organoids with an immune system. They are accomplishing this with the addition of macrophages differentiated from induced pluripotent stem cells, making them “designer” immune cells. Fraunhofer ITEM researcher Prof. Dr. Nico Lachmann has succeeded in producing mature immune cells such as macrophages in scalable systems, i.e., from the small lab scale up to industrial use. Macrophages are an important part of the human immune response, fighting pathogens such as bacteria by “eating” them. Adding this extra cell type is proven to improve the functioning of the artificial heart tissue. It has been proven that the implementation of this extra cell type promotes the functional characteristics of artificial heart tissues. “Adding the macrophages and thus incorporating immune competence into the cardiac organoid allows us to do research that is even closer to the actual human heart enabeling more reliable translational research,” Mohr says.

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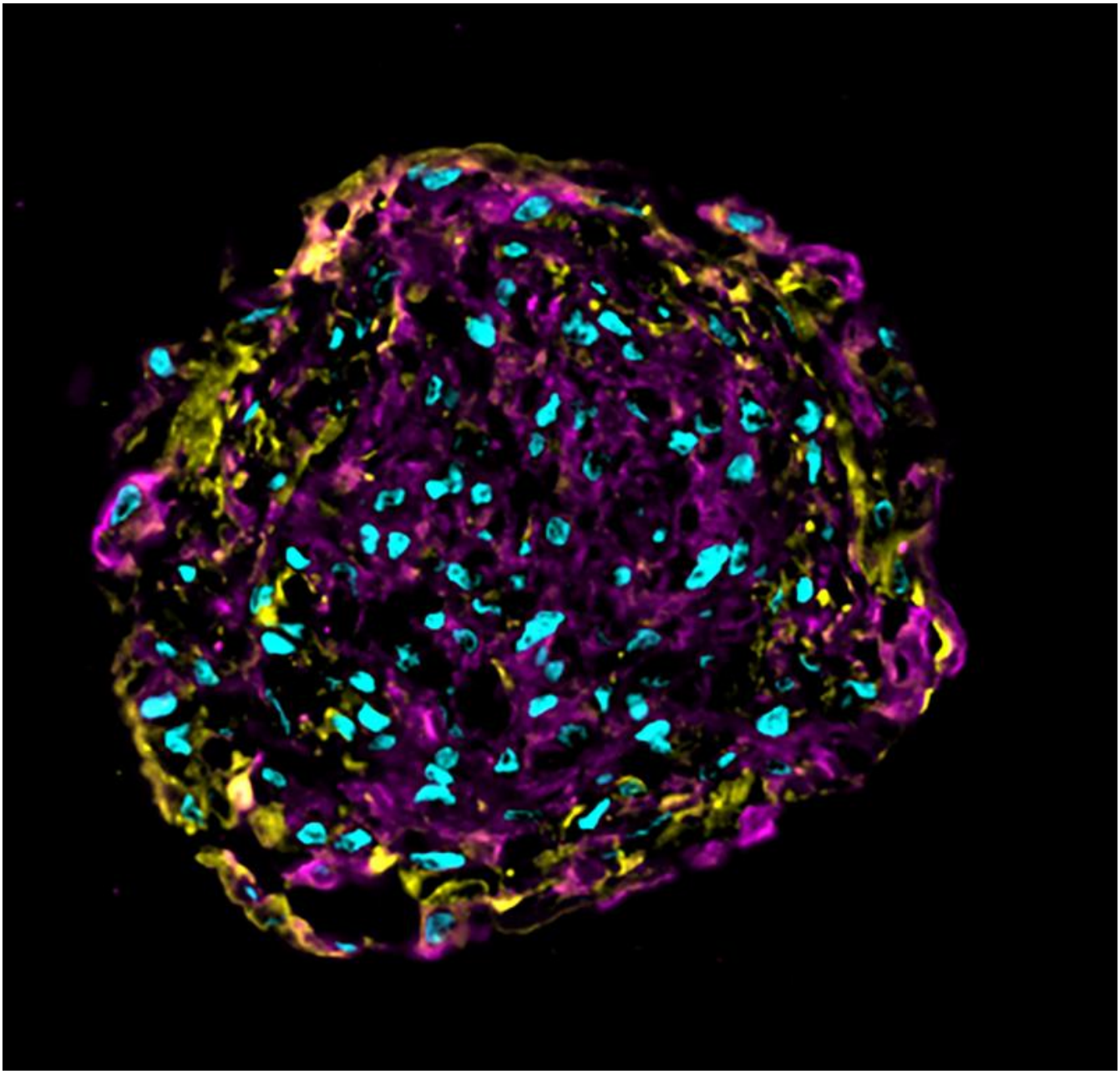

Mini heart: a functional, independently beating organoid consisting of heart muscle cells, cardiac fibroblasts and endothelial cells.