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The miniPUMP: A New Way to Get a Close-Up View of the Heart

Dr. Butler:
There is currently no safe way to get a closeup view of the human heart, which is exactly why a team of Boston University researchers created a device to mimic the human organ. So how does the new device called miniPUMP work? And how was it developed?

Welcome to *Heart Matters* on ReachMD. I'm Dr. Javed Butler. And joining me today to discuss the miniPUMP is Dr. Alice White and Dr. Christopher Chen from Boston University. Dr. White is the Chair of Mechanical Engineering, and Dr. Chen is the William F. Warren Distinguished Professor at the College of Engineering.

Dr. White and Dr. Chen, welcome to the program.

Dr. White:
Thanks. I'm really glad to be here.

Dr. Chen:
Thank you for having me.

Dr. Butler:
Pleasure. So let me first start with you, Dr. Chen. Can you describe to us what is the miniPUMP, and what was the problem that you were trying to solve with this invention?

Dr. Chen:
Sure. I'd be happy to. The miniPUMP is a small device that contains a millimeter- scale, engineered cardiac chamber along with valves that lets us basically model the way the heart actually works using living cells. Cardiomyocytes, which are the muscle cells of the heart, are known to respond to the different forces and pressures that they experience during daily life, but it's been really difficult to study because these cells die when you take them out of the heart to try to study them, but in the past decade, scientists have figured out how to take other cells, like skin cells for example, and induce them into stem cells and then redifferentiate them into a cardiomyocyte-like cell. And with that technology now we have a source of cells that behave like human heart cells, and what we wanted to do is to take these cells and get them back into a tissue-like structure that experiences forces similar to what happens in real heart so that we can start to study them and understand how they behave in this lifelike context.

Dr. Butler:
That's really fascinating. So, Dr. White, can you sort of walk us through from this concept to how actually the miniPUMP was developed? And how does it work?

Dr. White:

I'm going to say that the key to this work was actually a PhD student, Christos Michas, who was co-advised by me and Chris and had background both in biomedical engineering, tissue engineering, but also nanotechnology and mechanical engineering. He was working on a heart tube project where heart cells were connected in a tube-like configuration, and he realized that using nanoscale 3D printing he could actually make a more biomimetic chamber. And I think Chris and I probably thought it was a little bit too ambitious, but he headed off to do that. And in the end, because he had the engineering skills and because of the advantages of the nanoscale 3D printer that we have, he was able to quickly iterate designs, test them out; and quickly get to something that worked.

He did a number of designs for the chamber that Chris mentioned. Some were actually not strong enough to support the cardiomyocytes, and others as he iterated with mechanical design actually did support the compacting cells and exhibit with contraction some fluid flow so he was able to do both the fabrication of the scaffold as well as the seating of the cells on that scaffold, and that meant that he could work very quickly to get something that actually worked.

In terms of the actual working of the pump, the cells are seated onto the scaffold which was placed in a microfluidic device, which provided the afterload and preload, and the cells were able to contract, and there was bidirectional fluid flow. Christos realized that using the same tool he could also fabricate miniature valves to recapitulate the function of the valves in the heart, and with that he was able to rectify the flow and demonstrate the full pressure volume curve in this miniature heart model.

Dr. Butler:
Well, this is really, really fascinating. Let me ask you a couple of questions. So I'm trying to sort of visualize this. A scaffold is only one chamber, right? So this is not a complete heart model. It's just sort of one chamber, correct?

Dr. White: That's correct. It's a ventricular model, so the cells are ventricular cardiomyocytes, yes.

Dr. Butler:
So, you know, the heart syncytium has sort of a special orientation of the fibers as well. So were you able to sort of replicate the orientation of the fibers that also mimic the normal heart?

Dr. Chen:
We were able to build a scaffold where the scaffolding structure was optimized for the contractile function of the chamber, but in the future, we hope to be able to use that same scaffolding design specifically to organize the alignment of the fibers of the cells themselves so that we can capture that aspect of the heart tissue.

Dr. Butler:
Super. So let me keep with you, Dr. Chen. So now that we know how the miniPUMP works, can you explain to us how it can be used to test potential new drugs for heart failure? And actually, not only drug and its effect on cardiomyocyte, but I would assume that there are ways on by which you could sort of vary the preload and the afterload and see the effect of that on the cardiomyocyte as well.

Dr. Chen:
Yeah. You're absolutely right. We can model different types of heart disease either using, for example, cells with mutations that are associated with different types of heart conditions: for example, hypertrophic or dilated cardiomyopathy-type cells, and then we can study what types of interventions might improve heart function, whether that's using it as a way to screen different types of drugs or molecular interventions to see what would improve function, but even from a physiology standpoint, we still don't understand, for example, why cardiomyocytes respond to preload or afterload differently. Even though we know that mechanical forces impact the cells, we don't understand why different types of mechanical loading impacts cells differently, and so even from a basic physiology standpoint, we think we have a model that can be used to give us insight in those areas.

And then one of the other areas that we found maybe wasn't something we were initially thinking about but that a lot of folks in the pharmaceutical industry have talked to us about is that simply modeling normal heart tissue is something that is of high interest to that industry because then they can use it to monitor safety or toxicity of noncardiac drugs. I hadn't appreciated that 40% of drugs that now

reach humans for testing or even are approved then turn out to be cardiotoxic and are pulled from the market, and that's a very high number. And we hope that having, human heart models like this would allow for companies to down-select and avoid some of those compounds before they reach humans.

Dr. Butler:
For those just joining us, you're listening to *Heart Matters* on ReachMD. I am Dr. Javed Butler, and I'm speaking with Drs. Alice White and Christopher Chen about the recently developed miniPUMP device.

So my next question is coming from a place of complete ignorance, so I apologize if it's really simplistic. But is there anything stopping you from making the scaffolding for the entire heart and the 4 chambers?

Dr. White:
I'll jump in there and say that I think that one of the things that we've done here is a proof of concept, and that expanding this to larger systems is definitely part of our future research program. The chamber itself is only a millimeter in height and less than a millimeter in diameter, and the entire fluidic circuit that we developed is about the size of a postage stamp, so it is possible. We'd like to be able to reproduce this at large scale and also to think about expanding both to the full heart and potentially to other organs. So the miniPUMP is a proof of concept, if you will.

Dr. Chen:
And I would just say that in addition to the challenges of fabricating chambers with the right geometries or alignment or structure, the other big challenge is having the right cell types to form the different chambers, and that's an area of ongoing research. There have been some breakthroughs to develop iPS, induced pluripotent stem cell-derived cardiomyocytes that are specialized to the left heart or the right heart or the atrial versus ventricular cardiomyocytes, but it's work that's still ongoing. And even today, these cardiomyocytes that are differentiated from stem cells are still more like second trimester fetal cardiomyocytes than they are adult cardiomyocytes, and so as the cell technology continues to improve, that will help us in building these models in a more sophisticated way.

Dr. Butler:
Very nice. So, Dr. White, keeping on with this theme, what are some of the next steps that your group is pursuing?

Dr. White:
We're very pleased that the technology is as reproducible as it is, and it would be nice to make more of these devices, especially if we're thinking about drug tests and trying to align the cardiomyocyte, the cardiac tissue in a way that is more biomimetic. The program that we are part of has a mission of creating a cardiac patch, so this is in the direction of that as well.

Dr. Butler:
Well, great. This has literally been a fascinating look at the new invention of the miniPUMP and its potential to aid heart disease research in the future. And I'd like to really thank my guests for sharing their insights and their expertise. Dr. White, thank you so much for joining me today.

Dr. White:
Thank you. It's been great. What a fun project this has been.

Dr. Butler:
And, Dr. Chen, it's been a pleasure talking with you as well.

Dr. Chen:
Thank you so much. I really appreciate it. It was fun.

Dr. Butler:
For ReachMD, I'm Dr. Javed Butler. To access this and other episodes in our series, visit ReachMD.com/HeartMatters where you can Be Part of the Knowledge. Thanks for listening.