How hiPSCs Can Fix an Achy-Breaky Heart

By Sarah Zeigler

Heart disease is a global economic and health burden leading to 1 death every 40 seconds in the United States [1]. The sinoatrial node is located in the top right region of your heart and functions as the primary pacemaker of your heart. This causes your heart to beat at the correct pace to pump blood throughout your whole body while you go about your daily life. Pretty cool, huh?

However, if there is a problem with your sinoatrial node, this can cause a wide range of diseases such as atrial fibrillation. Atrial fibrillation is the most common type of rhythm dysfunction, which is when the heart beats either too fast, too slow, or at an irregular pace [2]. A common treatment is an implanted pacemaker; but these devices have drawbacks such as high cost, device lifespan, and surgical risks. For example, the battery on a pacemaker only lasts, on average, 10-15 years before requiring a surgical procedure to be replaced.

Human induced pluripotent stem cells (hiPSCs) are a special type of cell that can become any cell type in the body, including cardiomyocytes, or heart cells. You may be wondering, "why not just use those newly engineered cardiomyocytes to fix the sinoatrial node?" Well, the sinoatrial node is made up of a special subtype of cardiomyocytes called pacemaking cells, which are not so easy to generate. If you are interested in studying any type of sinoatrial node diseases, you need the cells native to that area to design an effective treatment. There are actually three subtypes of cardiomyocytes: pacemaking, atrial, and ventricular [3]. When you program hiPSCs into cardiomyocytes, all three subtypes are generated—with pacemaking cells being the minority population [3].

Fortunately, there's a promising new line of research investigating how to grow hiPSCs into pacemaking cells in order to design therapies to treat various sinoatrial node diseases, such as atrial fibrillation. Typically, hiPSCs are grown in a petri dish. However, the native environment of the heart requires more than what a simple petri dish can offer! It is made up of collagen, elastin, and other proteins that make the heart the muscle what it is [4]. These proteins create a microenvironment that likely provides the structural and biochemical support that enable different subtypes of cardiomyocytes to grow in different regions of the heart [4]. You can think of the

sinoatrial node as the pacemaking cell's home. This is the environment our pacemaking cells are used to living in!

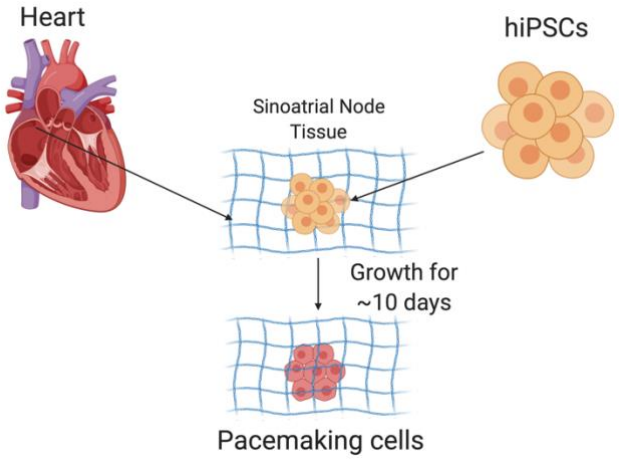

Figure 1: Growing hiPSCs on decellularized sinoatrial node tissue sections.

Dr. Deborah Lieu's lab at UC Davis is researching the growth of cardiomyocytes grown from hiPSCs. We are working on transplanting the hiPSC cardiomyocytes onto pig heart sinoatrial node decellularized tissues. "Decellularized" just means that we remove the existing cells so that we can implant our own hiPSC cardiomyocytes onto the sinoatrial node tissue. This process will allow us to see if a larger population of pacemaking cells can be achieved by allowing the cardiomyocytes to develop in their "home" (Figure 1). If we can achieve a more uniform population, the future of bioengineered pacemakers for patients that otherwise do not have many options looks promising.

Previous evidence has shown that the human left ventricle has helped direct cardiomyocyte growth from hiPSCs [5]. This gives us hope that mimicking the pacemaking home environment found in the sinoatrial node will give rise to a greater number of pacemaking cells. These could then be used for therapeutic efforts to treat sinoatrial node rhythm dysfunction, such as tissue engineering that could revolutionize treatment for many types of heart disease, including sinoatrial node dysfunction!

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al (2016) Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 133:e38–360

2. CDC (2019) Atrial Fibrillation | cdc.gov. In: Centers for Disease Control and Prevention. https://www.cdc.gov/heartdisease/atrial_fibrillation.htm. Accessed 1 May 2020

3. Yechikov S, Copaciu R, Gluck JM, et al (2016) Same-single-cell analysis of pacemaker-specific markers in human induced pluripotent stem cell-derived cardiomyocyte subtypes classified by electrophysiology. Stem Cells 34:2670–2680

4. Gluck JM, Herren AW, Yechikov S, et al (2017) Biochemical and biomechanical properties of the pacemaking sinoatrial

node extracellular matrix are distinct from contractile left ventricular matrix. PLoS One 12:e0185125

5. Oberwallner B, Brodarac A, Anić P, et al (2015) Human cardiac extracellular matrix supports myocardial lineage commitment of pluripotent stem cells. Eur J Cardiothorac Surg 47:416–25; discussion 425