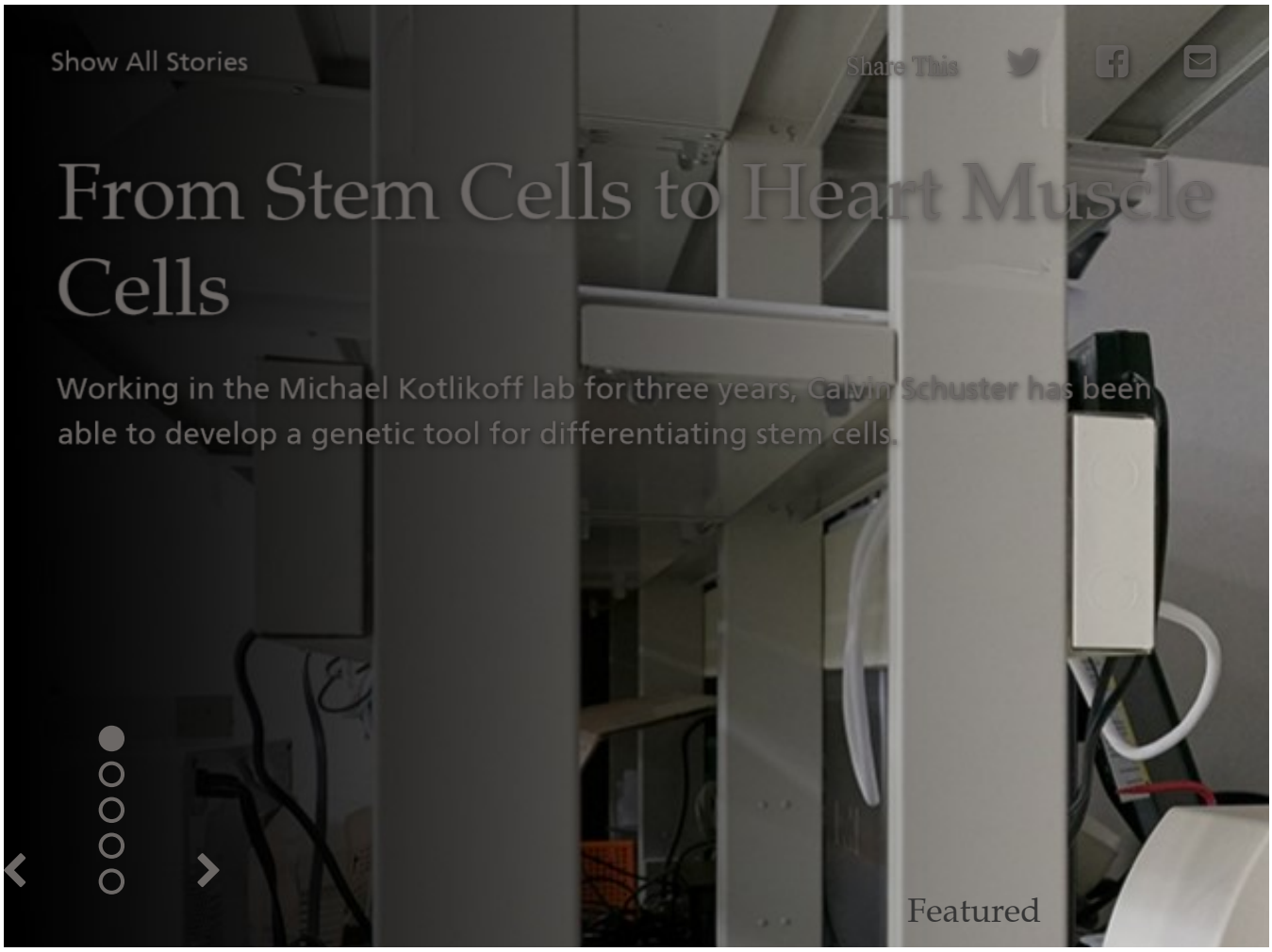

by Colton Poore '20

"These cells should start beating, like a heart, on the plate," explains Calvin Schuster, an undergraduate researcher in Michael I. Kotlikoff's lab, Biomedical Sciences. "And if the tool we designed works, they should begin to flash green with each beat."

Schuster's work centers around the use of induced pluripotent stem cells (iPSCs). These cells begin as adult somatic (body) cells and are subsequently modified to become pluripotent stem cells. That is, they become

Calvin Schuster '19
Undergraduate Researcher

Highlights

cells that can differentiate into any number of different cell types. They can become blood cells, muscle cells, or gastrointestinal cells, and others. Schuster is specifically interested in differentiating these stem cells so they become cardiomyocytes—heart muscle cells.

Schuster first became interested in iPSCs as a high school senior. He took a class that showcased biotechnology research and saw boundless potential and applications for stem cell research. This class sparked his interest in pursuing research at Cornell University.

Differentiating Cardiomyocytes

His work in the Kotlikoff lab is a continuation of undergraduates before him to create a tool that allows a researcher to identify and quantify iPSCs that successfully differentiated into cardiomyocytes. “Currently, there is no way to measure the actual differentiation of cardiomyocytes. You can eyeball it and look to make sure that the cells are beating, but that only gives an estimate.”

Schuster’s work addresses the need for a tool that allows the quantification of successful cardiomyocyte differentiation. Such tool would enable researchers working with stem cells to study different methods for differentiation. The goal is to optimize differentiation efficiency. Since undifferentiated stem cells lead to uncontrolled cell growth, or tumor formation, when injected into the heart, the development of an optimized differentiation protocol could have significant clinical applications.

The Making of a Robust Tool

Schuster’s project addresses this need by inserting genes into the iPSCs that causes them to fluoresce only after they differentiate into cardiomyocytes. In order to do this, Joseph Neumeyer, a past undergraduate in the lab, created a DNA construct that codes for a specific sequence. The first important gene encodes GCaMP, which is a protein that glows when it interacts with calcium. Calcium ions are critical to the proper functioning of the heart. A release of calcium ions is responsible for the heart’s contraction.

If the cardiomyocytes are contracting and have taken up the construct, they should glow. The construct also contains a promoter sequence (which signals the cell to start transcribing a gene) upstream of the GCaMP gene specific to cardiomyocytes. This ensures that GCaMP will only be expressed if the cell has actually differentiated into a cardiomyocyte. If it remains undifferentiated or if it differentiates into cells other than cardiomyocytes, then the promoter sequence will remain inactive. The GCaMP will not be expressed, so fluorescence will not occur even when calcium is present.

After the initial construct was created, another previous undergraduate researcher, Bayan Yazdi, inserted the construct into a plasmid. A plasmid is a small molecule of DNA that is separate from the cell's own DNA and can replicate itself independently from the cell. By having the construct on a plasmid, Schuster is able to insert the plasmid into the stem cells through a process known as transfection. In stem cells, transfection can pose many challenges.

"If your transfection method disrupts the environment of the stem cells in a particular way, they can lose their pluripotent status by differentiating prematurely into cells that aren't cardiomyocytes. I have to be conscious of the environment that I'm creating for them."

Some methods of gene insertion include electroporation, TALEN, and CRISPR/Cas9. Schuster explains, however, that these methods of targeted gene insertion are often not easily accessible or must be designed ahead of time. In this experiment, however, it is very easy to screen iPSC cells that differentiated successfully.

Schuster, therefore, sought a transfection method that was more accessible and common, such as the chemical reagent lipofectamine, which does not require specific machinery or much advanced planning to use. If lipofectamine was an effective way to create a highly useful, differentiated cell line, it would demonstrate an accessible method for researchers to utilize when they are conducting future research on cardiomyocytes.

"At Cornell, we always talk about wanting to bring minds together. And I think that there's

no other place on campus where you can have quite the same level of intellectual collaboration that you can have in research."

Confirming Stem Cell Differentiation

Schuster's work would create a tool that allows researchers to measure and confirm stem cell differentiation reliably (only heart cells will exhibit green flashes as they start to develop regular contractions). In the short term, this will aid current research efforts in optimizing different methods of stem cell differentiation by allowing researchers to quantify their results. In the long term, this could lead to the development of a differentiation protocol that could more efficiently generate cardiomyocytes from iPSCs.

A method that perfectly differentiates stem cells may one day allow doctors to inject a patient's own differentiated stem cells into their body. "The idea is that the cells would come from the patients themselves, so we know that the body would accept them," Schuster explains. "It would be personalized medicine."

The Research Experience, Continued

As a student who has always dreamed of conducting stem cell research, Schuster has greatly enjoyed being a part of the Kotlikoff Lab. He has worked as an undergraduate researcher in the Kotlikoff lab for three years, joining in his second year at Cornell.

"At Cornell, we always talk about wanting to bring minds together. And I think that there's no other place on campus where you can have quite the same level of intellectual collaboration that you can have in research. It's a really creative and collaborative space."

Schuster is leaving permanent marks on the world of stem cell research. "I've always liked the idea of using gene modification and genetic models in unique ways in research. I came to Cornell specifically wanting to do something creative with stem cells. Now I'm finishing a thesis on them."

After graduating in May 2019, Schuster will be continuing his research experience. For the next two years, he will work in the Robert Flaumenhaft lab at Beth Israel Hospital in Boston, conducting hematology research. After these two gap years, he will attend medical school.

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