HSCI HARVARD STEM CELL INSTITUTE

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Stem Cell Lines

For friends and supporters of the Harvard Stem Cell Institute

The ALS challenge continues

HSCI scientists are using stem cells to redefine what it means to study this deadly disease

Professor Kevin Eggan was mid-sentence, discussing the importance of raising awareness for ALS research, when members of his lab dumped five buckets of freezing water over his head. Eggan recovered, gave the camera crew a smile and, soaking wet, nominated Howard Hughes Medical Institute President Robert Tjian, long-time collaborator Christopher Henderson at Columbia Medical Center, and Harvard biochemist Adam Cohen to do the same.

It was only a matter of time before Eggan did an ALS Ice Bucket Challenge video. The viral fundraising/awareness campaign has brought in over $100 million for the ALS Association, which is a regular supporter of the Eggan Lab.

Harvard President Drew Faust also took part and was doused by Eggan in honor of a friend she recently lost to the disease. "We have a long way to go," she said, as the members of the Eggan Lab looked on in the background. "But the people who are behind me today are testimony that we are making real progress."

Kevin Eggan, wearing a blue fleece, and lab members chat with Harvard President Drew Faust before their ALS Ice Bucket Challenges

For years, HSCI researchers have been exploring new platforms to illuminate the complexities of neurodegenerative diseases like ALS, short for amyotrophic lateral sclerosis. These platforms have not only made clear how the disease destroys a person's motor neurons, but have revealed new strategies for slowing cell death.

In 2008, Professor Eggan first raised the possibility of growing ALS patient-derived stem cells in a laboratory dish. At that time, there was no way to directly access and study living human tissue with the disease. Patient-grown stem cells have since allowed scientists to explore how specific mutations cause the disease and screen for drugs that might fix these problems. This year, the Eggan Lab reported two major findings as a result of their work.

First, there is a direct link between a group of inflammatory molecules, called prostanoids, and the damage to motor neurons done by ALS. By removing prostanoid receptors in glial cells—the background cells of the nervous system—it is possible to slow the progression of the disease. In mouse models, this increased survival time by 5-10 percent.

Second, Professor Eggan, working with Dr. Clifford Woolf at Boston Children's Hospital, found that many of the mutations that cause ALS may be linked by an ability to trigger abnormally high excitability in motor neurons, so that they send electrical signals more readily. The research team then conducted studies of the anti-epilepsy medication, retigabine, on patient neurons in a dish and found that it reduced the hyperexcitability of the cells.

All eyes are now on an ongoing Phase I clinical trial of this epilepsy drug at Massachusetts General Hospital, which could prove that patient stem cells are the path forward for finding new therapies for ALS and other diseases. ■

$1M gift to aid Harvard stem cell science

Edmund "Ed" Grossman wasn't a science-focused person. An English major at the University of Connecticut in the 1950s, he went on to Harvard Business School and built a career in the world of advertising and retail. For many years, he served as founder, president, and CEO of Marketing Resource, a company involved in the wholesaling of closeout merchandise and remainder books. But when cancer struck, he and his late wife Arlene found comfort (and lasting friends) in the world of medical research.

Their names now line the walls outside a multi-purpose hub on the third floor of the Harvard Department of Stem Cell and Regenerative Biology's Sherman Fairchild Laboratory, renamed in recognition of a $1 million commitment to Harvard's stem cell science initiatives.

The "Edmund and Arlene Grossman Meeting Center" is the heart of the department, where stem cell scientists—from undergraduates to senior investigators—meet to discuss work over coffee, conduct workshops, and foster interactions that support collaboration.

"Besides cancer, there are a couple of other 'C' words in the medical research lexicon that are of a great interest to me," said Ed Grossman. "One is curiosity and the other is collaboration, which is why the meeting center seemed to be an appropriate way to be memorialized."

Honoring Arlene Grossman, who died from breast cancer more than two years ago, the gift will also aid HSCI in expanding its Cancer Program, as well as in

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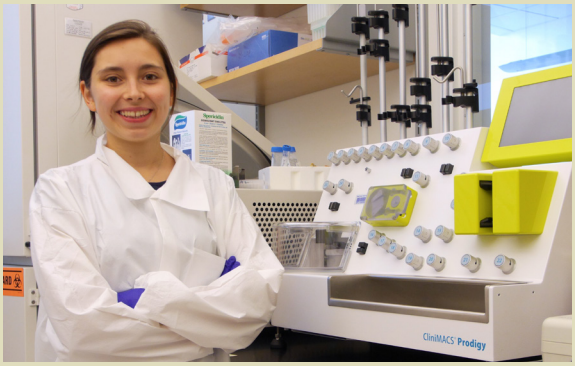
Meet international intern, Elizabeth Cheeseman

Elizabeth "Lizzie" Cheeseman, a chemical engineering student at Loughborough University in England, earned a coveted spot in the 2014 HSCI Internship Program by winning a UK-wide competition sponsored by the EPSRC Centre for Innovative Manufacturing in Regenerative Medicine. As her prize, Cheeseman spent ten weeks in the Center for Human Cell Therapy at Boston Children's Hospital, where she worked with her mentors to develop a way to label lung stem cells using iron particles, which would allow the cells to be tracked with MRI scanners if infused in a patient with a disease like emphysema. She spoke with *Stem Cell Lines* about her summer experience:



Loughborough student Elizabeth Cheeseman in the Center for Human Cell Therapy at Boston Children's Hospital

Q: As an engineering student, what inspired you to apply for a stem cell internship?
Cheeseman: I've had an interest in healthcare from a young age. My grandmother was diagnosed with renal failure when I was about ten, and my mom used to take me to the hospital with her. I met with all of my grandmother's doctors and they would explain to me all the different tablets she had to take and why.

I knew that I couldn't go into medicine, however, because I was terribly squeamish. My grandmother developed diabetes as well, and when I used to help her take the blood tests I would have to sit down after seeing even the tiniest drop of blood. I ended up going into chemical engineering because it gave me other options to do healthcare. I was looking to do a semester-long project at the EPSRC and came across this internship, and it's just gone from there.

Q: What was the most unexpected part of working in a biology lab?
Cheeseman: I'd say the clinical things were weird for me. The Center for Human Cell Therapy is a translational lab, and so they help different researchers and organizations get their drugs to be FDA-approved. They'd get, for example, mobilized peripheral blood—blood that has a lot of white blood cells—and then find techniques to improve how it's used in the clinic. The lab also gets things like corneas. I tried to watch one of my colleagues do a dissection and I just felt the color drain out of me.

Q: Do you feel like the lab was a good match for you?
Cheeseman: The lab was the perfect match for me; not just in terms of the project that I worked on, but the overall goal of trying to translate basic research for the clinic.

Even on my final day of the internship, the novelty never wore off. I was as excited to come into the lab as I was on the first day. I experienced some issues—ultimately my project yielded mixed results—but I enjoyed the challenge. Even if I had negative results, it'd still be a result. It's almost as if there is no failure in science, because you're continually adding to this breadth of knowledge. I just find it fascinating.

Q: Has using the scientific method made you a better engineer?
Cheeseman: I think so. It gives you a different approach to things—a more flexible view. Engineers tend to think in binary terms; it either is or it isn't. Biologists are more comfortable dealing with gray areas and complexity, and so I tried to take some of that attitude back with me.

Q: What do you see yourself doing in the future?
Cheeseman: I've gone from not really knowing what I want to do for a career this time last year to being dead set on doing a PhD and some sort of research experience. I don't know where it's going to take me in the long term, but I know that I'll love what I'm doing. ■

Ed Grossman, continued from page 1.

hastening translational research to prevent and treat a range of other conditions.

Ed Grossman sees enormous potential economic benefits from investing in stem cell research, which could lead to the reduction or even elimination of costs associated with managing many chronic diseases. His main motivation for giving to organizations like HSCI, however, remains more personal. "Going through a ravaging disease with my wife touched me very deeply," he said. "I would like, if at all possible, to see the pain and suffering that Arlene experienced, alleviated or prevented for as many people as possible." ■

HSCI Executive Director Brock Reeve, HSCI Co-directors David Scadden and Doug Melton, Ed Grossman, and HSCRB Executive Director M. William Lensch (left to right) at the unveiling of the renamed meeting center in June.

CRISPR/Cas9: How a new genome-editing tool could help patients

Scientists have made great strides in gene therapy over the last decade. Patients are already benefitting from technologies that add new genes or correct misbehaving ones, but concerns still linger about these procedures' safety and cost. Since 2013, researchers at HSCI and MIT have been developing an alternative genome-editing tool, called the CRISPR/CAS9 system, which may address some of gene therapy's hurdles. This new approach to altering genomes was inspired by nature, specifically, bacteria.

The bacterial immune system

Bacteria may be germs, but they can also catch a virus. Viruses that latch onto a healthy bacterium will inject their genetic code into their victim. The code integrates itself into the bacterium's DNA and transforms the bacterium's genetic machinery into a virus factory. The bacterium soon fills with newly formed viruses and bursts.

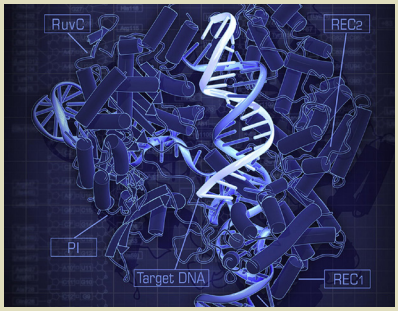
In the 2000s, researchers found that bacteria that carry the CRISPR gene locus—more than half of all bacteria—seemed to have more immunity to viruses. Upon closer inspection, scientists learned that CRISPR allows these bacteria to incorporate the DNA from a virus into their own genomes, in a way building a memory of an infection. Bacteria use this information and an enzyme, Cas9, to target viral DNA and chop it up.

"It's an adaptive immune system for bacteria," said HSCI Principal Faculty member Chad Cowan, PhD, a co-founder of startup CRISPR Therapeutics. "And it didn't take long for some very smart people to consider that it might possible to use this CRISPR/Cas9 system to cleave the mammalian genome."

A discovery in Cambridge

Harvard geneticist George Church, PhD, and Feng Zhang, PhD, working independently at the MIT and Broad Institute, were the first to translate CRISPR/Cas9 technology into mammalian cells. They demonstrated how to guide the Cas9 enzymes to the genome of a human or mouse cell and cause the DNA to break, allowing any mutation to be made or repaired.

"People use it all the time now in human cell lines," Cowan said. "People at Harvard have been trying to use this system as a gene therapeutic tool, where you could direct the CRISPR/Cas9 system to correct a mutation that's causing a disease."



Cas9 cleaves its target DNA

Current and future applications

In 2013, the HSCI iPS Core began to offer CRISPR/Cas9 genome editing in addition to reprogramming services. "It's wonderful because you no longer have to spend years or months of a postdoc's time to make these cells," said Cowan, who also acts as the Core's Co-director.

Several HSCI faculty members are already taking advantage of the resource, exploring how the tool can help patients with diabetes, HIV, or sickle-cell anemia, as well as those susceptible to heart attacks.

A June 2014 study from Kiran Musunuru, PhD, and colleagues in Harvard's Department of Stem Cell and Regenerative Biology showed that using CRISPR/Cas9 to mutate a gene in the livers of mice could reduce cholesterol levels, which over the lifetime of the individual would prevent heart attacks by up to 90 percent.

According to Professor Cowan, expect more exciting discoveries to be published in the months to come. ■

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HSCI news briefs

HSCI finds new home in Bauer Lab

The two key components of Harvard Stem Cell Science are finally together under one roof. Over the summer, the Harvard Stem Cell Institute's core administrative team moved to their new home in the Bauer Laboratory in Cambridge, joining the staff of Harvard University's Department of Stem Cell and Regenerative Biology (HSCRB). "I'm excited that HSCI is here with us in Bauer and look forward to seeing how our efforts synergize on behalf of stem cell science at Harvard," said HSCRB Executive Director M. William Lensch, PhD. "I anticipate an even richer working environment in the years ahead."

Spinal cord injury think-tank

HSCI is taking the first steps toward building a community of scientists, clinicians, and foundations that will specifically study spinal cord injury and repair. At a July "think-tank," co-organized by neuroscientists Qiao Zhou, PhD, and Zhigang He, PhD, experts met to identify some of the main research questions that need to be addressed regarding spinal cord injury, and discussed how the HSCI network could collaborate to find answers. Representatives from spinal cord research foundations Wings for Life and the Craig H. Neilsen Foundation were also present to lend their knowledge and support. "There are a lot of steps between being fully paraplegic or tetraplegic and being able to walk again," said HSCI Program Director Claudia Rizzini, PhD. "This initiative is another example of how HSCI brings together leading researchers to find new ways to help patients."

New tool to map out cell differentiation

There are many recipes that turn a stem cell into a specialized cell, but not every recipe produces cells that have the same properties as those that naturally arise in the human body. A new resource called CellNet can now act as quality assurance. The tool provides a roadmap for scientists looking to generate the "truest" human stem cells to model diseases, test potential drugs, and use as treatments. CellNet was co-developed by HSCI Executive Committee member George Daley, MD, PhD, at Boston Children's Hospital, along with scientists at the Wyss Institute for Biologically Inspired Engineering at Harvard University and Boston University. ■

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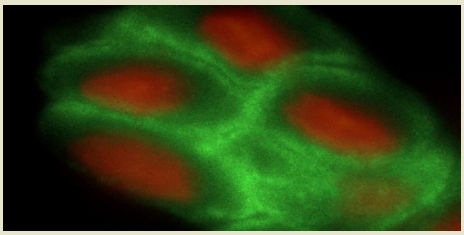
1000 SCIENTISTS. ONE GOAL. REINVENTING HEALTH.

HSCI researchers work to improve cornea transplants

A Boston-based scientific collaborative, led by HSCI researchers at Massachusetts Eye and Ear/ Schepens Eye Research Institute has discovered a way to collect the best cell type for regenerating a damaged cornea—the clear membrane that covers the pupil and directs light into the back of the eye.

Corneal blindness is a clouding of vision that results when blood vessels grow into the cornea. It can be caused by an injury, infection, or autoimmune disease that destroys an actively regenerating population of stem cells located in an area behind the cornea, called the limbus. At present, limbal stem cell transplants from an uninjured eye or deceased organ donor have had promising, yet inconsistent, results.

The investigators found that transplant success is greatly improved by purifying the limbal stem cells. The team is now pursuing FDA-approval for the technique before moving on to clinical trials.



Stem cells within the limbus of the eye can now be purified with the help of an antibody.

"Previously, work on limbal cell grafts showed that when more than three percent of transplanted cells were stem cells, transplants were successful—less than three percent and the transplants were not," said co-senior investigator Natasha Frank, MD. "The question in the field then was whether we could enrich the limbal stem cells. But until this study there was no specific marker that could isolate these cells," she added.

The biological marker the researchers found is the ABCB5 protein, which is located on the surface of limbal stem cells. The team then developed an antibody that could tag limbal stem cells, making it possible to purify only the cells responsible for successful limbal cell transplants.

A second team of scientists led by HSCI's Ula Jurkanas, MD, also at Massachusetts Eye and Ear, is investigating how to use patient limbal stem cells for the treatment of limbal stem cell deficiency. They are collaborating with the Center for Human Cell Therapy at Boston Children's Hospital to translate the work for the clinic. ■