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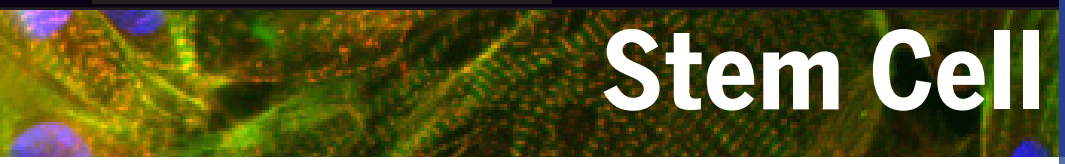

Stem Cell Lines

For friends and supporters of the Harvard Stem Cell Institute

The little fish that could

Zebrafish help HSCI researchers fight human disease

Leonard Zon, MD, could be called HSCI's most prolific aquarist. The Executive Committee Chair estimates that he has over 300,000 fish spread throughout his laboratories at the Harvard Department of Stem Cell and Regenerative Biology and Boston Children's Hospital.

His collection isn't very diverse, composed as it is entirely of zebrafish—minnow-like, freshwater, tropical fish that grow about an inch-and-a-half long. But Zon isn't interested in winning best in show. Instead, he is leading a scientific movement to show that his striped fish could be humanity's new animal of choice for drug discovery and studying disease.

Not only does the zebrafish require fewer facility resources than science's go-to-organism, the mouse, but fish are quicker to reproduce, easier to experimentally manipulate, and at least 70 percent of human protein-coding genes have analogs in the zebrafish, including those related to skin cancer, muscular dystrophy, and T cell leukemia.

The zebfrafish (Danio rerio)

"The zebrafish is now emerging as another powerful organism for the modeling and study of human diseases, and it is conceivable that zebrafish models will complement mouse models in the future," Zon wrote in the December issue of *Trends in Cell Biology*, pointing out the accelerating increase in studies on zebrafish, from about 150 in 1995 to over 2,000 in 2013.

As a pediatric oncologist, Zon's main purpose in using zebrafish is to help cancer patients. He is the first scientist to successfully apply basic research from the zebrafish to develop an FDA-approved treatment for human melanoma, and is now applying similar methods to find therapies for muscle and blood cancers.

One cancer Zon is pursuing is rhabdomyosarcoma, a rare muscle cancer diagnosed primarily in early childhood. Zebrafish, under certain conditions, develop tumors very similar to the human disease. He is currently using zebrafish embryos to identify which genes transform a normal muscle stem cell into a malignant tumor, as well as searching for factors that might suppress the cancer.

"One of the things that's really interesting in zebrafish is that the embryos are completely transparent and you can watch the tumors invade the normal tissues," he said. "That's a process that you can't study in any other organism."

Postdocs in Zon's lab can expose the zebrafish embryos to multiple chemicals and literally watch changes in the fish's development. In 2007, this technique led to the discovery of a type of prostaglandin that expands blood stem cells about 300 to 400 percent. Last fall, the prostaglandin found in Zon's lab passed Phase Ib clinical trials as a therapy that increases the success of cord blood transplants.

A similar screen led to a major paper last November, in which Zon and fellow HSCI Executive Committee member Amy Wagers, PhD, showed that the same chemicals that stimulate muscle development in

Continued on page 2.

2013 interns reflect on their summer at HSCI

On July 25, Tirth Patel awoke shortly before six in the morning to the sound of fire alarms in his apartment building. The Northwestern University student rushed out with no time to grab his laptop or other belongings. Within hours, his Somerville residence had burned to the ground. Patel, who had come to Massachusetts to be part of the HSCI Internship Program, was among the 45 people displaced by the blaze.

"It was a little scary at first because I was alone," he said. "But I knew the people in my program and my lab would be there to support me."

Instead of returning home, Patel was provided temporary housing at Harvard and finished his summer project barcoding blood stem cells in the Boston Children's Hospital laboratory of HSCI Principal Faculty member Fernando Camargo, PhD. Patel said he stayed because the internship was unlike anything he'd had before.

"When the interns assemble at HSCI in June, we become a family within the larger Harvard family, and it's really endearing to see how these 'strangers' immediately bond and look out for each other," said HSCI Program and Administrative Director Maureen Herrmann. "After hearing Tirth's story, all the other interns in the program were texting me, 'I have an extra pillow,' 'I can share my microfridge,' 'Would Tirth like to join us for dinner?' If that isn't family, I don't know what is."

In 2013, 44 undergraduates were accepted into HSCI's 10-week summer internship program. Students came from Harvard, as well as other national and international

Continued on page 2.

Meet the Boston Single-Cell Network

In the spring of 2013, HSCI Affiliated Faculty member Peter Kharchenko, PhD, a computational biologist at Harvard Medical School, and Lev Silberstein, MD, PhD, a clinician at Massachusetts General Hospital, joined forces to start the first collaborative network for Boston researchers who use single-cell analysis as a laboratory tool.

Silberstein and Karchenko

Single-cell analysis is a technique still very much in development, and Karchenko and Silberstein are hoping to speed up its effectiveness with a regular seminar series that allows scientists to present their work and share protocols. They spoke with Stem Cell Lines about single-cell science and the goals of the Boston Single-Cell Network:

Q: What is single-cell science?
Kharchenko: Any chunk of an organism you take is going to have many cells of different types in it. When you are studying a mixture of different cells, you look at averages. But, similar to looking at average temperature in a hospital, sometimes it's a poor indicator of what actually goes on. Maybe some of the cells are acting in different ways, but you can't tell because you're looking at an average. There's recently been very substantial progress in terms of techniques that could be applied to smaller and smaller samples, and now there's a possibility of looking at individual cells.

Q: How does single-cell science benefit patients?
Silberstein: From a clinical point of view, there are two main applications of single-cell analysis: cancer and prenatal diagnosis. In cancer, the ability to examine individual cells and compare their genetic makeup is extremely important to understand how different cancer cells in the same patient are related to each other.

Kharchenko: Prenatal diagnosis is more direct because you actually want to get the genome and analyze potential risk factors with as few cells as possible, ideally with one cell or even with fragments of DNA that's floating in the mother's blood.

Q: What is the intent of the Boston Single-Cell Network?
Silberstein: It is a community building exercise. Single-cell research is very technically challenging and resource demanding. Boston is one of the very few places in the world where a single-cell community can grow rapidly. By sharing experience and expertise, people will essentially get to work together on developing new methods and solving problems.

Q: Where do you see the Boston Single-Cell Network in a year?
Kharchenko: I'm looking forward to hearing about work collaborations that have been established somehow because of the network. ■

Interns continued from page 1

institutions. The internship, one of the most popular in the world for stem cell research, attracted corporate sponsorship for the first time in 2013. Biogen Idec, EMD Millipore, GlaxoSmithKline, the Novartis Institutes for BioMedical Research, and Sanofi Aventis supported the program, both financially and by sharing career advice with the interns.

Harvard senior Marissa Suchyta used her summer to conduct thesis research on salamander regeneration in the Department of Stem Cell and Regenerative Biology laboratory of HSCI Co-director Douglas Melton, PhD. Her goal, still ongoing, is to understand what allows an axolotl—a Mexican salamander that can regenerate almost any part of its body—to initiate regeneration of a lost limb, and to identify the factors that ensure the correct cell types are replaced.

As a participant in the HSCI internship program, she was able to pursue her research interests alongside others just as passionate about stem cell biology.

"The opportunity to interact with students from so many different backgrounds and hear their take on research was incredible," Suchyta said. "The daily interactions you had at the coffee machine transformed into new ideas for experiments."

International applicant Can Aztekin, who came to the program from Sabanci University in Turkey, was overwhelmed—and a little surprised—by how friendly and warm the people of Harvard were to him.

Aztekin credits his mentors in the Brigham and Women's Hospital laboratory of HSCI Cancer Program Leader Benjamin Ebert, MD, for treating him more like a colleague than an intern. Inspired by the level of determination that his lab mates showed when they approached a question they wanted to solve, he was pushed to do his best.

"I knew that I wanted to pursue my PhD, but I wasn't sure whether I am ready or not," Aztekin said. "But with this internship, I became really confident with myself." ■

Zebrafish continued from page 1

zebrafish can also be used to differentiate human stem cells into muscle cells in the laboratory, an historically challenging task that, now overcome, makes muscle cell therapy a more realistic possibility.

"This research demonstrates that over 300 million years of evolution, the pathways used in the fish are conserved through vertebrates all the way up to the human," Zon said.

His passion for and success with zebrafish has helped make the animal a staple in HSCI faculty member laboratories across Boston, and an unexpected symbol for stem cell research. ■

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Leadership Gifts Our deepest gratitude goes to the donors listed below for their profound commitment to stem cell science at Harvard. We recognize these top supporters, whose cumulative gifts and pledges total $100,000 or more as of the fiscal year that ended June 30, 2013. Their enduring leadership helps Harvard sustain its excellence in stem cell science.

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HSCI news briefs

Second Annual Deans' Challenge

"I think the single most important element of any new biotech remains the scientific validity of its work," HSCI Executive Committee member George Daley, MD, PhD, told those attending the 2nd Annual Dean's Health & Life Sciences Challenge opening kickoff at the Harvard Innovation Lab on October 28. Daley shared his experience crossing the line from academia to industry as the scientific co-founder of iPierian, Inc., a biopharmaceutical focused on neurological diseases. The university-wide Deans' challenge invites teams of Harvard students and postdoctoral fellows to develop startups that improve health delivery and patient lives. HSCI-affiliated scientists won the inaugural competition with their plan for MatriTarg Laboratories, now developing therapeutics for fibrosis.

Cancer symposium highlights program's success

HSCI Cancer Program co-leaders Benjamin Ebert, MD, and Ramesh Shivdasani, MD, marked four years of cumulative efforts to fund creative research with a half-day symposium on November 8. Seven HSCI-funded labs presented and received critique of their work, which included new insights into the link between circadian rhythm genes and leukemia, and the role of stem cells in stomach cancer. Keynote speaker Cédric Blanpain, MD, PhD, from the Université libre de Bruxelles, closed the symposium with a discussion of the mechanisms that differentiate skin cancer from normal cellular turnover.

Evotec & HSCI form new collaborations

German biotech Evotec AG entered into two strategic partnerships with HSCI researchers last fall. The first collaboration, "Cure Motor Neuron," will identify compounds that prevent or slow down the loss of motor neurons, which is characteristic of amyotrophic lateral sclerosis, also known as Lou Gehrig's Disease. The compounds will be found using drug-screening techniques developed by HSCI Executive Committee member Lee Rubin, PhD, and Principal Faculty member Kevin Eggan, PhD. The second research collaboration, "Target Enteroendocrine Mechanisms," with HSCI Co-director Douglas Melton, PhD, will look for biological pathways and signals that could be therapeutically relevant to diabetic patients. ■

Stem Cell Lines

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HSCI researchers discover self-healing mice

Turning on a single dormant gene in mice gives them heretofore known powers of regeneration, found a team of researchers led by HSCI Executive Committee member George Daley, MD, PhD. The gene, *Lin28a*, is normally active during embryo formation, but if re-expressed in mice up to six weeks old, the animals gain the ability to regrow hair and repair soft tissues.

The investigators found that by engineering a fully-grown mouse to express *Lin28a*, they could speed up the animal's cellular metabolism, causing it to function like that of a much younger, developing animal. When the researchers perforated the ears or clipped the toes of the *Lin28a* mice, the lost tissue kept regenerating. "Efforts to improve wound healing and tissue repair have mostly failed, but altering metabolism provides a new strategy which we hope will prove successful," said Daley, who is also director of Boston Children Hospital's Stem Cell Transplantation Program.

Mice engineered to express the gene Lin28a **could regrow hair and regenerate soft tissues and bone**

Further experiments, published in the journal *Cell*, showed that bypassing *Lin28a* and directly activating an animal's cellular metabolism with a small molecule also had the effect of enhancing wound healing. This suggests the possibility of inducing regeneration and promoting tissue repair with drugs.

Lin28a didn't universally induce regeneration in all tissues. Heart tissue showed little effect, and while the researchers were able to enhance the regrowth of finger tips in newborn mice, they could not in adults.

"*Lin28a* could be a key factor in constituting a healing cocktail," said PhD candidate Shyh-Chang, "but there are other embryonic factors that remain to be found." ■