



## Stem Cell Central

*September 1, 2009*

*By Meredith W. Salisbury*

Advances in stem cell research have been coming fast and furious in recent years, and the Harvard Stem Cell Institute has been right in the middle of the fray. Founded by scientific co-directors David Scadden and Doug Melton just five years ago, the institute was conceived as "a convening force" that would "bring together people who work on different parts of the large portfolio of research in stem cell biology and stem cell ethics and other aspects," Scadden says. A hematologist and oncologist by training, Scadden says his perspective at the time was informed by how clinically useful stem cells appeared to be, while Melton came from a developmental biology background and had an appreciation for what the research community could do.

Taking those views together, and working with the support of Harvard and their colleagues, Melton and Scadden envisioned the institute as a place that could bring "people together in a coordinated way," Scadden says, "rather than just have it be by chance that people would interact." To help facilitate that, Harvard faculty members who were interested in joining HSCI were asked to assemble themselves into a sort of matrix, by disease type and by research approach. Another factor that was important, Scadden says, was investing in core facilities "to try to enhance the ability of individual investigators to work in this field." Those resources include labs for flow cytometry, making induced pluripotent stem cells, and a therapeutic screening center.

Throughout the first five years — which included what Scadden calls the "community formation" phase — the institute kept an eye on the big goal: clinical impact. HSCI members are encouraged to consider opportunities for data sharing and, where possible, to think about "deliverables" such as a cell that might be handed off to the cell processing center and turned into a resource for the rest of the faculty. At this point in the institute's life cycle, Scadden says the focus is heavily on application of all this research: "As part of that, we are establishing collaborative relationships with biopharma," he adds. Last year, the institute inked a deal with GlaxoSmithKline under which the pharma pays \$25 million over five years in exchange for a research alliance with HSCI scientists aimed at developing treatments for a range of diseases. Another victory was establishing a stem cell and regenerative biology department at Harvard, giving faculty members a way to engage undergraduates in their science.

Getting that faculty to act in concert, rather than as 70 different PIs with independent labs, has led to a number of initiatives at the institute. "This is largely a volunteer army," Scadden says. HSCI hosts retreats, symposia, interlab meetings, and monthly whiteboard sessions to give faculty opportunities to get familiar with each other's work and brainstorm ways to team up. Additionally, to encourage bold ideas, the institute provides seed funding grants each year to projects that likely wouldn't be fundable through other mechanisms, Scadden says. This year, seed grants went to Sharad Ramanathan to study decision making in embryonic stem cells and to David Weinstock to look into DNA double-stranded break repair in human pluripotent cells,

among several other recipients. Another component in bringing faculty together is more logistical: HSCI will relocate to a new building to enable scientists to interact more organically. That building is slated to be finished in 2011.

### **Building assays**

A significant part of HSCI is the therapeutic screening center, set up by Lee Rubin a little more than two years ago. Rubin, a neurobiologist who focuses on orphan diseases worked at a biotech company founded by Doug Melton prior to joining HSCI, where he is now director of translational medicine. At the biotech company, he says, work on the hedgehog signaling pathway shed light on a means of making motor neurons from embryonic stem cells, offering "the ability to generate large numbers of well-defined neural populations."

That turned out to be a key breakthrough in screening and designing assays. Pharmas often screen cells that aren't directly related to the disease in question — for instance, in studies of spinal muscular atrophy, a primarily genetic disease that kills motor neurons in children, standard screens involve taking fibroblasts from patients with the disease and looking for a reaction in a particular protein, Rubin says. But the obvious question is, wouldn't results be more relevant if that screening were actually performed in motor neurons, which are the only cells affected by the disease?

When Rubin joined the institute three years ago, he proposed building the therapeutic screening center to run these kinds of assays — built around cells that offer clear insight into a disease state. While useful for his own research, the center would also be available for other investigators. Less than a year later, the center was up and running, and clinically relevant findings are already coming from it. For instance, in a major project on spinal muscular atrophy where Rubin wanted to study motor neurons instead of standard-issue fibroblasts, he worked to derive embryonic stem cells from mice with the disease, differentiate them into motor neurons, and carry out a "microscope-based screen looking for small molecules that increase the level of the protein that is decreased in the disease," he says. "We really wanted to identify pathways ... that regulate the level of this protein." He set up functional screens with the motor neuron cells and worked with those. In what he calls "a good proof of principle," Rubin and his team found several small molecules including known drugs that can increase protein levels and prevent motor neuron death. These molecules are now being tested on human motor neurons also produced from embryonic stem cells.

Other scientists have indeed availed themselves of Rubin's screening center, which is run less as a service facility and more as a partnership. Because so much of the screening revolves around image-based results using cells that would be considered difficult to grow and assess by normal standards, Rubin says, he prefers arrangements where collaborating labs send a scientist to work with his team on developing and running the screens. Much of the center's work so far has been around trying to produce various differentiated cells from embryonic stem cells, he says.

Harvard Stem Cell Institute  
Boston, Mass.