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Innovations

Hydra Biosciences

Inducing Nature's Regenerative Power

Although Hydra Biosciences is in the business of finding new ways to repair and regenerate injured heart cell tissues, they are not a cell-based therapy company. This means no stem cells. Instead, this 20-person Cambridge, MA-based company is hot in pursuit of proteins and small molecules to do the job instead. The idea is to change the balance of normal biologic function to enhance proliferation of the cardiac myocytes where it is needed—and impede it where it could be harmful.

"Much of the interest in the company is due to the fact that lots of people are interested in the promise of regeneration medicine and the controversy associated with the ethics of stem cell biology," says Dr. Dean Y. Li, MD, PhD, Scientific Cofounder of Hydra and Associate Professor of Medicine, University of Utah. "The drive behind embryonic stem cells is to guide them into forming heart cells, for example, and delivering them to a patient." But he believes delivering cells, which also includes whole organ heart transplants, in his view, is difficult to achieve in practice. Instead, Hydra focuses on developing and delivering a medicine, not cells, to induce the body's own heart cells to regenerate. The approach would be less intimidating ethically and, they hope, easier for physicians to put into practice. "Delivering a small molecule or biologic is much easier and can affect more lives," says Dr. Li.

Academic, Now Business, Partners

As with many start-up biotech companies, most of Hydra's four founders first became associated through their work in academic labs: Dean Li and Mark Keating, PhD at Utah, and David Clapham, PhD at Harvard (who recruited Keating to Harvard in 2001). Laurie Keating joined the team to provide business development structure and to initiate venture financing—successfully achieved through VC funding and a collaboration with Abbott Laboratories. Series B funding was complete in December 2003. While at Utah, Li and Keating were involved in vascular regeneration and cardiac regeneration, respectively. Hence, the regeneration-based company was established in 2001. Many of the first employees at Hydra have since migrated from the Clapham/Keating lab at Harvard.

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"Hydra has three major projects, the primary being the regeneration project," explains Matthew Gantz, Hydra's President and CEO. Much of the foundational work on this project was performed through Mark Keating's academic research on cardiac myocyte regeneration in zebrafish. He proved that zebrafish heart muscle could regenerate, and he identified a way to dedifferentiate skeletal myocytes. "The whole rush was to actually prove you could cause cardiac myocytes to grow," says Dr. Li. Keating published this work in *Science* (*298*, pp. 2188–2190, "Heart regeneration in zebrafish"). Specifically, Keating and colleagues proved that zebrafish fully regenerate hearts within 2 months of 20% ventricular resection. "But we have moved beyond that to a point where have developed a mammalian-based assay that enables us to screen primary adult and neonatal cardiomyocytes," explains Mr. Gantz.

The zebrafish and newt are good organisms for an academic lab to study the process of regeneration. But, as Dr. Li points out, "treating zebrafish isn't high on my list of things to pursue within a company, but understanding and harnessing mammalian regeneration is." So the company is turning exclusively to mammalian models. Others have already provided evidence that human cardiac myocytes, once injured, can regenerate to some point. (For further details, see Beltrami, A.P. et al., N. Engl. J. Med. *344*, pp. 1750–1757, "Evidence that human cardiac myocytes divide after myocardial infarction.") "For mammalian cardiac regeneration to work, you may have to give extra of some factors that are highly expressed in fetal cardiac myocytes that aren't so much in adult heart cells," says Dr. Li. This is how he screens for factors at Hydra Biosciences. "But you may also have to block a competing process, such as cardiac fibrosis or scarring," he says. "For a maximal response, we'll have to find nuance to balance both."

Hydra is now trying to prove if they can get a factor to induce mammalian cardiomyocytes to grow in an animal model. Just as bone heals after an injury, Hydra believes there is a regeneration process that normally tries to occur in the heart after trauma. "But it may not have advanced to the same extent with cardiomyocytes, so the process is not fast enough," says Glenn R. Larsen, PhD, Chief Scientific Officer at Hydra.

Though Hydra is not disclosing the specific mechanisms, growth factors, or small molecules it has discovered, they have developed a body of evidence showing rodent cardiac myocytes grow in culture systems. So while zebrafish need the cell-cycle regulator Mps1—what Keating et al. describe as a "mitotic checkpoint kinase upregulated in many proliferative cell types"—to repair their injured hearts, not unexpectedly, the Hydra team has discovered that mammalian systems require different factors. "The factors we've identified are capable of promoting cardiac myocyte growth from cells that have been iso-

lated from mammalian hearts," says Dr. Larsen. The company developed what they call "high-content assays" of mature, differentiated mammalian cardiomyocytes to test the effectiveness of these growth factors and small molecules. "We anticipate these factors to correlate with their potential to regenerate in whole animals," says Dr. Larsen. "We are in a position now where we are no longer concerned if we can find factors that induce cardiac myocytes to grow in culture but whether those factors are effective in vivo."

Vascular Wall Regeneration

Further on in development is a project on vascular wall regeneration, initially developed in collaboration with Abbott and based on the work at Li's and Keating's labs. "I am studying vessel wall regeneration and the means to help it regenerate correctly," explains Dr. Li. "In coronary restenosis, it is a case of uncontrolled regeneration," he explains of his research in identifying the natural biological factors controlling excess regeneration. Hydra's efforts on this front include a project designed to prevent post-injury restenosis with drug-eluting stents, such as those championed in the last year through the Cordis Cypher sirolimus-eluting stent (available since April 2003) and Boston Scientific's Taxus paclitaxel-eluting stent, just FDA approved in March 2004. The success of these products is not to be underestimated. Following its first full quarter of availability, Cypher stents generated US sales of $429 million. The company is currently seeking partners for continued development of this project.

Hydra is focusing on the cardiovascular market now. "We can imagine having each patient who has suffered from a heart attack, of which there are over 800,000 each year in the US alone, treated with our drugs to help stimulate a normal repair process following cardiac injury," says Dr. Larsen. Adds Mr. Gantz, "And if we're successful in the cardiac regeneration program, the implications for future applications are obvious." Other potential areas may include retinal cell regeneration to treat macular degeneration, other diseased muscle cells, and pancreatic cell regeneration.

Hydra is also developing high-throughput screenings against select ion channels to develop drugs for cardiovascular and inflammatory diseases. Explains Dr. Larsen, "David Clapham is world class in ion channel physiology." Clapham's most recent publication on ion channels was published in *Nature* (*426*, pp. 517–524, "TRP channels as cellular sensors"). "This is a highly druggable target class both in terms of identifying small molecule agonists and antagonists to ion flux in cells," says Larsen. As with the vascular regeneration project, Hydra is seeking partnerships for this program.

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