Cell

Stem Cell Biotech: Seeking a Piece of the Action

Venture capital groups and big pharma have largely held back from investing in biotech companies focused on regenerative medicine. Will it take a clinical bull's eye to bring venture capitalists and big pharma into the cell therapy arena?

Four years ago, when Gregory Bonfiglio was writing a business plan for a venture capital group dedicated to companies pursuing stem cell therapies and regenerative medicine, "there were less than 100 that could be legitimately called regenerative or stem cell companies," Bonfiglio notes. Today, the newly established Proteus Venture Partners, where Bonfiglio is the Managing Partner, is tracking about 1000 companies in over ten countries. While at least half of these, he acknowledges, are mid-sized to large pharma companies with multifold interests, "300 to 400 are focused solely on regenerative medicine."

Cell therapy companies range from those developing therapies using human embryonic stem (ES) cells, like Geron and Advanced Cell Technology (ACT), to companies like Mesoblast and Cytori that are pursuing treatments derived from adult stem cells and their precursors. There are also tissue engineering firms such as Tengion, which just announced a phase II trial for NeoBladder made from a patient's own bladder epithelial cells. Tool companies represent a third category. Some, like VistaGen, produce cells for drug discovery and toxicity testing, whereas others make the instruments and devices, "the picks and shovels," as Bonfiglio calls them, that will help to manufacture cell therapies. Examples include StemCor Systems, which received approval from the US Food and Drug Administration (FDA) several months ago to market its new device for extracting bone marrow, and Novathera, which has designed a bioreactor that allows the three-dimensional culture of stem and progenitor cells. Finally, there are companies that concentrate principally on bioaesthetics, such as Organogenesis and its skin rejuvenation and repair products and Intercytex, whose hair regeneration procedure depends on expanding cells from human hair follicles in culture.

Chris Mason, Director of the Stem Cell and Regenerative Medicine Bioprocess Group at University College London, remarks how things have changed since the first wave of cell-and-tissue companies came and went between 1985 and 2002, an era he refers to as RegenMed 1.0. "We've seen this expansion before," he notes, "but back then, companies were so busy doing basic science, they had no solid business plans." About 70 tissue engineering companies failed to live up to their early promise including Advanced Tissue Sciences (ATS), which at one point had a market cap in excess of one billion dollars, with $600 million raised from venture capital and public markets. ATS and Organogenesis, another pioneer, stirred up excitement, only to eventually file Chapter 11 in late 2002. Curis, Ortec International, Genzyme Tissue Repair, and others similarly closed, reorganized, or merged, while regulatory and other problems kept most products of this era from reaching the marketplace.

Now as we enter "RegenMed 2.0," commercialization is much more of a priority for cell therapy businesses. "The universities are doing great research on regenerative medicine science, and this allows the companies to do great translation/commercialization. We're beginning to see innovative companies with strong business plans spring up all over the world, and this time around it's moved from being an American sport to being a global sport," says Mason.

Where's the Beef?

The sobering reality is, however, that for many stem cell biotechs, the future will depend on making the leap from start-up funds to the large cash infusions that can propel their products through clinical trials. For this to happen, they will have to prove as best they can that their therapies are medically valuable and cost effective. "I think everyone is sitting on the fence waiting for something good to happen," says Lutz Giebel, Managing Partner of SV Life Sciences Advisers and former cofounder and CEO of Cythera, now part of the stem cell engineering firm Novocell. "Quite frankly, every disease a mouse could possibly get has been cured by various stem cell biotechnologies, but the biggest problem is that little has materialized in the clinic that shows these approaches are successful." Giebel compares it to the early days of monoclonal antibody translational research, which people knew eventually would make a difference in drug development. "Investors who invested early lost money. Investors who invested when the time was right made good money."

Ed Field, the President and COO of Aldagen, similarly believes that the biggest boost for regenerative medicine biotech companies would be a few significant clinical bull's eyes. "What my company needs most," more than even money or technology, "is to show in well designed clinical trials that our products are efficacious in humans, and for others to show theirs are." Such clinical successes might better earn the trust of venture capitalists and pharmaceutical companies, who largely have hung back from bankrolling stem cell companies, although in the case of Aldagen, the record shows that if you have what investors like, venture capital need not be elusive. Since its establishment in 2001, this Durham, North Carolina company has received $45 million from venture backers. Three Aldagen products comprising progenitor and adult stem cells derived from bone marrow and peripheral blood are currently in clinical trials for treating heart failure and limb ischemia and for improving cord-blood transplantation.

Some contend that the field is getting close to scoring a winner. For example, Osiris, based in Columbia, Maryland, has three therapies based on a proprietary mesenchymal stem cell product derived from adult bone marrow. The product is formulated differently according to the disorder: Prochymal is delivered intravenously; OsteoCel, one of the field's earliest approved products, is for bone matrix; and Chondrogen is an injectible for treating knee injuries. Phase III trials have received fast-track status by the FDA for testing Prochymal in patients with acute Graft versus Host Disease (GVHD) and the intestinal disorder Crohn's disease. And last month, the US Department of Defense awarded a $224.7 million contract to Osiris to advance Prochymal as a therapy for treating gastrointestinal injury due to radiation exposure.

Meanwhile, Chris Mason points to the success of a tissue-engineered bilayered skin product called Apligraf, manufactured by Organogenesis. Comprising a layer of collagen and neonatal fibroblasts overlain with living keratinocytes, Apligraf has been used to treat venous leg ulcers and diabetic foot ulcers in 200,000 patients since it received FDA approval 9 years ago. "When Organogenesis emerged from Chapter 11, it came out very strongly, and has prospered by strongly focusing on its skin products," Mason notes. Organogenesis, in Mason's opinion, exemplifies the three factors that will help ensure a company's success in this new era of commercialization: "expert business management, simpler but superior products, and scalability of manufacture." In a similar vein, Advanced Tissue Sciences, after rescue from Chapter 11, was sold to Advanced BioHealing, which relaunched ATS's product Dermagraft, a wound-healing dermal substitute derived from newborn foreskin.

Overcoming Hurdles

Cell therapy companies have the twin hardships of showing that a cell therapy is efficacious in humans and demonstrating by phase III how the product will be produced according to Good Manufacturing Practice (GMP) regulations. Given this, it is not surprising that investors remain wary. Making a chemical drug as opposed to developing a cell therapy "is a lot easier because it's a chemical…and not a complex thing like a cell," notes Giebel. Just how much of the biology has to be elucidated before a clinical trial can take place? The Investigational New Drug (IND) application that Geron expects to file this year to test neural stem cells for treating spinal-cord injury will be between 20,000 and 30,000 pages in length, testimony to the very high bar required for moving cell therapy products into clinical trials, especially those involving the nervous system.

Despite the length of time it can take to prove that a particular cell therapy has a desired effect—and not just once but time after time—examples exist of biological advances being made and investments following. At Novocell in San Diego, years of experiments to efficiently differentiate human ES cells into pancreatic endocrine cells are starting to pay off, according to Chief Scientific Officer (CSO) Emmanuel Baetge. Complex culture conditions are required first to turn human ES cells into definitive endoderm (as opposed to extra-embryonic endoderm), then posterior foregut (and not anterior foregut), then pancreatic endoderm (as opposed to gastric or intestinal endoderm), then endocrine precursor cells, then finally the pancreatic islet beta cells that produce insulin. As for multiplying a small batch of cells into billions, "No one has mastered that yet," says Baetge. "While differentiation strategies are making good progress, scaling up the cells will depend on defining cell purification procedures for clinically relevant patient populations" to ensure safe transplants. A proprietary technology that coats islet cells and protects them from immune attack is one of two technologies in Novocell's portfolio that keeps the company pushing forward and attracting funding. Last July, Novocell raised another $25 million in venture capital, its total to date being $60 million, according to Baetge.

A Helping Hand at the Start

For start-up companies, a diversity of funding sources in the $1 to $5 million range exists, especially in the United States. The funds come from university-sponsored start-up funds, state grants and bonds, patient advocacy groups, family foundations, individual angel donors and venture capital, DARPA and other federal agencies, as well as less traditional fare such as grants from the US Small Business Innovation Research (SBIR) program and the Small Business Technology Transfer (STTR) program. A portion of the annual budgets of eleven federal departments and agencies are put aside for SBIR grants, which in turn go to small businesses with innovative and technical merit. Five federal groups similarly save funds for STTR programs, which are meant to kindle partnerships between small businesses and prominent research institutions. Administered by the US Small Business Administration, the SBIR program was launched in 1983, and the STTR program in 1992.

Four-year-old Arteriocyte, which initially focused on using several types of stem cells to grow blood vessels for reestablishing cardiac function, started with $250,000 of venture seed funds from Case Western Reserve University; since then it has received federal, state, and local grants, including three SBIR-STTR grants. Consequently, this Cleveland, Ohio-based company has been able to expand to developing four cell-based products derived from adult bone marrow for treating ischemic diseases and acute and chronic wounds, thus enlarging its future chances for revenue.

"Since the market rolled over in 2001, venture capitalists are delaying their investments until a technology is at phase II or later. There's more watchful waiting going on," observes Arteriocyte CEO Donald Brown. "That's why non-dilutive grant mechanisms like SBIRs and STTRs are so valuable to start-ups." StemCells, Inc., Athersys, MacroPore (now a division of Cytori Therapeutics), Osiris, and other stem cell businesses have also received these federal infusions of funds.

State grants and venture funding helped to launch Cellular Dynamics International (CDI) and Stem Cell Products (SCP), started by James Thomson of the University of Wisconsin and colleagues in 2005 and 2006, respectively. CDI produces ES cell-derived cardiomyocytes for testing the effects of drugs on heart electrophysiology. The models routinely used "are Purkinje fibers from the heart of the dog or guinea pig," says Nicholas Seay, COO of both companies. "We think cells from human would be a better model, because the animals don't have the same electrophysiological response as the human heart." Meanwhile, SCP has the more complex goal of steering human ES cells down the hematopoietic differentiation pathway to form platelets and red

blood cells, products that in the future could do away with the need for blood donations. "We're actually pretty good at making platelets and red blood cells," says Thomson, although the company so far can turn out only very small quantities. The "non-trivial exercise" ahead, says Seay, is to ramp up the production process by several orders of magnitude while holding down costs. Seay sees an automated future where robots "would be culturing cells and automating a process to produce differentiated cells."

Generating immense numbers of cells for the eventual treatment of large patient populations is one of the toughest tasks that companies face. Most people working with adult stem cells "can generate only a limited amount of cells," says John Sinden, CSO of ReNeuron, a UK-based cell therapy company. ReNeuron has the goal of using neural stem cells from fetal tissue to treat stroke patients with chronic disabilities. Because "we're a research and development engine and not ourselves geared up to do clinical manufacture," notes Sinden, ReNeuron collaborates with the UK's two leading contract manufacturing organizations—Angel Biotechnology and BioReliance. Cells from the biotech's small cell bank are transferred to these processing facilities, where they are expanded and then stored in a master cell bank, ready for transplant. "We ourselves aren't big enough to do anything more than proof of concept in patients beyond Phase II," points out Sinden. "We'd be looking for a larger biotech or pharma to carry this forward."

The Next Billion?

A make-it-or-break-it question for a biotech company focused on stem cell therapies is where, after receiving its initial millions, will the company's next billion come from? Douglas Fambrough, a general partner with the venture capital firm Oxford Bioscience Partners, suggests that public market investors are not likely to support earlier clinical stage research, nor are pharmaceutical companies, who "don't yet care about cell therapy" because no cell product has generated $500 million. That leaves venture capital "holding the bag," he notes. Cell therapies that have come to market—Genzyme's Epicel and Carticel and Osiris's OsteoCel—are used by small patient populations and generate only modest revenues. OsteoCel's 2006 sales, for instance, were reportedly $8.3 million.

Oxford Bioscience Partners has been actively scrutinizing stem cell companies but has yet to invest in one. What does it take to convince venture capitalists? Fambrough says that, along with a strong medical need, a savvy management team and intellectual property that lets you protect your position; "speaking personally, I need to see all the dots connected. I need to see that what you've got today can turn into a product used by physicians." He feels that with ES cell companies, in particular, the dots are hard to connect, such as the ability to "reproducibly differentiate cells to precisely the mature cell you want, in an irreversible fashion." With companies that are developing autologous therapies, neither does he grasp how cells can be efficiently extracted, expanded, differentiated in vitro, and then delivered back into the patient. "We don't have a commercial medical delivery infrastructure that does that."

Some investors maintain that autologous cell therapies will be less commercially viable than allogeneic therapies. "You have to bring in the patient and harvest the cells, expand them, and then bring the patient back in for transplantation," notes Giebel. "For a pharmaceutical company and its profit margins, it would be much better if you can mass manufacture one product-fits-all." But allogeneic therapies also have problems because transplanting cells from one person to another runs the risk of immune rejection of the cell transplant. Bonfiglio, meanwhile, takes a different view, predicting that "a substantial number of therapies developed will likely be autologous, which will require you have some sort of cell processing device at the point of care or cell-therapy centers."

Robert Lanza, CSO of ACT, believes that the field is closing in on solutions for allogeneic treatments and immune rejection. "If you look at tissue types in the U.S., you find that 100 lines would give you a complete haplotype match for fifty percent of the population." Those cell lines could be produced through somatic cell nuclear transfer or by reprogramming adult somatic cells, but until such a bank of cell lines exists, immune rejection will continue to be a problem. ACT will soon file an IND to test its ES cell-derived retinal cells for treating macular degeneration; in this case, immune rejection is less likely because the eye is an immunoprivileged site.

Although big pharma has not yet shown major interest in stem cell biotech companies, some onlookers believe there are increasing signs of partnering. AstraZeneca, for instance, has joined EpiStem to study how a physiological link between hair follicles and intestinal stem cells can be used to assess the side effects of certain cancer drugs. Meanwhile, Roche Venture Fund and Novartis Venture Fund entered a multi-million-dollar round of financing for Cellerix, a Spanish company that has clinical trials underway for cell therapies that treat fistulas and skin disorders; and Johnson & Johnson Development Corporation (the venture capital subsidiary of J&J) led Novocell's latest round of venture financing. Cytori has a joint venture with the Japanese medical device maker Olympus Corporation to commercialize its Celution System, a medical device that processes adipose tissue stem cells from patients for autologous transplant. And several months ago, Arteriocyte's medical systems division formed a partnership with Medtronic, acquiring its Magellan System, a technology for separating platelets from peripheral blood that will be "the ideal delivery vehicle for our stem cell therapies into damaged tissue," according to Arteriocyte CEO Donald Brown.

The Road Ahead

Some say that a confluence of forces is driving regenerative medicine forward, from the push of innovative technologies coming out of universities, to the pull of the marketplace brought on by big pharma's growing need for effective new treatments. Only time will tell if "RegenMed 2.0" will indeed prevail or whether it will go the way of RegenMed 1.0.

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