

Little Biotech on the Prairie

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Fargo, North Dakota, has a lot of horizontal space. In adjoining Moorhead, Minnesota, is a Viking ship that was built by a junior high school guidance counselor and sailed to Norway and back by family members. In a similar can-do spirit, Mike Chambers, co-founder of Aldevron (www.aldevron.com), thought North Dakota was a fine place to set up a plasmid farming operation.

While entrepreneurs like Chambers prove biotech can sprout up anywhere, the Midwest still lacks the venture capital that lubricates places like Boston or the Bay Area/San Diego. Biotechs outside established clusters may appear more like service providers, as they

in partnership with one of its clients as well as a high throughput vaccine platform with Redwood City, California-based Maxygen (www.maxygen.com). "In 2003, we made the world's first DNA vaccine to be used outside of a trial setting," said Chambers. "It was used to immunize the California condor against West Nile virus." There are a few other biotechs in Fargo now, funded by angel investors. "When we started out Aldevron, the investment committee wasn't attuned to high tech," Chambers noted. "But now people successful in the manufacturing sector are willing to fund high risk ventures."

Madison, Wisconsin, is the home of the Wisconsin Alumni Research Fund (WARF), which commercializes the research from the University of Wisconsin. Biotech development is also encouraged by such entities as the State of Wisconsin Investment Board and several angel investor networks. Sister city Milwaukee has GE Healthcare and the Medical College of Wisconsin. "GE Healthcare brings in world-class people, and sometimes those world-class people want to leave GE and do other things," says Teresa Esser, managing director of Silicon Pastures, a Milwaukee-based angel network. "They come to me with their resume. GE doesn't acquire companies under \$100 million. We are trying to bridge that gap."

A Silicon Pastures investment is Madison-based NeoClone Biotechnology International (www.neoclone.com), which makes monoclonal antibodies (mAbs) for research and diagnostics using a retrovirus and immortalized antibody lines instead of the standard hybridoma fusions. The now ten person company was founded in 1999 by a couple of University of Wisconsin-Madison graduates, Deven McGlenn and Richard Burgess, Ph.D., and licensed mAbs production technology from WARF. NeoClone has customers in over 30 countries and anticipates total sales north of \$1.2 million.

"The biotech community has a great deal of influence because, relatively speaking, it is a major industry here," said McGlenn. Ten years ago, it was difficult to recruit skilled labor, but since then Madison has experienced a number of biotech financial successes (such as NimbleGen Systems, Inc., a maker of high-density DNA microarrays that was acquired by Roche for \$272.5 million, and TomoTherapy, Inc., which makes imaging and radiation treatment systems for cancer and raised \$222 million in an IPO in May). Major players such as Promega

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have to generate revenue to support their R&D. Although states are offering incentives to develop local biotech clusters, how big nascent companies can grow before they have to seek their fortunes elsewhere remains an issue.

Pharma Farming

Chambers, a North Dakota native, and John Ballantyne, a New Zealander and fellow science student at North Dakota State University, founded Aldevron "with creative use of credit cards" in 1998. The two entrepreneurs at first incubated the company in lab space from NDSU while bootstrapping its development by contract manufacturing DNA plasmids, proteins, and antibodies for biotech companies. Aldevron now totals 50 people, including Genovac, a German company acquired in 2004. The company plows its profits back into internal development projects including a therapeutic vaccine for lung cancer developed

The Treachery of Distance

According to Dan Broderick, partner at Prolog Ventures, a St. Louis, Missouri, venture capital firm, every biotech job creates a multiplier effect of 3.1 other jobs. "The quality of the deals is high right now," says Broderick. "What you need is technology with a market, talent, and capital. Those three things are in the Midwest. We are a little light in entrepreneurial or C level talent. We are looking for people who want to come home."

According to Broderick, costs are low compared to the coasts. Laboratory space rents in Wisconsin for \$25 a square foot versus Boston's \$45 and New York's \$66. A lab tech in Wisconsin can be hired for \$40,000 and senior scientists in the \$60,000 range. "The thing we need to deal with in the Midwest is the treachery of distance," Broderick said. "Most innovation and commercialization takes place in urban areas."

Corporation, Sigma-Aldrich, Covance, and Invitrogen are locating there. "In terms of research institutions, we really don't lack," said McGlenn. "WARF has huge experience in licensing." But lack of venture capital and experienced management are persistent concerns.

Take your Vitamins

Madison-based Deltanoid Pharmaceuticals (www.deltanoid.com) develops treatments based on vitamin D analogs for osteoporosis, renal osteodystrophy, psoriasis, and other diseases. The company was cofounded by Hector DeLuca, the Harry Steenbock Research Professor of Biochemistry at the University of Wisconsin-Madison, and Dr. Margaret Clagett-Dame, his wife. DeLuca has generated patents prolifically in the course of five decades of research on vitamins A and D: over 150 in the U.S. and more than 1000 worldwide, producing more than \$150 million for WARF in licensing fees. He was involved in developing eight drugs, including Alfarol, Zemplar, Rocaltrol, and the eponymous Hectorol, which exceeded \$5 billion in pharmaceutical sales.

DeLuca had existing connections with pharma companies, a long-term relationship with WARF through his own work, and good enough data in animals to get venture capital investment for Deltanoid, led by Dan Broderick (formerly at Mason Wells) as well as Venture Investors, LLC. In 2004, Deltanoid signed collaborations with Abbott Laboratories to develop Vitamin D Receptor Activators (VDRAs) for the treatment of kidney disease and licensed to Pfizer its lead compound 2MD [2-methylene-19-nor-20(S)-1 α , 25-dihydroxyvitamin D 3] to treat postmenopausal osteoporosis for \$42.5 million in upfront and milestone payments. But Pfizer abandoned the collaboration in the following year. Deltanoid decided to continue on its own and is recruiting patients for the phase II trials. Now the company is going back to investors for a second round of funding.

Fortifying Rat Chow

Vitamin D hormone as well as parathyroid hormone and calcitonin regulate

the body's calcium and phosphorus levels. At too high a dose, vitamin D is toxic. But if it is lacking, the body cannot absorb enough calcium and phosphorus from food for bone building. In children, vitamin D deficiency causes rickets; in adults, it causes osteoporosis.

While the effects of vitamin deficiencies were known for centuries, the puzzle of how micronutrients worked was put together incrementally by teams of scientists around the world. In 1913, Harry Steenbock, (who also founded WARF) and E.B. Hart made a link between sun exposure and rickets when they discovered that a herd of lactating goats kept inside lost bone mass, compared to their brethren kept outdoors. In the 1920s, Steenbock and others followed up with experiments that showed irradiating rat chow prevented rickets in animals. DeLuca, one of Steenbock's students, led a team at the University of Wisconsin that isolated the active hormone derived from vitamin D, 1,25-hydroxyvitamin D₃, which is produced in sequence by the liver and kidney. Vitamin D is carried in the blood by proteins. In the early 1990s, DeLuca's lab also established that vitamin D could affect the immune system.

"There are two difficult problems we are trying to solve," said DeLuca. "We are trying to bring out a vitamin D compound that has bone-building activity." Osteoporosis treatments currently on the market mineralize bone but have no anabolic effects. Deltanoid is also trying to use a vitamin D analog to treat autoimmune diseases such as multiple sclerosis and lupus and is conducting research on how vitamin D compounds inhibit cancer both in vitro and in vivo. "In addition, we are always trying to improve drugs we have out there" said DeLuca. DeLuca's discoveries had spurred the formation of two prior companies: Bone Care International, whose injectable drug Hectorol (Doxercalciferol), which prevents secondary hyperparathyroidism (overproduction of parathyroid hormone associated with chronic kidney disease), was bought by Genzyme in 2005; and Tetronics, which manufactured complex active phar-

maceutical ingredients and intermediates, bought by Sigma Aldrich. Deltanoid is also developing a successor to Zemplar, produced by Abbott Laboratories, another vitamin D analog to treat secondary hyperparathyroidism in kidney dialysis patients that won't raise blood calcium levels.

"We have to investigate why blood calcium goes up," said DeLuca. "And what is the molecular basis of suppression of autoimmune function. It does something to the immune system that suppresses the cells that chew up their own tissue. It is not simply being an immune suppressant. We are targeting what is going wrong in autoimmune therapy." Raised blood calcium calcifies tissues in the kidneys, heart, and cardiovascular systems. "If we find an analog that does what it does in the immune system and that doesn't, at doses required, raise blood calcium, then we are golden." DeLuca said.

Deltanoid also has a topical compound, becocalcidiol, a vitamin D analog for treatment of psoriasis, sublicensed originally to QuatRx Pharmaceuticals. In addition, Deltanoid is working on a preclinical compound that controls blood phosphorus in dialysis patients to compete with Genzyme's Renagel, which prevents phosphates from being absorbed from the diet.

Knitting It All Together

The Midwest, formerly considered fly-over country, is getting an increasing amount of attention and investment from East and West Coast venture capitalists. So far in 2007, Ohio companies received \$244.3 million in healthcare investment. Minnesota, a traditional center of medical devices, garnered \$126 million, and Wisconsin \$16 million. According to Baiju Shah, president of Cleveland's Bioenterprise (www.bioenterprise.com), the Midwest generates \$8 billion of national, peer-reviewed NIH research, but research institutions need to step up their rate of technology transfer if they want to commercialize their research. To combat the paucity of venture capital, the states are kicking in funding, such as Ohio's \$1.6 billion Third Frontier Fund and Michigan's \$2.1 billion 21st Century Jobs Fund. Shah cautions that states get in trouble

when they make direct investments in companies, as the temptation is to make politically driven decisions. Awards in Ohio go through peer review by the National Academy of Sciences and then evaluation by venture capitalists from outside Ohio.

Shah cites Copernicus Therapeutics (www.cgsys.com), which is developing

a cure for cystic fibrosis, and Athersys (www.athersys.com), a Cleveland biotech and stem cell company that is going public through a reverse merger, both of which have benefited from state support in their development. "It is too early to declare victory," Shah said. "We have notable exits in the Midwest, such as Esperion Therapeu-

tics in Ann Arbor, which was sold to Pfizer for \$1.3 billion after having gone public, but we still have a few biotech companies leaving the Midwest for late-stage development."

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