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Innovations

ZymoGenetics

A Quiet Powerhouse Emerges

Drug Discovery: For most, the expression conjures up thoughts of big pharma and the hunt for "small-molecule drugs" to treat cancer and other human diseases. And rightly so; this is big business that continues to produce important drugs with huge implications for human health and society—think Gleevec, Prozac, Lipitor, or Allegra. Although the technologies of this type of drug discovery have become much more sophisticated since aspirin hit the market more than 100 years ago, the modus operandi remains relatively unchanged. Screen a series of synthetic or natural molecules for interaction with a drug target (usually a protein) that plays a pivotal role in a biochemical pathway involved in the molecular pathogenesis of human disease. The ultimate prize at the end of this costly and painstaking process is a drug lead that modifies the activity of the protein in the body to treat or prevent the disease—and significant revenues for the company if the market for the drug is sufficiently large.

However, the availability today of the catalog of known and putative human proteins in the form of the genome—coupled with powerful new bioinformatics tools—has given rise to an additional paradigm in drug discovery. This fundamentally different strategy, sometimes called the "gene first" approach, is one on which a Seattle-based biotechnology company called ZymoGenetics has bet its future. Rather than creating and screening new chemical entities, ZymoGenetics plans to harness the therapeutic potential that exists inherently in specific categories of human protein. "Proteins as drugs" is a therapeutic modality that is complementary to the action of small-molecule inhibitors. Protein therapeutics generally involves a gain-of-function effect rather than the inhibition of a key enzyme.

A focus on proteins as therapeutics also provides important advantages on the business side. A hefty portion of the expense in the drug discovery process comes relatively late in the development pipeline—during clinical trials. A major reason for drug failure is unforeseen toxicities or poor bioavailability. However, most therapeutic proteins occur naturally in the human body, making them less likely to trigger adverse effects. Another key advantage is that it is difficult to create a "generic version" of a protein. "The Holy Grail of the pharma industry is exclusivity," explains ZymoGenetics President and CEO Bruce L.A. Carter, "and proteins provide a better opportunity to achieve this than small-molecule drugs."

"A small number of protein families are providing the most valuable intellectual property coming out of genomics today" –Patrick O'Hara, Vice President of Bioinformatics.

This approach may be relatively new, but ZymoGenetics is no "new kid on the block." Founded more than 20 years ago by Earl Davie and Benjamin Hall of the University of Washington and the late Nobel laureate Michael Smith of the University of British Columbia, ZymoGenetics' early focus was on the development of production systems for recombinant proteins. "The original impetus behind the foundation of ZymoGenetics was the desire to commercialize our yeast protein production system," explains Hall. Their expertise in the area led to a collaboration with Denmark's pharmaceutical giant, Novo Nordisk A/S, which was looking for a partner to produce its own version of recombinant insulin to compete with the Eli Lilly-Genentech Humulin protein, produced in *E. coli*. The relationship grew, and ZymoGenetics was soon absorbed as the U.S. R&D arm of Novo Nordisk in 1988, providing the former with a much-needed infusion of cash.

Retaining both their name and a significant degree of independence, ZymoGenetics benefited greatly from the financial security that Novo provided. Largely buffeted from the commercial pressures weighing upon other genomics companies in the 90s, they were able to nurture a top-notch bioinformatics group that built upon the company's base in protein biochemistry. They created and honed computational strategies to query genomic databases, allowing them to focus on the relatively small fraction of human genes with an arguably greater potential for therapeutic exploitation—for example, growth factors or cytokines. The logic was to probe databases with sophisticated, proprietary digital representations of key protein motifs and structure prediction algorithms to look for putative proteins similar to those that had already proven themselves in the market. Armed with these tools, the company has zeroed in on hundreds of genes rather than the thousands in the sights of its competitors. "A small number of protein families are providing the most valuable intellectual property coming out of genomics today," explains Patrick O'Hara, Vice President of Bioinformatics.

And intellectual property they have. After a private placement offering of $150 million, ZymoGenetics was reestablished as an independent company in November 2000 and currently holds more than 225 issued U.S. patents. Such a portfolio puts the company in the same league as better-known competitors Human Genome Sciences and Genentech. Under a collaborative licensing agreement in effect over the next four years, Novo retains options to license up to eight proteins resulting from discoveries made at ZymoGenetics. According to this agreement,

ZymoGenetics retains exclusive rights to the proteins for North America, whereas Novo may obtain a license in the rest of the world. Because ZymoGenetics intends to focus its development and marketing activities in North America, the agreement gives ZymoGenetics a crucial and seasoned product development, production, and marketing partner outside North America. "This agreement provides ZymoGenetics a built-in partnership with one of the world's largest manufactures of recombinant proteins," said Charles E. Hart, Senior Director of Corporate Communications and Investor Relations. "We see this as a real benefit as we advance our pipeline of product candidates."

But ZymoGenetics' newfound independence has also provided the company with the leeway to pursue drug candidates with partners whose focus and expertise better matches the potential therapeutic application at hand. Indeed, part of the rational for the spin-off was borne out of the fact that many of ZymoGenetics' current and future product leads were unlikely to fit into Novo's strong focus on diabetes. "Our bioinformatics-driven strategy has allowed us to make discoveries in many different therapeutic areas rather than a single area of human disease," commented Carter. "Having the flexibility to work with the appropriate partner for a given therapeutic area will allow us to optimally advance our product candidates into clinical trials and to the market."

As part of Novo, ZymoGenetics participated in the discovery or development of five brand-name medical products that together led to sales in 2001 in excess of $2 billion. These sales provided ZymoGenetics with approximately $10 million in royalties—a healthy income, but this still left them $37 million in the red in the last fiscal year. The key determinant of ZymoGenetics' ability to survive the next decade hinges on the ability of the company's discovery and development engine to bear fruit in the form of marketable products. The investors are optimistic. ZymoGenetics pulled off its first public offering in the days following September 11—hardly good timing. Although they missed their price target, they raised another $110 million, providing needed cash as they move their products toward the clinic.

The first two candidates that ZymoGenetics is advancing toward clinical studies are recombinant human (rh) Factor XIII and rh Thrombin. These two molecules, which are key proteins in the blood coagulation cascade, are being developed to treat bleeding complications associated with surgery. ZymoGenetics intends to file investigational new drug applications (INDs) with the FDA for rh Factor XIII in late 2002 and for rh Thrombin in early 2003, paving the way for Phase I clinical studies in patients.

Although the primary commercialization strategy for ZymoGenetics is internal development and marketing, the company is also aggressively leveraging its extensive patent portfolio with various licensing and partnership deals. Recent examples include the establishment of collaboration with Switzerland's Serono S.A. to develop TACI-Ig for the treatment of autoimmune disease. TACI is a cell surface receptor that drives proliferation of B cells. Fusion of the extracellular domain of receptor to a piece of an immunoglobulin protein produces TACI-Ig—effectively a decoy protein that sops up TACI's natural ligand to prevent aberrant receptor activation and B-cell proliferation that occurs in autoimmune disorders.

Additionally, Novo Nordisk has exercised options to license three proteins discovered from ZymoGenetics' bioinformatics activities. The proteins are IL-21, a potential anticancer drug, and IL-20 and its receptor, being studied for the treatment of psoriasis. IL-21 is a cytokine that appears to regulate levels of antibody-producing B cells and also stimulates natural killer (NK) cells—the immune system's scavenger cells that roam the body in search of cancerous prey. IL-20 is a cytokine that acts on epidermal cells in the skin. It has been implicated in the development of psoriasis in animal models of the disease. Various other proteins in preclinical development are described on the ZymoGenetics website at www.zymogenetics.com.

Those following drug discovery in the coming years will certainly be paying attention to ZymoGenetics. With a solid research and discovery record, a rich horde of IP, and a seasoned management team, the company is well placed to make good on its aggressive goal of being a leader in protein therapeutics. Big pharma? Not quite yet, but ZymoGenetics has quietly laid the groundwork to aim for their ranks.

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