Innovations

Trust me, it will work

Small Molecule Therapeutics, Inc.

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The first sign that Small Molecule Therapeutics, Inc. (SMT; Monmouth Junction, New Jersey) is unique is its name. This drug company is going to search for small molecule drugs. And that's it. No fancy founding technology to draw in the scientifically knowledgeable investors, and no catchy story to sell to the general public. Indeed, in an interview shortly before the company opened for business in 1997, the CEO and founder stated: "We have not decided to focus on any one therapeutic area or technology platform. Our goal is to identify [drugs for] unmet medical needs."

Language like this is endemic in industry press releases that aim to obfuscate, but few CEOs will say such things in real life. Prabhavathi Fernandes was making an exception that day because she really didn't have anything concrete to say, at least in public. Fernandes had left her job as vice-president of biomedical screening at Bristol Myers Squibb (BMS; Princeton, New Jersey) to set up SMT and, as she says, "coming out of a major company you have to start from scratch."

The one thing she had was a substantial reputation. "She's very energetic and very enthusiastic," says Daniel Chu, vice-president of discovery research at KOSAN Biosciences, Inc. (Hayward, California), and a former co-worker at Abbott Laboratories (Abbott Park, Illinois). "She has the momentum and strength to make things happen. And she's very knowledgeable as a scientist."

On the basis of that reputation, which includes the research that led to four approved drugs, Fernandes was given the money to start SMT. Now all she needed was some science to go with it.

Confidence breeds confidence

Fernandes was born in Bangalore, India, and studied in India, Belgium and the United States. In the pharmaceutical industry it was Richard Sykes, now the CEO of Glaxo, who showed her that drug hunting was a viable option. "I realized that you could do good science within major companies," she says. She oversaw antimicrobial screens at Abbott, then moved to BMS to direct a variety of screening efforts.

Eventually her enthusiasm for big pharma began to wane. "I like big companies — I have grown a lot there — but I was there for 20 years, and 20 years is a long time," she says. "I thought I could move things along faster in a small company."

SMT is a company founded on reputation alone.

The next step was to find money. "A lot of venture capitalists knew me, so when I called and presented what we could do they were enthusiastic," says Fernandes. Her presentation centered on one major theme: in her words, "We've done it before, and we can do it again." Money arrived in July 1997 (US$2 million) and January 1998 (US$8 million). Rolf Menzel left BMS with Fernandes to become executive vice-president, and the laboratories opened in November 1997.

Building on the old

Although Fernandes couldn't take any specific intellectual property away from her previous employers, she could still use her considerable knowledge of successful, and unsuccessful screening strategies. This is particularly true with screens for antibiotics. As more antibiotics have been discovered (in response to the growing numbers of antibiotic-resistant bacteria), antibiotic hunts have increasingly turned up the same, or similar molecules. At Abbott, Fernandes had pushed the "variation on a theme" line successfully, developing a blockbuster macrolide called clarithromycin in the process. But now the easy modifications have been covered, and resistant bugs are throwing out multiple related chemicals in one hit. New targets are needed.

SMT has selected bacterial topoisomerase I as its first candidate target. Inhibitors of this enzyme should work like the extremely successful quinolones, which Fernandes worked on when she was at Abbott. Quinolones trap DNA in a cleaved state by inhibiting a late step in the cycle of DNA gyrase (topoisomerase II). SMT has used a proprietary functional screen with bacterial cells to detect antibacterial compounds that specifically inhibit topoisomerase I, and confirmed that they inhibit the enzyme *in vitro*. Similar screens are planned with other targets such as RNA polymerase.

New strategies: interaction disruption

The centerpiece of SMT's science is a pair of techniques designed to make sense of the mountain of genomics data that is overwhelming the drug industry. Genomics can, for example, yield a comprehensive list of proteins that are over-produced in a diseased tissue. Turning off one or more or those proteins might reverse the disease process, but the list is no help in determining which of the many proteins might be the best candidate for inhibition.

The best way to tell is to come up with an inhibitor for each protein. Traditional inhibitors block active sites of enzymes, but much of the cell's business involves protein–protein interactions. These interactions govern the assembly of countless cellular machines, and inhibition of

them could provide a way to attack many disease processes. Several companies are generating exhaustive lists of protein–protein interactions, but what is needed is a way of defining which of the interactions is functionally important in disease.

A technique called Functional Interactive Screening Technology (FIST) is SMT's solution to these dual problems. The method begins with two-hybrid analysis to define a protein–protein interaction. (In the standard two-hybrid technique, a transcription activator is fused to one protein partner, and a DNA-binding domain is fused to another; interaction of the two proteins is detected as a transcriptional read-out when the DNA-binding protein brings the activator protein to a promoter.) The gene encoding one of the interacting proteins is then sheared randomly, and the fragments are expressed with both interacting proteins. A fragment that disrupts the interaction of the full-length proteins (a dominant-negative protein fragment) is termed a functional domain; this fragment can then be expressed in a disease tissue or cell to test whether disruption of the protein–protein interaction reverts the disease. If it does, SMT starts another two-hybrid screen — to search for a small molecule that can mimic the disruption by the functional domain.

The alternative to FIST is traditional molecular biology — defining the exact function of the protein and therefore the likelihood of its involvement in a disease. In comparison, says Fernandes, FIST can be seen as high-throughput. SMT recently completed FIST analysis for three major proteins in one month.

Looking outside the cell

Just as communication networks inside the cell rely largely on protein–protein interactions, communication outside the cell relies on membrane-bound receptors. Thanks to their importance and accessibility, membrane receptors are the target of up to 70% of all drugs, according to Fernandes. SMT has developed its second key technology — the *Escherichia coli* Dimer Detection System (EDDS) — to monitor the status of one subset of these proteins — the single transmembrane receptors.

In mammalian cells, binding of ligand to these receptors triggers dimerization and activation of signal transduction pathways. In EDDS, the extracellular portion of the mammalian receptor is fused to the CadC protein of *E. coli*. CadC normally detects pH change, and when dimerized it acts directly as a transcriptional activator. The fusion proteins made by SMT produce this transcriptional readout in bacteria in the presence of ligands such as insulin and erythropoietin.

EDDS has two main uses. The first is to define the ligands for orphan receptors. These receptors typically turn up in genomics efforts, but have no known ligand. The ligand can be found by fusing the receptor to CadC, and co-expressing a library of extracellular proteins in bacteria. In bacteria that make the appropriate ligand, the ligand will dimerize the receptor and turn on a reporter gene. In this screen, says Fernandes, 10,000 clones can easily be screened in one night.

Newly discovered ligands have potential as protein therapeutics, but EDDS can also be used to screen for small molecule replacements for both new and well-known ligands. EDDS finds small molecules that either mimic or interfere with the dimerizing effect of a ligand like insulin.

The big question is whether small molecules have enough heft to do the job of proteins — be it disrupting protein–protein interactions or inducing dimerization. Fernandes cites the recent success of the granulocyte-colony stimulating factor (G-CSF) mimetic made by Ligand Pharmaceuticals, Inc. (San Diego, California) and Smith Kline Beecham, and believes that similar molecules are on the way. One key, she says, is ignoring the structure of the original ligand. "If we stop looking for a structural mimetic and start looking for a functional mimetic, we believe we will be successful," she says.

A family-based business strategy

Producing drugs involves much more than clever assays. SMT's approach, says Fernandes, is to "be the drug-discovery arm for companies with clinical and marketing prowess." Other partners will provide genomics data, and add to the in-house chemistry.

"We would like to keep it small," says Fernandes. "Flexibility is a very big issue — we need to move fast. We prefer to do a lot by partnering. We keep our burn-rate low and get the job done."

Partnering also yields choice. "In a large company you have one CNS group, one anti-infective group, but if you are a small company you can shop the project around to the best possible partner," says Fernandes. SMT hopes to finalize deals soon. "We did think people might fund us for ideas, but those times have come and gone — people want data," says Fernandes. "We are working hard to get data."

The small size of the company — 32 at present, and estimated to double eventually — has its pluses and minuses. "We are still very much part of a family," says Fernandes, and decisions are made by those who really know about the work. But with a new company comes responsibility. "Normally you worry about yourself and your family," says Fernandes. When you start something like this you want to be successful for 31 other people. You really acquire a large family."

Not that Fernandes seems too worried. "Security comes from within," she says. "In a big company, no one cares if you succeed. Here, why would you want to fail when everyone is watching?"

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