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BioCentury

THE BERNSTEIN REPORT ON BIOBUSINESS™

Tools & Techniques

Unnatural selection

By Susan Schaeffer
Senior Editor

Since 2004 **Sutro Biopharma Inc.** has quietly been building a cell-free protein synthesis platform and working on early research projects with undisclosed partners. Now that it has hired a new CSO and received an injection of venture money, the company will turn to building an internal pipeline of "biosuperiors," compounds that improve upon marketed protein therapeutics.

While the idea of biosuperiors isn't new, Sutro says its biochemical protein synthesis technology will allow it to make modifications that are difficult, if not impossible, to do with cell-based synthesis systems. Last week, it announced a multiyear collaboration with **Pfizer Inc.** focused on peptides that have been difficult to produce using conventional technologies.

"When Sutro came along, it opened up a protein space that had been completely inaccessible to drug developers like myself. It has the ability to introduce non-natural amino acids to bring real diversity into protein therapeutics," CSO Trevor Hallam told BioCentury.

Hallam joined Sutro in December. He has spent more than 25 years in drug discovery and development, most recently as EVP of R&D at **Palatin Technologies Inc.** One of Palatin's technologies allows it to develop peptides with novel amino acid mimetics in place of selected amino acids.

Sutro brings a similar ability to proteins, with a platform that allows for cell-free synthesis of whole proteins on a much larger scale than has been possible.

CEO William Newell said research kits that can perform transcription and translation in a cell-free environment have been available for many years, but are not scalable. The main limitation, he said, has been the cost of the energy source needed to drive the synthesis reaction.

"With smaller kits, even if you could scale up, you'd have to purchase such large amounts of ATP, at exorbitant prices, that you couldn't make clinical quantities of a protein cost effectively," Newell told BioCentury.

Sutro's technology, exclusively licensed from **Stanford University**, uses an extract of *Escherichia coli* that contains fully functional ribosomes, as well as a fully functional catalytic ATP generation system in an inverted vesicle.

Newell said the technology can produce proteins with a COGS in the range between that of *E. coli*- and CHO cell-based systems. But while *E. coli* can make only relatively simple proteins that don't have disulfide bonds, and it produces unfolded proteins, Sutro says its biochemical protein synthesis technology can make more complex proteins with very little downstream processing.

To provide proof of concept, the company first synthesized human GM-CSF. It has since moved on to more complex proteins, including antibody derivatives such as Fabs and Fc-fusion proteins, and even full-length IgG.

"We showed we can increase in complexity, not only homodimers, but also heterodimers — and our biochemical protein synthesis is scalable," Lesley Stolz, VP of business development, told BioCentury.

"We've been able to show we can do 10 runs in a row and get exactly the same expression efficiency," she said. "And it's linearly scalable from 10 microliters to 100 liters at 1 gram per liter, with very little process development."

According to Newell, Sutro can make protein at small scale in about four hours and can do a 100-liter run to get 1 g/L or more in about 12 hours. "It can take days to weeks to get to those levels in cell-based expression systems, depending on the complexity of the protein," he said.

See next page

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Tools & Techniques,
from previous page

"We have analytic tools that can monitor very precisely that the extract is reproducibly the same, and that will help us with FDA," he said. "Regardless of what protein you make, it's the same standardized extract. Once we get through the regulatory cycle once, [regulators] will have 'passed' the extract. The next time around, there will be a reference to the previous filing."

Using the platform to stock Sutro's internal pipeline will be Hallam's priority. The company is not ready to say what specific proteins or diseases it plans to work on. But his initial goal is to identify indications where Sutro can quickly enter the clinic with protein therapeutics that are engineered to have improved pharmaceutical properties via the introduction of non-natural amino acids, or amino acids that are not contained in the genetic code, at specific locations.

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>
> **Trevor Hallam, Sutro Biopharma**

To overcome challenges associated with incorporating nonnatural amino acids into proteins in conventional cell-based systems, Sutro's technology uses charged tRNA that is directed to a specific codon to deliver the nonnatural amino acid to the desired location on the protein.

"We can use a wide variety of nonnatural amino acid side chains, because we don't have to get through a cell membrane and because we can approach the process of attaching the amino acid differently than you could within a cell. Additionally, we are only overexpressing one protein, not the other cellular proteins, which results in greater control and greater fidelity," Stolz said.

Sutro has the option to incorporate a nonnatural amino acid that has a chemical "handle," which could allow site-specific modifications including pegylation, glycosylation or addition of cell-targeting moieties.

In November, Sutro raised the first $20 million of a planned $36.5 million series C round. The second tranche is conditioned upon development steps including "demonstrating the power of nonnatural amino acids" and manufacturing scalability, investor Leon Chen from Skyline Ventures told BioCentury *(see BioCentury, Nov. 22, 2010)*.

In total, Sutro expects the round to provide enough money to be able to get a biosuperior candidate into the clinic and have additional candidates in preclinical development.

"Ultimately, we will look to partner our products. 'When' depends upon the product opportunity," said Newell.

"We are going to pursue a business strategy that recognizes the platform is our core," he added. Sutro thus will engage in selected collaborations where the biotech's technology can enable a partner to do research that could not otherwise be performed."

"We've transformed protein chemistry into something that's more like medicinal chemistry. If a protein engineer, a researcher, has an idea for a novel molecule but wants to explore a lot of variations, in a 96-well plate over the course of a day, we can beat out all those ideas and give you basic data," Newell said.

Also, he said, "once we're free from the constraints that cells place on protein synthesis, we can explore inaccessible proteins cells don't like to make, for example, proteins that are toxic."

By enabling work on products that partners could not otherwise explore, Sutro expects the economics of its deals to be more favorable than what it could command for conventional biomanufacturing services.

Under the Pfizer deal, Sutro will receive an undisclosed upfront payment and research funding. The biotech also is eligible for milestones and royalties.

"We're not going to be a contract manufacturing organization," Newell said. "We will differentiate ourselves by striking relationships that give partners product opportunities such as biosuperiors that aren't possible today."

COMPANIES AND INSTITUTIONS MENTIONED

Palatin Technologies Inc. (NYSE-A:PTN), Princeton, N.J.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Stanford University, Stanford, Calif.
Sutro Biopharma Inc., South San Francisco, Calif.