

BIOTECHNOLOGY

Sutro Biopharma Inc.

Scalable cell-free protein synthesis

Research scientists have long tinkered with cell-free methods of protein synthesis, but turning their lab-bench discoveries into commercially actionable ones is usually a tedious affair that ultimately requires return to traditional cell-line development. “There is a lot of frustration in the industry with currently available research tools... a lot of talk about innovative proteins being abandoned because people can’t make them in sufficient quantities,” says Bill Newell, CEO of **Sutro Biopharma Inc.**

Now San Francisco-based Sutro claims to have developed a speedy cell-free way of producing proteins that can swiftly shift from laboratory to commercial scale. The company recently announced it had achieved yields of over a gram of protein per litre, at a scale of 100 litres, with the very same kinetics that work in micro-titre plates. Rather than packaging the process for widespread use by researchers, Sutro is seeking to collaborate with partners intent on creating biopharmaceuticals—ideally, companies interested in high-throughput protein engineering.

The method invented and patented by company co-founder Jim Swartz, for years now a Stanford University professor after a long career at Genentech Inc., relies on low-cost raw materials and is “quite robust,” says Daniel Gold, PhD, Sutro’s president and COO. He explains that Swartz figured out a way to prepare an extract from *E. coli* that contains transcription and translation machinery sufficient to produce protein from nearly any DNA message put into the solution. The extract is filterable and freezable, and preserves the key energy-generating oxidative phosphorylation capability found in *E. coli*, a scientific workhorse. Whereas most cell-free protein synthesis approaches require a supply of expensive ingredients such as ATP and high-energy bond reagents—materials affordable at bench-scale but not for commercial purposes—Gold says Sutro’s open system does the job with inexpensive ingredients.

Sutro’s system effectively turns each well of a micro-titre dish into a bioreactor, Newell declares, adding, “If we can make the molecule in the plate, we know we can get to gram quantities.” The scalability means scientists can

do high-throughput selection and screening of proteins, confident they can make enough within days for *in vitro* or *in vivo* testing—without shifting production to cell lines.

Newell says Sutro has used its extract to make many different kinds of proteins, including cytokines and antibody fragments, fusion proteins, membrane proteins, and enzymes. Yields are similar to what one expects of cell-based systems, he declares, noting, “It’s unusual for a cell-free system to get that kind of productivity.” Because cell debris has already been removed from Sutro’s extract, Newell and Gold maintain that purifying protein products from their system is easier than breaking open whole cells. The method produces few variants, they say, so purified products are pharmaceutical-grade in terms of purity and activity.

Beyond economic advantages and scalability, Newell says Sutro’s synthesis process has the benefit of similarity to standard *E. coli* production processes with which many people are already acquainted. “The host strains we use, as well as the equipment, will be very familiar to the FDA as well as to researchers,” he asserts.

As yet, Sutro has no peer-reviewed publications documenting its method’s scalability, but going forward the company does intend to emphasize “strong science-to-science connections” in its promotions. Meanwhile, Sutro’s business development activities are focused on reaching out to and educating certain Big Pharma and biotech companies that have already demonstrated commitment to producing proteins. “We’re looking for an area that’s ready to explode,” Newell says: “We could make the difference to a partner, by allowing them to make lots and lots of novel proteins and protein variants.”

People working with scaffolds for binding are likely to be interested in Sutro’s method, as are those looking to make antibody fragments bind more tightly to a receptor, Gold suggests. “This method allows you to go in and rapidly synthetically change the sequence at the site of interest, then efficiently screen variants on a plate, and then when you’ve found what you want go ahead and make it. It’s a very valuable tool,” he says. Once a partner company has

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Founded: June 2003
Founders: James Swartz, ScD; Sutanto Widjaja
Employees: 23
Financing to Date: \$23.6 million
Investors: SV Life Sciences; Alta Partners
Board of Directors: William J. Newell; V. Bryan Lawlis, PhD (Itero Biopharmaceuticals); David Mack, PhD (Alta Partners); Daniel Petree (P2 Partners); Michael Ross, PhD (SV Life Sciences); James Swartz (Stanford University)

identified a lead drug candidate, Sutro could help optimize the expression system specifically for it. Ordinarily, Newell points out, efforts to maximize production capacity have to wait until production is already at large-scale.

“Because this is an open system, there’s a lot of capability for making multi-factorial improvements,” Gold says. “You’d start with the same extract, but vary things like chaperones or change redox potential, to help assure proper folding of the protein.” He reckons optimization could be achieved in a matter of days—which is practically “lightning speed for protein researchers” who can spend months manipulating a mammalian cell system to yield gram quantities of a desired protein.

Although it’s tempting to mull the sorts of manufacturing manipulations possible when “you’re no longer bound by what can get into and out of a cell,” or even to contemplate how this platform might benefit other industries, Newell realizes that Sutro must focus first on making a success of its existing technology with biopharmaceutical partners. Newell believes Sutro could conceivably help collaborators “accelerate the path to market for a protein therapeutic by a year or more, and unlock new molecules they couldn’t access previously.” For now, Sutro is simply spreading the word that linear scalability has been achieved with its method of cell-free protein synthesis.

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—DEBORAH ERICKSON