Sutro Biopharma
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Precision protein engineering to target oncology

Sutro Biopharma combines its powerful cell-free protein synthesis platform with click chemistry to develop precisely engineered bioconjugate therapeutics for oncology.

Sutro Biopharma, a drug development and manufacturing company headquartered in South San Francisco, is transforming biotherapeutics discovery with a novel platform for cell-free protein synthesis combined with site-specific conjugation to non-natural amino acids (nnAAs), which together allow for the precise design and rapid expression of homogeneous therapeutic bioconjugates (Fig. 1).

XpressCF: the power of going cell-free

Designing and producing complex proteins using cell-based systems is expensive and time-consuming, often taking years from concept to clinic. Sutro reinvented this process using a cell-free platform, XpressCF, to produce discovery proteins consistently and quickly, allowing for the screening of thousands of variants of a molecule to get to an optimized lead.

Core to XpressCF is Sutro's proprietary cell-free extract manufactured from a highly engineered bacterial cell line, which contains all the transcriptional and translational machinery needed to rapidly express any desired protein from an encoding plasmid. The synthesis of proteins with XpressCF can be achieved overnight and does away with the need to make a new cell line for every new molecule, as required in traditional cell-based expression systems. With protein expression reduced to a liquid-handling operation and the ability to produce and screen thousands of protein variants in parallel overnight reactions, the drug discovery process is greatly sped up and simplified.

Sutro's complementary XpressCF+ platform further augments the cell-free process by incorporating nnAAs at specific sites as a chemical handle to attach payloads selectively via highly efficient click chemistry conjugation. This capability enabled Sutro to create highly optimized clinical-stage antibody–drug conjugates (ADCs), bispecific ADCs and early-stage immunostimulatory ADCs. The process leaves natural amino acids unmodified—resulting in a homogeneous and well-controlled drug product. The combination of the two platform technologies allows Sutro to screen many variants with different positioning of nnAAs in the protein sequence, permitting empirical identification of the optimal molecule.

"Sutro's XpressCF technology uses a proprietary cellular extract, which is a key element that guarantees robust protein manufacturing," said Trevor Hallam, CSO of Sutro. "That, in combination with our ability to make a single homogenous therapy, sets our technology apart—not only from a drug development standpoint, but also in our ability to supply the therapy needed to power our clinical trials without cell-based limitations."

The ability of Sutro's platform to selectively conjugate payloads precisely at specific sites in proteins is key to overcoming a problem that besets other approaches: heterogeneity in a single drug. Standard approaches, in which payloads are conjugated to natural amino acids, lack control over the exact location of conjugation and how many payloads are added to each protein, resulting in a drug product that is a mixture of a number of different protein conjugates.

By contrast, for Sutro, the end result is a precisely engineered, fully optimized and homogeneous drug product, which Sutro believes translates to a broader therapeutic window and better patient outcomes.

"Sutro is working to address unmet needs by developing targeted therapies that can evolve with ever-changing cancer cells," said Bill Newell, CEO of Sutro. "Our technology enables precision and speed."

Amongst Sutro's pipeline are four unique ADCs. STRO-002 is an ADC targeting folate receptor-α with four cleavable hemiasterlin linker-warheads per antibody currently in phase 1/1b in advanced ovarian cancers. STRO-002 has shown good patient tolerability with no ocular toxicity and a potentially better therapeutic index than other ADCs in development for ovarian and endometrial cancers. STRO-001, an ADC targeting CD74 with two non-cleavable maytansinoid linker-warheads, is currently in phase 1a studies for lymphomas and multiple myeloma. While STRO-001 continues in dose escalation, it has shown signs of an improved therapeutic index versus other ADCs in hematological cancers and also exhibits no ocular toxicity. In collaboration with Bristol Myers Squibb, CC-99712, an ADC against B cell maturation antigen, is being studied in phase 1/1b trials for multiple myeloma, and, in a separate collaboration with Merck KGaA, (operating as EMD Serono in the US and Canada), M1231, a bispecific ADC that targets MUC1 and EGFR, is in phase 1/1b trials for non-small-cell lung cancer and esophageal cancer.

Additional drug candidates enabled by Sutro's platform currently in development are cytokine derivatives, in collaboration with Merck & Co., and a 24-valent *Pneumococcal* conjugate vaccine being developed by its spinout, Vaxcyte, Inc.

Sutro has established the world's only cell-free protein production GMP facility in San Carlos, California, which can produce engineered proteins of consistent quality at scale and provide drug material through clinical development. Recently, dry powder formulations of the cell-free extract have further optimized the manufacturing process, enabling large-scale extract production with ease of shipping and flexibility of use for future product commercialization.

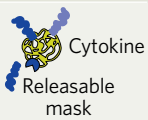
	Bispecific antibody		Conjugated antibody			Cytokine derivative
Modality	Immune cell engager		ADC or ISAC	iADC	Bispecific ADC	Masked cytokine derivative
Target	Tumor or stromal antigen	Immune cell engager	Tumor antigen	Tumor antigen	Dual tumor antigens	Tumor selective mask
Structure						
Drug properties	Optimized format and affinity; improved specificity for optimized therapeutic window		ISAC: Immune-stimulating ADC: targeting novel payloads	Site-specific dual drug conjugate with complementary modalities (TME modulator ± immune modulator)	Enhanced tumor targeting of cytotoxic payloads	Masked cytokine targeting functional cytokine to tumor

Fig. 1 | Sutro Biopharma's deep R&D arsenal. The precise design drives adaptive and protective immunity. ADC, antibody–drug conjugate; iADC, immunostimulatory ADC; ISAC, immune-stimulating ADC.

Moving forward

Sutro seeks to expand its partnerships with pharmaceutical companies, whose long-standing expertise in disease biology has synergistically combined with the power of Sutro's differentiating biologic design, discovery and manufacturing technology. "Our ultimate goal is to leverage these powerful collaborations to create best-in-class therapeutics and help fill the unmet needs of cancer patients with more targeted therapies", said Newell.

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