



Photo courtesy of Ambrx

Creating Better Medicines through Better Conjugation

Clinical-stage biopharmaceutical company Ambrx leverages its site-specific bioconjugation technology through partnerships to bring drugs with enhanced stability and bioactivity to market.

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The pharmaceutical industry is evolving, and what is occurring today in the biopharmaceutical sector is similar to what occurred with small molecule drugs over the previous three to four decades, according to Ho Cho, chief technology officer of clinical-stage biopharmaceutical company Ambrx.

“We initially began deriving medicinal benefits from natural products, attaining the ability to extract and purify the active pharmaceutical ingredients. Medicinal chemists then developed the capabilities necessary for the careful and precise manipulation of the structure and chemistry of active ingredients, thus making better therapeutic drugs. A similar evolution has taken place in the biologics space as well. Originally, insulin was

isolated from pigs and human growth hormone from the pituitary of cadavers. Next, recombinant DNA technology now allowed the production of numerous types of proteins and antibodies using recombinant host systems such as *Escherichia coli* and Chinese hamster ovary cells.

Today, this natural evolution has led to the convergence of these two modalities where, through precise bioconjugation, one is able to assemble proteins and antibodies empowered with effective molecules that can be small molecules or peptide ligands that really can help create better medicines,” he explains.

With core technology that enables bioconjugations using chemistry that does not exist in the native 20 amino acids, Cho believes that Ambrx

is well positioned to achieve its goal of becoming the premier bioconjugation company. “It is all about using better bioconjugation to create better medicines,” he asserts.

FOCUSED ON BIOCONJUGATION

Proteins and antibodies that are currently created by nature have limited therapeutic utility, Cho explains. In some cases, they are suitable for treating a disease, but often they are insufficiently potent. “At Ambrx, we create better bioconjugates through the site-specific incorporation of non-native amino acids with chemical functionality that allows us to do bioorthogonal modifications, and through these bioconjugations we are able to attach a variety of different effective molecules. Some can add to the time of action of a protein, while others may be highly potent cytotoxic payloads used to create antibody drug conjugates for treating cancer.”

With its site-specific conjugation approach, which Cho calls protein medicinal chemistry, Ambrx is able to fully optimize the different aspects of an antibody drug conjugate, namely the chosen antibody and binding molecule, which is optimized for specificity to tumor cells as well as internalization and delivery of the payload. “More specifically, with our conjugation technology, we can optimize the linker payload configuration such that it has optimal stability during circulation and releases the payload only once the antibody drug conjugate has been internalized into the tumor cell,” observes Cho.

In addition, because its core technology is inherently a recombinant DNA technology, Ambrx

can rapidly generate a variety of different molecules based on a given starting protein or antibody and do rapid structure-activity relationship studies, thus allowing the preclinical selection of the bioconjugates that have the right properties from both a biophysical and disease-modifying perspective. “We want to create antibody drug conjugates that have very high tumor specific potency, but are also very safe for normal cells. By having a wide therapeutic window, we can advance molecules that we have reason to believe will benefit patients the most,” Cho says.

INTERNAL AND EXTERNAL PROGRAMS

Ambrx also maximizes its opportunities for advancing candidates through clinical trials by pursuing a variety of programs in partnership with major pharmaceutical and biopharmaceutical firms as well as on its own. Thus, research programs are underway at Ambrx and with leading companies such as Bristol-Myers Squibb (BMS), Merck & Co., Astellas Pharma, and Eli Lilly and Company.

Most recently, according to Cho, Ambrx entered into a collaboration with the Chinese pharmaceutical company Zhejiang Medicines Corporation, with the actual research in China conducted at WuXi AppTec. “We have science not only going on at Ambrx, but we have scientists at BMS, Merck, Astellas, and in China working on molecules that have been enabled by our core technology. Importantly, we are able to integrate all of the great science that is being done at these different organizations and use these learnings to further optimize our core technology and apply the them to specific prod-

Company Stats

Company
Ambrx

Headquarters
San Diego, CA

Top Management
Lawson Macartney, CEO
Peter Kiener, chief science officer
Simon Allen, chief business officer
Cris Calsada, vice-president of finance
Ho Sung Cho, chief technology officer
Feng Tien, head of Ambrx China
John W. Wallen III, vice-president, intellectual property

No. of Employees
66

Technology
Protein Medicinal Chemistry, or the combination of site-specific conjugation with proprietary linkers, payloads and PK extenders to create a single molecular species that is optimized for safety, efficacy, and biophysical properties.

Key Partnerships
Merck
Bristol-Myers Squibb
Astellas
Eli Lilly and Company
Zhejiang Medicine Co. Ltd.
California Biomedical Research Institute

Leading candidates
ARX788 for Her2-positive breast cancer (with Zhejiang Medicine Co.)
ARX201 for growth deficiency
ARX434 for multiple sclerosis
ARX618 for diabetes (with BMS)
Relaxin for heart failure (with BMS)
Protein bioconjugates for undisclosed targets (with Merck)

ucts on a collaboration-by-collaboration basis,” Cho notes.

PARTNERSHIPS KEY TO DEVELOPMENT AND MANUFACTURING

Partnerships, in fact, are incredibly important for Ambrx, both

in terms of its R&D and commercialization efforts. “On the development side, our partners bring a wealth of scientific expertise to the collaboration, so they can help guide us in terms of specific collaboration programs that can be advanced into the clinic and beyond,” Cho asserts. They are also highly lucrative for the company, and the financials that are provided by Ambrx’s partners are leveraged to develop its own pipeline programs and further strengthen its core technology. “By having these partnerships, we can advance our internal programs, strengthen our technology, and gain great scientific insights from all of the data that are generated from these world-class pharmaceutical companies,” he adds.

With respect to commercialization, Ambrx’s current strategy is not to have its own GMP manufacturing capability. The company’s large pharmaceutical partners already have established manufacturing capabilities and the expertise to select the most efficient and effective manufacturing approach.

For its internal initiatives, Ambrx typically takes a program to the point where it can designate a preclinical candidate with a defined composition of matter and then works with world-class CMOs, such as Boehringer Ingelheim, Lonza, Fujifilm Diosynth, and Wuxi Apptech, to do the drug-substance and drug-product manufacturing. “We believe that this strategy provides Ambrx the opportunity to focus on our core strength, which is to do the early research and further enhance and build

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additional robustness into our technology while leveraging external capabilities through partnerships at CMOs and with our pharmaceutical partners,” states Cho.

RECENT RELATIONSHIPS

Ambrx has, in fact, been very busy in the past 18 months, securing and expanding several partnerships. The company is now working with Astellas on antibody drug conjugates for oncology, and has extended an existing collaboration with BMS that focused on long-acting protein programs around FGF-21 and Relaxin to include antibody drug conjugates. In both cases, Cho indicates that Ambrx has made great progress in terms of delivering material and enabling the production and testing of a variety of different antibody drug conjugates for oncology.

In that same 18-month period, Ambrx has collaborated with Merck to develop a range of bioconjugates using its site-specific technology that have generated results in preclinical testing. “Unfortunately, I can’t say specifically what those programs are, but I do believe that Merck is highly encouraged with respect to the types of molecules we have been able to create,” says Cho.

FILLING THE PIPELINE

The versatility of Ambrx’s bioconjugation technology provides the company with significant advantages with respect to possible pipeline candidates. “One of the luxuries we have with our base technology is that it enables a variety of different products depending on the specific therapeutic area that we are interested in pursuing. We have scientists at Ambrx creating specific bioconjugates for both oncology and non-oncology applications,” Cho explains.

Relationships are also important to Ambrx when it comes to filling its pipeline. Recently, for example, the company entered into collaboration with the California Biomedical Research Institute to create molecules that might be of interest. In addition, Ambrx currently has a strong cash balance thanks to the successful partnerships it has pursued over the past couple of years. Ambrx is exploring relationships with younger companies that perhaps have novel targeting molecules and interesting new mechanism-of-action payloads. While no deals have been signed yet, Cho notes that Ambrx is actively speaking with companies with technologies that have the potential to help populate its pipeline in the next couple of years. **BP**