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TOOLS & TECHNIQUES

ON YOUR MARKS

By Lauren Martz, Senior Writer

With less fanfare than the first two waves, a quiet rise in activity is driving a revival of interest in epigenetics, despite little progress in solving the fundamental challenges that have dogged the field from the start.

Although a host of new chromatin-regulators have been identified over the last five years, few of the targets have been touched by drug developers. Instead, preclinical innovation has been springboarding off positive clinical data by devising workarounds to selectively hit validated targets and explore uses for them beyond cancer (see "New Epigenetic Targets").

And while companies may be missing opportunities by not jumping on the new targets, preclinical progress in the field has clearly been sufficient to sustain enthusiasm among investors, who have been steadily backing new opportunities created out of the earlier waves.

In the last five years, at least 12 epigenetic companies have been formed, raising more than $428.5 million between them. Of those, nine are going after epigenetic targets already in the clinic, including HDACs and BET bromodomain proteins. Two have not disclosed targets and one is working on diagnostics based on epigenetic profiles (see "New Epigenetic Companies").

Approval of the first pan-HDAC inhibitor in 2006 launched the initial era of epigenetics; since then seven more pan-HDAC inhibitors have been approved and at least 30 more are in clinical development, along with the first isoform-selective versions, which should have less widespread effects across the genome.

The second epigenetics surge kicked off five years ago when BET bromodomain inhibitors were shown to have exceptional clinical efficacy in NUT midline carcinoma — a rare genetic disease caused by rearrangement of the NUT gene that often results in generation of BRD-NUT fusion proteins. At least 11 BET inhibitors are now in the clinic for various cancers.

The advent of HDACs, and then BET bromodomain proteins, was met with broad enthusiasm, but the idea that regulating the agents that regulate gene expression could make major inroads into treating cancer proved harder than anticipated to realize.

In 2013, a collection of epigenetic experts at BioCentury's SciBX Summit on Innovation in Drug Discovery & Development highlighted

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ALPHAMAB'S SOUP

BY MICHAEL LEVITEN, SENIOR WRITER

Chinese protein engineering company Alphamab is building a one-stop antibody production facility housing a slew of multispecific antibody-generating technologies and its own GMP plant under construction. The company has its own spin on the well-trodden territory of bispecifics production and is bringing innovation to the space with mix-mAb and nanobody platforms that can produce multiple, multifunctional antibodies in a single cell line.

According to CEO Ting Xu, **Suzhou Alphamab Co. Ltd.** not only plans to make a variety of antibody types but will combine antibody modules with other types of protein modules to make novel biologics.

"Our technologies give us building blocks we can play with, and we are putting antibodies together with other proteins like cytokines and chemokines for targeted delivery," and other purposes, said Xu.

Alphamab's lead product **KN035** is an injectable form of a camel-derived, single-domain anti-**PD-L1** antibody. However, Xu told BioCentury the company's primarily focus is on multispecific protein therapeutics that exploit its three core technologies: single-domain camel antibody or nanobody library screening; bispecific production; and its mix-mAb strategy, which allows up to four antibodies to be made in a single cell line.

The camel antibody library lets researchers quickly find small single-domain antibodies (dAbs) with biological activity that are roughly one tenth the size of a standard antibody. Xu said these molecules can be turned into stand-alone therapeutics like KN035 or become building blocks for larger multifunctional therapies.

Alphamab's bispecific platform is based on a charge repulsion induced bispecific (CRIB) strategy that uses knob-and-hole technology analogous to **Roche** (SIX:ROG; OTCQX:RHHBY)'s CrossMab platform. The CRIB strategy involves engineering charges into the Fc region that ensure heterodimer formation and hence dual specificity. With the technology, Alphamab gets 3 g/L production concentrations, close to the 4-5 g/L considered optimal for antibodies. In addition to adding new charges, the company also has methods for altering the endogenous surface charge of the Fc regions to further facilitate heterodimer formation, Xu said.

Alphamab validated its bispecific platform developing **KN026**, a preclinical bispecific comprised of distinct **HER2**-targeting antibodies that is meant to mimic the synergistic effects of Roche's **Herceptin** trastuzumab and **Perjeta** pertuzumab. Roche and **Chugai Pharmaceutical Co. Ltd.** (Tokyo:4519) market Herceptin and Perjeta for breast and gastric cancer.

"Our technologies give us building blocks we can play with, and we are putting antibodies together with other proteins like cytokines and chemokines for targeted delivery."

Ting Xu, Alphamab

The company's mix-mAb platform goes in the opposite direction. While it also uses knob-and-hole technology to create dimer pairs, mix-Mab favors monospecific homodimers instead of bispecifics, but is able to generate two distinct antibodies against different targets in the same cell line. The platform also has been optimized to dial in the desired antibody ratio.

In addition to housing more antibody platforms under one roof than most of its competitors, perhaps the most striking difference between Alphamab and its U.S. competitors is Alphamab's GMP capabilities. While most U.S. biotechs don't manufacture their own antibodies, Alphamab has a pilot plant to feed clinical trials and is building a plant for commercial-scale production.

According to Xu, China lacks CMOs because the country's regulations stipulate that a drug's NDA holder must be its manufacturer. While that regulation creates a burden for small companies, it gives them more control when timing their batches.

He said Alphamab has 180 R&D personnel at its main site in Suzhou, which focuses on autoimmune and metabolic

diseases, and another 20 at its immuno-oncology Suzhou subsidiary, Dingfu Biotarget Co. Ltd. He added that the commercial-scale plant will employ 250 people, when complete.

KN035, which is partnered with **3DMed**, has nearly completed a Phase Ia study to treat solid tumors in China; next, the partners will conduct a short Phase Ib/IIa before starting a Phase III trial by 3Q18. In 2016, KN035 began a U.S. open label Phase I ascending dose trial in solid tumors.

Alphamab also has **KN015**, a long-lasting human follicular stimulating hormone (FSH), in a Phase I trial to treat infertility. KN026 is in preclinical testing, as is **KN046**, a bispecific targeting PD-L1 and **cytotoxic T-lymphocyte associated protein 4 (CTLA-4; CTLA4; CD152)** for cancer.

Zymeworks Inc. (NYSE:ZYME; TSX:ZYME) has **ZW25**, a HER2-targeting bispecific, in Phase I testing in the U.S.

Ablynx N.V. (Euronext:ABLX) is Alphamab's largest competitor in the nanobody arena, while **Qilu Puget Sound Biotherapeutics Corp.** has a competing mix-mAb platform (see **"Antibodies in Stereo."** *BioCentury Innovations* (Aug. 2, 2017)).

According to Xu, Alphamab has secured $300 million for its new manufacturing facility, including a $100 million bank loan; he did not disclose the source of the other $200 million.

He added Alphamab has invested a total of $50 million in its research programs to date: $20 million that it raised from two private investors in 2011 and the other $30 million from biosimilar partnerships. The company hopes to raise a $150 million in series A round by February, he said.