BioCentury
WEEK OF JULY 27, 2015

5 PRODUCT DEVELOPMENT: IRONWOOD'S LOCAL NOTION
Ironwood is dialing in tissue-specific biodistribution to confer additional activity or enable new indications for sGC and GCC modulators.

7 EMERGING COMPANY PROFILE: CONFO(RMATION) ACTIVE
Confo Therapeutics is using antibody fragments to stabilize GPCRs in their active state, opening up new binding sites for agonists.

8 GUEST COMMENTARY: CLARION CALL FOR DIAGNOSTICS
FIND's Mark Kessel on why and how alternative funding should be tapped to develop rapid diagnostics to ensure world health security.

10 EBB & FLOW: FROM PORE TO RICH
Oxford Nanopore's private haul. Plus: Athyrium's structured finance sweet spot; and Sofinnova Ventures' asset-centric arrival.

RULES OF COMPETITION

BY STEPHEN HANSEN, ASSOCIATE EDITOR

Competing in gene therapy is unlikely to follow the same rules as competing in other therapeutic categories where — even in Orphan diseases — a better product can steal market share. The reason is that if the first gene therapies to market deliver on the promise of a functional cure, there may not be any patients left to treat.

Investors have poured at least $3 billion into 20 companies developing gene therapies for Orphan indications that have one or more competitors working on the same gene — including $1 billion to bluebird bio Inc. alone. Most of these companies have touted potential benefits of their products over more advanced competitors targeting the same genes.

But in Orphan indications, if the first-to-market therapy addresses a large proportion of the prevalent patient population, it could be difficult for followers to even enroll clinical trials. And it is unknown whether the risk of immunogenicity to the vector or the transgene protein product would preclude re-treating patients who received a first-generation product.

"If there is an approved gene therapy that is providing a functional cure, I think it will be hard for some of these companies to enroll trials," Spark Therapeutics Inc. CFO Stephen Webster told BioCentury.

However, when the gene therapy delivers a therapeutic protein that doesn't address the underlying pathology of the disease — and therefore isn't a cure — improvements in efficacy or safety can potentially supplant first-in-class therapies.

And even in Orphan indications, there could be room for followers with new vectors if the first to market uses a vector to which a large enough proportion of the population has a pre-existing, natural immunity.

For companies pursuing larger indications, the rules of competition should be similar to those in other drug classes. Here, followers may be able to compete based on advances in vectors, gene expression levels,

EMERGING COMPANY PROFILE

CONFO(RMATION) ACTIVE

BY STEPHEN HANSEN, ASSOCIATE EDITOR

Drug discovery against GPCRs can be difficult because the proteins quickly fall apart when removed from their natural membrane environment. Confo Therapeutics N.V. has developed Confobodies, which mimic the role of the G protein to stabilize GPCRs in a soluble form for use in screening assays.

The concept for Confobodies came out of the academic lab of co-founder and CSO Jan Steyaert at Vrije Universiteit Brussel (VUB) and Flanders Institute for Biotechnology (VIB). A Confobody is a single-domain antibody fragment lacking a light chain that is derived from a camelid antibody.

It is no coincidence that Confobodies have the same structure as the Nanobodies developed by Ablynx N.V., as both companies were spun out of the same institutions and co-founded by Steyaert.

Where they differ is that while Ablynx uses Nanobodies for therapeutic applications, Confo is using Confobodies solely for drug discovery purposes.

CEO Stephane van Rooijen noted that in cellular assays most GPCRs remain in their basal conformation. Screening for antagonists is possible, but screening for agonists can be very difficult because the receptor requires the G protein and ligand to be converted to the active conformation. By mimicking the role of the G protein, Confobodies lock the GPCR in its active conformation, which allows the stabilized protein to be used in high throughput screening methods, such as biophysical assays.

"We are able to take GPCRs from their basal state into an active state, with the Confobodies stabilizing the proteins, and make undruggable GPCRs druggable," van Rooijen said.

CONFO THERAPEUTICS N.V.
Brussels, Belgium

Technology: Confobodies for stabilization of GPCRs

Disease focus: Undisclosed

Clinical status: Discovery

Founded: 2015 by Jan Steyaert, Toon Laeremans, Flanders Institute for Biotechnology (VIB), Vrije Universiteit Brussel (VUB), and Capricorn Venture Partners

University collaborators: VIB, VUB, Stanford University, University of Michigan

Corporate partners: None

Number of employees: 6

Funds raised: €3 million ($3.4 million)

Investors: Capricorn Venture Partners, PMV N.V., Qbic Arkiv Fund

CEO: Stephane van Rooijen

Patents: None issued

Van Rooijen said because of Confo's ability to stabilize GPCRs with a high affinity for agonists, the newco will focus on developing an internal pipeline of small molecule agonists. It is not disclosing specific targets or disease areas.

A €3 million ($3.4 million) seed round raised in June should generate lead molecules from two or three drug discovery programs.

Van Rooijen noted the Confobody technology achieves a similar result as the StaR technology from the Heptares Therapeutics Ltd. unit of Sosei Group Corp. Heptares uses point mutations to stabilize a GPCR outside its native cell membrane for use in drug discovery.

Heptares co-founder and CSO Fiona Marshall told BioCentury the StaR technology can stabilize the receptor in a variety of conformations that have high affinities for both agonists and antagonists. However, she acknowledged StaR cannot produce a GPCR in its fully activated, G protein-coupled conformation.

Steyaert added that Confobodies could also be developed to mimic beta arrestin proteins. Similar to G proteins, beta arrestin proteins alter and activate GPCRs into conformations that differ from their G protein-coupled conformations, potentially opening up additional binding sites.

The technology still faces some challenges, which Confo is working on. Co-founder and Head of Technology Toon Laeremans said the technology relies on access to purified GPCRs. That means wild-type proteins that are naturally unstable — and therefore difficult to purify — could prove to be more difficult targets to use.

Laeremans said Confo is working on a method for generating Confobodies using GPCRs in their native cell membrane, which would remove the need for prior GPCR purification. In addition, he said that as the knowledge of GPCR structures continues to grow, "I expect that it will be possible to purify any GPCR in the future." bc

COMPANIES AND INSTITUTIONS MENTIONED

Ablynx N.V. (Euronext:ABLX), Ghent, Belgium
Confo Therapeutics N.V., Brussels, Belgium
Sosei Group Corp. (Tokyo:4565), Tokyo, Japan

REFERENCES

Hansen, S. "Heptares: Stabilizing GPCR discovery." *BioCentury* (2008)