BioCentury
REPRINT FROM AUGUST 17, 2015

PRODUCT DEVELOPMENT

STRUCTURE KNOWS BEST

BY STEPHEN HANSEN, ASSOCIATE EDITOR

Although most of Heptares' compounds are against clinically validated targets, and only one currently boasts first-in-class potential, the structure-based drug design company is building a case for its ability to expand targets into new indications, or improve upon the efficacy and/or safety profiles of more advanced candidates.

In the wake of being acquired by Sosei Group Corp. in February, Heptares landed new partner AstraZeneca plc this month, with the pharma taking an exclusive, worldwide license to the biotech's HTL1071 immuno-oncology program.

According to Heptares co-founder, Chairman and CEO Malcolm Weir, the unit built its StaR platform for GPCR drug discovery to create best-in-class molecules.

"Our platform is designed to take difficult targets that have not previously had very good chemistry or very good molecules developed against them, and make more selective compounds that are likely more amenable for development in the clinic," he said.

StaR uses point mutations to stabilize GPCRs in their native, functional form, allowing them to be isolated and purified outside their native cell membrane and used in either high throughput screening or X-ray crystallography to determine their structure. Without stabilization, GPCRs lose their functional form when removed from the cell membrane.

According to Weir, the ability to generate crystal structures of GPCR targets enables Heptares to design small molecules with improved pharmacological properties that could translate into a clinical benefit and a best-in-class profile: whether it is improved selectivity to avoid side effects or greater potency to increase efficacy.

Of Heptares' seven programs, only one has first-in-class potential as a glucagon-like peptide-1 (GLP-1) antagonist in a space populated by agonist players. Among the others, Heptares' muscarinic and orexin programs are examples of molecules where the company is expanding targets into indications that couldn't have been addressed before, while two others seek to improve upon the efficacy or safety of more advanced molecules (see "Heptares' Pipeline," page 7).

This potential for best-in-class design prompted Sosei to turn Heptares into its R&D engine by acquiring the U.K. biotech in February for $180 million up front and up to $220 million in milestones.

> "THE MUSCARINIC PROGRAM IS A CLEAR CUT EXAMPLE WHERE STRUCTURE-BASED DESIGN GAVE YOU SELECTIVITY WHERE NO OTHER METHOD OR EMPIRICAL MEDICINAL CHEMISTRY COULD."
>
> MALCOLM WEIR, HEPTARES

STRUCTURAL EXPANSION

In its muscarinic and orexin programs, Heptares is seeking to develop more selective molecules to expand the targets into indications that couldn't be or hadn't been explored by more advanced compounds in the same class.

Lead program HTL9936 is an example, where Heptares is building agonists to work where antagonists have failed.

HTL9936 is a muscarinic acetylcholine receptor M1 (CHRM1; HM1) agonist for cognitive impairment in Alzheimer's disease and schizophrenia, indications where previous pan-muscarinic antagonists have failed because of side effects.

HTL9936 has completed a Phase Ia trial in healthy volunteers.

Weir said a clear Phase II efficacy signal for pan-muscarinic agonists prompted Heptares to start its own development programs in the space.

He pointed to data from a Phase II trial of Eli Lilly and Co.'s xanomeline to treat AD in the 1990s. That study showed a statistically significant benefit on cognition in AD patients. A smaller trial of the compound in schizophrenia showed a clinical benefit on psychosis.

Xanomeline was not very selective, however.

"Xanomeline is a relatively non-specific muscarinic agonist," Weir said. "It may have a bit more M1 and M4 activity than it does M2 and M3, but it is not super selective."

As a result, 52% of patients receiving the high dose of xanomeline in the AD trial discontinued treatment due to adverse events, primarily nausea, vomiting and diarrhea. Lilly discontinued development because of the side effect profile.

Weir said researchers later discovered the side effects were due to the activity on M2 and M3, while the cognitive benefit was via M1 agonism and the psychosis benefit was via M4 agonism.

"The whole industry got stuck because they couldn't get selectivity between the M1 and M4 over and above M2 and M3," he said.

To solve the problem, Heptares first created crystal structures of all four muscarinic receptors, which helped discover why others were struggling

HEPTARES' PIPELINE

Of the seven molecules in the pipeline of the Heptares unit of **Sosei Group Corp.** (Tokyo:4565), only one — the GLP-1 antagonist — has first-in-class potential. Of the other six, only two are likely to face competition from more advanced molecules in the same class: HTL1071, an adenosine A2A receptor (ADORA2A) inhibitor, and the calcitonin gene-related peptide (CGRP) receptor antagonist program. *Sources: BCIQ: BioCentury Online Intelligence, company press releases and websites*

Company	Product	Indication	Status
Heptares' pipeline			
Sosei Group Corp. (Tokyo:4565)	HTL9936, a muscarinic acetylcholine receptor M1 (CHRM1; HM1) agonist	Alzheimer's disease (AD); schizophrenia	Ph Ib
Sosei	Muscarinic acetylcholine receptor M4 (CHRM4; HM4) agonist	AD; psychosis in schizophrenia	Preclin
Sosei	Dual muscarinic M1/M4 agonist	Psychosis and cognitive impairment in AD, schizophrenia and other diseases	Preclin
Sosei	Calcitonin gene-related peptide (CGRP) receptor antagonist	Migraine	Preclin
Sosei	Glucagon-like peptide-1 (GLP-1) antagonist	Congenital hyperinsulinemia	Preclin
Sosei	Orexin 1 receptor (HCRTR1; OX1R) antagonist	Binge eating disorder, nicotine addiction	Preclin
Sosei / **AstraZeneca plc** (LSE:AZN; NYSE:AZN)	HTL1071, an adenosine A2A receptor (ADORA2A) inhibitor	Cancer	Preclin
CGRP or CGRP receptor antagonists in the clinic			
Amgen Inc. (NASDAQ:AMGN)	AMG 334 mAb	Migraine	Ph III
Eli Lilly and Co. (NYSE:LLY)	LY2951742 mAb	Migraine	Ph III
Alder Biopharmaceuticals Inc. (NASDAQ:ALDR)	ALD403 mAb IV	Migraine	Ph II
Allergan plc (NYSE:AGN) / **Merck & Co. Inc.** (NYSE:MRK)	MK-1602	Migraine	Ph II
Teva Pharmaceutical Industries Ltd. (NASDAQ:TEVA)	TEV-48125 mAb (formerly LBR-101 / RN-307)	Migraine	Ph II
Alder Biopharmaceuticals Inc. (NASDAQ:ALDR)	ALD403 mAb subcutaneous	Migraine	Ph I
Allergan plc (NYSE:AGN) / **Merck & Co. Inc.** (NYSE:MRK)	MK-8031	Migraine	Ph I
ADORA2A antagonists in the clinic			
Kyowa Hakko Kirin Co. Ltd. (Tokyo:4151)	Nouriast istradefylline	Parkinson's disease (PD)	Mkt in Japan; Ph III in North America and EU
Biotie Therapies Corp. (HSE:BTH1V; NASDAQ:BITI)	Tozadenant (SYN-115)	PD	Ph III
Vernalis plc (LSE:VER)	V81444	ADHD	Ph I/II

to identify highly selective molecules: the amino acid side chains lining the binding pockets of all four receptors were identical.

According to Weir, using a typical drug discovery screening assay to find a selective muscarinic agonist would be akin to finding a needle in a haystack.

"Making even tens of thousands of compounds empirically only scratches the surface of this problem, because there are simply too many combinations of chemical possibilities to work through to find the right ones unless you are very lucky," he said.

Heptares could design around the problem because it knew the structure of the muscarinic receptors, according to Weir.

"The way we get selectivity is by exploiting very fine differences the structure tells us are there in the size, shape and electrostatics of those binding pockets," he said. This work resulted in HTL9936, which is about 1,000x more selective for M1 than other muscarinic receptors.

"THE WHOLE INDUSTRY GOT STUCK BECAUSE THEY COULDN'T GET SELECTIVITY BETWEEN THE M1 AND M4 OVER AND ABOVE M2 AND M3."

MALCOLM WEIR, HEPTARES

"The muscarinic program is a clear cut example where structure-based design gave you selectivity where no other method or empirical medicinal chemistry could," Weir said.

Weir said the design of HTL9936 should allow Heptares to pursue the AD indication, where marketed muscarinic agonists likely couldn't be developed.

The four marketed muscarinic agonists, which are non-selective, are indicated to treat overactive bladder (OAB) or chronic severe drooling.

In June, Heptares reported data from a Phase Ia trial of its compound in 84 healthy volunteers that showed no adverse events. The trial also showed increased brain activity associated with cognition as measured by electroencephalography (EEG).

Heptares also has two preclinical muscarinic programs, one of which is expected to enter the clinic by YE16.

Heptares also has orexin 1 receptor (HCRTR1; OX1R) antagonists in preclinical development for addiction. As with the muscarinic programs, Heptares used the crystal structure of the receptor to develop a molecule selective for OX1R.

Weir said OX1R is the predominant receptor involved with compulsive behavior, making it an attractive target for addiction.

More advanced dual OX1R/OX2R antagonists target insomnia, with the most advanced being Merck & Co. Inc.'s Belsomra suvorexant, which is marketed for the sleep disorder.

ENTER AZ

In its adenosine A2A receptor (ADORA2A) inhibitor and calcitonin gene-related peptide (CGRP) receptor antagonist programs, Heptares sought to generate best-in-class molecules compared with more advanced compounds going after the same indications.

Heptares partnered the A2A program with AstraZeneca on Aug. 6, licensing exclusive, worldwide rights to HTL1071 to the pharma for all indications. Sosei will receive $10 million up front and is eligible for up to $500 million in development and commercialization milestones, plus double-digit royalties.

In HTL1071's case, the problem Heptares sought to solve wasn't related to selectivity, but rather a need to avoid using a potentially toxic chemical moiety while maintaining the molecule's potency.

Weir said more advanced A2A antagonists required a furan group to be added to their chemical structure to boost potency. But he noted furan groups also can lead to liver toxicity.

"Furans increase the probability that your drug will be a toxic drug," he said.

Heptares used its crystal structure of the A2A receptor to design a molecule with high receptor affinity, but without the furan group.

"That's why our molecule has best-in-class potential," said Weir, who acknowledged there has been no published data demonstrating dose-limiting liver toxicity for other A2A antagonists.

There are two approved A2A antagonists: Gilead Sciences Inc.'s Lexiscan regadenoson, which is marketed as a pharmacologic stress agent for cardiac perfusion imaging studies; and Nouriast istradefylline from Kyowa Hakko Kirin Co. Ltd., which in 2013 was approved in Japan to treat Parkinson's disease.

Weir said Heptares started working on A2A for PD, but then moved into ADHD, which prompted a 2011 deal with Shire plc. But the rights to HTL1071 were returned last year after Shire stopped doing early R&D in ADHD.

Weir said Heptares had planned to continue development for the indication, but AZ's interest in the compound in immuno-oncology changed those plans.

Adenosine signaling through A2A receptors stops T cells from proliferating and reduces their ability to destroy tumor cells. Weir said the pharmacological profile of HTL1071 — its lack of a furan group, selectivity and potency — were factors in driving AstraZeneca's interest in licensing the program.

AZ's immuno-oncology assets include MEDI4736, a mAb against PD-L1 that is in Phase III for non-small cell lung cancer (NSCLC); and tremelimumab, a mAb against CTLA-4 (CD152) that is in Phase II testing for various cancer indications.

HTL1071 will likely be the second A2A antagonist to enter the clinic for cancer. According to ClinicalTrials.gov, Palobiofarma S.L. in July started a Phase I trial of A2A antagonist PBF-509 to treat NSCLC.

Weir said the Heptares compound is Phase I ready, but did not disclose a timeline.

MIGRAINE COMPETITION

Heptares' CGRP receptor antagonist program for migraine will enter a more crowded space when it goes in the clinic. According to Weir,

the company is aiming to develop an intranasal or subcutaneous small molecule CGRP antagonist that will fill a gap between more advanced mAb and oral programs.

At least four mAbs targeting CGRP are in the clinic for migraine, with the most advanced in Phase III testing. In addition, Merck has two oral CGRP antagonists in Phase I and Phase II development for the indication.

Weir said mAbs are primarily positioned as prophylactic therapy for more severe migraine patients in part because of the long half-life of the mAbs and slow onset of action.

While oral therapy could be an option for acute treatment, he said there are two drawbacks. First, gastrointestinal absorption of CGRP antagonists is associated with compound-related liver toxicity. Merck had previously discontinued development of two other oral CGRP compounds due to side effects. Second, he said, "about 30% of people with migraines have problems with gastric stasis or vomiting, so you take the pill but it is poorly absorbed or you vomit it up again."

Weir said a CGRP antagonist would have an advantage for acute treatment if it could be administered via a route that avoids the potential liver toxicity and vomiting.

While Heptares is investigating development of an oral CGRP antagonist, its subcutaneous and intranasal formulations are more advanced.

SWITCHING SIDES IN GLP-1

In contrast to CGRP, Heptares' GLP-1 antagonist program doesn't appear to have any competitive pressure in the compound class, as other approaches are focused on agonists.

Weir said the program was initially focused on developing an oral GLP-1 agonist to treat diabetes. But as Heptares generated the crystal structure for GLP-1, it also was able to design antagonists against the receptor.

"That made us think what could you do with an antagonist here, as well as an agonist?" he said.

The preclinical program is being developed to treat the Orphan indication of congenital hyperinsulinemia, where high insulin levels can have detrimental effects in the development of infants. bc

COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.
Kyowa Hakko Kirin Co. Ltd. (Tokyo:4151), Tokyo, Japan
Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
Palobiofarma S.L., Barcelona, Spain
Shire plc (LSE:SHP; NASDAQ:SHPG), Dublin, Ireland
Sosei Group Corp. (Tokyo:4565), Tokyo, Japan

REFERENCES

Hansen, S. "Heptares: Stabilizing GPCR discovery." *BioCentury* (2008)
Hansen, S. "Sosei finds its R&D engine." *BioCentury* (2015)

BIOCENTURY PUBLICATIONS, INC.

NEWSROOM
pressreleases@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM
+44 (0)1865-512184; Fax: +1 650-595-5589