Using silicon medicinal chemistry in drug design

Paradigm Therapeutics Ltd has acquired new chemistry technology based on the understanding of how the introduction of the silicon atom into key drug classes can be used to generate novel, improved clinical candidates. The company's director of development, Graham Showell, describes its drug discovery programme.

Paradigm Therapeutics Ltd has focused on the identification of novel, small-molecule tractable targets with defined therapeutic utility within key gene families such as G-protein coupled receptors (GPCRs), ion channels and proteases. The company has developed a drug discovery pipeline comprising targets and late-stage preclinical projects in key areas of unmet medical need in pain, central nervous system (CNS) disorders, hormone-dependent diseases such as prostate and breast cancer, and metabolic diseases such as diabetes, hyperlipidemias, obesity and osteoporosis.

"Novel candidates are verified by determining their expression profile and full genomic structures," explains Graham Showell, Paradigm's director of development. "Concurrently, the mammalian function of the genes is determined *in vivo* by mutating the gene in embryonic stem cells, generating knockout lines and by carrying out a structured phenotypic analysis programme. Establishment of novel therapeutic utility is key to Paradigm's success. The breadth and depth to which the company performs the phenotyping analysis provides Paradigm with a competitive edge and the company has embarked on drug discovery collaborations with Takeda Pharmaceuticals in the area of CNS disorders and Ortho-McNeil Pharmaceuticals in pain and urology."

> "The recent move has improved the scope for interaction between biologists and chemists"

Paradigm recently moved into a larger facility on the Cambridge Science Park, Cambridge, UK. Currently the company employs 50 staff in Cambridge with a further 15 scientists at the new Biopolis facility in Singapore. "The recent move in the Cambridge Science Park has improved the scope for better interaction between the biologists and chemists as well as providing a first-class environment for the company's planned expansion," says Showell.

Technological expertise

Paradigm was founded in 1999 as a spin-out from the University of Cambridge, and has established world-class target identification and validation capabilities based on gene knockout technology and *in vivo* pharmacology. The key founders, Mark Carlton and Sam Aparicio, are still highly involved with the company: Carlton is chief scientific officer and Aparicio is co-chair of the Scientific Advisory Board. Both scientists are experts in their field using this technology. In collaboration with the Reproductive Endocrine Unit of the Massachusetts General Hospital, Boston, USA, the company reported the identification and validation of the cell surface receptor GPR54, required for regulation of sex hormone secretion. Gene mutations that disrupt the normal function of this receptor cause a lack of production of hormones from the pituitary gland, and have been shown to result in failure to reach sexual maturation in both mice and humans. The findings were published in the *New England Journal of Medicine* in 2003.

Last year the company acquired Amedis Pharmaceuticals, a company with considerable expertise in silicon medicinal chemistry. Showell explains the reasoning behind the acquisition:

"Three years ago Paradigm was a biology-focused company that was looking to build a medicinal chemistry capability to carry its projects forward. Amedis not only had an experienced

MEET GRAHAM SHOWELL OF PARADIGM THERAPEUTICS

Graham A. Showell entered the pharmaceutical industry in 1976, working as a research chemist with Beecham Pharmaceuticals on cardiovascular projects, and then in 1980 with Smith Kline & French on thyroid hormone analogues. In 1984 he joined the Neuroscience Research Centre of Merck Sharp & Dohme, and focused his medicinal chemistry efforts in the area of GPCR targets for CNS disorders.

In 1997 he joined the medicinal chemistry service company Cambridge Combinatorial, later named Cambridge Discovery Chemistry. During the rapid growth of the chemistry department he was appointed Director of Chemistry, joining the company's management team and being responsible for the organisation and delivery of medicinal chemistry projects with collaborators in Japan, Europe and the USA.

In 2000, Cambridge Discovery Chemistry was acquired by Millennium Pharmaceuticals Inc, and Showell became responsible for the Discovery Chemistry and Analytical Sciences departments in the UK, progressing NCEs in a variety of biologically-validated targets from screening hits through hit-to-lead and into lead optimisation.

He joined Amedis Pharmaceuticals in September 2002 as Director of Chemistry and in January 2005, Amedis Pharmaceuticals was acquired by Paradigm Therapeutics with Showell having responsibility for all aspects of medicinal chemistry from hit identification to clinical development candidate. In November 2005 he was appointed Director of Development and, in addition to chemistry, acquired the added responsibility for assay development and screening within the company.

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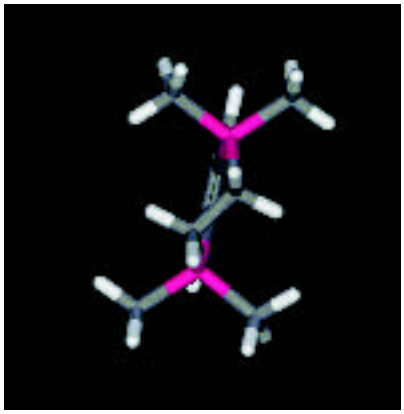
Paradigm Therapeutics just recently moved into new facilities on the Cambridge Science Park, Cambridge, UK.

medicinal chemistry and drug discovery and development group but also had expertise in silicon medicinal chemistry that once again would give Paradigm a competitive advantage. Amedis was acquired by Paradigm in January 2005 and the companies' drug discovery portfolios were amalgamated.

"Amedis's drug discovery platform was built around validated targets and a fast-follower strategy. Silicon was used to add an advantage to known chemotypes that existed in drug-like molecules. The advantage that silicon may offer could be one of the following: a) improved pharmacokinetic profiles; b) increased lipophilicity (if required, for example for improved brain penetration); and c) novelty.

"The GnRH antagonist programme has shown how successful this approach can be"

"Paradigm's chemists have expertise in building silicon-containing drug-like compounds in the areas of GnRH antagonists, monoamine re-uptake inhibitors, retinoids, kinase inhibitors and protease inhibitors. The use of silicon to build stable, drug-like compounds requires the understanding of silicon chemistry rules. By closely working with experts in the field, Ian Fleming of the University of Cambridge, UK, now retired, and Reinhold Tacke of the University of Würzburg, the chemists at Paradigm now have sufficient silicon medicinal chemistry know-how to exploit this technology to the full. The GnRH antagonist programme, currently in preclinical development and on schedule for entering Phase I clinical trials in 2007, has shown how successful this approach can be," he says.



Incorporation of one or two silicon atoms into carbocyclic ring systems provides novelty and a change of shape not always possible with carbon equivalents. This part structure, containing two silicon atoms, is from an X-ray crystallography study. Crystallography is an important tool for understanding the conformational changes imparted by the incorporation of silicon.

The GnRH antagonist programme is based on a validated target. The development compound on this project was identified by synthesising small focused sets of compounds within 18 months of full project initiation. Paradigm's novel pipeline has generated targets that are at the small-molecule hit identification and lead identification stage.

Collaborative programmes and licensing opportunities

As mentioned above by Showell, Paradigm's collaborative programmes are with Takeda Pharmaceuticals in the CNS area and with Ortho-McNeil Pharmaceuticals in pain and urology. Paradigm is providing to Takeda exclusive access to proprietary drug targets in defined CNS fields, with selected targets being subject to further validation by Paradigm and subsequent screening and development carried out at Takeda. The deal anticipates the identification of multiple targets through each year of the collaboration. "This approach further validates the use of Paradigm's gene knockout technology in drug discovery," says Showell.

"Amedis had experience in silicon medicinal chemistry that would give Paradigm a competitive advantage"

In its collaboration with Ortho-McNeil, Paradigm has provided an exclusive licence to one of its proprietary discovery programmes with potential utility in the treatment of chronic pain and urinary incontinence.

Licensing opportunities are available for a number of Paradigm's drug discovery programmes, including: a) proprietary target and drug discovery programmes in the therapeutic areas of pain and metabolic diseases; and b) preclinical drug discovery programmes such as the GnRH antagonist programme.

"Paradigm is a private company funded by venture captial. The company is in a strong position with investors who believe in its technologies and its ability to deliver drug development candidates in a realistic timeframe. The company aims to find suitable partners within the pharmaceutical industry to ensure fast progression of its pipeline," says Showell. sp^2

FURTHER INFORMATION

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