

## Lectus Therapeutics: driving channels forwards

In the realm of ion channel modulators an emerging young biopharmaceutical company is challenging the perception that this sector is too difficult to embrace. *BVV* talks to Dr Roland Kozlowski, CEO of **Lectus Therapeutics**, about how Lectus' new proteomics approach could overcome some of the problems in creating next generation ion channel modulator-based therapeutics.

Lectus began its operations in the summer of 2003 with a management team of six. The company was set up in light of the lack of success in getting first generation ion channel modulators into the clinic. The big issue is the side effects caused. "One of the main problems associated with developing ion channel modulators is their lack of tissue specificity for the intended ion channel target. This can ultimately lead to a number of unwanted effects in the clinic. Although the side effects depend on the sort of compounds that you are looking at, the success of the next generation of ion channel modulators will focus on increasing their tissue specificity," Kozlowski explains.

Although the number of companies concentrating on ion channel drugs is small, the earning potential is enormous. There are currently 18 ion channel therapeutics on the market with annual revenues in excess of \$8.3Bn, led by Pfizer's Norvasc. This alone should make it a worthwhile venture.

### ...immobilise and identify

Lectus is focusing on discovering and developing novel drugs for diseases associated with smooth muscle hyper-reactivity, including bladder disorders. "For urinary incontinence, we are trying to reduce the excitability of bladder smooth muscle by opening a potassium channel. The problem is that the sorts of potassium channels found in the bladder are also present in the circulatory system and so opening these channels can lead to massive hypertension and a sweeping drop in blood pressure," he explains.

Currently, many companies use patch clamp technologies to measure ion channel expression. Patch clamping can be carried out using a glass pipette or chip to record ion channels opening and closing. The problem is that patch clamping is laborious, suffers from relatively low-throughput and is reliant on cell-based assays using cloned pore-forming domains of ion channels. Lectus believes its proteomics-based platform LEPTICS (Leveraged Enabling Proteomics

Technology for Ion Channel Screening) offers a new approach to discovering channel modulators that cannot be identified using conventional methods.

LEPTICS works by immobilising ion channel accessory proteins on a solid surface. Small molecules are screened against these proteins to identify compounds that modulate the interaction between their accessory proteins and pore-forming domains of the channel involved. "In other words what we have developed is a high-throughput screening assay that enables you to identify modulators of ion channel function that act on the accessory protein. Depending on the ion channel, we would look for a differential effect that enhances inhibition or activation kinetics. The action involved would then be confirmed using electrophysiological methods in native cells," Kozlowski clarifies.

### ...difficult but important

Lectus' disease areas are bladder disorders, angina and hypertension. Kozlowski believes that finding specific ion channel modulators in these areas will be easier than in other diseases. "There are some good precedents particularly in the urinary incontinence sector and we feel our approach will yield more specific compounds. The next disease areas we plan to look at are angina and hypertension, which are also huge markets. The second reason to focus here is that these diseases offer targets that are externally validated, and have a well defined approach and measurable endpoints, which will assist progress into the clinic," he says. Kozlowski anticipates having developmental candidates this time next year.

In spite of the difficulties inherent to ion channel therapeutics, companies are emerging to become active in the sector. Discovery companies involved in looking for new therapeutic agents include Xention Discovery, Ionix Pharmaceuticals (both Cambridge, England) and Icagen (Research Triangle Park, NC). There are also a number of companies producing high-throughput

patch clamp systems such as Nanion (Munich, Germany) and Sophion (Copenhagen, Denmark). Additionally, virtually every major pharmaceutical company has ion channel projects.

However, there are only 6–7 companies in competition with Lectus in ion channel modulation, which is a small number for such a large therapeutic sector. "I think the reason is that people perceive ion channels to be a difficult area. However, there are well over 400 genes that encode ion channels and, since the genomic revolution, there is great breadth of information and a multitude of diversities between tissue types and cell types," he states.

### ...aggressive strategy

The company's main aim is to develop therapeutics, although it will also be aggressively seeking partnerships with pharma or large biotech to develop compounds identified in-house. Kozlowski believes that owing to the strength of Lectus' platform, and the fact that there are so many different ion channels, the company is in a strong position to partner and generate early revenues. "The idea is to be in a position to be able to mitigate the burn rate if necessary. Ultimately we want to retain as much value as possible within the business. Early stage deals will offer further valuable endorsement of our technology and business approach and allow us to expand our R&D base," he reveals.

At the moment, Lectus is outsourcing its R&D efforts and has temporary facilities at the University of Bristol. "We are outsourcing our development work to minimise burn rate but anticipate moving to permanent premises later this year," says Kozlowski.

Lectus received an undisclosed sum in seed financing from the SULIS seedcorn fund last year, which provides support for early stage commercialisation of research from the Universities of Bath, Bristol and Southampton. "We are using the seed funding to advance our initial programmes and allow us to perform some corporate development. Currently we are in the middle of our first financing round, which should be complete by Q2/2004," he concludes. – COB

*For more information, contact Dr Roland Kozlowski on tel: +44 (0)1993 810 029, or e-mail: roland.kozlowski@lectusth.com*