Screening technology for fragment-based discovery

Selcia has launched its new Fragment Screening Platform, based on the CE Screen pioneered by the former Cetek Corporation, which it has adapted for fragment screening. The company believes that the CE Screen is one of the most powerful technologies available today for fragment-based drug discovery.

Selcia Discovery, which has a track record of delivering robust clinical candidates, and Selcia Radiolabelling, which specialises in 14C custom synthesis, are the operating divisions of UK company Selcia. These recently-formed divisions are supported by a GLP MHRA-accredited laboratory where the company's analysts, with experience in structural biology, structural elucidation and impurity profiling, operate with state-of-the-art equipment to provide discovery and synthesis services. According to Dr Hans Fliri, the company's managing director, the re-brand and launch of the Discovery division are the latest initiatives in efforts to take Selcia's client partnership proposition and service quality to the next level:

"We think our bold new brand and website better reflect our core values, describing what we do and what we stand for, helping to encapsulate our passion for client delivery and world-class standards in radiolabelling and drug discovery," he says.

"When I took over Scynexis Europe in 2003, we had a small radiochemistry unit and the main focus of the company was the synthesis of compound libraries," he explains. "The latter was making losses and had no future. So we closed the library activity, streamlined the company and started to focus on radiochemistry. A Board decision to divest the then Scynexis Europe eventually led to an MBO in December 2005 and the creation of Selcia. It had always been my plan to relaunch a chemistry-based drug discovery activity. The question was how to go about it as a small newcomer with limited capital in a well-served market, with several established competitors, some a few miles from our doorstep, offering a complete service including chemistry and biology.

"So we developed our own business model for short-term survival and a long-term strategy for income generation and value growth. Clearly, that strategy had to be adapted to the demands of the market, and it had to contain some unique elements that none of our competitors had. It took a few years to generate the funds to do it and to develop a strategy we all believe in. Now we are confident of our strong offering which secures us a competitive position in the market and provides us with an exciting future for our company."

Integrated drug discovery services

Selcia now offers integrated drug discovery services with screening, biology and chemistry units. The establishment of the Selcia Fragment Library was followed by an alliance that gives the company access to some very unusual microbial extracts to screen against customer targets. Selcia can now take a customer's therapeutic target, discover hit compounds either from the customer's or Selcia's libraries, and optimise these into robust drug candidates that can succeed in the clinic.

"Along with this, we provide all the information enabling solid patent protection," says Fliri. "Most of the capabilities required for this process have been established in-house, and what we don't have – such as the capability of doing *in-vivo* work – we do through trusted partners. Most of our services are offered on a fee-for-service basis, that is, all IP belongs to the client and we do not ask for milestones or royalties.

"We also have a business model we call 'MedChemPlus'. In this model, Selcia invests its own capital to generate a package containing a proprietary chemical family, biological data and a patent application. This package is then offered to customers for a deal involving research funding and small success-dependent payments as the project progresses towards the market. Its main objective is to secure research funding," he says.

"The CE screen is something I had been involved with in the past when I was VP of Drug Discovery for Cetek, a Massachusetts

Meet Hans Fliri of Selcia

Dr Hans Fliri is a highly experienced pharmaceutical, health care and biotechnology professional, with a career spanning 30 years in five countries. He has many international contacts across the academic, industrial, commercial, R&D and financial sectors. He is a former biotechnology company research director, with an international reputation for advancing drug research and development, with particular emphasis on infectious diseases and immune system disorders. He led the MBO that formed Selcia Ltd.

Dr Fliri has been Managing Director of Selcia Ltd since 2003, and from 2001-2002 was Vice President Drug Discovery at Cetek Corporation. Prior to that, he held senior positions in drug discovery at Rhône-Poulenc Rorer and Aventis, and from 1990 to 1994 was Associate Director, Immunology Research at Novartis Pharma, where he started his career as a medicinal chemist in 1977. Dr Fliri was awarded his PhD by the University of Innsbruck in 1972 and completed postdoctoral work at ETH Zurich and MIT from 1972 and 1977.

company founded on using capillary electrophoresis for screening," adds Fliri. "Cetek had been operating for ten years and built a very successful business on the CE screen. The fact that Cetek closed down in 2006 was entirely due to strategic and not technical reasons. Thus I knew the strengths and limitations of the CE screen, and recognised its potential for fragment screening. In fact, I believe that fragment screening is a much better application for the CE screen than conventional HTS.

"CE also has some distinct advantages over other technologies used for fragment screening, in particular for certain targets, for example, protein-protein interactions. CE is an enormously powerful technology with multiple applications in drug discovery and we intend to exploit this in every possible aspect.

"When Cetek closed down, the whole IP estate reverted to Northeastern University from which Selcia took a licence. We also recruited some of the former Cetek scientists and engineers and established a small unit near Boston which we call 'Selcia West'. Having started, we found that we had to develop some new ways of doing the CE screen to make it work with fragments, for which we also filed a patent application. I'm very optimistic that in a few years' time, CE will be used as the fragment screening technology of choice. With six granted patents and one new application, we now have an extremely strong position in that area," he says.

R&D grant – a turning point

In March 2008, the East of England Development Agency (EEDA) awarded Selcia a Research and Development Grant for one year, covering 60 per cent of project costs. The award of the grant, along with the commissioning of a Class II GM containment cell biology laboratory, provided the basis of the first joint in-house biology and chemistry project and represented a turning point in the Selcia business model towards drug discovery. The company had hypothesised that the compound SEL-100130, which was known in the literature for antiviral activity, might also have anti-inflammatory properties. The grant enabled Selcia Discovery to establish a set of screens detecting the inhibition of events downstream of cytokine receptors, that is, of anti-inflammatory activity.

In the course of the project, not only could it be verified that SEL-100130 did have the hypothesised properties (for example, potent inhibition of IL-1b stimulated IL-8 secretion from endothelial cells such as HUVEC) without being toxic to the cells, it was also possible to establish synthetic procedures for a range of analogues and to study structure-activity relationships. Finally, it was also verified that SEL-100130 acts as a potent inflammation inhibitor *in vivo* upon topical administration to the skin.

Selcia's brand new state-of-the-art radiosynthesis laboratory was commissioned in August this year

"Thus, with the help of the EEDA grant it was possible to verify that SEL-100130 is a potent anti-inflammatory agent *in vitro* and *in vivo*," says Fliri. "The activity appears to be of a novel type, but the actual biological mechanism of this activity remains as yet unidentified. The results obtained enabled the filing of a patent application on a new therapeutic application of this compound family. Selcia is continuing to investigate this new class of agents with the aim of developing a new category of anti-inflammatory agents, initially for topical therapy."

Selecting target types

Selcia's CE fragment screen at this time works best with protein targets that are soluble, irrespective of their molecular size. The company is working to find ways to work with GPCRs and other membrane targets such as ion channels or transporters. The principle is that a molecule moving in an electric field is monitored and that binding of the monitored molecule to another, for example, the target, alters its movement characteristics and these changes are measured.

"Which molecule is chosen to be monitored depends on the particular case, but in general it can be the target, ligands, or complexes between target and ligand," explains Fliri. "There is enormous flexibility which makes the technology so powerful. One advantage is that the target proteins do not have to be highly pure, and CE works particularly well with natural extracts which are commonly complex mixtures that often contain coloured or fluorescent compounds whose presence is incompatible with most other screening formats."

Fliri says fragment screening is fast becoming the tool of choice to find a chemical starting point acting on a therapeutic target of interest:

"Medicinal chemists are very talented in making original and innovative drugs out of seemingly trivial and known chemicals. The key is finding the activity in the first place, which for very small molecules, that is, fragments, is usually very weak. Thus, fragment screening depends crucially on a method detecting weak affinities between the target and small molecules. The approaches currently used are either based on structure determinations like X-ray crystallography or NMR, or biophysical methods such as surface plasmon resonance. All have advantages and disadvantages: both NMR and X-ray methods require relatively large amounts of pure protein and are relatively slow, on the other hand they provide structural information of the interaction, which is what chemists need to build on. Our CE screen has a number of strong advantages over the other techniques: it requires very little target protein, which does not have to be highly pure and which does not have to be immobilised or otherwise modified. Assay development is fast, the screen is very sensitive, provides IC_{50} data and very few false positives."

14C custom synthesis

Compounds with a 14C label are widely used as radiotracers for analytical purposes. During the development of a new drug they are used to determine the absorption,

distribution and metabolism of drug candidate compounds in the body. The REACH regulation, which came into force in Europe in 2007 and aims to protect human health and the environment, requires manufacturers and importers of chemicals to submit data on the impact and fate of their products in the environment. Again, to generate this data requires the use of radiotracers ('No data, no market').

A radiochemist at Selcia preparing reagents in order to set up a reaction

"Then, there is an ongoing consolidation in the pharmaceutical sector," says Fliri. "Big Pharma companies typically have their own in-house radiolabelling groups, but they are usually a bit like orphans in the organisation and get eliminated during mergers. It is much more cost-effective to outsource this activity to a reliable provider of top-quality services than to maintain it in-house. And Selcia has been very successful in building a worldwide reputation for quality and reliability.

"Selcia has a very strong position in 14C custom synthesis, but as far as synergies with Selcia Discovery goes, there is very little," he says. "The only common aspect is the requirement for synthetic chemistry in both divisions and they both use the same analytical and chemistry support. But the common ground ends there. Radiochemistry is about making molecules; when the molecule is made, the job is done. Medicinal chemistry is about making properties, and the molecule one chooses to make is of almost secondary importance; success is in achieving the property profile. Both activities require different mindsets and personalities. Our Radiolabelling Division came initially out of the former Rhône-Poulenc and Aventis radiochemistry groups and played only a minor role in the business strategy of the former Scynexis Europe. However, having the expertise, the laboratory, the facility licence and waste disposal contracts in place meant that the main entrance barriers into a niche market with few players did not exist for us and we exploited that opportunity as aggressively as we could. Within four years we have more than quintupled the number of synthetic radiochemists and continue recruiting. And we have succeeded in establishing Selcia Radiolabelling as one of the top companies for 14C labelling worldwide."

Pharma and academic collaborations

Selcia has several collaborations with US pharmaceutical companies as well as with UK academic institutions. These mostly involve lead discovery and optimisation projects. The company is currently working on a complex natural product, as well as on an improved follow-up compound to a client's blockbuster, and on another project that concerns very challenging carbohydrate chemistry, all in different therapeutic areas. Fliri comments: "With the launch of the CE screen and Selcia West in the USA, we expect our customer base to broaden significantly. Presently, our industrial clients are almost exclusively from the USA, but we have established a good reputation with UK academic institutions and their sponsors. Most of our work does not involve milestones or royalties, but there are exceptions.

"As a newcomer in a well served market with limited capital, we had to be creative to acquire business. Initially, we specifically targeted companies that we knew had projects that could benefit from our experience or specific knowledge. Later, when radiochemistry started to generate cash, we used it to put our first MedChemPlus package in place, which generated substantial revenues. Our mid-term plans are to take some of our own projects into the clinic and license them out after human proof of concept.

"We are working on two anti-inflammatory projects that nobody else is working on and that will both be first-in-class agents. Obviously, that is the type of project that carries the highest risk but also the highest rewards, but we have a strategy to address this.

"We believe Selcia is now in an enviable position. We have become nicely profitable, have no debt, and operate within achieveable boundaries, which affords us the liberty to do work on some very exciting projects. Of course we have to be cautious, but we have every reason to be extremely optimistic for the future," he concludes. sp²

Further information

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