# Changing Shapes: From Proteins to Business Models


Simon Kerr, CEO at Cypralis, Harriet Fear and Dr Hans Fliri, Chairman of Cypralis and Selcia

Cypralis was spun out from parent company Selcia to exploit its extensive expertise and know-how in targeting a large family of protein targets involved in many acute and chronic diseases. We hear from Dr Hans Fliri, Chairman of Selcia and Cypralis and Simon Kerr, CEO at Cypralis, about the company and the importance of peptidyl-prolyl isomerases, known as PPIases

**Tell us a little about Selcia and how the Cypralis spin-out came about**

**Hans Fliri (HF):** Selcia was founded in 2005 as an MBO from Scynexis Europe Ltd. We immediately reoriented the business model and focused on USP and niche activities. We started with a small 14-carbon radiolabelling group of four people. Custom labelling using 14-carbon is an activity with high entry barriers for newcomers (which we had already overcome), so the main challenge was growing the business in a market with only one other major global competitor. We implemented high quality (GLP, GMP) standards and consistently generated year-on-year double-digit growth. Selcia is now firmly established as the second largest provider of isotope labelling (14-carbon and stable isotopes) services worldwide.

At the time of the MBO, we also had a small group of in-house medicinal chemists. In my previous career at Novartis and Aventis, I had recognised that PPIase inhibitors had a large, underexploited therapeutic potential and followed the field closely. This provided Selcia with our USP in medicinal chemistry. Selcia established a major collaboration with a US biopharma company and the business became profitable in 2007. With the help of an EEDA grant, we created a biology unit and began to establish our own IP, in the area of cyclophilins. This led to a second major pharma collaboration with Gilead Sciences Inc, generating two preclinical candidates. During this time, the science around cyclophilins and their role in disease grew exponentially, indicating roles in diseases that had not been recognised before. Simultaneously, Selcia developed an unrivalled understanding of SAR (structure-activity relationships) and generated several new chemical families with selectivity for cyclophilin subtypes.

So, Selcia had a CRO business with exceptional growth and a strong market position and we had a unique drug discovery platform with broad therapeutic and commercial potential, but we needed a significant injection of capital to exploit it fully. We created Cypralis to focus upon IP generating activities, whilst Selcia's CRO business focused on the 14-carbon radiolabelling business and contract drug discovery services.

**Simon Kerr (SK):** I was introduced to Hans shortly after the Selcia Board had taken the decision to create Cypralis. The opportunity seemed to fit well with my experience in building biotech companies and Selcia's depth of expertise within the cyclophilin field appealed to me. The breadth of potential indications where cyclophilin inhibition could make a difference was exciting. However, we needed to develop a strategy to secure long-term support from investors and collaborators. We also completed a deal with Scynexis Inc to acquire their compound library and now have an unmatched collection of cyclophilin inhibitors, with the potential for sub-type selective, first-in-class drugs to treat several acute and chronic degenerative diseases. The next stage will be to raise significant capital from VCs, whilst continuing to pursue capital from sources such as pharma collaborations and grants.

**The two companies maintain a strong relationship – practically how does this work?**

**SK:** Cypralis operates separately from Selcia but collaborates closely on the chemistry and biology required to support our drug discovery efforts. All of Selcia's cyclophilin-based IP has been transferred to Cypralis, but the key scientists remain employees of Selcia, providing medicinal chemistry services to Cypralis under a Master Services Agreement. We have exclusive rights to Selcia's cyclophilin chemistry, although

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PPIase assay services are offered to other companies on a fee-for-service basis.

We took the decision early on that Cypralis should be based at arms-length from Selcia, which is headquartered near Ongar, Essex. Cypralis has an office at the Babraham Research Campus in South Cambridge with the intention of establishing biology labs there once funding has been secured. Mike Peel (CSO) and I are based at Babraham but chemistry will remain at Selcia under sub-contract, for the foreseeable future. We meet face-to-face with the Selcia team at least once per week, although we usually communicate daily.

Hans is chairman of both companies, and we are also fortunate to have Nicola Baker-Munton and Andreas Rummelt on our Board. Nicola is CEO of Stratagem IPM and runs all of our IP; Andreas is CEO of InterPharmaLink AG and was previously CEO of Sandoz and a Member of the Novartis Executive Committee.

**PPIases are known to be involved in many acute and chronic diseases - what are they and what do they do?**

**HF:** PPIases facilitate shape changes in client proteins and by doing so, they act as 'functional switches' that induce, or block, the activity of such client proteins. They include the cyclophilin family and several have been successfully crystalized, allowing the rational design of new inhibitors. Over the last few years, a number of knock-down studies have demonstrated a clear link between certain cyclophilins and several disease states. These properties combine to make cyclophilins attractive and tractable targets for drug discovery. They play fundamental roles in signal transduction, cell growth and differentiation, in cell death mechanisms, and are used by infectious pathogens as virulence factors or for replication. PPIases inhibitors have activity as antivirals (HCV, HIV) and as anti-inflammatory agents. They could be valuable in preventing cell death in degenerative diseases such as Alzheimer's, Parkinson's and muscular dystrophies. A role for cyclophilin inhibitors in cancer has also been described.

**What are your research priorities?**

**SK:** Acute indications that require a short duration of treatment, as a rational pathway to clinical proof of concept. The first indication we're pursuing is acute pancreatitis. Risk factors include many of the hallmarks of a western diet and lifestyle including hyperlipidemia, obesity and alcohol use. The incidence of acute pancreatitis is rising fast globally. It accounts for 500,000 hospital admissions in the EU and US per year and it's very expensive to manage. There are currently no disease-modifying therapies available. However, Professor Sutton at the Liverpool Pancreas Biomedical Research Unit has provided solid evidence for the role of cyclophilin D in the initiation and progression of acute pancreatitis, using cyclophilin D knockout mice and small molecule cyclophilin inhibitors. We believe there is a significant opportunity for a new cyclophilin inhibitor drug, delivered by the intravenous route, as a disease-modifying treatment for mild to moderate acute pancreatitis. We're collaborating closely with Professor Sutton and have already demonstrated excellent cell protection in several assays, including in vivo models of tissue damage.

The next step is to nominate a pre-clinical candidate for our lead programme and move towards entry into the clinic from mid-2018. Our objective is to take the lead compound to clinical proof of concept whilst building our pipeline of earlier stage programmes. If we achieve that objective, we expect to open up several pathways for other hospital-based indications, driven by the same mitochondrial mechanism.

**Cypralis actively seeks to establish collaborations with Pharma/Biotech – can you update us on a few ongoing projects?**

**SK:** In addition to our lead programme in acute pancreatitis, there are many other potential chronic diseases where cyclophilin inhibition offers the opportunity for disease-modification. However, we are unlikely to have sufficient funding to progress more than two programmes, at least within the next three years. With this in mind, we are exploring partnership opportunities in chronic diseases that could include mitochondrial DNA mediated diseases such as Leber's Hereditary Optic Neuropathy, pancreatic degeneration resulting from diabetes and liver fibrosis. We already have an agreement with Gilead Sciences Inc, based upon the previous successful collaboration with Selcia. We also announced an early-stage deal with Janssen Pharmaceuticals Inc in December 2015; a joint research programme to generate a new class of CNS penetrant, selective inhibitors of cyclophilin D that can target degenerative diseases including CNS degeneration. The medicinal chemistry and PPIase screening has been sub-contracted to Selcia. Clearly, this is an area of enormous potential but is also high-risk, so it needs the major resources that a big pharma can bring. We have other ideas in the pipeline too.

**HF:** This is an exciting time for both companies, in different ways. I think the decision to focus our efforts on two distinct business models was the right one, but I am very pleased we continue to work together so closely. Long may this continue!

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