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Andy Southan talks about ion channel research services at BioFocus

Interviewed by Steve Carney

Could you give our readers some information about your company?
BioFocus was founded in 1997 as a provider of chemistry services and libraries to the pharmaceutical and biotechnology communities. The acquisition of Cambridge Drug Discovery by BioFocus in 2001 added biological assay development and screening services to BioFocus' activities, positioning the company as an integrated service provider in small-molecule drug discovery.

In 2005, we became part of the Belgian–Dutch company Galapagos. By incorporating the former service arm (Galadeno) of Galapagos, the BioFocus organization has been able to add to the range of services available to clients and, as the service and products' provider of Galapagos, BioFocus retains its own identity. BioFocus now operates at two sites – Chesterford Park in the UK and Leiden in the Netherlands – separate from the Galapagos headquarters in Mechelen, Belgium. BioFocus designs and sells high-quality focused libraries based on targeting particular biological classes of proteins (the SoftFocus® brand, including libraries focused against ion channel targets) or on other criteria, such as very unusual compound classes of significant interest to medicinal chemists (Azetidine, ThemePair and C-Nucleoside libraries are recent examples).

Andy Southan
Head of Ion Channel Pharmacology, BioFocus

After graduating with a PhD in Pharmacology from University College London in 1991, Southan joined the UK division of Wyeth Research and worked on a variety of ion channel-related drug discovery programmes. He then moved to Imperial College, London, studying the ion channels involved in cerebellar inhibitory synaptic transmission. This work resulted in publication of the first electrophysiological recordings from identified inhibitory synaptic nerve terminals. He then joined CeNeS Pharmaceuticals, in Cambridge (UK), and served as Head of the Electrophysiology Group, with responsibility for instigating and managing the company's internal ion channel discovery research programmes. As one of the first employees of Ionix Pharmaceuticals, another start-up company in Cambridge (UK), he established the electrophysiology laboratory and was also responsible for managing one of the company's research programmes, which involved extensive contact with external collaborators and resulted in the identification of a number of novel peptides blockers of mechanosensitive ion channels implicated in pain pathways. His current responsibilities at BioFocus include overseeing the ion channel group and maintaining one of the company's long term collaborations with a major US company. Since joining BioFocus, he has been responsible for further strengthening their ion channel biology capabilities by investing in automated electrophysiology.

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BioFocus can offer high-technology medicinal chemistry, biology (assay development and screening), computational chemistry and ADME-Tox services in drug discovery and, through the former Galadeno operation of Galapagos, now offers a target-discovery service. This entails the use of proprietary siRNA technology and reagents for target validation, including access to both gene-product knockdown and knockin siRNA, using adenoviral vectors to access primary cell lines of interest to those involved in biological target discovery and biological target validation. Galapagos (in Belgium) conducts in-house target discovery and drug discovery research on bone-disease targets and also has an Alzheimer's disease portfolio of novel biological targets available for license.

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Do you find that the Biofocus ion-channel-targeted libraries give an above normal hit rate for something like hERG, for example?
Obviously the potential for hERG interaction is a concern, particularly for libraries such as the Softfocus® ion-channel-directed (SFI) libraries where we are seeking to enhance the probability of molecules interacting with ion channel proteins. Our chemists have applied a novel chemogenomic strategy to ion channel ligand design that inherently requires an understanding of the underlying drug fragment recognition. This has enabled 'engineering out' (as far as possible) the potential for hERG interaction. Because these libraries are a relatively new approach we are closely monitoring the results we obtain using our SFI libraries and will modify our approach towards scaffold design, should it prove necessary.

The industry as a whole is really only just beginning to address ion channels as a diverse and valuable target class and we believe the SoftFocus® approach is an efficient way to identify hit compounds. What I can say from our work to date is that we, and our clients, are seeing an enriched rate at the primary screening target when using SFI libraries, thus validating our original design hypothesis. We have received no adverse feedback to date regarding the hERG liability for our SFI library compounds.

Do you have an intention to set up drug discovery programmes that you can run independently?
In early 2005 the long-term vision for BioFocus was to build upon our profitable service-based business and invest our intellectual property portfolio and milestone payments up to the point where the business had sufficient cash resources to run our own independent discovery research. Our recent acquisition by Galapagos has meant that this long-term vision can be accelerated and, although the integration of the business is still within the early stages, we can see how BioFocus will be contributing not only towards our existing external collaborations, but also to current and new research programmes that Galapagos already subcontracts to BioFocus. The strengths and synergies of the two companies coming together have been widely recognized by both the financial sector and our existing collaborators.

Why do you think clients find your company attractive?
From a chemistry point of view, BioFocus libraries are well known for their excellent purity and novelty. For example, our SoftFocus® libraries involve a lot of advanced planning and database searching to ensure that all the structures are based around novel scaffolds (at least at the time of synthesis!) and we generate the libraries in such a way that high purity is guaranteed. It is possible to obtain libraries from other sources for less financial outlay but, generally, they will not have the same degree of purity or novelty that our libraries offer.

'BioFocus libraries are well known for their excellent purity and novelty.'

Our diverse range of Biology Division services complements our chemistry capabilities, allowing us not only to offer screening services across a number of therapeutic target areas (e.g. GPCR, kinase and ion channels), but also to follow up with chemistry input should the client require it.

Our clients can nominate a target that we can clone, then we can create stable cell lines, validate assays, perform a high-throughput screen and follow up with chemistry from the hit molecules (right through to optimized leads).

Are you selecting compounds from other sources or are they all made in-house?
Our broad spectrum, 100 000 compound, diverse library has been built up from a number of sources. All of the SoftFocus® libraries have been designed by BioFocus using our proprietary software tools and they are synthesized by our Discovery Products Division.

You have mentioned some of your collaborations – what about your involvement with Molecular Devices? Do you have any particular involvement with them because obviously they are one of the leaders in the field?
We don't have a formal agreement with the company but we do have a very good working relationship with them. They invited us to present at their high-throughput electrophysiology webinar in June and I recently gave a presentation at a seminar organized by them at the Society for Biomolecular Screening meeting in Geneva. It's good for us to have that kind of relationship, the presentations help to raise client awareness for BioFocus and Molecular Devices keep us informed on new technology developments, which helps us to ensure that we are working with the most appropriate technology. I had seen Quattro™ in action under CDA, before it was officially launched, which was enough to convince me that this particular form of high-throughput electrophysiology was well-suited to BioFocus.

BioFocus was the first company to purchase IonWorks®Quattro™ and this technology allows us to reliably screen small libraries, of around 1000 compounds, in a day. Focused screening of libraries between 10 000 and 15 000 compounds is now possible in the electrophysiology format, this is a really exciting development – both in terms of hit identification and follow on selectivity profiling.

Going back to your ion channel libraries, do you find that they're particularly good for particular ion channels? For example, do you have a preponderance of hits against sodium and potassium, rather than calcium, channels?
Our libraries are designed around the recently published crystal structure of a potassium channel but our complementary software tools [Helical Domain Recognition Analysis (HDRA™)] allow us to design-in enhanced potential for interactions with other channel types, such as sodium and calcium channels. By linking primary sequence alignment and site-directed mutagenesis data directly to SAR, followed by mapping using the published X-ray data, we can design molecules directed towards a number of channel types. Experiments using compounds from SFI01 showed not only good hit rates, but identified compounds with selectivity profiles too.

Where do you see the company going in the next five years?
My personal goal is to establish the BioFocus Ion Channel Group as the leading choice for

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companies seeking collaborative ion channel discovery research services. The preferred route would be extensive multi-FTE collaborations with partners, allowing us to build up the business with stable long-term relationships, in much the same way as we have with Amgen.

'The preferred route would be extensive multi-FTE collaborations with partners, allowing us to build up the business...'

If you were to ask somebody in the business how they saw BioFocus, how do you think they would describe you as a company?
Historically, people would have probably recognized us as a library sales or contract chemistry company. As we move forward, our strength is that we can now offer a much broader range of services encompassing both biology and chemistry. Our market research shows that clients associate us with delivering quality products, having good levels of communication and delivering on our promises. Importantly, we give people the good and the bad news if progress isn't going well, something that is essential to allow meaningful problem solving and programme progression.

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How would you like them to see you in five years? If you had a one-liner as to what they would say about BioFocus in 2010, what would it be?
The highest quality, innovative, integrated drug and biological target-discovery business.

If you had a message that you would like to get out to our readership, what would it be?
That BioFocus provides a complete early stage drug discovery package, in a range of therapeutic areas. We are a company that delivers, from target identification through to optimized lead compounds, using our combined chemistry and biology resources. Our diverse range of technologies, including early stage ADME-Tox, and our extensive experience of collaborative discovery research mean we can offer a very high-quality service to our clients.

'...we give people the good and the bad news if progress isn't going well.'

What would your preference be as a company – to work in partnerships, so that you get the best for your clients, or as a service provider?
It is preferable to work in a stable, long-term partnership. Obviously we have to be sensitive to the needs of each individual client but, if at all possible, we like to build some long-term value for BioFocus into our agreements (milestone payments for products going into the clinic, etc.). This benefits both parties because our commitment extends beyond the simple fee-for-service model.

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