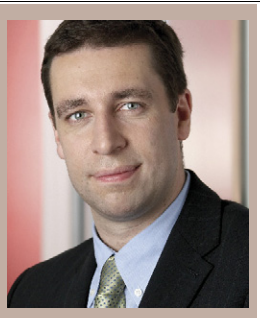
interview

Steve Carney talks to Mark Ashton and Mark Whittaker about Evotec and their approach to fragment-based drug discovery

Interviewed by **Steve Carney**

Mark Ashton



Mark Ashton has been Executive Vice President Business Development Services Division since 2005 and a Member of the Executive Committee of Evotec since 2004. Before taking over responsibility for Business Development, he held a number of positions within Operations at Evotec. He is now responsible for all of Evotec's commercial and marketing activities for the Companies' Drug Discovery and Development Services Division. Dr Ashton is trained as a medicinal chemist and completed a medicinal chemistry post-doctoral at Bath University.

Mark Whittaker

Mark Whittaker is Senior Vice President Drug Discovery at Evotec where he manages a large drug discovery collaboration and the groups of computational chemistry and structural biology. Before joining Evotec in 2001, Mark spent 13 years at British Biotech Pharmaceuticals where he led a number of medicinal chemistry programmes and was latterly Director of Chemistry. At British Biotech, Mark contributed to the discovery and development of six compounds that have progressed into human clinical trials. Before his career at British Biotech, Mark carried out post-doctoral research at the University of Oxford and at York University, Toronto and obtained a D. Phil in Chemistry from the University of York.

How do you feel Evotec is perceived externally? How would you like to be viewed?

Mark Ashton

We have a unique business model, whereby we are supporting pharmaceutical and biotechnology companies through collaborative research on their internal programmes or through the partnering of programmes developed within Evotec. Both activities are targeted at optimally supporting the pharmaceutical industry. Programmes and expertise developed within Evotec are based around CNS diseases and targets or non-CNS targets based on our proprietary platform. Everything we do is aimed at partnership, so we hope that we would be perceived as a partner that offers high value services where we can really bring value to the table and get involved in high value partnerships.

We see medicinal chemistry as being our core expertise

We see medicinal chemistry as being our core expertise, with a focus on understanding how biological targets and pathways interrelate with diseases, and how one can target them from a small molecule perspective to create potential drug candidates. In everything that we do we are seeking to maximize value for our clients by progressing projects through the earlier stages of screening to identify initial chemical matter and lead optimization to identify subsequent development candidates.

Do you feel that there is a gap developing where VCs are not willing to fund early

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biotech, yet they can only attract Pharma capital at the stage where active, later stage molecules have been identified? Is that a gap that Evotec, through partnerships, can fill?

Mark Ashton

The historical funders of biotech are all looking for a much shorter return time

That is indeed one area that Evotec can support Pharmaceutical companies. It is true that Pharma companies are being challenged to improve their pipeline and be more innovative in terms of identifying and developing drugs against particular biological targets. On the contrary, traditionally, they have accessed this innovation from Biotech, but at the moment, the focus of Biotech, in terms of building their own value, is having products in the clinic. The historical founders of Biotech, venture capitalists and investors, are all looking for a much shorter return time on their investment, two to three years, rather than the five to six years expected a while back. If they are going to get return on their investment in a two to three year time period, then really, there is pressure on the Biotechs to have a clinical product quickly. This has the danger of creating a lot of me-too compounds and causing a lack of innovation. So, I would say there is a gap. Where traditionally, Biotechs would pick up interesting science from an academic group and then have five to six years to mature that science; they no longer have that comfort. So there is a lot of innovation and intellectual property (IP) resting in Academia that we see value in. We are trying to bridge the gap between Pharma companies and Academics and/or early-stage Biotechs, to very quickly build value on some of the early IP that exists, and then look to partner with pharmaceutical companies down the line through business models such as results-based deals whereby we get downstream participation in a programme that we bring to the table.

Where are you going in the future with respect to results-based deals?

Mark Ashton

We are trying to build downstream value

We are confident in the drug discovery and development platform that we have developed. As the market has matured, we have tended to try not to commoditize our offering but to differentiate our offering, as we believe very much in bringing high value solutions to our partners. We have got quite a significant drug discovery engine now for small molecule drug discovery. We have got capabilities from high-throughput screening through medicinal chemistry and into clinical development. We have essentially got all the capabilities one would expect of a drug discovery and development company to have to be able to move from target to clinic; what we are doing now is try to seek partners, with whom to implement business models and collaborations, where we are willing to share some of the early risk associated with drug discovery (such as the deal we announced a couple of years back with Boehringer Ingelheim). In return for that, we are trying to build downstream value—create value for our shareholders in terms of sharing the success of compounds once they move into the clinic. Our collaboration with Boehringer Ingelheim is an example of such a business model, but we are looking to build rapidly on that collaboration and introduce other collaborations where we are working more in partnership with our clients rather than in a pure fee-for-service model, sharing some of the early risk associated with attrition or IP issues and then share in the downstream value as well. We announced a deal past year with Roche, where we are effectively co-funding a CNS target research project up to pre-clinical development. At pre-clinical development, Roche has options to take that programme on internally, and we will get significantly higher milestones and royalties than we would expect from a corresponding fee-for-service deal.

Big Pharma seem to be licensing assets earlier and earlier; how has that affected Evotec?

Mark Ashton

Ultimately, that is good news; we have been expecting this, and we have been working with a number of Pharma companies over the years, and they have been telling us that they are looking for earlier and earlier assets. It plays into our hands, because we believe that our core strength is around medicinal chemistry for the rapid optimization of hit molecules to clinical development candidates. We talk about our IND engine, because we believe that we are very experienced and, through our track record and capabilities, extremely successful in taking compounds from the hit stage, through to the initiation of clinical development. This is something we are going to exploit by utilizing our CNS biology expertise and also our platform USPs to try and develop early stage projects at our cost and look to partner those early on, for instance at the stage of leads or optimized leads. In terms of our fragment-based drug discovery platform, we will initiate a number of programmes this year, where we will screen our fragment library using our EVOlutionTM technology in order to identify active fragments against challenging, high-interest targets that we will then optimize and seek partners for. This is in addition to a number of pre-clinical CNS programmes that we are running. We will look to partner a number of these programmes at an early stage.

Evotec has made a number of recent announcements with respect to partnerships (with Roche, Solvay, Boeringer Ingelheim and Interprotein); how do you see the future for the company? As one that has a core competency in CNS drug development with a strong partnering element, or as a company that becomes less dependant upon partnerships at the screening level?

Mark Ashton

Partnership, for us, is core to everything that we do

Partnership for us is core to everything that we do. We will develop a platform, our expertise, and our capabilities in order to provide high value partnerships with our clients. The partnerships will follow different business models, but many partnerships will still rely very much on our fee-for-service model, because with a fee-for-service model, we generate revenue on a daily basis. This helps us to further improve our capabilities and invest in some of the R&D that we are doing. Looking forwards, we will look to build more results-based partnerships in areas where we are open to take on some of the early stage risk but share some of the downstream value as well. Complementing this, in our internal CNS research, we are taking the up front risk ourselves and then seeking to partner from an early stage in discovery to before Phase IIb in clinical development.

We are also fully committed to establishing key areas of innovation that we believe will add value to the drug discovery process. In line with this, earlier this year we established an Innovation Centre for fragment-based drug discovery based on our proprietary platform and expertise.

Where do you see Evotec in 5 years? In 10 years?

Mark Ashton

That is a good question, if only we had a crystal ball! I think that if a Pharmaceutical or Biotechnology company wants to seek a partnership in drug discovery, we would like Evotec to be first and foremost in their minds in terms of value creation and quality. What we want to try and do is ensure that we continue to build on our engine for drug discovery and development; we are looking to add differentiating technologies to bring innovation to drug discovery such as our Innovation Centre for fragment-based drug discovery. We are looking to build additional Innovation Centres around innovative technologies that we believe will enhance current drug discovery. In addition, we are looking to take risk and build a pipeline of programmes within CNS and also outside the CNS, where the projects are compatible with our technology platforms, and partner those at very early stages. What we hope for in 5 or 10 years time is that we have a number of ongoing programmes partnered with different clients where we share in the downstream value. We have already demonstrated our technology expertise and our innovative technology in terms of fragment-based drug discovery and other innovative technologies such as high content screening, and we truly believe that we are the premier partner for drug discovery and development.

Could you outline what you see as the major advantages of a fragment-based screening approach to drug discovery compared with standard library screening?

Mark Whittaker

Often, fragment hits provide greater opportunity for moving into novel IP space

We think the power of fragment-based screening is when it is coupled with structure-based design, to provide fragment-based drug discovery projects. Fragment-based screening effectively finds low molecular weight starting points, and it is the determination of their binding modes to the target protein, usually by X-ray crystallography, that provides the insight for medicinal chemists to rapidly improve potency, through fragment evolution and fragment linking approaches. This provides one of the first advantages of fragment-based drug discovery and that is the speed of the overall process, but there are other advantages as well; the inherent high diversity and diversity coverage of fragment libraries can provide practical starting points for those targets that give low hit rates in standard library screening. This might apply to certain protein–protein interaction targets, for example. Conversely, for those targets that may give high hit rates in standard screening, there can be problems with the chemical IP space being crowded, and a case in point would be kinases. So fragment screening, in these circumstances, is highly useful as, often, fragment hits provide greater opportunity for moving into novel IP space. Although the fragment starting points are less active, structure-based optimization is, in our experience, a more rapid process for developing lead series compared with optimization of HTS hits for targets with no structural information. However, HTS methods remain the approach of choice, in our view, for targets that are currently not amenable to structural studies, such as membrane-associated proteins and certain complex cell-based assays.

Could you tell me how your approach to fragment-based drug discovery varies from that of your competitors, for example, Astex?

Mark Whittaker

Well, there are a number of ways of conducting fragment screening, and we can break down the fragment-based discovery process into screening and structural determination. Dealing first with fragment screening, this can be done by NMR, surface plasmon resonance (SPR), X-ray crystallography and also the approach of tethering. Our approach has been to use biochemical assays predicated upon a highly sensitive assay technology that we have built up over a number of years at Evotec. In particular, we are using single molecule detection in the context of fluorescence confocal spectroscopy. This allows us to run assays with a very low hit threshold setting, which means that we can identify weakly active compounds with good precision. Now, in terms of comparison with other methods, each has its advantages and disadvantages, but we believe our biochemical approach to be faster, more sensitive and more biologically relevant. We have chosen to add a capability in protein NMR as an orthogonal label-free method and, so recently we have integrated into our offering the NMR fragment screening capability that we acquired from Combinature Biopharm. This provides us with a team with a proven track record in NMR-based screening methods including the SAR-by-NMR™ methodology licensed from Abbott. SAR-by-NMR™ is a profoundly reliable and sensitive technique for the identification of even weak fragment binders whereby the binding affinity and binding site information can be experimentally generated. Our sensitive biochemical assay technology allows us to identify fragments with activities (IC_{50}) on the target in the order of 1 mM. The challenges to the methods are the time lines to developing a sensitive assay for the biochemical approach and to producing sufficient high quality protein for the NMR approach. For targets where there is limited access to protein we recommend the biochemical screening approach with subsequent hit verification by NMR. Where sufficient protein is available we recommend a dual approach of screening by NMR and biochemical assay in parallel with different but complementary fragment libraries being used for each method and hit verification by the orthogonal method. If sufficient protein can be obtained but assay development is not straightforward then we would recommend an NMR-screening approach with subsequent verification by biochemical assay once that is on line. So one can see our approach is unique with respect to its flexibility, sensitivity, speed and access to novel chemical matter.

Does an NMR-based approach help you in your future SAR?

Mark Whittaker

Yes and no; NMR can confirm, reliably, Kd values, but at the end of the day, you are measuring a binding event and not a functional event. Biochemical assays and NMR, we would say, are two approaches that are complementary. Surface Plasmon Resonance is fast, but we believe is less suitable as it does require a secondary assay to determine functional relevance and can give rise to false positives. It is also necessary to tether either the protein or a set of fragment molecules. We understand that Astex, and companies such as Structural Genomics, are using X-ray crystallography as a primary screening step. This involves identifying a robust crystallographic system, whereby mixtures of fragments are soaked into preformed crystals of the apo form of an enzyme or protein. Then the presence of a bound fragment is determined by high-throughput crystallography from the presence of additional electron density. This method does require deconvolution of mixtures. Using NMR, and/or biochemical screening up front, allows one to select compounds for the crystallographic step, which can be conducted not only by soaking but also by co-crystallization. There are certain examples in the

literature and from our own experience, where structures of fragments in complex with a protein can only be obtained by co-crystallization and not by soaking.

Do you find it places more work on the medicinal chemist later in the process?

Mark Whittaker

Not necessarily, because the medicinal chemists make well-informed choices as to which compounds to make by having the insights from X-ray crystallography information on how the weakly active fragments bind to the target protein. This allows them to make very precise structural changes to enhance activity and other properties of the molecule. So, in fact, we run our fragment-based drug discovery programmes with fewer chemists than, say, a traditional GPCR programme.

Mark Ashton

Without wanting to trivialize medicinal chemistry, a non-structural approach can be a little bit hit-and-miss. So making decisions about what part of the molecule to omit and what parts of the molecule to introduce additional functionality is pure guesswork until you build up a good picture of the SAR. With a structural approach, very early on, because you have the 3-D structure of the ligand interacting with the protein, you are no longer playing hit-and-miss, you know to what part of the molecule you want to add functionality and where you want to delete functionality.

Do you find that the technology is more applicable to some targets rather than others? Can you give examples of those that are more successful?

Mark Whittaker

We think that the technology is best suited to soluble protein targets, whose X-ray structure can be determined, and so, a key criterion for us to progress a fragment-based programme is to have a reliable X-ray crystallographic system. We have experienced good successes with ATPases, for example HSP-90, with proteases, such as renin and protein–protein interactions, such as Bcl-2/Bcl-X_L, and, of course, kinases. In our experience, to date, so long as we can get that robust crystallographic system set up in the first place, then there are no obvious limitations, in terms of progressing targets through a fragment-based approach.

What proportion of your screening is now fragment-based, and how much is directed against more orthodox libraries? Is that likely to change in the future?

Mark Ashton

For us, the focus is very much not on building a particular technology; the focus is on ensuring that we have a toolbox of technologies for a range of biological targets. As mentioned earlier the fragment-based approach is excellent for targets such as enzymes, and for enzyme targets involved in CNS disorders we will primarily look at a fragment-based drug discovery approach. Having said that, there may be certain enzyme targets that we feel a high-throughput screening approach may be more appropriate. We ensure that we have the appropriate toolbox of technologies to be able to approach different targets from different angles and to really create innovative solutions to finding drugs against those targets.

Could you outline the rules that you use for compound selection? How do you develop an in-house approach to selecting compounds rich in functionality?

Mark Whittaker

One of the key advantages to our approach to fragment-based drug discovery is that we can utilize high-throughput methods to screen a large number of fragments. Our competitors, using X-ray crystallographic methods, will typically be screening in the order of 500–1000 fragments per screening campaign. For our biochemical approach we have built up what we consider to be one of the larger, known collection of fragments, which is 20 000 carefully selected compounds. We have done this in a very careful manner; the process that we have gone through is to select compounds from external sources, as well as in-house sources. We have then profiled those compounds *in silico*, and we have removed all compounds with undesirable features, such as reactive groups, toxicophores, and so on. Then *in silico* applied a set of filters that are a modified version of the Astex 'rule of three', so we restrict the molecular weight to be between 150 and 350 Da, and the average molecular weight is around 250 Da; the clogP is between 0 and 3; the number of hydrogen bond donors is 3 or less; the number of hydrogen bond acceptors is 4 or less; the number of rotatable bonds is 5 or less, and the polar surface area is 70 $Å^2$ or less. We have utilized an in-house QSAR model for aqueous solubility, and we have found this is a very useful filter to select only those molecules that are predicted to be soluble in the aqueous environment at the millimolar level, as ultimately, these compounds are going to be screened at high assay concentrations. This has provided a large set of compounds from which we have made a diverse selection, using proprietary 'hole-filling' software, which maximizes the diversity. We have then had medicinal chemists review every single fragment for their scaffold-like attributes and suitability for analoging by parallel chemistry; this has led to a large number of rejections. We have gone through four iterations of this process, so we have minimized the effect on diversity, after medicinal chemist rejections, and then before being accepted into our library, all fragments have been analyzed by high-throughput LC–MS and only accepted if purity is greater than 85%. How we present the library to the fragment-based screen is by a proprietary storage system, which we term a Nanostore™, which was developed together with scientists from Pfizer. It allows us to run our screens in the absence of DMSO, and we have validated this approach in a number of contexts, both in high-throughput screening and in fragment-based drug discovery.

For NMR screening we have a separate library of 20 000 compounds that have again been selected very carefully by making extensive use of *in silico* tools. This collection has proven a rich source of fragment chemical starting points over the past six years or so. The overlap between the two fragment collections is less than 1000 compounds. For NMR screening we screen fragment mixtures with subsequent identification of the active fragment from an active mixture and while we can screen the full set of 20 000 compounds we more usually screen a diverse subset of 5000 compounds.

Do you think that a FBDD approach is more satisfying for the medicinal chemist? Does it offer more, and more interesting, challenges than the more orthodox library screening approaches?

Mark Whittaker

The big challenge of the future will be to obtain structures for membrane-bound protein targets

At Evotec I have been involved in fragment-based and GPCR drug discovery projects and each has its own particular challenges. The structural insight from fragment programmes allow the development of hypotheses using computational methods, with a high degree of precision, whereas GPCR projects and other programmes that lack structural information require a flair for developing ligand-based hypotheses, which

perhaps are not so precise, but are still intellectually stimulating. The big challenge of the future will be to obtain structures for membrane-bound protein targets, so that we can apply fragment approaches to those as well.

Of the drugs in the Evotec pipeline, which do you think is the most interesting and why?

Mark Ashton

Well, I think they are all interesting! But obviously EVT-201 is one that we are very excited about, really because the therapeutic area and indication; it is in insomnia, which we believe is a very interesting area at the moment. We believe that our compound is differentiated from a lot of the competition, and we hope to show that when we get the full Phase II data later this year. In addition, we have a lot of hope for EVT-302, a MAO-B inhibitor. Initially, we are going to focus on smoking cessation, but we also are very excited about their potential role in modifying Alzheimer's disease. In clinical and pre-clinical, we have some other exciting programmes that we are looking to progress in the next 12 months. We have got a programme against bradykinin B1, which is for pain and inflammation that we are hoping to move into pre-clinical development later this year plus a CB1 programme for obesity. Some of the earlier stage programmes use a fragment-based approach, for example our BACE inhibitor programme, for Alzheimer's. We think that BACE is a very difficult target—a lot of Pharmaceutical companies have tried to find compounds active against BACE and the challenge is to find a small molecule with good drug-like properties. We hope that our fragment-based approach is going to be successful in doing that.