

# BioFocus DPI

www.biofocusdpi.com

In August 2008, BioFocus DPI acquired the structural biology business of Sareum. From an integrated, high-technology provider, clients can now access all of the following: target discovery and target validation, biological screening, structural biology, medicinal chemistry, ADME/PK studies, compound library production, and corporate compound library management.

## Accelerating Drug Discovery

As the trend for outsourcing drug discovery grows in the pharmaceutical sector and the virtual biotechnology model focuses investment into building intellectual property rather than infrastructure, BioFocus DPI is strengthening its portfolio of capabilities by integrating structural biology into its service offering. Through the acquisition of the X-ray crystallography structural biology group of Sareum, BioFocus DPI is now able to offer integrated structure-based drug discovery and support the latest in hit finding technologies, such as fragment-based drug discovery.

### Facilitating structure-based drug discovery

Structure-based drug discovery is a standard approach for multiple target families that are amenable to X-ray crystallographic structure determination — such as soluble enzymes (for example kinases, proteases, transferases, polymerases, esterases), and nuclear hormone receptors. Structure-based drug discovery can also assist in finding drugs that interfere with protein/protein interactions. Using the atomic structure information of ligands bound to their target proteins, structure activity relationships can be understood and medicinal chemistry optimization of hits and leads accelerated. For example, the information can be used to optimize ligand potency, maximize target selectivity and identify sites for the attachment of groups that may modify the physico-chemical properties of the ligand. In addition, this information can be used for lead hopping strategies for the exploration of novel chemical space. By integrating the structural biology group into BioFocus DPI, atomic information can be immediately available to medicinal chemists, thereby enabling rapid progression through the optimization phase.

### Supporting fragment-based approaches

Another area of drug discovery that is increasingly important for targets that are amenable to X-ray crystallography is fragment-based drug discovery. This approach utilizes the atomic information provided by the X-ray crystallography platform in a similar way to a hit- and lead-optimization strategy in order to identify fragment “hits” for a target of interest. In this case, the protein target/fragment structure for multiple fragments (usually defined as ligands with molecular mass between 150 and 350 Daltons) is determined. In order to optimize this process, BioFocus DPI utilizes additional methods including target bioassays to enrich the pool with fragments that are known to bind to the target.

Obtaining a crystal of a protein-fragment complex can often be challenging as the binding affinity of fragments is typically very weak (high micromolar range) and, consequently, high solubility of the fragment in the crystallization conditions is critical. Therefore, in addition to the now accepted definitions of diversity and lead potential for fragments, the so called “Rule of Three”, fragment libraries are selected with high aqueous solubility as a key factor. With this in mind, BioFocus DPI has carefully selected a fragment library from its own exclusive ThemePair™ brand of chemogenomically designed libraries, the acquired Sareum fragment library and other commercial sources, ensuring the chosen fragments fulfill the lead potential criteria, optimize chemical diversity and, importantly, are thoroughly characterized for solubility.

### Achieving uniform protein packing

A key factor in the success of a protein crystallography program is obtaining the protein in a form that packs uniformly in the crystal lattice, creating a high quality ordered crystal that diffracts to high resolution. Variations in the N- and C-termini of the protein can greatly affect this by introducing areas of mobility in the polypeptide. It is therefore accepted that the best strategy is one that investigates multiple forms of the protein, with variations in N- and C-termini or amino acid mutations in surface loops, to identify a protein form that can reproducibly produce robust crystals. BioFocus DPI has a high-throughput parallel processing platform where 48 or 96 different constructs of a target are examined routinely for expression in both *Escherichia coli* and baculovirus vectors in insect cells.

An automated multi-column purification process is used for purification of the multiple variants. Protein forms showing high expression and solubility are then taken forward into crystallization trials. Once the protein forms that crystallize are identified, further optimization of the crystallization process is undertaken using robotic plat-



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forms to identify the crystal form most suitable for the generation of high resolution protein/ligand complexes. Cryopreservation of the crystal is then optimized and data is collected either in house, on a high resolution X-ray source, or at one of a number of European synchrotron sources, allowing multiple crystal structures to be solved

rapidly and efficiently. Overall, BioFocus DPI has one of the most automated platforms for structure-based activities in the drug discovery service industry.

### Seamlessly integrated drug discovery services

Within a seamlessly integrated offering overseen by a dedicated project management team of skilled drug discovery scientists, BioFocus DPI provides medicinal chemistry, structural biology, biological screening and ADME/PK. Due to the single location of these capabilities, the compound design and synthesis cycle time can be minimized allowing programs to progress extremely rapidly. By working with BioFocus DPI, clients have access to these specialized skills without incurring their own fixed costs and can operate in a dynamic, flexible manner that suits the competitive commercial environment of drug discovery.

With a client base that spans the major pharma, large biotechnology, small biotechnology and the “not-for-profit” sector, BioFocus DPI has the experience to successfully deliver preclinical candidates.

## AN INTEGRATED SOLUTION TO DRUG DISCOVERY

**BioFocus DPI is the service division of Galapagos, with over 300 employees operating in four countries.**

### TARGET DISCOVERY

The target discovery platform is based on adenoviruses that efficiently introduce human cDNA or shRNA constructs into a wide variety of human primary cells to knock-in or knock-down specific human genes. High-throughput assays are then used to select for those proteins that have an effect on the disease phenotype. After undergoing further validation studies, these targets form the basis for the development of drugs or biological therapeutics.

### BIOLOGICAL SCREENING

Results are generated using an “Intelligent Screening” approach which focuses on combining the know-how and expertise of BioFocus DPI’s scientists with extensive high-throughput and information-rich screening capabilities. Services include:

- cell line generation
- assay development
- PrimePath™: screening in human primary cells
- medium and high throughput screening
- compound profiling
- high-content screening
- multi-parameter screening

### STRUCTURAL BIOLOGY

This platform is able to support structure-based drug discovery programs with protein purification, crystallization and structure determination by X-ray crystallography. This may be as part of an integrated drug discovery project or as support for a client’s lead optimization or fragment discovery program. BioFocus DPI is also able to offer fragment-based NMR technologies through a worldwide marketing and sales agreement with ZoBio. ZoBio has extensive experience in fragment-based screening using its patented Target Immobilized NMR

Screening (TINS) technology. TINS allows rapid screening of drug fragment libraries with high sensitivity using only a few mg of target protein. An additional advantage of TINS screening is that it can be achieved in a few weeks, accelerating the drug discovery process.

### MEDICINAL CHEMISTRY

BioFocus DPI delivers a fully integrated medicinal chemistry contract research service complemented by structural biology, biology screening and comprehensive ADME profiling. The medicinal chemistry division combines world class project management with extensive experience in collaborating with global pharma and biotechs as well as non-profit organizations, to deliver drug candidates in all major therapeutic areas and gene families.

### ADME/PK

A consultative approach combines industry experienced ADME specialists and modern, high-throughput facilities to deliver high quality ADME data rapidly.

### COMPOUND MANAGEMENT

BioFocus DPI’s recently renovated compound management facility is home to the National Institutes of Health Molecular Libraries Small Molecule Repository. Capabilities on offer:

- capacity up to 2,000,000 compounds
- inert, processing and low temperature storage
- high throughput compound QC
- multi-format plating and reformatting
- expert compound selection and procurement
- rapid delivery to screening centers

### COMPOUND LIBRARIES

The libraries use advanced techniques to ensure they are designed to modulate biological targets whilst adhering to drug-like or lead-like criteria. The intelligent design results in higher quality compounds that lead to the faster generation of novel clinical candidates.

“ **BioFocus DPI have consistently proved to be excellent collaborators. They are sensitive to our needs and they have delivered against agreed timelines most effectively. It is a pleasure to work with them.** ”

*David Brown PhD, FRSC  
Senior Advisor  
Head of Drug Discovery  
Institute for OneWorld Health*

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