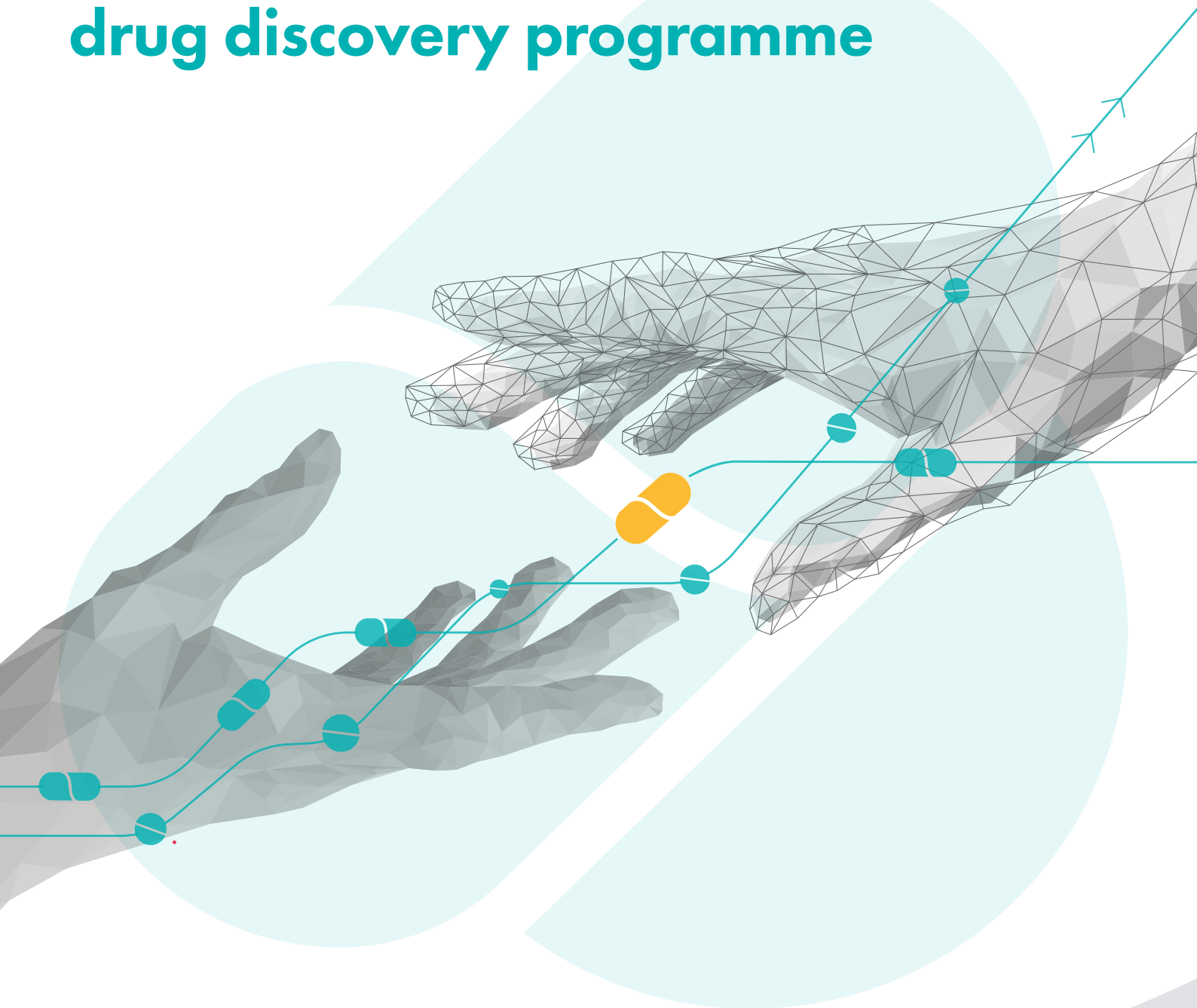
Structural Biology

Revealing New Dimensions

High-resolution protein structures to progress your drug discovery programme



Domainex

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It is increasingly the case that our clients regard structure-based drug design (SBDD) as a vital component of their projects. Domainex has been a long-standing and a leading proponent of SBDD, so it's not surprising that we have a strong in-house team of structural biologists including expert X-ray crystallographers, cryogenic electron microscopists and molecular modellers.

We can obtain high-resolution datasets for your target proteins (apo or ligand-bound) and process this data to solve the structures and present them to you in a variety of formats suitable for computational modelling.

X-ray crystallography is currently the gold-standard in terms of protein/protein-ligand structure generation. However, cryogenic electron microscopy (cryo-EM) is the method of choice for large proteins or protein complexes particularly when crystallisation has proved challenging. A combination of cryo-EM and X-ray crystallography can be useful when resolution is limiting, fitting small X-ray structures into cryo-EM density. Our experts will discuss your needs and recommend the right approach for your project.

X-ray Crystallography

X-ray crystallography is currently the gold-standard for protein/protein-ligand structure generation and can be applied to proteins with a broad range of molecular weights.

To generate an X-ray crystal structure, samples are first crystallised and then an X-ray beam is used to create a diffraction pattern from which the position of each atom in the crystallised molecule is determined. Domainex has extensive expertise and the facilities in-house to undertake high-throughput screening of thousands of crystallisation conditions. Through a network of world-class synchrotron facilities across Europe, with whom we have established access agreements, including the Diamond Light Source (Oxfordshire, UK), we will obtain high-resolution datasets for your target proteins (both apo or ligand-bound).

Figure 1 *X-ray crystal structure generated at Domainex of CD73 bound to adenosine 5'-(α,β-methylene) diphosphate (AMPCP), a CD73 inhibitor (dataset resolution 1.7Å). The structure was generated using protein produced at Domainex and overlays well with the apo open conformation structure which was also solved.*

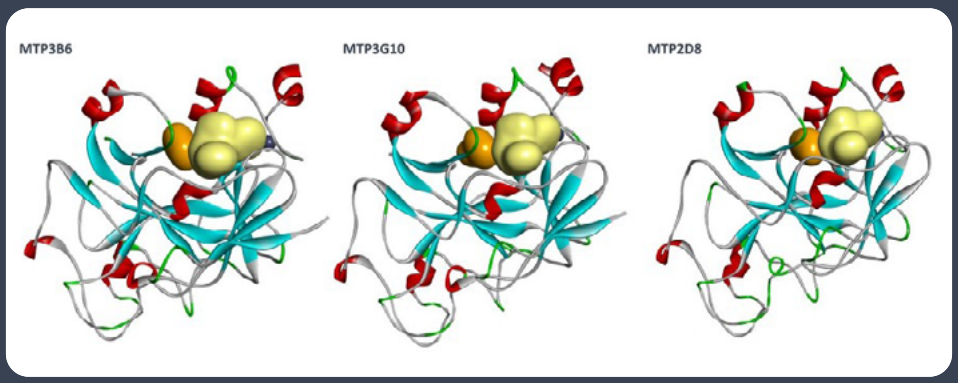

Figure 2 *X-ray crystal structures of G9a bound to three different fragments (MTP3B6, MTP3G10 and MTP2D8) generated at Domainex. G9a protein was produced at Domainex and the structures enabled a structure-guided fragment expansion programme. The fragments are shown in orange and S-adenosyl methionine (SAM) is shown in yellow.*

Cryogenic electron microscopy (cryo-EM)

Cryo-EM is a microscopy technique applied to samples cooled to cryogenic temperatures. Samples are rapidly frozen (vitrified), preserving the sample in its native state. A transmission electron microscope (TEM) is then used to capture two-dimensional projections, which are combined to make a 3D model. The technique is applicable to a wide range of protein targets including membrane proteins, such as GPCRs and ion channels, and does not require crystallisation of the protein which allows flexible conformations to be observed.

Cryo-EM is the method of choice for large proteins or protein complexes, particularly when crystallisation has proved challenging. Proteins with molecular weights >100 kDa are preferred, as proteins with smaller molecular weights can be challenging. However, this can often be overcome by the addition of fiducial markers.

Our in-house expert microscopists will generate cryo-EM structures for your project using external state-of-the-art data collection facilities accessed through our partner agreements.

Advantages of cryo-EM

- The rapid vitrification treatment of the sample maintains its closer-to-native state
- A relatively small amount of sample material is required compared to X-ray crystallography
- Captures flexible conformations
- Can determine structures of heterogenous protein complexes
- No extensive construct optimisation required, such as removal of post-translational modifications
- It does not require the protein to crystallise
- High sample purity is not required
- Can be combined with our PoLiPa technology to generate structures of membrane proteins

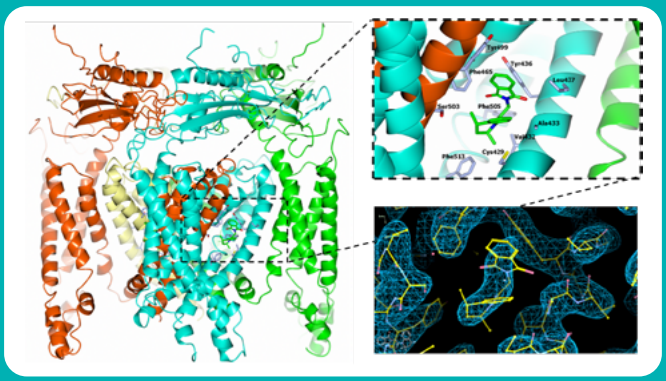

***Figure 3**: Cryo-EM structure, generated by Domainex on behalf of Samsara Therapeutics, of ML-SA1 (a published inhibitor) bound to TRPML1 in a hydrophobic cavity at 2.97Å resolution (ribbon representation generated using CCP4MG). Top right hand side image shows a close-up view of ML-SA1 while the bottom right hand side image shows the electron density map.*

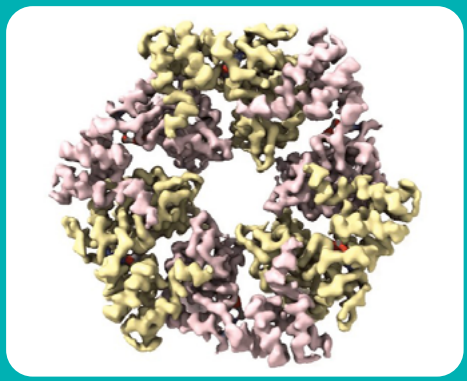

***Figure 4**: 3D 3.3Å Map of RuvBL1/2 in a hetero-hexameric ring conformation visualised using ChimeraX. Protein is colour coded by RuvB monomer with RUVBL1 monomers in yellow and RUVBL2 monomers in pink. Adenosine diphosphate (ADP) is seen in the active site coloured in red.*

Protein Supply

Our highly skilled protein science team can prepare high-quality proteins using various expression systems, to support your structural studies, if required.

Structure Based Drug Design

By coupling our structural biology know-how to our capabilities in fragment and structure-based drug design, you can access our state-of-the-art approaches to rapid compound optimisation. Our medicinal, computational and analytical chemists are skilled in the use of this invaluable information throughout the drug discovery process to optimise ligand design, assess any off-target liabilities and produce the most effective candidate molecules.

About Domainex

Domainex is a fully integrated drug discovery service company based in Cambridge, UK. We serve a wide range of pharmaceutical, biotechnology, academic organisations and patient foundations globally. We have ambitious growth plans and currently have over 100 scientists. We provide integrated services, from disease target selection to candidate drug nomination. We have a very strong reputation for contributing innovative ideas, undertaking high-quality experiments and for generating intellectual property on behalf of our clients. We strive to build strong, dynamic relationships and work with our clients to provide customised services.

How Can Domainex Help Your Drug Discovery Project?

Our highly experienced, multi-disciplined scientists – molecular biologists, protein biochemists, assay biologists, structural biologists, medicinal, computational and bio/analytical chemists, *in vitro* pharmacologists and ADME scientists – will support you to advance your drug discovery projects towards drug development effectively and efficiently. We provide customised programmes to address your specific needs at each stage of the pre-clinical drug discovery process. We draw from a wealth of expertise built up over the last 20 years across a wide range of drug targets and therapeutic areas. From our sites within Europe's leading bioscience hub at Cambridge, UK and with access to the very latest cutting-edge technologies, we are able to help you realise your goals and enrich your discovery pipeline.

Contact

If you would like to know more about Domainex's discovery services, or speak to us regarding your own drug discovery needs, please contact us at enquiries@domainex.co.uk

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