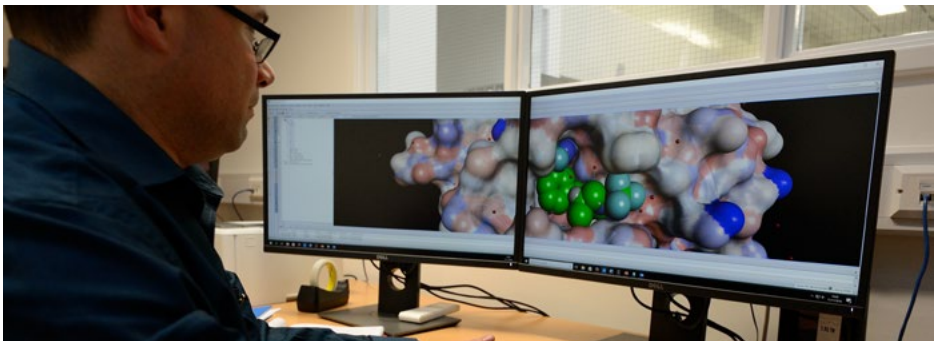
Integrated drug discovery services designed to meet your needs

Choose an integrated approach from Domainex for the faster route to drug discovery

Customised solutions from protein expression to lead optimisation of your candidate drug



Target selection through to candidate drug up to **30% faster**

Domainex's world-class discovery team delivers high-quality, innovative results, hits, leads and pre-clinical candidates

domainex
the faster route to drug discovery

www.domainex.co.uk

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Introduction

'Every compound counts'. It's not a slogan, it's the way we work. Drug research is a complex process, but our aim is simple: we'll help you convert ideas and discoveries into new treatments for patients, **effectively and efficiently**. That means getting there faster, and using fewer resources.

Our integrated science-led approach to drug research brings together the talent, creativity and expertise of our multi-disciplinary team, proprietary technologies, and a highly collaborative approach, to **deliver results.** And it works: our team enjoys an exceptional and unrivalled track record of delivering an average of one candidate drug every year on behalf of our clients.

Integrated drug discovery

Sir Simon Campbell with Tom Mander, Domainex COO, at the opening of the Domainex Medicines Research Centre (November 2016).

The 20,000 sq ft facility is located in the Cambridge bioscience hub, and includes more than 50 chemistry fume hoods and dedicated biology labs, including cell culture facilities.

30%
FASTER

We will take you from target selection through to candidate drug up to 30% faster and more cost effectively than industry standards.

Work with us to access a world-class team built to meet your requirements

50 the **number of patents** that we are cited as inventors on

110 the **number of peer-reviewed papers** we have authored

90% of our 70 staff who are **active scientists**

>70% of our scientists who are **PhD qualified**

>10 the average number of **years' experience** our scientists have in medicines research

3 the number of candidate drugs our clients have **progressed in to clinical trials**

4 the number of **candidate drugs we've helped invent** in pre-clinical development

2001

Domainex was founded by Laurence Pearl, Paul Driscoll, Chris Prodromou, Mark McAllister and Renos Savva, to develop and exploit Combinatorial Domain Hunting: a novel technology for the expression of difficult drug proteins

2006

Merged with NCE Discovery, a medicinal chemistry services company founded by Dave Selwood, Dave Madge and Chris Sharman

2007

New company moved to a single site in Cambridge to provide an integrated medicines research capability

2011

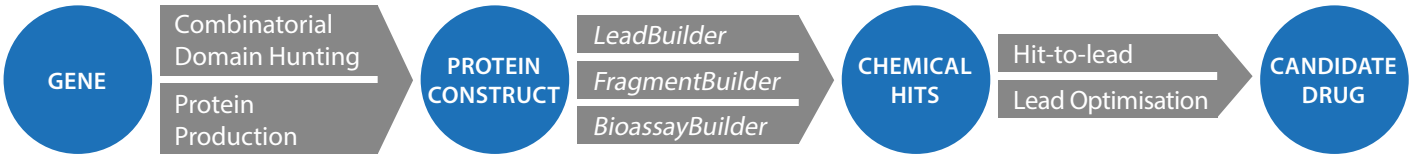
Expansion of bioassay services in biochemistry and cell biology. Moved to larger premises in Cambridge

2016

Doubling of lab capacity in chemistry and biology at the new Domainex Medicines Research Centre on Chesterford Research Park

Our Integrated Drug Discovery Approach

Domainex offers a range of drug discovery services from protein production and assay development through to medicinal chemistry for lead optimisation. Your dedicated project leader will listen to your needs and provide tailored and well-considered scientific solutions to support your project every step of the way. Our integrated approach, when applied from target protein through to candidate drug, has been proven to be up to 30% faster than conventional methods, saving you time and money.



Protein production and assay development

CDH Combinatorial Domain Hunting

Our patented Combinatorial Domain Hunting (CDH) technology enables efficient drug discovery. For even the most challenging of targets, CDH can supply high-quality and soluble protein domains for X-ray crystallography, bioassay development, biophysical analysis and fragment-based drug discovery as well as for the analysis of antibodies under preclinical development.

Bioassay Builder

BioassayBuilder is our integrated biology platform, offering a comprehensive suite of services, including assay development, screening, and compound characterisation / ADME testing of candidate drugs.

Hit screening

A critical factor for efficient prosecution of a successful drug discovery project is the quality of the starting point. Domainex offers rapid and cost-effective hit screening services to match your needs.

Lead Builder

Virtual screening the Domainex way. Using minimal structural information, *LeadBuilder* brings together a uniquely filtered 'NICE' compound collection (containing 1.5 million 'ideal screening hits'), protein modelling and virtual screening to provide you with a highly tailored series of hits, suitable for efficient lead optimisation and progression to candidate drugs.

Fragment Builder

Fragment screening offers a practical alternative to high-throughput screening. *FragmentBuilder* is the leading fragment screening platform with MicroScale Thermophoresis at its core. Combined with our exclusive fragment library and a surprisingly small sample of your pure protein, this high-throughput technique can generate high-quality compounds for your drug discovery programme.

Hit-to-lead and Lead Optimisation

Armed with our 'every compound counts' philosophy, we will carefully design >make >purify >test compounds in pursuit of your next optimised drug candidate. We strive to shorten this invention cycle, and to minimise the number of iterations needed to find your candidate. We'll place a particular emphasis on early DMPK, analytical and physical chemistry profiling to quickly identify which of your leads exhibits the greatest potential, and we'll apply computational chemistry approaches to inform our structure-based drug design. Our aim is to find your drug candidate more quickly and efficiently than you thought was possible.

From our use of state-of–the-art drug design software including tools from BIOVIA, CCDC, Dotmatics and Reaxys; to our well-equipped chemistry, analytical and biology laboratories; and the simple fact that all our teams are housed within the same building and are sharing information, learning new skills and improving processes together – all our work is supported by the high-quality infrastructure that you would expect from a leading drug research services provider.

Case Study 1

Target: Der p 1

Domainex expertise

- Medicinal Chemistry
- Computational Chemistry
- DMPK

Disease area: Asthma

Der p 1 is a cysteine protease excreted by house dust mites and is a major cause of allergic asthma. Our client needed us to identify a candidate drug suitable for delivery by dry powder inhaler (DPI). The starting point was an irreversible peptide-based inhibitor deemed unsuitable for long-term administration in the allergy setting owing to concerns about its potential safety profile.

The Domainex team successfully designed a replacement for the irreversible pharmacophore by employing a reversible, covalent binding group that retained the benefits of a slow off-rate, but without the risk of adverse events. The computational chemistry team used structural information from published crystal structures of Der p 1 and related human cysteine peptidases to design-in exquisite selectivity, and improved stability to proteases in the lung. Physicochemical properties were fine-tuned to optimise lung retention, and this was confirmed by the long duration of action shown in allergy models where rodents were exposed to house dust mite pellets. Metabolic, plasma protein binding and oral absorption properties were also optimised to ensure low levels of systemic exposure, and hence reduced risks of adverse effects. The Domainex team demonstrated that compounds were compatible for use with DPI by identifying compounds with stable crystalline forms that could be micronised to give particles of a size appropriate for inhaled delivery.

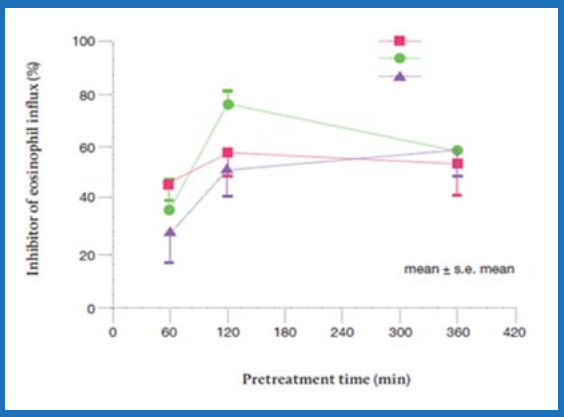


Figure 1: Bronchoalveolar lavage shows that ADI compounds inhibit HDM-induced eosinophil influx when dosed intratracheally (i.t.) up to six hours before allergen challenge

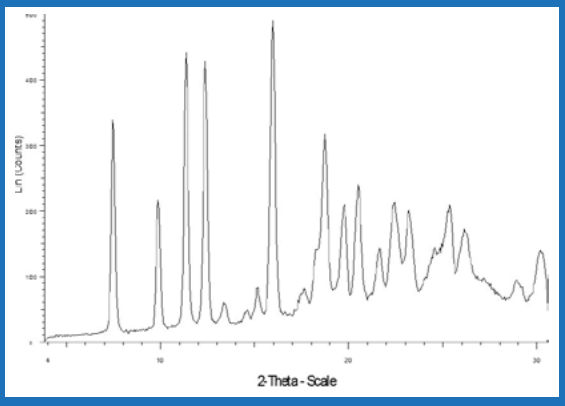


Figure 2: Exemplar of X-ray powder diffraction (XRPD) showing the crystalline form of one of our compounds

Reference

Newton G *et al.* (2014),The discovery of potent, selective, and reversible inhibitors of the house dust mite peptidase allergen Der p 1: an innovative approach to the treatment of allergic asthma. *J. Med. Chem.*, **57 (22)**, 9447-9462

What was the successful outcome?

A candidate drug and a number of credible back-up compounds were identified from the primary series.

Work on the follow-up programme led to a differentiated series with a non-covalent binding mode which demonstrated *in vivo* efficacy.

Case Study 2

Target: Tankyrase

Domainex expertise

- Virtual Screening via *LeadBuilder*
- X-ray Crystallography
- Structure-based Drug Design
- DMPK
- Medicinal Chemistry
- Lead Optimisation

Disease area: Oncology

Tankyrase is a member of the PARP family which has been shown to play an important role in the Wnt signalling pathway.

LeadBuilder was used to identify hit compounds that acted as tankyrase inhibitors. Previously published crystal structures showed tankyrase in a closed form, in which the active site was inaccessible to ligands. Domainex built a homology model of tankyrase using the closed conformation and a published crystal structure of PARP1 in an open conformation. This model was used to screen a 900K sub-set of Domainex's NICE database of ~1.5 million commercially available compounds, from which ~1000 compounds were purchased. 59 hits were identified with IC_{50} values between 100 nM and 10 µM (Figure 1).

Several chemical series of potent tankyrase inhibitors, including the "IQ" series (Figure 2), were progressed through an integrated medicinal chemistry programme. The leads identified were potent (<20nM tankyrase inhibition in a biochemical assay), exhibited good cellular activity (<100nM in a Wnt reporter assay) and had excellent selectivity over PARP1 (>30-fold). They also showed required DMPK properties (e.g. oral bioavailability in rodents of >50%). The programme was supported throughout by structure-based drug design and X-ray crystallography data (Figure 3).

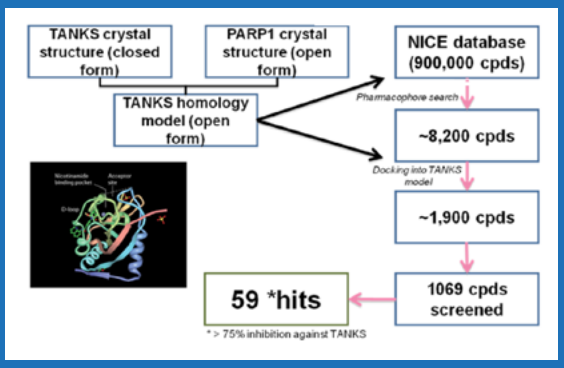
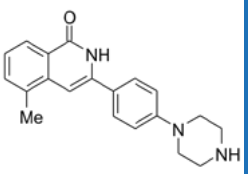


Figure 1: Schematic of *LeadBuilder* process leading to the discovery of a set of tankyrase inhibitors

IQ series analogue



TANKS IC_{50}	12 nM
Wnt-Luc reporter IC_{50}	14 nM
Cell inhibition SF_{50} (APC_{mut})	291 nM
MW	319
AlogP	2.5
Ligand Lipophilicity Efficiency (LLE) pIC_{50} (TANKS) – AlogP	5.4

Figure 2: Key properties of one of the identified tankyrase lead series

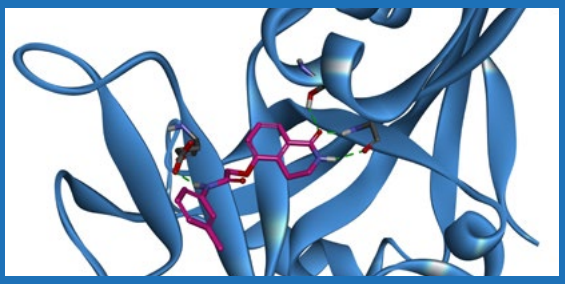


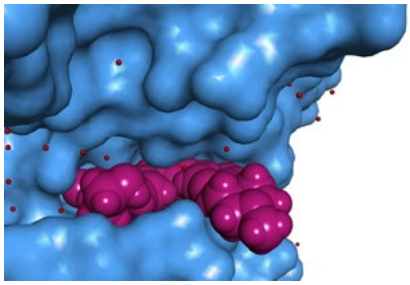
Figure 3: X-ray crystal structure of one of our compounds bound to tankyrase

Reference

Elliott R, Ashley J *et al.* (2015), Design and discovery of 3-aryl-5-substituted-isoquinolin-1-ones as potent tankyrase inhibitors. Med. Chem. Commun., **6**, 1687-1692

What was the successful outcome?

In less than 3 years, a small team went from hit to candidate drug in less than 400 compounds. The project received further funding to generate a back-up candidate, and was subsequently out-licensed to a major pharmaceutical company to develop these compounds as anti-cancer drugs.



Case Study 3

Target class: Lysine Methyltransferases

Domainex expertise

- Assay Development via *BioassayBuilder*
- Hit Screening via *LeadBuilder* and *FragmentBuilder*
- Protein Production and Combinatorial Domain Hunting (CDH)
- X-ray Crystallography

Disease area: Oncology

Lysine methyltransferases (KMTs) play an important role in the progression of solid tumours, promoting cell proliferation and survival under hypoxic conditions, as well as metastasis, therefore making them an important class of cancer targets.

Domainex has addressed the key technical challenges associated with KMTs, including generation of a number of X-ray crystal structures, assays and a KMT specific chemical library of small-molecule inhibitors. For example, EZH2 screening assays were developed using a peptide substrate and the more physiologically relevant substrate H3/H4 tetramer (Figure 1). Screening of our KMT library, selected using virtual screening via *LeadBuilder*, has identified specific chemotypes for methyltransferases such as EZH2, SMYD2, SMYD3, G9a and NSD2.

We utilised our protein production platform to produce several milligrams of full-length G9a and were able to show the absence of post-translational modifications. *FragmentBuilder* was used to screen a 320 compound sub-set of the Domainex fragment library against G9a by MicroScale Thermophoresis (MST), with a hit rate of 5%. Screening the same fragments using Differential Scanning Fluorimetry (DSF) yielded only a 0.3% hit rate, due to the small shift (0.5-1C) observed in DSF using this ternary system. Eleven fragment hits identified by MST were taken into secondary screening to determine their binding affinity (K_d) to the G9a-SAM complex (Figure 3). Unlike some other biophysical methods, MST is able to identify both high and low affinity binders, and provide an affinity-based ranking. As a follow-up, the K_d values for nine of the fragment hits were determined in the absence of the co-factor SAM. This revealed different mechanisms of action and highlighted the value of being able to study a ternary system using this technique. Orthogonal confirmation of hit binding to G9a was demonstrated by Saturation Transfer Difference (STD) NMR spectroscopy.

What was the successful outcome?

The team at Domainex are now using a proprietary crystal structure of a G9a-ligand complex to drive the hit-to-lead programme.

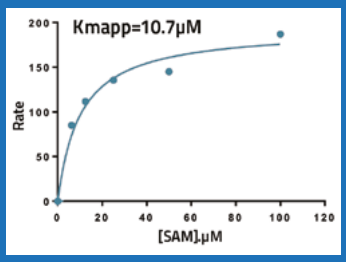


Figure 1: Development of an EZH2 AlphaScreen assay. Purified recombinant EZH2 complex was tested for its ability to methylate histone-based substrates and resolve SAM ATP K_{mapp}. Rate of reaction was elucidated from a serial dilution of SAM in the presence of fixed concentrations of biotinylated peptide and EZH2 complex. Methylation was detected using Alpha-donor streptavidin and Alpha-acceptor anti-H3K27me3 beads.

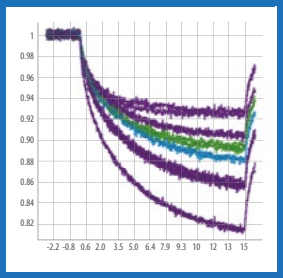


Figure 2: MicroScale Thermophoresis (MST) traces of selected fragments, positive control and DMSO.

	Kd + SAM	Kd - SAM	Comment
Ligand Name	Kd [µM]	Kd [µM]	MOA
MTP3B6	17	109	SAM dependent
MTP2C3	56	No Saturation at 1 mM	SAM dependent
MTP4E1	117	94	SAM independent
MTP3G10	195	No Saturation at 1 mM	SAM dependent
MTP2D8	534	No Binder	SAM dependent
MTP2H9	564	No Binder	SAM dependent
MTP3G1	718	518	SAM independent

Figure 3: Summary table of fragments taken into secondary and tertiary screening.

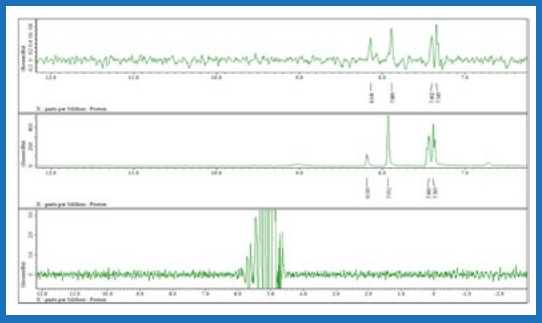
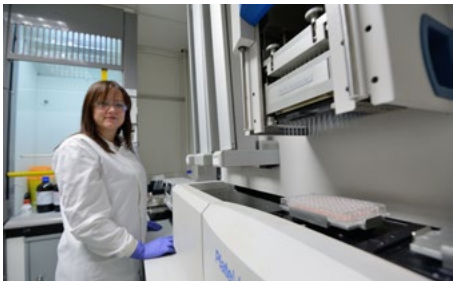


Figure 4: STD NMR spectra showing the binding of one of our MST hits to G9a.



Building partnerships

Domainex has an established track record and is proud to have worked with global companies in all sectors including large pharmaceutical companies, biotechs and start-ups, as well as leading academic groups.

Imperial College London

Domainex is in partnership with Professor Michael Schneider and his research group from Imperial College London to discover novel therapies that reduce heart muscle damage during heart attacks.

What was the key challenge of the project, and why did you choose to work with Domainex?

A principal challenge for us, seeking an inhibitor of a protein kinase that mediates human cardiac muscle cell death, was that most ATP-competitive inhibitors are very promiscuous. We needed to improve our tool compound's bioavailability, without sacrificing potency and selectivity. Domainex are experienced with other kinase targets, and their emphasis on structure-guided medicinal chemistry was indispensable to my success.

How would you describe working with the team at Domainex?

For me, partnering with Domainex was nothing short of ideal. The skill set, alacrity, knowledge base, effort, responsiveness and effectiveness of all team members is superb, at every level of seniority. I always look forward to our monthly project team meetings, and learn from them immensely.

What was the successful outcome of the project?

We successfully created novel small-molecule inhibitors of the stress-activated protein kinase MAP4K4, which inhibit the death of human heart muscle cells grown in the lab and successfully suppress the damage caused by heart attacks in mice. Our collaboration has resulted in £7M of Wellcome Trust Seeding Drug Discovery support.

Would you work with Domainex on future projects?

I would gladly work with Domainex again and indeed have a nascent collaboration that just was funded. Ready, willing, and very, very able.

auspherix

Domainex works closely with Dr Neil Miller and his team at Auspherix, providing medicinal chemistry support. Auspherix, a UK-based anti-infectives biotech, discovers and develops novel organogold-based antibiotics for the treatment of serious bacterial infections. Auspherix anticipate a development candidate molecule from a current lead series targeting complicated urinary tract infections, progressing into clinical studies by early 2019.

What technical expertise has Domainex been able to provide you?

Auspherix operates a semi-virtual drug discovery model and, following a rigorous search, selected Domainex as our preferred partner to provide medicinal chemistry support. This choice was based on the specific synthetic and analytical chemistry expertise Domainex offers, and on the belief that the two organisations shared similar philosophies and could work effectively together.

What have been the key ingredients to a successful partnership with Domainex?

The full integration of the Domainex scientists into the project team has been crucial. They have shown real commitment to the project and have been instrumental in helping solve a number of key scientific challenges we have faced over the last 2-3 years. Their passion to do the very best science and to help achieve the project's objectives has been very clear from the start.

What are your aspirations for Auspherix in the future?

The rising global spread of anti-microbial resistance (AMR) is a clear threat to human healthcare. Our vision is to deliver the first class of Gram-negative antibiotics in over 40 years to the market, helping to save the lives of patients suffering from life-threatening bacterial infections. We very much hope that Domainex and our other partners will be part of this successful endeavour.

About Domainex

Domainex is a fully integrated drug discovery service company based near Cambridge, UK serving pharmaceutical, biotechnology, academic and patient foundations globally. Domainex's drug discovery service business was established in 2001 and since that time has continued to expand to serve a wider range of clients across the world including UCB, FORMA Therapeutics, St George's University, The Institute of Cancer Research and Auspherix. Our expertise and commitment to providing high-quality services has resulted in a strong success record in drug discovery, delivering an average of one candidate drug every year for the past six years.

How Can Domainex Help Your Drug Discovery Project?

Domainex's highly experienced molecular biologists, assay biologists, medicinal, computational and analytical chemists can be leveraged through our CRO services. Domainex provides highly efficient and well considered scientific solutions to enable successful drug discovery programmes against a wide range of drug targets. Whether your project is at an early stage of drug discovery or has already identified chemical matter, our processes have been shown to result in a 30% time-saving compared to industry standards and use less resource, allowing prudent management of your own budget.

Contacts

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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