

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

Social

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Integrated drug discovery services from Domainex

The research partner that creates innovative solutions



Introduction

'Every compound counts'. It's not a slogan, it's the way we work. Medicines research is a complex process, but our aim is simple: we'll provide innovation in partnership to help you convert ideas and discoveries into blockbuster treatments for patients, **effectively and efficiently**. This means deploying our considerable brainpower, experience, cutting-edge technologies and established processes to make therapeutic breakthroughs on your behalf.

Domainex scientists have experience in working across different therapeutic areas, including cancer, immuno-oncology, inflammation, cardiovascular, central nervous system and respiratory diseases. Our integrated science-led approach to medicines research brings together the talent, creativity and expertise of our multi-disciplinary team, proprietary technologies, and a highly collaborative approach, to **deliver results**.

Forming dynamic relationships

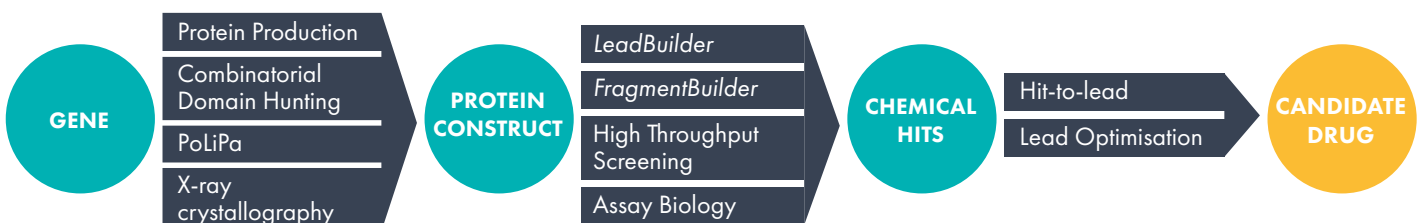
In 2021 we served over 60 clients from the UK, Europe, the United States, Japan and Australia and had a project continuation rate of **over 80%** to the next stage of the process

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

- >150 the **number of patents** that our scientists are cited as inventors on
- >10 the average number of **years' experience** our scientists have in medicines research
- >350 the number of **peer-reviewed papers** our scientists have authored
- 3 the number of candidate drugs our clients have **progressed into clinical trials**
- >75% of our scientists who are **PhD qualified**
- 4 the number of **candidate drugs we've helped invent** in pre-clinical development

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 on a journey of discovery. Our integrated approach has a proven record of success in delivering timely and cost-effective solutions, and generating new intellectual property for our clients.



Protein production and assay development



If you need well-characterised, **high-quality protein** for your drug discovery programmes or for other purposes, then Domainex's team of highly experienced protein scientists are at your disposal. We can offer you a complete solution, including construct design, cloning, protein expression (*E. coli*, insect cells, or mammalian cells), purification and characterisation. We are able to produce and purify proteins in multi-milligram quantities, and our expertise in protein characterisation means that you can have confidence that we will deliver you high quality protein that has passed our rigorous quality control process.



Our scientists will often use literature-informed or bioinformatics approaches for expression construct design, but our Combinatorial Domain Hunting (CDH) technology can be used for more challenging proteins. **CDH** is our patented technology for generating many thousands of variants of target proteins to identify suitable **novel constructs**, which can be used in assays or for structural biology.



Polymer Lipid Particle (**PoLiPa**) is our established generic platform for the efficient preparation of stable and highly purified **membrane proteins**, such as GPCRs, for use in drug discovery. Without the need for thermostabilising mutations or detergents, our technology enables rapid access to pharmacologically intact membrane targets with versatile applications that are stable over several months.



Whether you are looking for high-quality assay biology solutions based on established techniques, or for more innovative assays, we will strive to deliver what you need. We offer a comprehensive suite of **assay development** services, including bespoke biophysical, biochemical and cell-based assays.

Hit identification

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



LeadBuilder is Domainex's novel approach to **virtual screening**. At its heart is our NICE (Number of Interesting Chemical Entities) virtual database of 4.9 million compounds that has been assembled from known commercial vendor collections and filtered so that only compounds with lead-like properties remain. This collection can be screened in as little as 2 weeks to generate a virtual hit list of 500 – 1000 compounds.



FragmentBuilder is Domainex's **Fragment-Based Drug Design (FBDD)** platform that enables us to identify rapidly hits against your chosen target. Starting from a target gene, Domainex deploys its FBDD expertise in protein science, assay biology and medicinal chemistry to discover tractable, patentable leads cost-effectively.



At Domainex we offer high throughput screening using a **variety of assay formats** (biochemical, cell-based) in 384- or 1536-well format. We can access commercially available **diversity libraries** of lead-like compounds or focussed compounds directed towards target classes, modalities or therapeutic area, on your behalf. Various library sizes are available, to suit your budget and project needs. Alternatively, if you would prefer to provide your own library, Domainex would be happy to screen it for you.



Our structural biologists can generate high-resolution **X-ray crystal structures** providing invaluable information for your programme and enabling a structure guided hit-to-lead phase.

Hit-to-lead and lead optimisation



At the hit-to-lead stage of your project, our aim is to establish the potential of each of your hits to be developed into patentable leads as efficiently as possible, in order to focus our subsequent lead optimisation work on the most promising chemical series. We will provide a **fully integrated, multi-disciplinary team**, including **medicinal, computational and analytical chemists** to design, synthesise and purify novel compounds, as well as **in vitro pharmacologists** and **in vitro ADME/PK scientists** to devise the optimum screening cascade for your project and carry out just-in-time compound screening.

Our **in vitro pharmacologists** are fully enabled to run suites of biochemical, biophysical and cell-based assays in miniaturised (384-well typically) formats to minimise reagent consumption and maximise the flow of project-enabling data. They work closely with our medicinal chemists to minimize cycle times, thus facilitating real-time decision making on where to deploy chemistry resource to further enhance the pharmaceutical properties both within and across several series of compounds in parallel.

In addition, we have built a comprehensive platform of **in vitro ADME/PK assays** that generally utilize highly sensitive mass spectrometry read-outs. Our *in vitro* pharmacology and ADME/PK teams work very closely together to co-ordinate the running of multiple assays in parallel, providing information-rich data sets to our chemists.

Computational chemistry expertise can significantly improve the efficiency of your drug discovery project by helping to design compounds that have a high probability of binding to your target and the right molecular and physical properties to ultimately demonstrate good bioavailability. Our **Computer-Assisted Drug Design (CADD)** experts use state-of-the-art software and proactively develop new insights that are tailored to the particular characteristics of the binding pocket of your disease target.

Building partnerships

With an unrivalled track record of solving research challenges, our highly experienced scientific team delivers successful outcomes efficiently and quickly.

We work closely and collaboratively with ambitious life science organisations globally. See what some of them have to say about working with Domainex:



Professor Helen Philippou – Professor of Translational Medicine, Lunac Therapeutics

“Domainex have provided us with integrated drug discovery services including medicinal chemistry, assay biology and ADME. The team were great to work with in a collaborative partnership. The scientists have contributed strategic insight and intellectual input across a range of disciplines. This support was invaluable in areas of expertise on the overall drug discovery process. I’ve really enjoyed working together with such a dedicated, highly skilled and professional team.”

I would recommend Domainex to anyone looking for a provider of drug discovery services.”



Professor Daniel Longley – Deputy Director of the Patrick G. Johnston Centre for Cancer Research, Queen's University Belfast

“It has been an absolute pleasure working with Dr Boffey and the Domainex team on this project. Without their first class medicinal chemistry expertise and the use of their Leadbuilder virtual screening platform at the outset of the programme, we would not have been able to secure the support of The Wellcome Trust and advance the programme to the stage it has now reached.”



Marc Gleeson – CEO, Azura Ophthalmics

“Domainex with their deep industry experience, have been able to solve complex synthetic, medicinal and analytical chemistry challenges to deliver project outcomes for Azura in a timely and efficient manner. They’ve been able to flexibly resource our program to deliver high quality results and support tight patent timelines.”



Dr Jack Kennefick - Co-founder & Chief Executive Officer, Tagomics

“We have been really impressed with the service at Domainex, from initial discussion to delivery of the project. The Domainex team are attentive, well organised, and knowledgeable. They always take the time to understand our exact needs and consistently deliver high-quality results, in a time efficient manner.”

Case Study 1

Domainex expertise

- Medicinal chemistry
- Computational chemistry
- ADME
- Structure-based drug design
- Lead optimisation

Disease area: Asthma

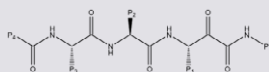
Der p 1 is a cysteine protease excreted by house dust mites (HDM) and is a major cause of allergic asthma. In collaboration with St George's University London and the University of Manchester, we set out to identify a candidate drug suitable for delivery by dry powder inhaler (DPI). The starting point 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 designed successfully 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 dry powder inhalers by identifying compounds with stable crystalline forms that could be micronised to give particles of a size appropriate for inhaled delivery.

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.











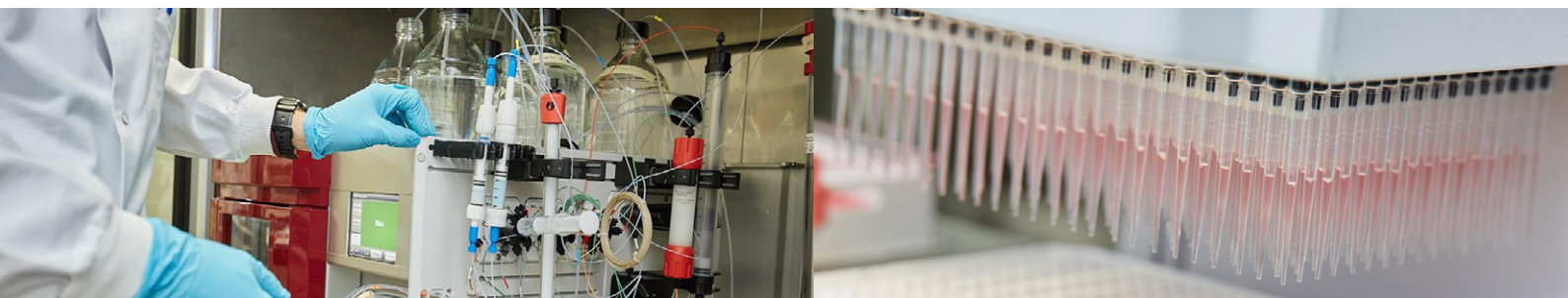
Compound	P1	P2	P3	P4	P'	Der p 1 IC ₅₀ (nM)	Cat B IC ₅₀ (nM)	LogD _{7,4}
4	n-Bu	Me	benzyl	Ph	cyclohexyl	8	17	
5	i-Pr	Me	benzyl	Ph	cyclohexyl	18	52	
6	i-Pr	Me	benzyl	Ph	benzyl	12	50	
7	t-bu	Me	benzyl	Ph	cyclohexyl	9167	Not determined	
8	i-Pr	Me	t-butyl	Ph	cyclohexyl	14	378	3.9
9	i-Pr	Me	C(Me) ₂ Ph	Ph	benzyl	42	446	
10	i-Pr	n-Pr	benzyl	Ph	cyclohexyl	164	67	
11	i-Pr	Me	t-butyl		benzyl	18	>2500	3.4
12	i-Pr	Me	t-butyl		Benzyl	6	274	-0.9
13	i-Pr	Me	t-butyl		cyclohexyl	13	231	2.8
14	i-Pr	Me	t-butyl	Ph	CH ₂ Ph	9	512	3.2
15	i-Pr	Me	benzyl	Ph		14	544	1.3
16	i-Pr	Me	t-butyl	Ph		14	>2500	1.0
17	i-Pr	Me	benzyl	Ph		9	88	1.7
18	i-Pr	Me	benzyl	Ph		17	>2500	-0.6
19	i-Pr	Me	benzyl			20	540	2.0

Table 1: The impact of modifying P1, P2 and P3 on selectivity over Cathepsin B

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



Case Study 2

Domainex expertise

- Virtual screening via *LeadBuilder*
- Hit identification
- Structure-based drug design
- ADME
- 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 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 μ M.

Supported by X-ray crystallography, a subsequent structure-based drug design programme (incorporating integrated ADME to inform each iteration of medicinal chemistry, and early screening for other liabilities) generated several series of potent tankyrase inhibitors (< 20 nM tankyrase, < 100 nM in a Wnt reporter cell assay), with excellent selectivity over PARP1 (> 30 fold), and good ADME properties (e.g. oral bioavailability in rodents of > 50%). Lead compounds were shown to inhibit the growth of APC-null tumour xenografts.

What was the successful outcome?

The project 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.

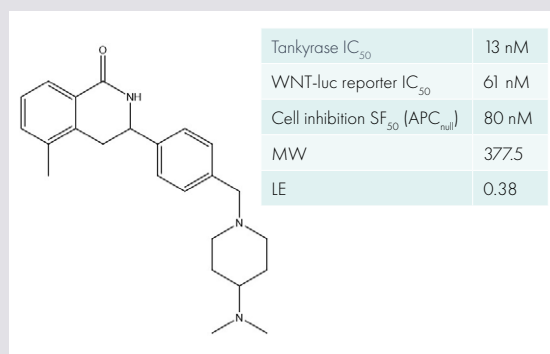


Figure 1: Example of an isoquinolone tankyrase inhibitor designed and synthesised at Domainex

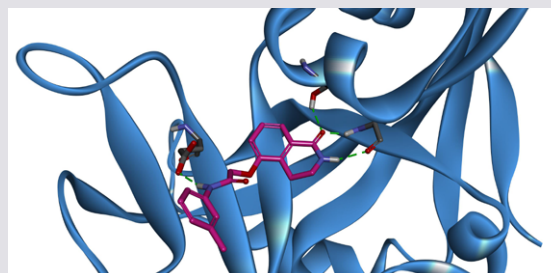


Figure 2: X-ray crystal structure of one of our compounds bound to tankyrase

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



Case Study 3

Domainex expertise

- Computational chemistry
- Medicinal chemistry
- Assay biology
- Lead optimisation
- ADME
- X-ray crystallography

Disease area: Heart disease

Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4), a serine-threonine kinase which activates the JNK signalling pathway, is activated in failing human hearts and relevant rodent models. Therefore, Professor Michael Schneider and his team at Imperial College London postulated that an inhibitor of MAP4K4 would be able to suppress human cardiac cell death, offering the possibility of cardioprotection following heart attacks.

An empirical screen was carried out against human MAP4K4 using about 1800 bioactive compounds, and the initial hit, DMX-4640 (Figure 1), was identified as a starting point for medicinal chemistry studies. We then undertook a programme of rational drug design, including X-ray crystallography, to produce DMX-5804, a compound with a significantly greater water solubility and reduced metabolic clearance.

We demonstrated that MAP4K4 inhibition by DMX-5804 confers protection in hiPSC-CMs (Figure 2) and reduces ischemia-reperfusion injury in mice by >50% (Figure 3). The solubility and pharmacokinetic properties of DMX-5804 were insufficient for a human drug candidate in acute ischemic injury, where rapid intravenous infusion is desired. However, further structural modifications led to compounds with properties suitable for clinical candidates (Figure 1).

What was the successful outcome?

Using hiPSC-CMs as the most relevant platform for gene silencing and drug discovery, we designed small-molecule inhibitors of MAP4K4. DMX-5804, a novel, potent, highly selective, small-molecule inhibitor of MAP4K4, was identified for proof of concept studies.

Additionally, we were able to further optimise the series and identified a number of compounds with properties suitable for a clinical candidate.

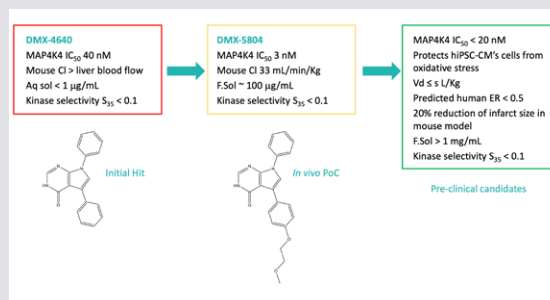


Figure 1: The medicinal chemistry progression from initial hit, DMX-4640, to the identification of pre-clinical candidates

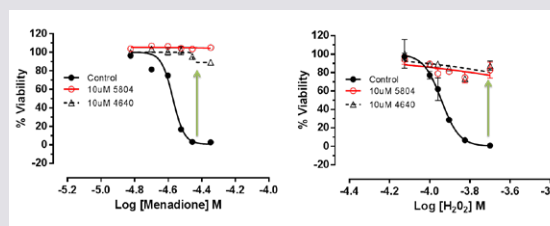


Figure 2: DMX-5804 confers 100% protection against two oxidative stress signals in cardiomyocyte stem cells

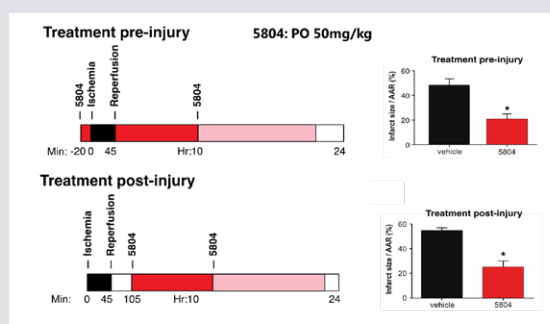


Figure 3: Initial proof of concept studies carried out in mice using 50mg/kg oral dose of DMX-5804

Reference

Schneider MD *et al.* (2019). MAP4K4 inhibition promotes survival of human stem cell-derived cardiomyocytes and reduces infarct size in vivo. *Cell Stem Cell*, **24** (4), 579-591

