Domainex
Enrich your Medicines Pipeline

Integrated drug discovery services from Domainex

The research partner that creates innovative solutions

Domainex

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 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 2020 we served over 50 clients drawn from the UK, Europe, the United States and Australia and had a project continuation rate of **over 70%** to the next stage of the process

Integrated drug discovery

Sir Simon Campbell with Tom Mander, Domainex CEO, 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.

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

>350 the number of **peer-reviewed papers** our scientists have authored

>85% of our 70 staff who are **active scientists**

>80% of our scientists who are **PhD qualified**

>8 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

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 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

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.

Combinatorial Domain Hunting
Unlocking 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.

PoLiPa
Accelerating Membrane Protein Research

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.

Assay Biology
Quality Data Throughout

Whether you are looking for high-quality assay biology solutions based on established techniques, or for more innovative assays, the talented Domainex team will strive to deliver what you need. We offer a comprehensive suite of services, including bespoke biophysical, biochemical and cell-based assays, screening, and ADME testing. Routinely, we run screening cascades of potency, selectivity, MOA and phenotypic assays to support each stage of medicines research.

Hit identification

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.

LeadBuilder
Taking a Rational Route to Leads

LeadBuilder is Domainex's novel approach to virtual screening. At its heart is our NICE (Number of Interesting Chemical Entities) virtual database of ~1.5 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
Efficient Fragments to Quality Leads

FragmentBuilder is Domainex's Fragment-Based Drug Discovery (FBDD) platform that enables us to rapidly identify 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.

Hit-to-lead and lead optimisation

Medicinal Chemistry
Delivering Drug Candidates

Analytical Chemistry
Reaching Peak Precision

Structural Biology
Revealing New Dimensions

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 leads as quickly as possible, in order to focus our subsequent lead optimisation work on the most promising chemical series. We can provide a fully integrated team, including medicinal, computational and analytical chemists to design, synthesise and purify novel compounds, as well as assay biologists to carry out compound screening and to devise the optimum screening cascade for your project.

Our structural biologists can generate high-resolution X-ray crystal structures which provide invaluable structural information for your programme. We also offer a wide range of *in-vitro* ADME services to profile your compounds and to ensure that only compounds with the highest chances of success are progressed.

St George's University of London

Case Study 1

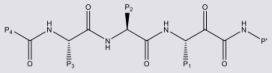
Domainex expertise

- Medicinal chemistry
- Computational chemistry
- DMPK
- 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 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 dry powder inhalers by identifying compounds with stable crystalline forms that could be micronised to give particles of a size appropriate for inhaled delivery.



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	$C(Me)_2Ph$	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	CH2Ph	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

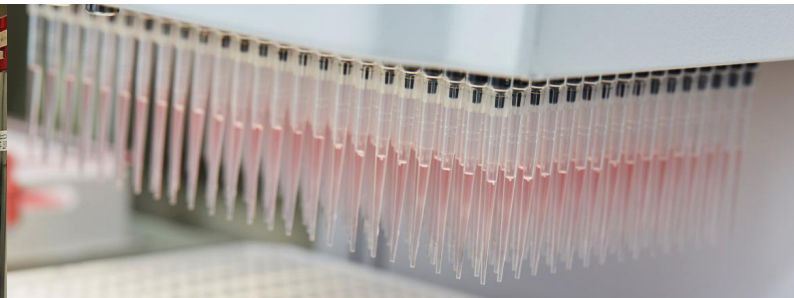
Reference

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

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.

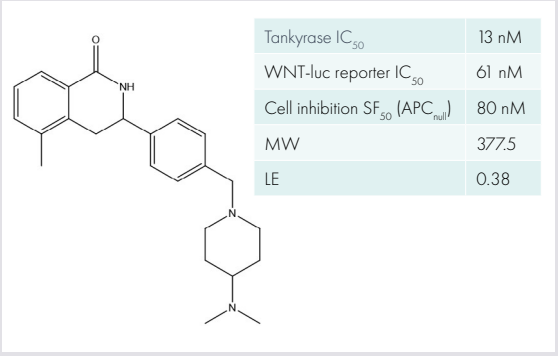


ICR The Institute of Cancer Research

Case Study 2

Domainex expertise

- Virtual screening via *LeadBuilder*
- Hit identification
- Structure-based drug design
- DMPK
- Medicinal chemistry
- Lead optimisation



Tankyrase IC_{50}	13 nM
WNT-luc reporter IC_{50}	61 nM
Cell inhibition SF_{50} (APC_{null})	80 nM
MW	377.5
LE	0.38

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

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 µM.

Supported by X-ray crystallography, a subsequent structure-based drug design programme (incorporating integrated DMPK 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 Wnt reporter cell assay), with excellent selectivity over PARP1 (> 30 fold), and good DMPK properties (e.g. oral bioavailability in rodents of > 50%). Lead compounds were shown to inhibit the growth of APC-null tumour xenografts.

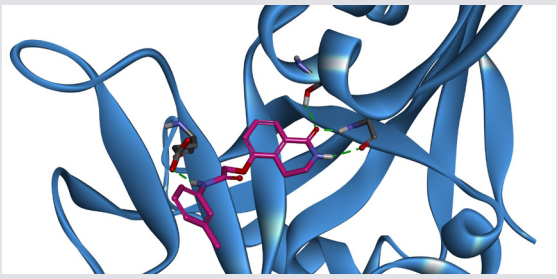


Figure 2: X-ray crystal structure of one of our compounds bound to tankyrase

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

What was the successful outcome?

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.

Imperial College London

Case Study 3

Domainex expertise

- Computational chemistry
- Medicinal chemistry
- Assay biology
- Lead optimisation
- DMPK
- 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).

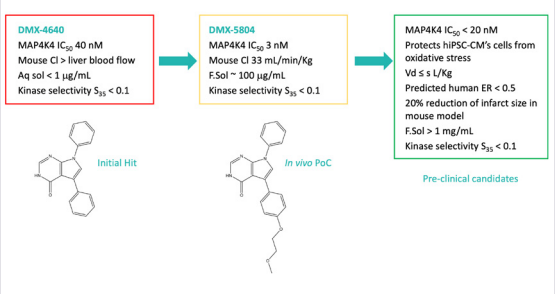


Figure 1: The medicinal chemistry progression from initial hit, DMX-4640, to the identification of pre-clinical candidates

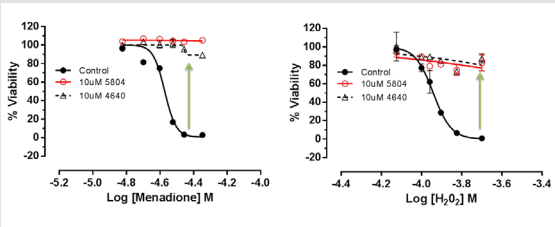


Figure 2: DMX-5804 confers 100% protection against two oxidative stress signals in cardiomyocyte stem cells

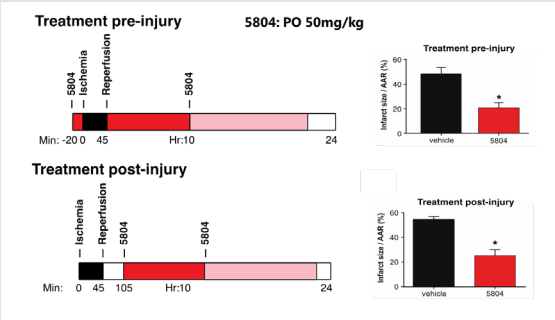


Figure 3: Initial proof of concept studies carried out in mice using 50mg/kg oral dose of DMX-5804

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

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.

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:

ICR The Institute of Cancer Research

Professor Alan Ashworth – Institute of Cancer Research (ICR)

"The Domainex team went far beyond our expectations of a service provider. They were proactive, knowledgeable, and true partners in what we were trying to achieve. I would work with them again without hesitation."

PHORE MOST
DRUGGING THE UNDRUGGABLE

Dr Rich Boyce – Senior Director of Research, PhoreMost Ltd.

"Domainex is a highly valuable partner in PhoreMost's drug discovery programmes. The company's expertise in virtual screening, through its LeadBuilder Platform, has allowed the identification of small molecule hits to challenging biological targets which are now being pursued at PhoreMost.

Domainex's deep knowledge and expertise in computational chemistry is enabling us to progress multiple projects quickly and cost effectively."

Imperial College London

Professor Michael Schneider – Imperial College

"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.

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

ucb Inspired by patients. Driven by science.

Dr Neil Weir – formerly Senior Vice President, Discovery Research UCB

"The partnership with Domainex has been invaluable for our MEK discovery program. Successful collaborations, such as this, are a key part of UCB's innovative and cutting-edge research. We hope that the novel class of MEK inhibitors which the UCB team discovered will bring benefits to patients."

About Domainex

Domainex is a fully integrated drug discovery service company based at Cambridge, UK. We serve pharmaceutical, biotechnology, academic organisations and patient foundations globally. With over 70 highly experienced biologists and chemists, we work in partnership with our clients from disease target through to candidate drug nomination. We have built a strong reputation for providing our clients with innovative ideas and undertaking high-quality, breakthrough experimental studies. We strive to build strong, dynamic relationships with our clients. In 2020 we served over 50 clients drawn from the UK, Europe, the United States and Australia and had a project renewal rate of over 70%.

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 analytical chemists – 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 drug discovery. We draw from a wealth of expertise built up over the last 20 years against a wide range of drug targets and therapeutic areas. Being based at a single location with access to the very latest cutting-edge technologies, we are able to help you realise your goals and enrich your discovery pipeline.

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

Alternatively we can be contacted directly as follows:

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