DOMAINEX: INTEGRATED DRUG DISCOVERY

Mark Stewart

Domainex
Enrich your medicines pipeline

Domainex's approaches to virtual screening, hit finding, hit-to-lead and lead optimisation have enabled successful delivery of pre-clinical candidates.

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.

Protein production and assay development

Combinatorial Domain Hunting
Unlocking Challenging Proteins

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.

Assay Biology
Quality Data Throughout

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

Hit Identification

LeadBuilder
Taking a Rational Route to Leads

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.

FragmentBuilder
Efficient Fragments to Quality Leads

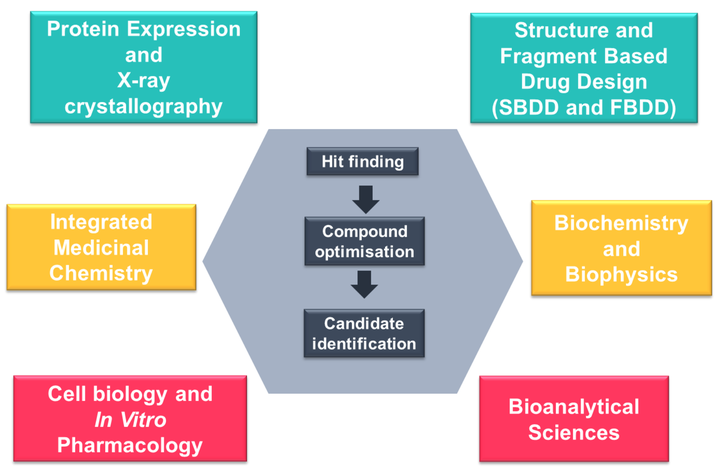
Fragment screening offers a practical alternative to high-throughput screening. *FragmentBuilder* is the leading fragment screening platform with MicroScaleThermophoresis at its core. Combined with our exclusive fragment library (including novel SpiroChem compounds) and a surprisingly small sample of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

Hit-to-Lead and Lead Optimisation

Medicinal Chemistry
Delivering Drug Candidates

Armed with our 'every compound counts' philosophy, we will carefully design >make >purify >test compounds in pursuit of your next drug candidate. We strive to shorten this invention cycle, and to minimise the number of iterations needed to find your candidate drug. We place a particular emphasis on early **DMPK**, analytical and physical chemistry profiling to quickly identify which of your leads exhibits the greatest potential. We have the ability to generate **high-resolution crystal structures** (all crystallisation trials and data analysis are performed in-house, and X-ray diffraction data is collected at the Diamond Light Source facility in Oxford where we have regular access to dedicated synchrotron beam time). We routinely apply **computational chemistry** approaches to inform our structure-based drug design.

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 enabling effective information sharing and learning– all our work is supported by the high-quality infrastructure that you would expect from a leading drug research services provider. **Our aim is to find your drug candidate more quickly and efficiently than you thought possible.**



Services / Contact

If you would like to learn more about applying our drug-discovery platforms, please contact:

ray.boffey@domainex.co.uk **www.domainex.co.uk**

Case Study: Discovery and Development of Potent Tankyrase Inhibitors

ICR The Institute of Cancer Research
wellcome
Domainex
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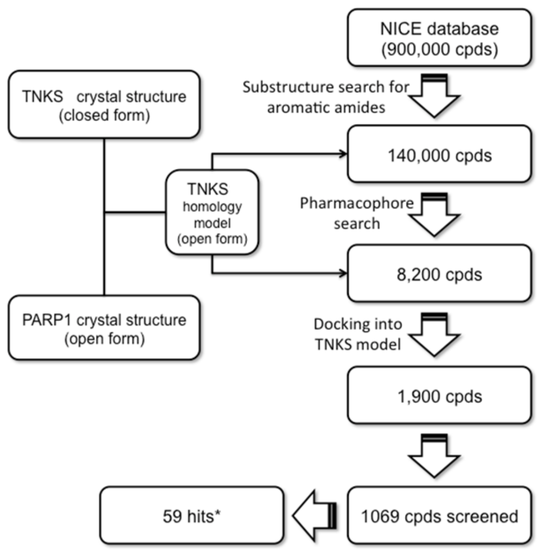
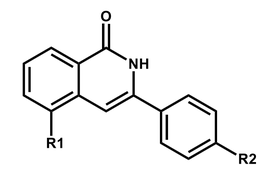
- **Funding: £3.9 million SDD grant received from Wellcome Trust**
- Collaboration with The Institute of Cancer Research
- TNKS/TNKS2 (PARP5/6) are novel targets which are involved in a range of cellular functions including telomere maintenance, control of the mitotic checkpoint and WNT signaling.
- Aim: Develop an orally administered drug for the treatment of WNT-dependent tumours

LeadBuilder to lead series

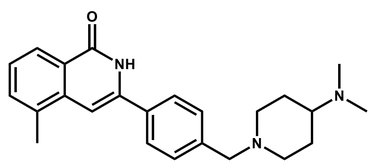


- Homology model of the open form of TNKS established based on a combination of PARP1 (open form) and TNKS (closed form)
- The Domainex '*LeadBuilder*' computational approach led to 1069 compounds screened and 59 hits (5% hit rate)
- Several hit series identified with 0.1-10μM potency against TNKS
- SBDD led to lead 'isoquinolin-1-one' series with <50nM enzyme potency
- R^1 = Me was chosen as the lead series since it was more metabolically stable than R^1 = OMe

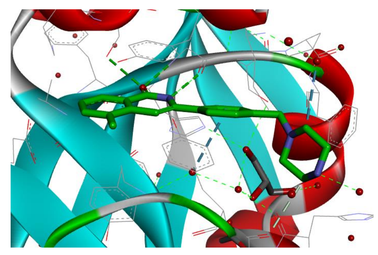


Development of 3-aryl-5-methyl isoquinolin-1-ones to give cell active compounds

- Optimisation of the series led to the discovery of compound **1** a potent Tankyrase inhibitor
- Good selectivity over PARP1 was observed for all tested analogues
- Excellent activity in a mechanistic WNT-Luc reporter assay for all analogues
- Compounds were able to inhibit growth of an *APC*-mutant colorectal cell line (DLD1)
- Several TNKS/ligand crystal structures were generated, confirming the binding mode as expected from previously published crystal structures and docking



Compound 1



- All ligands showed the same core set of hydrogen bonds: from the NH and carbonyl groups of the isoquinolin-1-one to Gly1185 and Ser1221
- Tyr1224 π-stacking interaction with the face of the isoquinoline-1-one core

Conclusions

- 3-Aryl isoquinolin-1-ones have been identified as potent inhibitors of TNKS
- Optimisation of these compounds led to compound **1**, a potent TNKS inhibitor which showed selective activity against *APC*-mutant cell lines
- Programme successfully out-licenced to Merck Serono
- **The work presented has been published in:** R. J. R. Elliott *et al. Med. Chem. Commun*., **2015**, 6, 1687

Other Funded Collaborations:

- Queen's University Belfast CRCCB: £10 million Wellcome Trust grant
- University of Oxford: Wellcome Trust grant
- Imperial College London: MRC confidence in concept award
- Imperial College London: BHF/Wellcome Trust funding
- Multiple projects funded by Innovate UK
- Supporting WT "Developing Concept Fund" application
- Domainex has supported many other academic institutions' funding applications

Queen's University Belfast
wellcome
UNIVERSITY OF OXFORD
Imperial College London
MRC Medical Research Council
Innovate UK
British Heart Foundation