Domainex

Enrich your Medicines Pipeline

Hit identification – selecting the best path to success

Domainex

Once you have selected your drug target, a critical determinant of the success of your research project is going to be the quality of your chemical hits.

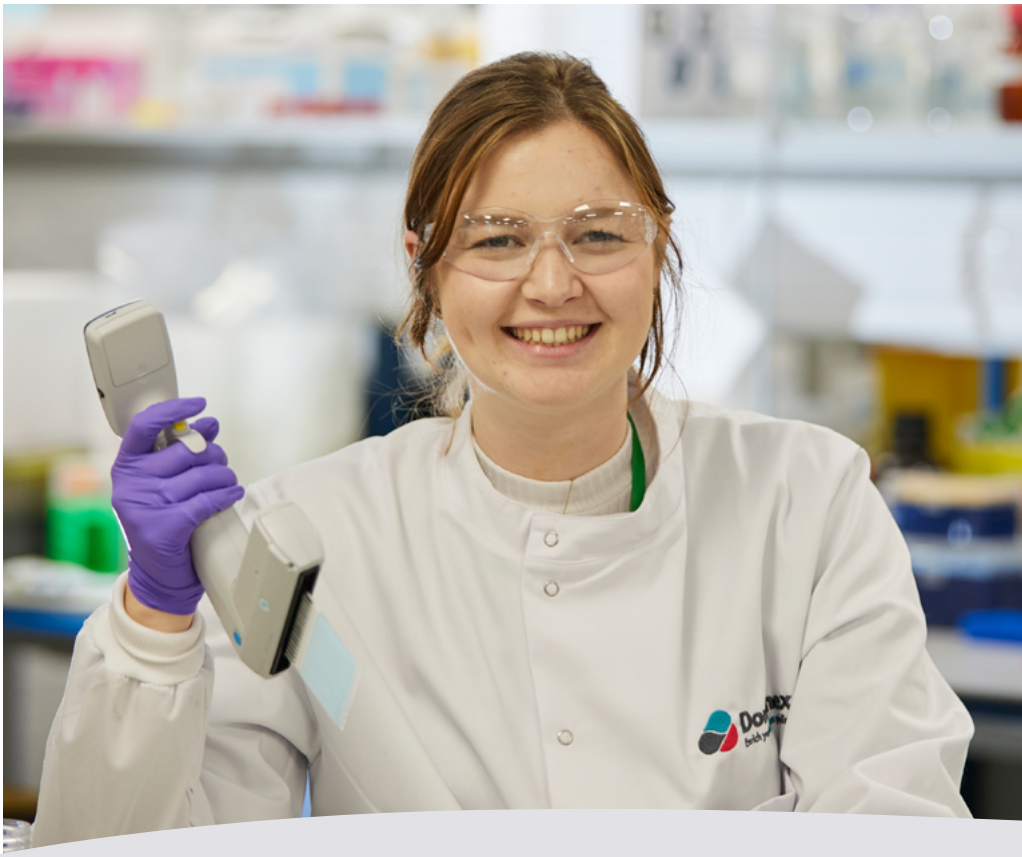
At Domainex, we believe that generating **high-quality hits** will ultimately result in **better drug candidates** being discovered more quickly. That will give you a superior end-product and save you time and money along the way.

What do we mean by high-quality hits? Well, we are looking for compounds that bind very efficiently to their target, that have good developability characteristics (e.g. favourable molecular and physical properties), and that are amenable to synthetic modification by our medicinal chemists to allow for rapid optimisation. Essentially, we are looking for starting points that already have many of the characteristics that you are looking for in your final drug.

Which hit identification approaches are best suited to your target?

Sometimes the best approach is to take one or more known ligands – for example a published or patented inhibitor – as the chemical starting point, and to carry out a knowledge-based ("**literature-to-lead**") design programme to identify related but different chemotypes by means of bioisosteric modification, scaffold-hopping, etc. Our aim here is to find you novel and patentable chemical matter that also confers biological advantages such as improved potency, selectivity, or pharmacokinetic properties over the prior art compounds. Our medicinal and computational chemists are very skilled at this, and several of our successful programmes have started in this way.

However, when there is no known ligand that is suitable for small-molecule drug design, or when you want to move into entirely new chemical space, the Domainex team offers three highly-refined and well-tested in-house technology platforms to identify novel chemical hits for your programme: **High-Throughput Screening (HTS), *FragmentBuilder* (fragment screening),** and ***LeadBuilder* (virtual screening)**. *LeadBuilder* virtual screening can be conducted in either ligand-based or protein-based modes – or both together – depending on what information is available for us to use.



High Throughput Screening
Casting the net wide

FragmentBuilder
Efficient Fragments to Quality Leads

LeadBuilder
Taking a Rational Route to Leads

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Domainex offers high throughput screening services to meet your needs with our sophisticated technology platforms & extensive capabilities.

- Variety of assay formats (biochemical, cell-based) in 384- or 1536-well format
- Various library sizes available, to suit your budget and project needs or we can screen your own library

Find out more by visiting our website: **https://www.domainex.co.uk/services/high-throughput-screening**

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.

Find out more by visiting our website: **https://www.domainex.co.uk/services/fragmentbuilder-fragment-based-drug-discovery-design** or ask for a copy of our ***FragmentBuilder* brochure**

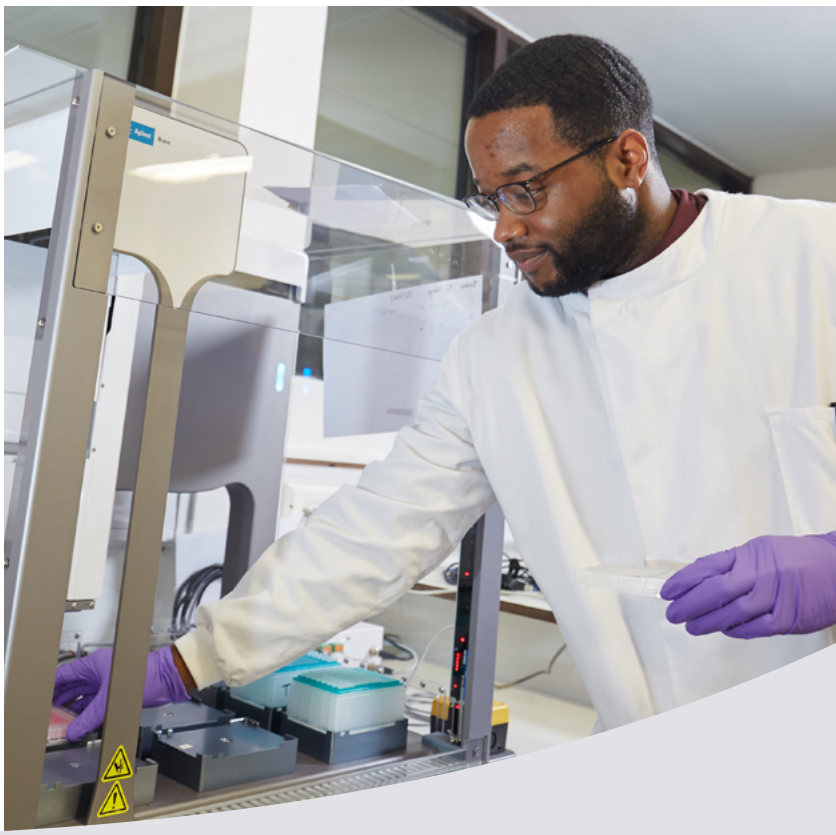
LeadBuilder
Taking a Rational Route to Leads

LeadBuilder is Domainex's virtual screening platform that allows us to identify small-molecule starting points on behalf of our clients against a diverse range of biological disease targets. Hits are pre-curated to ensure 'developability' and streamline hit-to-lead chemistry.

Find out more by visiting our website: **https://www.domainex.co.uk/services/leadbuilder-virtual-screening** or ask for a copy of our ***LeadBuilder* brochure**

Domainex scientists are experts in all these hit identification techniques, and we have **state-of-the-art capabilities** that you can find out more about on our website or in the individual brochures for each technology. These approaches can either be used **singly or in combination**, depending on what is known about your target, and how wide a range of hit matter you wish to identify.

With all of this hit-finding capability at your disposal, a question we are often asked is: "**which hit finding approach/approaches would you recommend for our target?**" As with most questions in drug discovery there is rarely a simple answer – but Domainex scientists have the experience and expertise, based on their proven track-record, to give you the best possible advice on this crucial point. This brochure will explain some of the key factors that should be taken into account when determining your hit-finding strategy.



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Target Information

Firstly, we have to consider what is known about the target and its ligands. Both *FragmentBuilder* and a protein-based *LeadBuilder* approach will benefit from a **3D structure of the target protein**, but this is unnecessary for HTS. If a 3D protein structure is not available, our expert structural biologists can look into the possibility of generating a structure on your behalf, using the techniques of **X-ray crystallography** or **cryo-electron microscopy (cryo-EM)**. Alternatively, our computational chemists can generate a **homology model** based on related protein structures.

Protein Supply

Protein supply should also be considered as the **different approaches have different demands for the quantity of target protein** – generally speaking, HTS requires the most protein, and *LeadBuilder* virtual screening requires the least. *FragmentBuilder* does not require a large quantity of protein for the screening stage, but more protein will be needed to obtain fragment-protein co-crystal structures for structure-guided follow-on medicinal chemistry.

Our protein science specialists can advise on what quantity and quality of protein supply is realistically achievable for your target.

Assays

Additionally, we have to evaluate what screening technologies can be applied to the target. Our assay biology team is skilled in evaluating the information available about your target and recommending what type of assay(s) to use for screening. Generally speaking, **biochemical or cell-based assays are well suited to HTS**, whereas **biophysical assays are more effective for the screening of fragments**. It should also be noted that when we move to implementing the selected screening technologies, known ligands are very valuable (but not essential) as positive controls for bioassay development.

Time and cost

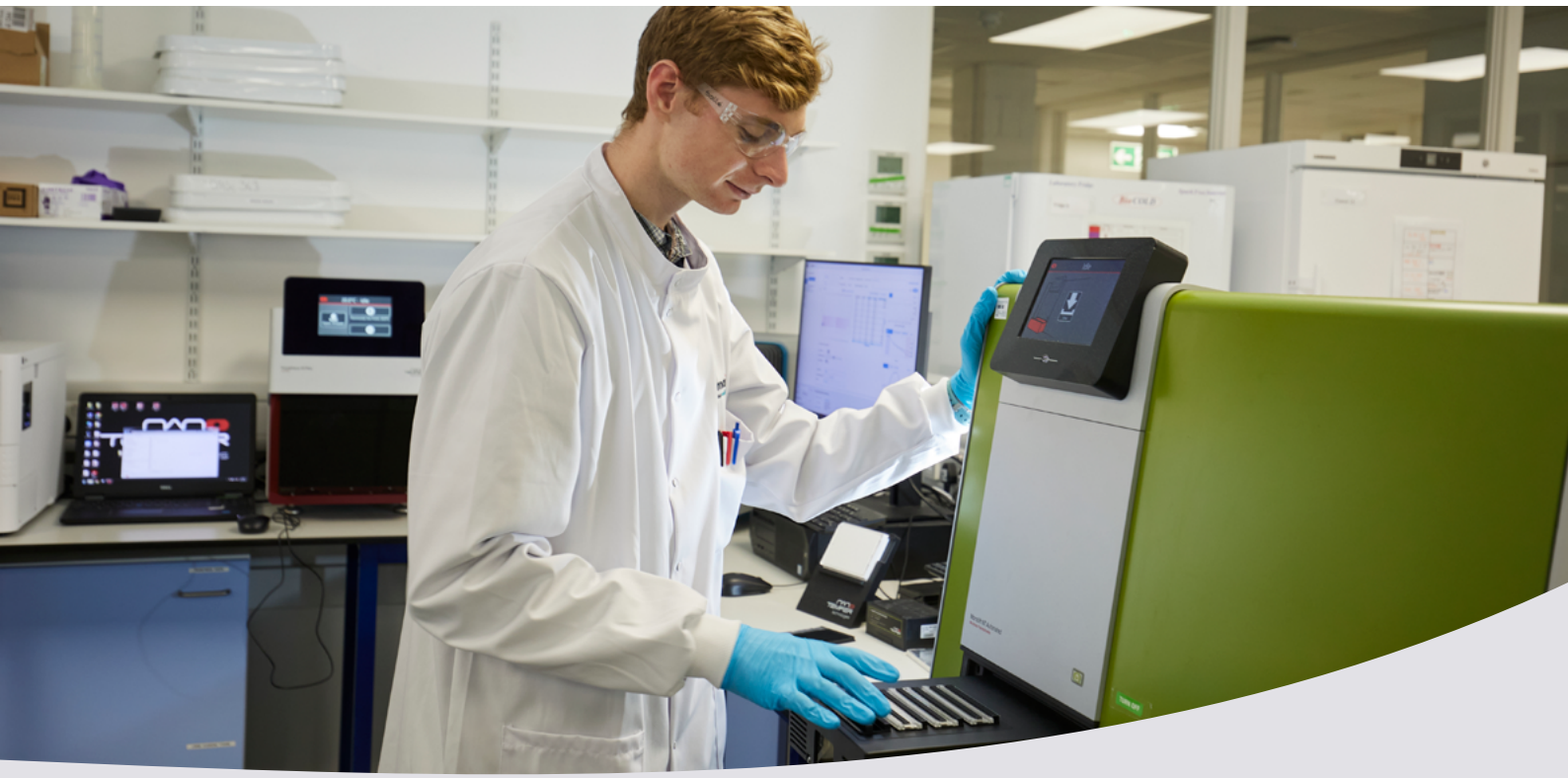
Finally, we have to keep in mind your expectations for the time and cost of this stage. Whilst a HTS campaign is the most widely applicable approach, it is likely to be the most expensive and time-consuming option (due to the scale and amount of data generated); whereas when the requisite information is available, a *LeadBuilder* approach will generally be the **fastest and most cost-effective technology**. *FragmentBuilder* is also a cost-effective approach in terms of identifying fragment hits, however, due to their smaller molecular size and weaker potency (typically the range 100-1000 μM), additional time is often required to reach lead optimisation.

Recommendation

Weighing up all these factors, **we will recommend which of these approaches are most applicable to your specific target protein**. Based on this advice, many of our clients decide that their optimum hit identification strategy is to deploy a combination of these technologies to maximise their chances of success, and to give them the greatest possible diversity of chemical starting points. It is also worth bearing in mind that there are often **synergies** to be found in applying more than one of these methods in parallel. For example, protein production for HTS can also be used for structural biology and for fragment screening; and biochemical assay development can drive both HTS and the wet-screening of the virtual hits from a *LeadBuilder* campaign.

	HTS	*FragmentBuilder*	*LeadBuilder*: Ligand-based approach	*LeadBuilder*: Protein-based approach
Quantity of target protein required?	High	Medium	Low	Low
Is the target protein 3D structure required?	No	Yes (to enable a follow-on structure-guided fragment expansion phase)	No	Yes, or structure of close homolog
Are known ligands required?	No	No	Yes	No
Screening by biochemical assay	Yes	Sometimes	Yes	Yes
Screening by biophysical assay	No	Yes	Yes	Yes
Screening by cell/ phenotypic assay	Yes	No	Yes	Yes
Typical number of compounds screened	>100,000	>1,000	500-1,000	500-1,000

The proven expertise and success of our scientists, and the hit identification capability they have developed, gives us a highly differentiated platform that allows you to gain an early edge over your competitors. And, once we have identified hits for your target of interest, we can continue supporting your project, for example by providing a **multi-disciplinary drug-hunting team** to move it seamlessly into the **hit-to-lead** and **lead optimisation** phases.



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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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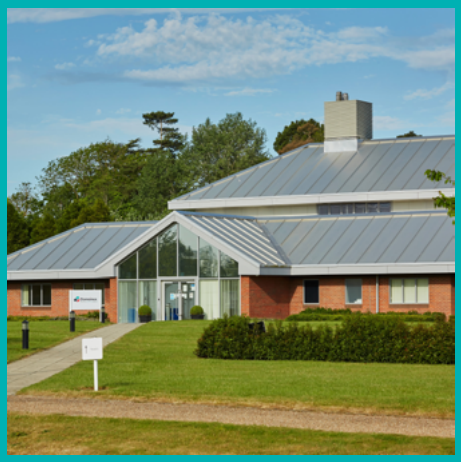

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