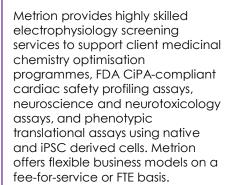




Metrion Biosciences is a specialist ion channel focused CRO delivering a range of high quality drug discovery services.











Domainex delivers highly innovative, integrated drug discovery outcomes from its **Medicines Research Centre** near Cambridge, UK.

Domainex provides protein expression, assay development, virtual and fragment screening to generate hit compounds. Our team of expert computational and medicinal chemists is able to design and optimise these hits. Simultaneously our bioassay scientists (and those from Metrion) and our analytical chemists provide in vitro pharmacology and ADME/tox support for the rapid identification of clinical drug candidates.







CASE STUDY

Identification of antagonists of the TRPA1 ion channel using a LeadBuilder approach



- Located close to Europe's leading bioscience hub in Cambridge, **Domainex** and **Metrion Biosciences** are partnering, so their complimentary expertise can benefit clients by offering a seamless, one stop solution.
- Domainex has an established proprietary virtual screening platform, LeadBuilder, for identifying novel hit matter for structure- or ligand-guided drug discovery projects.
- LeadBuilder has demonstrated success in identifying optimisable hit compounds.
- Metrion Biosciences offers access to a suite of high quality ion channel focused assays. We used our assay and drug discovery expertise to identify genuine TRPA1 antagonists as seed structures for this virtual screen.

As part of their strategic collaboration, Metrion and Domainex identified antagonists of the transient receptor potential cation channel TRPA1, which may have utility for treatment of pain and chronic cough.

Uncertainty of potential antagonist binding sites, led to the initiation of a ligand-based approach to hit ID.



Focus on compounds with desired receptor pharmacology.



Selected three chemotypes, confirmed at Metrion as true antagonists.

Confirmed Antagonist Chemotypes

Hvdra HC-030031

AMG-0902 IC₅₀

compound 31, IC₅₀ 17 nM

Pharmacophores used to search Domainex's NICE (Number of Interesting Chemical Entities) database. Matches shortlisted to give the final diverse set of drug-like compounds for purchase.



NMR structure of tarantula toxin Protoxin-I venom plus additional site-directed mutagenesis data was used to generate four further pharmacophores.



Collated SAR for each lead series. Analysed key pharmacophoric features. Undertook ligand conformational analysis to generate eight pharmacophores.



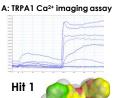
400 compounds assayed against hTRPA1 in a validated Ca2+ imaging assay.

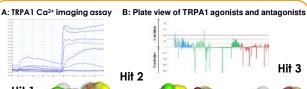


14 hits progressed to IC₅₀ titration; three genuine antagonists were confirmed.



Novel SAR identified around hit compounds.





Hydrogen Bond Acceptor Aromatic/hydrophobe, Shape of matching Shape component of pharmacophore

