e-therapeutics

Network-driven Drug Discovery

SMALL MOLECULE INHIBITORS OF TNFα PRODUCTION

BACKGROUND

Tumour Necrosis Factor alpha (TNFα) is a master regulator of inflammation. Excessive production of TNFα drives the damaging inflammation characteristic of multiple inflammatory diseases.

Inhibition of the effects of TNFα by TNFα blockers is efficacious in the treatment of a number of inflammatory conditions, including rheumatoid arthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis plaque psoriasis, Crohn's disease, and ulcerative colitis.

Our programme focuses on the discovery of small molecule TNFα suppressors which could potentially avoid the inconvenience, unwanted effects and the development of drug-resistance associated with anti-TNFα biologic therapies currently in use.

THE OPPORTUNITY

e-therapeutics has successfully applied its **Network-driven Drug Discovery** (NDD) platform to identify small-molecule inhibitors of TNFα production. The programme yielded four chemically distinct lead series suitable for further medicinal chemistry optimisation. The molecules were discovered using human protein interaction networks and showed activity in primary human immune cells.

e-therapeutics' platform can be used to discover novel and differentiated hits for subsequent hit-to-lead and lead optimisation.

THE APPROACH

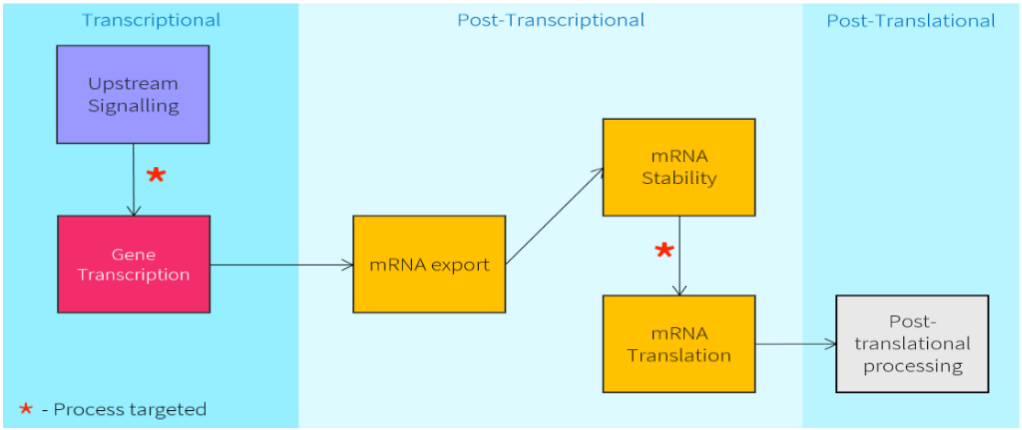
Network-driven Drug Discovery

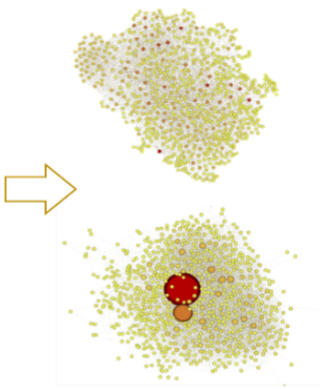
By combining biological expertise with a powerful computer-based platform, we create and analyse protein interaction network models to identify compounds that could effectively target disease. We believe that our approach more realistically reflects the true complexity of disease, with its multiple and often interconnected cellular pathways. In considering the entire pattern of connections between proteins associated with a disease, rather than isolated pathways, we are able to more efficiently select drug-like compounds for screening.

ACTIVITIES

Networks, Compounds, Screening and Medicinal Chemistry Optimisation

Protein interaction networks were constructed based on known regulatory mechanisms for TNFα production: transcription and post-transcriptional regulation; as well as genes differentially expressed in blood and tissues of patients with inflammatory diseases.



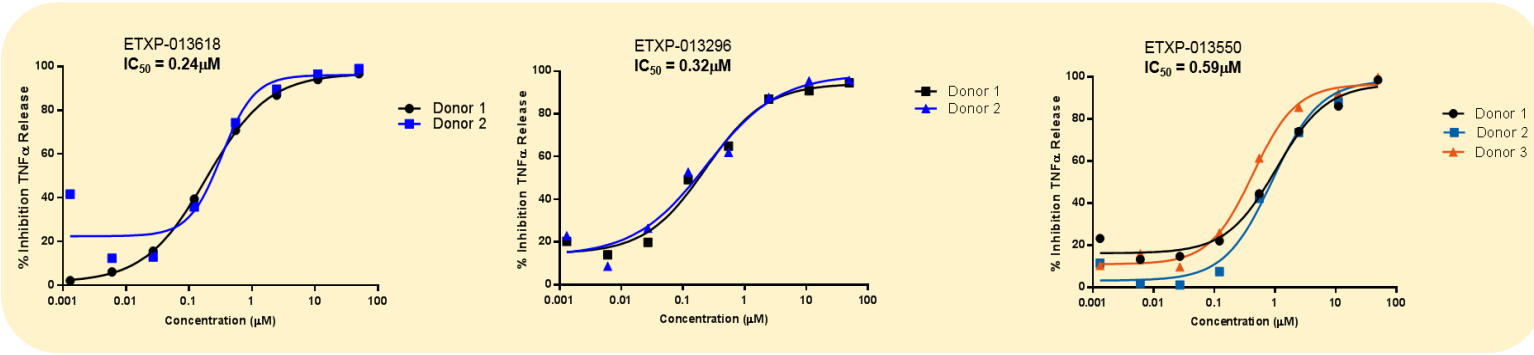


Using our proprietary network analysis tools, 356 compounds with desirable physicochemical characteristics were identified for *in vitro* testing. Compounds were initially screened for inhibitory effects on LPS-induced TNFα release from human peripheral blood mononuclear cells (PBMC). 153 of these compounds matched the selection criteria of IC_{50} < 10μM and no detected cytotoxicity

Assessment of the multiple chemotypes based on synthetic tractability and freedom to operate (FTO) led to the initial prioritization of four chemical series for hit-to-lead medicinal chemistry optimization. Screening of prioritised compounds for activity in a panel of 50 diverse kinases confirmed that they were not kinase inhibitors.

The medicinal chemistry programme subsequently focused mainly on improving the activity of a single chemotype series, yielding molecules with IC_{50} potencies of <500nM.

Although subsequent analysis of the mechanism of action for compounds from this series indicates the involvement of a previously recognised anti-inflammatory target, testing of representatives of the other, as yet unexplored, chemical series indicated distinct mechanisms that may be further explored and improved.



Small molecule TNFα inhibitors: Non-kinase inhibitors, simple chemical structure, low molecular weight, chemical tractability, and positive IP

Please Contact
Dr Ray Barlow, CEO
T +44(0)7387411612
ray.barlow@etherapeutics.co.uk

e-therapeutics
Network-driven Drug Discovery

17 Blenheim Office Park
Long Hanborough
Oxfordshire, UK