The European Lead Factory: A Collaborative Approach to Drug Discovery


For further information contact Frances MacLeod: francis.macleod@ox.ac.uk

The European Lead Factory

The European Lead Factory (ELF) is a public-private drug discovery partnership consisting of 30 organizations throughout Europe that is funded by the Innovative Medicines Initiative (IMI). The goal of the ELF is to enable pre-clinical drug discovery by identifying and validating new biological targets that are amenable to small molecule intervention.

Joint European Compound Library (JECL)

- The JECL is a high quality and diverse compound collection
- The collection is comprised of approximately 300,000 high quality, lead like compounds contributed by seven EFPIA partners
- A public compound collection (PCC) has been added to provide further 200,000 bespoke compounds to the JECL

The European Screening Centre (ESC)

- The ESC screens the target against the JECL to generate a Qualified Hit List (QHL) of up to 50 compounds
- Hit expansion activities are initiated by the medicinal chemistry team to provide an Improved Hit List (IHL)
- Compounds from the QHL or IHL may be used to gain crystallography, selectivity and NDM data
- The programme owner has exclusive rights to the structures and data generated for three years

Case Study 1: New Delhi Metallo-β-Lactamase 1 (NDM-1)

- Antibiotic resistance represents a major threat to global healthcare
- Metallo-β-lactamases (MBLs) are zinc dependent enzymes that catalyse the hydrolysis of β-lactam antibiotics
- NDM-1 is capable of hydrolysing antibiotics of last resort including the carbapenems
- Objective was to discover novel inhibitors of NDM-1
- Building in cross-MLL against VIM and IMP was also highly desirable

Screening

- QHL contained 50 compounds that consisted of 28 structural clusters - 15 were singletons
- Eighteen compounds were selected for reactivity - 13 confirmed activity
- Orthogonal SPr and $^{19}$F NMR assays confirmed binding

QHL to Improved Hit List

- ESC100003 prioritised for further SAR
- 137 analogues prepared
- Plausible inhibitors of NDM-1 developed
- Broad-based NEL activity observed
- Activity improvements of 100-fold vs NDM-1 and VIM-2 and 1000-fold vs IMP-1
- Protein crystallography confirmed binding mode
- Schofield and co-workers working with IMI ENABLE (European Gram-negative Antibacterial Engine) to develop these early stage compounds towards clinical trials

QHL Hit Characterisation

- Target activity: Biochemistry, Cell-based assays
- Target Engagement: Biophysics: SPR, MST, TSA
- Mode of Action: Peptidomimetics, Competitive, Kinetics

Case Study 2: Diacylglycerol Lipase-α (DAGL-α)

- DAGL-α is a serine hydrolase that hydrolyses diacylglycerol into the endocannabinoid 2-arachidonoylglycerol (2-AG) in the central nervous system.
- Enzyme inhibition was hypothesised to have therapeutic benefit for obesity/metabolic disorders and neurodegenerative disorders
- No potent, selective inhibitors of DAGL-α had been described and were required to validate the target

Screening

- 30255 compounds screened in primary assay
- CHL contained 46 compounds consisting of 30 structural clusters, of which 20 were singletons
- Orthogonal ABP profiling used to assess potency and serine hydrolase selectivity in mouse brain proteome

QHL to Improved Hit List: Triazole Urea Series

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