3Discovery platform: boosting hit-identification and lead-optimisation efficiency by merging fragment screening, virtual screening, parallel synthesis and chirally pure chemical space

I. Proietti Silvestri,[1] C. Chu,[1] B. Gill,[1] C. Legros,[2] P. Ratcliffe,[3] C. Swain[1]

[1] LCC, Chemistry Department, University of Liverpool, Crown Street, Liverpool, UK

[2] Eurofins Discovery, Celle-l'Evescault, 86600, France

[3] Eurofins Integrated Discovery UK Ltd, Essex, CM50GS, UK

Fragment-based drug discovery (FBDD) is a validated method for hit-identification which has driven tens of candidates entering the clinical stage and the approval by the FDA of several drugs [1]. Originally, fragment libraries were populated by low-complexity, sp^2-rich compounds but there is a growing interest in adding more 3D character to existing collections to increase molecular diversity and improve properties such as solubility and off-target activity.

LCC designed a 3D-rich fragment library of >1000 Ro3 compliant and highly developable compounds. Design principles, properties and analysis of the coverage of the chemical space will be presented. The fragment library includes >40% of enantiomerically pure compounds and is chemically-poised, which allows hits to be easily modified by parallel chemistry.

One of the key challenges in a FBDD campaign is the development of a fragment hit into a lead-like compound. LCC's 3Discovery lead-like virtual library is enumerated using LCC's 3D-rich poised fragment library compounds and, as such, it enables rapid fragment elaboration and hit expansion through parallel synthesis. These virtual compounds are available from well validated chemistry and in stock reagents, ensuring timely and efficient synthesis in the parallel synthesis lab. 3Discovery virtual library can be mined using a variety of 2D and 3D similarity scoring techniques, or used as an input for docking or de novo design strategies. The presence of single enantiomers and enantiopairs with absolute stereochemistry already determined is highly advantageous for rapid data analysis and hit follow-up studies.

Preliminary data from a case study on a kinase target will be presented. The fragment screening generated hits that were clustered into different classes. The initial round of hit expansion identified several related analogues, validating the initial fragment hit and offering vectors for further exploration.

[1] Erlanson, D., Fesik, S., Hubbard, R. *et al.* Twenty years on: the impact of fragments on drug discovery. *Nat Rev Drug Discov* , **15**, 605–619 (2016)