IDENTIFICATION AND VALIDATION OF NOVEL AND TRACTABLE PIM3 STARTING POINTS AND THEIR OPTIMISATION

Ilaria Proietti SilIlvestri[1] ; Paul Ratcliffe, PhD[2] ; Simon Pettit[2] ; José Manuel Villalgordo-Soto, PhD[3] ; Philippe Dupuis, PhD[4] ; Celine Legros, PhD[4].

(1) Liverpool ChiroChem Limited, Liverpool UK | (2) Eurofins DiscoveryOne, Ongar UK | Eurofins Villapharma Research, Murcia ES | (4) Eurofins Cerep, Celle l'Evescault FR.

The PIM serine/threonine kinases (PIM1/PIM2/PIM3) are downstream effectors of ABL, JAK2 and Flt-3 oncogenes and are required for tumorigenesis. Overexpression has been reported in haematological and solid tumours, myeloma, lymphoma, leukemia and adenocarcinoma. The first generation of PIM inhibitors to make it to the clinic such as SGI-1776, AZD1208 and PIM447 are known to be pan-PIM inhibitors, while the aim of this project was to identify novel & selective PIM3 inhibitors. To this end, HTS, Fragment and Virtual Screening approaches were employed to rapidly generate novel chemical matter which were assessed for their activity against PIM3 using a robust ADP-Glo assay.

Confirmed hits, from the HTS, were subsequently advanced into two orthogonal assays, a label free mass spectrometry based activity assay, and the second a cellular target engagement assay. Pleasingly, a good correlation between all three screening methodologies was observed. The confirmed hits were clustered, prioritised, and early ADME data generated. A set of clusters were selected for further optimisation based upon activity in the three assays, physico-chemical properties, novelty, and overall tractability.

A combined fragment library comprising the fully complementary Eurofins diversity and LCC's 3D-rich poised fragment libraries was employed. Fragments hits from the initial screen were confirmed by two orthogonal assays as described for the HTS hits. These fragment hits came from several unrelated structural classes, the majority of which were devoid of traditional hinge binding motifs. In a next step, taking advantage of LCC's 3Discovery virtual library, of which LCC's fragments represent a critical component, rapid fragment elaboration and hit expansion through parallel synthesis was enabled.

1. Swords et al. Curr. Drug Targets 2011, 14, 2059-2066