Abstract

Potential therapeutic targets are becoming ever more challenging, with limited literature precedent and unknown druggability. Binding pockets may be unknown and with no tool compounds available, activity-based screening approaches are difficult to develop. Embarking upon and investing in a full drug discovery campaign for such targets is therefore high risk.

Here, we describe how AstraZeneca has used DNA-Encoded Library (DEL) screening, prior to project investment, to further our understanding of these targets, asses their tractability and de-risk further investment. 20 targets were selected based on 3 criteria: priority to therapy areas; suitability for DEL screening; and feasibility of reagent generation. Over 30 protein constructs were designed, tested, and purified.

Successfully purified proteins were then subjected to rigorous quality control measures to determine suitability for DEL Screening. Suitable targets were screened in parallel to identify binders and this parallel screening approach allowed unrelated targets to act as off-target controls for each other. Data was analysed and representative compounds were resynthesized off-DNA before nanoDSF and SPR approaches were employed for hit confirmation. Here, we present the results from this pilot, discussing how we have increased confidence in target druggability, identified potential tool compounds for assay development and hope to positively influence investment decisions.