Criteria for New Compound Intake into preclinical probes sublibrary (REPO3)

Required:

- Structure is known and shareable
- Target(s) identified
- Evidence of activity in cell based assay

With your submission please provide a rationale for nomination:

- Is this compound targeting a mechanism not already represented in the collection OR is it significantly better than previous probe molecules?
- Why should it be included in the library based on the list of below criteria?

    - Biophysical/ biochemical activity demonstrated
    - Cellular target engagement biomarker modulation - modulates endpoint closely related to target engagement in cells
    - Selectivity / Specificity - Chemical matter preferentially modulates
    - Kinetic aqueous solubility >100 mM- Important for running in vitro assays and for in vivo delivery of drug
    - Stability in hepatic enzymes
        - Microsomal stability: CLint < 30 µl/min/mg - Liver microsomes contain membrane bound drug metabolizing enzymes. This assay measures compound clearance and can give an idea of how fast it will be cleared out in vivo
        - Hepatocytes stability: < 10 µl/min/million cells
    - Permeability:
        - MDCK II WT cells - MDCK cells transfected with the MDR1 gene, which encodes the efflux protein P glycoprotein (P-gp). An important efflux transporter in many tissues including intestine, kidney and brain, P-gp can be used to predict intestinal and brain permeability.
            - Passive permeability - Papp A-B: >1 x 10-6 cm/sec
        - Caco-2 cells - colon carcinoma cell line used to estimate permeability across intestinal epithelium, important for drug absorption from gut
            - Papp A-B: >0.5 x 10-6 cm/sec, Efflux ratio < 2
    - Hepatotoxicity - Human HepG2 cells can act as a surrogate for effects of toxicity on human liver, an important cause of drug failure in the clinic.
        - No effect at 50 x IC50 or EC50
    - Cellular Cytotoxicity (CC50)
        - limited non-specific cytotoxicity in non-target and/or target cell types of indications, reduce the likelihood of cellular toxicity in vivo
        - IC50 PD marker / CC50 target cell types ≥ 2-5x