1. Introduction

- The Hedgehog (Hh) pathway is an evolutionarily conserved signalling pathway which plays a key role in regulating embryonic development and tissue regeneration\(^1\). The improper activation of the pathway can lead to malignancy\(^2\) (particularly basal cell carcinoma, medulloblastoma, pancreatic, prostate and small cell lung cancer) and is also observed in fibrosis\(^3\), graft-versus-host disease\(^4\) and angiogenic disorders.
- The majority of pharmaceutical efforts to modulate the pathway in cancer have focused on the GPCR-like signal transducer Smoothened (SMO)\(^5\).
- Although SMO inhibitors\(^6\) are effective in the clinic, treatment-driven tumour evolution results in the emergence of drug-resistance and this restricts the overall impact of these molecules\(^7\).
- There is an unmet need for a new class of the Hh signaling pathway modulators that would overcome existing SMO-associated drug-resistance.
- e-Therapeutics have applied their network-driven drug discovery (NDD) platform to identify new pathway inhibitors which retain activity in resistant cells.

2. Compound Screening

- 1146 compounds screened
- 63 hit compounds
- 144 compounds active at <10µM in both cell lines with no cytotoxicity
- Multiple chemotypes (CTs) were recognized from NDD approach
- Based on SAR trends, existing IP and synthetic tractability assessment, four chemotypes were progressed for hit to lead optimization

3. Hit to Lead Medicinal Chemistry Campaign

- Compound cascade
  - Hh cellular activity / SMO binding
  - in vitro ADME screen (MLMs, MDOX, PPB, solubility and chronolog)
  - in vivo mouse PK (IV and PO)
  - >900 compounds synthesized
  - 3 patent applications filed

4. Representative Compound with Oral Bioavailability

5. No Loss of Activity in Vismodegib-resistant Cells

- The potency of Compound 8 is unaffected by tumour-associated SMO mutations

6. Literature

- The e-Therapeutics NDD platform technology provided a set of 1146 compounds from commercial sources, which were tested at Aurelia Bioscience for inhibition in orthogonal Hh cellular assays in the absence of SMO binding. 63 compounds met the HIT criteria.
- A subsequent medicinal chemistry campaign generated orally bioavailable compounds with potency in cellular assays equivalent to Vismodegib, superiority to Vismodegib in associated Vismodegib-resistant cells and activity in xenograft models.
- The outcome of the project in generating an orally bioavailable Hh inhibitor with in vivo efficacy confirms the validity of the NDD approach.

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