**BACKGROUND**

**Hedgehog Pathway in Cancer**

The Hedgehog pathway is activated in cancers through deletions, mutations and changes in DNA methylation of multiple key components and hence has attracted attention for therapeutic intervention.

Initial pharmaceutical approaches have focused on targeting the GPCR-like, SMO protein. The most advanced of these projects (Vismodegib & Sonidegib) have received approval for use in locally advanced and metastatic basal-cell carcinoma.

Although the initial responses are impressive, resistance is a frequent concern with the appearance of mutations in the target and clonal selection of cells with changes elsewhere in the pathway.

The existing small molecule inhibitors have validated the pathway as a target, but there is an opportunity to improve the clinical value if approaches can be found that reduce the occurrence of resistance.

**THE OPPORTUNITY**

e-Therapeutics have applied their **Network-driven Drug Discovery** process to identify and progress novel inhibitors of tumour Hedgehog pathway activity.

The compounds are active against cells that are resistant to the approved agent, Vismodegib. They demonstrate superior performance *in vivo* and appear to have a novel mechanism of action.

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**E-THERAPEUTICS APPROACH**

**Network-driven Drug Discovery**

By combining biological expertise with a powerful computer-based platform, we create and analyse network models of disease to identify the proteins that could be most effectively targeted to treat the disease.

We believe that our approach more realistically reflects the true complexity of disease, with its multiple and often interconnected cellular pathways. In considering the entire pattern of connections between proteins associated with a disease, rather than isolated pathways, we are able to more efficiently select the very best drug-like compounds for screening and for subsequent progression in medicinal chemistry and pre-clinical testing.
ACTIVITY
Screening and Medicinal Chemistry Optimisation

Thirty-three networks were constructed based upon data from multiple sources exploring pathway function and activity. From these, fourteen were selected for analysis and identified a compound set of 1146 for testing.

Screening revealed 63 compounds that matched the hit criteria (potency <10µM, no toxicity, no binding to SMO) across more than 20 chemotypes. Three structural classes were selected for medicinal chemistry exploration based upon their potency and selectivity, chemical tractability and a positive assessment of their IP status.

A medicinal chemistry programme improved potency to the levels of the clinically approved agents and optimised pharmacokinetic properties.

The compounds’ cellular activity is not directly related to affinity for SMO and they demonstrate superior activity in Vismodegib-resistant cell lines. Three representative compounds have demonstrated in vivo potency at least equivalent to Sonidegib in a Calu-6 xenograft pharmacodynamic model.