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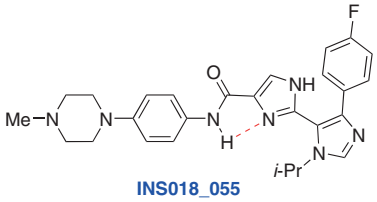
A Small-Molecule TNIK Inhibitor Targets Fibrosis in Preclinical and Clinical Models
Nat. Biotechnol. **2024**, DOI: 10.1038/s41587-024-02143-0.

Using Artificial Intelligence to Identify TRAF2- and NCK-Interacting Kinase as a Target for Fibrosis



INS018_055

Significance: Artificial intelligence (AI) and machine learning (ML) are being broadly adopted and applied in drug design. In this article, Insilico Medicine used their proprietary PandaOmics program to analyze multiomic data sets abstracted from patient samples combined with an analysis of the scientific literature to identify TRAF2-and NCK-interacting protein kinase (TNIK) as a potential target for the treatment of fibrosis, particularly idiopathic pulmonary fibrosis (IPF) for which the composite data suggested a close correlation. The proprietary Chemistry42 design platform was used to identify precursors to INS018_55 which were optimized for ADME properties. This article provides an interesting contemporary paradigm of applying AI to both the identification of disease-relevant targets and the design of new molecular entities in a process that was completed in just 18 months. The molecule affects both fibrotic and inflammatory pathways, suggesting a broader clinical application. Although INS018_55 is active in animal models of IPF, efficacy in a clinical setting is required to close the loop, studies that are ongoing following a successful Phase 1 clinical trial.

Comment: INS018_055 resulted from the application of Chemistry42, a structure-based drug design workflow driven driven by AI. The ATP-binding pocket was analyzed to facilitate the identification of compounds capable of establishing H-bonds with the NH of Cys108 of the TNIK hinge, with amide C=O of INS018_55 fulfilling that role. An intramolecular H-bond between the amide NH and pendent imidazole stabilizes a planar conformation. A hydrophobic parameter was applied to optimize occupancy of the back cavity of the enzyme, defined by Met105, Leu73, Leu103, Ala52 and Val104. Whilst the first iterative rounds of design identified inhibitors with nanomolar potency, optimization of several ADME properties that included CYP inhibition, poor solubility and high clearance was required to identify INS018_55. INS018_55 exhibited an IC_{50} of 31 nM toward TNIK with high kinase selectivity, although other kinases (ALK4, TGFBR1 and DDR1) that were inhibited at <1 µM were also implicated in fibrotic conditions. INS018_55 was active in a murine model of bleomycin-induced lung fibrosis, reducing markers by 50% at doses of 3 mpk BID and >75% at 10 and 30 mpk BID. An aerosolized formulation provided lung efficacy in the absence of systemic exposure when mice were treated with drug for 30 min/d for 21 days. In a murine model of kidney fibrosis (unilateral ureteral obstruction, UUO), INS018_55 ameliorated pathology at doses of 3, 10 and 30 mpk BID.

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Category
Innovative Drug Discovery and Development

Key words
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TRAF2- and NCK-interacting kinase inhibitor
anti-fibrotic activity

Synfact of the Month