A Novel Cancer Therapy Targeting KIF18A with AI-Designed Compound

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Insilico Medicine, a leader in AI-driven drug discovery, has developed a new preclinical candidate, ISM9682, aimed at treating advanced solid tumors. This innovative compound, designed to inhibit the mitotic kinesin KIF18A, shows potential in combating cancers characterized by chromosomal instability (CIN), including high-grade serous ovarian cancer (HGSOC), triple-negative breast cancer (TNBC), and non-small cell lung cancer (NSCLC).

CIN, a common feature of various cancers, results from errors in chromosome segregation during mitosis. KIF18A, a key player in this process, has emerged as a promising target for cancer therapy. Research indicates that inhibiting KIF18A can trigger the mitotic checkpoint, leading to the selective eradication of CIN-affected cancer cells.

ISM9682 stands out due to its high selectivity and potential as a leading small molecule inhibitor of KIF18A. The compound was conceived using Insilico's Chemistry42, a generative chemistry engine part of the company's Pharma.AI platform. Through this platform, the research team designed novel macrocyclic structures targeting KIF18A and, after synthesizing and testing around 110 compounds, selected ISM9682 as the preclinical candidate.

Preclinical evaluations have revealed ISM9682's broad anti-tumor efficacy across various CIN cell lines associated with HGSOC, TNBC, and NSCLC. Notably, the compound has demonstrated significant in vivo efficacy in multiple cancer-derived xenograft (CDX) models, alongside favorable oral bioavailability and safety profiles. Further investigations will assess ISM9682's combinatory potential with other mitotic/DNA repair inhibitors, such as Olaparib, and its application in a wider range of indications.

Feng Ren, PhD, co-CEO and Chief Scientific Officer of Insilico Medicine, highlighted the significance of targeting KIF18A for CIN cancers and the promising features of ISM9682, discovered through the innovative use of Chemistry42. As the compound progresses through IND-enabling studies, the team anticipates advancing it to clinical trials.

Insilico Medicine's approach combines AI technologies with human expertise to develop novel therapeutics. Since 2021, the company has nominated 17 preclinical candidate compounds (PCCs),
advancing five to clinical development stages and securing major global out-licensing deals, including partnerships with Exelixis and Menarini in 2023. The recent update to the Pharma.AI platform introduces the Copilot feature, enhancing the integration of large language models with proprietary AI frameworks, marking a significant step forward in drug discovery and development.

READ MORE: Insilico Medicine’s Generative AI Patent Provides Advantage in AI Drug Discovery Race

Insilico Medicine operates globally, focusing on leveraging generative AI to bridge the gap between biology, chemistry, and clinical trials. The company aims to revolutionize the discovery and development of drugs for a spectrum of diseases, including cancer, fibrosis, immune disorders, central nervous system conditions, infectious diseases, autoimmune diseases, and aging-related conditions.

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