



A small-molecule TNK inhibitor targets fibrosis in preclinical and clinical models

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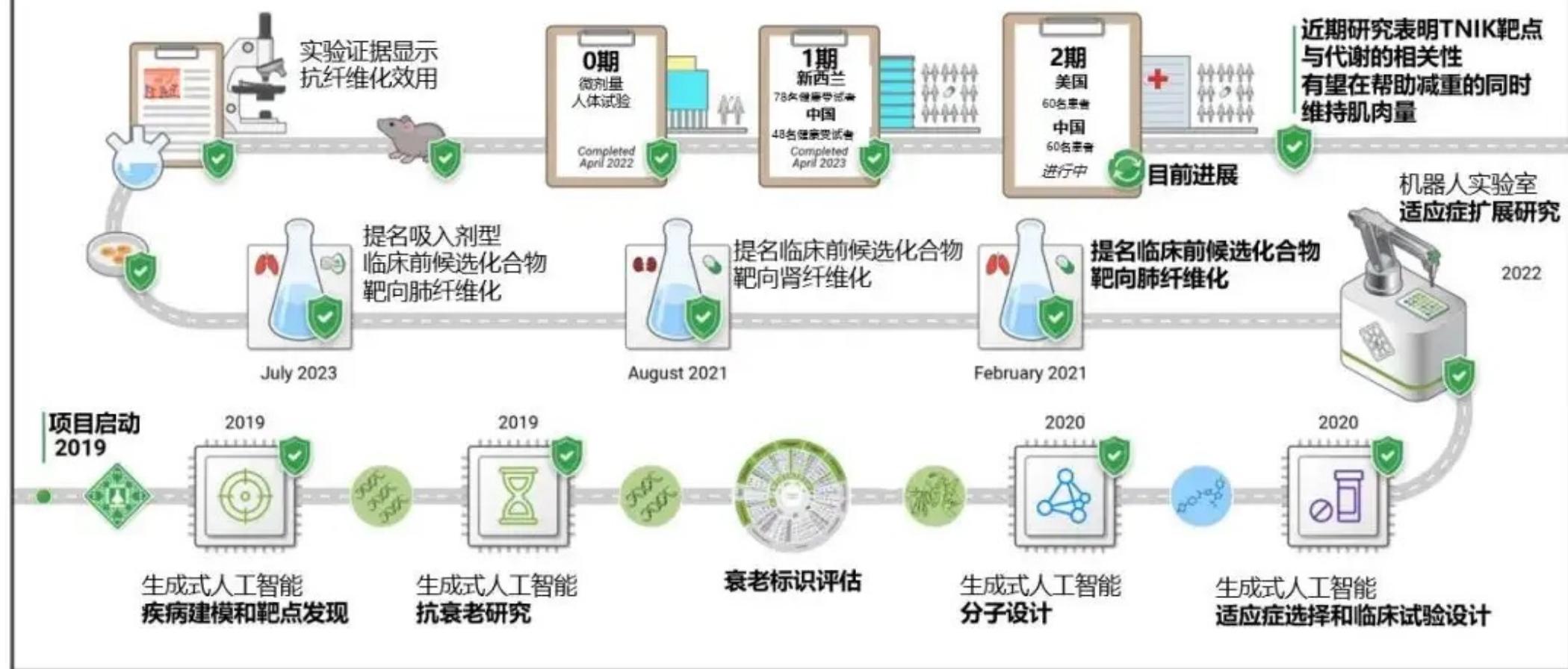


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AI驱动抗纤维化TNIK抑制剂研发流程



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PandaOmics

Discover and Prioritize

Novel Targets

Enabling multi-omics target discovery and deep biology analysis engine to considerably reduce required time

Chemistry42

Generate

Novel Molecules

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inClinico

Design and predict

Clinical Trials

Predict clinical trials success rate, recognize the weak points in trial design, while adopting the best practices in the industry

AI 驱动的药物治疗管线的开发，包括内部管线以及外部合作提供药物研发服务

PandaOmics: An AI-Driven Platform for Therapeutic Target and Biomarker Discovery

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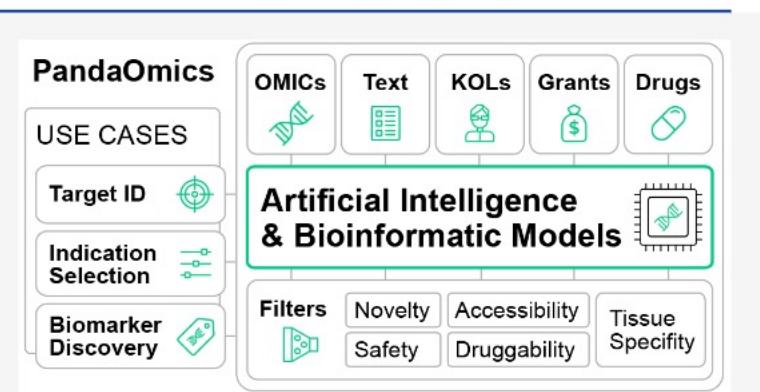
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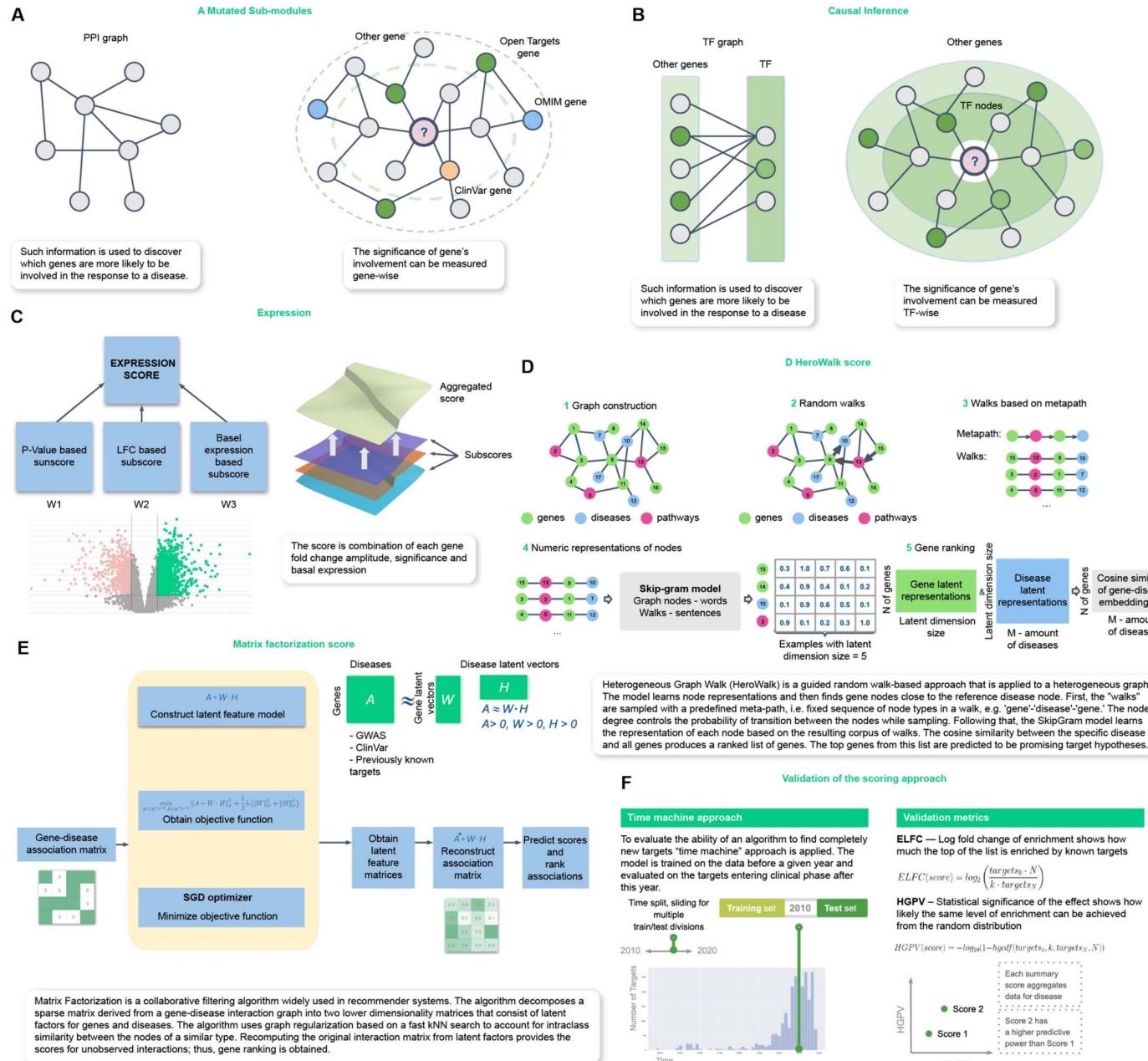
Article Recommendations

Supporting Information

ABSTRACT: PandaOmics is a cloud-based software platform that applies artificial intelligence and bioinformatics techniques to multimodal omics and biomedical text data for therapeutic target and biomarker discovery. PandaOmics generates novel and repurposed therapeutic target and biomarker hypotheses with the desired properties and is available through licensing or collaboration. Targets and biomarkers generated by the platform were previously validated in both *in vitro* and *in vivo* studies. PandaOmics is a core component of Insilico Medicine's Pharma.ai drug discovery suite, which also includes Chemistry42 for the *de novo* generation of novel small molecules, and inClinico—a data-driven multimodal platform that forecasts a clinical trial's probability of successful transition from phase 2 to phase 3. In this paper, we demonstrate how the PandaOmics platform can efficiently identify novel molecular targets and biomarkers for various diseases.



The PandaOmics target-discovery platform



network neighbors,
mutated submodules,
causal inference,
pathways,
interactome community,
expression,
heterogeneous graph walk
matrix factorization scores.

Matrix Factorization is a collaborative filtering algorithm widely used in recommender systems. The algorithm decomposes a sparse matrix derived from a gene-disease interaction graph into two lower dimensionality matrices that consist of latent factors for genes and diseases. The algorithm uses graph regularization based on a fast KNN search to account for intraclass similarity between the nodes of a similar type. Recomputing the original interaction matrix from latent factors provides the scores for unobserved interactions; thus, gene ranking is obtained.

products

候選產品	靶點	機制	適應症	發現	IND準備	開發階段		
						1 期	2 期	3 期
★ ISM001-055	TNIK	EMT、FMT、成纖維細胞巨噬細胞活化	特發性肺纖維化(IPF) ⁽¹⁾	中國(NMPA)、美國(FDA)				
			腎纖維化(KF)					
			IPF(吸入)					
ISM3091	USP1	合成致死	BRCA-突變體癌	美國(FDA)				
ISM3312	3CL ^{pro}	病毒複製	COVID-19	中國(NMPA)				
ISM8207	QPCTL	免疫調節	實體瘤和血液瘤	與復星合作開發				
ISM4808	PHD1/2	EPO誘導及鐵利用率	腎性貧血					
ISM5411		上皮完整性及抗炎	炎症性腸病(IBD)					
ISM6331	TEAD	細胞增殖與存活	實體瘤					
ISM5939	ENPP1	免疫調節	實體瘤					
ISM5043	KAT6	表觀遺傳學	ER+/HER2- 乳腺癌					
ISM3412	MAT2A	合成致死	MTAP ^{-/-} 癌					
ISM4312A	DGKA	免疫調節	實體瘤					
未披露	CDK12	腫瘤細胞增殖	實體瘤					
未披露	cMYC	腫瘤細胞增殖	實體瘤					

★ 核心產品

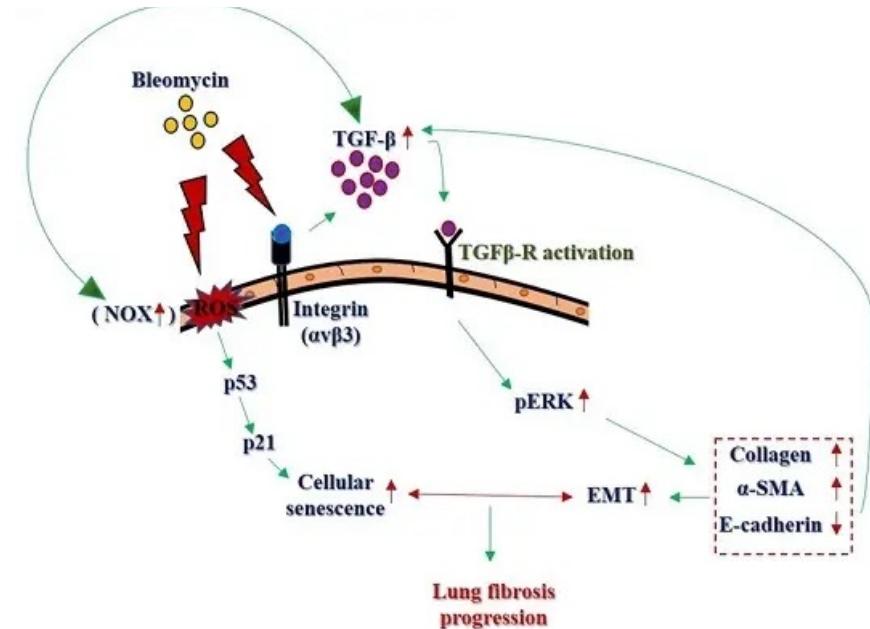
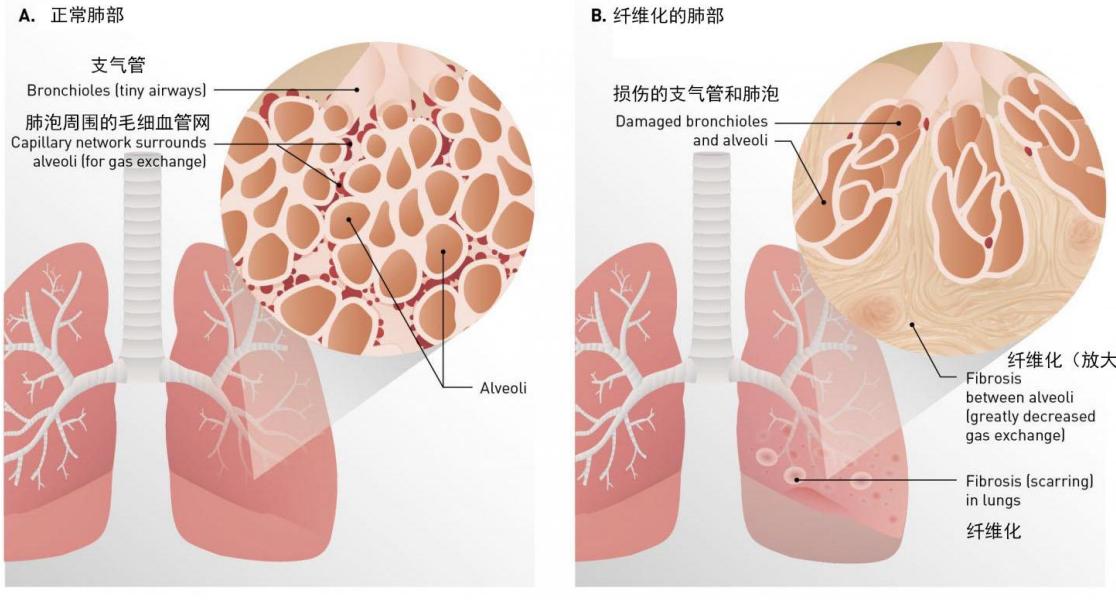
纖維化

腫瘤學

免疫學

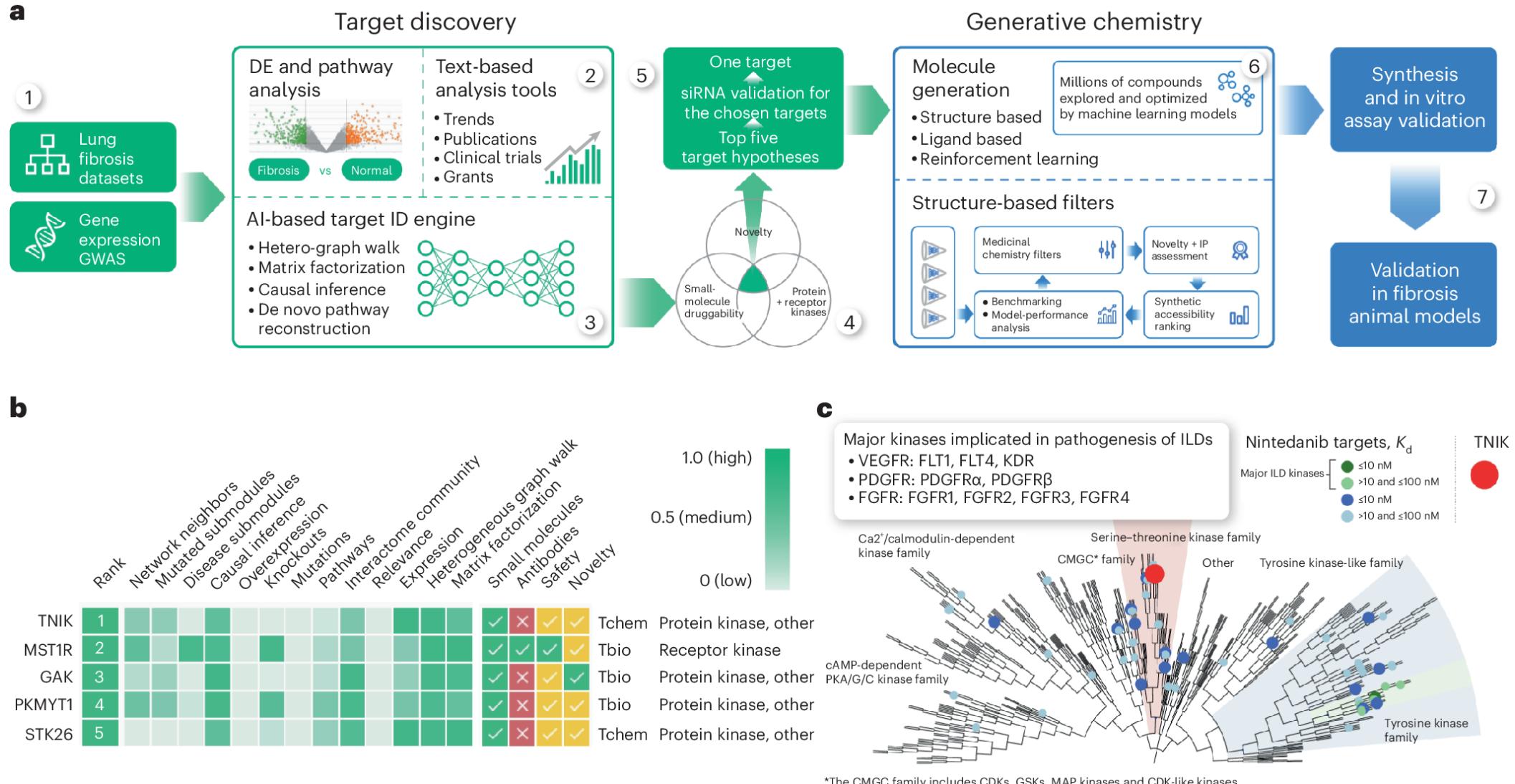
其他

Idiopathic Pulmonary Fibrosis, IPF



Current targeted treatment options for IPF are limited to nintedanib and pirfenidone

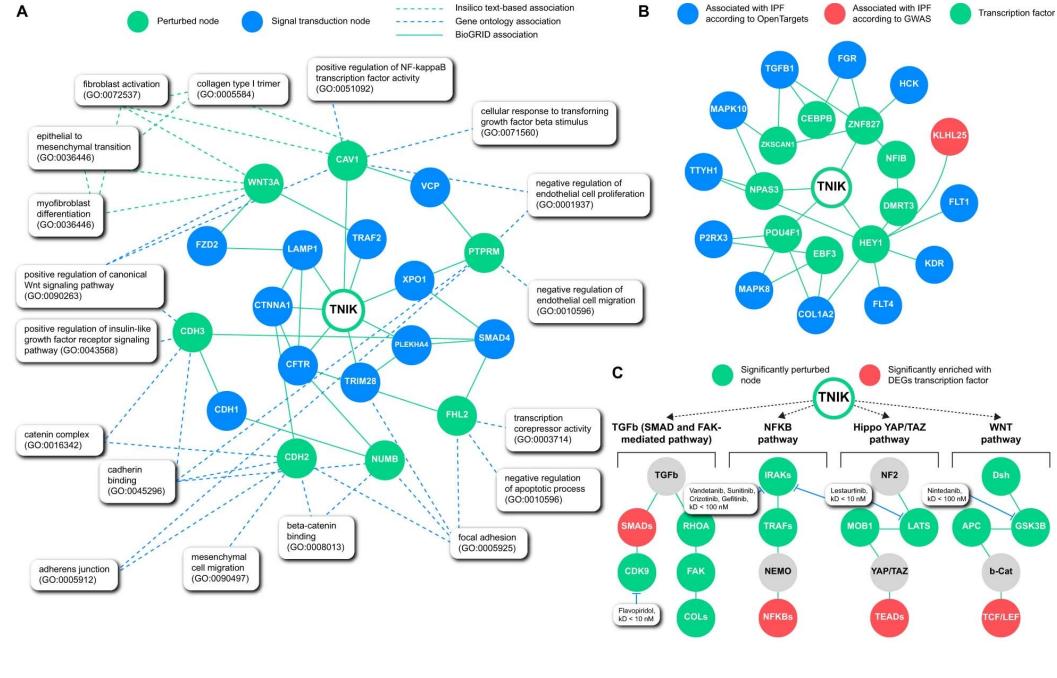
AI-augmented pipeline for target discovery



TRAF2- and NCK-interacting kinase (TNIK)

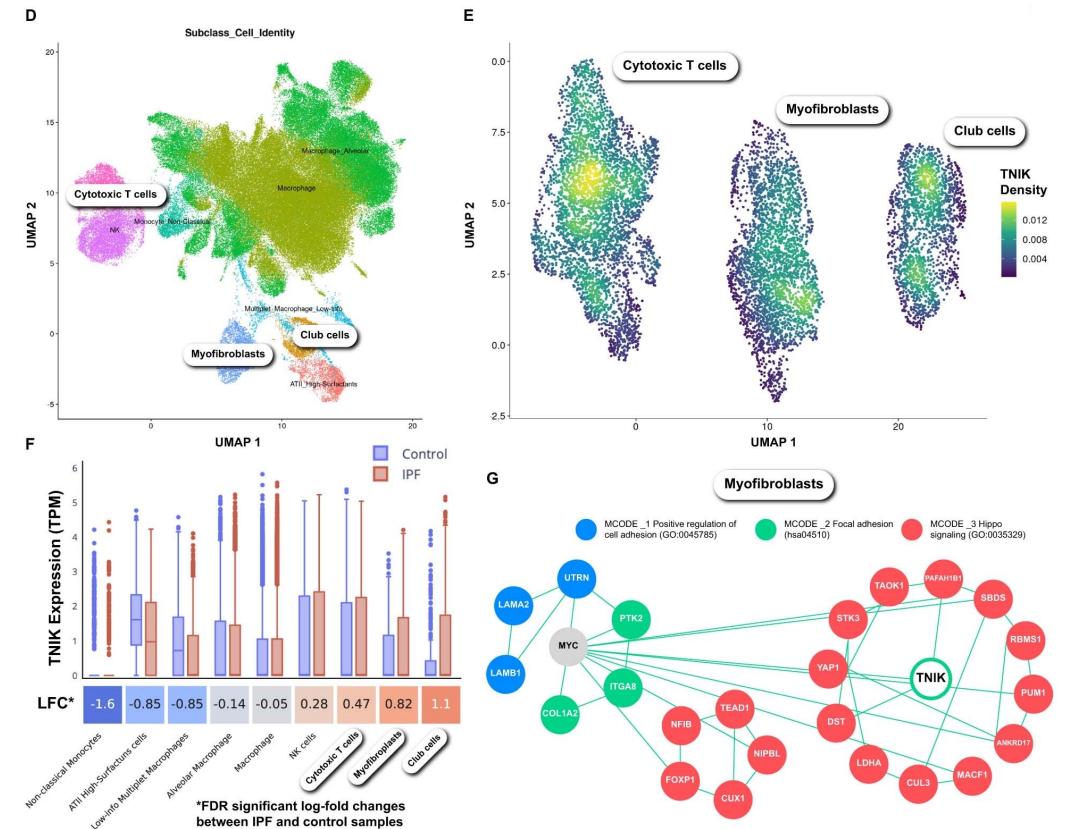
Transparency analysis

The interactome community transparency



AI-powered de novo pathway-reconstruction tool,

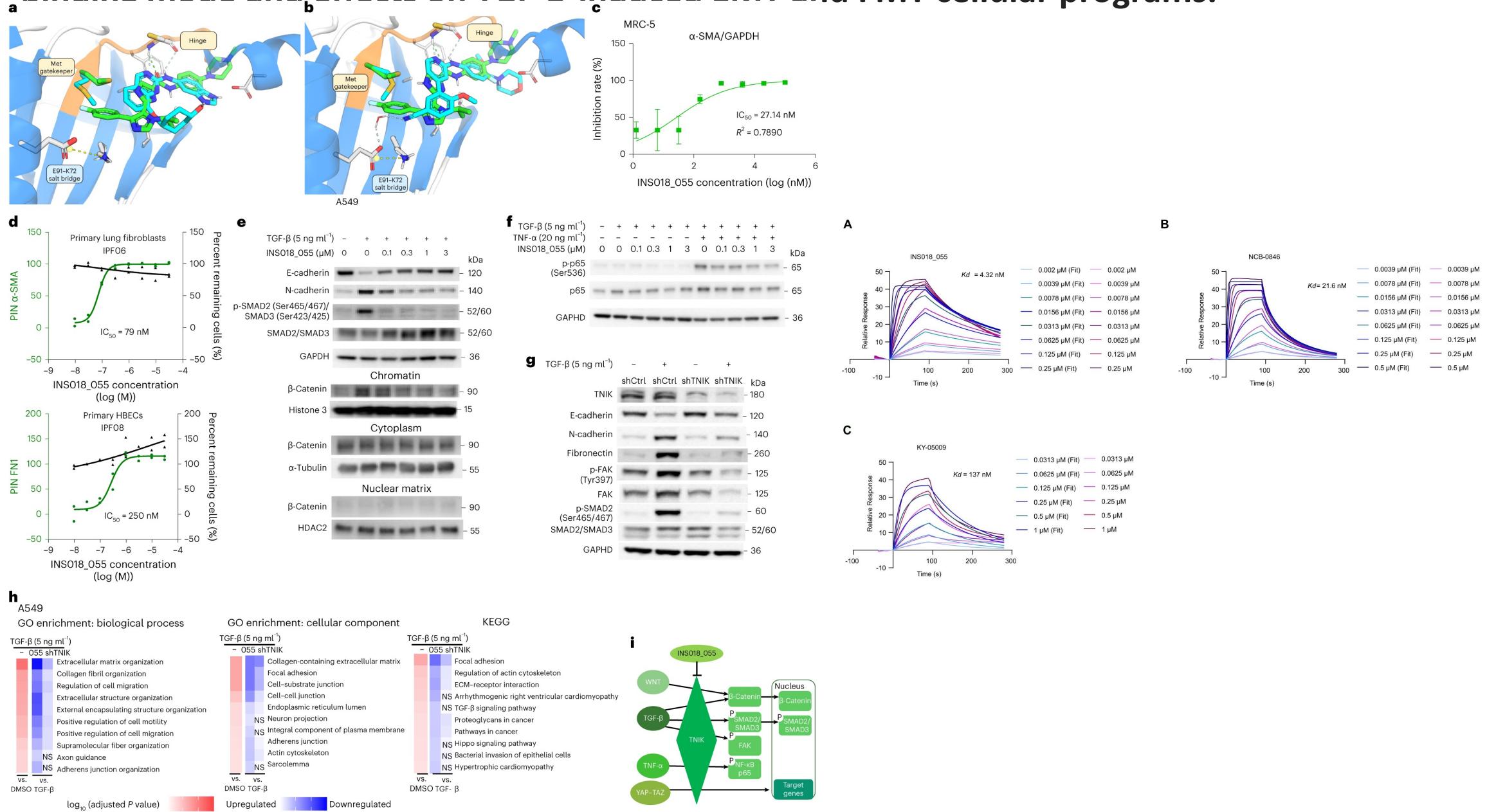
Causal inference transparency



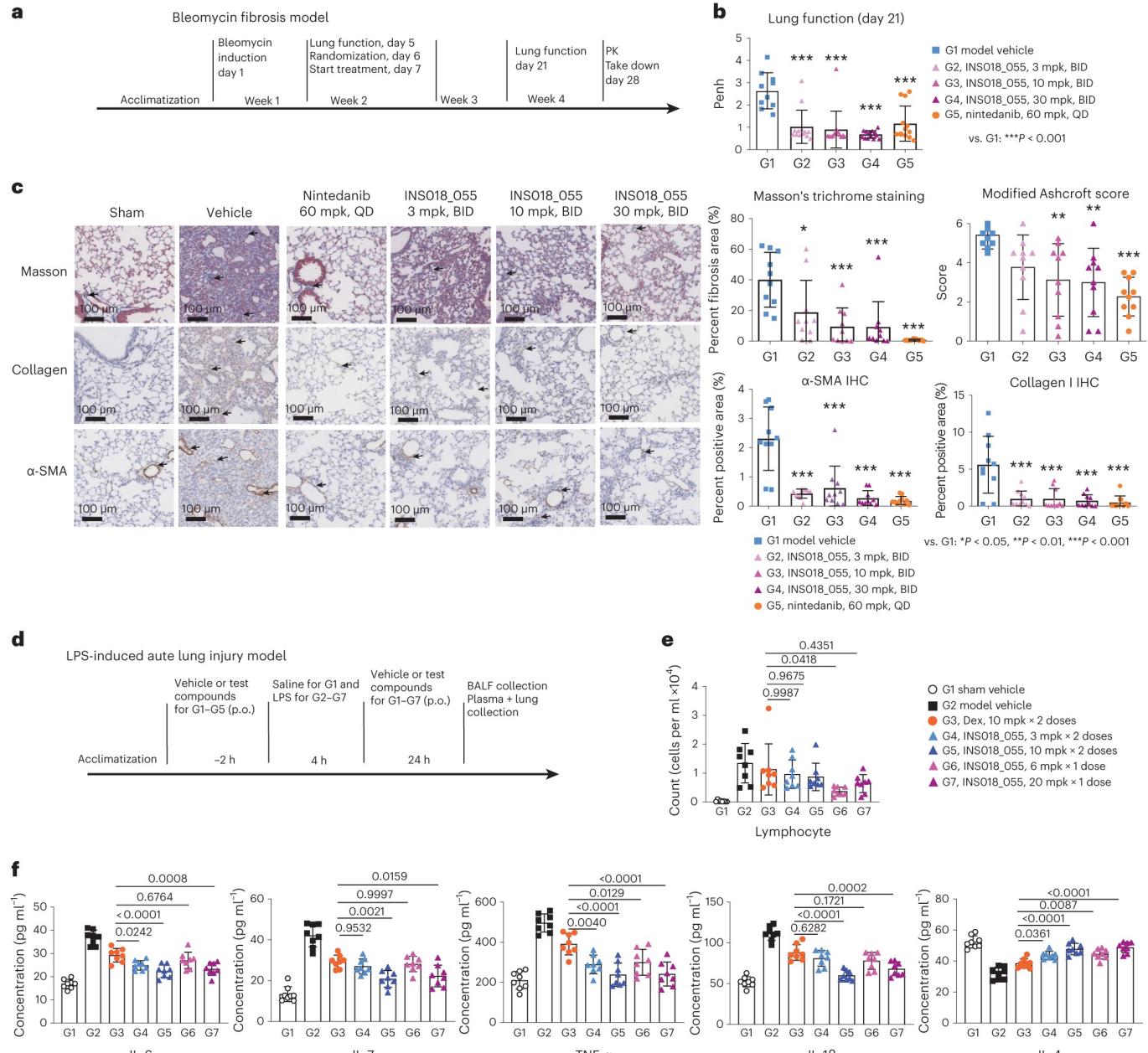
The interactome community transparency revealed that TNIK inhibition is connected to multiple biological processes known to be important for fibrosis progression

Inhibiting TNIK primarily activates Hippo signaling and, consequently, downregulates YAP–TAZ

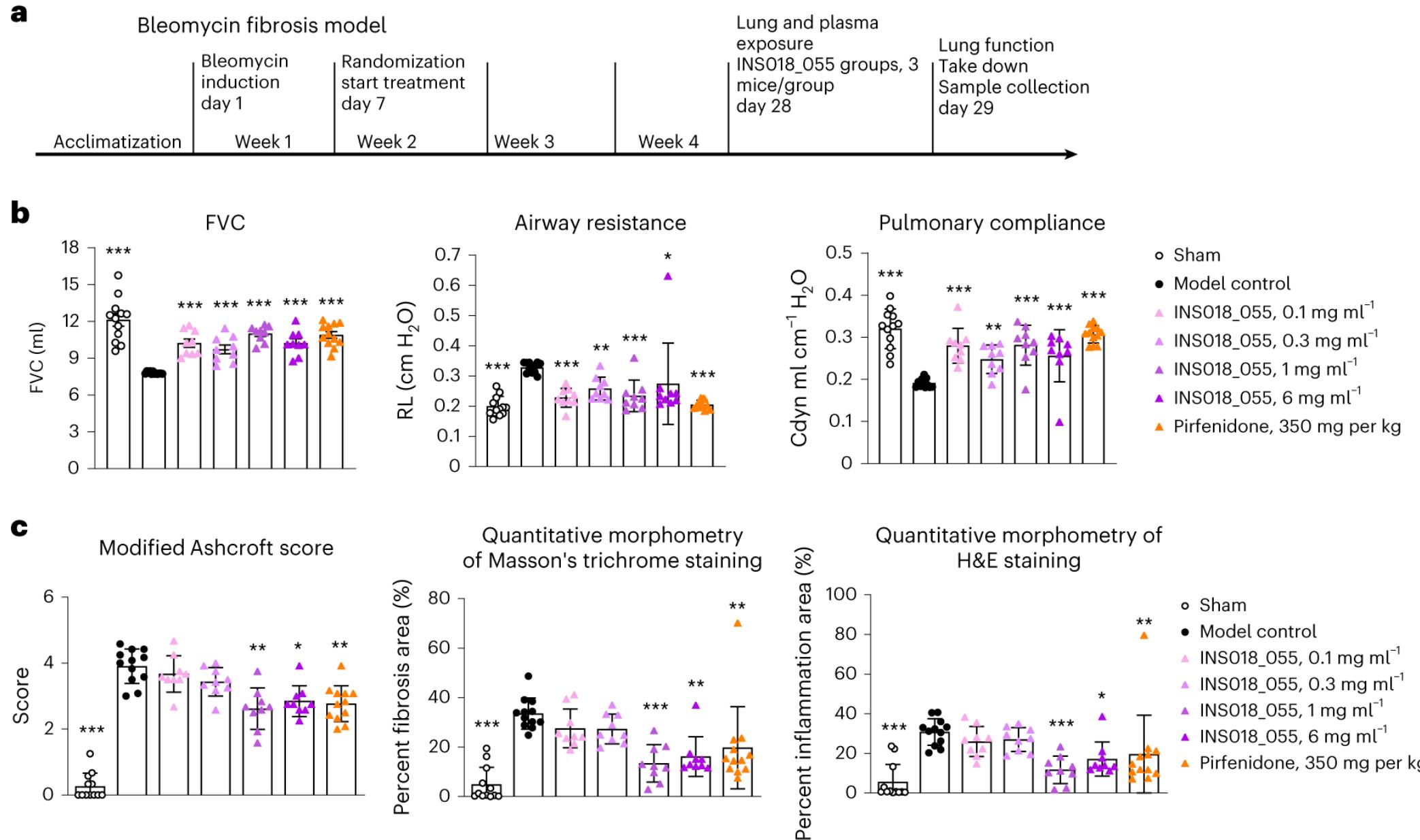
Architectural superposition of TNIK inhibitor structures with the predicted INS018_055-binding mode and effects on TGF- β -induced EMT and FMT cellular programs.



In vivo effects of INS018_055 treatment in mouse models of lung diseases.

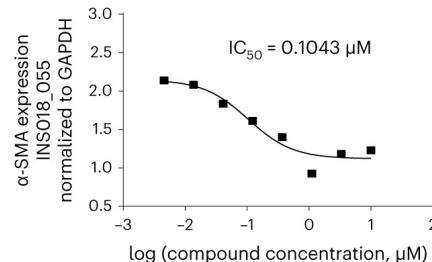
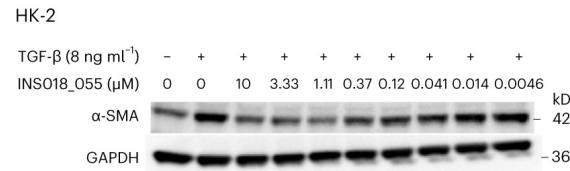


In vivo effects of INS018_055 treatment by inhalation in rat models of lung fibrosis.

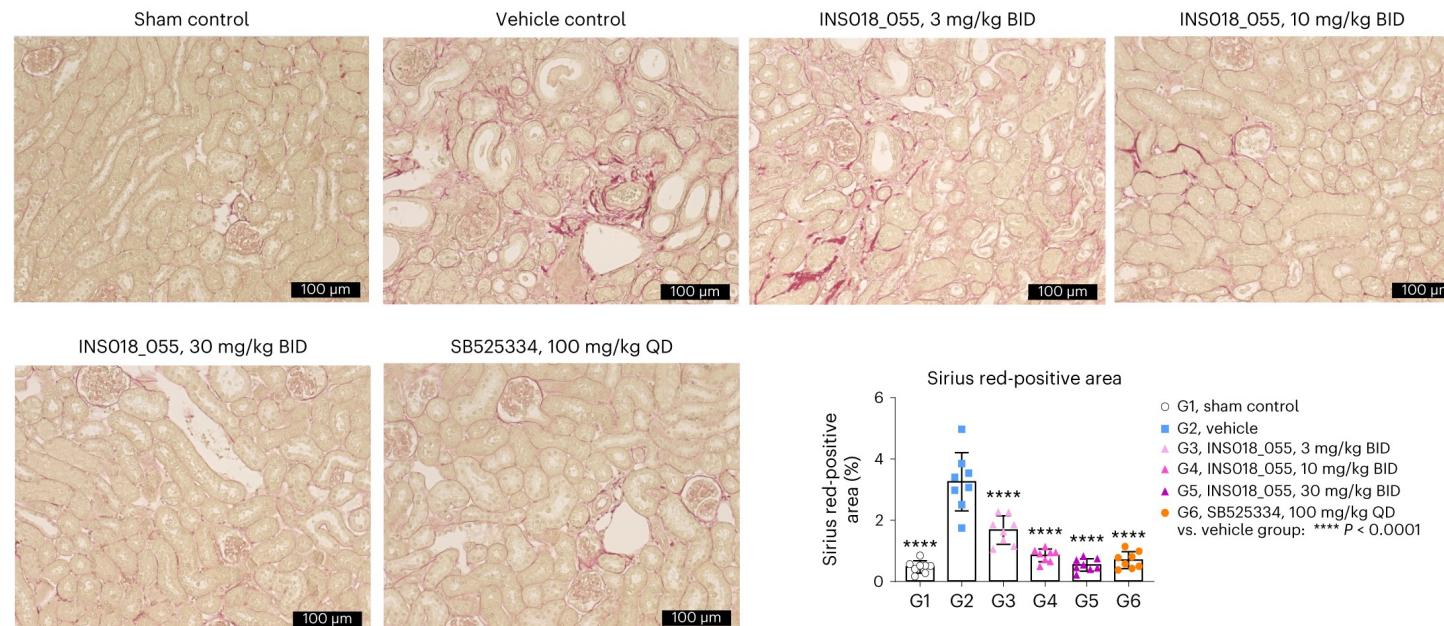


In vitro and in vivo studies on the effect of INS018_055 on kidney cells and the mouse model of kidney fibrosis.

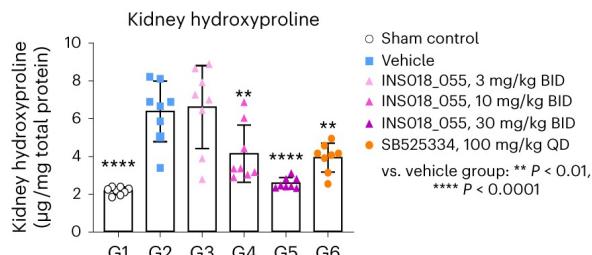
a



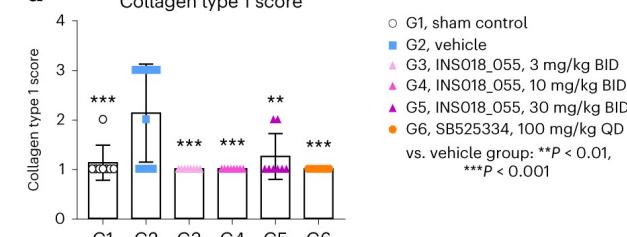
b UUO model (2 weeks)



c

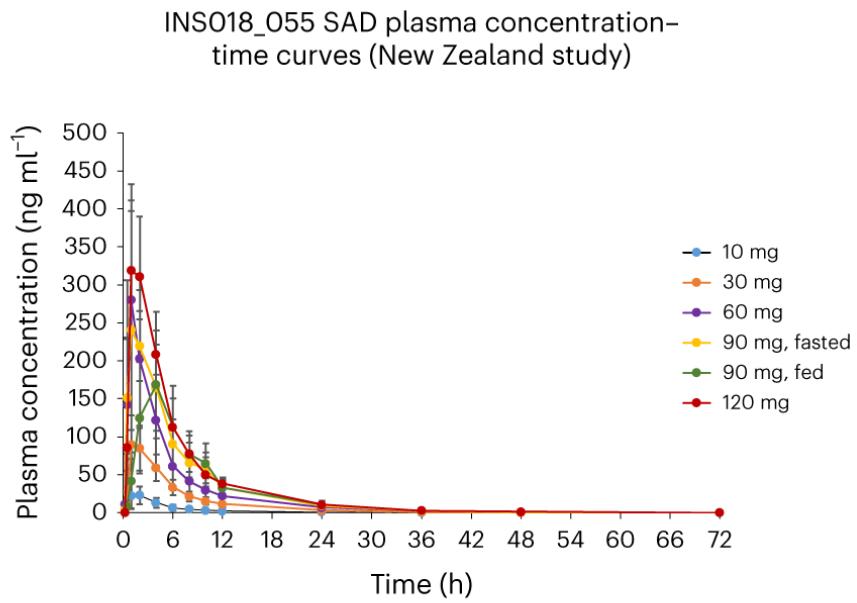


d Collagen type 1 score

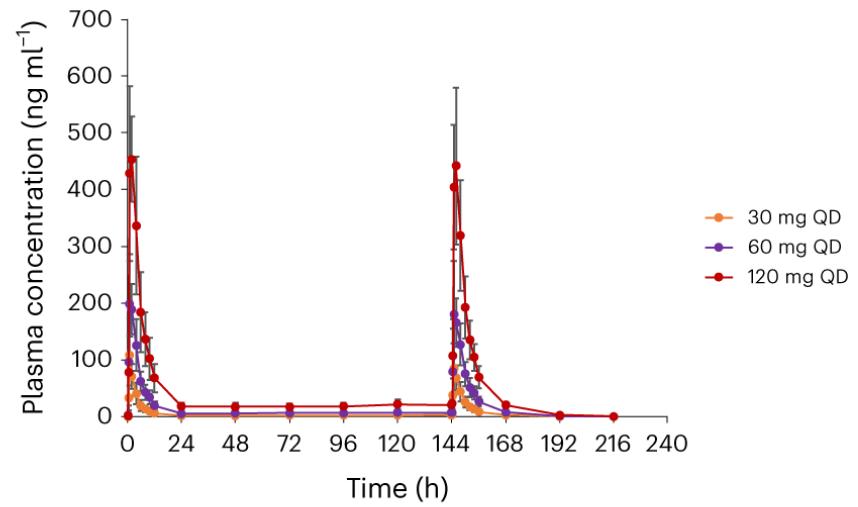


Pharmacokinetic analysis in the clinical phase I trial.

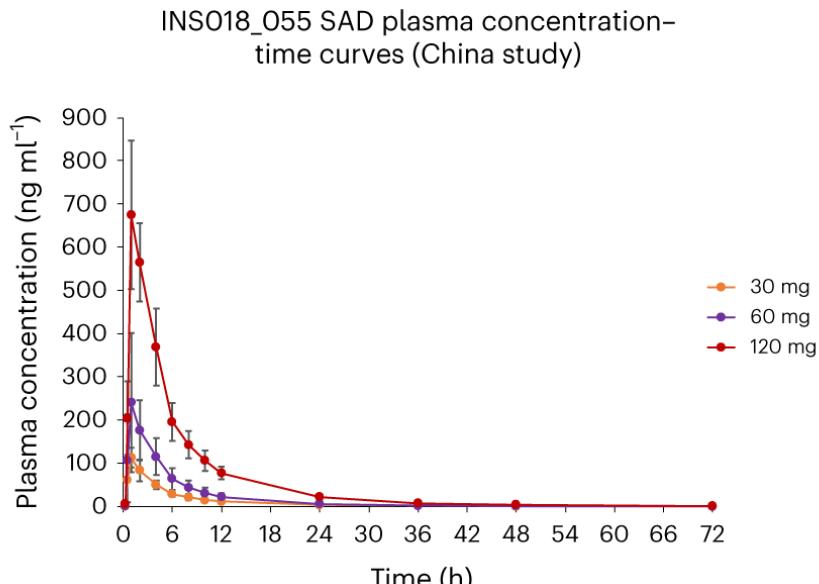
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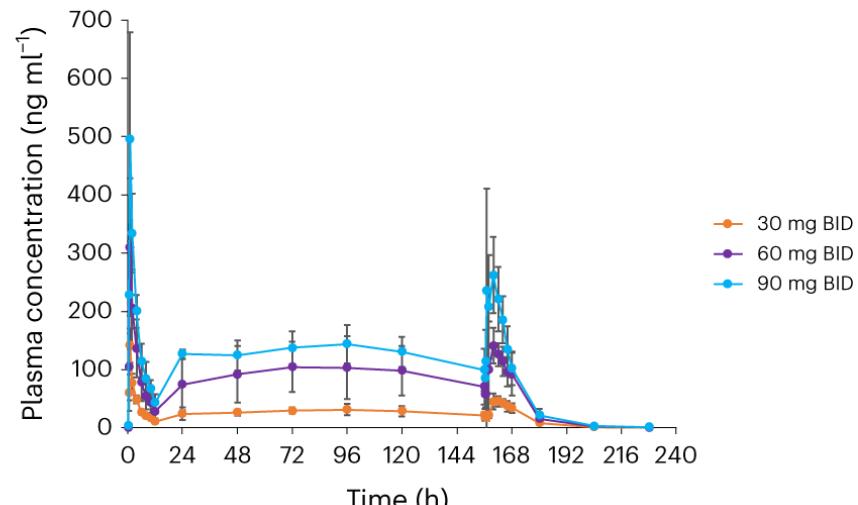
INS018_055 MAD plasma concentration-time curves (New Zealand study)



b



INS018_055 MAD plasma concentration-time curves (China study)



Summary

Using a comprehensive generative AI-driven drug-design technique, we designed a small-molecule inhibitor of TNIK, INS018_055. We demonstrate that TNIK inhibition effectively ameliorates fibrotic processes in vitro and in vivo in lung, kidney and skin fibrosis disease models.

Target discovery to preclinical candidate nomination took only 18 months to accomplish, with INS018_055 evaluated in two clinical phase I trials (NCT05154240 and CTR20221542).

We believe that this study underscores the strength of AI-enabled drug-discovery approaches, which will likely revolutionize drug discovery.