End-to-End AI-driven Robotic Drug Discovery and Case Study of the First AI-Discovered and AI-Designed Therapeutic in Human Clinical Trials

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Insilico Medicine

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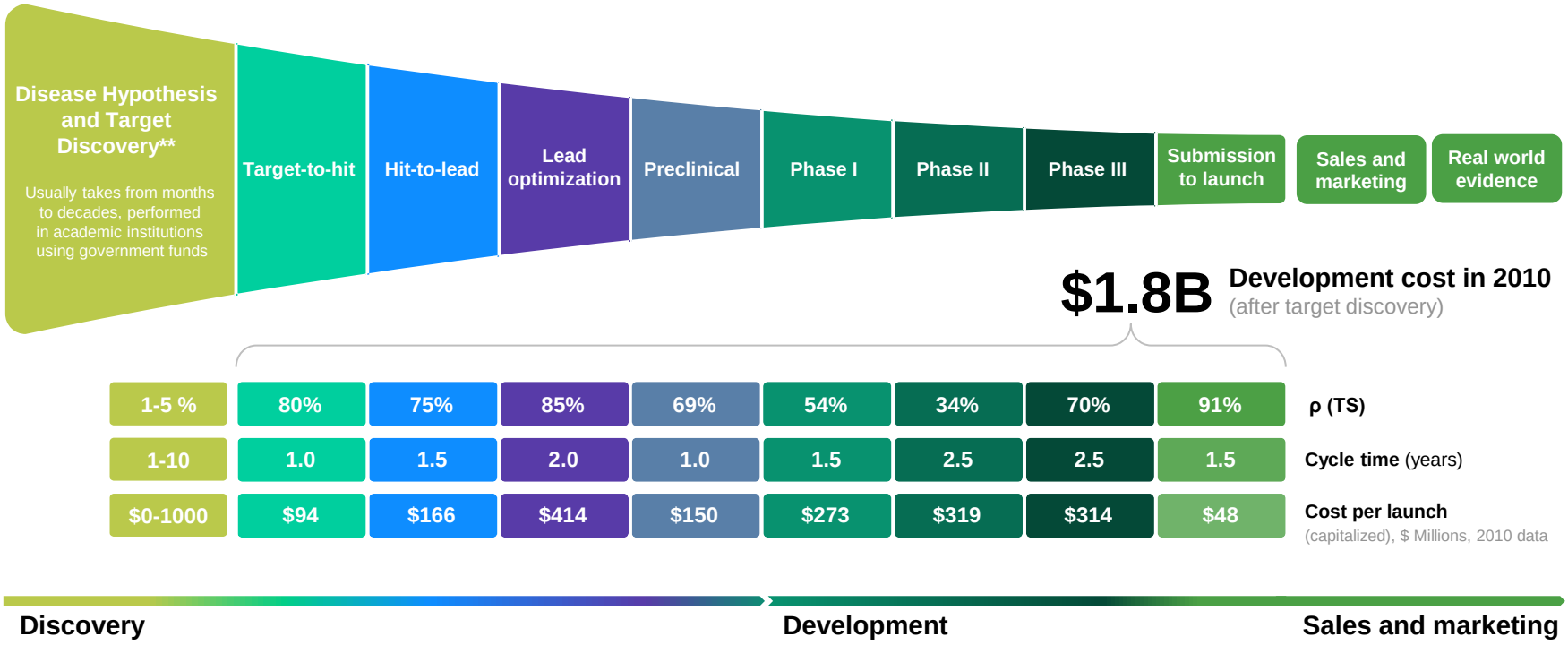
Insilico Medicine:
Transforming the drug discovery and development process with an *end-to-end next-generation AI platform*

- *Founded in 2014*
- *Global team and presence:*
  - *~250 scientists globally*
  - *70+ AI / ML experts*
  - *90+ drug hunters*
  - *210+ FTE scientists (biology + chemistry)*
  - *Expert C-Suite in the US*

Traditional drug R&D takes >10 years and >$2B*

From the discovery to the launch of a new drug



* Modified from Paul et al, How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Reviews Drug Discovery , 2010

** Based on interviews with the pharmaceutical industry executives

AI Platform ⟷ Pipeline of Therapeutics

Drug Discovery Team

AI, Compchem, Structural Biology and Medchem scientists provide context and valuable knowledge in the identification and validation of novel targets and molecules

- GPU HPC Team
- Generative Biology AI Team
- Generative Chemistry AI team
- Clinical Trial Prediction Team
- CADD / Quantum AI Team

AI Engines + Drug Discovery Team

- Novel target ID
- Novel molecules
- Synthetic route plan
- Clinical trial outcomes

AI-Powered Robotics

- Experimental data
- Expert review data

Clinical Operations & CRO Management Team

- Biology Team
- Med Chem Review
- CRO Prioritization and Planning
- Pre-clinical team
- CMC team
- Formulation Team

Clinical Operations & CRO Management Team

Streamlines and guides the discovery process and manages relationships with CROs

- In vivo CROs
- Synthetic Chemistry CROs
- Clinical Trial CROs
- In vitro, and in situ CROs
- Academic labs

- Over 80 CROs globally
- Over 40 CROs in China with dedicated managers from Insilico
- Expert CRO management, with local supervision, best FTE selection, security protocols, data and IP protection
- Focus on speed, quality, and accuracy with direct local supervision

Integrated AI-Driven End-to-End Drug Discovery and Development Platform

Insilico Medicine

PHARMA.AI

pandaOmics

SaaS

Broaden data analysis & visualization horizons

- Decipher & analyze any published OMICs data
- Discover and evaluate novel drug targets
- Uncover novel strategies for drug repurposing

LAUNCHED

Chemistry42

On-Premises Deployment

Explore uncharted chemical space

- An automated end-to-end machine learning platform
- Novel & diverse molecules for targets of interest
- Structure- and ligand-based drug design strategies

LAUNCHED

InClinico

Design & predict clinical trial outcomes

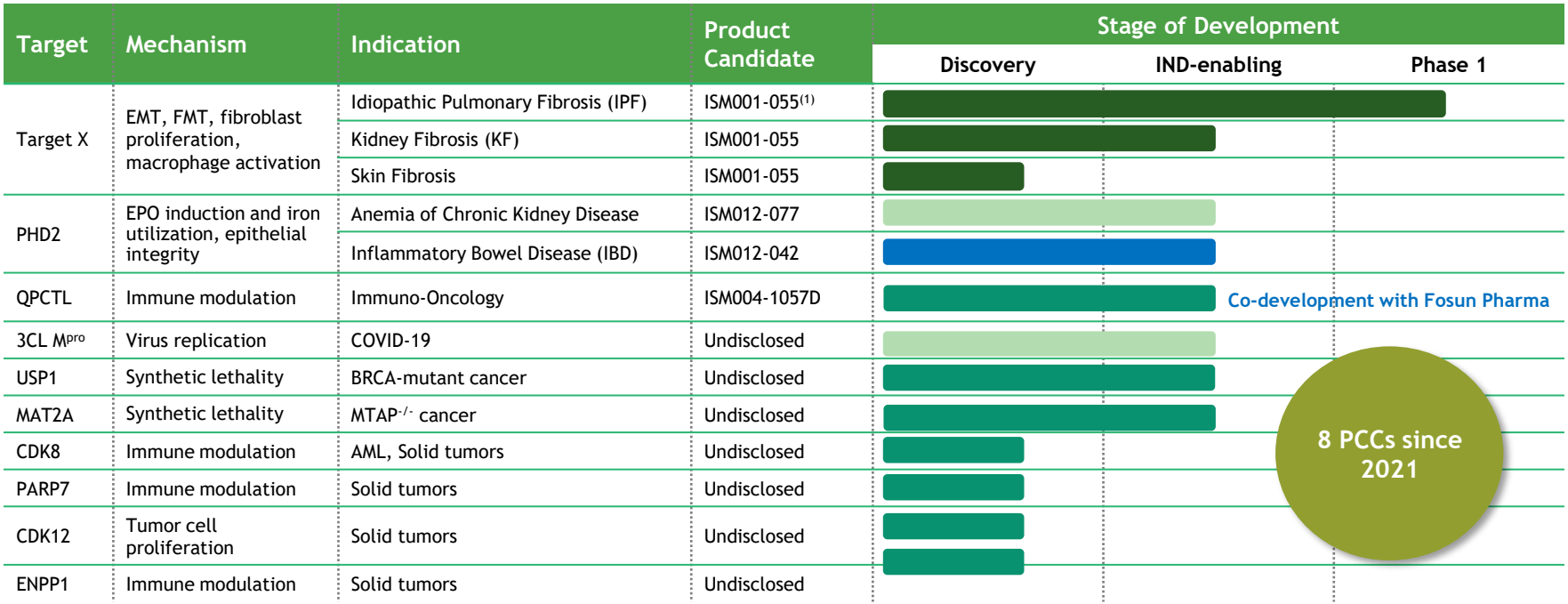
- Predict success rates of clinical trials
- Identify weak areas in trial design early
- Adopt best practices guided by InClinico

IN PROGRESS

Internal Pipeline Discovered Using Pharma.AI Platform

Multiple assets entering PCC in 2022

Target	Mechanism	Indication	Product Candidate	Stage of Development
Target X	EMT, FMT, fibroblast proliferation, macrophage activation	Idiopathic Pulmonary Fibrosis (IPF)	ISM001-055[1]	
		Kidney Fibrosis (KF)	ISM001-055	
		Skin Fibrosis	ISM001-055	
PHD2	EPO induction and iron utilization, epithelial integrity	Anemia of Chronic Kidney Disease	ISM012-077	
		Inflammatory Bowel Disease (IBD)	ISM012-042	
QPCTL	Immune modulation	Immuno-Oncology	ISM004-1057D	Co-development with Fosun Pharma
3CL M^{pro}	Virus replication	COVID-19	Undisclosed	
USP1	Synthetic lethality	BRCA-mutant cancer	Undisclosed	
MAT2A	Synthetic lethality	$MTAP^{-/-}$ cancer	Undisclosed	
CDK8	Immune modulation	AML, Solid tumors	Undisclosed	
PARP7	Immune modulation	Solid tumors	Undisclosed	
CDK12	Tumor cell proliferation	Solid tumors	Undisclosed	
ENPP1	Immune modulation	Solid tumors	Undisclosed	



1. ISM001-055, is currently being evaluated in a Phase 1, SAD / MAD study in New Zealand.
Note: Full pipeline consists of ~30 programs for 20+ drug targets; only selected programs have been listed above

8 Preclinical Candidates Nominated Since February 2021

Insilico Medicine

February 2021

Idiopathic Pulmonary Fibrosis

August 2021

Kidney Fibrosis

January 2022

Inflammatory Bowel Disease

January 2022

Anemia of Chronic Kidney Disease

February 2022

Immuno-Oncology

April 2022

BRCA-Mutant cancer

April 2022

MTAP-/- cancer

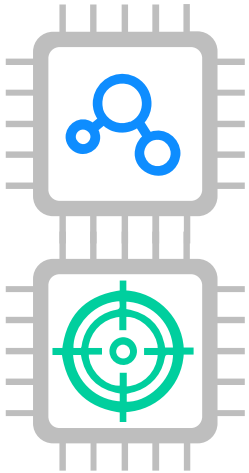
May 2022

COVID-19 3CL Protease

2020 - Can we link biology and chemistry to improve patient outcomes?

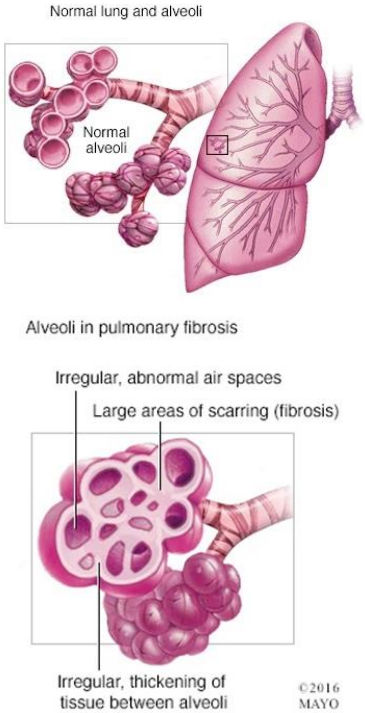
Can AI come up with
a **Novel Target** and **Novel Molecule**

for a broad disease with no cure
that may also target the fundamental
mechamisms of aging?



Idiopathic Pulmonary Fibrosis Disease Background

Idiopathic Pulmonary Fibrosis



IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP).

Symptoms

- Shortness of breath
- A severe dry cough.
- Others: Clubbing, fatigue, gradual unintended weight loss, generally feeling unwell, rapid shallow breathing.

Pathogenesis

The factors that induce the fibrotic process are unclear. Possible risk factors include smoke, history of pulmonary fibrosis, genes, certain viral infections, air pollution and some exposures in the workplace.

Prognosis

IPF is a progressive disease, fibrosis builds up over time causing a gradual breathlessness and the need for increasing amounts of oxygen. Eventually, lung failure (medically called “respiratory failure”) can develop, which is a life-threatening condition.

Complications

Depression and anxiety, lung cancer, pulmonary hypertension, gastroesophageal reflux disease, obesity, emphysema, and obstructive sleep apnea

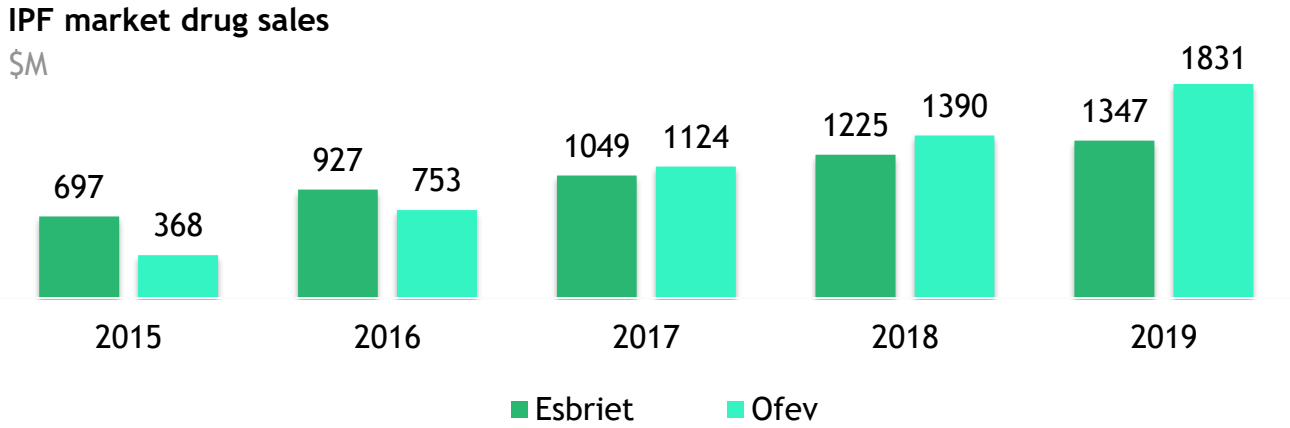
IPF Disease Background

Idiopathic Pulmonary Fibrosis

Boehringer Ingelheim

Roche

Current Therapy: Very limited treatments: Ofev (nintedanib) and Esbriet (pirfenidone) with 50% reduction of decline in forced vital capacity over 1 year, however, no oxygen saturation benefit.



ISM001: The Discovery of Novel Antifibrotic / Geroprotector

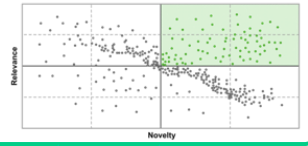
Fibrosis Target ID, Compound Generation and Validation in <18 months

Data Inventory of Omics Datasets

Related to tissue Fibrosis, annotated by Age and Sex

Omics and Clinical Data Sets

Novelty Assessment

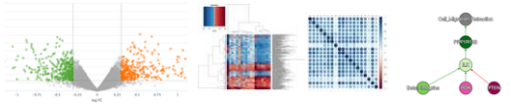


Relevant targets

Gene and Pathway scoring engine

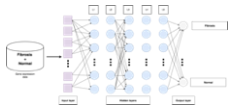
(with iPANDA)

Fibrosis vs Healthy



DL-based Target ID engine

- DFS
- PFI
- Causality inference
- *De novo* pathway reconstruction



Text-based analysis tools

- Patents
- Publications
- Clinical Trials
- Grants

20 Targets for validation
Multiple hits
Prioritized Top novel intracellular target — COMPLETE

***DE NOVO* COMPOUND GENERATION** — COMPLETE

Primary Assays — COMPLETE

Spec. & selectivity — COMPLETE

Fibrosis Assay

Collagen Production Assays — COMPLETE

Fibrosis *In Vivo* Studies — COMPLETE

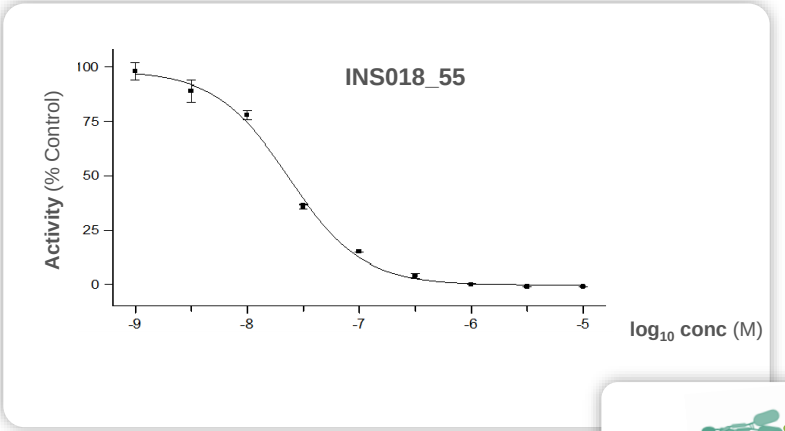
Target X is one of the targets identified by Insilico Medicine AI platform implicated in multiple fibrotic diseases

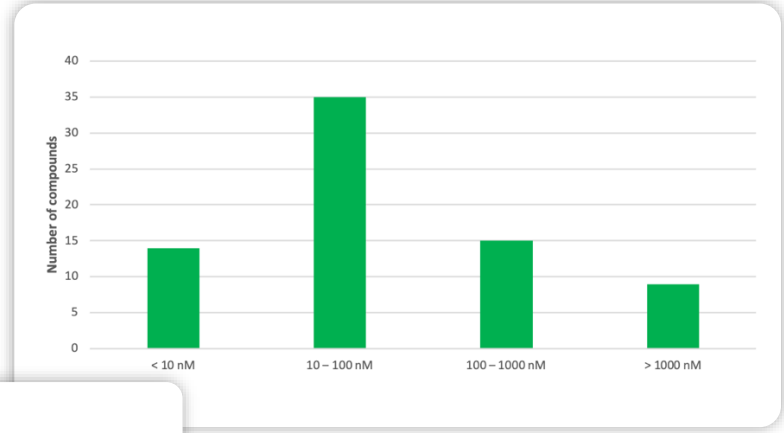
Confirmed Efficacy by Insilico Medicine

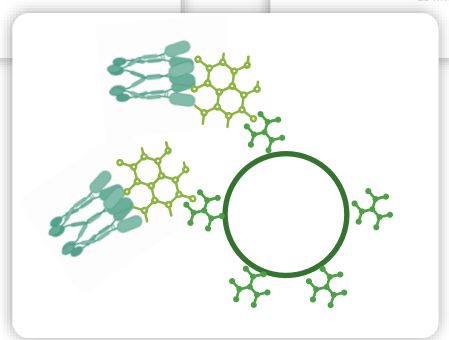
Potent target inhibition of ISM018_055

Novel small molecules generated using Chemistry42TM showed promising activity.

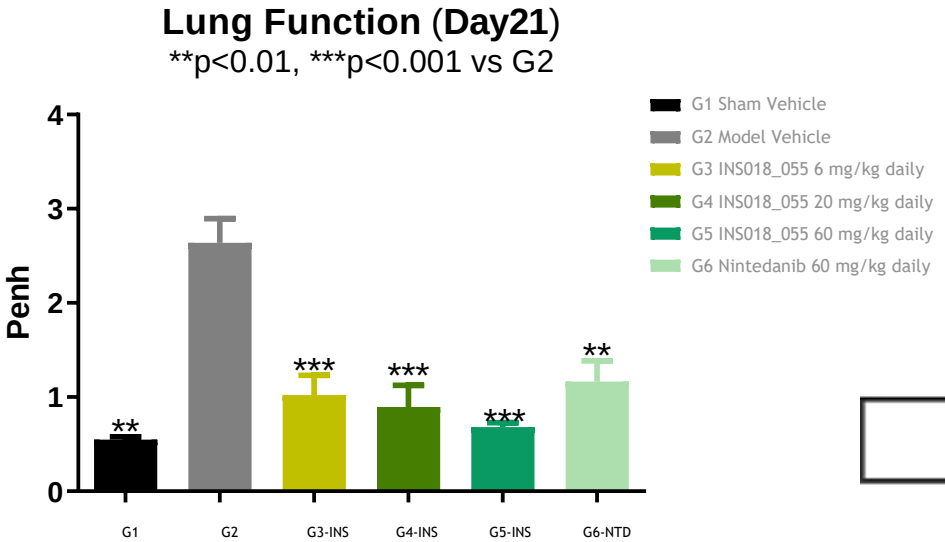
ISM001 series molecules showed potent inhibition of the target's activity with nM IC50 values.

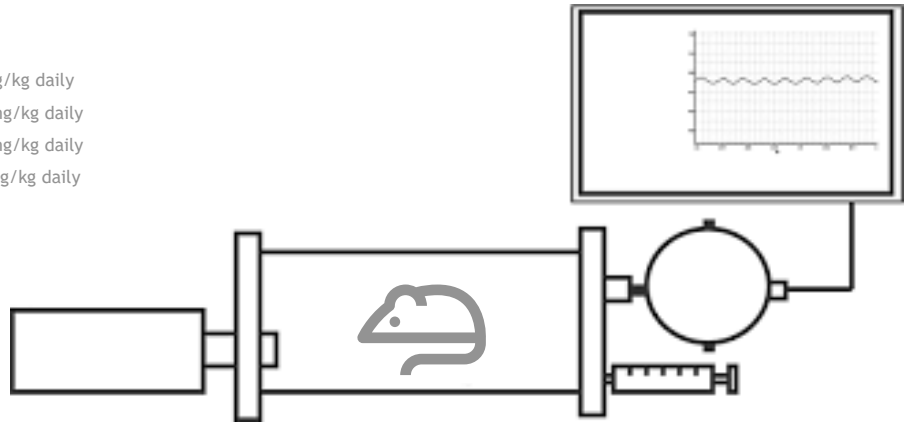






Lung function restored at low doses

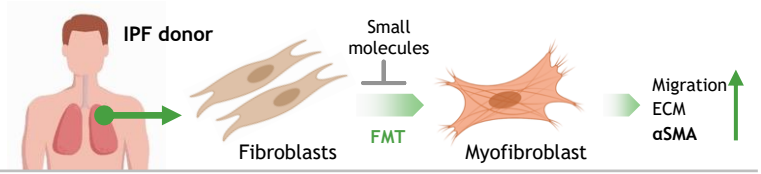




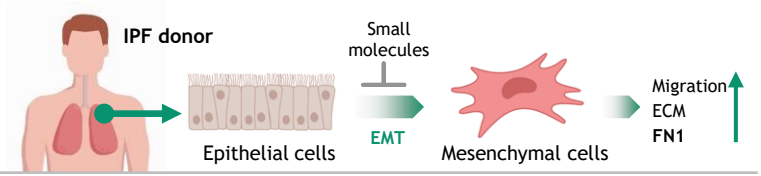
Histology data verified by independent, blinded analysis

Fibroblast-to-myofibroblast transition (FMT) and Epithelial-mesenchymal transition (EMT) in IPF human donors

FMT		INS018_055	Nintedanib
IPF donor	IPF05	50 nM	395 nM
	IPF06	79 nM	315 nM
	IPF08	63 nM	250 nM



EMT		INS018_055	Nintedanib
IPF donor	IPF05	395 nM	7800 nM
	IPF06	315 nM	6300 nM
	IPF08	250 nM	1500 nM



Myofibroblasts are thought to play a major role in fibrosis through excessive deposition of extra-cellular matrix during wound healing processes.

FMT & EMT are hallmark events in the pathobiology of IPF.

Average	INS018_055		Nintedanib	
	FMT	EMT	FMT	EMT
IC_{50}	64 nM	320 nM	320 nM	5200 nM

INS018_055 potently antagonized FMT and EMT in primary human lung epithelial cells and fibroblasts, respectively, derived from patients with idiopathic lung fibrosis.

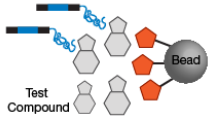
INS018_055 is **5-fold** more potent than Nintedanib on **FMT**, and **16-fold** more potent than Nintedanib on **EMT**.

Preclinical Candidate (PCC) preclinical experiments completed

Insilico Medicine

Enzymatic assay

AI-discovered,
highly selective & potent



In vitro cell-based assay
IC50 evaluation of fibrosis markers

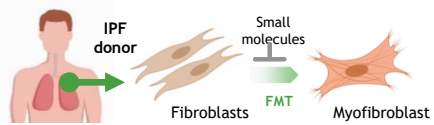
INS018_055

Collagen I & αSMA IC_{50} <100 nM

VS

IC_{50} > 600 nM of nintedanib

Fibroblast-to-myofibroblast transition
and Epithelial-mesenchymal transition



5- & 16- fold greater potency of INS018_055 than nintedanib in FMT & EMT respectively

In vivo efficacy study in **Bleomycin-induced lung fibrosis mouse model**

BLM

Equivalent efficacy at a lower dose (6-20 mg/kg) than nintedanib (60 mg/kg)

In vivo efficacy study: **Lung function**

Significant improvement in lung function

In vivo efficacy study: **Modified Ashcroft score**

Significant improvement in fibrosis status

In vivo efficacy study: **Immunohistochemistry for α-SMA & Collagen I**

equivalent efficacy in inhibiting α-SMA & Collagen I synthesis **at a lower doses**

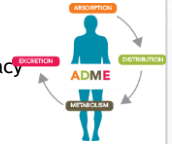
Toxicology study in mice

INS018_055

- No adverse effects was observed in doses up to 60 mg/kg daily in a 14-day non-GLP toxicity study in mice
- Safety factor of 8-10 in non-GLP 2-week toxicity study

ADME studies

- Forecasted clinical efficacy **at once-daily dosing**
- increase patient compliance and efficacy

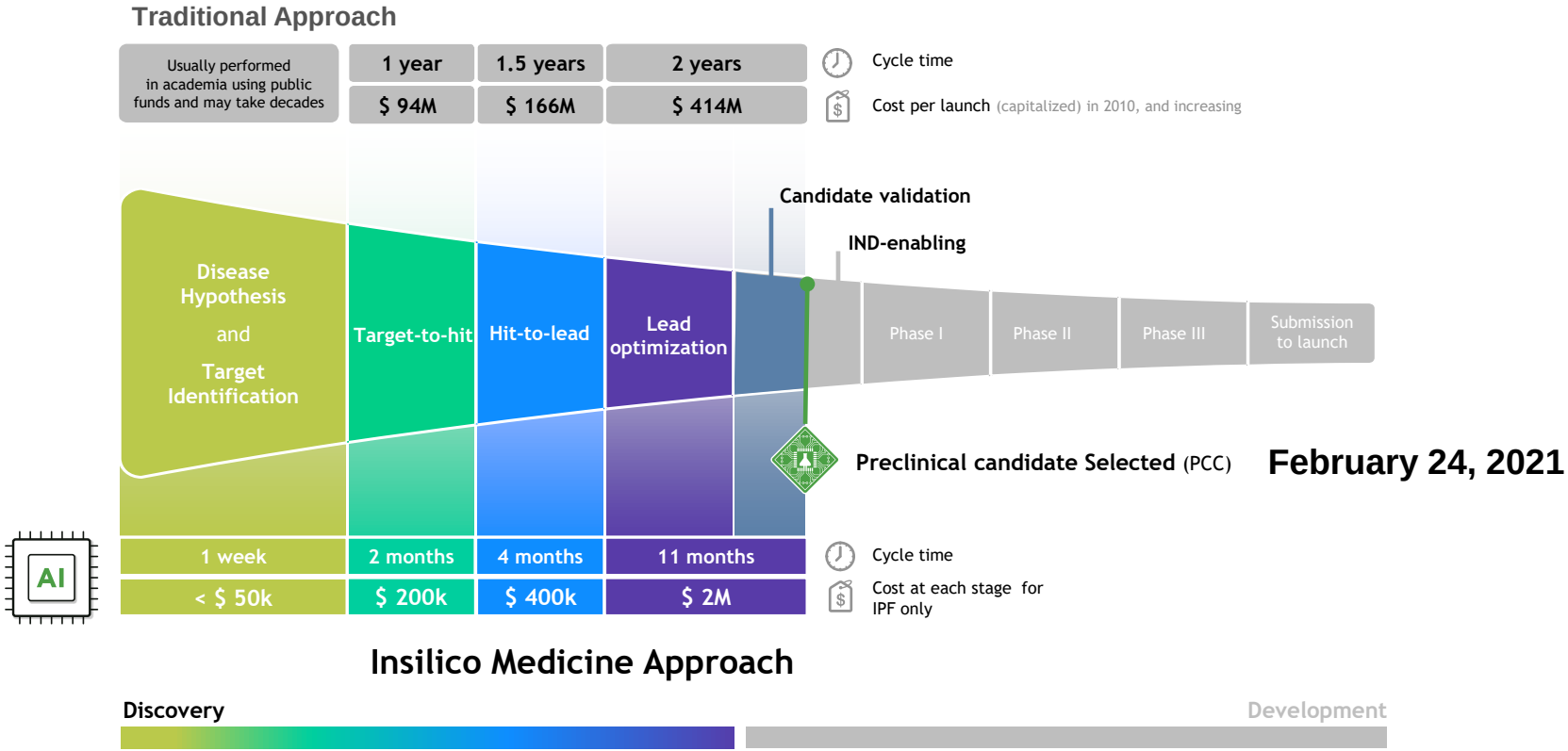


Predicted

Safety / Tolerability

- Greater tolerability to be confirmed in pivotal toxicity studies (Planned)
- Should be a preferred option, if tolerability is confirmed to be superior to nintedanib

Insilico Medicine AI platforms discovered a Novel target and designed a Novel preclinical candidate molecule

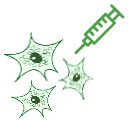


ISM001-055: Compelling Preclinical Package to Support CTA/IND Filing

Insilico Medicine

In vitro **cell-based assay**
IC_{50} evaluation of **fibrosis markers**

ISM001-055
Collagen I & αSMA **IC_{50} <100 nM**
vs
IC_{50} > 600 nM of Nintedanib



ISM001-055 observed to be 6-times more potent than Nintedanib

In vivo efficacy study for **combinations with Nintedanib & Pirfenidone**

Combination of suboptimal doses of ISM001-055 & Pirfenidone exhibited:

- ✓ Synergistic effect in the lung function restoration
- ✓ Synergistic anti-fibrotic effect
- ✓ Synergistic reductions in αSMA & Collagen I expression

Synergistic effect of ISM001-055 with Pirfenidone observed

BioMAP study in fibrosis panel demonstrated that ISM001-055:

- ✓ Was **active and non-cytotoxic**
- ✓ Mediated changes in key IPF biomarker parameters
- ✓ Showed a more pronounced effect compared to Nintedanib

ISM001-055 observed to cause significant changes of key biomarkers related to IPF

Toxicology studies in mice & dogs

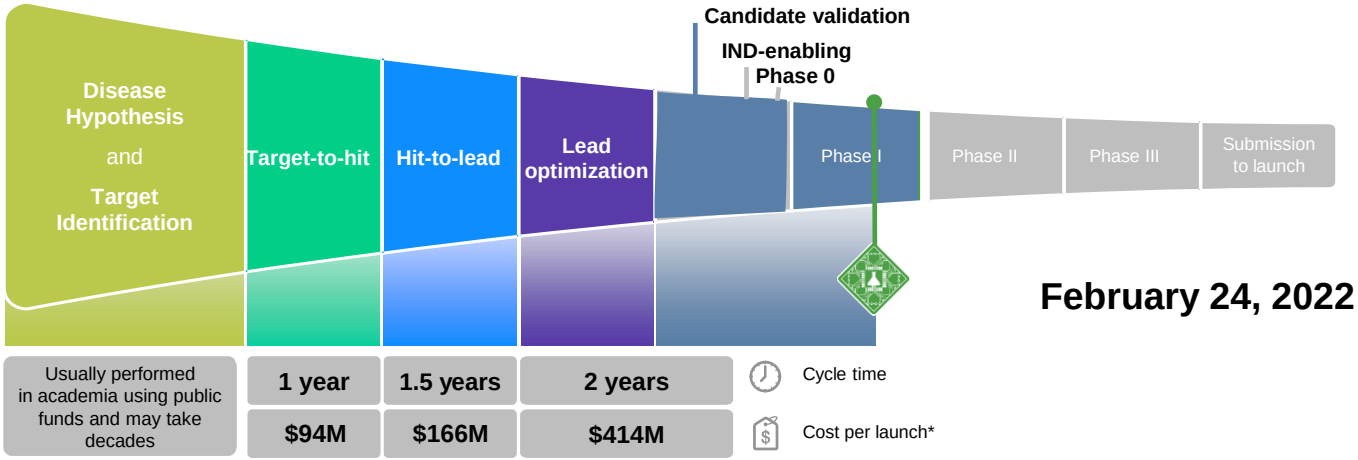
After 14-day oral repeat dose study:
- ✓ In mice: NOAEL considered to be 60 mg/kg/day
- ✓ In dogs: NOAEL considered to be 20 mg/kg/day

In the ongoing 28-day toxicology study:
- ✓ In mice: Top dose group showed dose-limiting toxicity; low and mid dose animals demonstrated only minor clinical findings
- ✓ In dogs: GI symptoms with increasing severity and reduced food intake observed mainly in high dose animals while not in low and mid dose groups

ISM001-055 observed to be well tolerated at low and mid doses

NOAEL = No Observed Adverse Effect Level

Example: AI-Discovered Novel Target and AI-Designed Novel Anti-Fibrotic Small Molecule with Multi-Purpose Target in Phase I in 30-months



* The cost per launch was capitalized in 2010, and is increasing

ISM001-073: Preclinical Data Supports Selection as a PCC for Kidney Fibrosis

Insilico Medicine

Highly active inhibitor of Target X with IC_{50} values in nM range

High efficacy in cell-based assay inhibiting α-SMA production in human kidney 2 cells with the nM IC_{50} values and μM CC_{50} values

In the BioMAP renal fibrosis system, inhibited inflammation, myofibroblast activation, fibrosis-related tissue remodeling and wound healing activity markers

Good efficacy in UUO *in vivo* model of kidney fibrosis:

- **Significant & dose dependent decrease** in hydroxyproline & fibrosis score
- **Significant decrease** in Collagen type 1, 3 & 4

Well-tolerated in 2-week toxicity study in mice

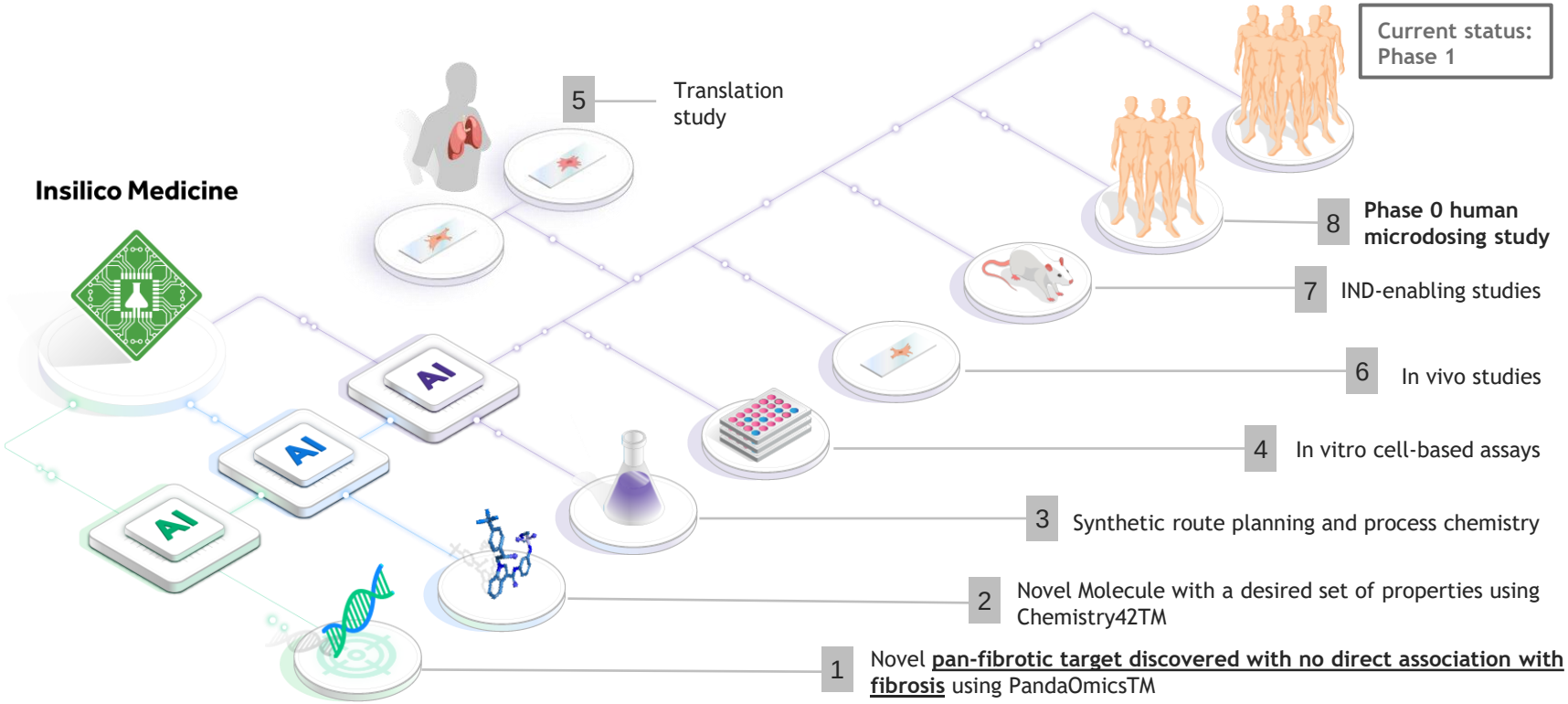
$$\text{Safety factor} = \frac{\text{Exposure at NOAEL}}{\text{Exposure at Pharmacological active dose}}$$

- Safety factor of ISM001-073 ≈ 12

Balanced ADMET properties suitable for further development in clinical trials

ADMET = Absorption, Distribution, Metabolism, Excretion and Toxicity

From Start to Phase 1 in 30 Months: Insilico's AI-Discovered & AI-Designed Potentially Geroprotective Anti-Fibrotic Drug

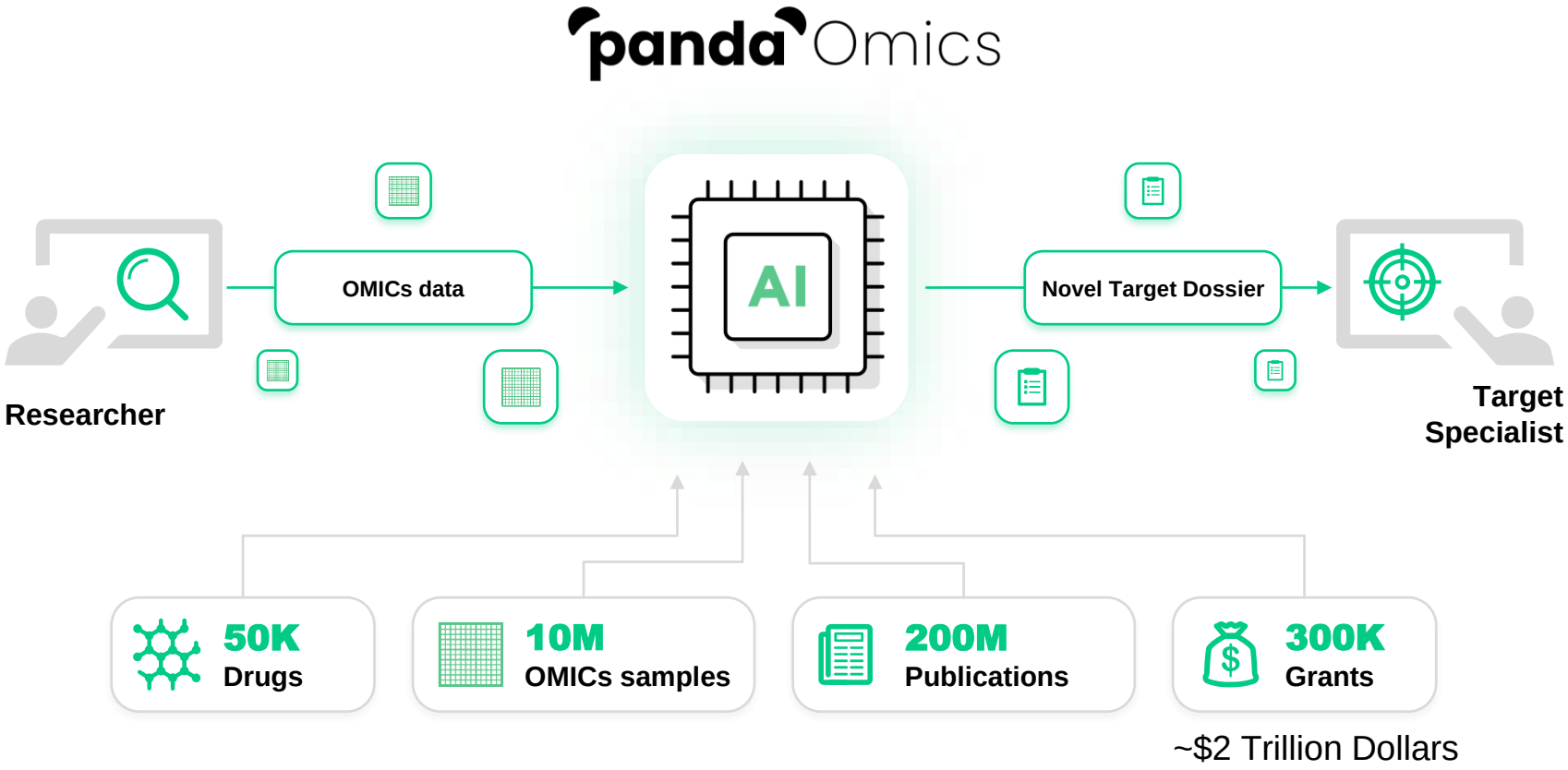


Autonomous AI-Driven Robotics Laboratory

Scaling Target Discovery With Robotics

Leverage OMICS and Meta Data for Novel Target Discovery

Insilico Medicine



AI-Driven and Self-driving Target Discovery and Validation Lab

Insilico Medicine

pandaOmics

Integrated system
with multiple workflows

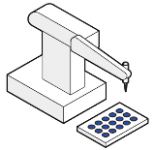
AI

Phenotype
High-resolution, High-content Imaging
Methylation Response
Transcriptional Response
Deep Phenotypic Response
HUMAN + ANIMAL

Sample culture

Hypothesis generation

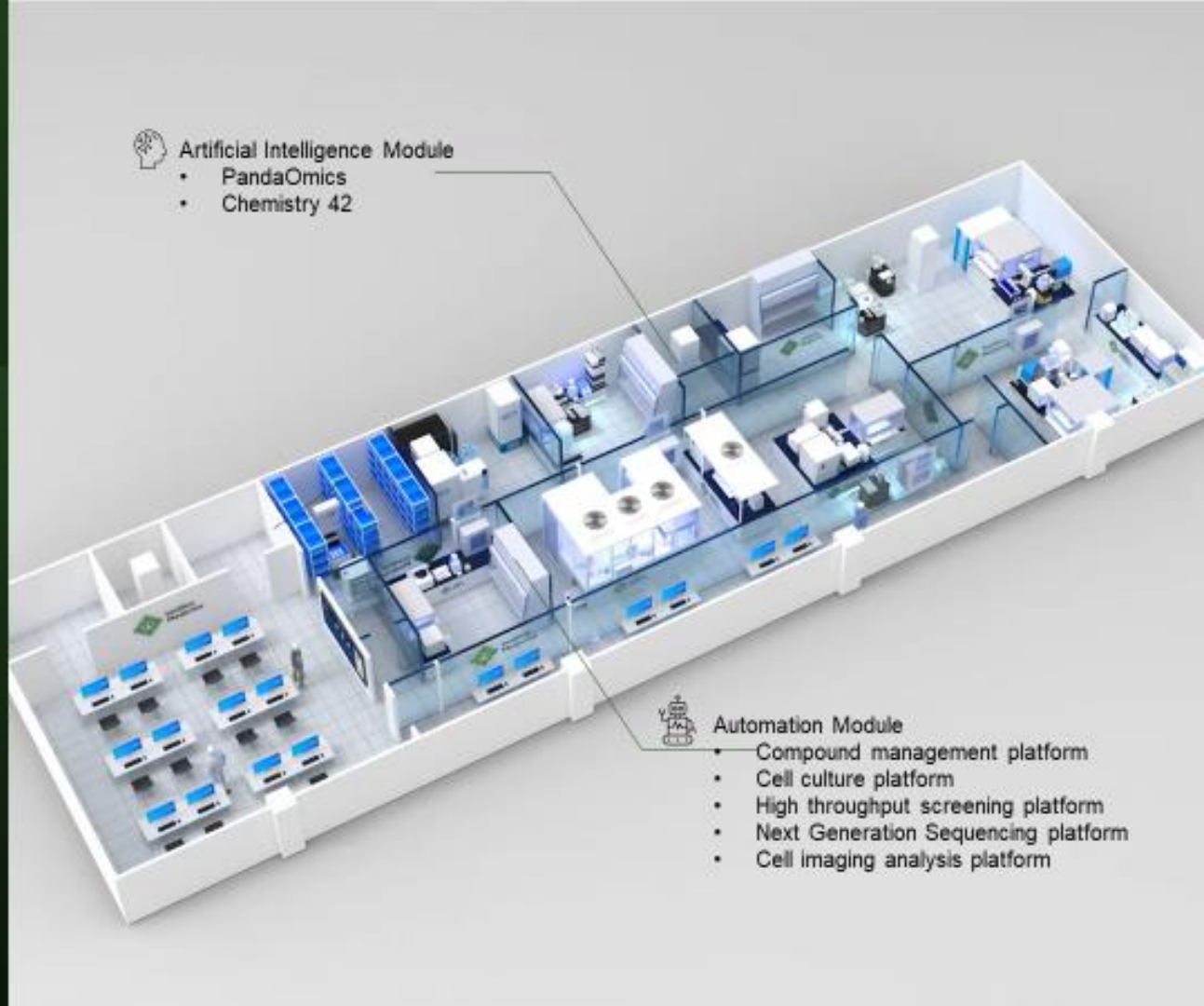
Perturbation



In Vitro Assays

NGS sequencing

End-to-End Integrated Solutions



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New York: Insilico Medicine, The Cure by Deerfield, 345 Park Avenue, New York

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Taipei: 20th Floor, No.333, Sec. 1, Keelung Rd., Xinyi District, Taipei

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A QUEST FOR AGING WITHOUT LOSING
AND CONTINUOUS IMPROVEMENT

www.LongevityPledge.org

www.aging-us.com AGING 2022, Vol. 14, Advance

Research Paper

Hallmarks of aging-based dual-purpose disease and age-associated targets predicted using PandaOmics AI-powered discovery engine

Frank W. Pun[1,*], Geoffrey Ho Duen Leung[1,*], Hoi Wing Leung[1,*], Bonnie Hei Man Liu[1], Xi Long[1], Ivan V. Ozerov[1], Ju Wang[1], Feng Ren[1], Alexander Aliper[1], Evgeny Izumchenko[2], Alexey Moskalev[3], João Pedro de Magalhães[4], Alex Zhavoronkov[1,5]

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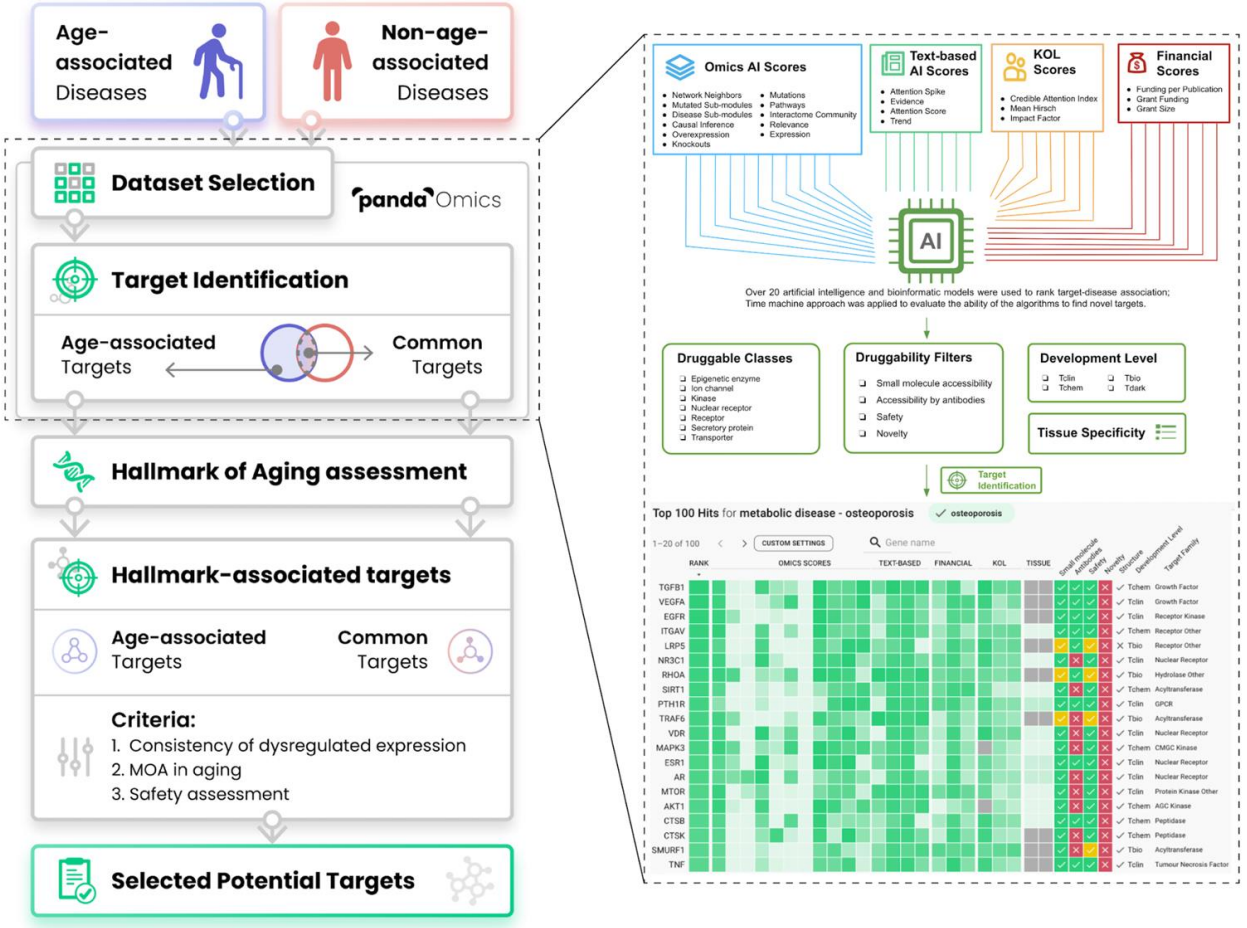
Workflow of the present study



List of diseases and datasets employed

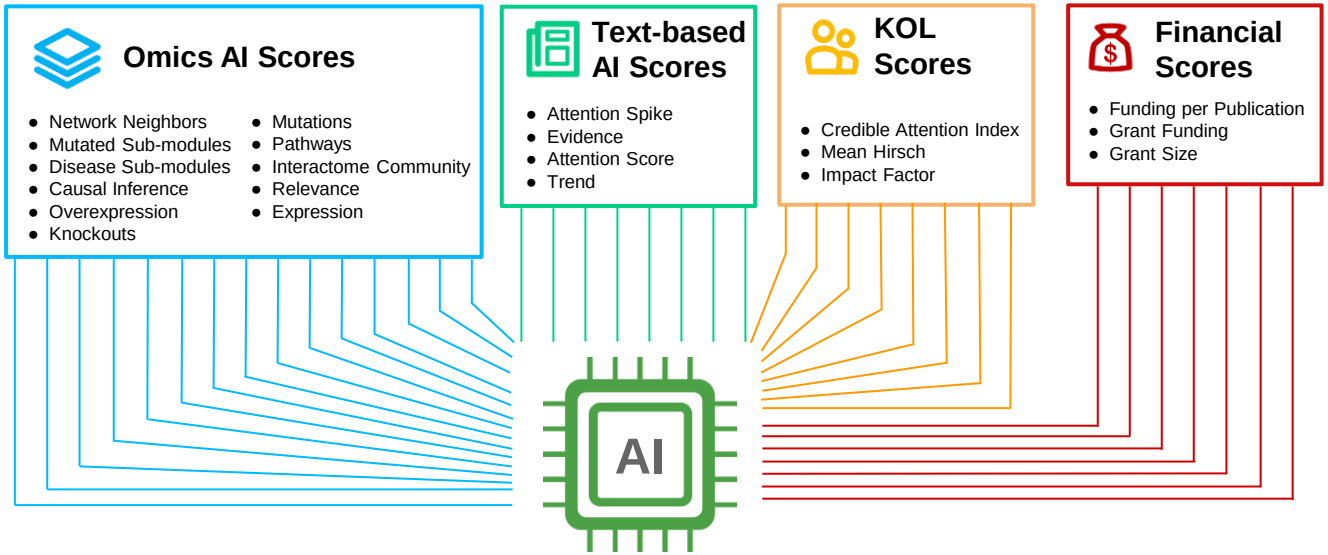
Non-age-associated diseases (NAADs) (n = 19)		
Disease	**Disease Class**	**Number of datasets**
Acromegaly	Metabolic	2
Asthma	Inflammation & Immunology	13
Bipolar disorder	Neurological	4
Celiac disease	Inflammation & Immunology	3
Crohn's disease	Inflammation & Immunology	8
Cystic fibrosis	Fibrotic	5
Hepatitis, alcoholic	Metabolic	3
Hepatitis C virus infection	Infectious	2
Huntington's disease	Neurological	5
Infectious meningitis	Infectious	3
Influenza	Infectious	5
Multiple sclerosis	Fibrotic	11
Psoriasis	Inflammation & Immunology	11
Pulmonary tuberculosis	Infectious	7
Schizophrenia	Neurological	4
Systemic lupus erythematosus	Inflammation & Immunology	9
Systemic scleroderma	Inflammation & Immunology	6
Type I diabetes mellitus	Metabolic	12
Ulcerative colitis	Inflammation & Immunology	13
	Total	126

Age-associated diseases (AADs)[1,2] (n = 14)		
Disease	**Disease Class**	**Number of datasets**
Alzheimer's disease	Neurological	12
Amyotrophic lateral sclerosis	Neurological	10
Chronic kidney disease	Metabolic	7
Chronic obstructive pulmonary disease	Inflammation & Immunology	6
Cirrhosis of liver	Fibrotic	5
Idiopathic Pulmonary Fibrosis	Fibrotic	11
Obesity	Metabolic	10
Osteoarthritis	Inflammation & Immunology	5
Osteoporosis	Metabolic	2
Parkinson's disease	Neurological	4
Primary myelofibrosis	Fibrotic	2
Pulmonary arterial hypertension	Metabolic	5
Rheumatoid Arthritis	Inflammation & Immunology	4
Type II diabetes mellitus	Metabolic	4
	Total	87

[1] Diseases are classified as age-associated if age is a strong risk factor for the disease onset

[2] The rationale behind the exclusion of cancer and cardiovascular disease:

- common mechanistic root contributing to the insufficient blood supply to multiple organs among cardiovascular disease
- Some mechanisms of Hallmark of Aging in cancer and some aging-associated diseases are in opposite direction.



Over 20 artificial intelligence and bioinformatic models were used to rank target-disease association;
Time machine approach was applied to evaluate the ability of the algorithms to find novel targets.

Druggable Classes

- ❑ Epigenetic enzyme
- ❑ Ion channel
- ❑ Kinase
- ❑ Nuclear receptor
- ❑ Receptor
- ❑ Secretory protein
- ❑ Transporter

Druggability Filters

- ❑ Small molecule accessibility
- ❑ Accessibility by antibodies
- ❑ Safety
- ❑ Novelty

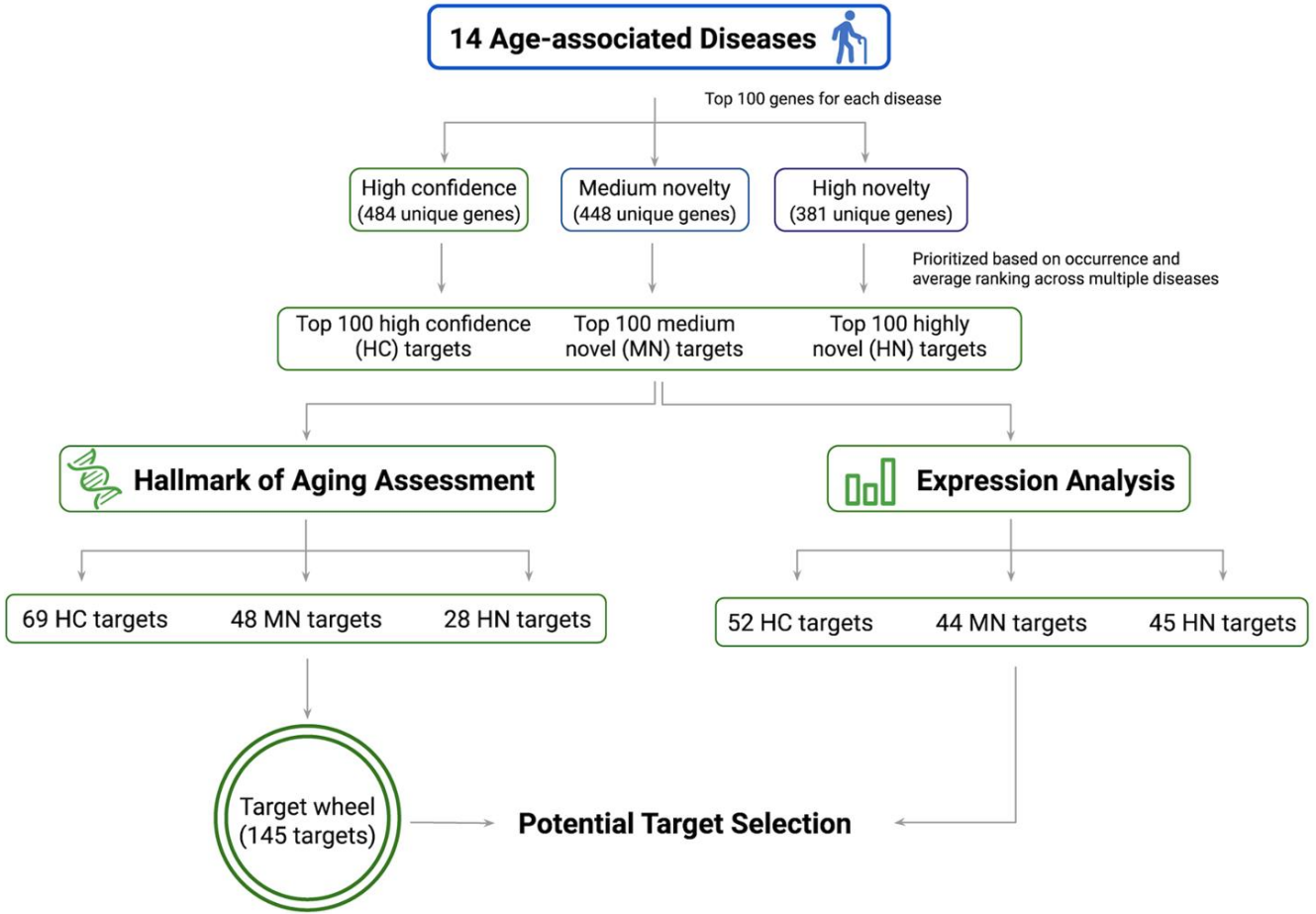
Development Level

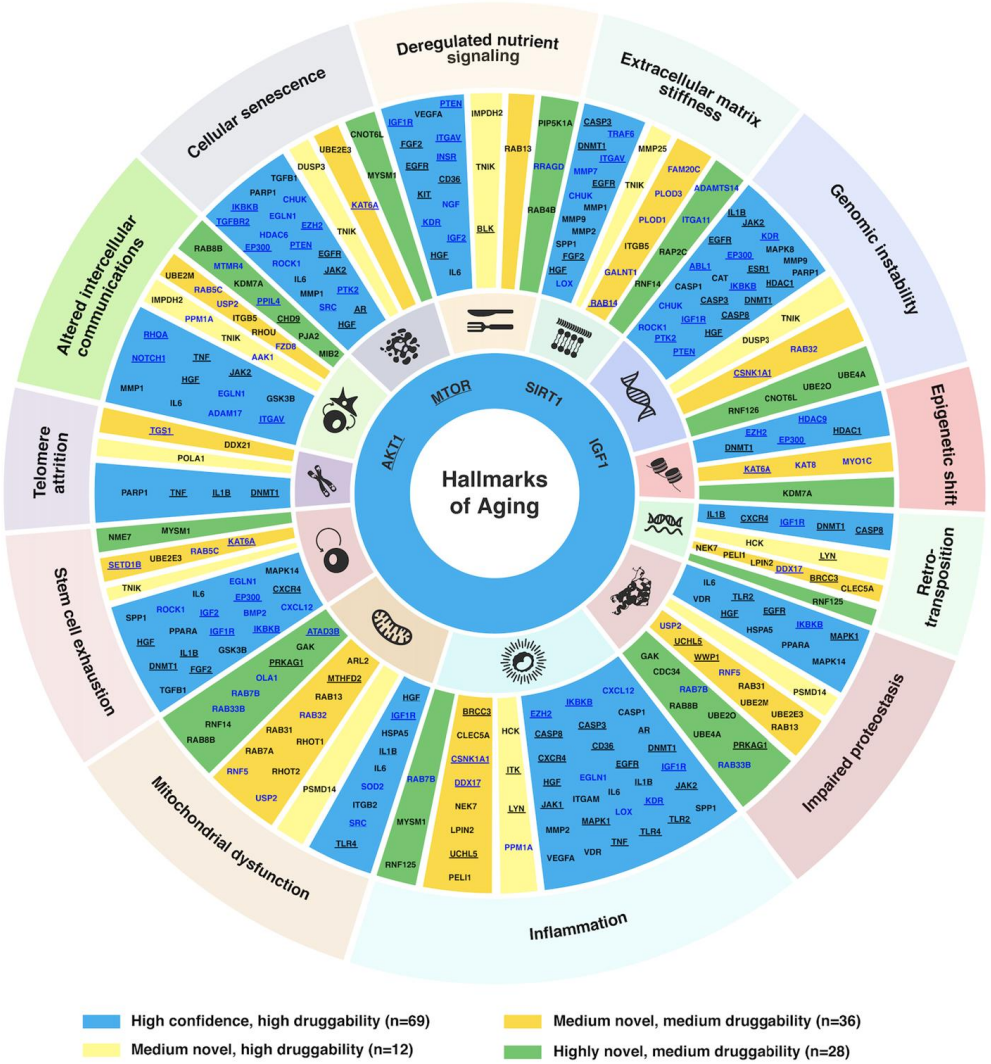
- ❑ Tclin
- ❑ Tchem
- ❑ Tbio
- ❑ Tdark

Tissue Specificity

Target Identification

Flowchart of the selection of dual-purpose targets from the 14 AADs



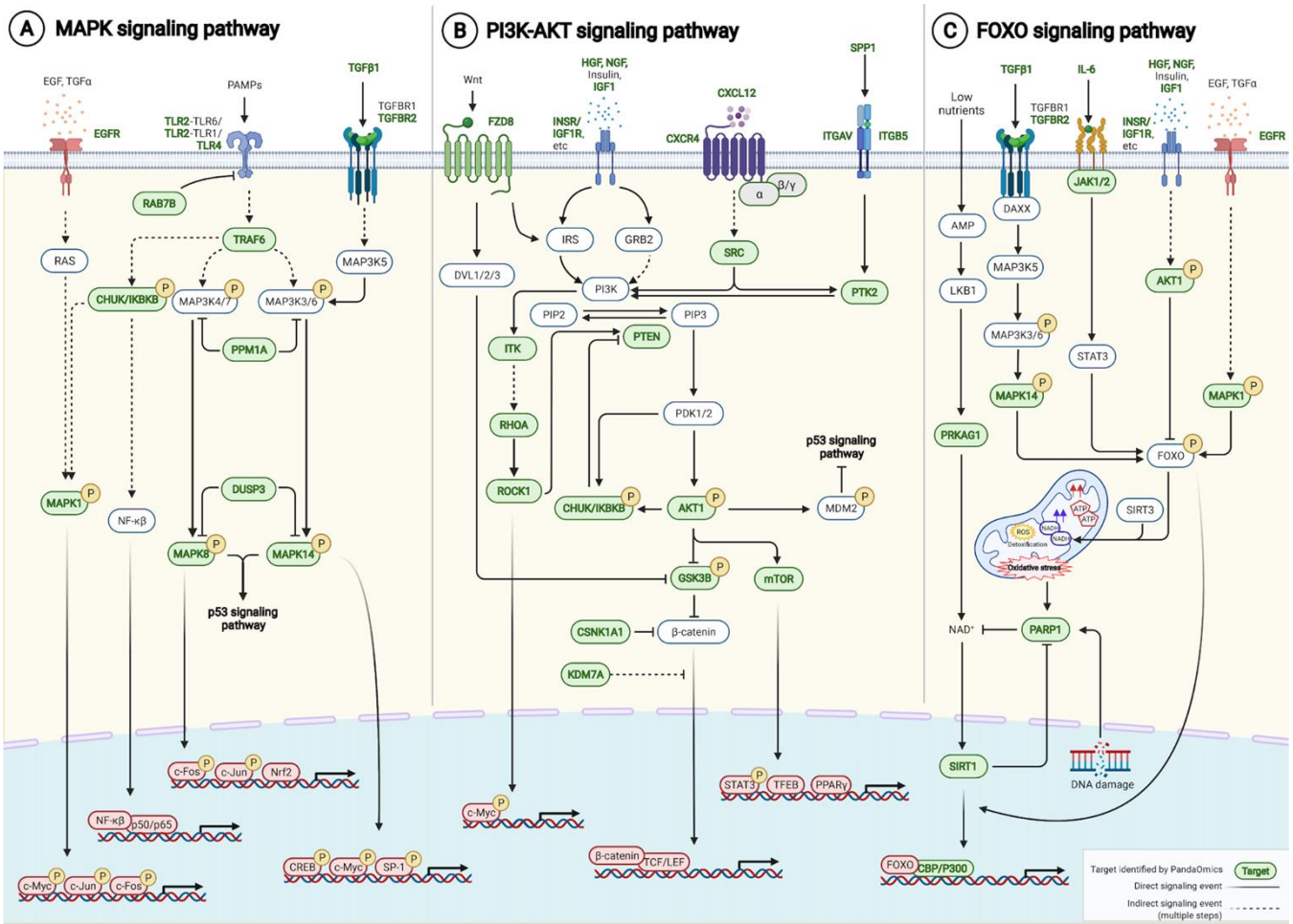


Targets associated with hallmarks of aging

Targets (*n* = 145) were mapped to the corresponding hallmark(s) of aging based on the literature. For novel targets, their participating pathways were also used for the assessment of their association with the hallmark(s) of aging.

Genes in inner circle: connected to all hallmarks
Genes in **Blue**: Age-associated disease targets
Genes in **Black**: Common targets
Genes **underlined**: Cancer drivers

AI-derived targets crosstalk to aging-associated signaling pathways



List of prioritized targets

Novelty	Target[1]	Protein family	Dysregulation in AAD classes	Therapy approach	Hallmarks of aging	Role in aging	Clinical trial status	Severe toxicity[3]	Reference (PMID)
High confidence	***CXCL12***	Cytokine	**ALL** Upregulated	Antagonist (pro-aging**)**	Inflammation, Stem cell exhaustion	CXCL12 is an aging-upregulated gene and a mediator of the crosstalk between vascular cells and many brain cell types	Completed phase 4	No evidence	23128103, 20833981
High confidence	***SPP1***	Chemokine	**ALL** Upregulated	Antagonist (pro-aging)	Extracellular matrix stiffness, Inflammation, Stem cell exhaustion	Age-dependent increase in SPP1 levels inhibited skeletal muscle regeneration	Completed phase 1/2	No evidence	28254837, 17392476
Medium novel	***ITGB5***	Receptor	**ALL** Upregulated	Antagonist (pro-aging)	Altered intercellular communications, Extracellular matrix stiffness	ITGB5 is a TGF-β activator. Inhibiting TGF-β signaling was shown to repress body size as well as lifespan *in vivo*	Completed phase 3	No evidence	29070608
Medium novel	*PPM1A*	Esterase	**ALL** Downregulated	Agonist (anti-aging[2])	Deregulated nutrient signaling, Inflammation	PPM1A stimulated macrophages to produce TNF through TLR4	N/A	No evidence; absence in DEG	31791585
Highly novel	*RAB7B*	Hydrolase	**ALL** Upregulated	Agonist (anti-aging)	Impaired proteostasis, Inflammation, Mitochondrial dysfunction	RAB7B negatively regulated TLR4 signaling in macrophages and autophagic flux as well as prevented inflammation and autophagy upon damage	N/A	No evidence; absence in DEG	28726776
Highly novel	***ADAMTS14***	Peptidase	Upregulated in neurological and fibrotic diseases	Antagonist (pro-aging)	Extracellular matrix stiffness	ADAMTS14 is responsible for the degradation of ECM collagen. Aged fibroblast-ECM interactions become disrupted due to the fragmentation of collagen fibrils. Fibroblasts synthesized fewer ECM proteins and more matrix-degrading metalloproteinases	N/A	No evidence, absence in DEG	11779638
Highly novel	*KDM7A*	Oxidoreductase	Downregulated in neurological and fibrotic diseases	Agonist (anti-aging)	Altered intercellular communications, Genome instability	Age-related neural dedifferentiation might contribute to many cognitive abilities decline with age. KDM7A regulated neural differentiation through FGF4, and was associated with Wnt signaling	N/A	No evidence	34395453, 30614617
Highly novel	*MYSM1*	Peptidase	Downregulated in neurological, fibrotic and metabolic diseases	Agonist (anti-aging)	Cellular senescence, Inflammation, Stem cell exhaustion	MYSM1 functionally reduced cellular senescence and the aging process. MYSM1 deficiency promoted the aging process and decreased lifespan while its overexpression inhibited the aging process and increased lifespan *in vivo*.	N/A	No evidence	33240758
Highly novel	*MTMR4*	Esterase	Downregulated in neurological, fibrotic and metabolic diseases	Agonist (anti-aging)	Altered intercellular communications	Skeletal muscle atrophy accompanies many chronic disease states and normal aging	N/A	No evidence	31543504

Note:
[1] Targets selected for comprehensive target review are in **BOLD**
[2] Based on its mechanism of action i.e. protective role
[3] Database of Essential Gene (DEG) is freely accessible from the website http://tubic.tju.edu.cn/deg