Insilico Medicine

Maximizing PTRS: Generative AI and Robotics for End-to-End Drug Discovery and Developme

SCRI SYMPOSIUM, SINGAPORE, JULY, 2024

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Insilico Medicine

A GLOBAL DEEP LEARNING-FIRST CLINICAL-STAGE GENERATIVE AI AND ROBOTICS COMPANY ESTABLISHED IN 2014

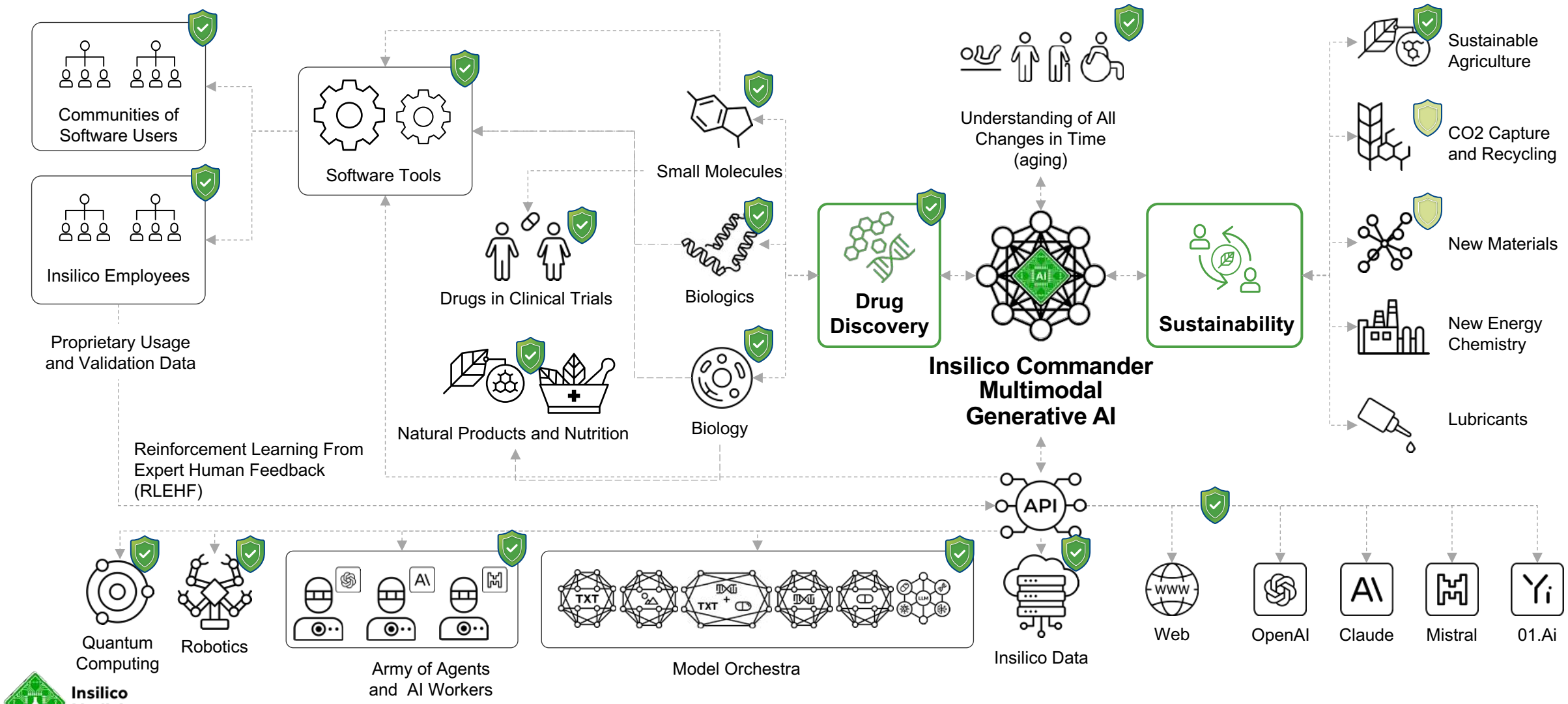
TO EXTEND HEALTHY PRODUCTIVE LONGEVITY FOR EVERYONE

VALUES

- PATIENT FIRST
- RELENTLESS INNOVATION
- TRANSPARENCY & INTEGRITY
- HIGHEST QUALITY & REPRODUCIBILITY

INSILICO.COM

Insilico Generalist Generative AI Platform For Multimodal Multi-Industry Multi-Domain Learning



Insilico Medicine

2024 Most Innovative Biotechnology Company Globally

FAST COMPANY

03-19-2024 | MOST INNOVATIVE COMPANIES 2024

The most innovative companies in biotech in 2024

Why Insilico Medicine, ElevateBio, Inato, and Exscientia are among Fast Company's Most Innovative Companies in biotech in 2024.

1. INSILICO MEDICINE

For zooming in on drug-disease targets

2. ELEVATEBIO

For catching genetic disorders at the root

3. PERSONALIS

For detecting cancers with precision

4. EXSCIENTIA

For using AI to personalize cancer treatments

5. ROCKET PHARMACEUTICALS

For targeting rare diseases with gene therapy

6. GUARDANT HEALTH

For doubling down on cancer detection

7. INATO

For bringing clinical trials to local hospitals

8. ELUCIDATA

For cleaning up messy biomedical data

9. MARAVAI LIFESCIENCES

For improving the safety of immunotherapy

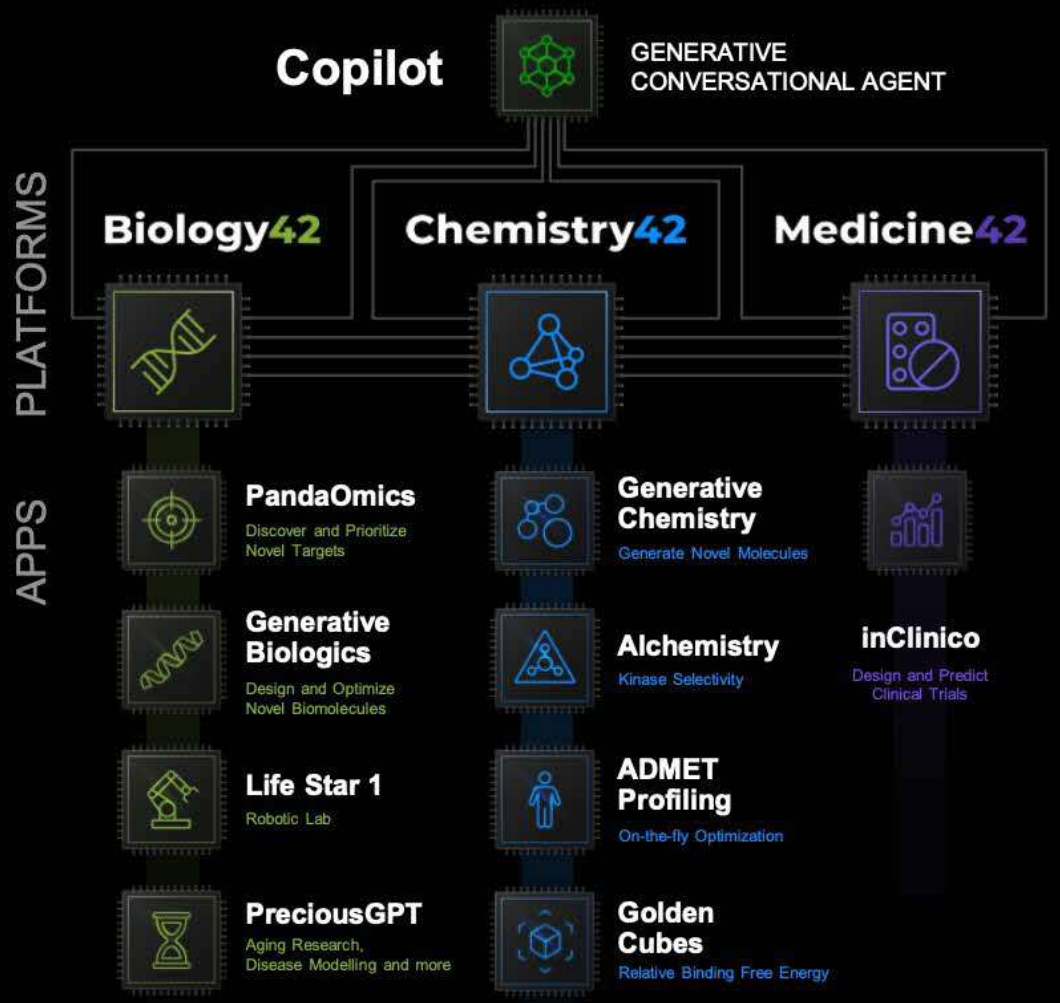
10. EMERALD CLOUD LAB

For providing 24/7 lab services in the cloud

Insilico Medicine

https://www.fastcompany.com/91034883/biotech-most-innovative-companies-2024

Pharma.AI Platform



Drug Discovery Pipeline

INDICATION	TARGET ID	HIT TO LEAD	LEAD OPT.	IND-ENABLING	PHASE I	PHASE II	
Idiopathic Pulmonary Fibrosis (IPF)	TNIK				New Zealand		US (FDA)
Idiopathic Pulmonary Fibrosis	TNIK				China		China (NMPA)
Kidney Fibrosis	TNIK						
IPF (Inhalable)	TNIK						
BRCA-mutant cancer	USP1						Out-licensed to Exelixis
Immuno-Oncology	QPCTL						Co-development with Fosun Pharma
Inflammatory Bowel Disease	PHD						Gut-restricted
Anemia of Chronic Kidney Disease	PHD						
MTAP-/- Cancer	MAT2A						IND clearance in US & CN
Mesothelioma, and Solid Tumors	TEAD						
Solid tumors	ENPP1						
ER+/HER2- breast cancer	KAT6						Out-licensed to Menarini
Solid tumors	DGKA						
Solid tumors	CDK12/13						
Solid tumors	FGFR2/3						
Solid tumors	KIF18A						
Solid tumors	WRN						
COVID-19	3CL^{PRO}						

Over 20 additional newly initiated programs in the discovery stage

*As of May 2024

Some Internal Benchmarks at Insilico Medicine

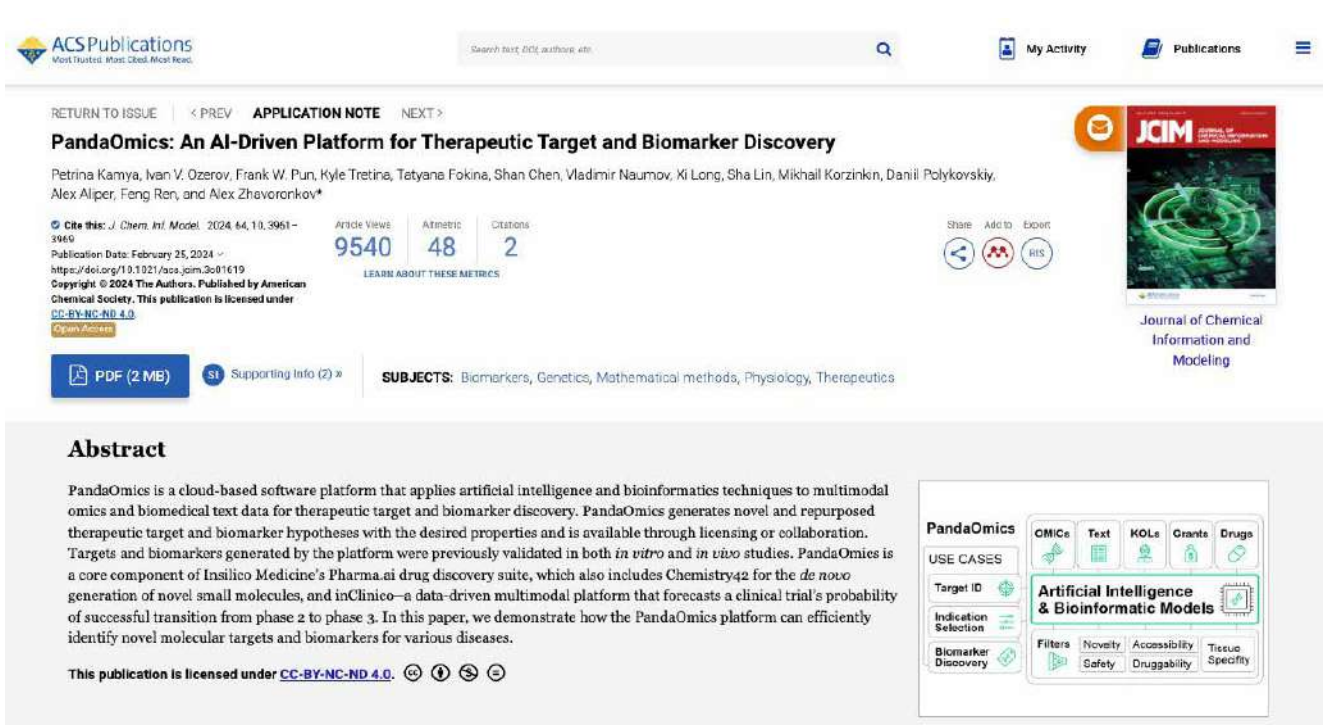
Started Internal Drug Discovery in 2019

- 18 Preclinical Candidates (PCC) Nominated
- 8 Human Clinical Trials
- 2 in Phase II
- Average Time to PCC is 13 Months
- Shortest Time to PCC – 9 Months
- Longest Time to PCC – 18 Months
- In 2022 Nominated 9 PCCs
- Annual Capacity ~ 12 PCCs

Biology42: Disease Modeling, Target Discovery andIndication Expansion Platform

60+ Target Discovery Philosophies
25+ AI Models

User Base: Biotechnology Companies, Pharma, Academics (thousands)

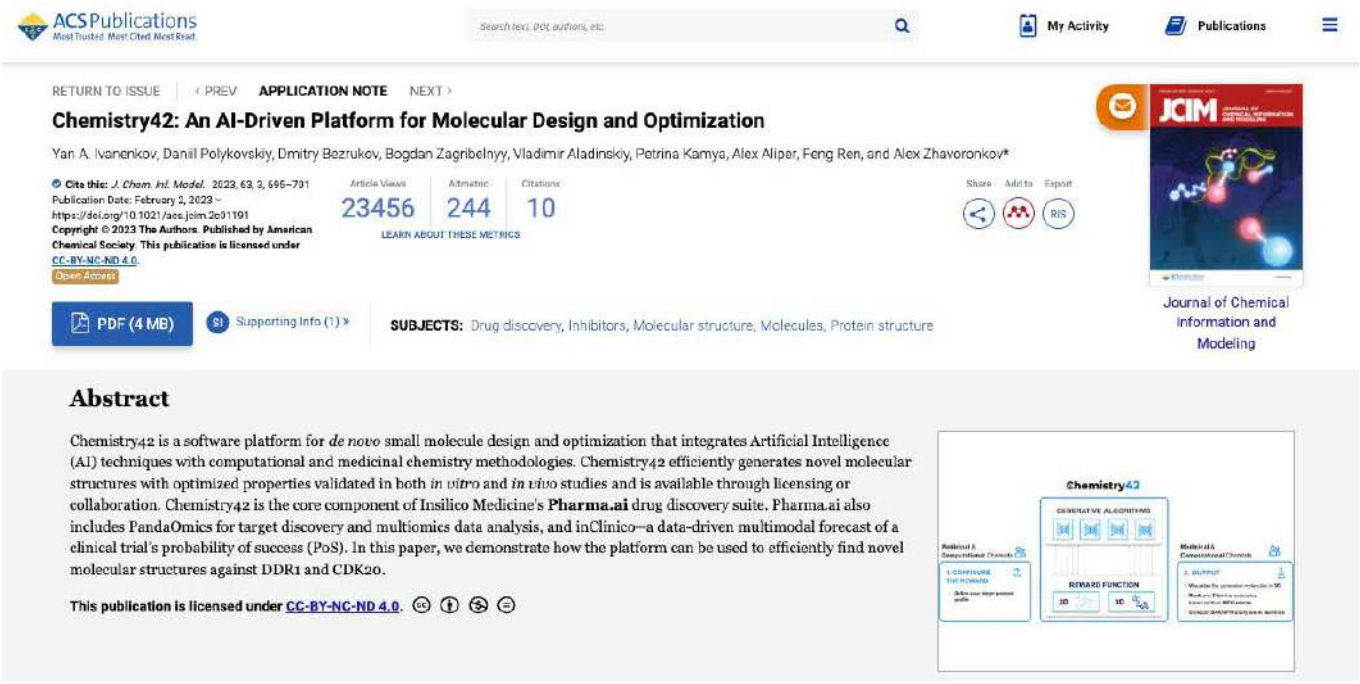


Chemistry42: Generative Chemistry Platform

40+ Generative Models
500+ Predictive Models

Alchemistry – quantum chemistry platform

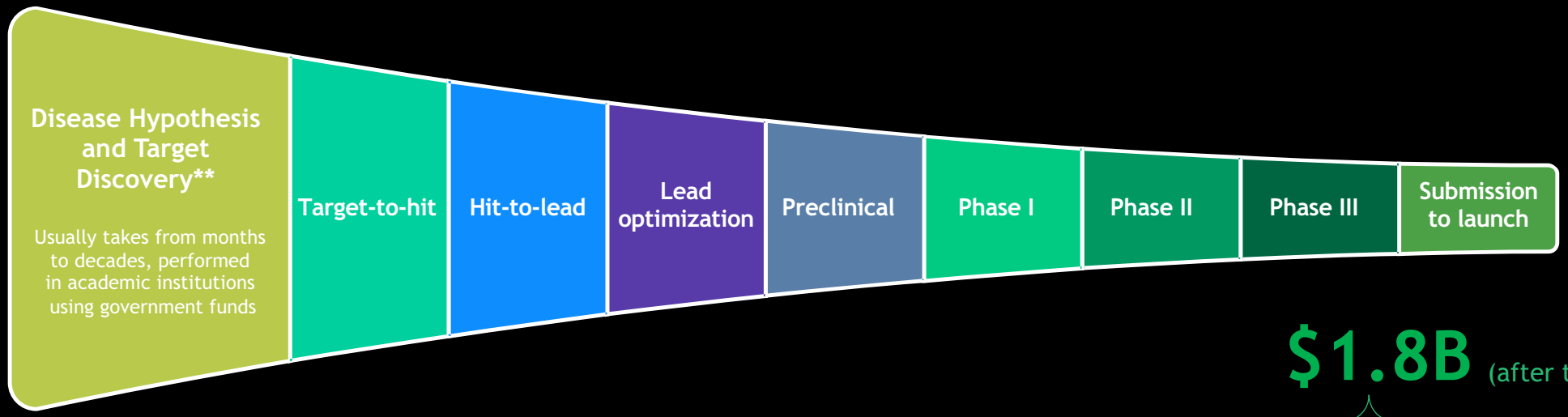
User Base: Pharma Companies (10 out of top 20)



Why End-to-End Drug Discovery and Development AI to Increase PTRS?

Why End-to-End Drug Discovery and Development AI?

- Click to edit Master text styles



$1.8B (after target discovery)

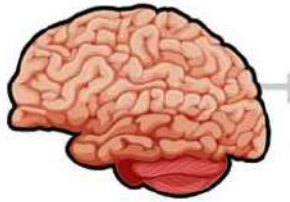
1-5 %	80%	75%	85%	69%	54%	34%	70%	91%	Probability of Success %
1-10	1.0	1.5	2.0	1.0	1.5	2.5	2.5	1.5	Cycle time (years)
$0-1000	$94	$166	$414	$150	$273	$319	$314	$48	Cost per launch (capitalized), $ Millions, 2010 data

* 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

What Can Generative AI Do For You Today?

It Can Discover and Prioritize Protein Targets

pandaOmics

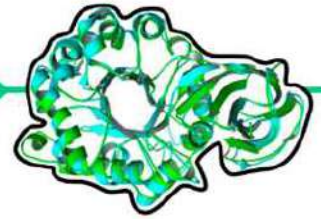


ALS patient brain samples

AnswerALS data

Other public ALS data

AI



New targets

Drugs to repurpose

Validated by experimental model

Frank Pun, PhD
Head, Insilico HK

Merit Cudlowicz, MD
Chief of Neurology and Director of the Healey & AMG Center for ALS at Mass General Hospital and Harvard Medical School

Jeffrey D. Rothstein, MD
Director, Robert Packard Center for ALS Research and Answer ALS

Bai Lu, PhD
Professor at Tsinghua University and founder of 4B Technologies

Ke Zhang, PhD
Professor of Neuroscience, Mayo Clinic

ALS.AI

In collaboration with Answer ALS, Johns Hopkins University and Mayo Clinic

OBJECTIVE

Apply Insilico AI-powered target discovery platform to search for novel targets and repurposed drugs for ALS

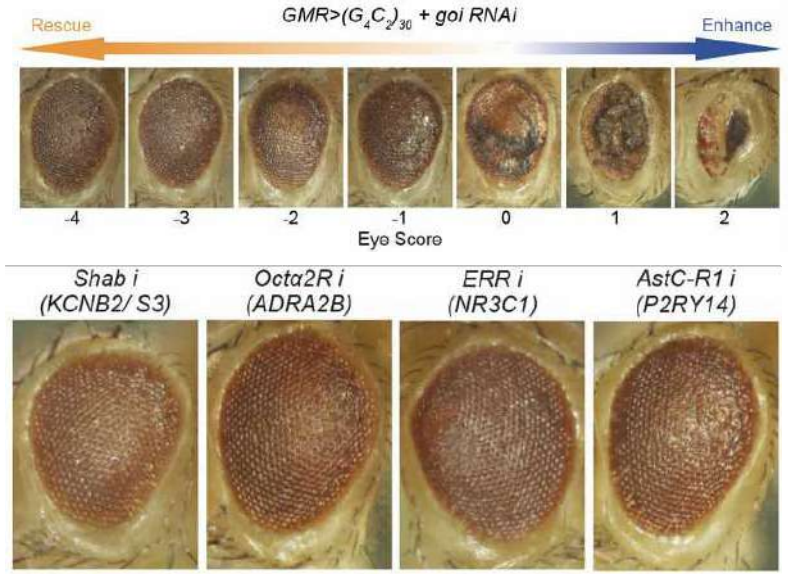
VALUE

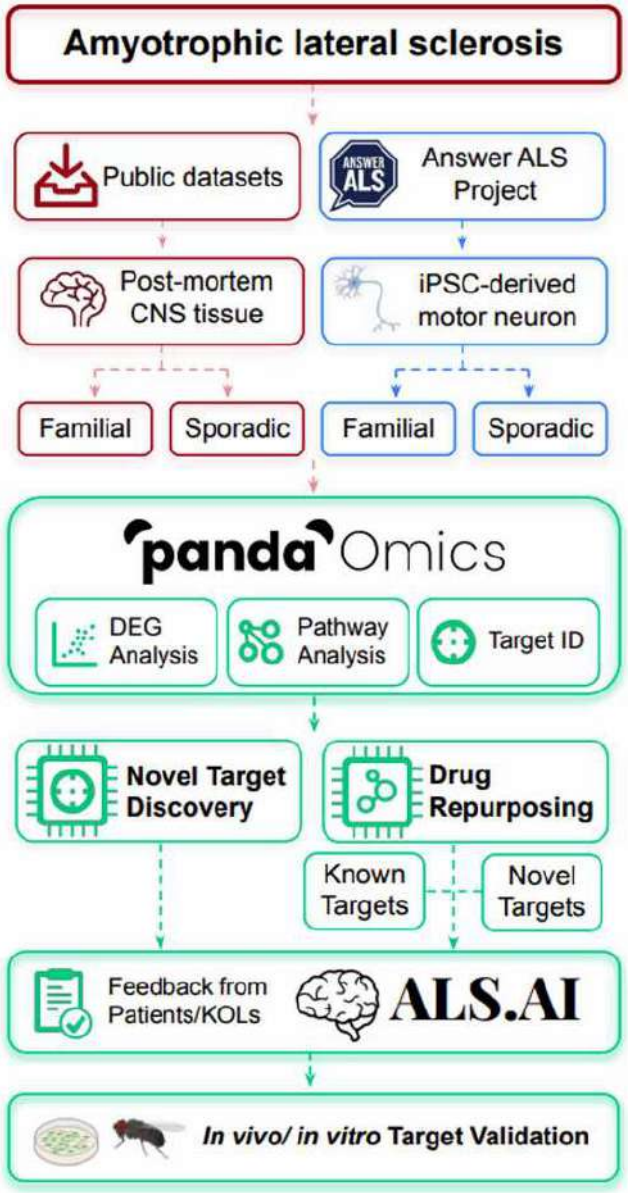
Our study exemplifies the full potential of PandaOmics for target discovery with *in vivo* validation

RESULT

Twenty-eight potential therapeutic targets that participate in a wide range of well-characterized ALS mechanisms were identified. Among the 26 proposed targets screened in the c9ALS *Drosophila* model, we verified 8 unreported genes whose perturbations strongly rescued eye neurodegeneration.

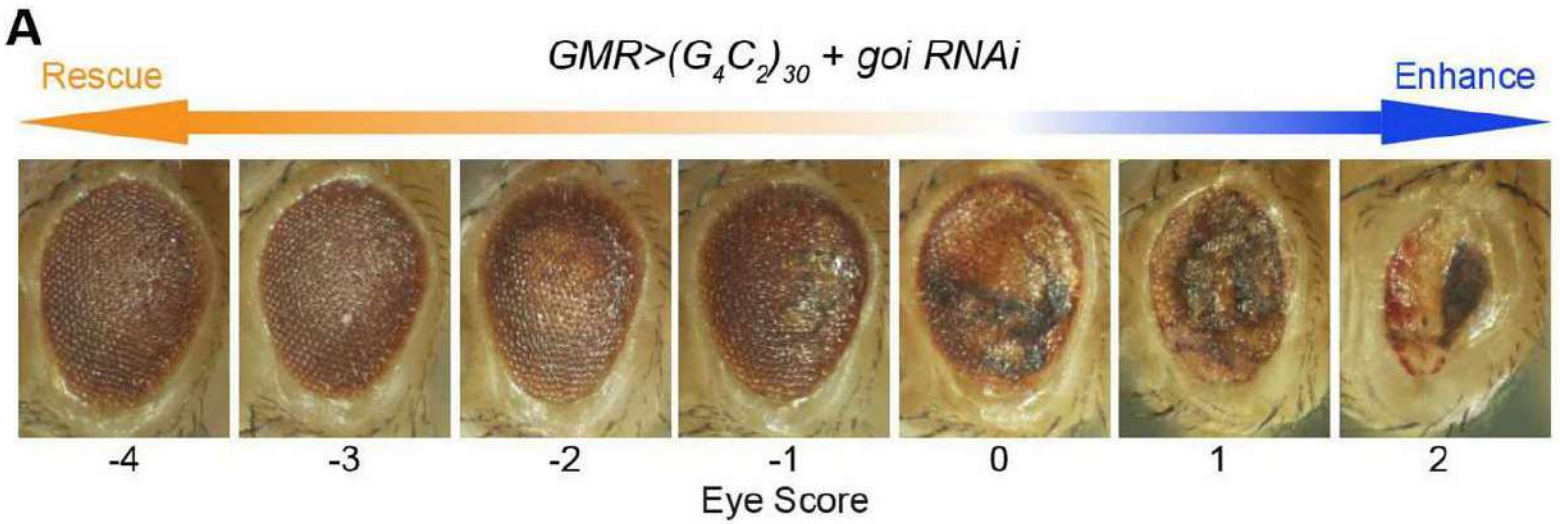
ALS.AI

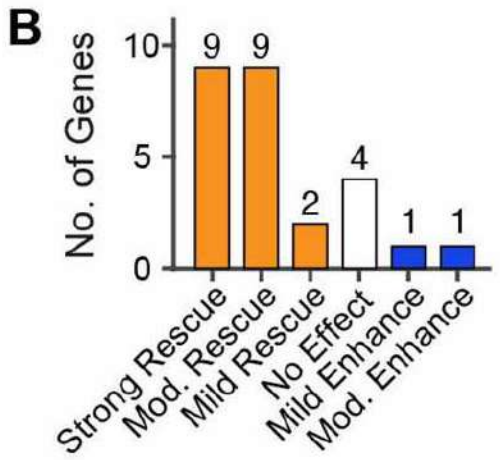




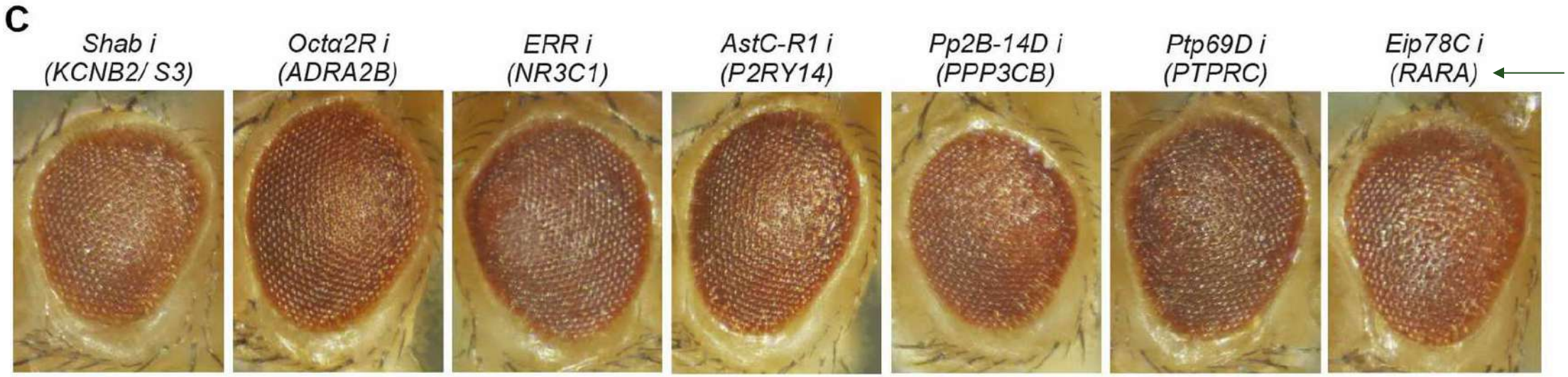
Pun *et al.*, **Front Aging Neurosci**, 2022.

Loss of 7 unreported fly orthologs, corresponding to 8 genes, strongly rescued $(G_4C_2)_{30}$- mediated neurodegeneration in a c9ALS *Drosophila* model





9 out of 26 screened genes (34.6%) reached score ≤ -3, indicating tha the **suppressions of these genes strongly rescue eye degeneration in the *Drosophila* model**



4B Technologies just enrolled ~64 patients in a clinical trial

From discovery into patients in <1 year

It Can Generate Compounds For Targets Without Crystal Structure

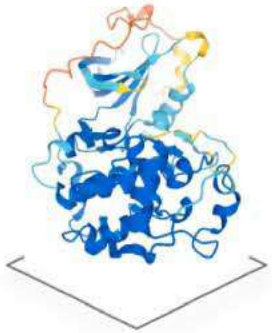
AI Discovers Target

pandaOmics

Identification of CDK20

AI Predicts Cystal

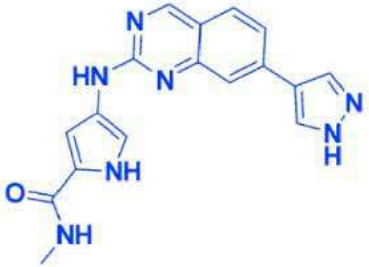
AlphaFold



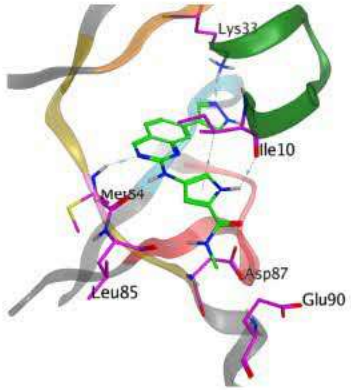
Predicted structure for dark target CDK20

AI Generates Molecules

Chemistry42

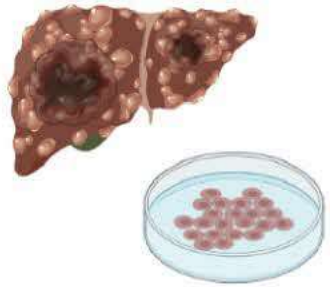


Novel Small Molecule Inhibitor ISM042-2-048



Predicted binding pose

Validation



In Vitro Validation Anti-proliferation Activity

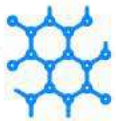
Issue 6, 2023

Chemical Science

AlphaFold accelerates artificial intelligence powered drug discovery: efficient discovery of a novel CDK20 small molecule inhibitor†

2 rounds of compound generation in Chemistry42

First round generated bioactive compounds
SBDD approach
KD (nM) = 7300



Second round enhanced compound activity
Privileged Structure approach
KD (nM) = 180

Feng Ren, Xiao Ding, Min Zheng, Mikhail Korzinkin, Xin Cai, Wei Zhu, Alexey Mantsyzov, Alex Aliper, Vladimir Aladinskiy , Zhongying Cao, Shanshan Kong, Xi Long, Bonnie Hei Man Liu, Yingtao Liu, Vladimir Naumov, Anastasia Shneyderman, Ivan V. Ozerov, Ju Wang, Frank W. Pun, Daniil Polykovskiy , Chong Sun, Michael Levitt, Alán Aspuru-Guzik and Alex Zhavoronkov

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Co-CEO & CSO,
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Michael Levitt, PhD
2013 Nobel Laureate in Chemistry
Professor, Stanford University,
Weizmann University

Alán Aspuru-Guzik, PhD
Professor and Director,
University of Toronto,
Former professor,
Harvard University

It Can Generate Compounds With The Desired Properties for a Broad Range of Targets

nature machine intelligence

Review article

https://doi.org/10.1038/s42256-024-00843-5

Machine learning-aided generative molecular design

Received: 19 July 2023

Accepted: 24 April 2024

Published online: 18 June 2024

Yuanqi Du [1,10], Arian R. Jamasb [2,3,9,10], Jeff Guo [4,5,10], Tianfan Fu [6], Charles Harris [3], Yingheng Wang [1], Chenru Duan [7], Pietro Liò [3], Philippe Schwaller [4,5], Tom L. Blundell [8]

Machine learning has provided a means to accelerate early-stage drug discovery by combining molecule generation and filtering steps in a single architecture that leverages the experience and design preferences of medicinal chemists. However, designing machine learning models that can achieve this on the fly to the satisfaction of medicinal chemists remains a challenge owing to the enormous search space. Researchers have addressed de novo design of molecules by decomposing the problem into a series of tasks determined by design criteria. Here we provide a comprehensive overview of the current state of the art in molecular design using machine learning models as well as important design decisions, such as the choice of molecular representations, generative methods and optimization strategies. Subsequently, we present a collection of practical applications in which the reviewed methodologies have been experimentally validated, encompassing both academic and industrial efforts. Finally, we draw attention to the theoretical, computational and empirical challenges in deploying generative machine learning and highlight future opportunities to better align such approaches to achieve realistic drug discovery end points.

https://www.nature.com/articles/s42256-024-00843-5

Table 4 | Experimentally validated small-molecule generative design case studies

Model	Input	Output	Design task	Target	Hit rate	Outcome	Publication year
Distribution learning							
LSTM RNN[146]	SMILES	SMILES	De novo	RXR	4/5 (80%)	nM agonist	2018
LSTM RNN[147]	SMILES	SMILES	De novo	RXR	2/4 (50%)	μM agonist	2018
GraphGMVAE[148]	Graph	SMILES	Scaffold hopping	JAK1	7/7 (100%)	nM inhibitor	2021
LSTM RNN[106]	SMILES	SMILES	De novo	LXR	17/25 (68%)	μM agonist	2021
LSTM RNN[149]	SMILES	SMILES	De novo	RORγ	3/3 (100%)	μM agonist	2021
LSTM RNN[150]	SMILES	SMILES	De novo	FLT-3	1/1 (100%)	μM inhibitor	2022
GGNN GNN[151]	Graph	Graph	Fragment linking	CDK8	9/43 (21%)	nM inhibitor	2022
GRU RNN[152]	SMILES	SMILES	De novo	Bacteria	0/1 (0%)[a]	μM inhibitor	2022
BiRNN encoder–decoder[153]	SMILES	SMILES	De novo	DDR1	2/2 (100%)	nM inhibitor	2021
GRU RNN[154]	SMILES	SMILES	Reaction-based de novo	MERTK	15/17 (88%)	μM inhibitor	2022
LSTM RNN[155]	SMILES	SMILES	De novo	PI3Kγ	3/18 (17%)	nM inhibitor	2023
Transformer[156]	SMILES	SMILES	Fragment linking	TBK1	1/1 (100%)	nM inhibitor	2023
VAE and transformer[157]	SMILES	SMILES	Fragment hopping/linking	CDK2	17/23 (74%)[c]	nM inhibitor (MC)[b]	2023
LSTM RNN[102]	SMILES	SMILES	De novo	Nurr1γ	2/6 (33%)	nM inhibitor	2023
Graph transformer-LSTM RNN[158]	Graph	SMILES	De novo	PPARγ	2/2 (100%)	μM agonist	2023
Goal oriented							
DNC[159]	SMILES	SMILES	De novo	Kinases	0[d]	μM inhibitor	2018
AAE (conditional)[160]	SMILES	SMILES	De novo	JAK3	1/1 (100%)	μM inhibitor	2018
VAE[18]	SMILES	SMILES	De novo	DDR1	4/6 (67%)	nM inhibitor[b]	2019
LSTM RNN[108]	SMILES	SMILES	De novo ligand based	DDR1	4/6 (67%)	nM inhibitor	2021
Stack-GRU RNN[161]	SMILES	SMILES	De novo	EGFR	4/15 (27%)	nM inhibitor	2022
LSTM RNN (conditional)[107]	SMILES	SMILES	De novo	RIPK1	4/8 (50%)	nM inhibitor[b]	2022
Chemistry42[50]	Mixed	Mixed	De novo structure based	CDK20	6/13 (46%)[a]	nM inhibitor	2023
Chemistry42[162]	Mixed	Mixed	De novo structure based	CDK8	1/1 (100%)	nM inhibitor[b]	2023
Chemistry42[105]	Mixed	Mixed	De novo structure based (R-group)	SIK2	6/6 (100%)	nM inhibitor	2023
VAE[163]	SMILES	SMILES	De novo structure based	KOR	2/5 (40%)	μM antagonist	2023
Chemistry42[164]	Mixed	Mixed	De novo structure based	PHD enzymes	1/1 (100%)	nM inhibitor[b]	2024
GRU RNN-transformer[165]	SMILES	SMILES	De novo activity model	NLRP3	0[e]	nM inhibitor[b]	2024
Transformer-VAE (conditional)[166]	Geometry-SMILES	SMILES	De novo	Tuberculosis ClpP	1/6 (17%)[a]	μM inhibitor	2024
QC-LSTM RNN-Chemistry42[167]	SMILES	SMILES	De novo structure based	KRAS	1/12 (8%)[a]	μM inhibitor	2024
Graph transformer[168]	Graph	Graph	De novo activity model	MGLL	1/3 (33%)[a]	μM inhibitor	2024
Chemistry42[169]	Mixed	Mixed	Fragment linking	Polθ	4/6 (67%)	μM inhibitor[b]	2024
Chemistry42[114,115]	Mixed	Mixed	De novo structure based	TNIK	Unknown[f]	nM inhibitor[b]	2024
Attention-convolution layers[170]	Substructure vector	SMILES	Scaffold based	Factor Xa	Unknown[g]	μM inhibitor	2024
Flow (conditional)[171]	Geometry	Geometry	De novo	HAT1 and YTHDC1	0/2 and 0/3 (0%)[a]	Both μM inhibitor[a]	2024
Activity model (MCTS)[42]	Variable	Variable	Reaction based	Bacteria	6/58 (10%)	μg inhibitor[b]	2024
Chemistry42[172]	Mixed	Mixed	De novo structure based	KIF18A	Unknown[h]	nM inhibitor[b]	2024
Diffusion (conditional)[173]	Geometry	Geometry	Lead optimization	CDK2	7/7 (100%)	nM inhibitor (MC)	2024

It Can Predict Outcomes of Some Clinical Trials and Help With Go-No-Go Decisions and Clinical Trial Design

inClinico

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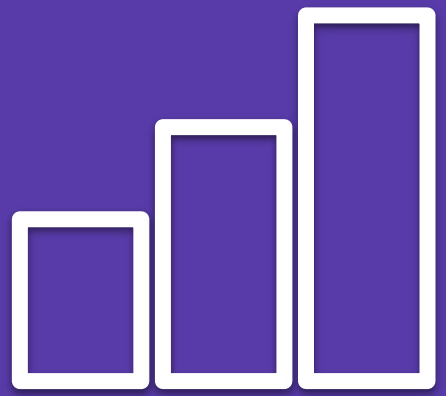
Multi-modal artificial intelligence platform for predicting and optimizing clinical trial outcomes



Platform capabilities

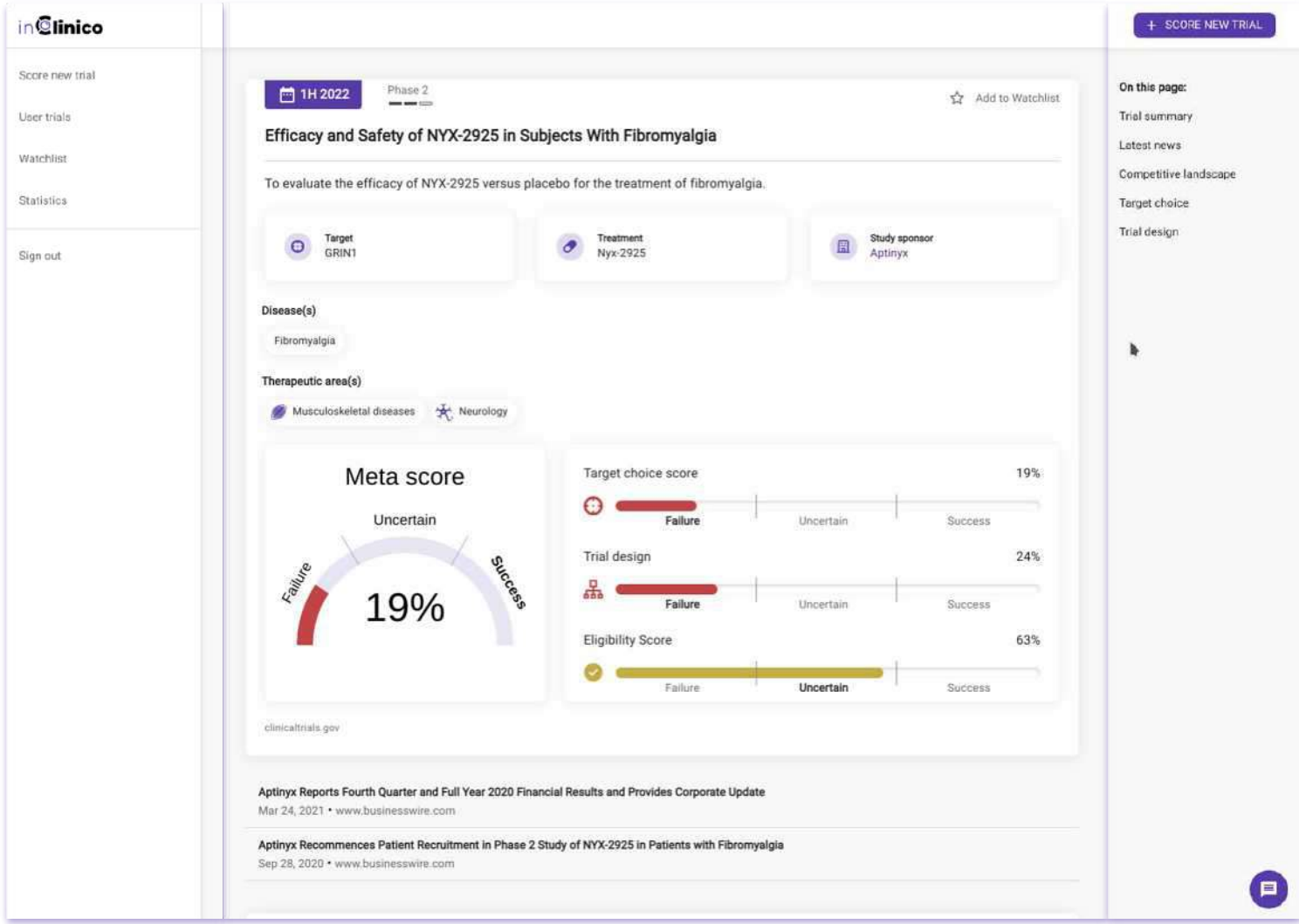
Insilico Medicine

Get **data-driven forecasts** of clinical trial outcomes

Explore and analyze clinical landscape for the given disease, therapeutic area

Score your trials, prioritize programs in early stages and optimize trial designs to improve probability of success

*Validated for Phase 2 clinical trials



Platform – approach

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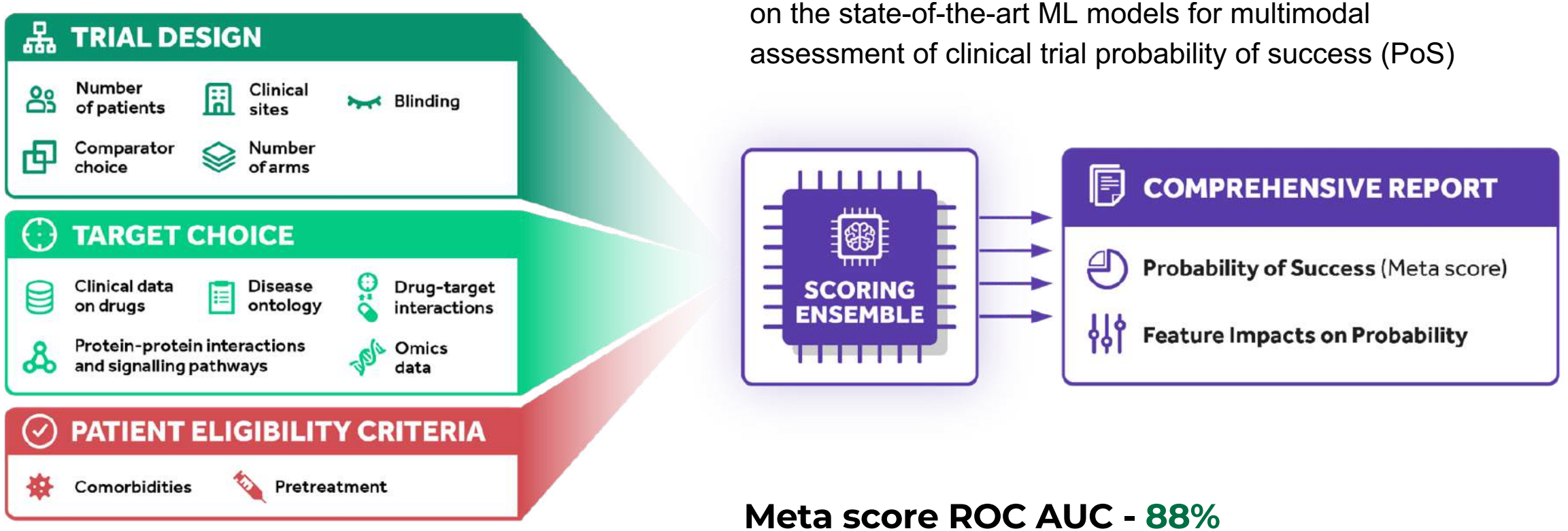


The **InClinico** platform scoring methods rely on the state-of-the-art ML models for multimodal assessment of clinical trial probability of success (PoS)

Meta score ROC AUC - 88%

Data

Insilico Medicine

Comprehensive dataset with extensive mappings on **multiple data sources**

150k
trials

41k
drugs

22k
conditions

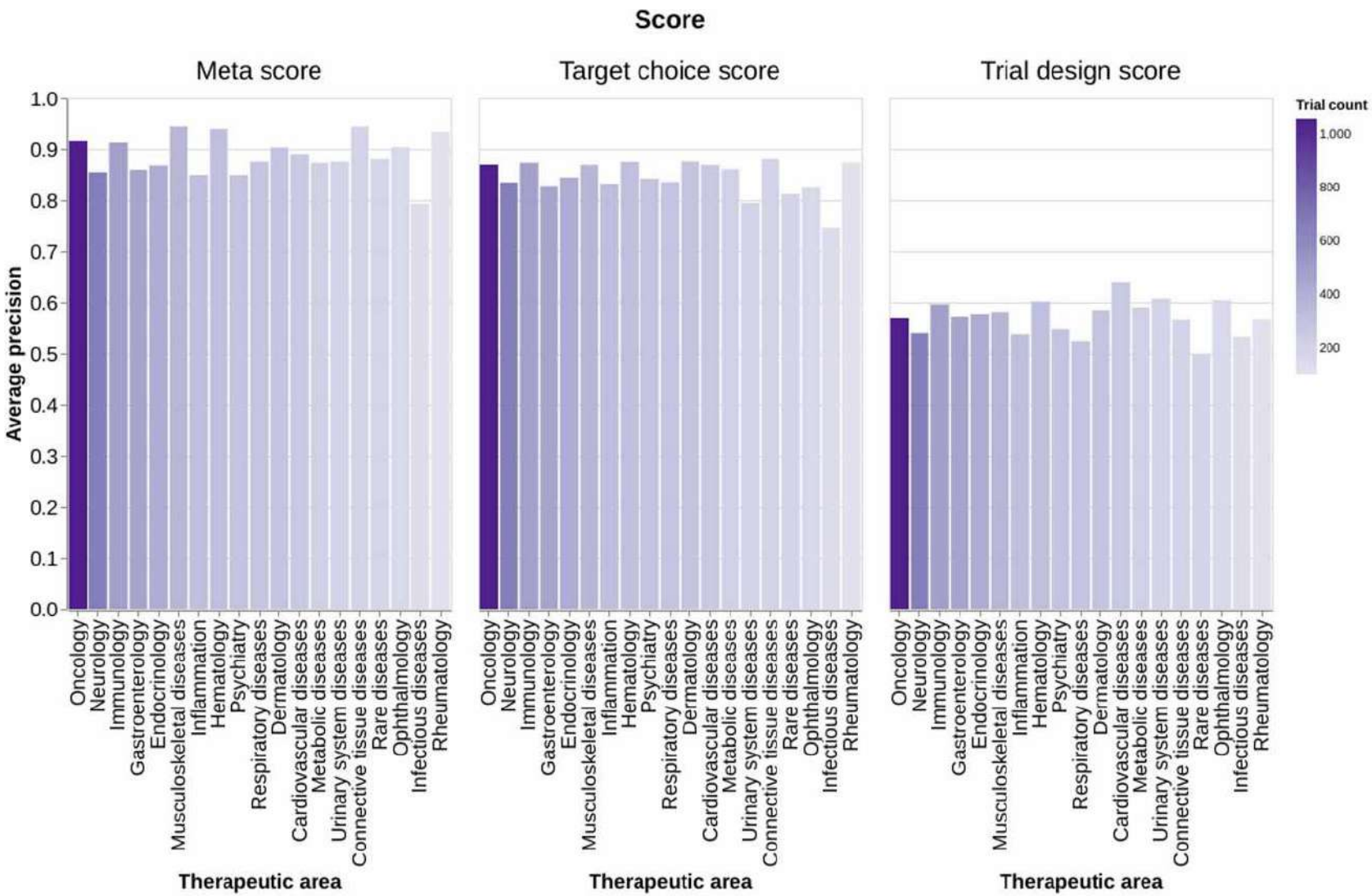
Validation

Insilico Medicine

Insilico models have been extensively **back tested**

We were able to correctly predict **more than 80%** of phase 2 ⇨ phase 3 transitions from 2018 to 2021

Quasi-Prospective Validation



Meta score ROC AUC

88%

Quasi-Prospective Validation – First-in-class drugs

	ROC AUC		Average precision	
	Overall	First-in-class	Overall	First-in-class
Meta score	0.882	0.724	0.879	0.731
Target choice score	0.841	0.697	0.841	0.701
Trial design score	0.582	0.591	0.545	0.581

Publications

Insilico Medicine

bioRxiv — December 29, 2016

Integrated deep learned transcriptomic and structure-based predictor of clinical trials outcomes

ResearchGate — April, 2020

Multimodal AI Engine for Clinical Trials Outcome Prediction: Prospective Case Study of Big Pharma for Q2 2020

Prospective forecasts for Novartis trials

ResearchGate — June, 2020

Multimodal AI Engine for Clinical Trials Outcome Prediction: Prospective Case Study Summer 2020

Prospective forecasts for Roche trials

ResearchGate — August, 2022

Multimodal AI Engine for Clinical Trials Outcome Prediction: Prospective Case Study H2 2022 -H2 2023

Prospective forecasts for small-cap and mid-cap pharma companies

Clinical Pharmacology & Therapeutics — July 22, 2023

Prediction of Clinical Trials Outcomes Based on Target Choice and Clinical Trial Design with Multi-Modal Artificial Intelligence

Analysis of prospective forecasts from August, 2022 paper and 2020 Novartis trials paper

2019

Successful pilot with Big pharma company

November 2022

inClinico 1.0 Release

June 2023

inClinico 1.1 Release

2016 2019 2020 2022 2023

Clinical Pharmacology & Therapeutics

Review | Open Access

Prediction of Clinical Trials Outcomes Based on Target Choice and Clinical Trial Design with Multi-Modal Artificial Intelligence

Alex Aliper, Roman Kudrin, Daniil Polykovskiy, Petrina Kamya, Elena Tutubalina, Shan Chen, Feng Ren, Alex Zhavoronkov

First published: 22 July 2023 | https://doi.org/10.1002/cpt.3008 | Citations: 2

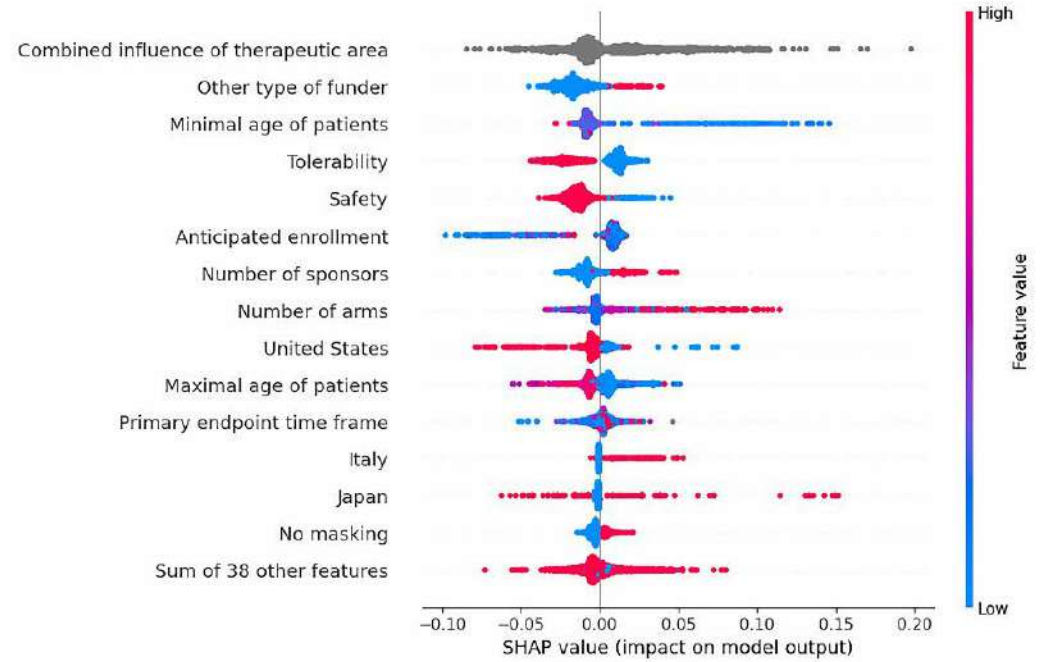


Figure 2 The features that impacted the probability of phase II clinical trial success the most as per SHAP values.[31,32] Full list of features and the descriptions are summarized in **Table S2**. SHAP, Shapley Additive Explanations.

Table 3 Prediction performance metrics for quasi-prospective validation dataset for the whole dataset of clinical trials and for clinical trials with first-in-class drugs

	ROC AUC		Average precision	
	Overall	First-in-class	Overall	First-in-class
Meta score	0.882	0.724	0.879	0.731
Target choice score	0.841	0.697	0.841	0.701
Trial design score	0.582	0.591	0.545	0.581

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

The following criteria were used simultaneously to determine if the phase II trial was successful (Table 3):

- Statistical and clinical significance of efficacy and safety end points;
- Company decision to transition drug program to phase III;
- Momentary increase of company's stock price in response to clinical trial results.

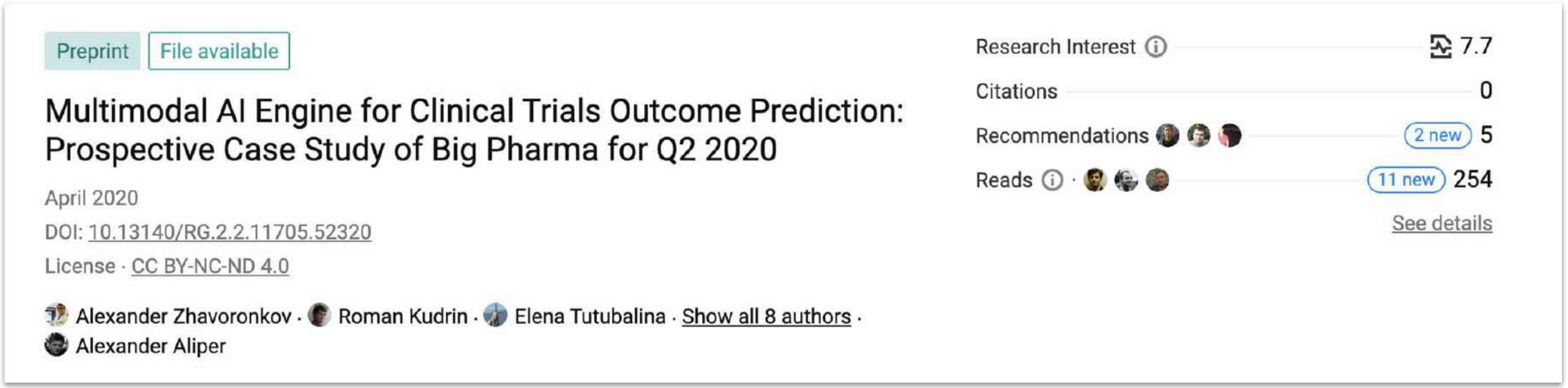
The results of trials listed in Table 4 are summarized in Table S3. It is important to note that the "success" cutoff for the inClinico meta score differs from 0.5 and is 0.48 instead. The threshold was selected by choosing the threshold which corresponded to the maximum of F1 score on a quasi-prospective validation set.

Case study—NYX-2925 for fibromyalgia conducted by Aptinyx. We used SHAP values to measure the impact of the trial design features to gain insights about the predictions. We provide SHAP values for the NYX-2925 phase II clinical trial in fibromyalgia (NCT04147858) in **Figure 4**. The main features influencing the probability of the NYX-2925 trial success are anticipated enrollment, primary type of funder, number of sponsors, tolerability, musculoskeletal system disease, safety, minimal age of patients, and location (USA). The NYX-2925 phase II clinical trial was a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of NYX-2925 in fibromyalgia. Fibromyalgia is a musculoskeletal system disease characterized by chronic widespread pain.[35] The indication of this trial, along with the absence of a tolerability measurement and several numbers of sponsors, improved the forecast probability of success. Other trial design characteristics negatively impact the probability of trial success. The expected enrollment for the NYX-2925 study was substantial for the phase II trial design (300 participants), which could increase the study duration and result in increased cost and resource utilization or failure to recruit the required number of patients. However, Aptynix was able to enroll the necessary number of participants in the allotted time.

Prospective Validation – 2020 paper

Insilico Medicine

Predict → **Publish** → **Wait** → **Compare** → **Improve the Predictor**



Preprint | File available

Multimodal AI Engine for Clinical Trials Outcome Prediction: Prospective Case Study of Big Pharma for Q2 2020

April 2020

DOI: 10.13140/RG.2.2.11705.52320

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Multimodal AI Engine for Clinical Trials Outcome Prediction: Prospective Case Study H2 2022 -H2 2023

August 2022

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Alex Aliper · Roman Kudrin · Ilya Bushmakin · Show all 9 authors · Alexander Zhavoronkov

Research Interest Score 2.1

Citations 0

Recommendations 0 new 3

Reads · 5 new 35

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Published forecasts for 40 ongoing clinical trials

19 predicted to **succeed**, **21** to **fail**

Prospective Validation — Comparison of inClinico's forecasts with actual trial outcomes

Insilico Medicine

Clinical Pharmacology & Therapeutics

Review | Open Access

Prediction of Clinical Trials Outcomes Based on Target Choice and Clinical Trial Design with Multi-Modal Artificial Intelligence

Alex Aliper, Roman Kudrin, Daniil Polykovskiy, Petrina Kamya, Elena Tutubalina, Shan Chen, Feng Ren, Alex Zhavoronkov

First published: 22 July 2023 | https://doi.org/10.1002/cpt.3008

Prospective Validation

Analysis is published in Clinical Pharmacology & Therapeutics

11 out of 14
outcomes (79%)
Predicted correctly

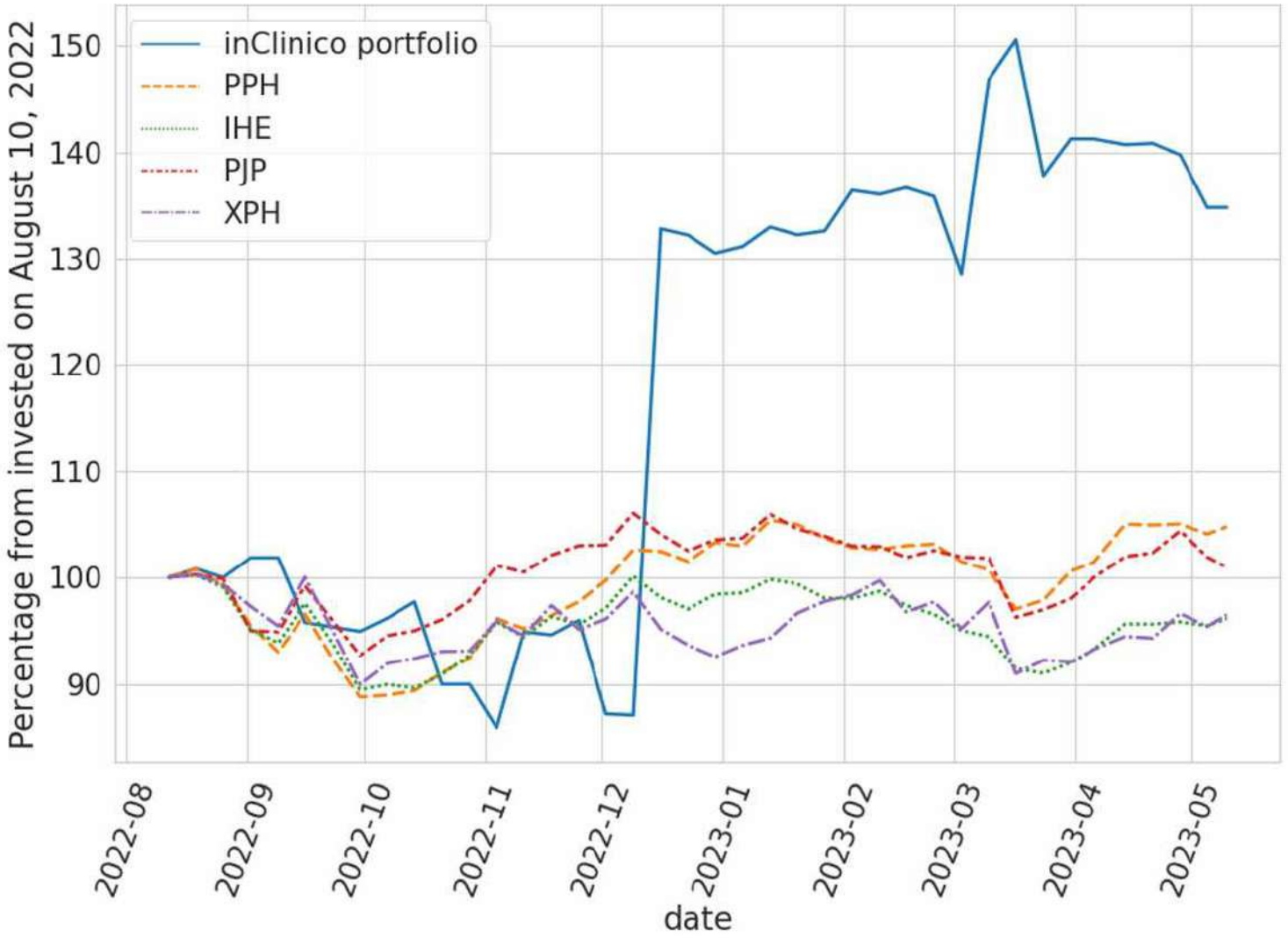
First-in-class drug for a rare disease

NCT ID	Company Ticker	Drug	inClinico Meta-score	Readout Date	Predicted Outcome	Outcome	Stock price, 10.08.2022	Stock price, Report date
NCT04456998	GOSS	Seralutinib	0.42	Q4 2022	Failure	Failure*	13.62	2.36 (-83%)
NCT04257929	HRMY	Pitolisant	0.27	H2 2022	Failure	Success	52.44	59.26 (12%)
NCT04030026	TRVI	Nalbuphine	0.37	Q3 2022	Failure	Failure*	4.26	2.45 (-42%)
NCT04147858	APTX	NYX-2925	0.09	Q3 2022	Failure	Failure	0.69	0.41 (-40%)
NCT04148391	APTX	NYX-458	0.35	Q1 2023	Failure	Failure	0.69	0.19 (-72%)
NCT04519658	AZN	Atuliflapon	0.57	H2 2022	Failure	Failure	-	-
NCT05137002	CINC	Baxdrostat	0.49	H2 2022	Success	Failure	33.35	14.11 (-58%)
NCT03818256	CORT	Miricorilant	0.42	Q4 2022	Failure	Failure	27.7	21.38 (-22%)
NCT04524403	CORT	Miricorlilant	0.42	Q4 2022	Failure	Failure	27.7	21.38 (-22%)
NCT05193409	BNOX	BNC210	0.56	Q4 2022	Success	Failure	6.32	5.89 (-7%)
NCT04265651	BBIO	Infigratinib	0.59	Q1 2023	Success	Success	11.99	18.55 (+55%)
NCT04112199	BIVI	Terlipressin	0.5	Q1 2023	Success	Success	2.05	9.2 (+349%)
NCT04109313	NVS	Remibrutinib	0.77	Q3 2022	Success	Success	-	-
NCT03896152	NVS	LNP029	0.79	Q2 2021	Success	Success	-	-

* Gossamer Bio's and Trevi Therapeutics's clinical readouts were statistically significant and presented as positive, the "Failure" assumption is based on the investment community reception

Prospective Validation

9-month Mid-& Small-cap CBOE option-based portfolio time-weighted return (TWR) – **35%**



PPH - VanEck Pharmaceutical ETF
IHE - iShares US Pharmaceuticals ETF
PJP - Invesco Dynamic Pharmaceuticals ETF
XPH - SPDR S&P Pharmaceuticals ETF

De-black-boxing

Impact of Clinical Trial Design Features on the Forecast

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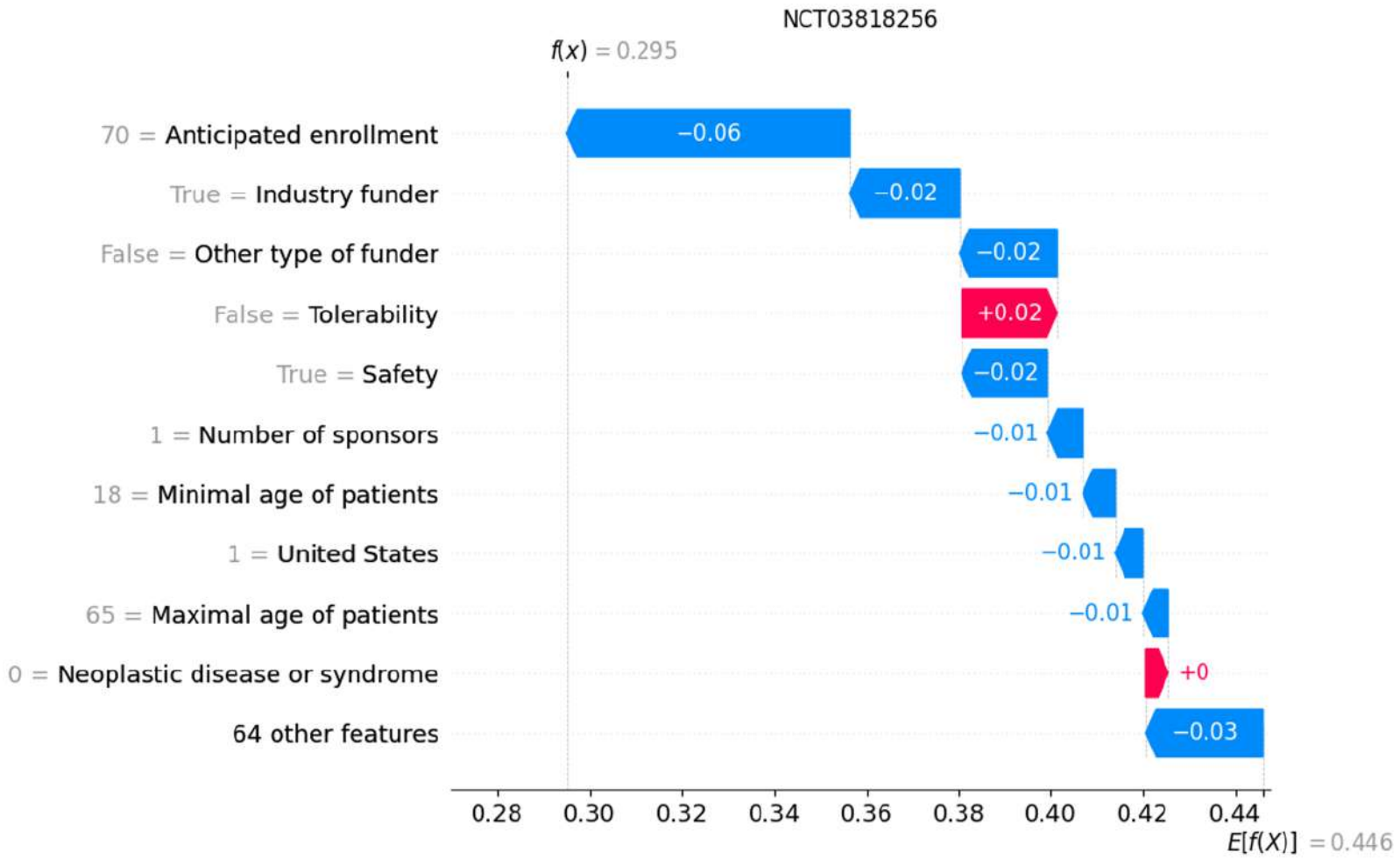
Condition	Anti-psychotic-induced weight gain
Target(s)	NR3C1, NR3C2
Organization	Corcept
NCT ID	NCT03818256
Phase	2
Readout date	December 8, 2022
Stock price change	**-22%**
Trial design score	**0.295**
Actual outcome	**Failure**



Common Use Cases

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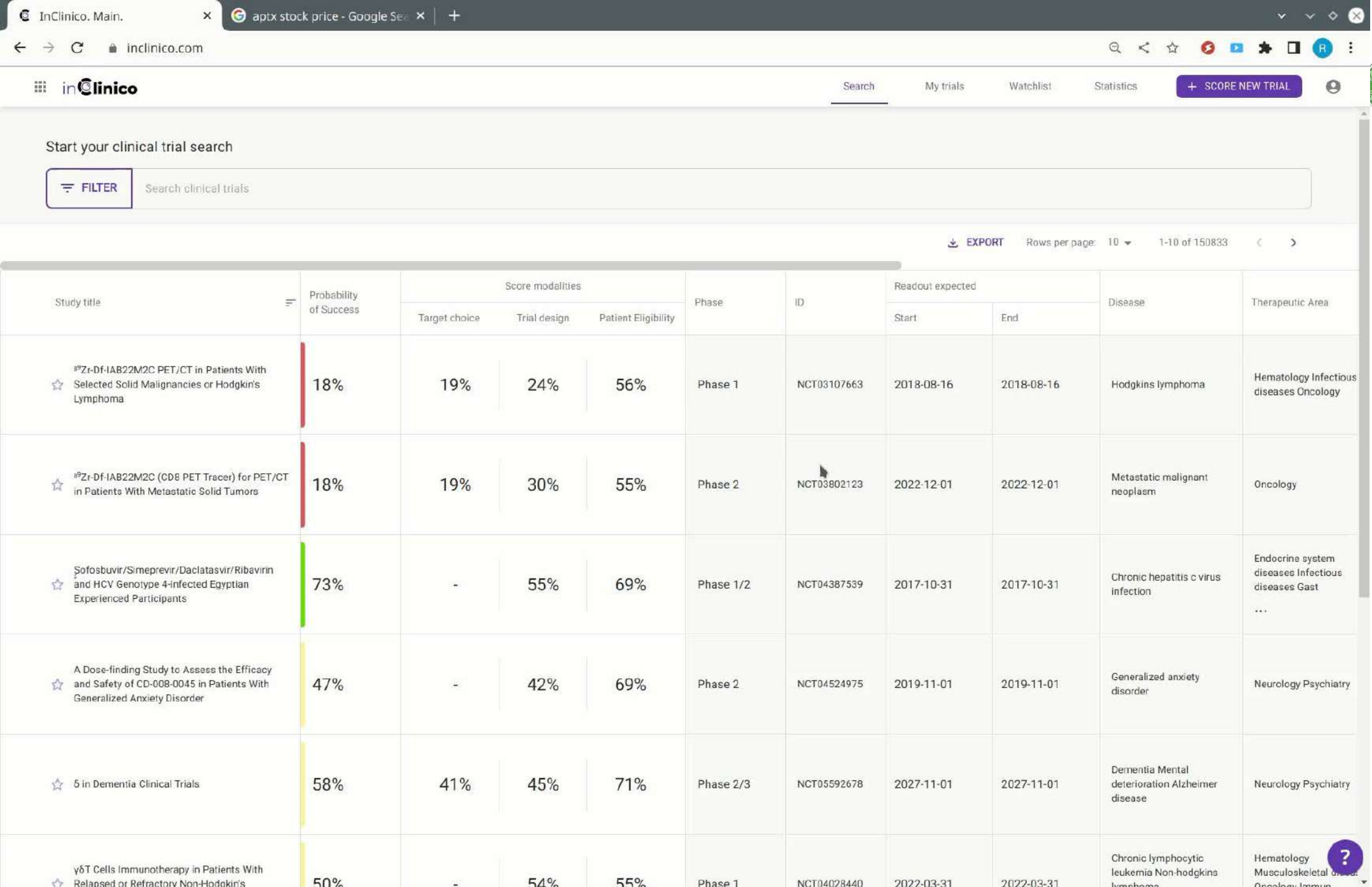
From Pharma's point of view

- Identify the red flags of current and ongoing trials to make corrections before the first patient is enrolled
- Prioritize clinical and preclinical programs
- Identify what went wrong with past trials
- Keep track of the competition

From an Investor's point of view

- Identify what companies or projects are likely to be successful
- Correctly adjust NPV for risk and value to generate greater returns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inClinico
Search
My trials
Watchlist
Statistics
SCORE NEW TRIAL
Start your clinical trial search
FILTER
Search clinical trials
EXPORT
Rows per page: 10
1-10 of 150833
Study title
Probability of Success
Score modalities
Target choice
Trial design
Patient Eligibility
Phase
ID
Readout expected
Start
End
Disease
Therapeutic Area
89Zr-Df-IAB22M2C PET/CT in Patients With Selected Solid Malignancies or Hodgkin's Lymphoma
18%
19%
24%
56%
Phase 1
NCT03107663
2018-08-16
2018-08-16
Hodgkins lymphoma
Hematology Infectious diseases Oncology
89Zr-Df-IAB22M2C (CD8 PET Tracer) for PET/CT in Patients With Metastatic Solid Tumors
18%
19%
30%
55%
Phase 2
NCT03802123
2022-12-01
2022-12-01
Metastatic malignant neoplasm
Oncology
Sofosbuvir/Simeprevir/Daclatasvir/Ribavirin and HCV Genotype 4-infected Egyptian Experienced Participants
73%
-
55%
69%
Phase 1/2
NCT04387539
2017-10-31
2017-10-31
Chronic hepatitis c virus infection
Endocrine system diseases Infectious diseases Gast ...
A Dose-finding Study to Assess the Efficacy and Safety of CD-008-0045 in Patients With Generalized Anxiety Disorder
47%
-
42%
69%
Phase 2
NCT04524975
2019-11-01
2019-11-01
Generalized anxiety disorder
Neurology Psychiatry
δ in Dementia Clinical Trials
58%
41%
45%
71%
Phase 2/3
NCT05592678
2027-11-01
2027-11-01
Dementia Mental deterioration Alzheimer disease
Neurology Psychiatry
γδT Cells Immunotherapy in Patients With Relapsed or Refractory Non-Hodgkin's
50%
-
54%
55%
Phase 1
NCT04028440
2022-03-31
2022-03-31
Chronic lymphocytic leukemia Non-hodgkins lymphoma
Hematology Musculoskeletal
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Can We Use AI to Discover a Novel Target, Generate Compounds With Desired Properties, and Predict PTRS For A Commercial Clinical Program?

nature biotechnology

Article

https://doi.org/10.1038/s41587-024-02143-0

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

Received: 26 June 2023

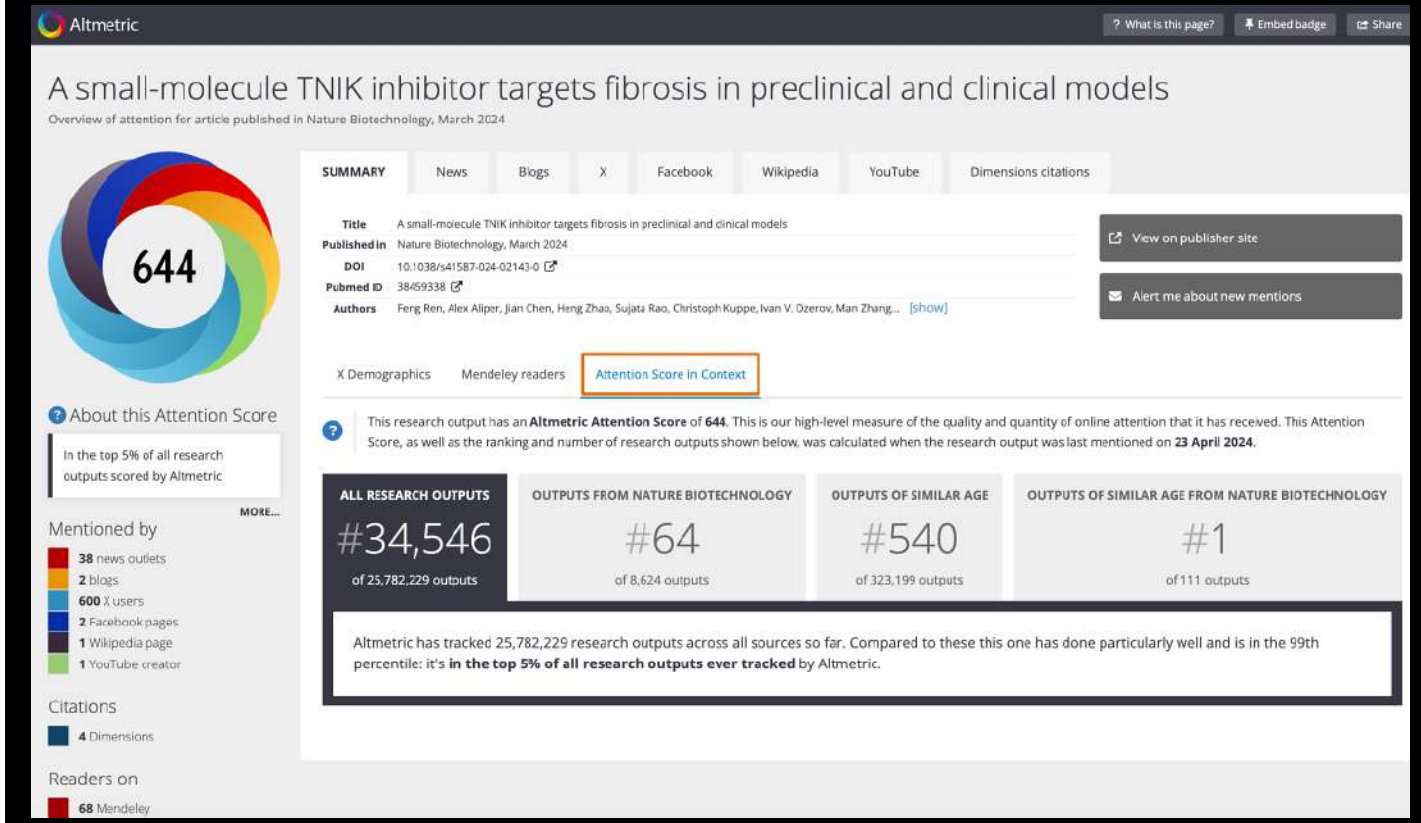
Accepted: 16 January 2024

Published online: 08 March 2024

Check for updates

Feng Ren[1,2], Alex Aliper[2,3], Jian Chen[4], Heng Zhao[1], Sujata Rao[5], Christoph Kuppe[6,7], Ivan V. Ozerov[3], Man Zhang[1], Klaus Witte[3], Chris Kruse[3], Vladimir Aladinskiy[2], Yan Ivanenkov[3], Daniil Polykovskiy[8], Yanyun Fu[1], Eugene Babin[2], Junwen Qiao[1], Xing Liang[1], Zhenzhen Mou[1], Hui Wang[1], Frank W. Pun[3], Pedro Torres Ayuso[9], Alexander Veviorskiy[2], Dandan Song[4], Sang Liu[1], Bei Zhang[1], Vladimir Naumov[3], Xiaoqiang Ding[10], Andrey Kukharenko[3], Evgeny Izumchenko[11] & Alex Zhavoronkov[2,3,5,8]

Idiopathic pulmonary fibrosis (IPF) is an aggressive interstitial lung disease with a high mortality rate. Putative drug targets in IPF have failed to translate into effective therapies at the clinical level. We identify TRAF2- and NCK-interacting kinase (TNIK) as an anti-fibrotic target using a predictive artificial intelligence (AI) approach. Using AI-driven methodology, we generated INS018_055, a small-molecule TNIK inhibitor, which exhibits desirable drug-like properties and anti-fibrotic activity across different organs in vivo through oral, inhaled or topical administration. INS018_055 possesses anti-inflammatory effects in addition to its anti-fibrotic profile, validated in multiple in vivo studies. Its safety and tolerability as well as pharmacokinetics were validated in a randomized, double-blinded, placebo-controlled phase I clinical trial (NCT05154240) involving 78 healthy participants. A separate phase I trial in China, CTR20221542, also demonstrated comparable safety and pharmacokinetic profiles. This work was completed in roughly 18 months from target discovery to preclinical candidate nomination and demonstrates the capabilities of our generative AI-driven drug-discovery pipeline.



Ren, F., Aliper, A., Chen, J. *et al.* A small-molecule TNIK inhibitor targets fibrosis in preclinical and clinical models. *Nat Biotechnol* (2024). https://doi.org/10.1038/s41587-024-02143-0
Published: March 8, 2024
https://www.nature.com/articles/s41587-024-02143-0

TNIK Discovery and Development Paper – Nature Biotechnology 2024

Documentary materials are available at ***insilico.com/docuthon***

Technology Development Phase 2014-2019

- ✓ Developed **Generative AI for Biology** (Published papers and patents)
- ✓ Developed **PandaOmics** (commercially available since 2019, limited-time free access, hundreds of KOL users, multiple application papers, >20 AI models, and >60 target discovery approaches)
- ✓ Developed **Generative AI for Chemistry** (Published papers and patents)
- ✓ Published **Generative Tensorial Reinforcement Learning** model (GENTRL) *Nature Biotechnology, 2019*
- ✓ Developed **Chemistry42** (commercially-available since 2020, multiple top 20 pharma companies as users, limited-time free access, >42 generative models, >500 predictive models)
- ✓ Developed **Predictor of Clinical Outcomes** (validated pilots with pharma)

- ✓ **Multiple Pilots and Projects with Pharmaceutical companies**
- ✓ **2019 – Decision made to test end-to-end PHARMA.AI platform with a focus on and substantial investment in experimental validation and indication expansion**

Lung fibrosis – Oral

- **SPR assay** for binding affinity
- **Selectivity assay** (enzyme profiling)
- **TNIK-knock down**
- **Inhibition of EMT, FMT** and fibrotic markers in cells
  - **MRC-5** cell line
  - **A549** cell line
  - Primary human **lung fibroblasts** 3 IPF + 3 healthy donors
  - Primary human **bronchial epithelial cells** 3 IPF + 3 healthy donors

Kidney fibrosis – Oral

- **HK-2** cell line

Skin fibrosis – Topical

- **NHDF** cells

Lung fibrosis – Oral

- **LPS-induced acute lung injury mouse model** Monotherapy study
- **Bleomycin-induced lung fibrosis mouse model**
  - **Monotherapy study**
  - **Combination study** of INS018_055 and pirfenidone
    - in **sub-therapeutic** doses
    - in **max-therapeutic** doses

Lung fibrosis – Inhalation

- **Bleomycin-induced lung fibrosis rat model** Monotherapy study

Kidney fibrosis – Oral

- **UUO-induced kidney fibrosis mouse model** Monotherapy study

Skin fibrosis – Topical

- **Bleomycin-induced skin fibrosis rat model** Monotherapy study

Phase 0
Australia
Completed April 2022

Phase 1
- **New Zealand** 78 healthy volunteers
- **China** 48 healthy volunteers

Completed April 2023

Phase 2a
- **US** 60 Patients
- **China** 60 Patients

Ongoing

insilico.com/Phase1

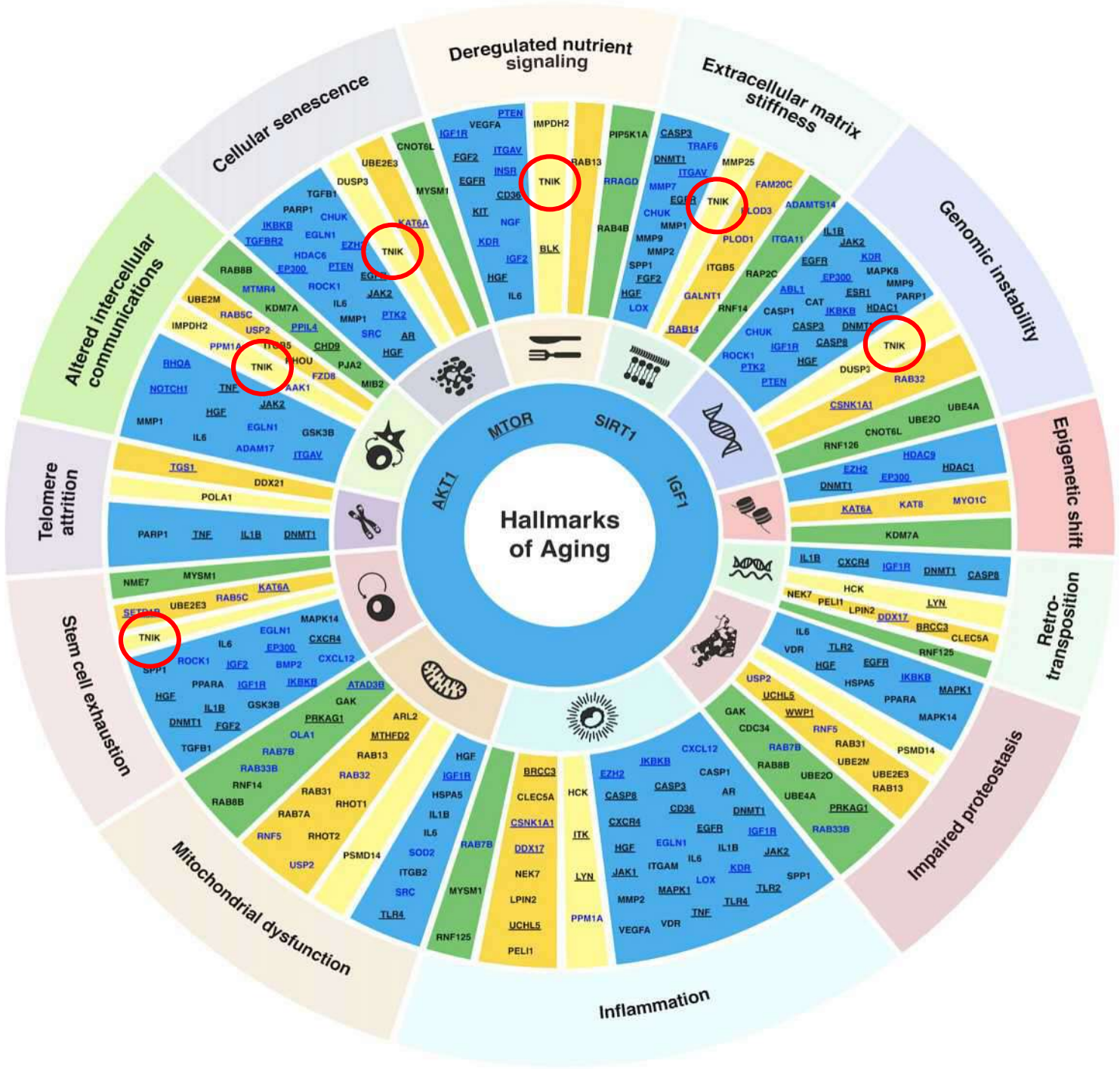
LifeStar1

Translational research
- ✓ INS018-055 study on aging & age-related diseases
- ✓ INS018-055 research on metabolite disorders

Lung Fibrosis Preclinical Candidate
February 2021 *insilico.com/blog/pcc*

Kidney Fibrosis Preclinical Candidate
August 2021 *insilico.com/blog/pcc_kidney*

Inhalation Preclinical Candidate
July 2023


Hallmarks of Aging
MTOR
SIRT1
IGF1
AKT1
Deregulated nutrient signaling
Extracellular matrix stiffness
Genomic instability
Epigenetic shift
Retro-transposition
Impaired proteostasis
Inflammation
Mitochondrial dysfunction
Stem cell exhaustion
Telomere attrition
Altered intercellular communications
Cellular senescence
TNIK
TNIK
TNIK
TNIK
TNIK

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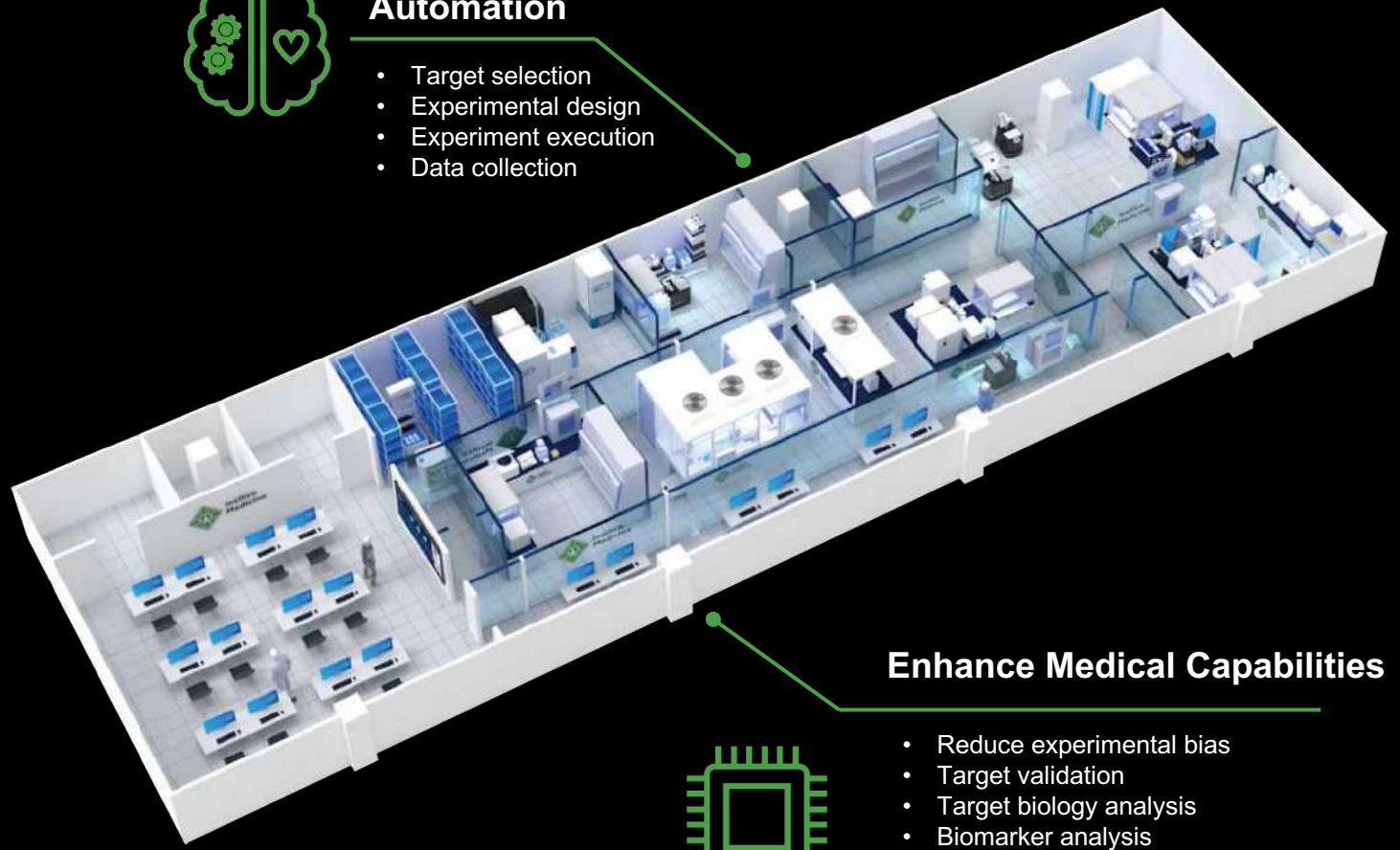
Next-gen Robotics Lab Expanding Research Capabilities

Phase out human intervention

Life Star 1 Robotics Lab

Automation

- Target selection
- Experimental design
- Experiment execution
- Data collection



Enhance Medical Capabilities

- Reduce experimental bias
- Target validation
- Target biology analysis
- Biomarker analysis
- Indication selection
- Combination strategy analysis

AI-driven Robotic Lab Has the Potential to Accelerate Early Stage Drug Discovery Process

pandaOmics

Chemistry42

RoboLab	RoboLab	RoboLab	RoboLab	RoboLab
Target Discovery	**Target Validation**	**Lead Generation**	**PCC Compound**	**Preclinical & Translational Research**
• PandaOmics predict novel targets • RoboLab discovers novel targets by 4 target ID platforms	• RNAi or CRISPR for target knock-down and knock-out • Functional assays to confirm phenotype	• Chemistry42 generates lead molecules • High-throughput hit compound screening in RoboLab for hits discovery	• Target-based, cell-based and organoid-based assays to evaluate activity of compounds • ADME assays to assess compound druggability	• Biomarker and MoA study • Indication: Large-scale cell panel sensitivity screening • Compound screening
Right Biology	**Right Target**	**Right Molecule**		**Right Patient**

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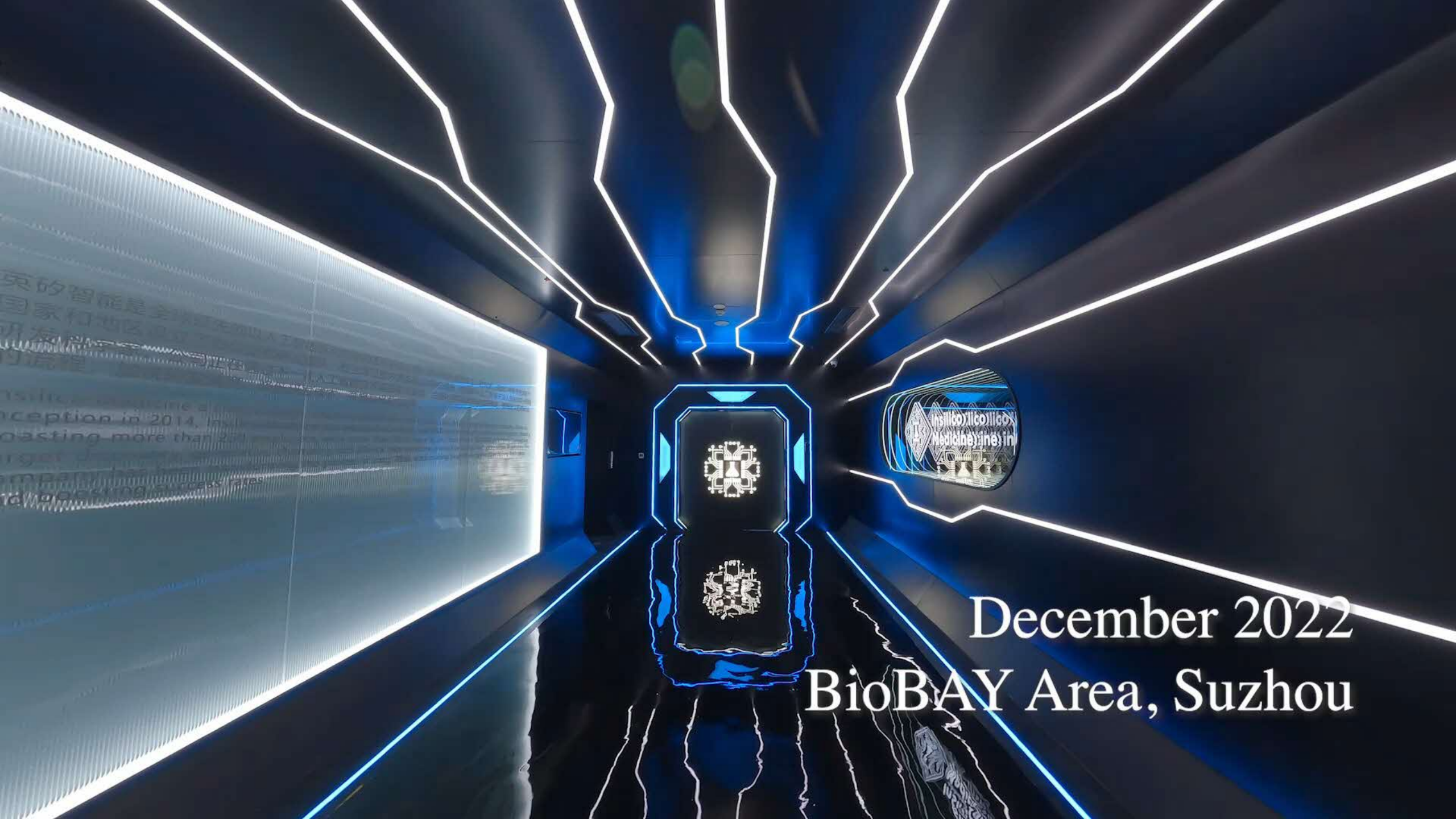
* For illustration purpose only


December 2022
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