ACCELERATING DRUG DISCOVERY AND DEVELOPMENT WITH ARTIFICIAL INTELLIGENCE
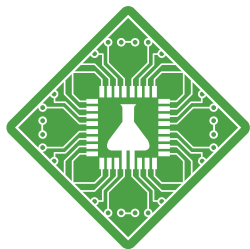
Insilico Medicine

BIOTECHNOLOGY
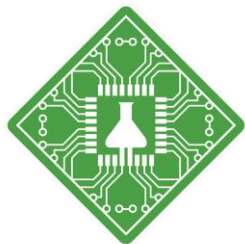
CHEMISTRY

CLINICAL TRIALS OUTCOME PREDICTIONS

Ján Szöllös, MBA
Senior Director AI Platforms BD

Insilico Medicine

An artificial intelligence (AI) drug discovery company founded in Baltimore, Maryland, in 2014

250+ employees worldwide with **70+ AI scientists, 60+ drug hunters** and **140+ scientists**

Headquarters in Hong Kong, and offices in the US, Europe and Asia

Raised **$ 395 million** in capital

At a Glance

Main AI strengths: development of **Generative Algorithms** and **Deep Learning techniques** for drug discovery and development

150+ peer-reviewed research papers since 2014

Develop AI-driven software platform – PHARMA.AI

Target discovery using omics, text and financial data

De novo design of **Novel Molecules**

Predicts **clinical trial outcomes**

30 Internal programs against 17 targets: 1 in Phase I, 8 at PCC

Insilico Medicine 1 of the **top 100 AI companies** in the world (CB Insights 2022)

Generative AI for de novo drug design

- ✓ GAN-based platforms
- ✓ Transformers
- ✓ Autoencoder-based models
- ✓ Language models (RNN-based)
- ✓ Genetic algorithms
- ✓ Combinatorial approaches
- ✓ Ensembles

All methods are combined with the Reinforcement Learning (RL) optimization, then integrated into unique end-to-end pipeline.

https://www.drugdiscoverytrends.com/a-i-to-generate-new-cancer-drugs-on-demand/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5355231/

Utilizing Generative AI in biology and small molecule chemistry since 2016!

DRUG
DISCOVERY & DEVELOPMENT®

DRUG DISCOVERY   WOMEN IN PHARMA AND BIOTECH   ONCOLOGY   NEUROLOGICAL DISEASE   INFECTIOUS DISEASE

A.I. to Generate New Cancer Drugs on Demand

By Insilico Medicine | December 22, 2016

BRIEF COMMUNICATION

https://doi.org/10.1038/s41587-019-0224-x

Deep learning enables rapid identification of potent DDR1 kinase inhibitors

Alex Zhavoronkov[1]*, Yan A. Ivanenkov[1], Alex Aliper[1], Mark S. Veselov[1], Vladimir A. Aladinskiy[1],
Anastasiya V. Aladinskaya[1], Victor A. Terentiev[1], Daniil A. Polykovskiy[1], Maksim D. Kuznetsov[1],
Arip Asadulaev[1], Yury Volkov[1], Artem Zholus[1], Rim R. Shayakhmetov[1], Alexander Zhebrak[1],
Lidiya I. Minaeva[1], Bogdan A. Zagribelnyy[1], Lennart H. Lee[2], Richard Soll[2], David Madge[2], Li Xin[2],
Tao Guo[2] and Alán Aspuru-Guzik[3,4,5,6]

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Insilico Medicine's AI uncovers 28 new potential drug targets for ALS
By Conor Hale · Jul 7, 2022 09:10am

TECH - CORONAVIRUS

Startup uses A.I. to identify molecules that could fight coronavirus

BY JEREMY KAHN
February 6, 2020 3:00 PM GMT+1

Issue 6, 2023   Previous Article

From the journal:
Chemical Science

Check fo

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

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 A. Polykovskiy, Chong Sun, Michael Levitt, Alán
Aspuru-Guzik and Alex Zhavoronkov

WSJ PRO

Biotech Companies Tap AI to Speed Path to Coronavirus Treatments

The hope is that AI can identify drug prospects to test on humans within months

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First Up A new recycling fee for Ontario consumers + why police ruled out a break-in in Sherman deaths

CANADA
U of T researchers used AI to discover a potential new cancer drug — in less than a month

The project, a collaboration between Insilico Medicine and the University of Toronto's Acceleration Consortium, used a revolutionary program to identify a weak point in liver cancer cells and synthesize a drug to attack it.

Insilico Medicine launches a 6th generation Intelligent Robotics Drug Discovery Laboratory

INSIDE PRECISION MEDICINE
Brought to you by Mary Ann Liebert, Inc., publishers

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Artificial Intelligence Patient Care Lung Diseases News & Features Topics

Insilico Medicine's AI-Designed Fibrosis Drug Passes Phase I Hurdle

January 10, 2023

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MEDTECH
Insilico Medicine begins first human trial of its AI-designed drug for pulmonary fibrosis
By Conor Hale · Nov 30, 2021 04:00pm
Artificial Intelligence clinical research drug discovery idiopathic pulmonary fibrosis

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BIOTECH
Amid 'biotech winter,' Insilico turns up the heat with Sanofi deal worth $1.2B in biobucks
By Gabrielle Masson · Nov 8, 2022 09:00am
Insilico Medicine Sanofi biotech deals drug discovery

World Class Management Team with Deep Expertise in AI and Drug R&D

Insilico Medicine

Alex Zhavoronkov, PhD
Founder & CEO

- 20 years experience in IT, HPC, bioinformatics
- Former Director, ATI Technologies (acquired by AMD for >$5bn)
- Former Adj. Professor, MIPT
- 150+ publications, 2 books
- B.S. from Queen's University,
- M.S. from Johns Hopkins University, PhD from MSU

Feng Ren, PhD
CSO & Co-CEO

- 14+ years experience across Pharma and CROs in both US and China
- Former SVP & Head of Drug Discovery Service, Medicilon
- Former Director & Head of Medicinal Chemistry, GSK, ND DPU
- PhD from Harvard University
- 30+ peer-reviewed publications

Alex Aliper, PhD
President

- 12+ years experience in Bioinformatics and Deep Learning
- Former Senior Bioinformatics Scientist, CPHOI
- Formerly with GeneGo (acquired by Thomson Reuters)
- 50+ peer-reviewed publications
- Endpoints "The 20 under 40 in Biopharma"
- PhD from SRC IBR

Nirav Jhaveri, CFA
Chief Financial Officer

- 15+ years experience in Finance
- Former CFO, Journey Medical Corp.
- Former VP of Business Development, Fortress Biotech
- Former analyst, equity research, Citigroup
- BA from University of Pennsylvania, MBA from NY

Michelle Chen, PhD
Chief Business Officer

- 20+ years experience in BD
- Former SVP of Corp Dev and Discovery BD, WuXi Biologics
- Former Executive Director, Business Development & Licensing, Merck
- Former Global Oncology Business Development Director, Roche
- PhD from University of Washington, Post-doc from UCSF

Surata Rao, MD
SVP- Head of Clinical Development

- 30+ years experience in extensive clinical development, academic and medical practice
- Former AVP of Global Clinical Development, Eli Lilly
- Former Immuno-Oncology Medical Leader and Oncology Scientific Advisor, Bristol-Myers Squibb
- Former Sr. Medical Director, Onyx (Amgen)
- MD from Jacobs School of Medicine and Biomedical Sciences

Advisory Board Comprised of AI Experts, Biologists, Chemists and Drug Hunters

Charles Cantor, PhD
Co-founder of Sequenom,
Professor, Boston University

Expert in Genomics
Former Principal Scientist
of Human Genome Project

Michael Levitt, PhD
Professor, Stanford University
Professor, Weizmann University

Expert in Computational Biology
and Structural Biology,
2013 Nobel Laureate in Chemistry

Kai-Fu Lee, PhD
Chairman and CEO, Sinovation Ventures,
President, Sinovation Venture's
Artificial Intelligence Institute

Expert in Artificial Intelligence

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

Expert in Generative Chemistry
and Quantum Computing

Klaus Witte, PhD
Co-founder of Sequenom,
Member of the German Society of Pharmacology
& Toxicology, Member of the Ethics Commission II,
University of Heidelberg

Expert in Genomics, Former Principal Scientist
of Human Genome Project

Stevan W Djuric, PhD
Adjunct Professor at the University of Kansas,
Former Vice President AbbVie

Expert in Medicinal Chemistry Technologies,
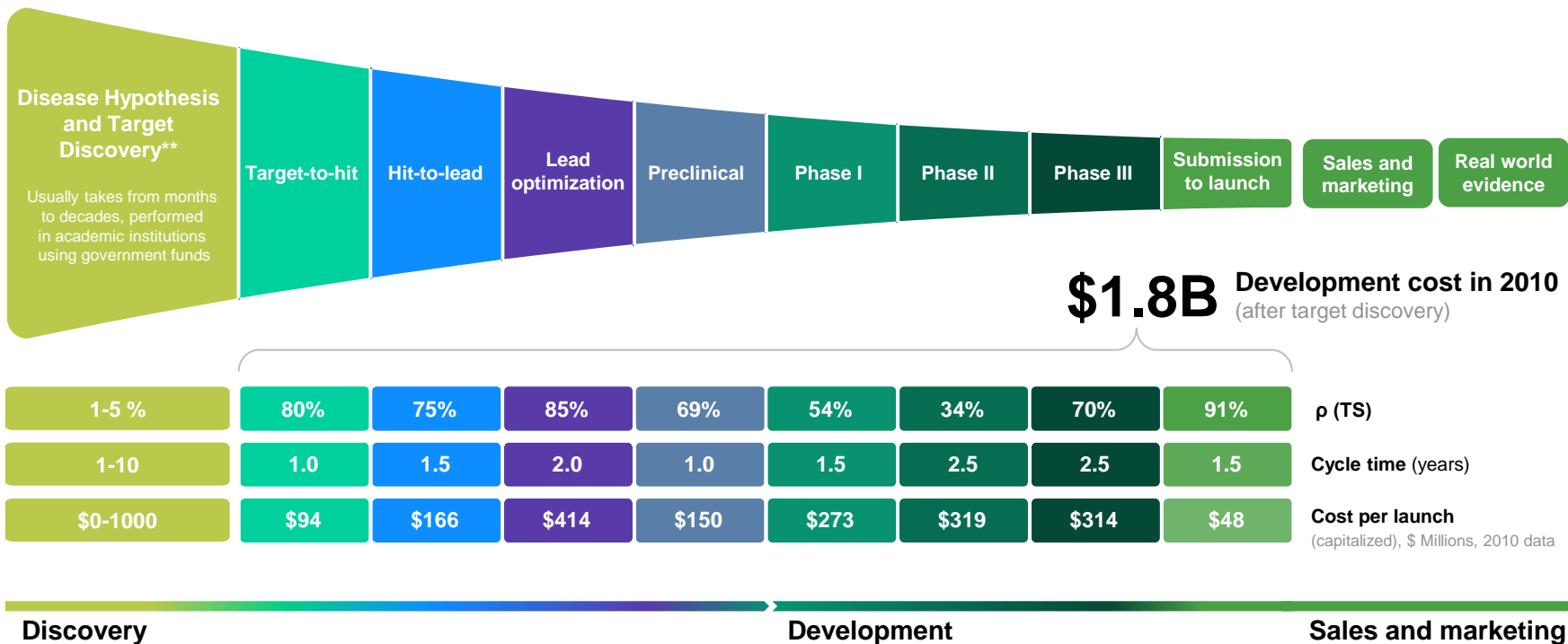Immunoinflammatory Disease Research

Bud Mishra, PhD
Professor at the Courant Institute,
Mathematical Sciences, New York University

Computer Scientist,
ISI highly cited researcher in Computer Science

Donald Small, MD, PhD
Director of Pediatric
Oncology and Professor,
Johns Hopkins Medical Institute (JHMI)

Expert in Pharmaceutical Research
in Target Discovery

Traditional drug R&D takes >10 years and >$2.0B

for a novel drug from discovery to launch (in 2010 and constantly increasing)

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Disease Hypothesis and Target Discovery**	Target-to-hit	Hit-to-lead	Lead optimization	Preclinical	Phase I	Phase II	Phase III	Submission to launch	Sales and marketing	Real world evidence
Usually takes from months to decades, performed in academic institutions using government funds										

$1.8B Development cost in 2010 (after target discovery)

1-5 %	80%	75%	85%	69%	54%	34%	70%	91%	ρ (TS)
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

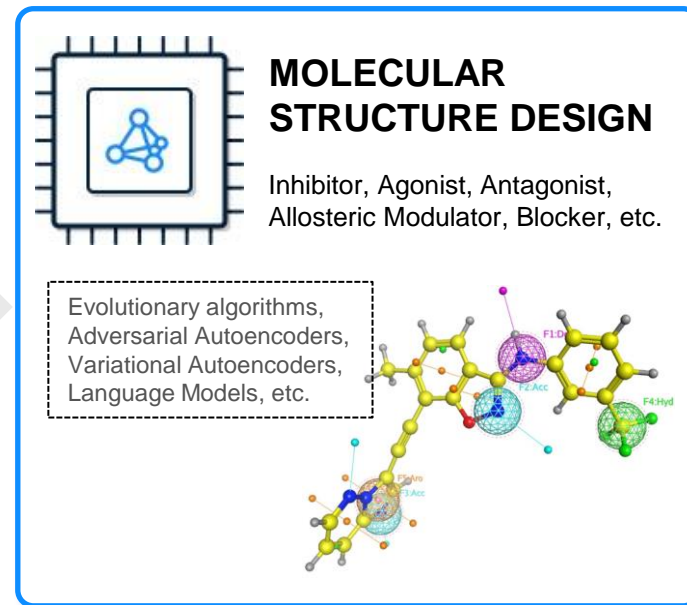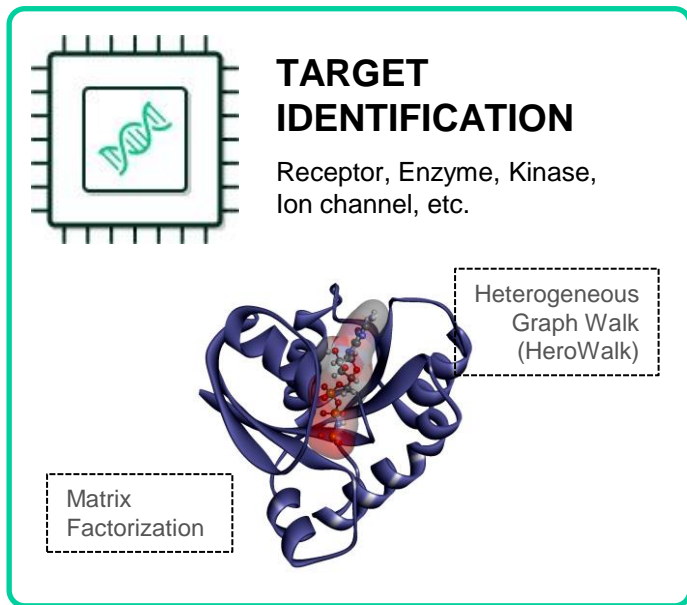**Discovery**   **Development**   **Sales and marketing**

* 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
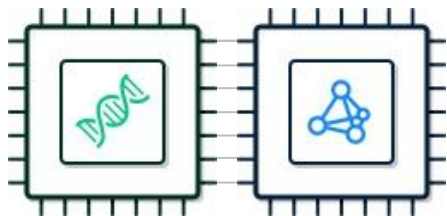
Traditional Drug Discovery Process: Expanded

Insilico Medicine

Preclinical Development | **Clinical Development**

Preclinical candidate (PCC)

Clinical Trial

Phase 1 | Phase 2 | Phase 3

| **Disease hypothesis** | **Target ID / Validation** | **Hit Identification** | **Lead optimization** | **IND-Enabling Studies** | **Safety & PK** | **Dose finding & efficacy** | **Efficacy** |

Phenotypic data analysis

Genetic data analysis

Transcriptomic and **Proteomics** data analysis

Competitive landscape

Competitors **safety & toxicity** analysis

In vitro Knock-down / Knock-out study

Assay **development**

Screening of compound / fragment libraries

Design from known compounds

Structural Biology

SAR**** study

In vitro **pharmacology**

Disease origin research

Disease causality research

Literature research

Clinical data analysis

Key opinion leader ideas

Drug effects research

Trial and error

Bioinformatics analysis

Target **structure**

Target **signaling**

Target **expression** and distribution

Target **physiology** function

Target **interaction**

Disease **association**

Preclinical assay and disease model

Obtain **crystal structure**

Compound **Synthesis**

In vitro **enzymatic** study

Cellular PD** study

Cellular Functional Study

Physicochemical property & **ADME***** ADME

Cellular **Toxicity**

Early **Developability** Assessment

In vivo **PK*** study (m, r, d, mk)

In vivo **PK*** / **PD**** study

In vivo **efficacy** study

Met ID analysis

In vitro **tox** counter-screenings

Pre-formulation

Solubility / **Permeability** evaluation

Human dose projection

Non-GLP tox study

Process **development**

Salt / Form screening

GLP tox batch synthesis

GMP batch manufacture (kg)

Formulation screening / selection

DMPK for IND

Pharmacology for IND

PK* / **PD**** for IND

GLP-Toxicology

*   PK: Pharmacokinetics
**   PD: Pharmacodynamics
*** ADME: Absorption, Distribution, Metabolism, Excretion
**** SAR: Structure-Activity-Relationship

Drug Discovery Process at glance

TARGET IDENTIFICATION

Receptor, Enzyme, Kinase, Ion channel, etc.

Heterogeneous Graph Walk (HeroWalk)

Matrix Factorization

Mechanism of Action

MOLECULAR STRUCTURE DESIGN

Inhibitor, Agonist, Antagonist, Allosteric Modulator, Blocker, etc.

Evolutionary algorithms, Adversarial Autoencoders, Variational Autoencoders, Language Models, etc.

Desired Phenotypic Effect

https://visualsonline.cancer.gov/details.cfm?imageid=11166

* Yan et al. Enhancing Molecular Shape Comparison by Weighted Gaussian Functions. J. Chem. Inf. Model. 2013, 53, 1967-1978

PHARMA.AI – End-to-End AI-powered Drug Discovery
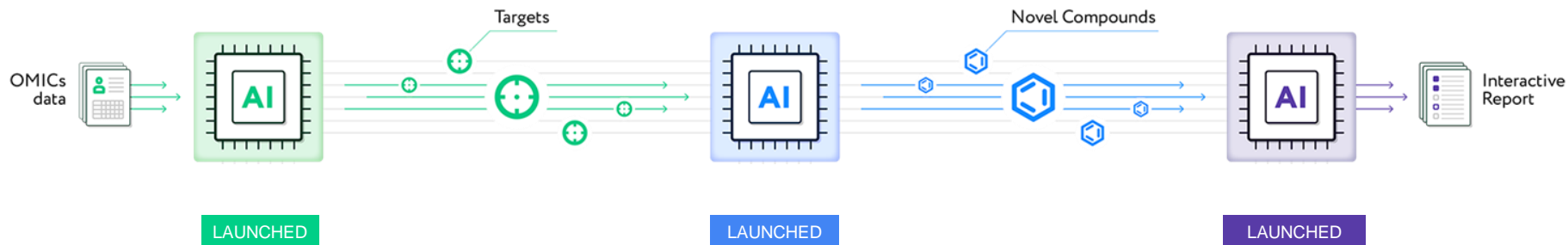
Insilico Medicine

panda Omics

Chemistry 42

in **Clinico**

**OMICs Research,
Target Identification,
Biomarker Identification**

De novo
**Small Molecule Generation
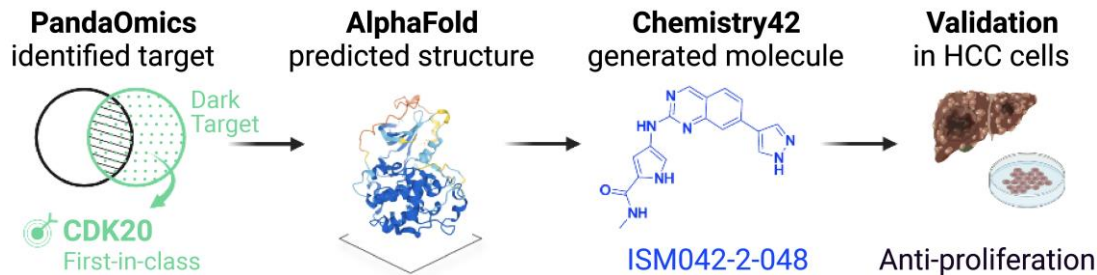and Virtual Screening**

**Clinical Trial
Outcomes Prediction**

OMICs data — AI — Targets

Novel Compounds — AI — Interactive Report

LAUNCHED

LAUNCHED

LAUNCHED

AI-Discovered Novel Target and AI-Designed Novel Anti-Fibrotic Small Molecule with Multi-Purpose Target in Phase I in 30-months
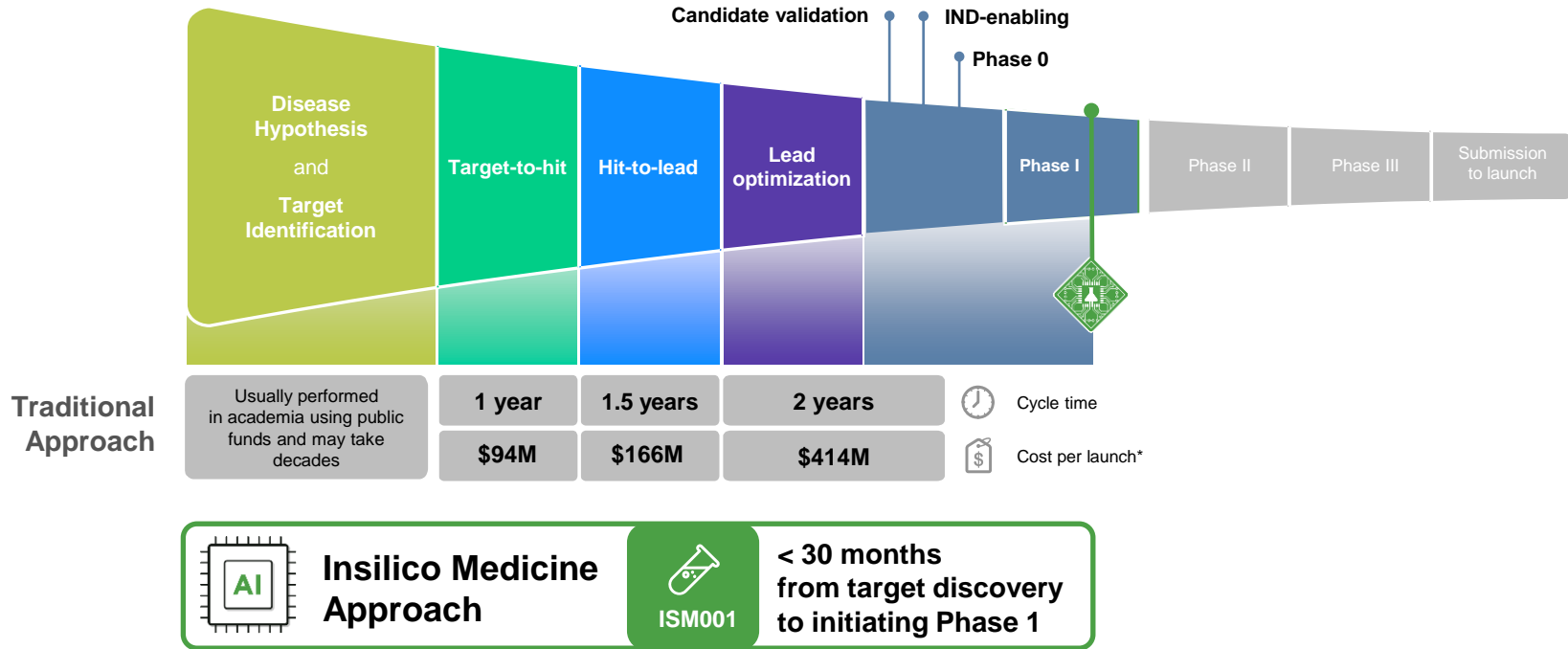
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Candidate validation   IND-enabling

Phase 0

| Disease Hypothesis and Target Identification | Target-to-hit | Hit-to-lead | Lead optimization | | Phase I | Phase II | Phase III | Submission to launch |

Traditional Approach

| Usually performed in academia using public funds and may take decades | 1 year | 1.5 years | 2 years | Cycle time |
| | $94M | $166M | $414M | Cost per launch* |

AI **Insilico Medicine Approach**   **ISM001**   **< 30 months from target discovery to initiating Phase 1**

Consortium of Researchers Used Different AI to Discover a Potential New Cancer Drug in Less than a Month

Insilico Medicine

PandaOmics identified target
Dark Target
CDK20 First-in-class

AlphaFold predicted structure

Chemistry42 generated molecule
ISM042-2-048

Validation in HCC cells
Anti-proliferation

✓ Potent hit molecule, **ISM042-2-048**, was discovered with an average Kd value of 566.7 ± 256.2 nM ($n = 3$) and an average IC_{50} value of 33.4 ± 22.6 nM ($n = 3$).

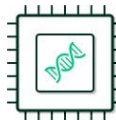✓ Good anti-proliferation activity in an HCC cell line Huh7
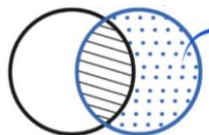
✓ Didn't induce indiscriminate cyto-toxicity

A
C-terminal
R305
M84

B
Phe81
Phe146
Met84
Asp87
Glu90

Model Confidence:
■ Very high (pLDDT > 90)
■ Confident (90 > pLDDT > 70)
■ Low (70 > pLDDT > 50)
■ Very low (pLDDT < 50)

ISM042-2-048
CDK20 KD (nM): 566.7 ± 256.2
CDK20/CycT1 IC_{50} (nM): 33.4 ± 22.6

ISM042-2-049
CDK20 KD (nM): 360.0 ± 14.1
CDK20/CycT1 IC_{50} (nM): 468.3 ± 6.0

ISM042-2-050
CDK20 KD (nM): 5333.3 ± 1189.8
CDK20/CycT1 IC_{50} (nM): 7103.3 ± 477.9

ISM042-2-052
CDK20 KD (nM): 18666.7 ± 6342.1
CDK20/CycT1 IC_{50} (nM): >6000

ISM042-2-053
CDK20 KD (nM): 17666.7 ± 4027.7
CDK20/CycT1 IC_{50} (nM): 7795.0 ± 125.0

ISM042-2-055
CDK20 KD (nM): 14333.3 ± 1699.7
CDK20/CycT1 IC_{50} (nM): 4085.0 ± 575.0

Insilico Medicine launches a 6th generation Intelligent Robotics Drug Discovery Laboratory

Insilico Medicine

→

| Fully automated storage and management for multiple formats | Receive compound from ambient hotel | Decapping tube rack | Compound plate preparation | Highly customized maintenance and management of various types cellular samples | Media exchange | Cell seeding |

| High-content imaging by Cx7 | Pre-scan or 'hit-like' well pick by Celigo | Full plate washing and dispensing by EL406 | Rapid and high-content imaging assays to enrich data outputs | Cell seeding to assay plate | Assay plate preparation by Echo 650T | Large scale of genomics/chemistry perturbation |

| Cell lysis and cDNA synthesis | Receive reagent plate | Multiple NGS workflow to generate comparable and highly consistent OMICs readouts | Library preparation | Concertation detection | qPCR quantitation | Fragment analysis |

PHARMA.AI

Sequencing by NovaSeq 6000

Closed Loop Biotech Innovation: **Fully-Automated Pharma R&D**
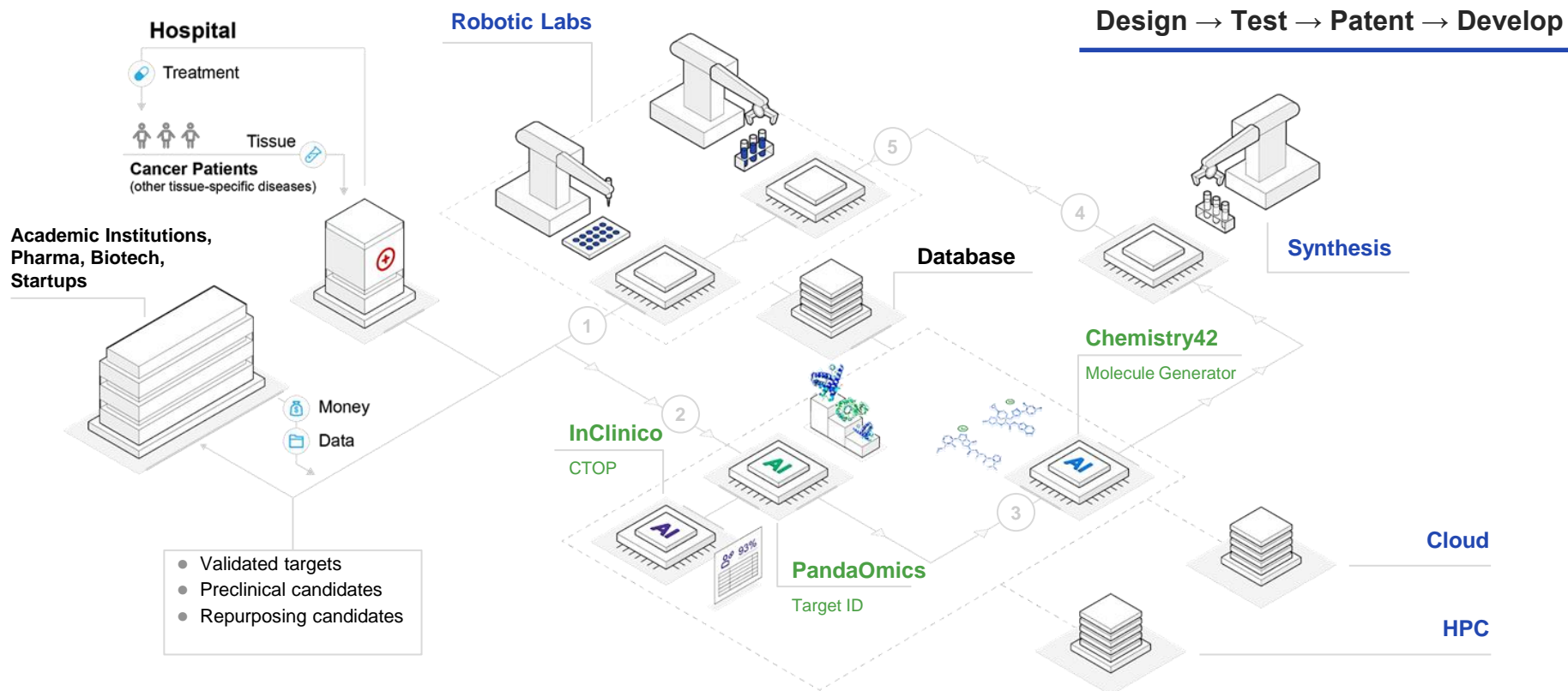
What does it all mean for the patient and the healthcare?

Insilico Medicine

Better medicines faster and cheaper

New treatments for diseases labelled as 'Unmet Medical Needs'

More therapeutic options, potential to combine different treatment for better outcomes

Targeted therapies through precise biomarker stratification of patient population

Easier repurposing of existing and approved drugs for new diseases

Precision and eventually personalised medicine accessible to everyone

External Validation Through BioPharma Collaborations Globally

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Pharma.AI Platform Users

pandaOmics
AI Software Platform to Discover and Prioritize Novel Targets

Universities, Biopharmaceutical Companies and Research Organizations

- Sumitomo Pharma
- FOSUN PHARMA
- INDIANA BIOSCIENCES RESEARCH INSTITUTE
- FERRING PHARMACEUTICALS
- UNIVERSITY OF CAMBRIDGE
- Engrail
- CrownBio

Chemistry42
AI Software Platform to Generate Novel Molecules

Top Pharmaceutical Companies

- MERCK
- FOSUN PHARMA
- ucb
- DEERFIELD Advancing Healthcare®

Plus, five other undisclosed pharmaceutical companies

Collaboration Partnerships
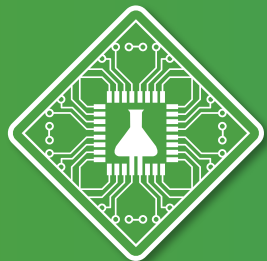
GLOBAL
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- FOSUN PHARMA
- teva
- Janssen
- ARVINAS
- Pfizer
- syngenta
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ASIA
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