DEEPCURE

Is AI in Drug Discovery trapped in the data of the past?

Thras Karydis, Chief Technology Officer

ChemTalks

In-person Conference

September 25, 2024

DEEPCURE

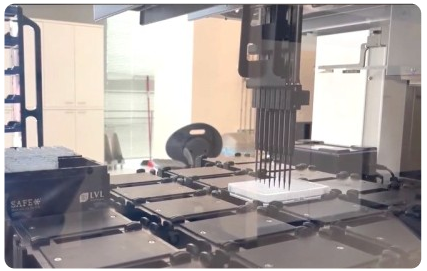
Leader in AI + robotic chemical synthesis for small molecule drug discovery

I&I Therapeutics

DeepCure with Generate Biomedicines, Scorpion Tx, & Valo Health

Leadership in AI

DeepCure with Relay Therapeutics, Exscientia, & Schrödinger



World's Most Advanced Chemistry Automation

Fully automated multi-step chemical synthesis

3
DRUG DISCOVERY PROGRAMS

2025
1st CLINICAL TRIAL

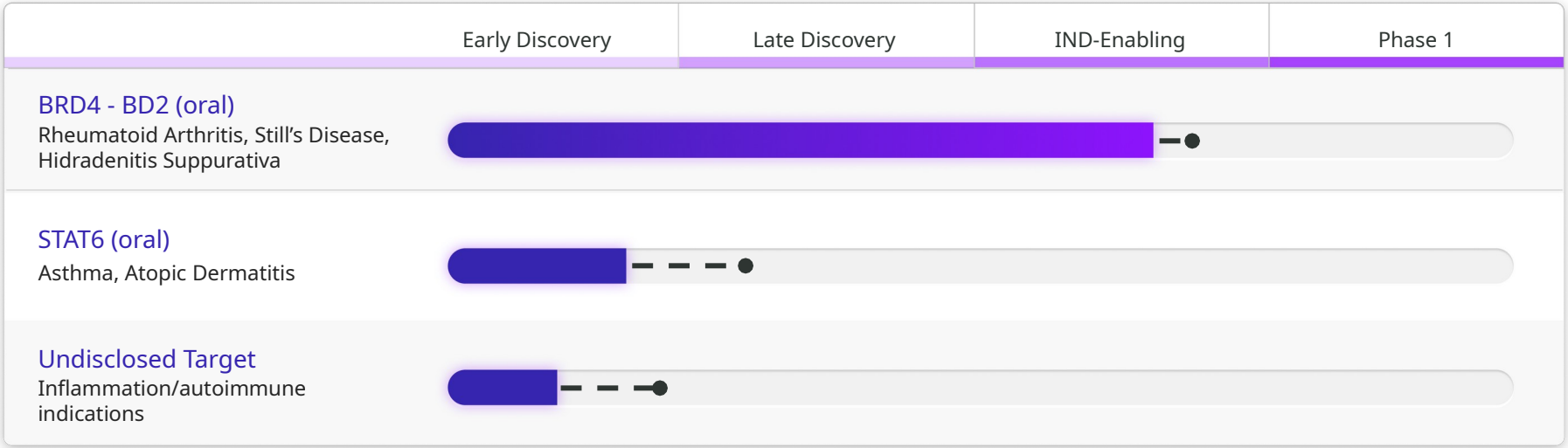
37
TEAM MEMBERS

$71M
RAISED

DEEPCURE

DEEPCURE

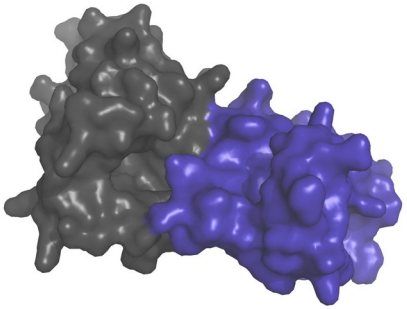
First- or best-in-class oral small molecule therapies



RA – Rheumatoid Arthritis; HS - Hidradenitis Suppurativa; SJIA - Systemic Juvenile Idiopathic Arthritis; AOSD - Adult-Onset Still's Disease; MAS - Macrophage Activation Syndrome; AD - Atopic Dermatitis; IBD - Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis).

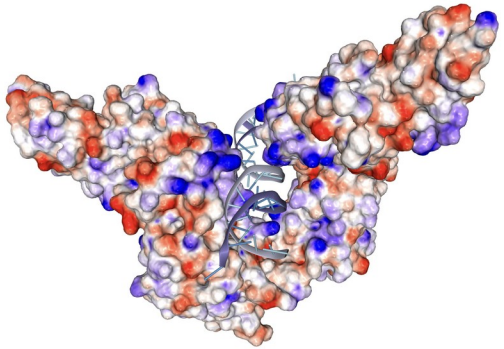
AI DRUG DISCOVERY

Immune targets pose new challenges for small molecule drug design



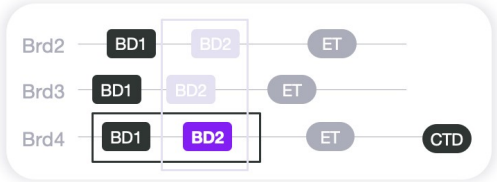
Protein-Protein Interactions

Requiring the design of larger, 3D-shaped drugs



Highly Charged Surfaces

Requiring careful balance of potency and PK



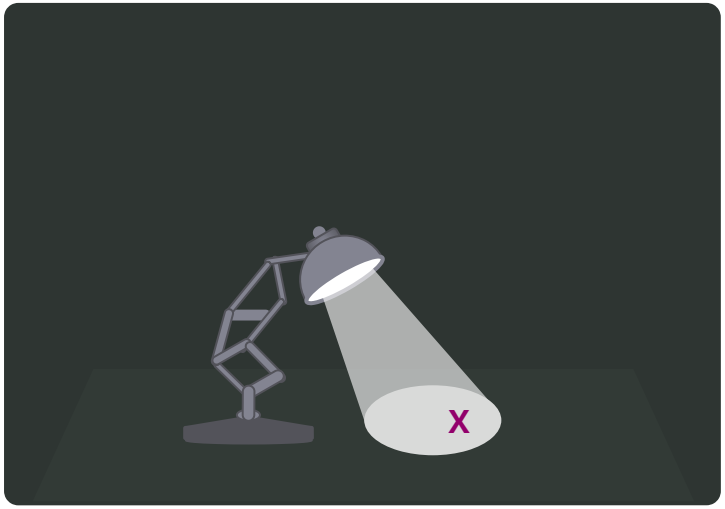
Precise Target Selectivity

Requiring unique interaction profiles

DEEPCURE

AI DRUG DISCOVERY

Can AI deliver on it’s promise to generate *novel* drugs for intractable targets? So far, no.



X = known ligand

Why? Because it’s hard to escape the data trap!

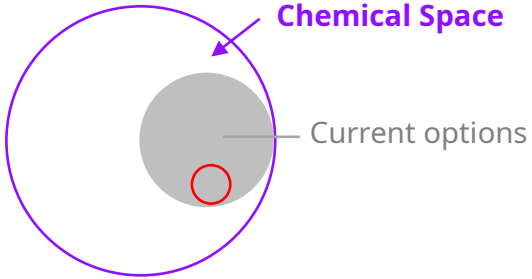
1. *Scientists and models focus on a known binding mode and existing chemical matter*

2. *Design biases from past data and established processes result in testing similar compounds again and again*

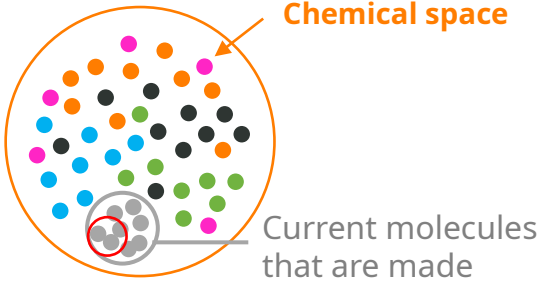
DEEPCURE

How can we develop technology to avoid these innovation pitfalls?

EXPAND SOLUTION SPACE



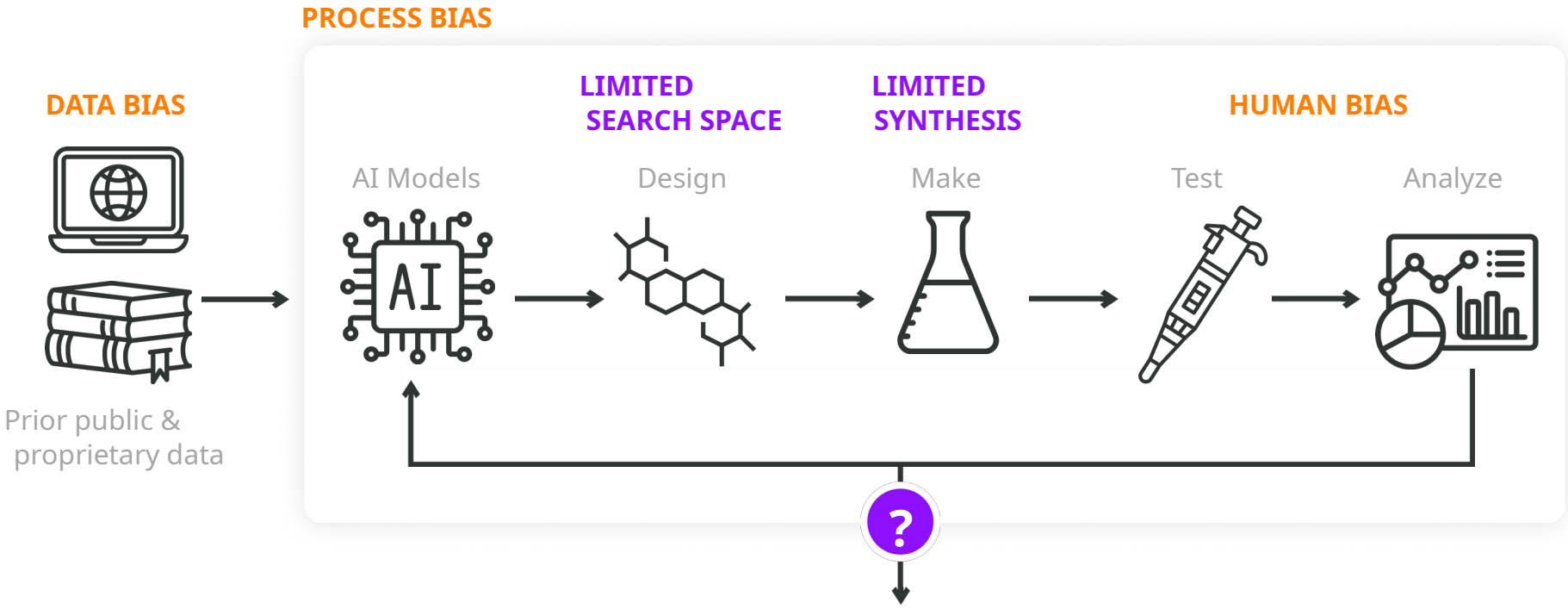
AVOID DESIGN BIASES



AI can innovate only if we expand the relevant solution space AND avoid design biases

AI DRUG DISCOVERY

Let’s take a closer look in the AI-driven drug discovery process

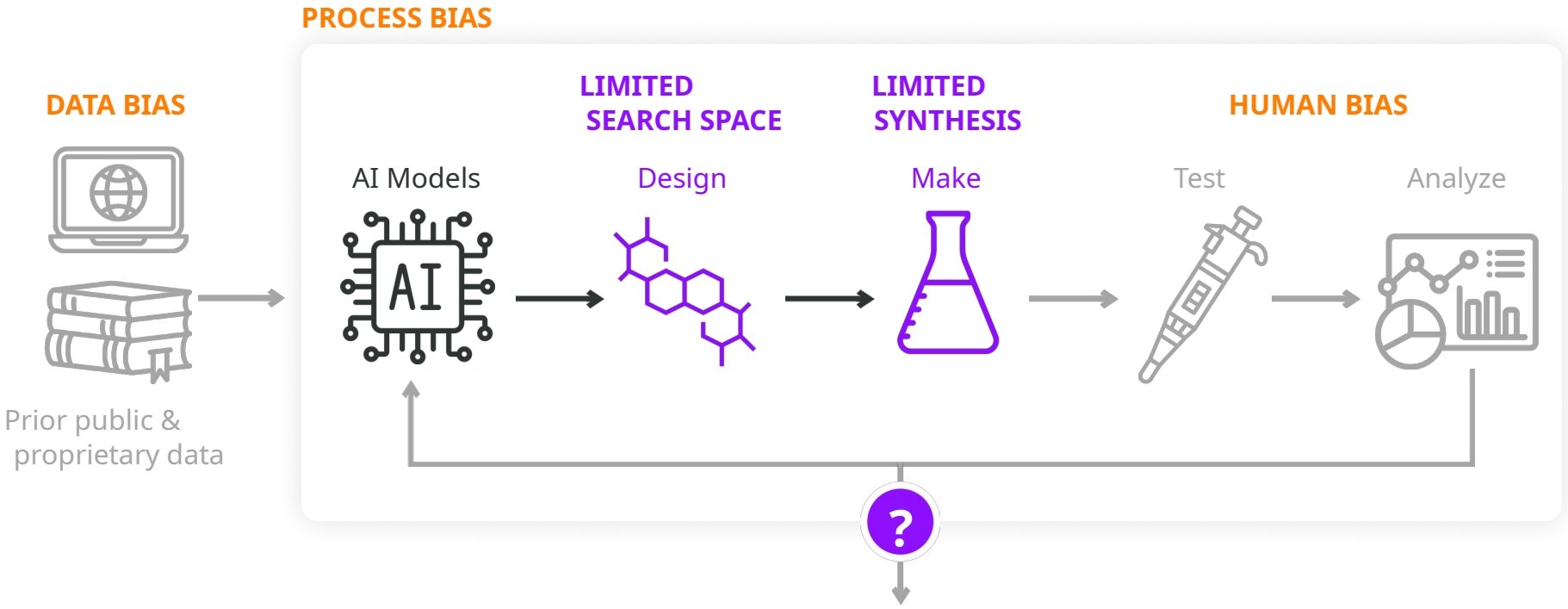


Output: ***Non-obvious*** small molecule drugs

DEEPCURE

AI DRUG DISCOVERY

Let’s take a closer look in the AI-driven drug discovery process



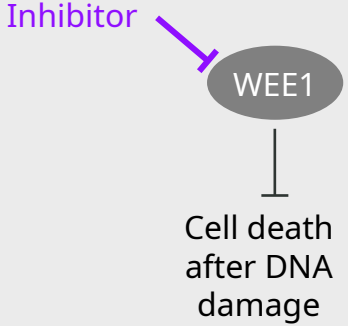
Output: ***Non-obvious*** small molecule drugs

DEEPCURE

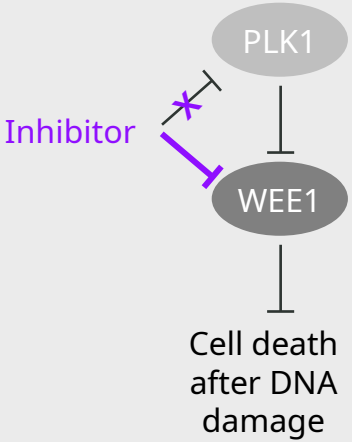
EXPAND SOLUTION SPACE

Case study on the importance of expanding the chemical space

1 Potent inhibitor



2 Selectivity



3 Brain penetrant

We built AI models to identify brain penetrant WEE1 inhibitors for brain tumors

DEEPCURE

EXPAND SOLUTION SPACE

Zero hits in commercial libraries offering limited chemical space

	Commercial Library *(20 billion compounds)*[1]
Hit rate @ 30 μM	6/262
Hit rate @ 100 nM	**0**/262
Hit rate @ 15 nM	**0**/262
Selectivity[2]	**not applicable**
Brain penetration[3]	**not applicable**
Synthesis cost	$22K - $25K

DEEPCURE

1 Commercial build on demand library with standard commercial building blocks and reactions. 262 compounds were tested and none were potent binders.

EXPAND SOLUTION SPACE

Immediate success when we expanded the chemical space by allowing custom synthesis of compounds top ranked by AI models

	Commercial Library *(20 billion compounds)*	**Custom Synthesis**
Hit rate @ 30 μM	6/262	7/12
Hit rate @ 100 nM	0/262	**7/12**
Hit rate @ 15 nM	0/262	**Yes (4/12)**
Selectivity[1]	not possible	**Yes (6/12)**
Brain penetration[2]	not possible	**Yes (4/12)**
Synthesis cost	$22K - $25K	$25K

Lessons:

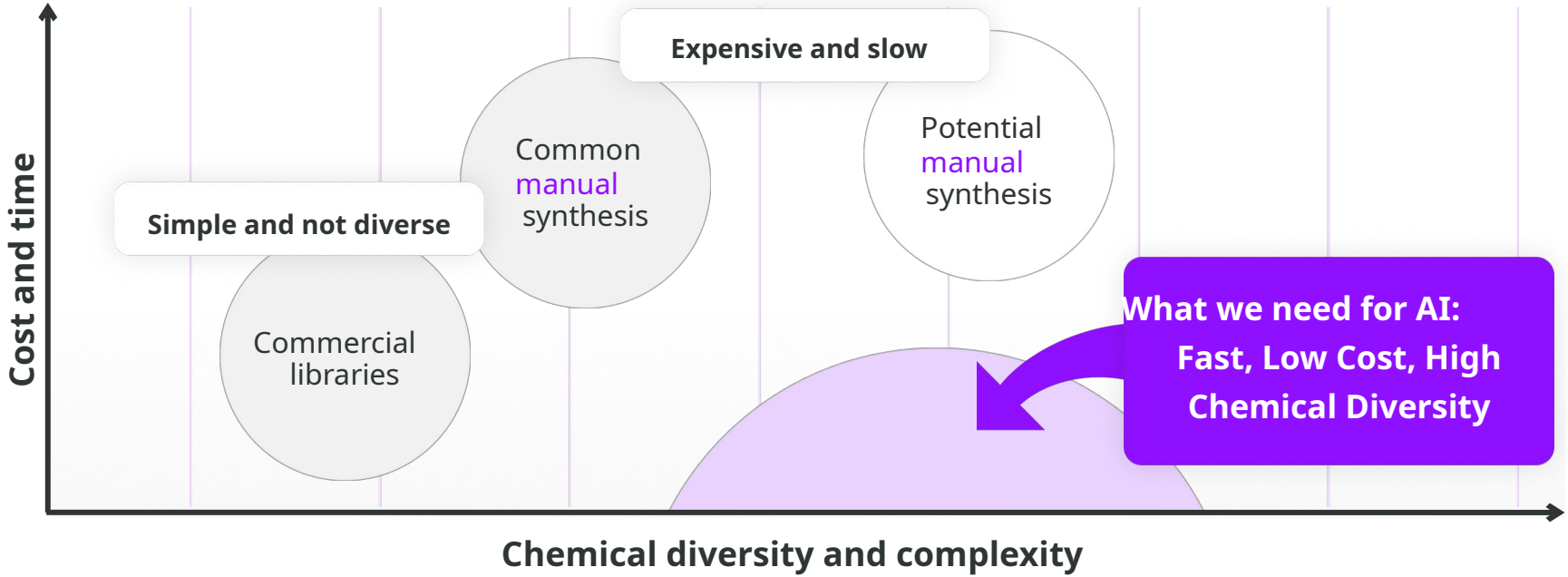
1. **Don’t assume AI is the problem!**
2. **AI will not help if the search space is limited**

DEEPCURE

1 IC50 for PLK1/Wee1 >35x | 2 Brain penetration predicted based on MDCK-MDR Efflux Ratio ⩽ 3.0.

EXPAND SOLUTION SPACE

We need custom libraries that unlock a larger chemical space and enable more compounds to be synthesized

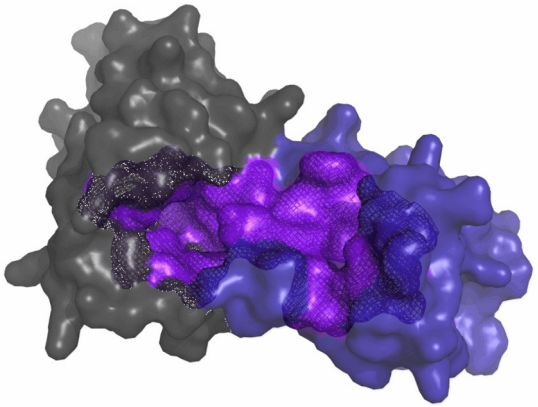


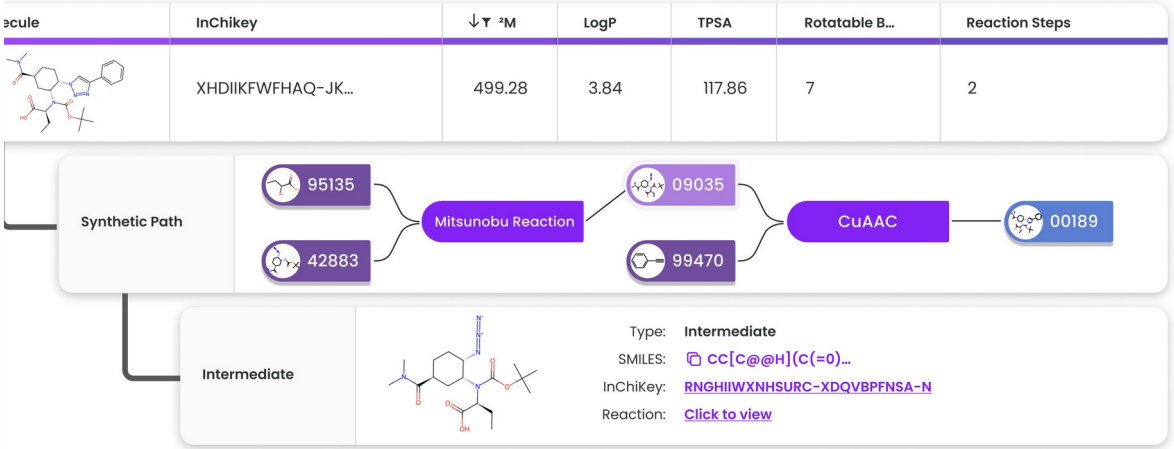
DEEPCURE

EXPAND SOLUTION SPACE

Using GenAI we can generate custom libraries of fit-for-purpose, synthesizable molecules

Unlocking GenAI creativity with physics and organic chemistry



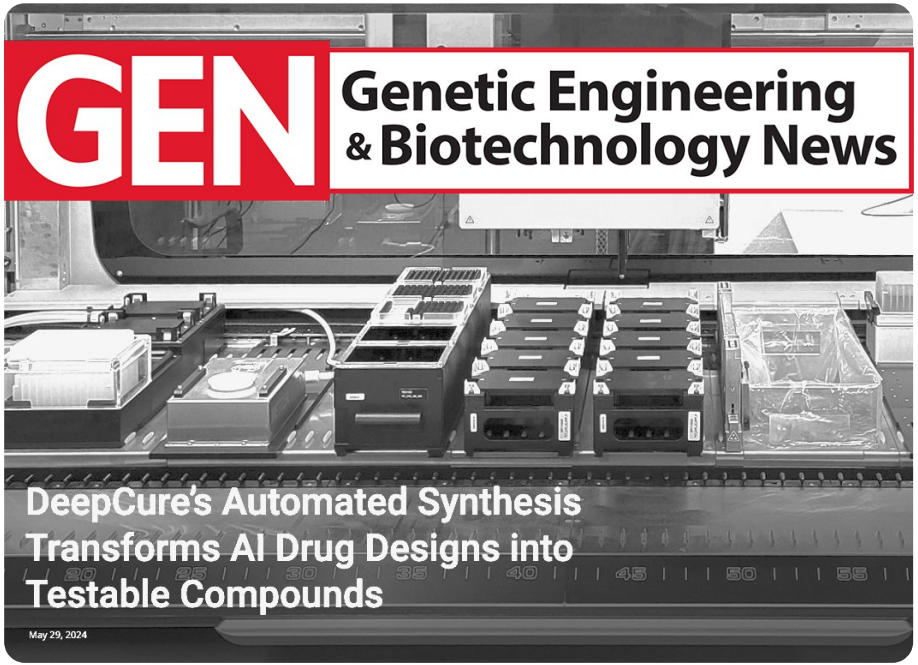


MolGen™

DEEPCURE

EXPAND SOLUTION SPACE

Robotic platform delivers high throughput synthesis **AND** complex compounds so that synthesis is not the bottleneck for AI-guided design



HIGH THROUGHPUT

10-1000x[1]

compared to a chemist

HIGH DIVERSITY AND COMPLEXITY

28 reaction types[2]

industry standard is <10 types

X

10 steps[3]

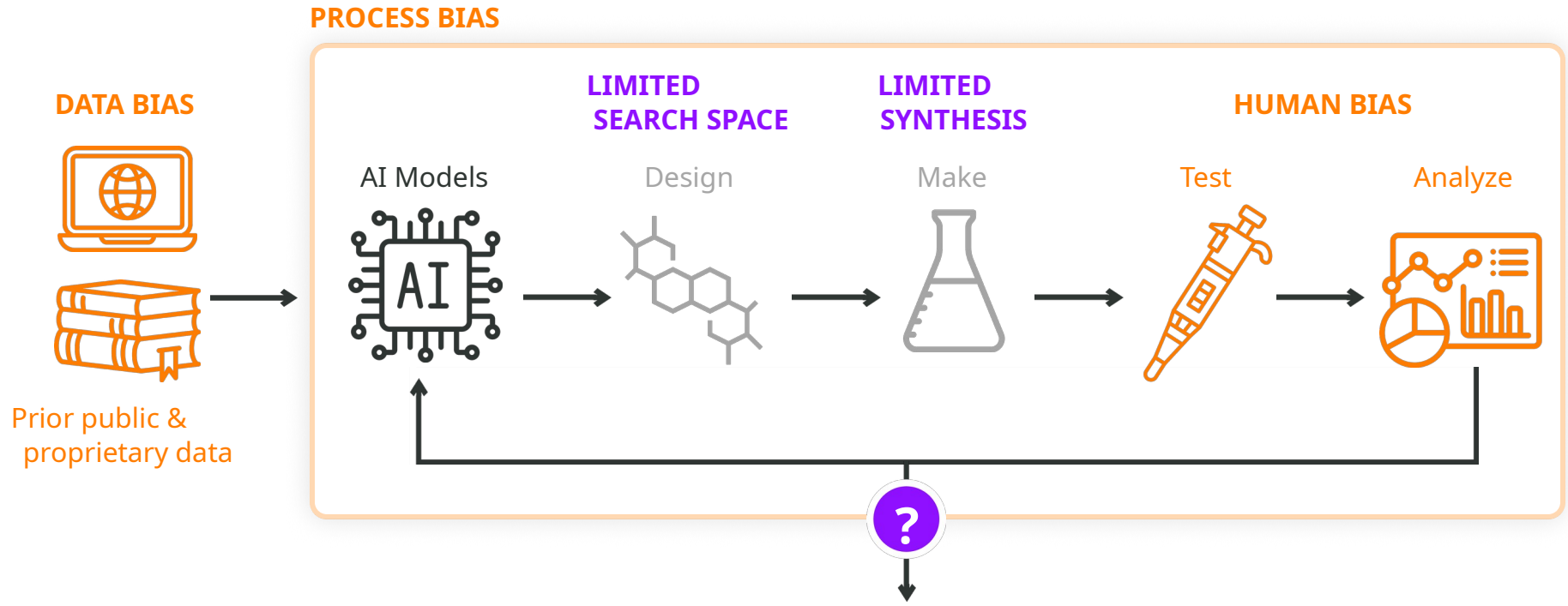
industry standard is 1 step

DEEPCURE

1 Currently at 10x an average chemist (~6 molecules/month) and expect up to 1000x by 2025 | 2 Currently 28 reaction types but expect 100 types by Q1 2026| 3 Current number of reaction steps is 10 (incl. 5 purifications), but more is feasible.

AVOID DESIGN BIAS

Let’s take a closer look in the AI-driven drug discovery process



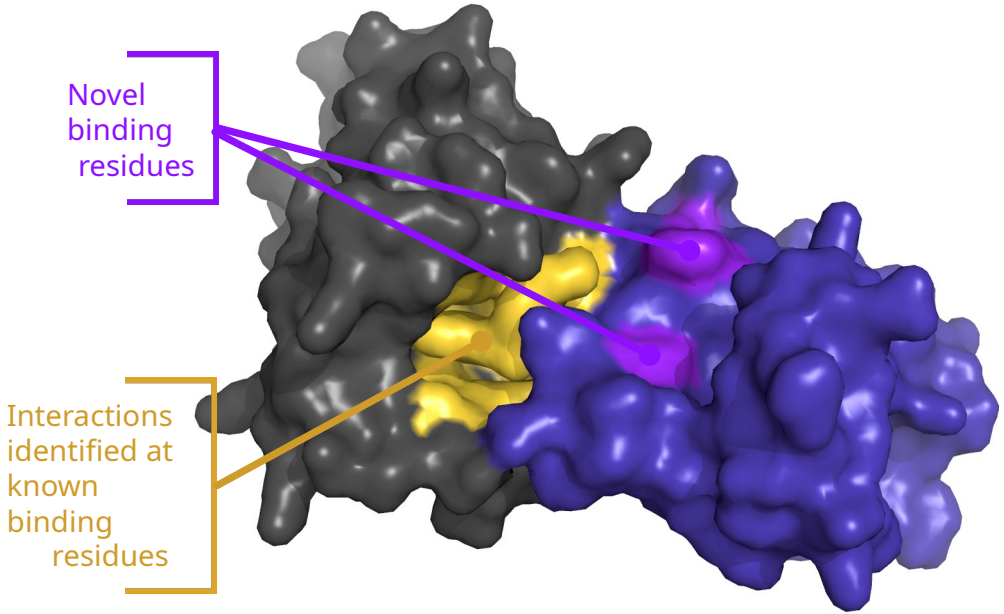
Output: ***Non-obvious*** small molecule drugs

DEEPCURE

AVOID DESIGN BIAS

Using first-principles derived hypotheses to eliminate the data bias towards known compounds

Exhaustive mapping of protein surface exposes untapped interactions



Residue	Interaction Type	Weight
LYS 544	cationpi:ligandpi	0.26
LYS 544	salt-bridge:ligand-protein+	0.1
SER 566	hbond:protein2ligand	0.32
ARG 562	salt-bridge:ligand-protein+	0.1
GLU 651	salt-bridge:ligand+protein-	0.48
ARG 667	cationpi:ligandpi	0.1
THR 672	hbond:protein2ligand	0.28
LEU 680	salt-bridge:ligand-protein+	0.09
THR 683	hbond:protein2ligand	0.04

DEEPCURE

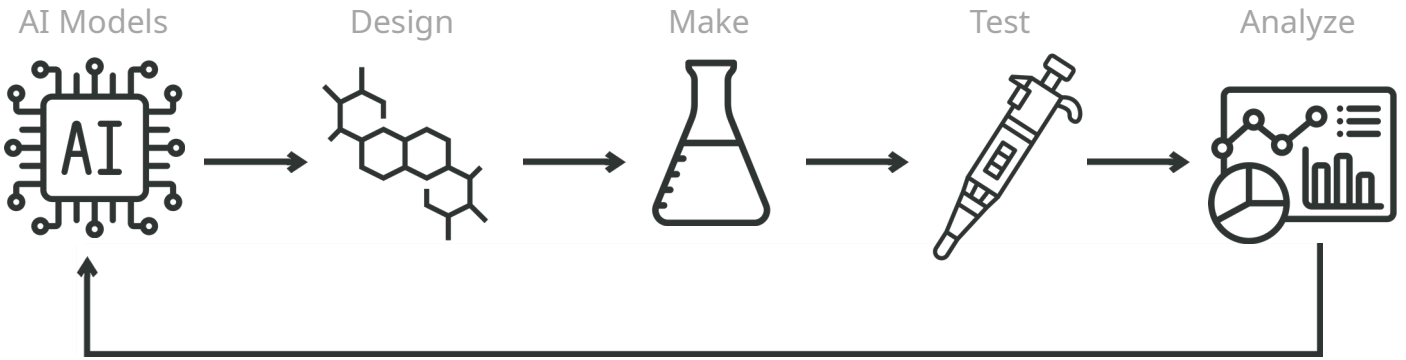
PocketExpander™

AVOID DESIGN BIAS

Innovative drug design constantly revisiting hypothesis, data and perspectives at every stage of the discovery process

Continuous update of hypotheses

Holistic evaluation of each molecule



More data and diverse molecules at each stage

DEEPCURE

ACKNOWLEDGMENTS

Team of drug hunters and innovators collaborating to advance small molecule discovery for challenging targets

LEADERSHIP

Kfir Schreiber
Co-Founder, CEO

Joseph Jacobson
Co-Founder, Chief Innovation Officer

Thras Karydis
Co-Founder, CTO

Luca Rastelli
CSO

Han Lim
CBO

DRUG DISCOVERY & DEVELOPMENT

Georg Duenstl
VP, Head of Discovery

Michal Segal Salto
Senior Director, Biology

Steven Ferrara
Director, Medicinal Chemistry

MJ Kim
Director, Translational Immunology

Kelvin Chan
Senior Director, DMPK

AI/ML & CHEMISTRY AUTOMATION

Derek Miller
VP, AI Research

Jon Kaufman
Associate Director, Physics-based AI

Mark Schroering
Associate Director, Engineering

Derrick Miyao
VP, Molecular Foundry

Heather Osswald
Associate Director, Automated Chemistry

DEEPCURE

THANK YOU!