CYCLICA
From molecule to medicine

Cyclica is the partner of choice for data-driven drug discovery.

We advance molecules that embrace the complexity of disease.

Cyclica is rooted in Canada, with a global team

2013
Founded in Toronto

Core technology developed at Cyclica

2014-2017
C$6.65M in Seed and Series A led by GreenSky Capital

2018
Launch of MatchMaker & Ligand Express

2019
Launch of POEM & Ligand Design

2020
C$23M in Series B led by Drive Capital with GreenSky Capital

2021
50+ global Employees (CAD, USA, UK)

Acknowledgements

Ranked as a top 100 AI Company Globally (the only AI Healthcare company in Canada)

A CIX Top 10 Growth Inductee 2021

Most Innovative AI-Based Drug Discovery Biotech Company 2020 (Canada)

A Top 20 AI-Based Drug Discovery Company in 2018

Cyclica is a founding member of the AAIH (Alliance for Artificial Intelligence in Healthcare)

From AAIH

Where is AI Having an Impact in Healthcare?

From AAIH

Where is AI Having an Impact in Healthcare?

From AAIH

Cyclica is a ***neo-biotech***: we are advancing the most sustainable pipeline of drug discovery programs at an unprecedented speed, scale and precision.

We have assembled an industry-leading leadership team with deep expertise in drug discovery and artificial intelligence

Naheed Kurji
President, CEO & Co-Founder

12+ years in tech and biotech innovation

EntheogeniX · AAIH · NineteenGale · PERTURBA

Dr. Mike Palovich
Chief Science Officer, Head of Drug Discovery

24 years of DD, 1 approved drug found in 3 medicines

GlaxoSmithKline · PERTURBA

Dr. Stephen Mackinnon
Chief Platforms Officer

10+ years in data science for drug discovery

CYCLICA

Dr. Andreas Windemuth
Chief Innovation Officer

25 years in life science technologies

abcam · Firefly BioWorks

Dr. Melissa Landon
Chief Strategy Officer

15 years in tech and pharma

SCHRÖDINGER. · CUBIST PHARMACEUTICALS

Dr. Vern De Biasi
Chief Partnerships Officer

30 years in big pharma drug development

GlaxoSmithKline · PERTURBA

Pratik Shah
Chief Financial Officer

10 years in biotech finance

hycasynth · ORGANIGRAM · MERUS LABS

Cyclica's Technology

We are more than just an
AI Drug Discovery company

Pharma is changing...

75%

of early stage drug discovery innovation is happening outside of the 4 walls of a pharma company.

This is up from 50% in the early 2000s.

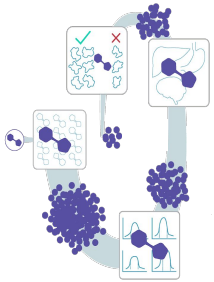
Only 11% and 23%

of J&J and Pfizer's product pipeline, respectively, were developed in house.

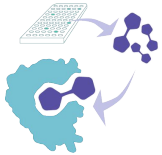
92.5%

of proteins remain undrugged.

Our platform addresses several challenges in preclinical drug discovery

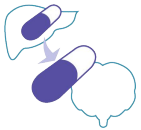


Multi-objective design of NCEs

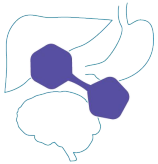


Target deconvolution

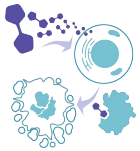
Hit and lead prioritization



Drug repurposing



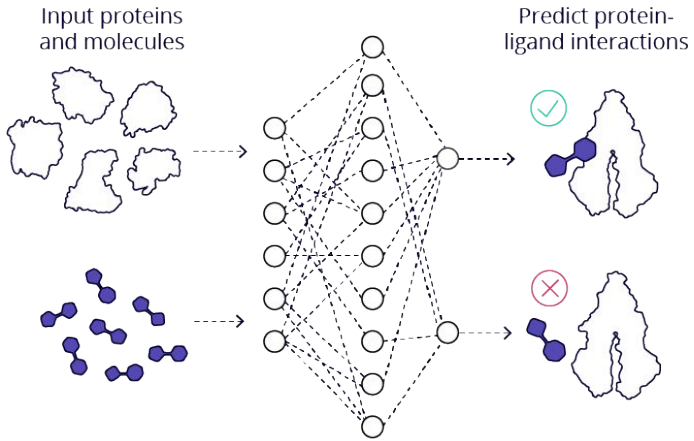
ADME prediction



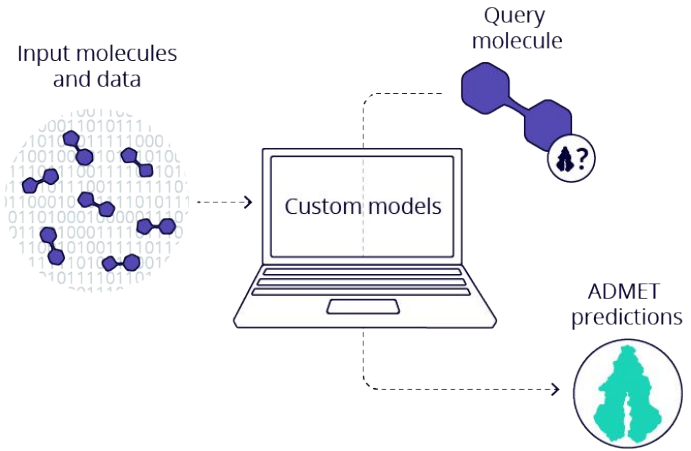
Target- mediated toxicity elucidation

Two machine learning engines underlie our platform

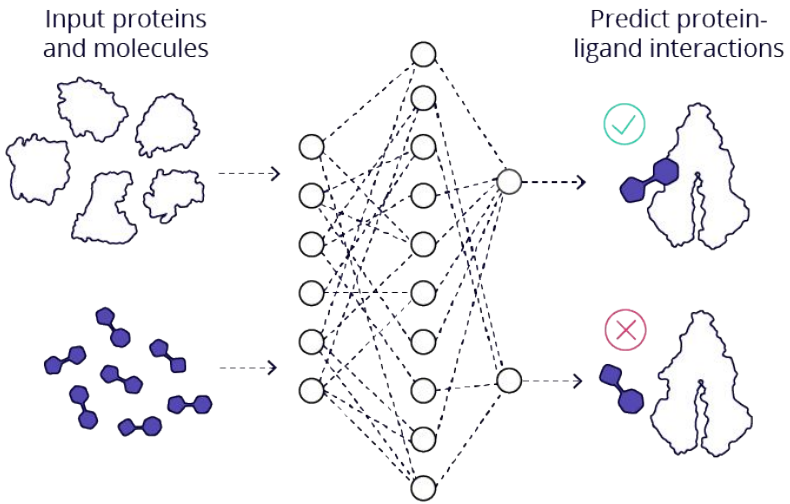
MatchMaker™
Deep learning engine for proteome-wide prediction of small molecule-target interactions



POEM™
ML framework for ADMET property model generation and application



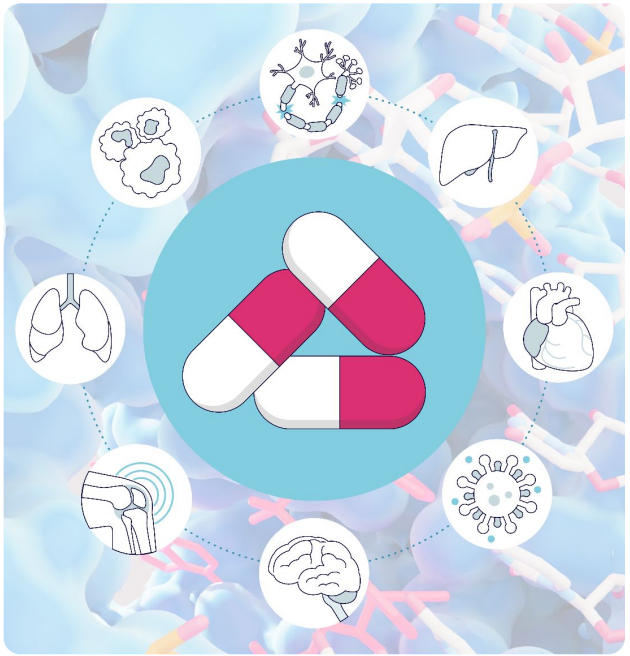
We built MatchMaker™ to enable proteome-wide evaluation of polypharmacology in real time



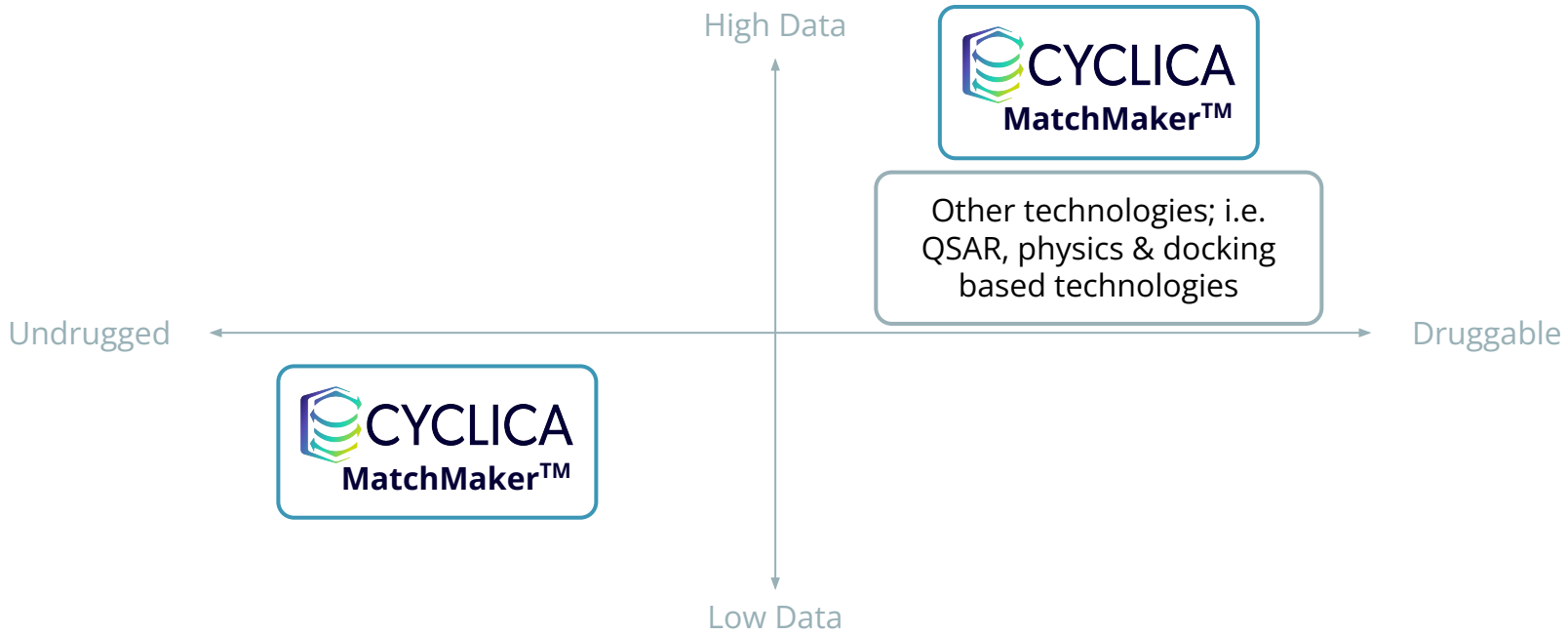
- Deep learning engine trained on millions of drug/target interactions as well as thousands of 3D structures
- Conducive for not only high data targets, but also low data targets using recent advances in 3D protein prediction technology (eg: AlphaFold2 structures)
- Design or screen a molecule across the human proteome takes a **fraction of a second**
- Improved accuracy as compared to other structure-based methods

We integrated AlphaFold2 into MatchMaker, creating the most powerful proteome wide screening capability in the industry

- Doubling our database at ~200K pockets from ~18K human proteins
- Created the largest known computational engine for proteome wide evaluation
- Enabling Cyclica to address human & other species **rapidly**
- Active prioritization of potential binders with off-target profile can **advance hundreds of drug discovery programs**
  - Key in therapeutic areas with high unmet medical needs



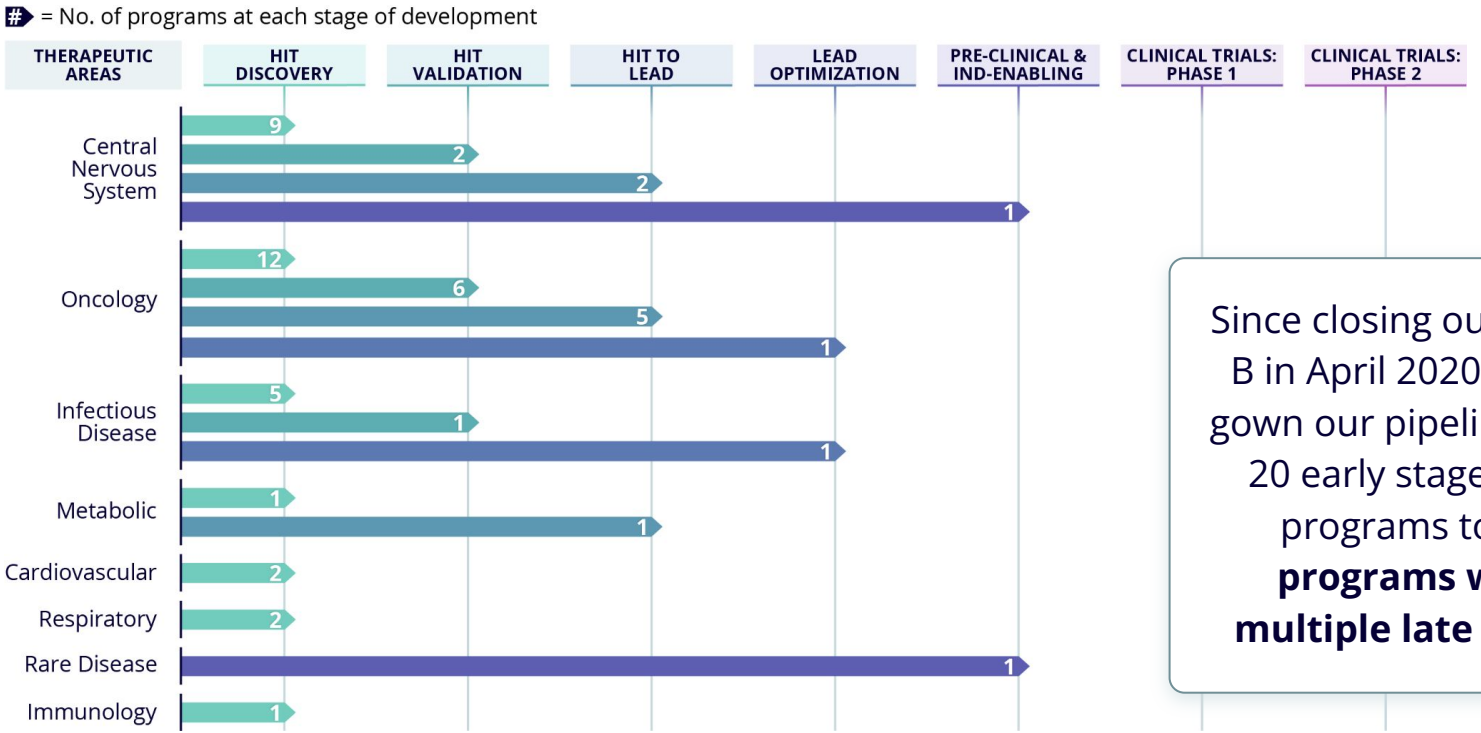
With MatchMaker, we're uniquely positioned to drive drug discovery programs for both high data and low data targets



Pipeline

Please refer to our data room for detailed examples on a number of our early and late stage programs

Over the *past* 3 years, we've established a pipeline of over 50 programs



Since closing our Series B in April 2020, we've gown our pipeline from 20 early stage drug programs to **50 programs with multiple late stage**.

We are *now* building a pipeline of programs for immuno-inflammation based diseases

Our focus is on the following therapeutic areas:

Autoimmune

CNS

Oncology

This strategy leverages Cyclica's technology advantages to deliver commercial opportunity:

Technological

Proteome-wide: Largest proteome wide capability in the industry is uniquely suited for polygenic based projects

Low data biological targets: Cyclica's platform capitalizes on advances in the field of 3D protein structure prediction

Repurposing + Fast Follower: Cyclica's platform has been used to deconvolute biological MoA, then identify new chemical matter

Commercial

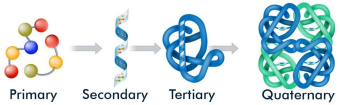
A multiple "shots on goal" disease opportunity for a given clinical molecule

Near term value: chemical IP for low data / intractable targets

Long term value: chemical assets with a viable path to the clinic

Example of low data project:
DCAF1

Protein Structure



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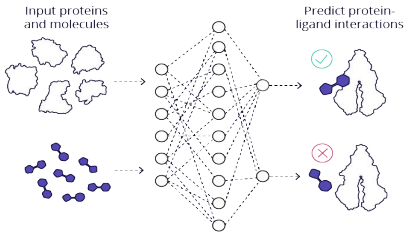
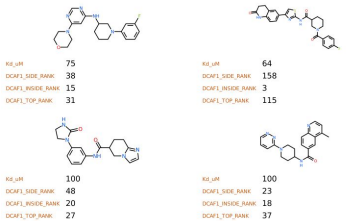
MatchMaker™



→

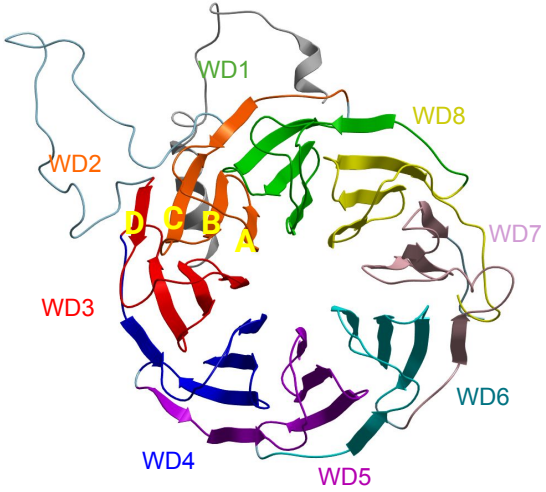
Novel chemical matter



WD40 & DCAF1 - overview

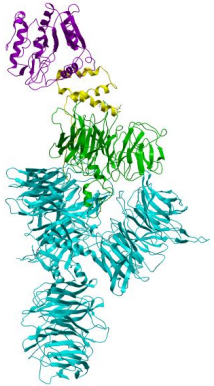
WD-40 repeats

- ~350 members - most lack protein structure and/or known small molecule binders
- Name derived from the conserved WD dipeptide and the length of approximately 40 amino acid residues in a single repeat.
- Usually assume a 7-8 bladed beta-propeller fold, but 4 to 16 exist.



DCAF1

- No published inhibitor.
- Substrate recognition component of an E3 ubiquitin-protein ligase complex.

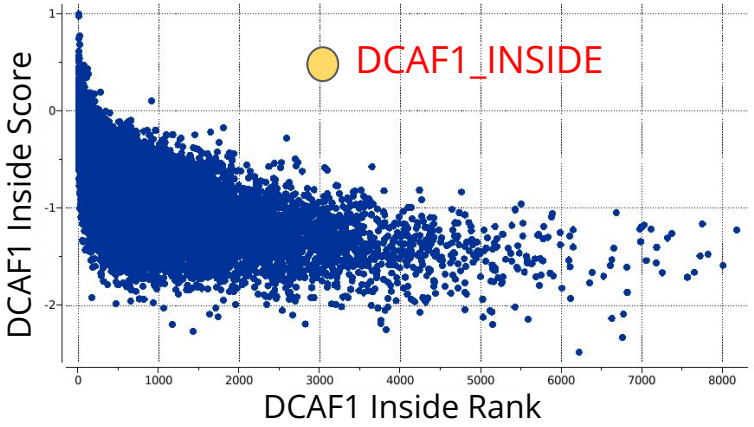


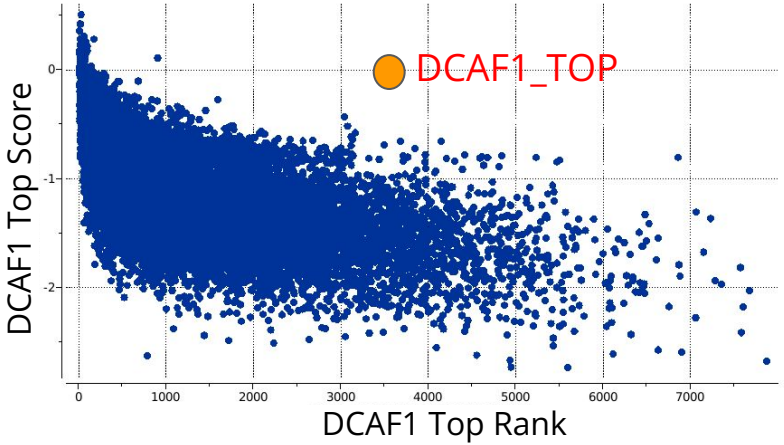
PDB 5JK7:

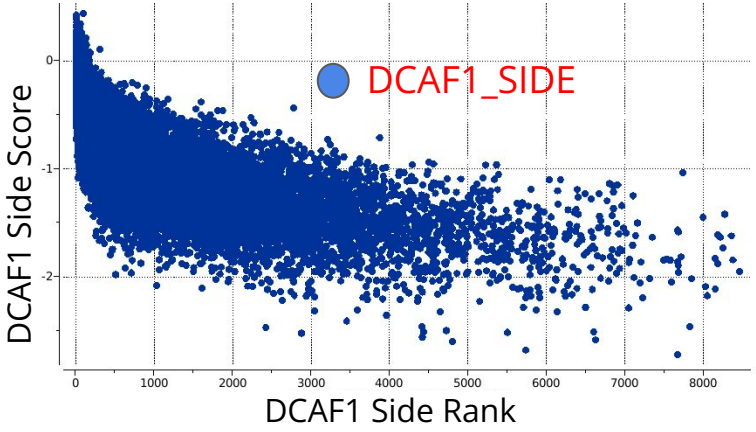
DCAF1, **DDB1**, **VPR**, **UNG2**

Xu, C., Min, J. Structure and function of WD40 domain proteins. *Protein Cell* 2, 202–214 (2011).

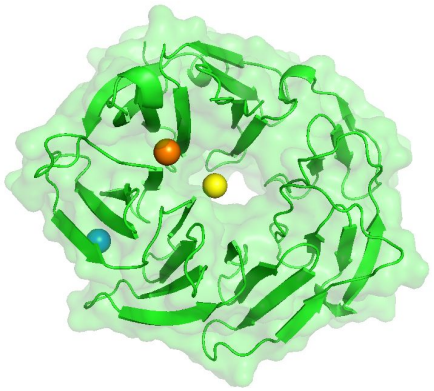
DCAF1 Subpockets



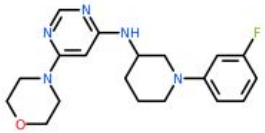




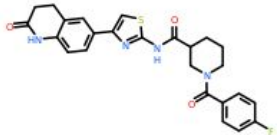
DCAF1_INSIDE
DCAF1_TOP
DCAF1_SIDE



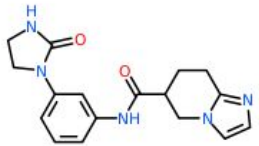
DCAF1 Initial Hits



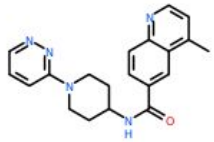
Kd (uM) : 75
DCAF1 Side Rank : 38
DCAF1 Inside Rank : 15
DCAF1 Top Rank : 31



Kd (uM) : 64
DCAF1 Side Rank : 158
DCAF1 Inside Rank : 3
DCAF1 Top Rank : 115

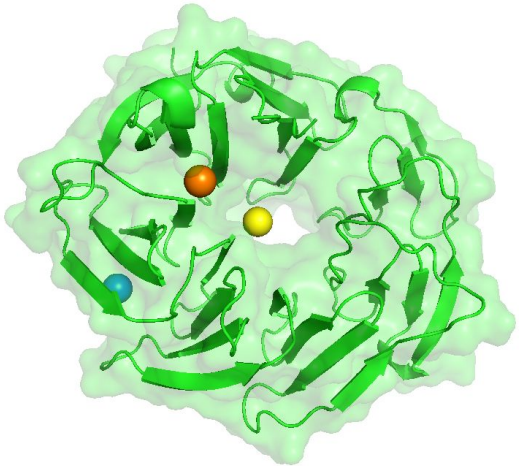


Kd (uM) : 100
DCAF1 Side Rank : 48
DCAF1 Inside Rank : 20
DCAF1 Top Rank : 27



Kd (uM) : 100
DCAF1 Side Rank : 23
DCAF1 Inside Rank : 18
DCAF1 Top Rank : 37

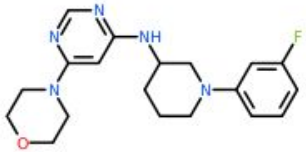
DCAF1_INSIDE
DCAF1_TOP
DCAF1_SIDE

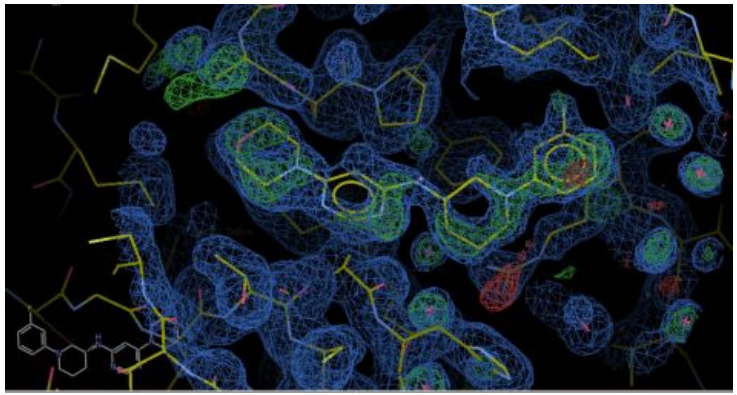


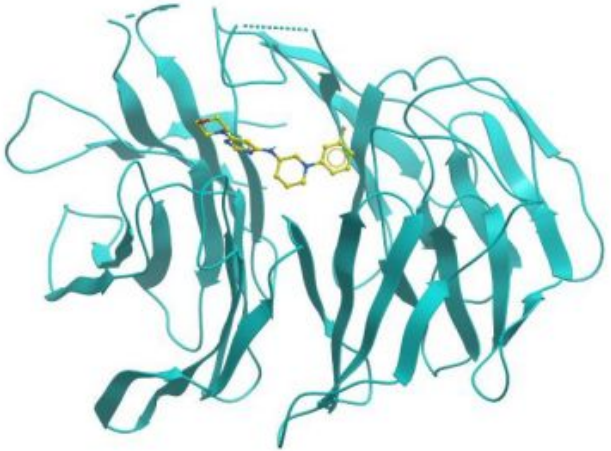
Co-crystal structure of DCAF1 in complex with CYCA-117-70 (PDB: 7SSE)

The SGC co-crystallized CYCA117-70 for DCAF-1 - **the first disclosed co-crystal structure of DCAF1** with a small molecule bound

IC_{50} = 75uM

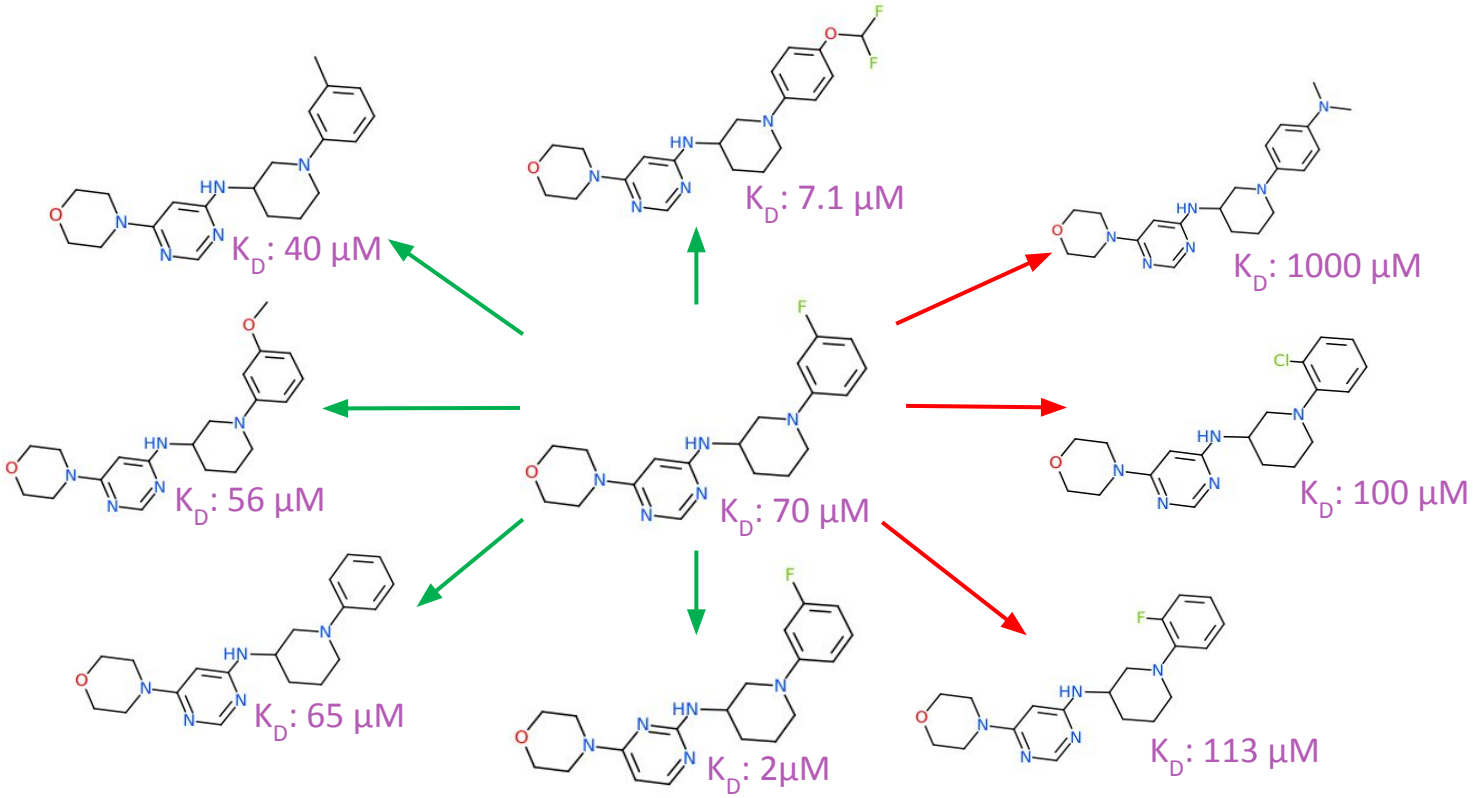






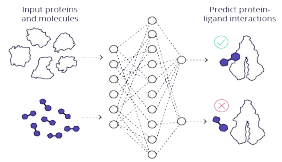
https://www.rcsb.org/structure/unreleased/7SSE
https://www.thesgc.org/structures/7SSE

Examples from hit expansion



Example of high data project:
Repurposing project SRC

MatchMaker™



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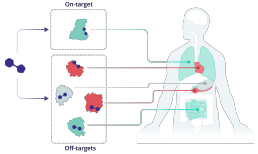
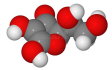
PolyPharmDB



Identify →

Drugs with repurposing potential



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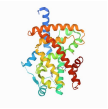
Repositioning targets



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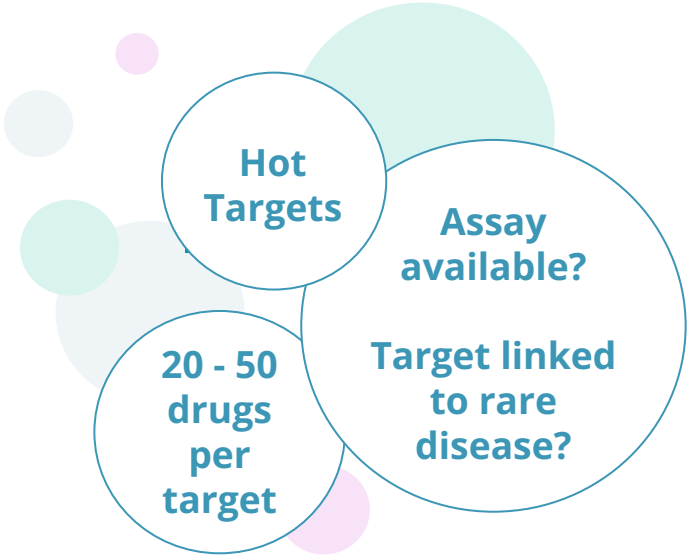
- Novel chemical matter
- Re- new- position existing drug

Implementing PolypharmDB

PolypharmDB	MatchMaker	Drug Selection	Target Selection
2,118 approved **2,242** clinical **5,547** pre-clinical Mapped targets to disease associations	**Proteome Screen** Rank every compounds against proteome	**MatchMaker Ranks** Rank < 25 MM Score > 1	**~ 2,000 Proteins**

Target selection



SRC Non-receptor tyrosine kinase

48 compounds passed our cut-offs

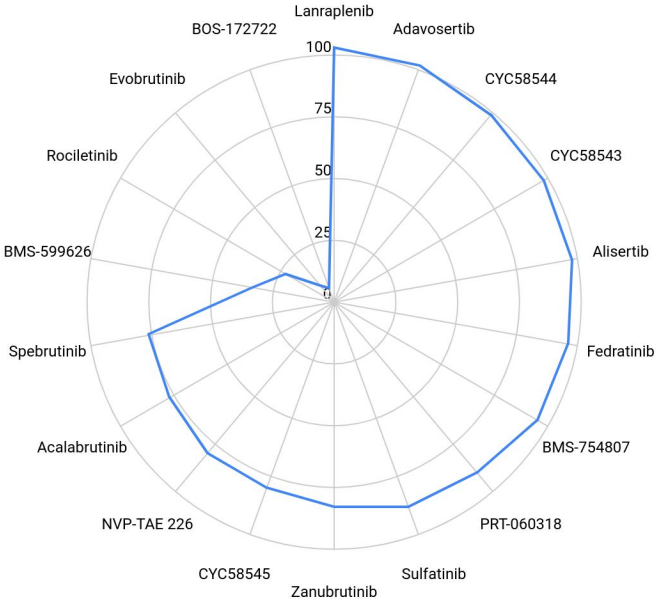
18 available for purchase

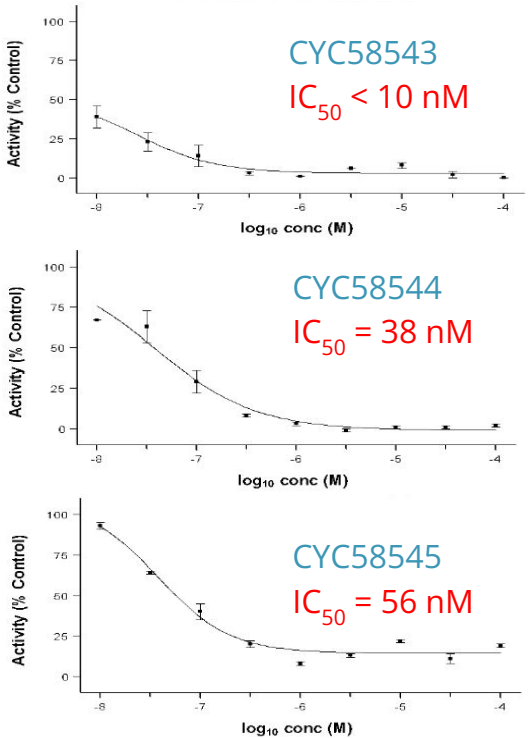
Gain-of-function mutation causes rare disease

Eurofins assay available

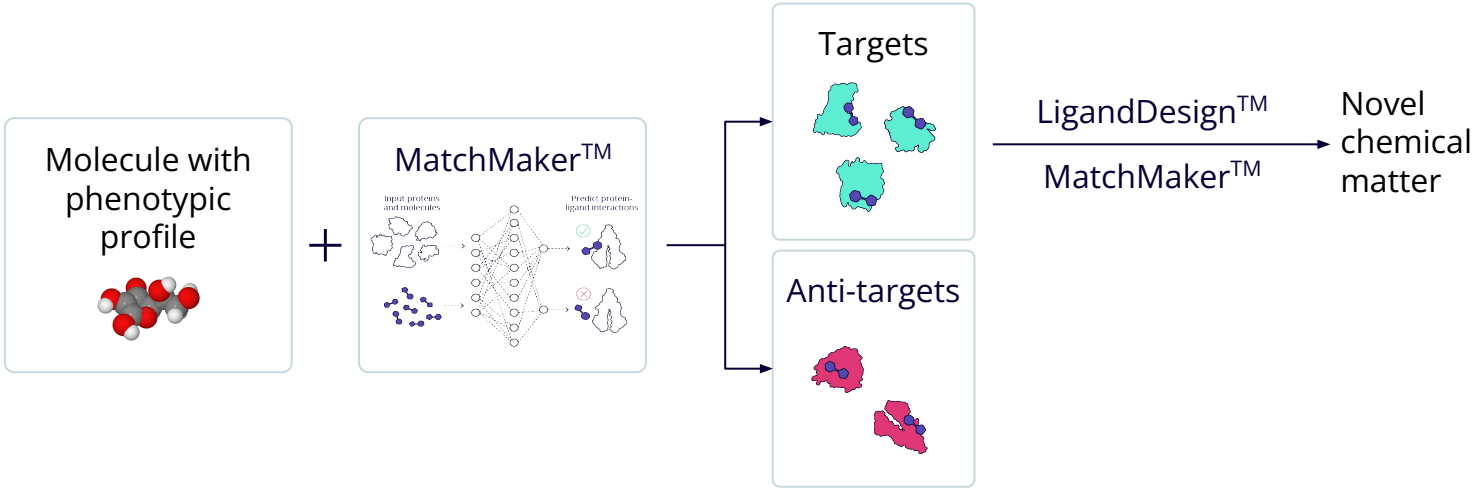
Screening outcomes...

14 of 18 compounds were strong inhibitors of SRC (Pct Inh > 70%)



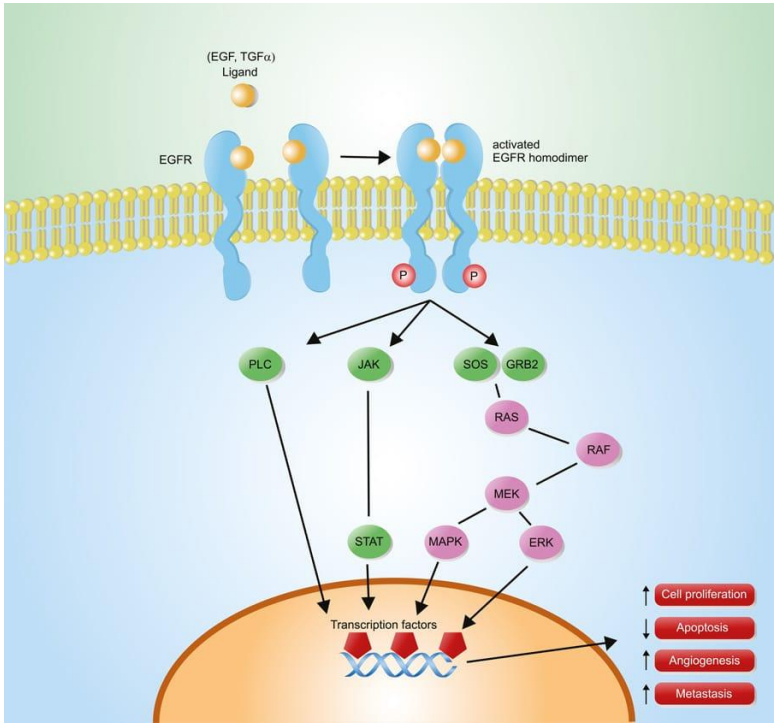


Example of a low data project:
EGFR triple mutant



Selective EGFR triple mutant inhibitor for NSCLC

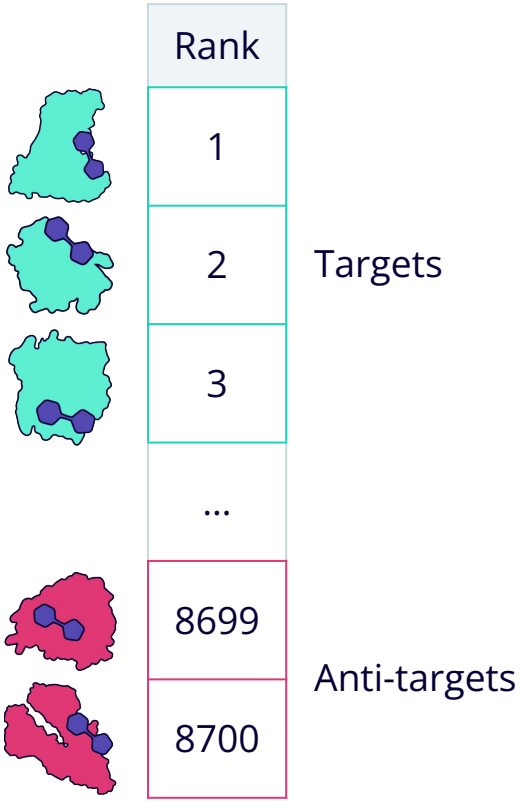
- **EGFR** is implicated in a variety of cancers, in particular non small cell lung cancer (NSCLC)
  - Mutations lead to activation
  - EGFR mutants expressed in many cancers, including NSCLC
- **EMI1** selectively inhibits EGFR triple mutant (L858R/ex19del - T790M -C797S) over WT
  - Discovered using specialized Mammalian Membrane Two-Hybrid assay (MaMTH) - Igor Stagljar's lab



Saron, P. *et al* A drug discovery platform to identify compounds that inhibit EGFR triple mutants. *Nat Chem Biol* **16**, 577-586 (2020)
https://researchoutreach.org/articles/understanding-egfr-mutation-aids-fight-lung-cancer/.

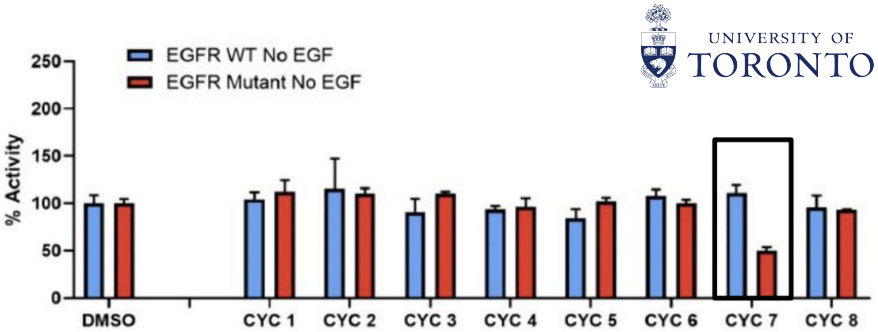
Proteome profile fingerprint and receptor panel

- Proteome Screening of EMI1 using MatchMaker creates a rank-ordered list of proteins
- Proteins located at the top became major **targets** of the Ligand Design run, with those at the bottom becoming **anti-targets**
- Ligand Design optimizes for molecules that match this profile
- Panel was also seeded with targets of biological relevance



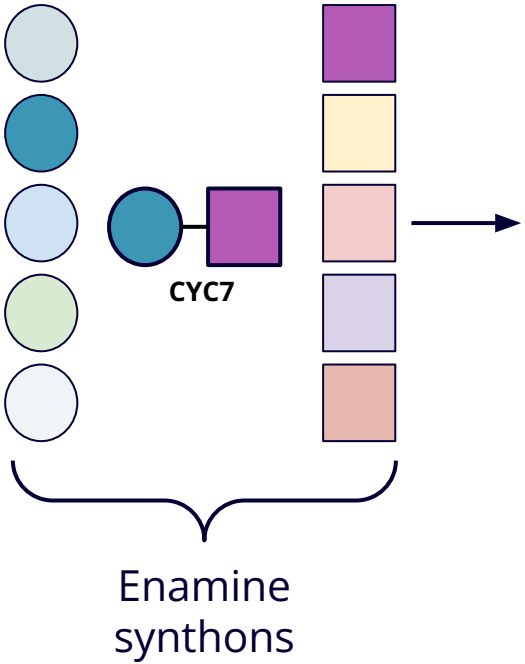
Selective EGFR triple mutant inhibitor identified within 6 weeks

- 8 molecules were synthesized based on predicted activity
- An initial hit **CYC7** showed measurable selectivity for mutant over wild-type



UNIVERSITY OF TORONTO

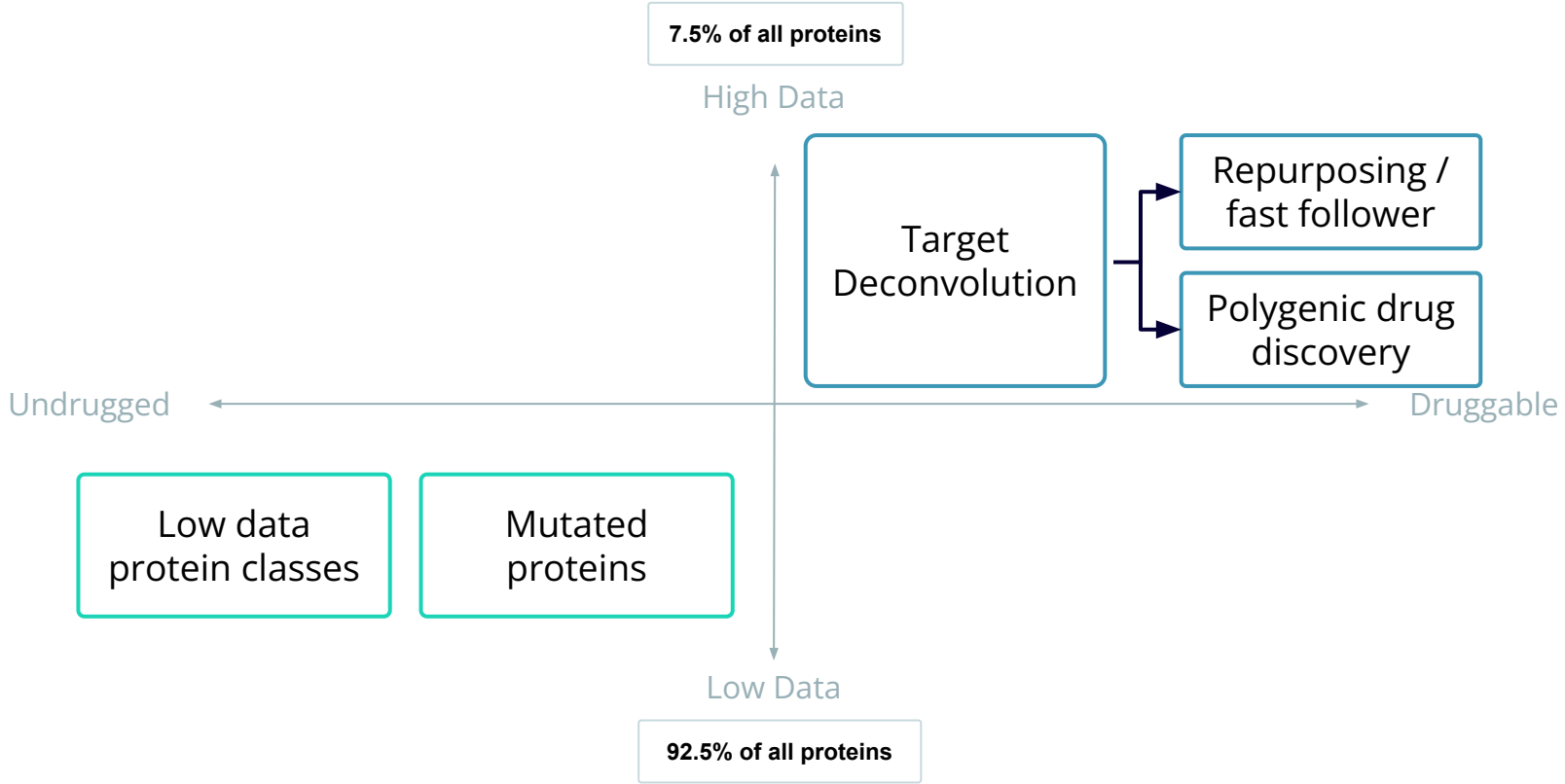
Hit expansion of CYC7 in Enamine REAL Space



- Apply filters:
  - score against polypharmacology panel
  - physicochemical properties
- Select by similarity to **CYC7**

- 30 compounds purchased
  - 14 synthon
  - 16 synthon
- 2 compounds demonstrated improved activity over **CYC7**

By approaching both high and low data targets with a thoughtful strategy, we will materially impact the discovery of medicines



Academic Partnerships

How Cyclica partners with academic institutions to translate basic research into viable drug discovery programs and publications

Cyclica Academic Partnership Program (CAPP)

- Engage with the University of Toronto research community to jointly advance small molecule drug discovery programs
- The goals of collaboration are to **pursue commercialization** and **joint publications**

1. **MatchMaker**: Protein Target(s) -------> Compounds from virtual screening

1. **POEM**: Compounds from virtual screening -------> ADMET predictions

CAPP: Partnership Goals

1. Grant Applications & Joint Publications
2. Lead Series
3. Clinical Candidates

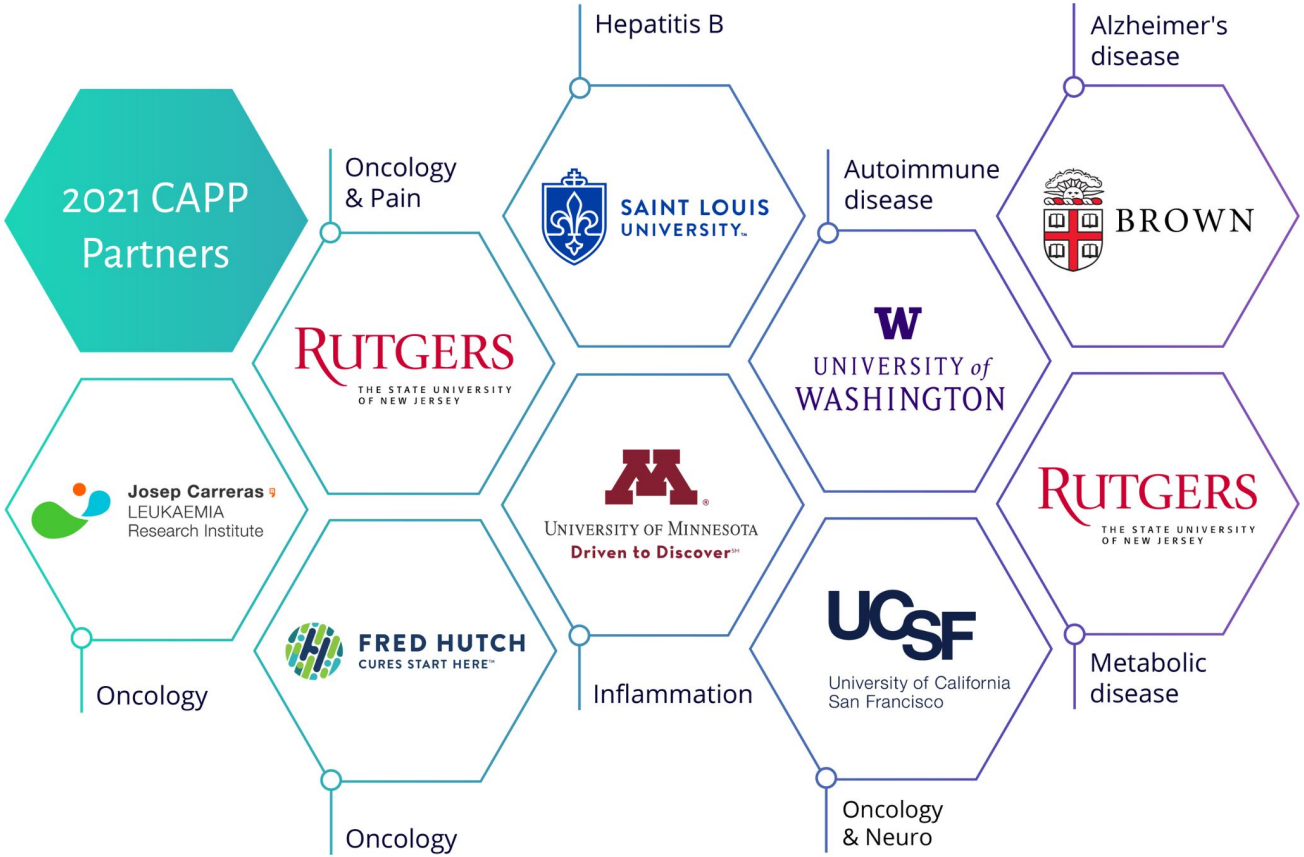
Cyclica is open to various forms of collaborations to pool resources and combine unique drug discovery capabilities

How we would like to collaborate with your lab

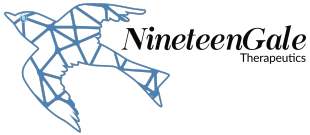
1. Identify novel compounds for therapeutically relevant protein targets from your lab
2. Development of novel assay systems and/or drug discovery technologies that augment Cyclica's capabilities and pipeline ambitions

What are the next steps?

1. Set up introductory meetings with Cyclica's Partnerships team to understand your needs/goals
2. Have an in-depth scientific discussion with Cyclica's Drug Discovery team for project feasibility and scoping
3. Sign partnership agreements and begin collaboration


2021 CAPP Partners
Hepatitis B
Saint Louis University
Alzheimer's disease
Brown
Oncology & Pain
Rutgers
The State University of New Jersey
Autoimmune disease
University of Washington
Josep Carreras Leukaemia Research Institute
Oncology
University of Minnesota
Driven to Discover
Inflammation
Rutgers
The State University of New Jersey
Metabolic disease
Fred Hutch
Cures Start Here
Oncology
UCSF
University of California San Francisco
Oncology & Neuro

And, a special thanks to our Canadian partners



At Cyclica, we **embrace the complexity of disease**.

CYCLICA
From molecule to medicine

Contact us to learn more

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@cyclica