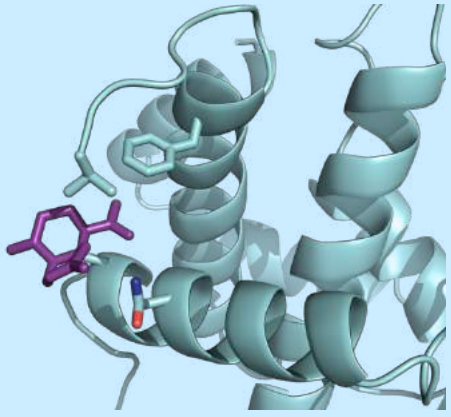
Think Bioscience

Nature-Inspired Drug Discovery



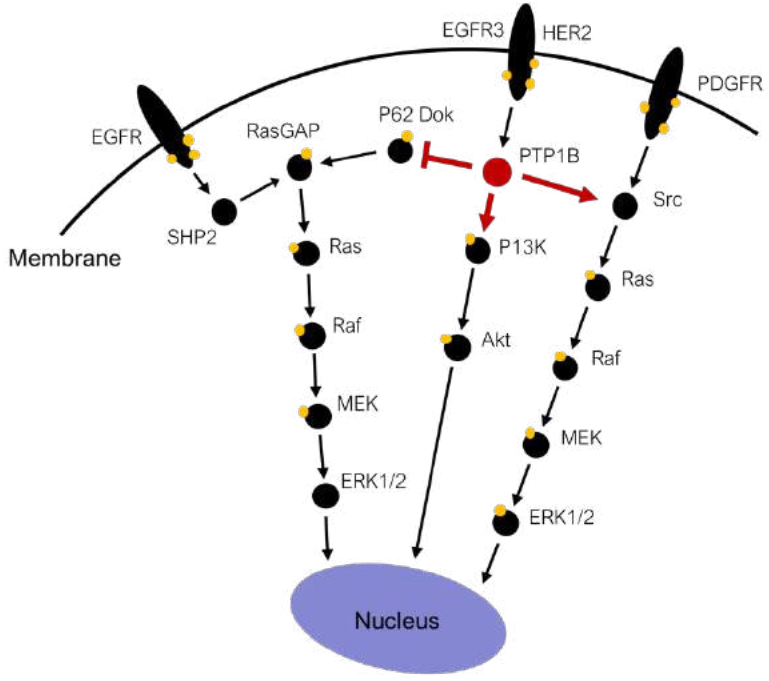
Drug Design is Exceedingly Difficult

Existing Challenges to Drug Discovery

- **Existing knowledge covers still only covers limited design space**
- **Subsequent functional assays**
- **Access to novel binding behavior**
- **Protein flexibility hard to model and entropic price**

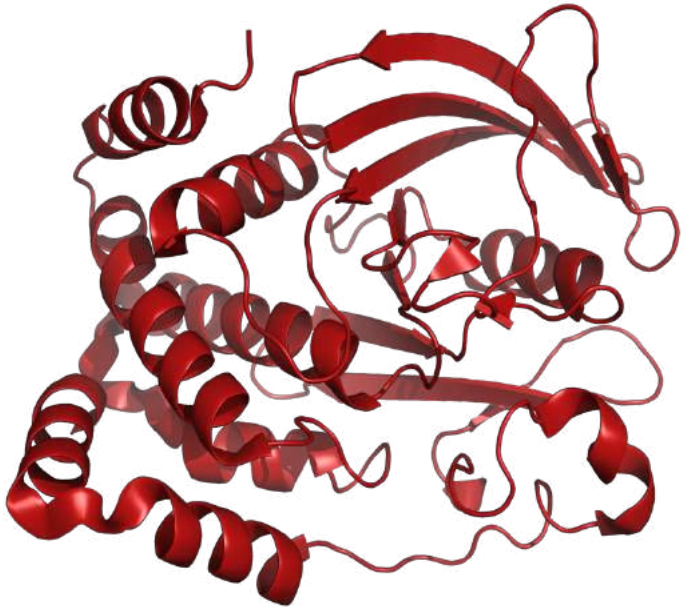
Goal: inhibit an overactive protein

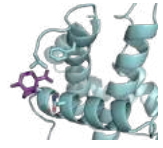
Tumorigenesis, growth, survival, and metastasis



Target: Protein tyrosine phosphatase 1B (PTP1B)

A selective inhibitor of PTP1B could treat type 2 diabetes, obesity, and HER2-positive breast cancer

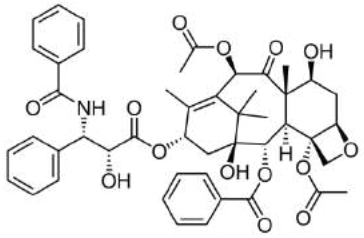


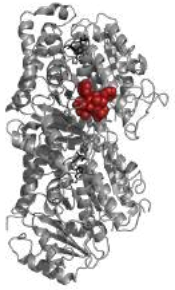


Nature provides a rich source of biologically active compounds

Paclitaxel (cancer)

Pacific yew
(Taxus brevifolia)

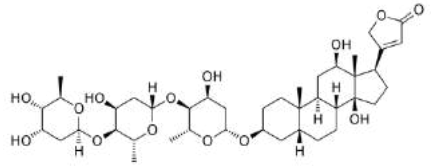


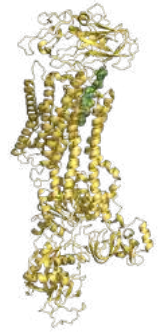


αβ tubulin

Digoxin (heart failure)

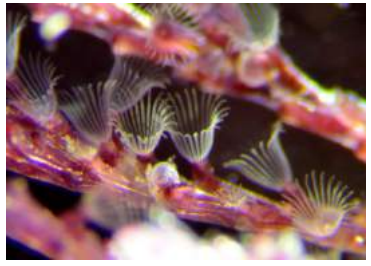
Foxglove
(Digitalis lanata)



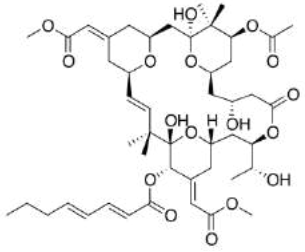


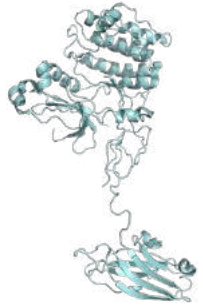
Na,K-ATPase

Bryostatin (cancer)



Brown bryozoan
(Bugula neritina)

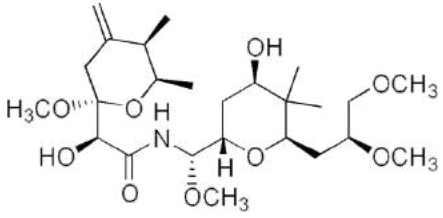


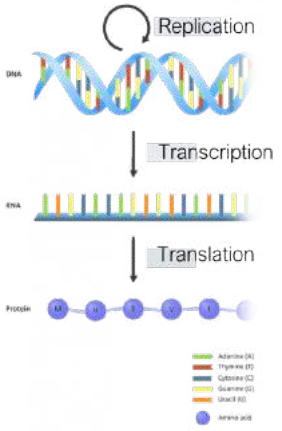


Protein kinase C

Pederin (cancer)

Paederus littoralis /
Pseudomonas



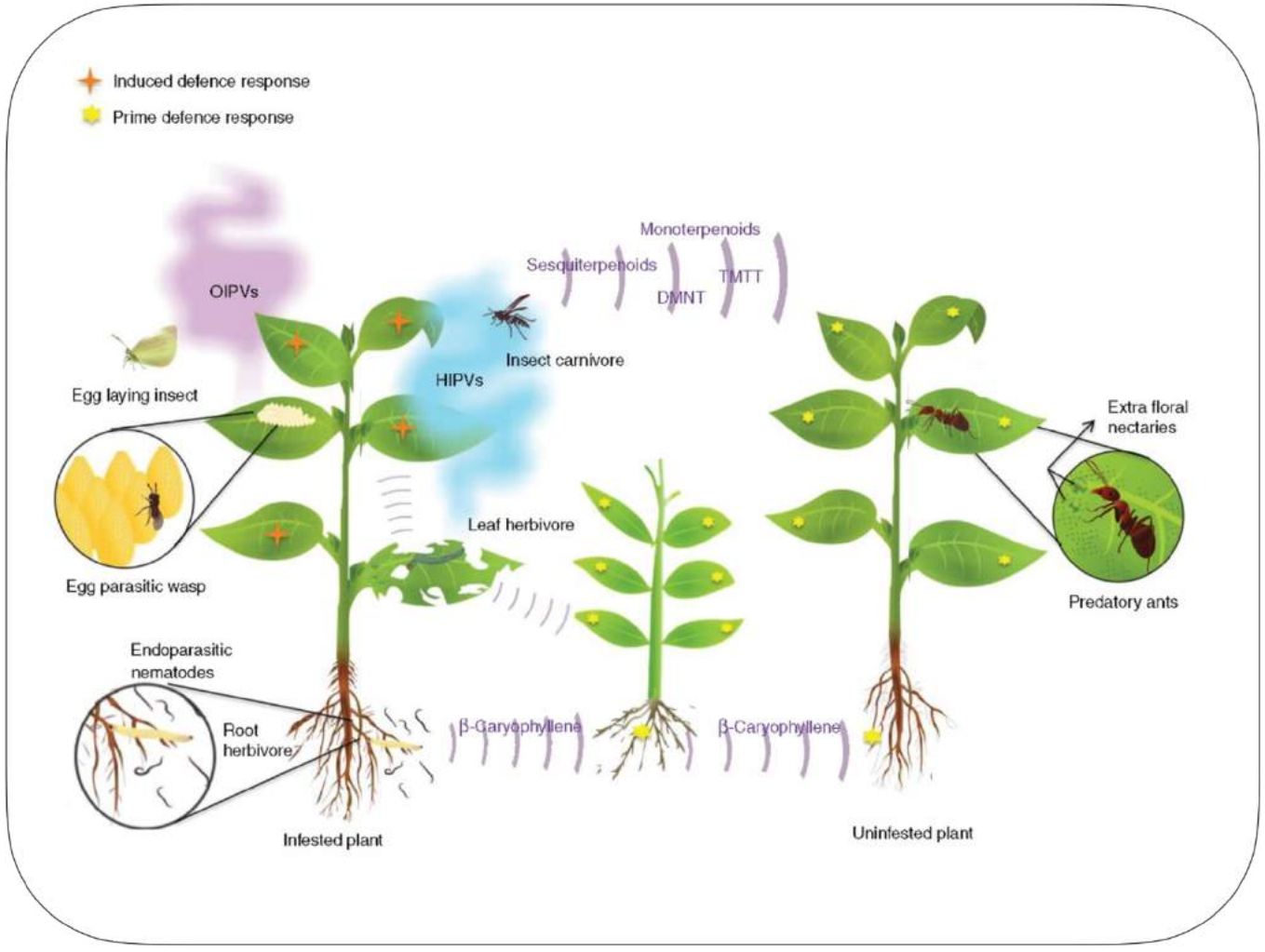


Western Yew Poising Dogs (2020). Available: https://wagwalking.com/condition/western-yew-poisoning; Growing Foxglove (2020). Available: https://www.almanac.com/plant/foxglove; Bryozoan (2020). Available: http://nathistoc.bio.uci.edu/Ectoprocta/Bugula%20neritina/index.html.; Wikimedia Commons: Paederus littoralis December 2016-1 (2020).; What is the 'Central Dogma' (2020). Available: https://www.yourgenome.org/facts/what-is-the-central-dogma

Evolution of Small Molecule Discovery | There still exists challenges to address current unmet need

	High Throughput Screening	AI Drug Discovery	Synthetic Biology Drug Discovery
Benefits	✓ Source of many approved drugs	✓ Screen larger chemical libraries ✓ Reduce cost and speed of hit/lead discovery	✓ Explore novel areas of chemical design space ✓ Requires less knowledge of target and crystal structure
Challenges	• Have already found low—hanging fruit • Existing chemical libraries cover a small portion of entire chemical design space	• Limited by quality of data • Biased to "existing solutions" and clear biological hypothesis • Typically require target structure	• Many existing companies focused on production of existing pharmacophores • Finding molecules with therapeutics effect that differ from native function
Examples Companies	Traditional Pharmaceutical Companies	BenevolentAI, BERG, RELAY THERAPEUTICS, Atomwise, SILICON Therapeutics, XtalPi, VERGE, RECURSION, AI Therapeutics, SCHRÖDINGER, Numerate, deep genomics	Think Bioscience, Hexagon Bio, ASIMOV, SyntheX

Natural products have evolved to achieve sophisticated ecological feats

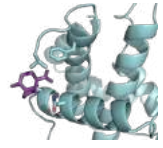


The plant's effective defense

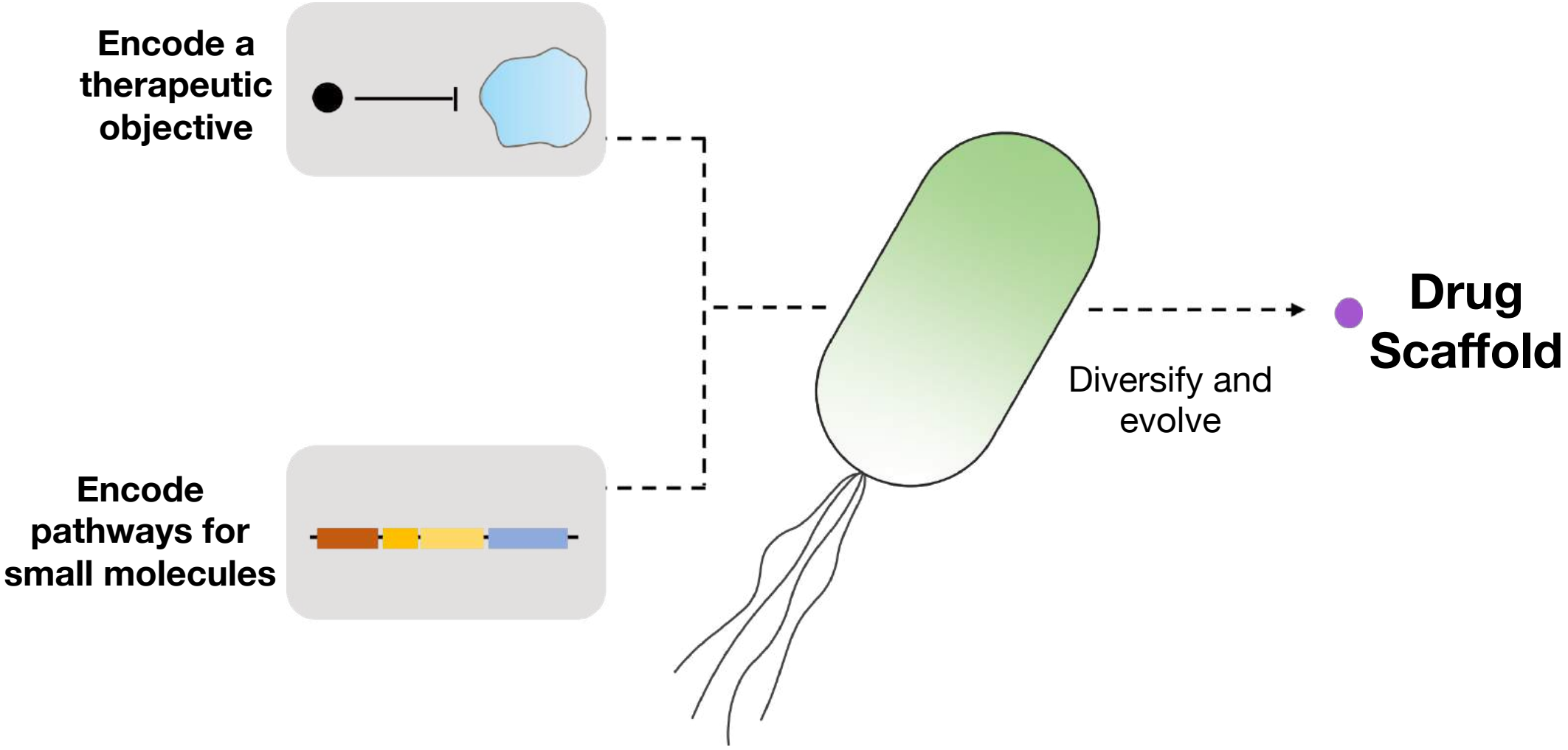
- Problem: herbivorous insects eat leaves
- Solution: plant generates terpenoids to attract predators
- Result: predators eat herbivors

Nature-Inspired Drug Discovery

Encode systems with a therapeutic challenge and use them to build molecules that solve it.

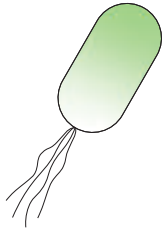


We use microbial systems to guide drug design



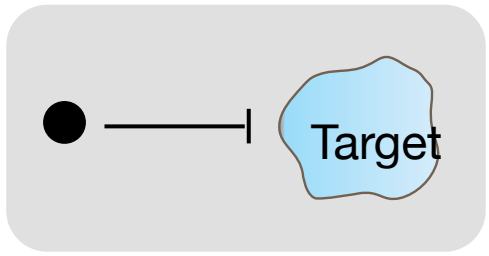
Think Bioscience Discovery Process

1 Find a suitable host



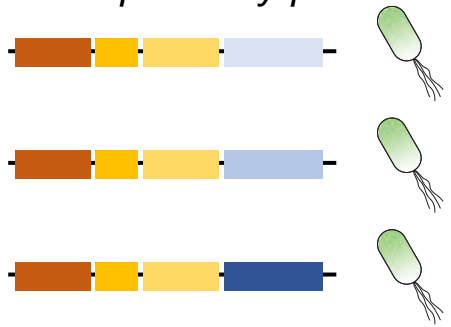
2 Encode a biochemical objective

inhibit target protein



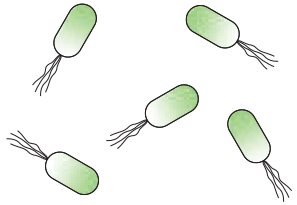
3 Encode biosynthetic pathways

one pathway per cell



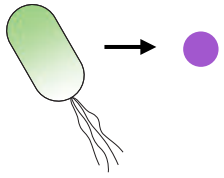
4 Grow population of cells under selection pressure

Each cell includes the same objective but a different pathway

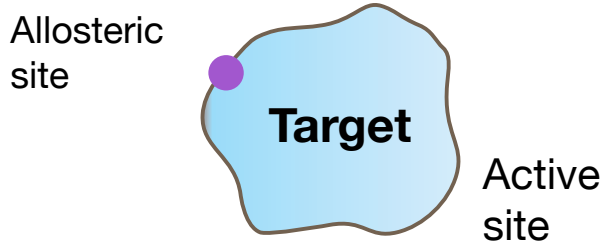


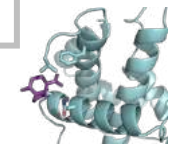
5 Surviving cells produce small-molecule modulators

Biosynthesis of protein inhibitors



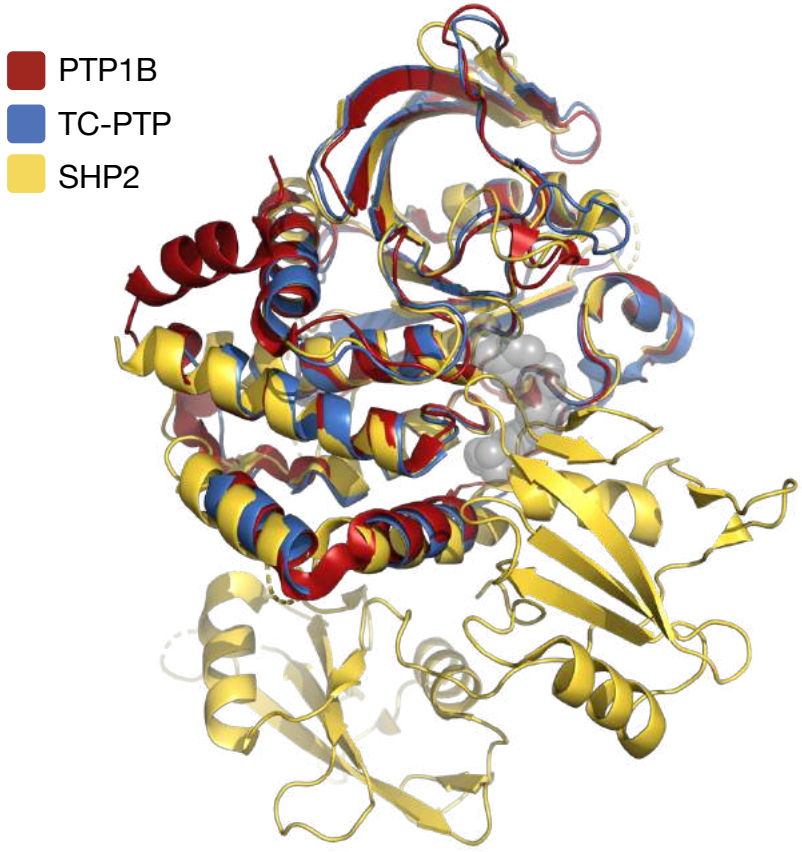
6 Drug Candidate Characterization



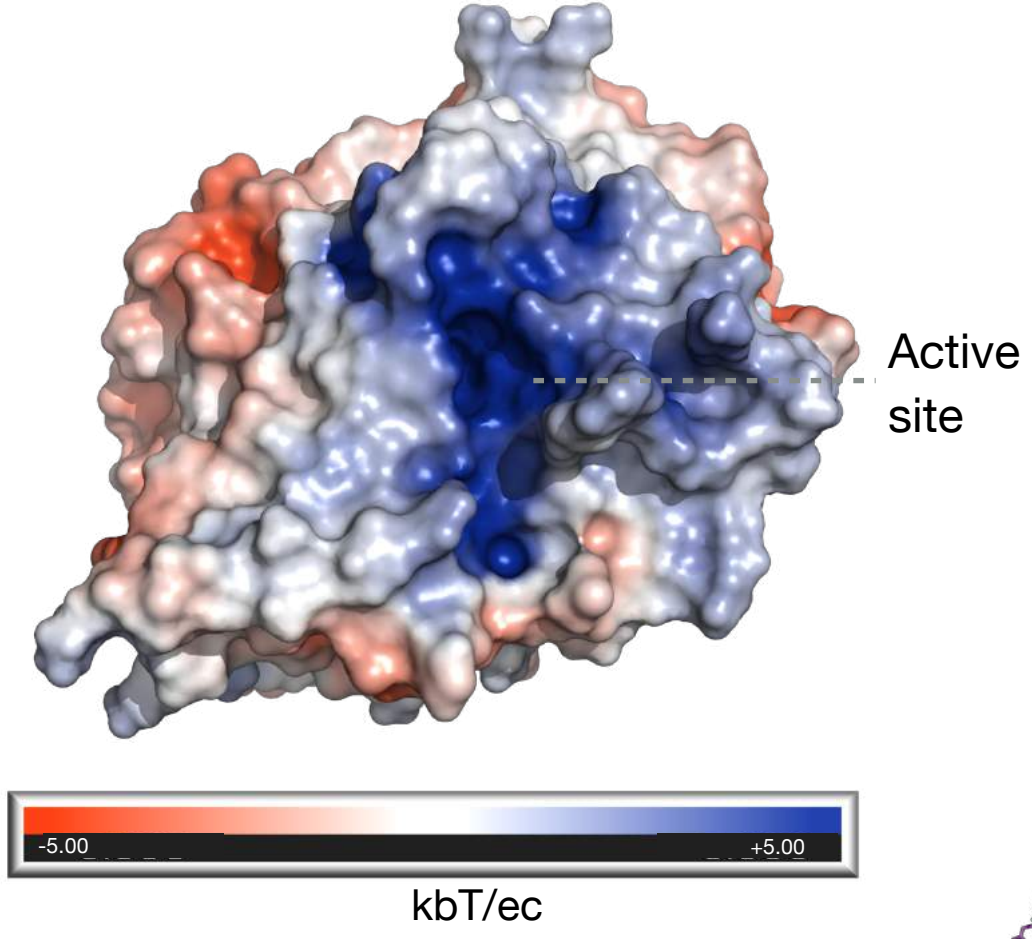


Platform Validation Case Study | Proof-of-Concept demonstrated in hard-to-drug PTP1B Target

Poor selectivity: conserved active site



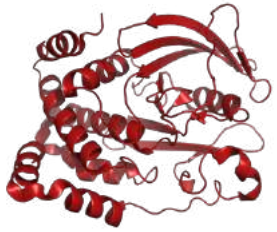
Poor membrane permeability: charged active site



Steps 1-2: Design a Genetically-Encoded Objective

Set Goal
Link therapeutic objective to cell survival

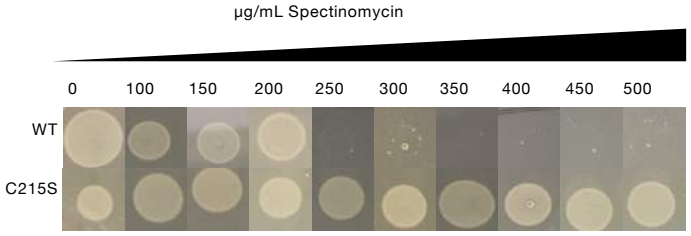
"Inhibit PTP1B"



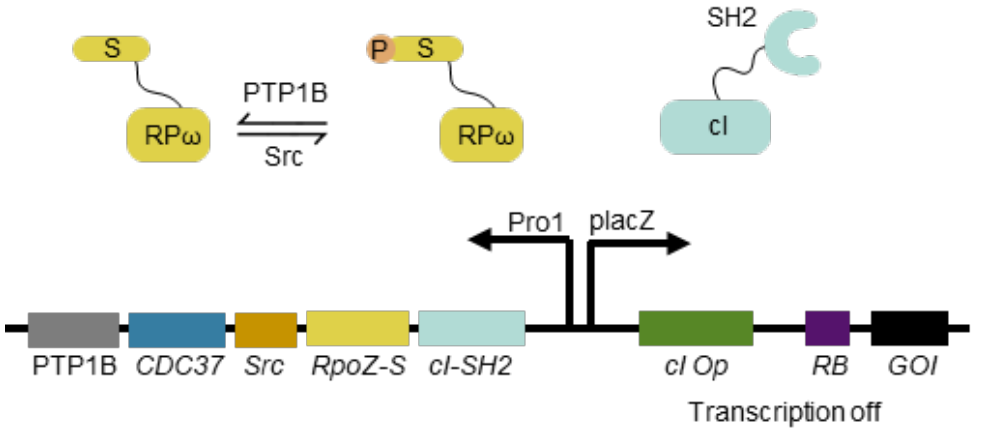
Protein tyrosine phosphatase 1B (PTP1B)

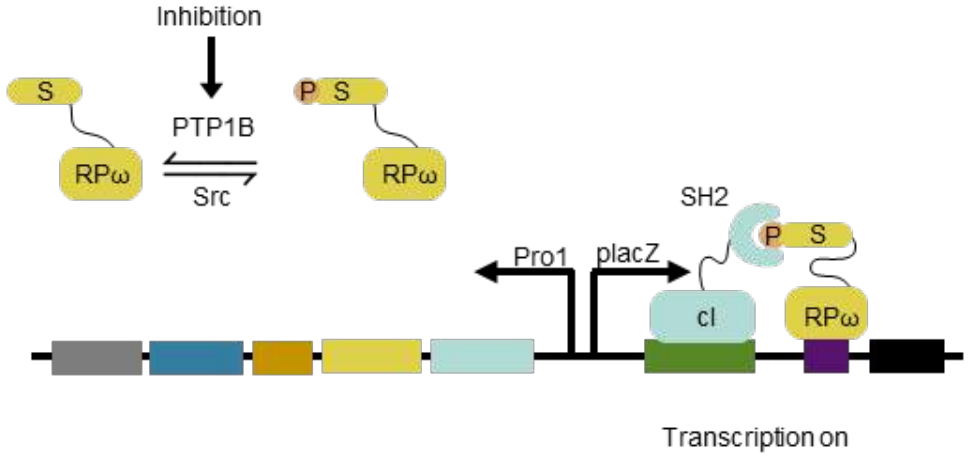
→ Toxic effects

Proof of concept:



Design Detection System
A bacterial two-hybrid system





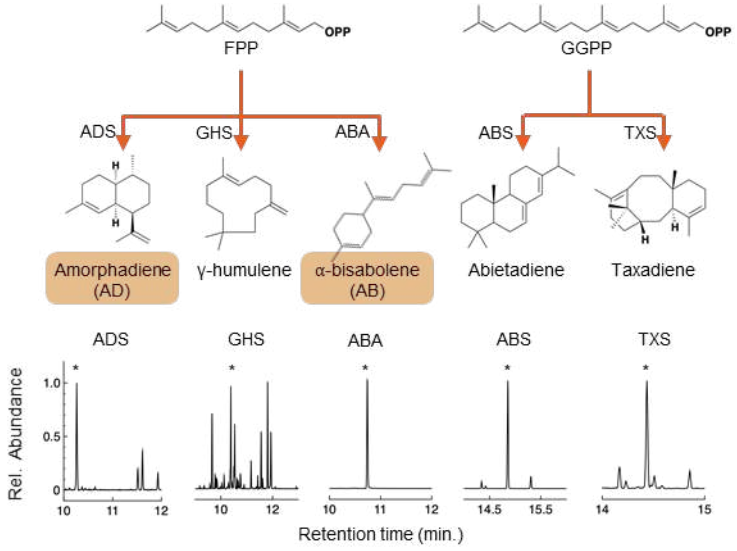
Sarkar et al. Submitted (2020)

Steps 3-5: Encode and Screen Biosynthetic Pathways

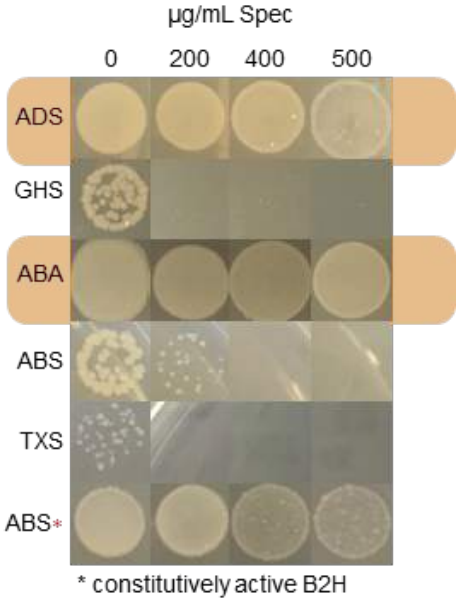
Design Biosynthetic Pathway for Target Molecule Class

Generate diverse set of terpenoids

Examine five structurally diverse terpenoids

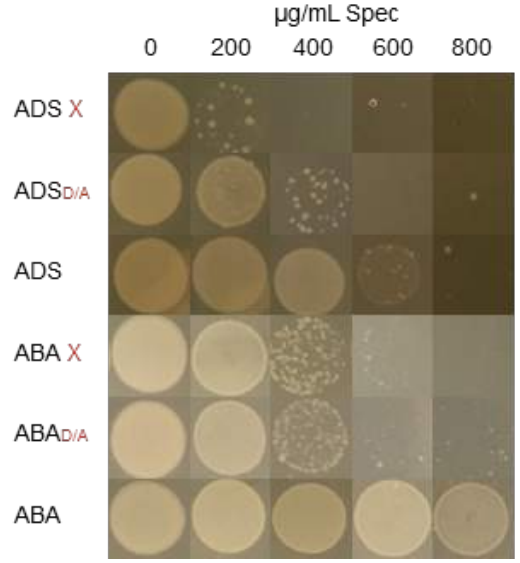


Do TSs confer survival?

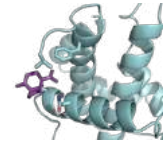


* constitutively active B2H

Does survival require an active TS and B2H?



D/A: inactive TS
X: inactive B2H

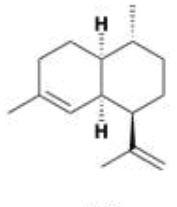


Sarkar et al. Submitted (2020)

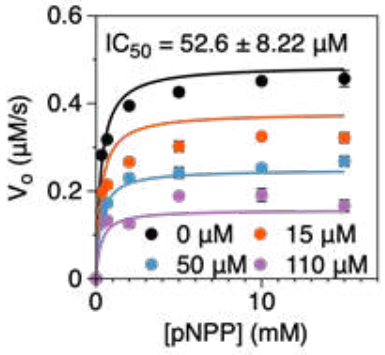
Step 6: Drug Candidate Characterization Part 1

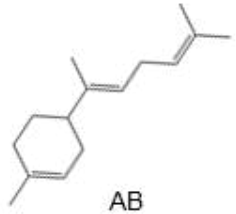
Validation Testing
Confirm Binding Activity

Confirmed Binding Activity with in vitro kinetic measurements

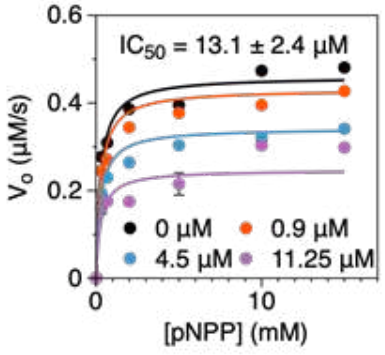


AD

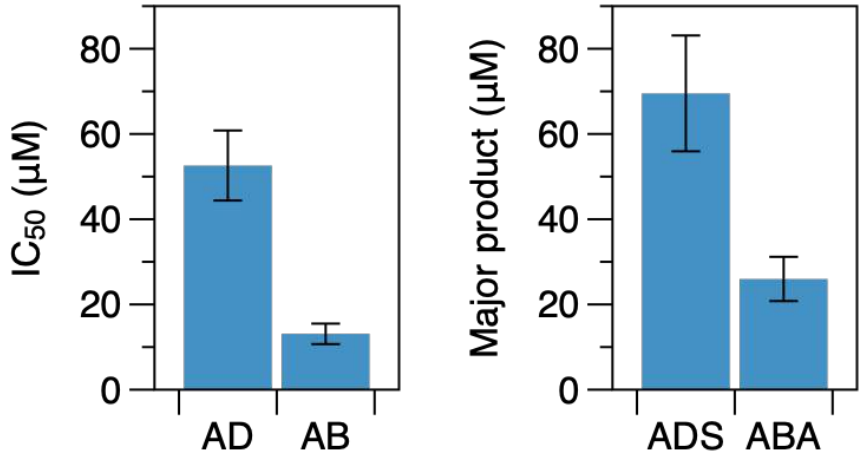




AB



Confirmed AD and AB activate B2H system by inhibiting PTP1B inside the cell



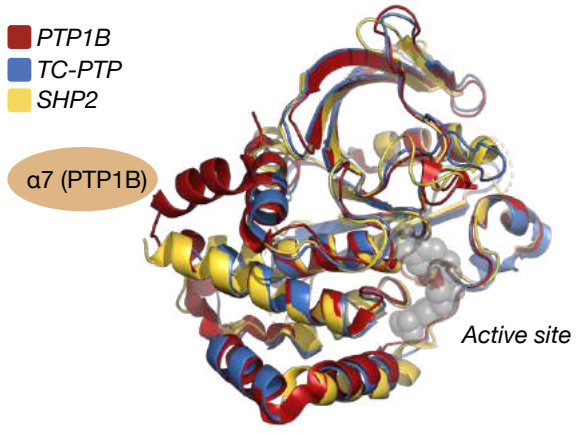
Both molecules could, in fact, inhibit PTP1B, and, intriguingly, their IC50s were similar to their concentrations in liquid culture.

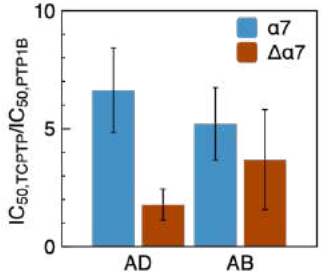
Sarkar et al. Submitted (2020)

Step 6: Drug Candidate Characterization Part 2

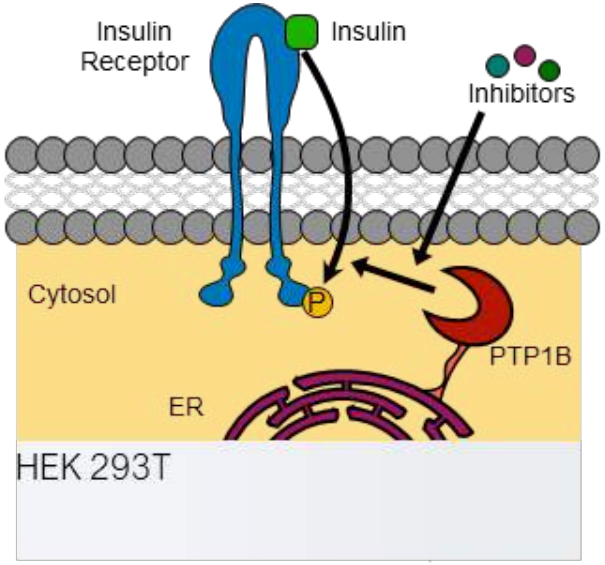
Validation Testing
Confirm Selectivity and Membrane Permeability

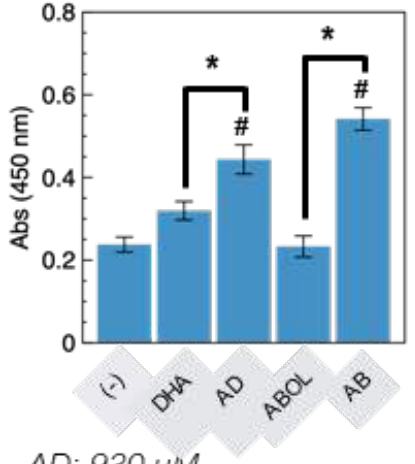
AD and AB Selectivity for PTP1B





AD and AB Cell Permeability





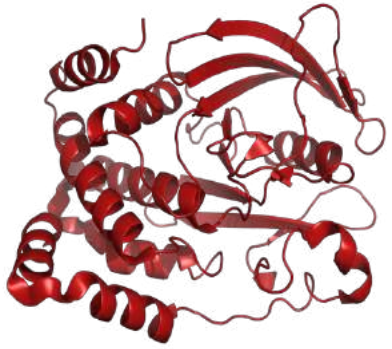
AD: 930 μM
DHA: 930 μM
AB: 405 μM
ABol: 405 μM

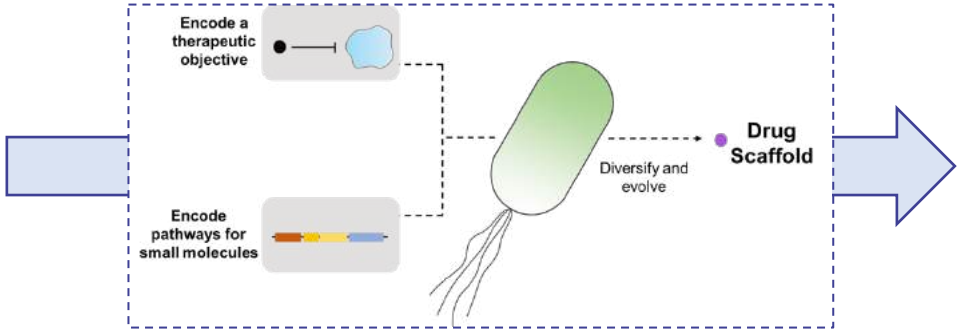
#: $p < 0.05$, compared to negative control
**: $p < 0.05$*

Sarkar et al. Submitted (2020)

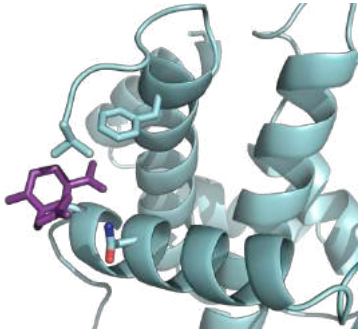
Use Case Summary | Established proof-of-concept in a challenging target

PTP1B

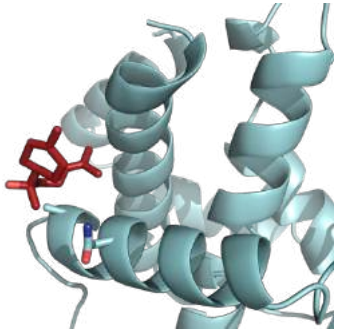




Amorphadiene



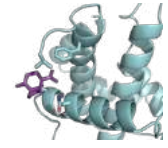
α-bisabolol



Resolution: 2.1 Å

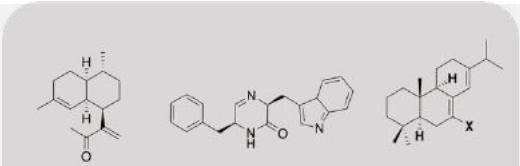
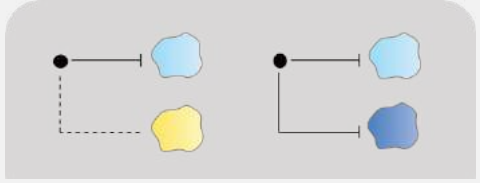
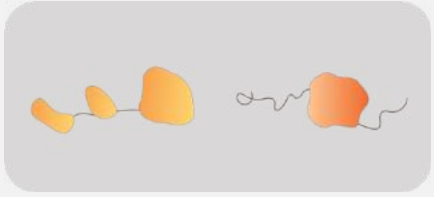
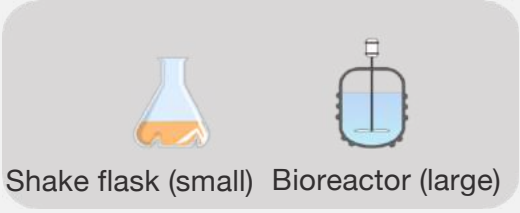
Next Steps

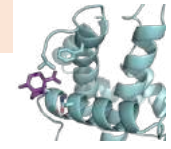
- ❑ Optimization of potency and biological activity of initial hits
- ❑ Further characterization of optimized hits with in vitro cell studies



We are continuing to expand on this approach to inhibitor discovery

Our approach yields targeted, readily synthesizable modulators of difficult-to-drug proteins

Address Structurally Complex Targets	 Terpenoids Peptides Halogenation	• Various pathways can be programmed into the microbe systems • Ability to address targets without well-understood biology
Incorporate Sophisticated Mechanisms	 Selective inhibition Multi-target inhibition	• Multiple objectives can be programmed • Platform knowledge leveraged for other targets
Access Molecular Diversity	 Multidomain Partially disordered	• Platform does not rely nor is biased by existing libraries • Access previously unexplored chemical design space
Rapid scale-up of molecular synthesis	 Shake flask (small) Bioreactor (large)	• Easily scaled to through cell culture (50-100 mg/L) • Further optimization can be conducted with CROs



Innovative drug discovery continues to a focus for biopharma companies

- Target ID
- Target Validation
- Lead Discovery
- Lead Optimization
- Preclinical Testing
- Clinical Testing

Think Bioscience Business Model

- Natural Scaffold for Drug Lead
- Med Chem Optimization
- In-Vitro Testing
- In-Vivo Testing

- **Expand Think Bioscience platform to broader range of target classes** (Phosphatases, kinases, proteases, transcription factors, etc...)
- **Optimize promising drug scaffolds to improve drug-like properties**
- **Leverage biopharma partnerships to deliver drugs to the clinic**

Example SHP2 Inhibitor Partnerships

Combo therapy with KRAS assets

REVOLUTION MEDICINES SANOFI RELAY THERAPEUTICS Genentech A Member of the Roche Group

July 2018: Revolution Medicines receives:

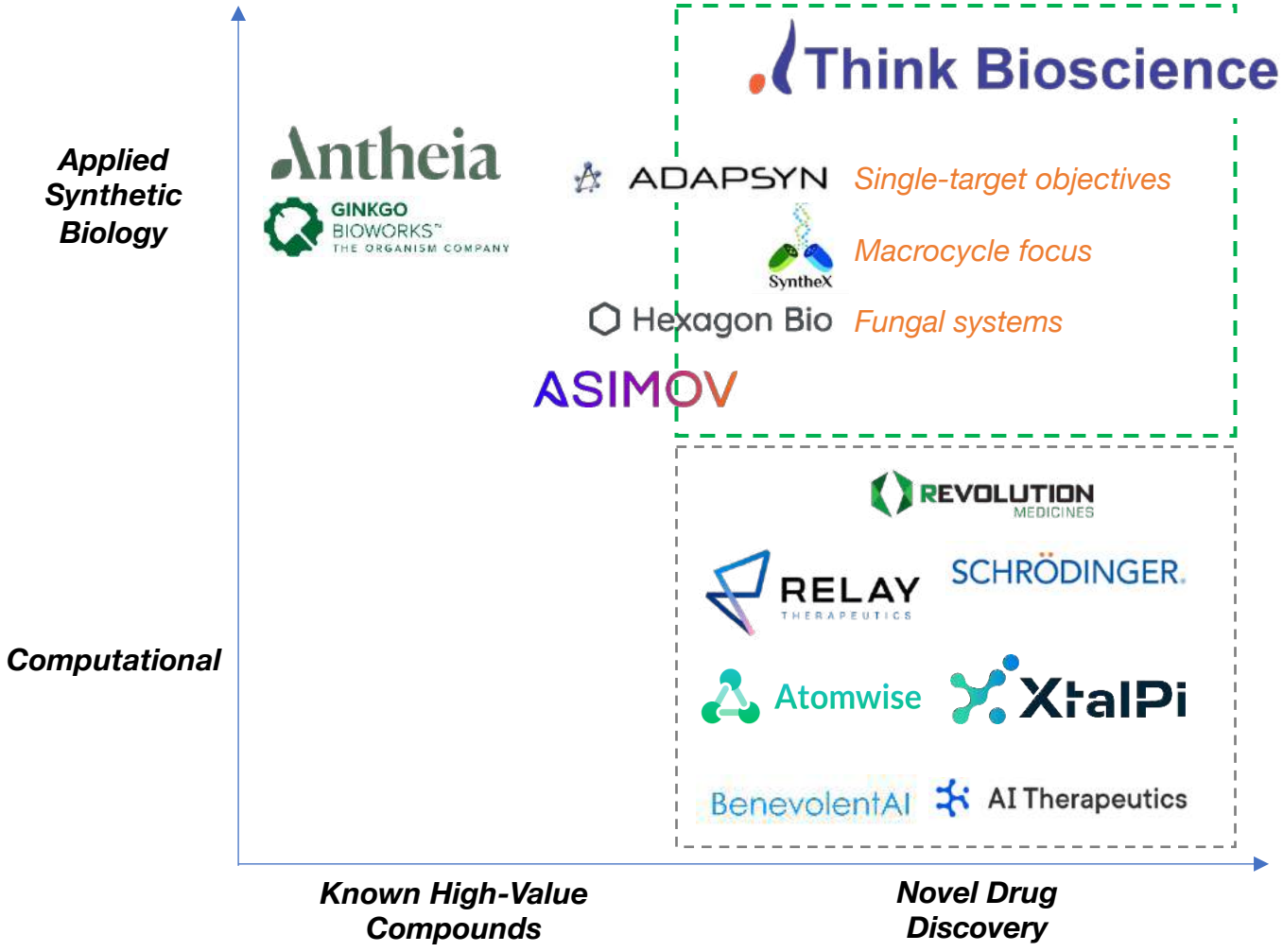
- $50M upfront and R&D costs
- $500M total potential milestone payments
- 50/50 profit and loss share (US)

Dec 2020: Relay receives:

- $75M upfront
- $25M near-term payments; up to $410M in milestone payments ($695 if full US dev/comm done by GNE)
- 50/50 profit and loss share (US)

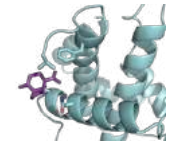
abbvie Jacobio AMGEN REVOLUTION MEDICINES

Competitive Landscape | Opportunity for synthetic biology driven platforms



- ✓ *Multi-target objectives*
- ✓ *Broad applicability across target classes*
- ✓ *Ability to uncover novel activity*

Company	Financing Activity
Adapsyn	Investment/Partner (2018): Up to $162M in bio-bucks
Synthex	Seed (2017): $6M
Hexagon Bio	Series A (2020): $47M
Asimov	Seed (2017): $4.7M
Revolution Medicines	Series A (2015): $45M Series B (2018): $56M Series C (2019): $100M IPO (2020): $273M
Relay	Series A (2016): $57M Series B (2017): $63M Series C (2018): $400M IPO (2020): $400M



Think Bioscience Team

Management Team

Jerome M. Fox, PhD
Interim CEO

University of Colorado Boulder

Philip Jeng
CBO

BLAVATNIK FELLOWSHIP IN LIFE SCIENCE ENTREPRENEURSHIP

Genentech
A Member of the Roche Group

Matt Traylor, PhD
Head of Pharm Dev

Mosaic Biosciences
Shire

Advisors

Harvey Blanch, PhD
Scientific Advisor

amyris

Ryan Gill, PhD
Scientific Advisor

INSCRIPTA
The Digital Genome Engineering Company

Stan Lapidus
Business Advisor

EXACT SCIENCES

Think Bioscience Milestones & Development Plan

2019-2020

Accomplishments

- Proof-of-concept demonstrated in PTP1B
- IP Protection: 1 PCT, 1 provisional, and 2 accelerated patents
- Exclusive option with CU

Non-Dilutive Funding

- Secured STTR ($256K) on antivirals recommended for funding
- Secured OEDIT 1:2 State Matching (up to $250k)
- Winner of CU Lab Venture Challenge ($125k)

2021

Company Dev

- Secure Seed funding
- Hire 1 lead scientist and 2 researchers
- Secure office and lab space

Platform Dev

- Further functionalization of PTP1B natural scaffold hit
- Proof-of-concept in two additional categories (proteases, transcription factors, etc…)
- 1st Pilot Study with Pharma company

2022

Company Dev

- Raise Series A
- 2nd Pilot Study with Pharma company
- Team expansion to include veteran drug developers

Platform Dev

- Complete in vitro studies for PTP1B and secure IP for lead molecule
- Optimize two additional hits for further lead optimization development