SANDERS TRI-INSTITUTIONAL THERAPEUTICS DISCOVERY INSTITUTE

Therapeutics Bridge Labs (TxBL)

Memorial Sloan Kettering Cancer Center

Drug Development and Target Validation
ENL YEATS as a Case Study

Peter T. Meinke

October 8, 2025

1

Outline

- Early Drug Development Stages
- Overview of the Discovery process
- Target identification and validation
- Assay development and screenings
- Lead identification, Optimization and candidate selection
- ADME and DMPK
- Drug delivery and scale up/manufacturing considerations

2

Target selection: The fundamental challenge

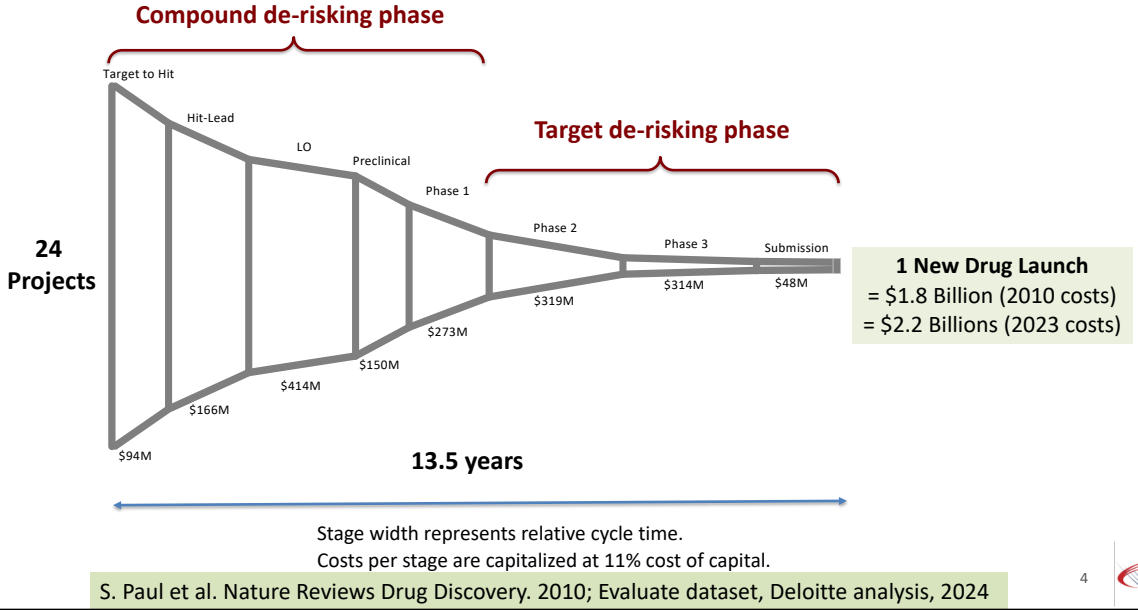
We think we know **where to aim**, however…

Human proof-of-concept studies are necessary to **validate them**

3

3

Current model: gradual, slow and costly



1 New Drug Launch
= $1.8 Billion (2010 costs)
= $2.2 Billions (2023 costs)

Stage width represents relative cycle time.
Costs per stage are capitalized at 11% cost of capital.

S. Paul et al. Nature Reviews Drug Discovery. 2010; Evaluate dataset, Deloitte analysis, 2024

4

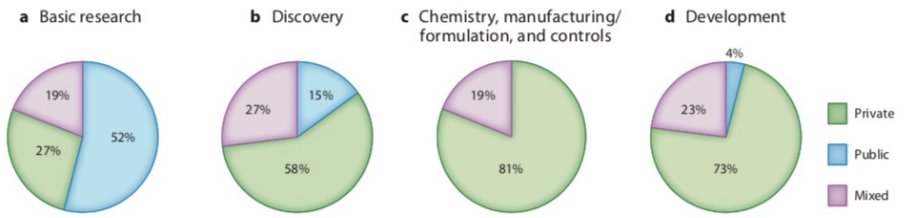
4

Drug Discovery

- Long and arduous and expensive process
- Most ideas fail
  - Wrong hypothesis
  - Animal model doesn't recapitulate human disease
  - Complex biology not fully understood
  - Compensation by other pathways or family member proteins
  - Toxicity: mechanism based or off target

5

Role of Academia in Basic Research and Discovering Drugs



- **Due to different drivers…**
  - Academia excels at basic research
  - Pharma increasingly dominates development
- Unfortunately, academic labs often lack the time, resources or expertise needed to advance insights into basic biology discoveries to therapeutics
- **Collaborate!!**
  - Translating basic science discoveries to animal proof-of-concept then to a drug requires different skills
  - Essential to identify colleagues and partners that fill resource and expertise gaps

https://www.annualreviews.org/doi/10.1146/annurev-pharmtox-010818-021625

6

Challenges in Academic Drug Discovery: Resources and Translational Expertise

Comprehensive data packages are highly valued by companies
The value proposition for licensing is ***highly nonlinear***

Project Stage at License	Research Program	Unoptimized Lead	Development Candidate	Clinical Program
Target identified	✅	✅	✅	✅
In vitro activity in biochemical, functional assays	✅	✅	✅	✅
In vivo efficacy in disease-relevant animal model		✅	✅	✅
Preliminary safety data safety in vitro			✅	✅
Preliminary safety data safety in vivo			✅	✅
IP established			✅	✅
Safety and tox studies				✅
Preliminary safety data safety				✅
Clinical studies				✅

7

7

Changing Gears…

…to Drug Development and Target Validation

- **Read the literature!**
  - Staying current with existing literature and new technologies is essential…

8

8

Nature Reviews: Guides to Drug Discovery

Advances in covalent drug discovery
Nat Rev Drug Discov. **2022** Dec;21(12):881-898

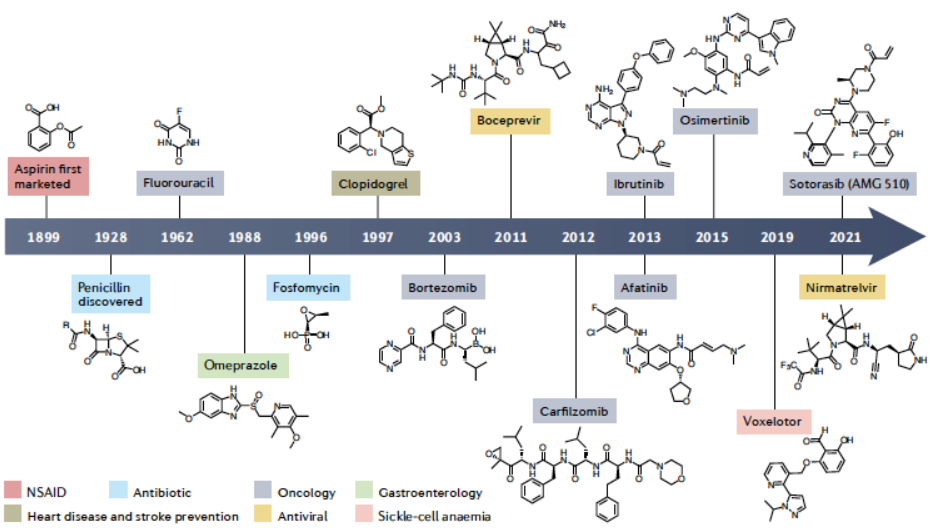


Fig. 1 | **Timeline of the development of major covalent drugs.** Each covalent drug is classified according to the drug type or type of disease it treats. Unless otherwise indicated, the date refers to the first approval by the US Food and Drug Administration. NSAID, non-steroidal anti-inflammatory drug.

9

9

Strategy For Drug Discovery

Distinct areas, but with much overlap

- **Basic Research** - molecular understanding of disease, target selection, screening, drug design and synthesis
- **Preclinical Research** - drug scale up, safety assessment, detailed metabolism
- **Clinical Research** - evaluation in humans (safety and tolerability, efficacy)

- **Case study: discovery of TDI-11055 for acute myeloid leukemia (AML)**
  - Opportunities for innovation at all stages

10

10

Basic Research Strategy

- Define the unmet medical need (disease)
- Understand the molecular mechanism of the disease
- Understand the biochemical pathway that contributes to that mechanism
- Identify a therapeutic target in that pathway
  - e.g., gene, key enzyme, receptor, ion-channel, nuclear receptor
- Validate the target
  - Use genetics, animal models, lead compounds
- Invent an assay to evaluate activity of compounds on the target
  - *in vitro* (e.g., enzyme assay)
  - *in vivo* (animal model or pharmacodynamic assay)

11

11

Challenges in Drug Discovery: Pharma's Prior Success

- **Economic drivers are equally significant**
  - Diabetes and dyslipidemia as examples
- **Dyslipidemia**
  - Statins: Lipid effects of Crestor > Lipitor > Zocor
  - Outcomes studies required for registration
  - Now generic, cost reduced to negligible levels per day
- **Diabetes**
  - Gliptins: Januvia ≈ Galvus ≈ Onglyza
  - Previously, outcomes studies were required for registration
    - FDA lifted this requirement
  - Soon to become generic (2026 onward), greatly reduced daily costs
- New therapeutics **MUST** compete on safety, efficacy and cost with generics
  - New mechanisms won't be introduced as they can be safe and effective but economic failures
  - Missed opportunities for unappreciated benefits from novel mechanisms or to select populations

12

12

Challenges in Drug Discovery: Safety Concerns

- Risk taking is integral to pharma's success (or lack thereof!)
  - Safety concerns are significant contributors to pharma strategies
  - **ALL** medicines have safety liabilities
- Concerns over rare / uncommon adverse effects
  - NSAIDs: non-steroidal anti-inflammatory drugs (asipirin, ibuprofen)
    - Non-selective COX-1, 2 inhibitors
    - Cause significant GI effects (bleeding) via COX 1
      - 17,000 deaths in 2005 in Spain alone in hospice settings
- Merck introduced painkiller Vioxx, a selective COX-2 inhibitor
  - No GI effects
  - Blockbuster drug (sales >$1B annually)
  - Merck withdrew Vioxx, paid $4.85 billion to settle nearly 27,000 lawsuits that claimed the arthritis drug caused heart attacks and strokes
  - Abandoned an entire research field
- **Many new potential therapies never reach clinic or get FDA approval for real or perceived safety concerns**

13

13

Mapping Human Microbiome Drug Metabolism by Gut Bacteria and Their Genes

Nature: doi:10.1038/s41586-019-1291-3

- Microbiome-encoded drug-metabolizing gene products explain drug metabolism of gut bacterial strains and communities
  - Previously unappreciated impact of microbiome on drug metabolism
  - Potential to monitor in advance as part of screening funnel for discovery
- Individuals vary widely in drug responses, which can be dangerous and expensive due to treatment delays and adverse effects.
  - Growing evidence implicates the gut microbiome in this variability, however the molecular mechanisms remain largely unknown.
- **Measured ability of 76 diverse human gut bacteria to metabolize 271 oral drugs**
  - **Many found to be chemically modified by microbes**.
  - Can explain drug-metabolizing activities of human gut bacteria and communities based on their genomic contents
  - Connects interpersonal microbiome variability to interpersonal differences in drug metabolism
- Implications for medical therapy and drug development across multiple disease indications

14

14

Validating therapeutic targets through human genetics

The support of human genetic evidence for approved drug indications

Nelson et al, Nature Genetics (2015), 856-860

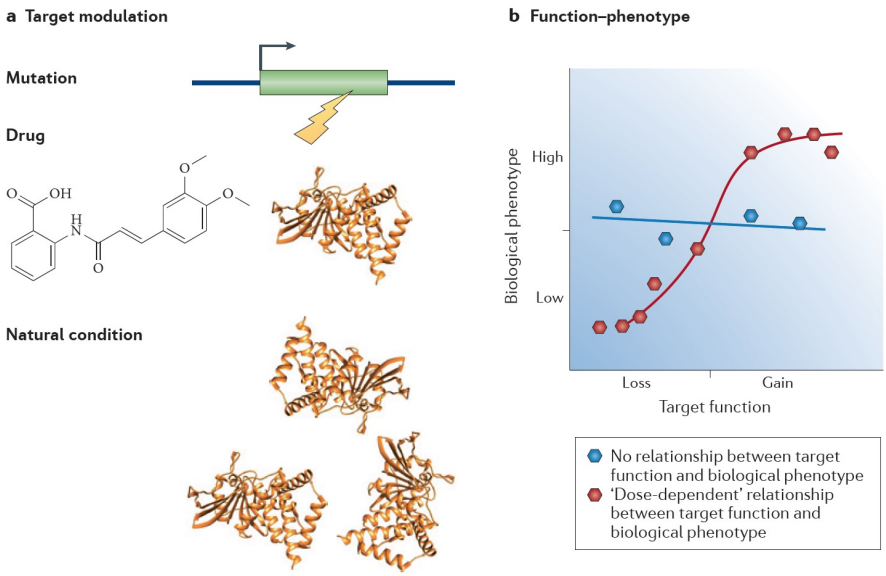
Matthew R Nelson[1], Hannah Tipney[2], Jeffery L Painter[1], Judong Shen[1], Paola Nicoletti[3], Yufeng Shen[3,4], Aris Floratos[3,4], Pak Chung Sham[5,6], Mulin Jun Li[6,7], Junwen Wang[6,7], Lon R Cardon[8], John C Whittaker[2] & Philippe Sanseau[2]

ABSTRACT: Over a quarter of drugs that enter clinical development fail because they are ineffective. Growing insight into genes that influence human disease may affect how drug targets and indications are selected. However, there is little guidance about how much weight should be given to genetic evidence in making these key decisions. To answer this question, we investigated how well the current archive of genetic evidence predicts drug mechanisms. We found that, among well-studied indications, the proportion of drug mechanisms with direct genetic support increases significantly across the drug development pipeline, from 2.0% at the preclinical stage to 8.2% among mechanisms for approved drugs, and varies dramatically among disease areas. We estimate that selecting genetically supported targets could double the success rate in clinical development. **Therefore, using the growing wealth of human genetic data to select the best targets and indications should have a measurable impact on the successful development of new drugs.**

15

Developing a Therapeutic Hypothesis

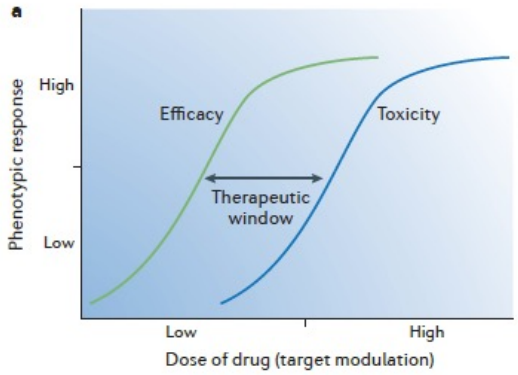
Validating therapeutic targets through human genetics, Plenge et al., *Nature Reviews Drug Discovery* volume 12, 581–594 (2013)



16

All Drugs Have Safety Liabilities

Validating therapeutic targets through human genetics, Plenge et al., *Nature Reviews Drug Discovery* volume 12, 581–594 (2013)



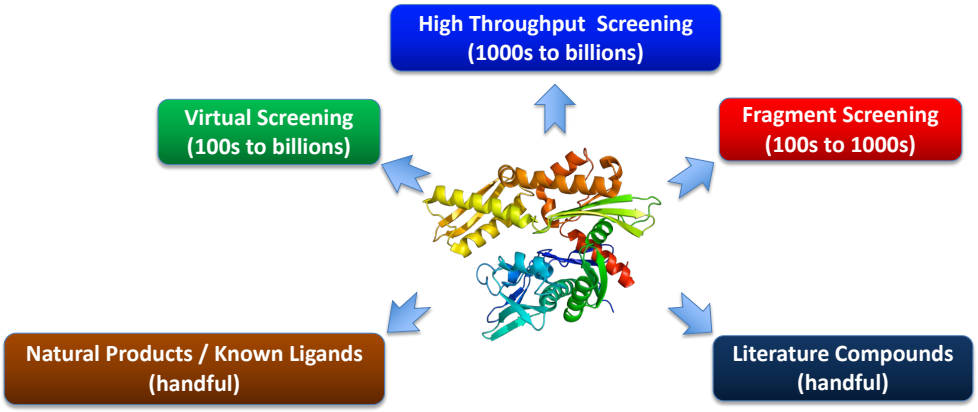
- **Therapeutic Index**
  - TC_{50} divided by EC_{50}
- **Therapeutic window**
  - Minimum effective concentration (MEC) represents the minimum blood level necessary to achieve a specified biological effect
  - Minimum toxic concentration represents the minimum blood level at which a toxic effect occurs
  - The range between these two values represents the therapeutic window

17

17

Introduction to Medicinal Chemistry: Hit Finding Methods

- The nature of the target will determine which options are feasible
- Each option has certain opportunities and challenges
- Utilizing multiple approaches in parallel is preferred – 'best chance' for finding multiple starting points



18

18

A Chemist's Guide to Lead Optimization

- Screening serves as the starting point
  - Understanding where you are going influences starting point
- What do you have to optimize in a lead compound?
  - Biological activity / selectivity
  - ADME / Solubility / Crystallinity
  - Safety
- What can you control as a chemist?
  - **Physical properties**

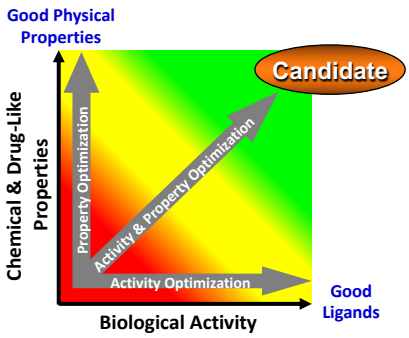
19

19

Drugs Generally Aren't Discovered Directly

ACS Combi. Sci. **2012**, *14* (11), 579 - 589

- Once a **lead compound** is identified
  - Prototype having desired activity but other undesirable characteristics, e.g. toxicity, off target activities, insolubility, metabolism problems, oral bioavailability
- Modify by synthesis
  - Amplify or introduce desired properties & eliminate undesired qualities
- Typical clinical candidate worthy of extensive evaluation:
  - Compromise between activity optimization (and minimization of undesired activities) and physical property optimization



20

20

ADMET and PKPD in Drug Discovery

Nature Biotechnology **2001**, **19**, 722–726

ADMET

- **A**bsorption
  - How much of the drug is absorbed and how quickly? (bioavailability)
- **Di**stribution
  - Where is the drug distributed within the body? What is the rate and extent of the distribution?
- **M**etabolism
  - How fast is the drug metabolized? What is the mechanism of action? What metabolite is formed and is it active or toxic?
- **E**limination
  - How is the drug excreted and how quickly?
- **T**oxicity
  - Does this drug have a toxic effect to body systems or organs?

- Pharmacokinetics-Pharmacodynamics (**PKPD**)
  - PK (pharmacokinetics): what the body does to the drug
  - PD (pharmacodynamics): what the drug does to the body / target

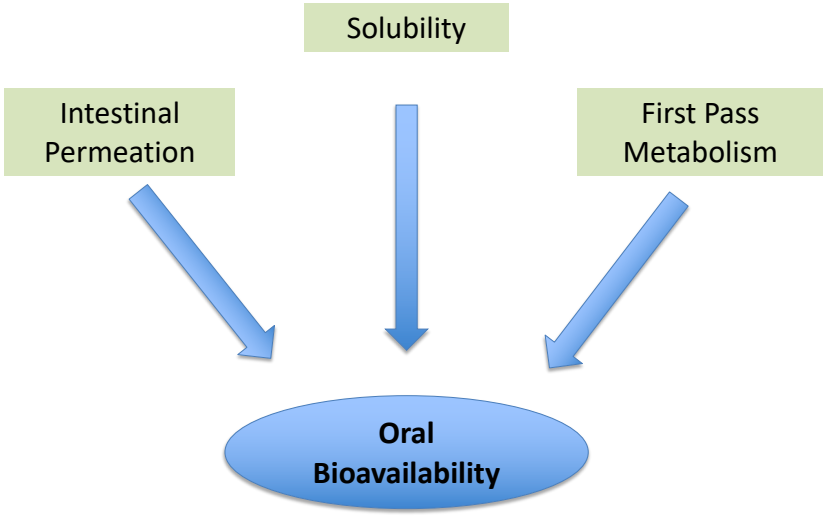
Pharm. Res. **2011**, *28* (7), 1460–1464

- Structural elements that pose safety risks in drugs or in metabolites
  - J Chem Inf Model. 2012 Aug 27; 52(8): 2310–2316

21

21

Designing for Oral Bioavailability



J. Med. Chem. **2019**, *53*, 1098-1108

22

22

Designing for Oral Bioavailability

"All models are wrong, but some are useful" George P. Box

- Property values impact oral bioavailability and drug-likeness
  - Promiscuity as a function of molecular weight and cLogP
  - Lipophilicity and molecular weight are major determinants of safety issues and off target activity
- Lipinski's Rules (Rule of 5): properties that ***decrease*** the likelihood of good oral absorption
  - Molecular weight >500
  - Lipophilicity >5 (calculated LogP)
  - Total hydrogen bond acceptors >10
  - Total hydrogen bond donors >5
- Different rules apply for CNS-, liver- or lung-targeting drugs
- Lipinski's rule of 5 evolved into more sophisticated models

Adv. Drug Deliv. Rev. 2001 Mar 1;46(1-3):3-26
Nature Rev. Drug Disc. **2007**, *6*, 881
J. Med. Chem. **2010**, 53 (3), 1098 - 1108
J. Med. Chem. **2018**, 61, 2636 - 2651

Small Molecule Drug Discovery – Key Considerations

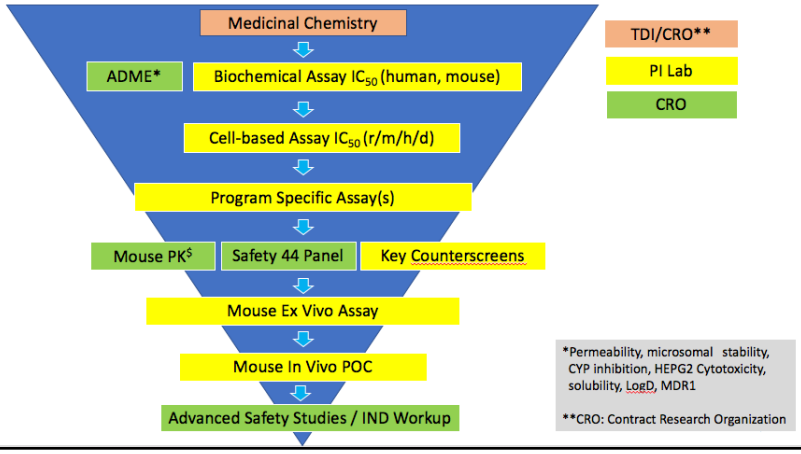
Target Candidate Profile (TCP) Requirements

- Patent Considerations
- Biochemistry / Pharmacology
- In Vitro ADME Characteristics
- Synthesis Considerations
- Structural / Physicochemical Properties
- Formulation
- Absorption Characteristics
- Drug / Drug Interaction Potential
- Pharmacokinetics
- Safety

- TCP articulates, in advance, key criteria that are integral for programmatic success and to facilitate IND-enabling studies
- A TCP is a living document, evolves over time

TCP Used to Create a Research Operating Plan (ROP)

- Screening funnel used to triage primary assays (resource sparing) to secondary and more advanced studies (resource intensive)
- Major failure at any step requires repeating **all studies** with new analogs
- Problematic assays get altered priority

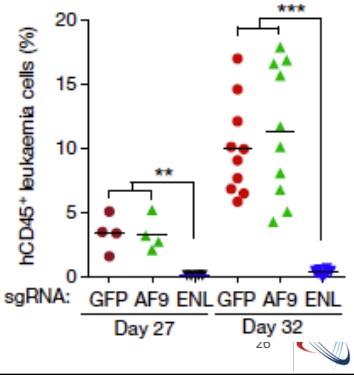


25

ENL links histone acetylation to oncogenic gene expression in acute myeloid leukaemia (Allis, RU, 2017)

Nature **2017** Mar 9, 543(7644), 265-269

- Cancer cells have aberrant epigenetic landscapes & exploit chromatin machinery to activate oncogenic gene expression
- Recognition of modified histones by 'reader' proteins constitutes a key mechanism underlying these processes; therefore, targeting such pathways holds clinical promise
- **YEATS domain identified as an acetyl-lysine-binding module, but its functional importance in human cancer remains unknown**
- The YEATS domain-containing protein ENL, but not its paralogue AF9, is required for disease maintenance in acute myeloid leukemia
- CRISPR–Cas9-mediated depletion of ENL led to anti-leukemic effects, including increased terminal myeloid differentiation and suppression of leukemia growth in vitro and in vivo

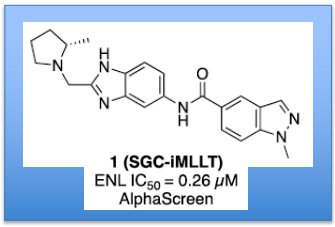


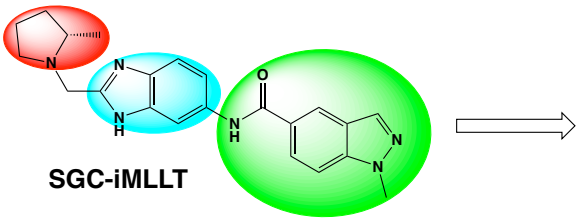
26

Lead Optimization of Small Molecule ENL YEATS Inhibitors to Enable In Vivo Studies: Discovery of TDI-11055 (2024)

ACS Med. Chem. Lett. **2024**, 15, 524–532

- Crystal structures of the ENL YEATS domain known
  - Virtual screen performed with Schrodinger – no progressible leads identified
- Multiple probes of ENL YEATS existed
  - SGC-iMLLT, derived from HTS
- Does SGC-iMLLT have flaws?
  - Modest potency (including cellular), poor permeability, poor PK profile
- Leverage structural data → superior analogs
  - Strategy: 3 regions readily modified





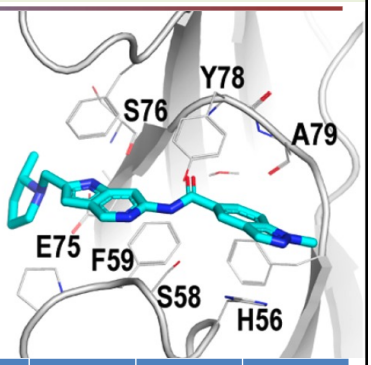
27

27

Lead Optimization of Small Molecule ENL YEATS Inhibitors to Enable In Vivo Studies: Discovery of TDI-11055 (2024)

ACS Med. Chem. Lett. **2024**, 15, 524–532

- **Red Region:** 5-membered rings optimal (azetidine **#15**, no
- **Green Region**
  - Transposed amide inactive (Cpd **#7**)
  - Alternative aryl groups tolerated
- **Blue Region**
  - Benzimidazole core substitutions tolerated
  - Nitrogen position impacts activity, permeability, "drug-likeness"
  - **Further optimization yielded TDI-11055**



ID	X_3	X_5	IC_{50} (uM)	FEP+ IC_{50} (uM)	MDR1 Ratio	MDR1 A → B	PAMPA pH 7.4
SGC	N	CH	0.12	0.12	15	13	91
15	N	CH	0.28	--	--	--	--
7	N	CH	54	17.1	150	2	106
9	CH	CH	0.39	0.11	1.8	84	185
TDI-11055	CH	N	0.05	0.01	1.4	71	261

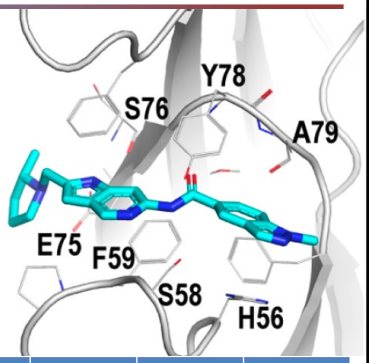
28

Lead Optimization of Small Molecule ENL YEATS Inhibitors to Enable In Vivo Studies: Discovery of TDI-11055 (2024)

ACS Med. Chem. Lett. **2024**, 15, 524–532

- **Red Region:** 5-membered rings optimal (azetidine **#15**, no
- **Green Region**
  - Transp[illegible]d amide inact[illegible] (Cpd **#7**)
  - Alternati[illegible]roups[illegible]d
- **Blue Region**
  - Be[illegible]
  - Nitroge[illegible]ug-likeness"
  - **Further op[illegible]**

2020 Rockefeller licensed program to Bridge Medicines!!



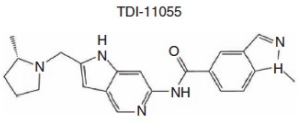
			(uM)	FEP+ IC_{50} (uM)	MDR1 Ratio	MDR1 A → B	PAMPA pH 7.4
[illegible]	[illegible]	[illegible]	0.12	0.12	15	13	91
[illegible]	**15**	[illegible]	0.28	--	--	--	--

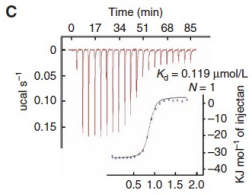
29

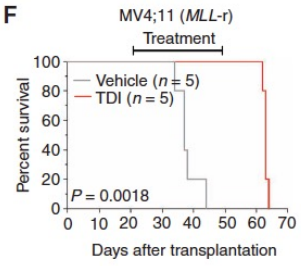
Small-Molecule Inhibition of ENL Is a Therapeutic Strategy against AML (2022)

Cancer Discov. **2022** Nov 2;12(11):2684-2709

- TDI-11055, a potent and orally bioavailable small-molecule inhibitor of ENL, displaces ENL from chromatin by blocking its YEATS domain interaction with acylated histones
- Cell lines and primary patient samples carrying MLL rearrangements or NPM1 mutations are responsive to TDI-11055
- CRISPR-Cas9–mediated mutagenesis screen uncovered an ENL mutation that confers resistance to TDI-11055, validating the compound's on-target activity
- TDI-11055 treatment rapidly decreases chromatin occupancy of ENL-associated complexes and impairs transcription elongation, leading to suppression of key oncogenic gene expression programs and induction of differentiation
- In vivo treatment with TDI-11055 blocks disease progression in cell line– and patient–derived xenograft models of MLL-rearranged and NPM1-mutated AML
- ENL displacement from chromatin: promising epigenetic therapy for molecularly defined AML subsets and supports the clinical translation of this approach







30

Galecto Acquires Acute Myeloid Leukemia Preclinical Asset from Bridge Medicines (2024)

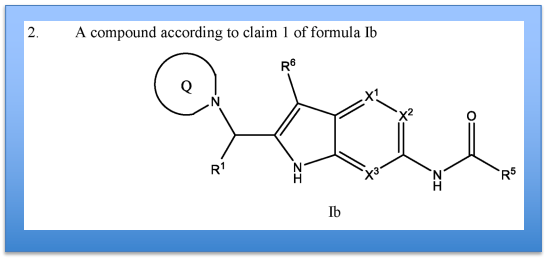
- Galecto, Inc. (NASDAQ: GLTO) acquired global rights to BRM-1420
- BRM-1420 is a potent and selective ENL-YEATS and FLT3 inhibitor of multiple genetic subsets of AML
  - In animal models, BRM-1420 exhibited superior efficacy to both FLT3 and menin inhibitors and was shown to inhibit cell proliferation in primary AML patient samples across multiple genotypes
  - These mutations are often seen in AML and, in total, could account for greater than 30% of the AML patient population
- Many of these mutations difficult to treat, represents a significant unmet medical need
  - BRM-1420 could be additive or synergistic when used in combination with the current standard of care (azacitidine, venetoclax, cytarabine, gilteritinib), as well as current therapies under development, such as menin inhibitors
- **Galecto plans to file an IND for BRM-1420 in the US in late 2025 or early 2026 and initiate clinical studies in patients with AML thereafter**

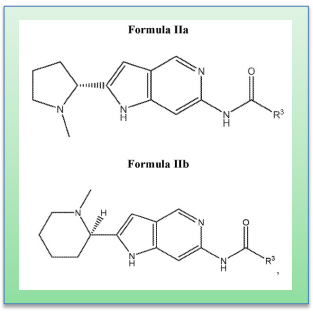
31

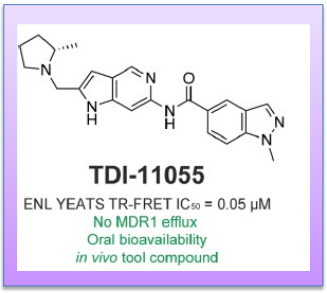
31

Rockefeller & Bridge Medicines ENL YEATS Patents

- Two published patents
  - WO2021127166A1 – Inhibitors of ENL YEATS (The Rockefeller University with TDI co-inventors)
    - Claim 2
  - WO2022240830A1 – C-Linked Inhibitors of ENL / AF9 YEATS (Bridge Medicines with TDI co-inventors)
    - Formula IIa & Formula IIb







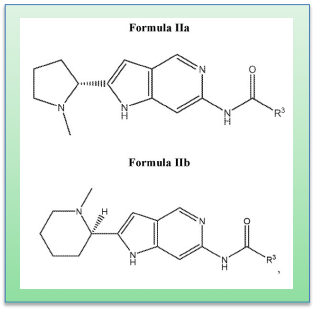
- Are these compounds different than those in Wan's paper?

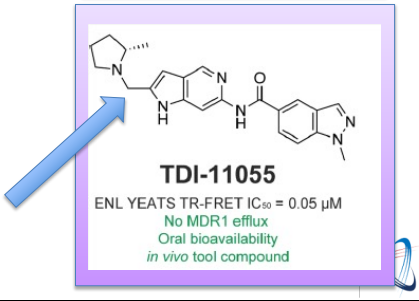
32

32

Bridge Medicines ENL YEATS Patent

- Some ways to determine 'best' compounds
  - Specific compound claims (Formula IIa, IIb)
  - Number of analogs in a series
    - Pyrrolidines: 74 cpds (pg 162 – 212 & 221 – 224)
    - Piperidines: 25 cpds (pg 221 – 234)
  - Bioactivity
    - Biochemical: 57 cpds <100nM (pg 257)
    - Cellular: 14 cpds <100nM (pg 260)
  - Scale of synthesis or in vivo data
- Could there be a selection patent from either patent?
  - Yes!
- Does the Bridge Medicines patent address a med chem issue?
  - Yes!





33

Potential Next Steps for Galecto on the Path to Registration

Needed for BRM-1420 (if not performed by Bridge Medicines):	
Non-Clinical Studies (1.5 yrs)	Preliminary non-GLP safety studies (rat, dog) Pilot process research for efficient scaleup (includes salt selection, form selection, stability studies)
Safety Assessment (1.5 yrs)	GMP drug manufacture GLP safety studies (rat, dog) GLP reproductive toxicity studies (if required by FDA)
Regulatory	Regulatory engagement with the FDA
Clinical Studies (>5 yrs)	Phase 1 (12 – 80 normal volunteers or patients) Safety, absorption & metabolism, biomarker measurements, preliminary dose selection
	Phase 2 (100 – 300 patients) 2a: Proof of concept 2b: Dose ranging Goals: Effectiveness in treating disease & short-term side effects in patients
	Phase 3 (1,000 – 30,000) Safety & efficacy in patients Less common & longer term side effects Labeling information
Registration	New drug application (NDA), worldwide marketing application (WMA)

34

Thank you!

Questions?