From Target to Translational Funding: *The journey from academic discovery to an investable therapeutic*

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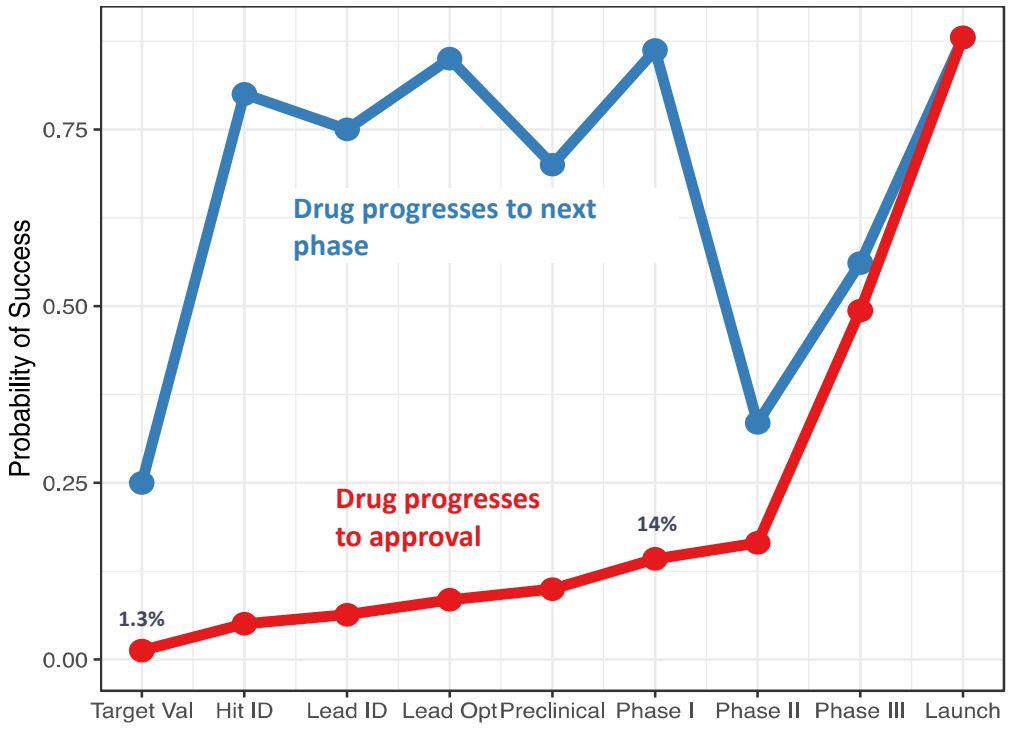
Presentation overview

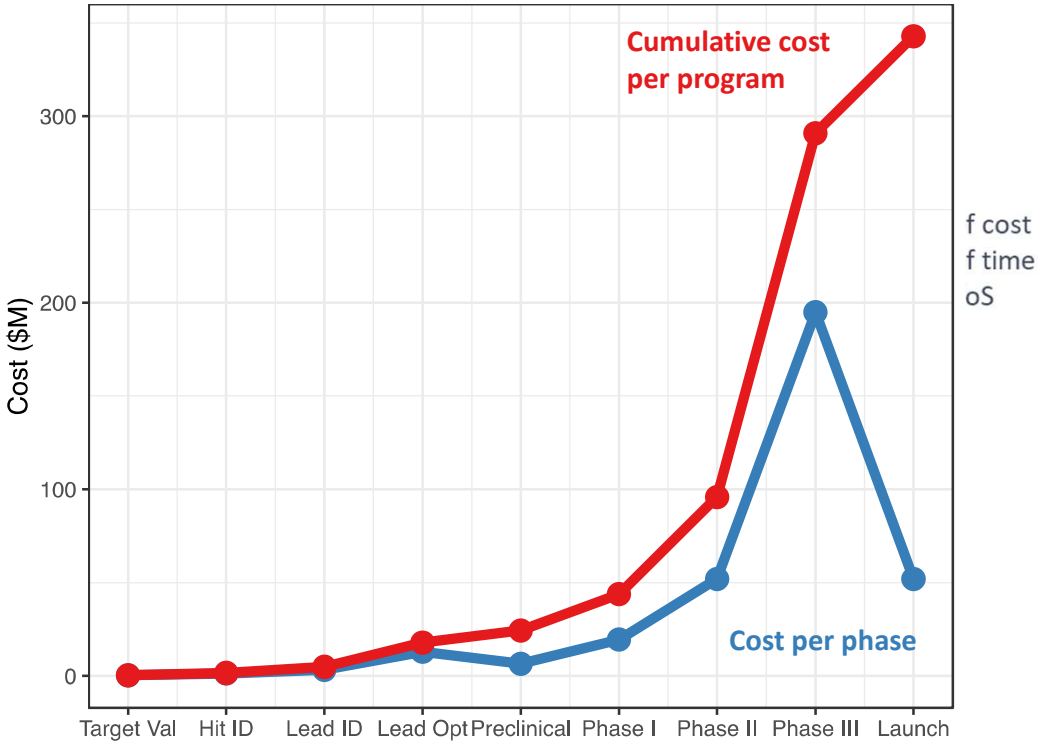
- *Begin with the end goal in mind!*
- *Drug development cost, failure, and risk*
- *Targets & Target Validation*
- *Unmet need & the medicine proposition*
- *Commercial considerations*
- *Translational funding landscape*

The Target Product Profile (TPP): A living document

Product Targets	Preferred	Minimum
Therapeutic Modality		
Primary Product Indication		
Patient Population		
Mechanism of Action (MOA)		
Treatment Duration		
Route of Administration		
Dosage Form		
Dose Regimen		
Efficacy		
Safety Profile		
Product Stability and Storage		

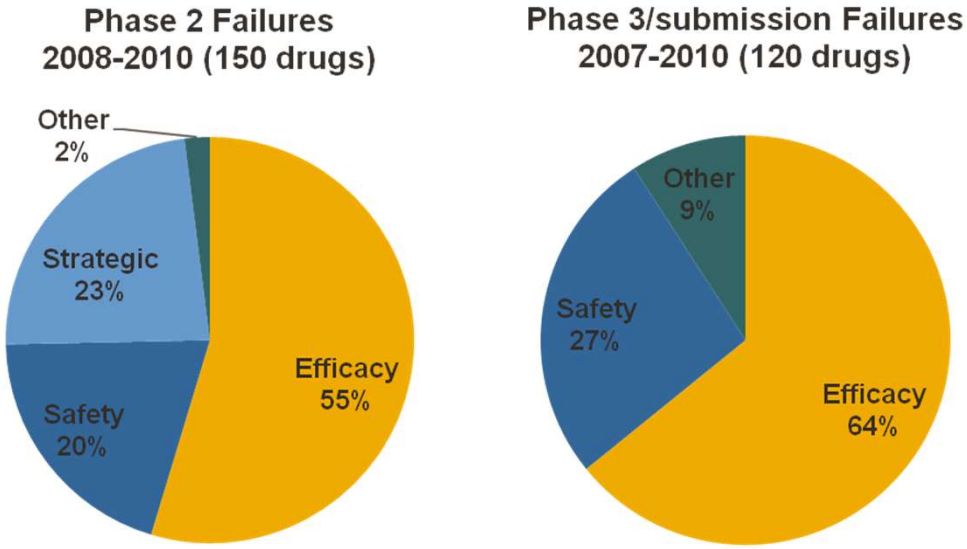
Drug discovery & development is risky and expensive (mAb example)





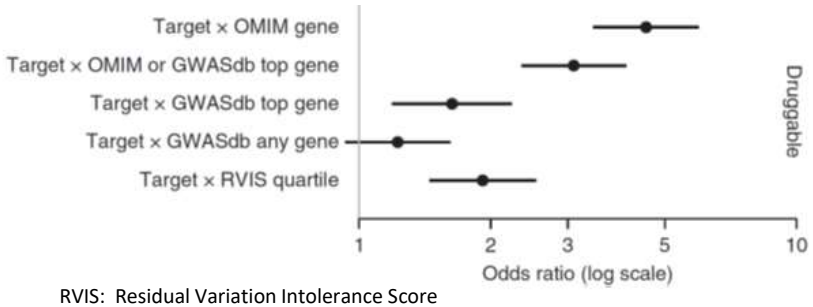
Clinical probabilities & costs for novel non-oncology mAb programs
Paul et al. (2010) Nat Rev Genet 9:203-14
Custom clinical probabilities of success

Why do drugs fail? How to mitigate this risk?



Hay et al. (2014) Nat. Biotech. 32:40-51
Arrowsmith & Miller (2013) Nat. Rev. Drug. Disc. 12:569

Targets for successful drugs are significantly enriched for genetic evidence



RVIS: Residual Variation Intolerance Score

	p(progress|genetic support)/(progress|no genetic support)		
Progression	GWASdb and OMIM	GWASdb	OMIM
Phase I to phase II	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Phase II to phase III	1.5 (1.3–1.7)	1.4 (1.2–1.7)	1.6 (1.3–1.9)
Phase III to approval	1.1 (1.0–1.2)	1.0 (0.8–1.2)	1.1 (0.9–1.3)
Phase I to phase III	1.8 (1.5–2.1)	1.8 (1.4–2.1)	1.9 (1.5–2.3)
Phase I to approval	2.0 (1.6–2.4)	1.8 (1.3–2.3)	2.2 (1.6–2.8)

Nelson et al. (2015) Nat Genet 47:856-60
Plenge et al, (2013) Nat Rev Drug Disc: 12: 581-594

Support of genetic evidence for the most prescribed and top grossing drugs

9 of 17 (53%) targets for the 20 most prescribed drugs in the US have supporting genetic evidence

	Drug	Primary Indication	US Rx (Millions)	Target(s)
✓	Atorvastatin/Simvastatin	Hyperlipidemia	162	HMGCR
✓	Levothyroxine	Hypothyroidism	114	THRA; THRB
✓	Lisinopril	Hypertension	111	ACE
✓	Metoprolol/Atenolol	Hypertension	101	ADRB1
	Metformin Hydrochloride	Type 2 Diabetes	81	GPDH; AMPK
	Amlodipine Besylate	Hypertension	75	CACNA1C
	Omeprazole	Gastric Reflux	71	ATP4A
✓	Losartan Potassium	Hypertension	49	AGTR1
✓	Albuterol	Asthma, COPD	47	ADRB2
	Gabapentin	Epilepsy	44	CACNA2D1
	Hydrochlorothiazide	Hypertension	43	SLC12A3
✓	Acetaminophen; Hydrocodone	Pain	43	PTGS1/2; OPRM1/D1/K1
	Sertraline Hydrochloride	Depression	37	SLC6A4
✓	Furosemide	Hypertension	33	SLC12A1;SLC12A2
✓	Fluticasone	Asthma, Allergy	30	NR3C1
	Acetaminophen	Pain	29	PTGS1;PTGS2
	~~Amoxicillin~~	~~Bacterial Infection~~	28	–
	Alprazolam	Anxiety	27	GABRA1/2/3/5

From ClinCalc.com DrugStats Database, accessed on 10/04/2019

Support of genetic evidence for the top grossing drugs

	Drug	Primary Indication	US Sales ($ Billions)	Target(s)
✓	Humira/Enbrel/Remicade	Autoimmune	22.2	TNF
✓	Victoza/Trulicity	Type 2 Diabetes	5.2	GLP1R
✓	Eylea	Macular Degeneration	4.1	VEGFA;PGF
✓	Neulasta	Neutropenia	3.9	CSF3R
✓	Eliquis	Stroke, DVT	3.8	F10
	Lyrica	Epilepsy, Pain	3.6	CACNA2D1
✓	Stelara	Autoimmune	3.5	IL12B;IL23A

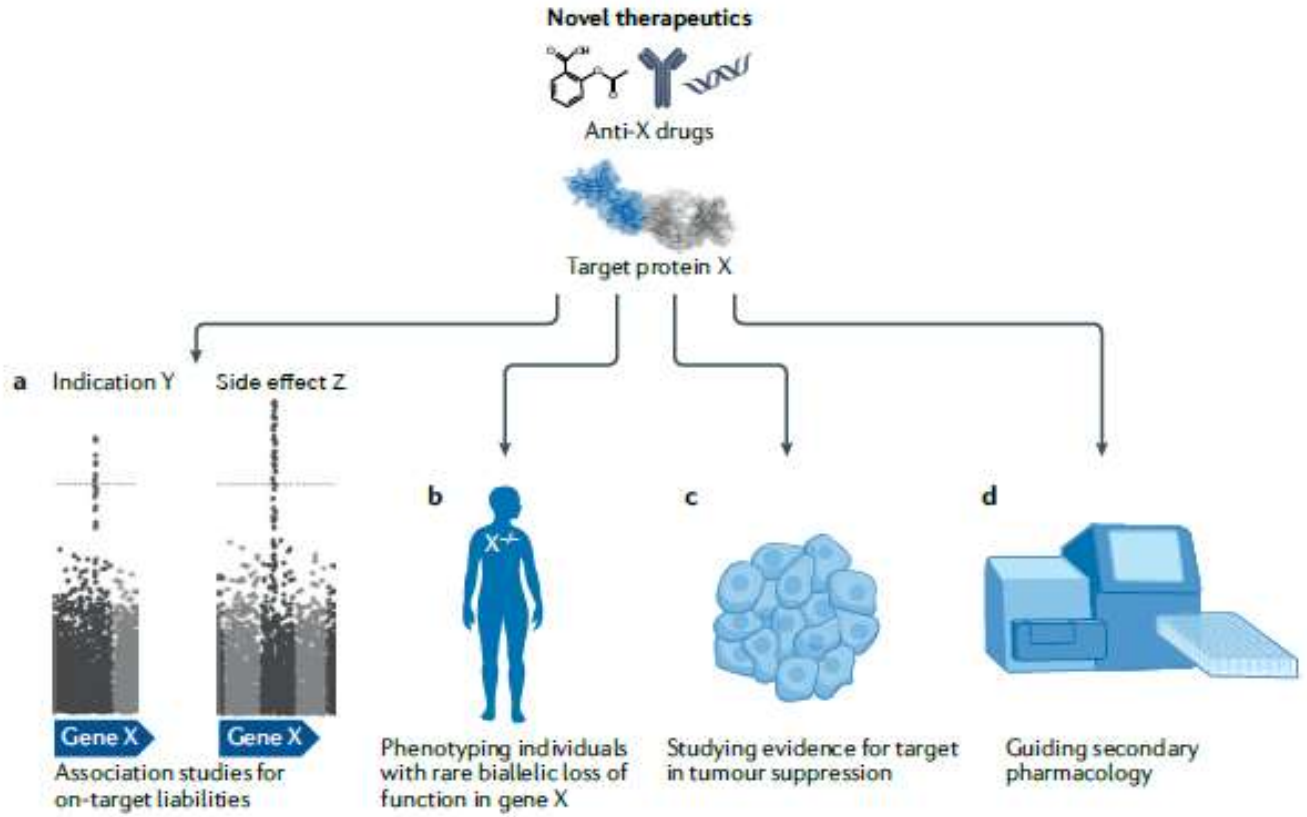
8 of top 20 are for oncology indications ($32B; not shown)

2 of top 20 are for HIV ($6.2B; not shown)

Remaining 10 represent 7 unique mechanisms

6 of 7 (86%) are supported by human genetic evidence

Human genetics data & assessment of target safety



Carss et al. (2023) Nat Rev Drug Discovery, 22: 145-162

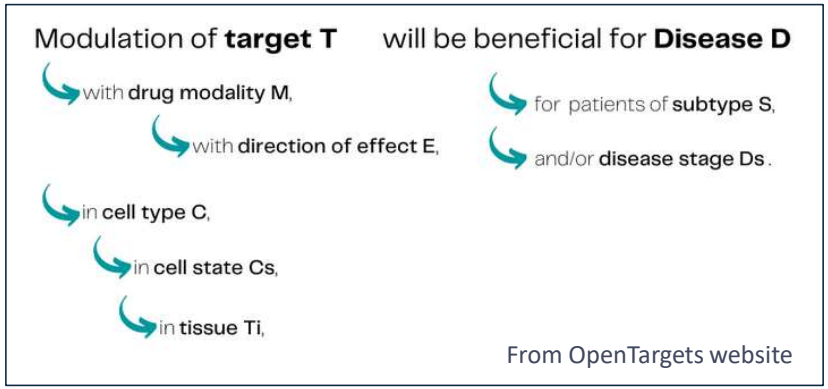
Target validation is critical

Does a potential drug target have a key role in a disease process?

Will modulation of the target be effective in a defined patient population?

Establishing target-disease linkage:

- Human genetic data → Functional consequences?
- Existing human POC or other human translational data
- Target signaling pathways and implication in disease
- Direct interacting partners of target that are genetically or clinically implicated in disease
- Genetic and/or pharmacological target manipulation in in vitro and in vivo systems → ideally humanized or using patient-derived samples
- Potential compensatory pathways or modes of action that could affect treatment
- Resistance mechanisms



Tool compounds & target validation: Quality matters!

Pharmacological manipulation of the target to assess:

- Linkage to disease biology
- Is there a target or chemotype-related safety issue

It is paramount that the tool compound be of sufficient quality to assess the above points

- Binding
  - IC_{50} < 100 nM
  - Molecular pharmacology is understood
- Selectivity over related targets
  - Minimally >10x, preferably >100x
- Solubility
  - >0.05 ug/mL in low % DMSO solutions
  - Soluble at relevant concentrations used in assays
- Cell penetrance for intracellular targets
  - Permeable
  - Minimal transporter efflux (Pgp)
- LogP: high LogP leads to promiscuity & increased risk of toxicity
- Is not chemically reactive, unless the intended MoA – needs to be selective and well characterized
- A structurally-related inactive analog can be a great negative control

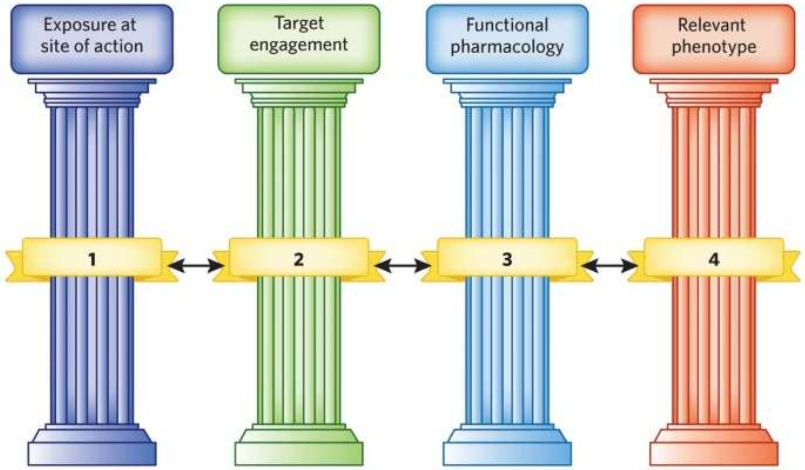
Pillars of pharmacological tool validation

1. Exposure at site of action
   - Biochemical and whole-cell activities correlation
   - Confirm pharmacologically-relevant intracellular concentrations inside cells (LCMS as an example)

2. Target engagement
   - Functional probes or endpoints to measure intracellular occupancy (small molecule: enzyme product or substrate levels)
   - Proteomics methods (small molecule: CETSA)
   - Can be challenging

3. Functional pharmacology
   - Measurement of <u>proximal</u> biomarker (phosphorylated kinase, methylated histone, levels of secreted protein)

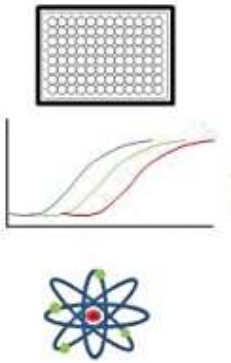
4. Desired phenotypic perturbation
   - Disease-relevant changes in naïve tissues and cell systems (bronchorelaxation of airway tissue)
   - Ideal to have high degree of confidence in clinical translatability



Modified from Jones, et al, Nature Chemical Biology, 2013, 9, 195-199

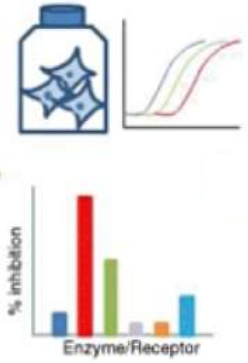
Building the preclinical assays

Compound Screening



- Robustness of assays for screening & SAR, ideally with +/- controls
- Reliability, signal-to-noise, background
- See: NIH Assay Guidance Manual
- Virtual screening is a viable option for structurally-enabled targets

Secondary Assays



- Quality of chemical matter
- 2^{o} and orthogonal assays to validate target engagement is specific (PAINS, aggregators, insoluble compounds, fluorescence interferers)
- Selectivity assays
- Cell-based assays with disease-relevant readouts
- Biomarkers of target engagement
- Physicochemical & ADME/DMPK assays

In vivo analysis

- PK studies to support design of efficacy studies and understand plasma and tissue exposures
- Development of biomarkers of target engagement
- Development of translational disease biomarkers
- Efficacy in translationally-relevant animal models
- Development of PK/PD relationship

Preclinical tractability

What is the **best modality** for a therapeutic (small molecule, antibody or other)?

Small Molecule	Biologic
• Chemically synthesized	• From living cells
• Low molecular weight ➢ Extensive distribution	• High molecular weight ➢ Limited distribution
• Metabolism important ➢ Active or toxic metabolites	• Metabolism not a concern ➢ Peptides, amino acids, inactive
• Immunogenicity not typically a concern	• Immunogenicity can be a concern
• Less targeted ➢ Off target toxicity possible from parent drug or metabolites	• Highly targeted ➢ Effects related to desired target; toxicity typically due to exaggerated pharmacology
• Generally active in many species	• Activity limited to relevant species ➢ Typically non-human primates

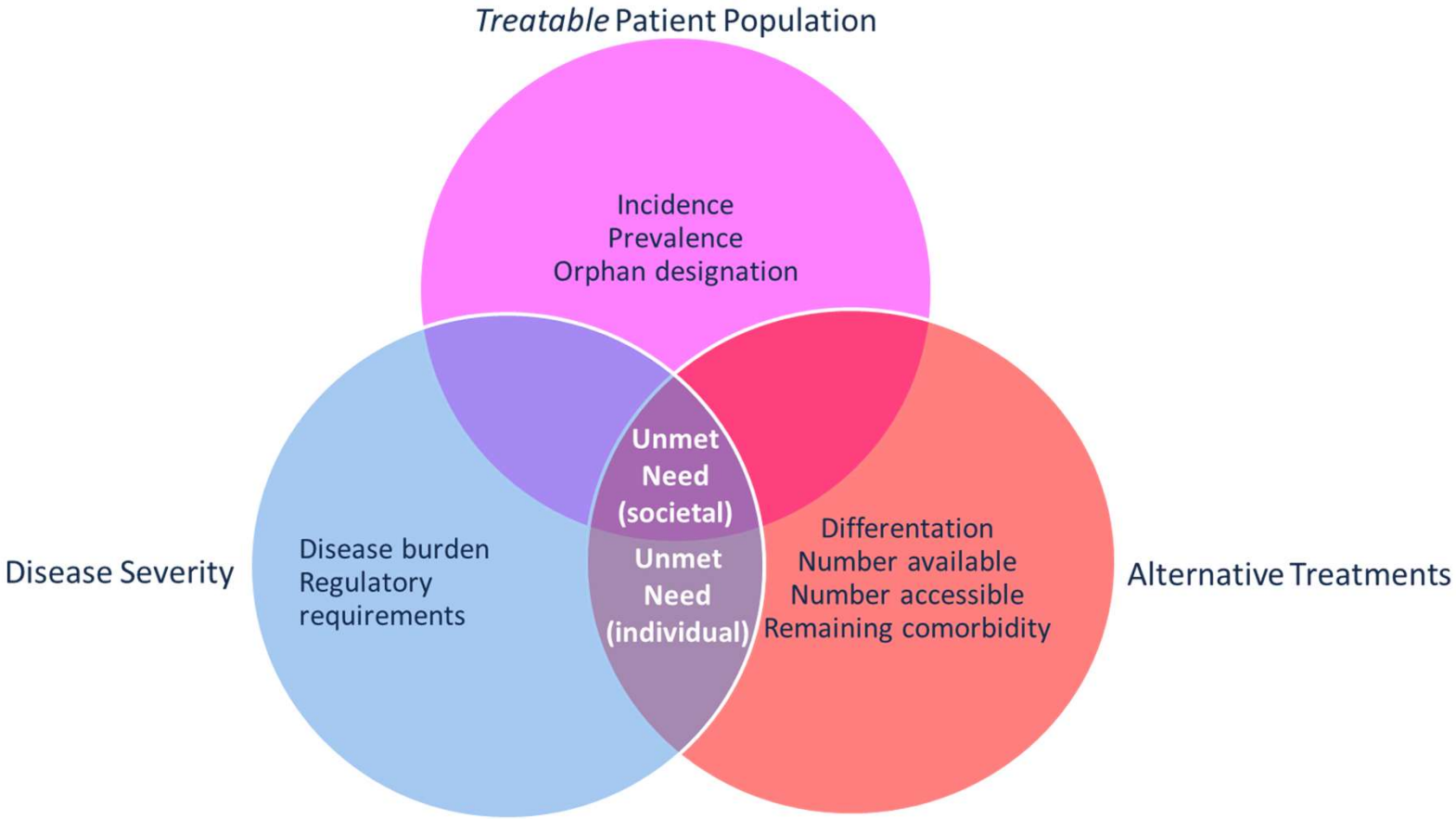
2x higher PoS to Phase 2 with an antibody versus a small molecule
>50% of FDA-approved drugs in 2023 were small molecules

Clinical tractability

- Is the proposed indication the best for the proposed molecular approach? Are there expansion indications?
- What is the size of the *treatable* patient population?
- Are there patient selection biomarkers to identify patients who will respond to treatment?
- Are there robust biomarkers to confirm adequate drug exposure to engage the target and induce the desired pharmacology?
- What are the clinical endpoints that will be required to gain FDA approval for the lead indication? How many patients will be needed to enroll? What is the estimated cost and timeline for Phase I and II studies?
- Does the unmet need for the proposed indication justify the risks associated with the approach?

Phase I	Phase II
• 20-50 healthy volunteers • Exposure • Dose finding • PK/PD • Safety	• Proof of Concept • 100-300 patients • Efficacy • Safety

Unmet need & the medicine proposition



Commercial Considerations

- Path to Intellectual Property
- Competitive landscape analysis (target and indication) to include marketed and pre-market pipeline
- Differentiation versus SoC & target-focused assets in clinical development
- Current market feedback from “friendly” VC community
- Value/de-risking profile

Target Product Profile for Addiction (Example)

Product Targets	Minimum	Preferred
Therapeutic Modality	Small molecule drug	Small molecule drug
Primary Product Indication	Prevention of relapse from opioid addiction	Prevention of relapse from all substances of abuse, including opioids, cocaine, ETOH, nicotine, etc.
Patient Population	Adults with opioid use disorder in or after rehab/detox	Adolescent and Adult patient populations with substance use disorders in or after rehab/detox
Treatment Duration	Chronic (1 month- 2 years)	Chronic (1 month- 2 years)
Route of Administration	patch, injection	Oral + patch + injection
Dosage Form	Combination with SOC	Monotherapy + Combination with SOC
Dose Regimen	Daily or weekly or monthly, chronic	1-2 times per day acute, weekly, monthly chronic
Efficacy	Better than SOC when given alone or in combination with FDA approved maintenance/detox therapies for opioid abuse including Suboxone (buprenorphine and naloxone), Vivitrol (naltrexone), naloxone	Better than SOC decrease in relapse behaviors
Safety Profile	No significant adverse effects given alone or in combination with FDA approved maintenance/detox therapies for opioid abuse including Suboxone (buprenorphine and naloxone), Vivitrol (naltrexone), naloxone	No significant adverse effects given alone or in combination with FDA approved SOCs
Product Stability and Storage	Stable in long term pharmacy storage	Stable in long term pharmacy storage

The Target Development Candidate Profile (TCP)

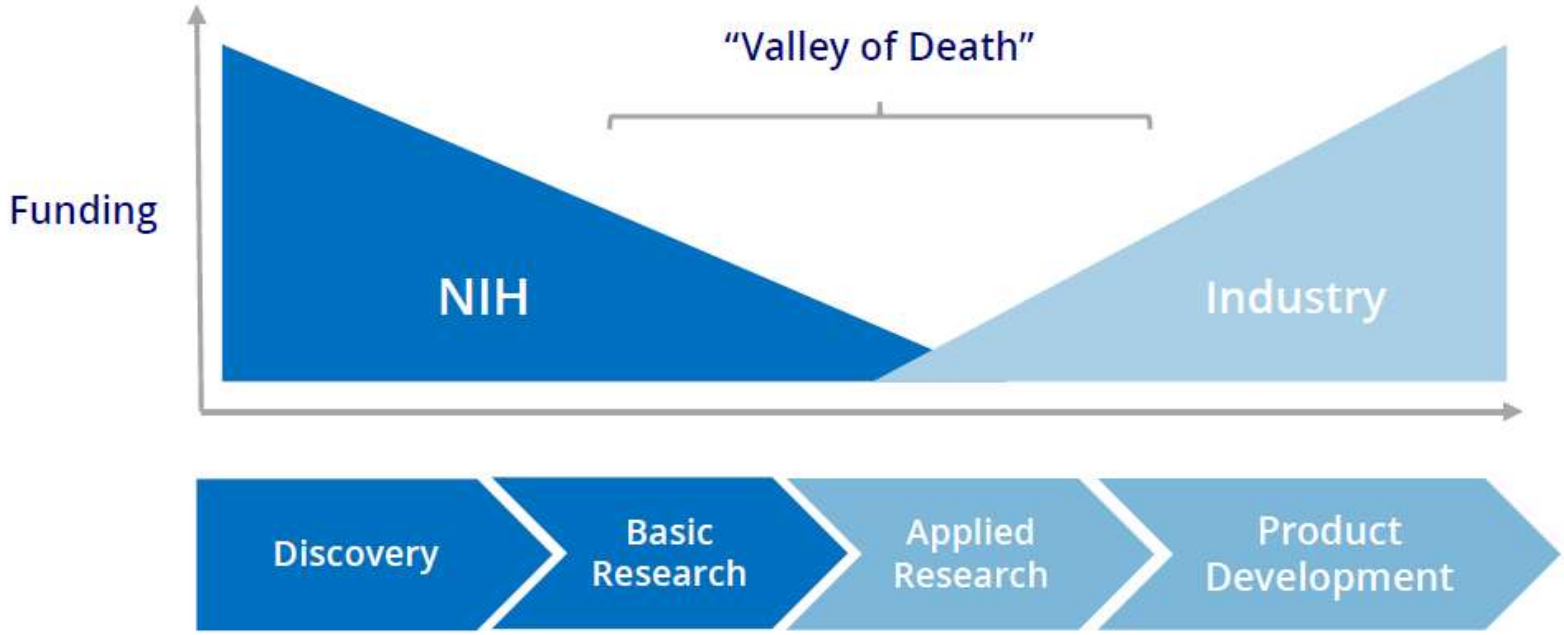
Small molecule example

	PARAMETER	VALUE	OPTIMAL
In-Vitro Activity	Biochemical EC_{50}		≤ 10 nM
	Cell Assay IC_{50}		≤ 100 nM
In Vivo Activity	Single Agent Efficacy		≤50 mg/kg/day
CYP Profiling	CYP Inhibition IC_{50}		> 10 µM
	TDI IC_{50}		No IC_{50} shift
	CYP Induction		None
Selectivity	hERG IC_{20} (µM)		> 50 µM
	Selectivity (as appropriate)		> 100-fold
	Receptor profiling		< 50% inhibition at 10 µM
	Ames Test		Not mutagenic
ADME	Solubility PBS pH 7		> 30 µM
	PPB (% free fraction)		Measurable and similar across species
	Hepatocytes *in vitro* % remaining @ 2h		> 50%
	Metabolite profiling		Tox species needs to produce metabolites produced in humans
	Transporter Studies (P-gP, BCRP, Substrate & Inhibition)		>10 µM IC_{50}
PK Single Dose	Mouse (AUC, CL, $t_{1/2}$, V_d, F%)		Orally bioavailable Appropriate for QD dosing Dose proportional up to 1 g/Kg Similar across species
	Rat (AUC, CL, $t_{1/2}$, V_d, F%)		
	Monkey or Dog (AUC, CL, $t_{1/2}$, V_d, F%)		
Tolerability Studies	Two species 10-14 day, 3 dose levels non-GLP		Tolerated with > 10x T.I.
Clinical Studies	Human Dose: projection based on preclinical ADME/PK/Efficacy		< 1000 mg daily
	Target Engagement biomarker assay developed for use in clinic		

mAb example

Parameter	Criteria
Binding and Selectivity	• Binding to target: K_D < 0.2 nM • Crossreactivity to cynomolgus and mouse targets: within 3-fold of human • No binding to isoform 2 of target at 1 µM
In vitro Potency	• Inhibition of ligand binding: IC_{90} < 0.5 nM • Reduction in cytokine secretion: IC_{50} < 0.5 nM
In vivo Efficacy	• Disease-relevant mouse model: > 50% reduction in tissue damage
Preclinical Safety	• No toxicity at doses up to 50 mg/kg in cynomolgus monkeys
Pharmacokinetics	• Cynomolgus PK profile that supports 1x monthly s.c. dosing
Manufacturability	• Favorable CMC (Chemistry, Manufacturing and Control) profile for large-scale production and high-concentration liquid formulation

Translational funding, How do I get there?



Examples of Translational Funding vehicles for Therapeutics (Retained IP rights)

Funding Agency	Therapeutic Modality	Indication	Funding Amount and time period	Entry criteria	Funding intervals
NHLBI (Catalyze)	Product: Drugs, devices, diagnostics, biologics, and enabling technologies	Heart, Lung, Blood and Sleep	R61: ≤ $350,000 direct costs per year –R33: ≤ $350,000 direct costs per year	R61 (product definition phase): Early stage ok, but preliminary data needed -R33 minimum of a 0.25:1 non-Federal cash match	Feb, July, and Nov each year (different for AIDS)
Deerfield	SM, ATB, Gene Therapy	Agnostic	Full development, Stage gated	Academic consortium member	Monthly submissions
C-Path TRxA	SM, ATB, ADC, Peptides proteins	Agnostic	$250K-1M	Early lead or later	January-Open call October-Award initiation
NATA	Nucleic Acid Therapies	Agnostic	TBD- Joint project with academic partners	POC in animal model	N/A
CARB-X	Antibiotics, vaccines, rapid diagnostics	Agnostic-Drug resistant bacteria	TBD	Hit-to-lead is minimum criteria	N/A
NCBC TRG	Agnostic	Agnostic	Up to $144K to include PM	Clear commercial de-risking AIMs. Academic only. Non-optioned or licensed IP.	Cycle 1- August Cycle2- January

* NCATS, Harrington Discovery, SBIR/STTR, etc.

Hallmark criteria for Translational Granting mechanisms

- Hits at a minimum
- Additional characterization a plus
- End-product visualization (Therapeutic Hypothesis)
- High level competitive landscape and differentiation thesis
- Unencumbered IP
- development plan framework
- Most funding agencies provide ongoing development and business related guidance

End