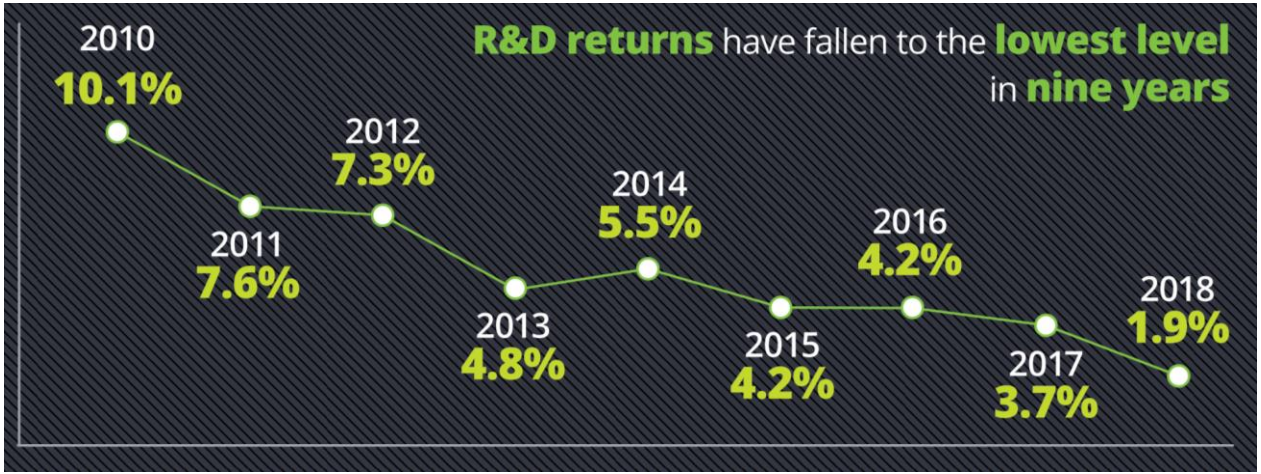
Creating a data package for biopharm/biotech

November 19, 2021

Carolyn Buser
VP of Novel Human Genetics Research Unit

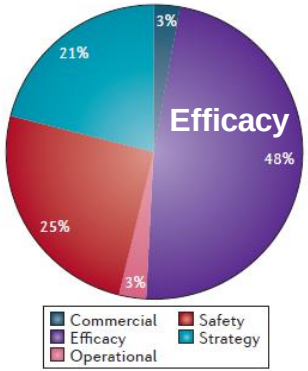
Challenges to pharmaceutical R&D



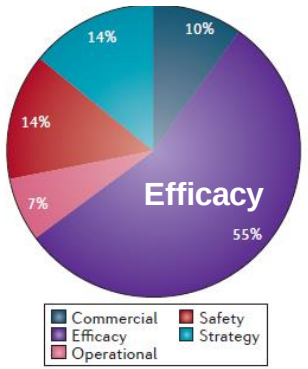
Deloitte 2018

- Realities
  - Cost of developing new molecular entities to approved therapies range from $3b to $10b across major pharmaceutical companies
  - Only ~8% of candidate NMEs (across all indications) in Ph 1 are eventually approved
  - Cost of failure contributes to cost of success
  - Most drugs fail Ph 2 and 3 clinical trials due to lack of efficacy

Ph 2 Failure



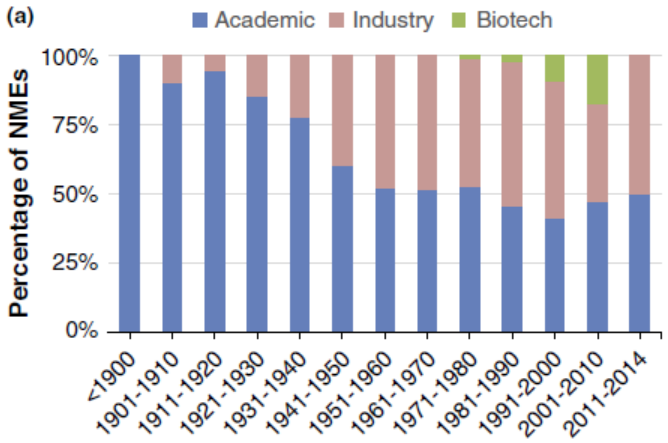
Ph 3 Failure



King *et al.* (2019) bioRxiv; http://dx.doi.org/10.1101/513945 (and references therein)
Harrison (2016) *Nature Rev. Drug Discovery 15*, 817-818

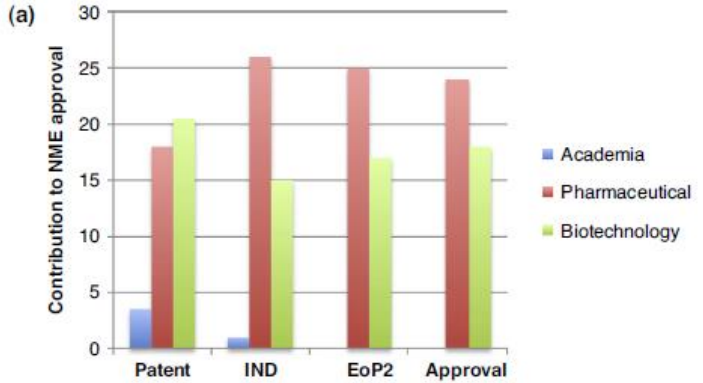
Challenges to academic drug development

Academia contributes significantly to target discovery but not medicine launches



The origin of the 1453 US FDA-approved NMEs for each sector, charted by the year of each first publication.

Patridge et al. (2015) *Drug Discovery Today*



Of the 42 FDA-approved new molecular entities in 2014, academia was involved in a single IND filing and not in any NDA filings (Kinch, 2015).

Kinch (2015) *Drug Discovery Today*

Academic research combined with Pharma execution for Covid-19 solutions

VIR – GSK Collaboration

- Lead mAb, Sotrovimab (VIR-7831) progressed from preclinical to Ph 3 start in just 6 mo and has achieved EUA.
- Academic collaborations were key to the preclinical characterization of Sotrovimab, resulting in several publications in *Science* and *Nature*.
- VIR-7832 (a modified version of VIR-7831) is engineered to optimize Fcγ receptor interactions to enhance immune mediated killing of SARS-CoV2, a concept created in collaboration with Rockefeller University.
- VIR-GSK are collaborating with the academic AGILE platform to evaluate VIR-7832 in a Ph 1b/2a trial.

GSK and Vir Biotechnology announce sotrovimab (VIR-7831) receives Emergency Use Authorization from the US FDA for treatment of mild-to-moderate COVID-19 in high-risk adults and paediatric patients | GSK

Oxford – Astrazeneca vaccine

- Developed in a collaboration between Oxford University's Jenner Institute and Vaccitech (private company spun out from Oxford) with financing from Oxford Sciences Innovation, Google Ventures, Sequoia Capital, and others.
- February 2020, Jenner Institute collaborated with Advent Srl to produce a batch of 1000 doses for clinical trials.
- UK government encouraged collaboration between Oxford and AstraZeneca with 1 billion doses secured in May 2020.
- Funding - at least 97% public, mostly UK government, British and US scientific institutes, and EU Commission and charities.

UK approves Oxford/AstraZeneca vaccine | Financial Times (ft.com)

Molnupiravir – Merck treatment

- Originally developed for treatment of influenza at Emory University as part of the Drug Innovation Ventures at Emory (DRIVE).
- EIDD-2801 identified in an anti-viral screen for equine encephalitis virus and later shown to be active against other RNA viruses, including influenza, Ebola, Chikungunya, and various coronaviruses.
- Acquired by Miami-based Ridgeback Biotherapeutics, who later partnered with Merck & Co. to develop the drug further.

Merck seeks FDA emergency use authorization for antiviral Covid-19 treatment molnupiravir | Coronavirus News | WPSD Local 6

Oxford–AstraZeneca COVID-19 vaccine – Wikipedia

Molnupiravir - Wikipedia

Academia + Pharma/Biotech

1 + 1 = 3

Address challenges with internal and external innovation

FIMBRION THERAPEUTICS
VIR
JHU-GSK (MrgX2)
ICAGEN
sosei HEPTARES
ALECTOR

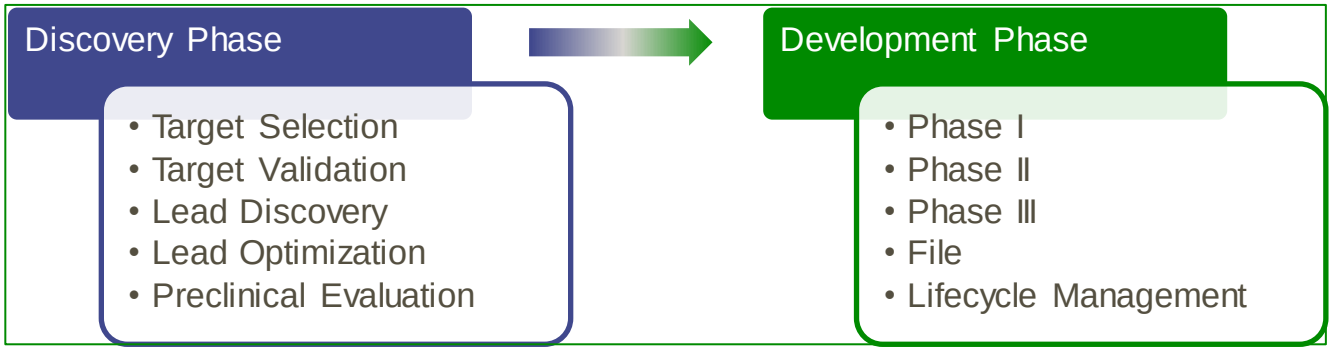
New assets
Genetic databases
Translational Data
Functional genomics
AI/ML

FINNGEN
biobank uk
Genes & Health
23andMe
BROAD INSTITUTE
Laboratory for Genomics Research
ADRESTIA THERAPEUTICS
Open Targets
ALTIVS
CERTARA
IBD PLEXUS

Many types of collaborations are of high interest to Pharmaceutical R&D!

From Target to Medicine

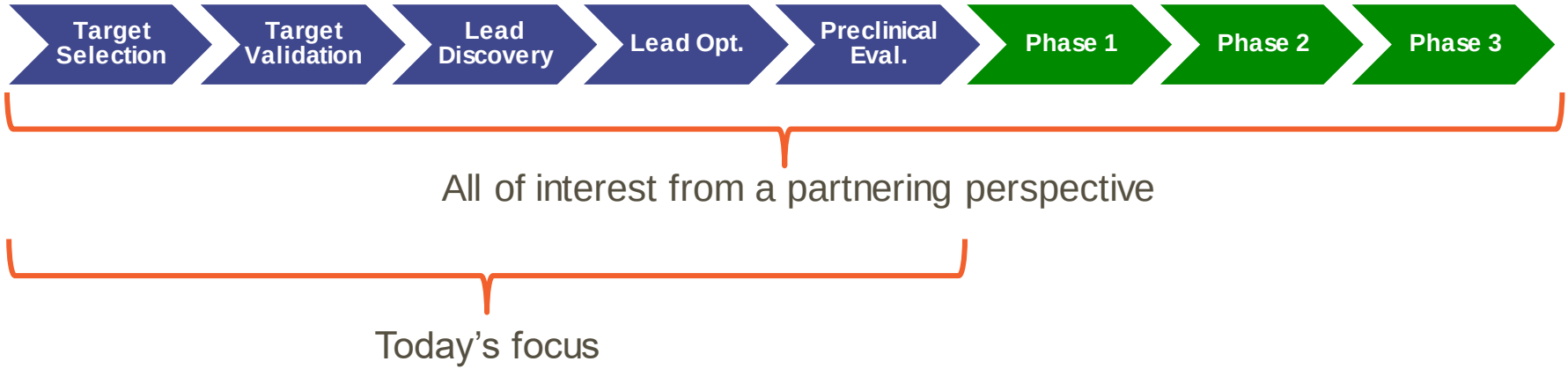
The ultimate goal: A safe, effective medicine to treat diseases of unmet need



At each phase transition, we review data and proposed plans to assess probability of future success and resourcing

Creating a data package for biopharm / biotech

– Seeking similar data package(s) as we build for our internal projects
– Similar ‘what’ but interested in the diversity of ‘how’



Target identification

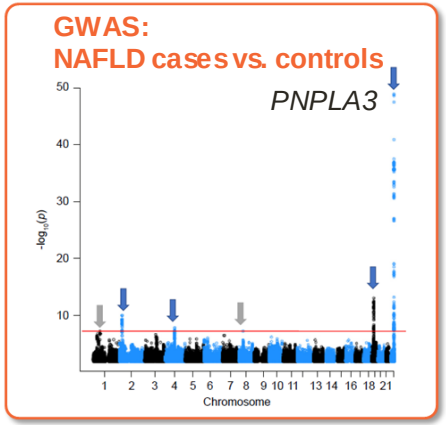
Target Selection | Target Validation | Lead Discovery | Lead Opt. | Preclinical Eval. | Phase 1 | Phase 2 | Phase 3

First step: **Target identification** (where do the targets come from?)

- Scientific publications and presentations
- External collaborations or partnerships
- Phenotypic / functional genomic screens
- Bioinformatics
- Genetic analyses (i.e., GWAS, FxG)

	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)

Values give the ratio of the probability of a target-indication pair progressing given genetic support to the probability of progressing without genetic support; 95% confidence intervals are given in parentheses.



Nelson, *et al.* (2015) *Nat. Genet.*
King, *et al.* (2019) *PLoS Genet*
Anstee, *et al.* (2020) *J. Hepatol.*

Target Identification at GSK – Internal Focus
Triumvirate of Human Genetics x Functional Genomics x AI/ML

Human Genetics
2x increase in clinical success

Metric	23andMe	UKB	FinnGen*
Sample size	5M+	500K	150K
Defined traits	>1K	>2.5K	>1K
Associations	>60K	>30K	>0.1K

Functional Genomics
Translate to targets and patient insights

- Functional Genomics
- Disease/tissue 'omics

Open Targets

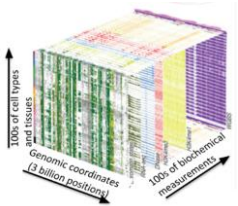
LGR

ALTIVS

BROAD INSTITUTE

AI/ML
Insights from increasingly complex data

- Molecule Disease Characterization Initiative
- Deconvolution of genetic signals
- Insights from preclinical and clinical imaging



Target identification with increased probability to a successful medicine

*FinnGen is expected to grow to 500k population

Target selection

- **Upfront considerations**
  - Strength of genetic signal (or FxG target validation)
  - Mechanism of action
  - Druggability (tractability)
  - Unmet medical need
- **Medicine vision**
  - *Example: "Inhibition of TG2 activity in patients with celiac disease on gluten free diet who remain symptomatic will lower production of the driving antigen, reduce inflammation and thereby reduce symptoms and improve mucosal health."*
  - Develop target medicine profile and progression path to demonstrate therapeutic hypothesis
- **Additional important considerations**
  - Tolerability, PheWAS
  - Preclinical tractability
  - Predictive biomarkers
  - Clinical path

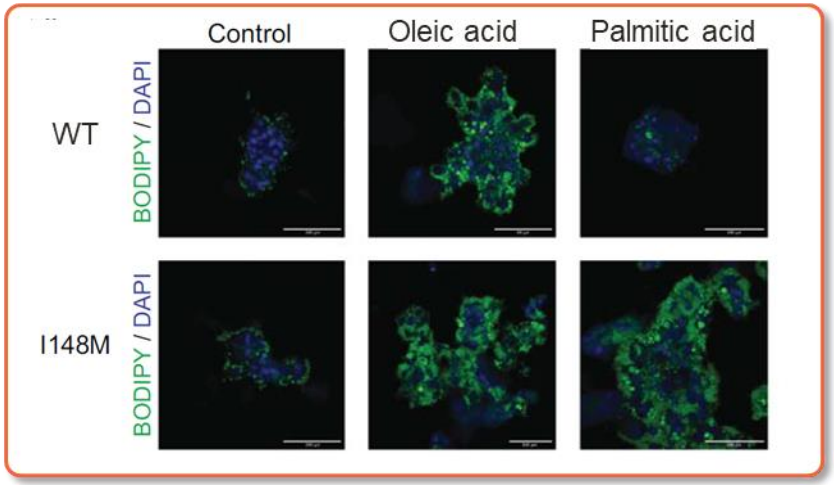
Target validation

Objective: Accumulate evidence for target in planned indication

Target Selection | **Target Validation** | Lead Discovery | Lead Opt. | Preclinical Eval. | Phase 1 | Phase 2 | Phase 3

- **Accumulate evidence for target in planned indication**
  - Human genetics provides indication
  - 'Omics can provide data on expression (RNA, protein) in tissue and cell type (ideally also disease-derived data)
  - Existing literature and hypothesis-driven research

- **Establish target validation using evidence from**
  - Cellular studies with tool compounds, genome editing, RNAi
    - Transformed cell lines
    - iPSc-derived
    - Organoid



Tilson, *et al.* (2021) *Hepatol.*

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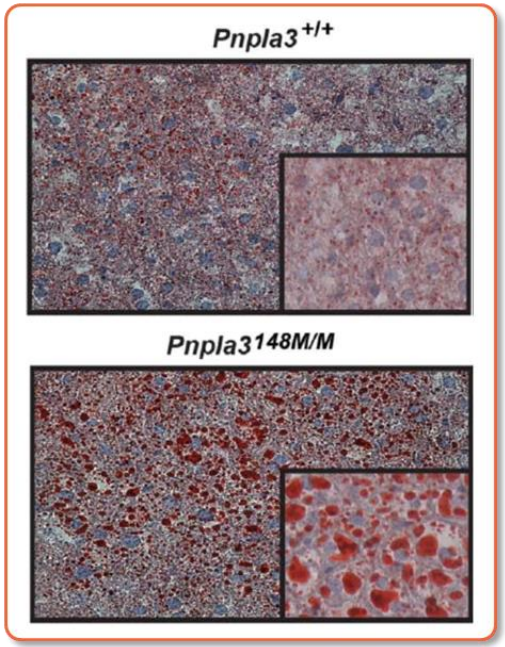
- **Establish target validation using evidence from**
  - Cellular studies with tool compounds, genome editing, RNAi
    - Transformed cell lines
    - iPSc-derived
    - Organoid
  - In vivo models
    - Genetically engineered mouse KI/KO (assuming target is expressed similarly)
    - Disease-models
  - Human disease derived data

A target is not truly validated until it becomes a medicine!

Mouse KI of PNPLA3 I148M/M

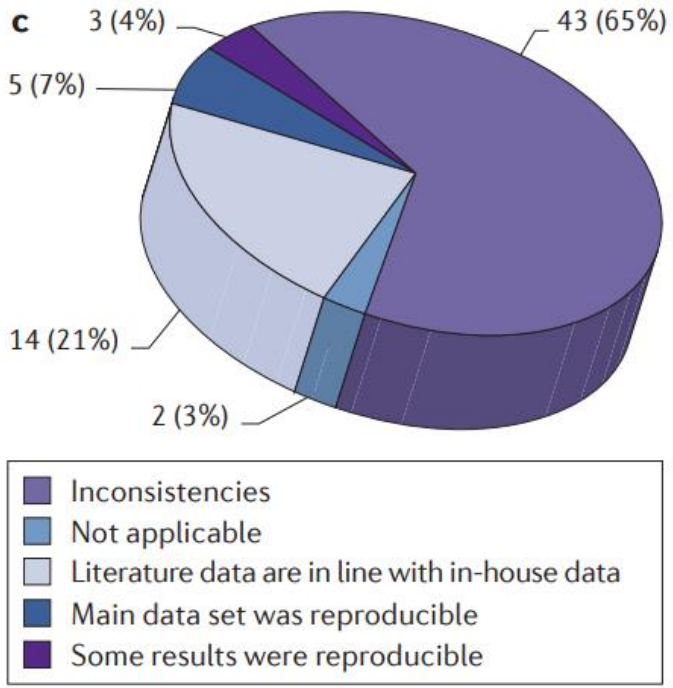


Smagris, *et al.* (2015) *Hepatol.*

The reproducibility problem

Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah



Prinz, *et al. Nature Rev Drug Disc* (2011) **10**:712

Target validation

Objective: Accumulate evidence for target tractability

Establishing target **tractability**

- Known assets in development?
- Known tool compounds?
- Structure (experimental, model) known?
- Cellular localization of target?

Tractability is linked to desired **modality**:

- Small molecule
- Antibody (monoclonal, bispecific, etc.)
- Oligonucleotide (RNAi, anti-sense oligo)
- Cell and gene therapies
- …others

Lead discovery

Identification of leads for further discovery

Lead molecule: Small molecule or antibody that interacts with the target of interest

- Positives from screen
- Reproducible
- Concentration-dependent

- Hits of sufficient quality and number to progress

Screen → **Hits** → **Hit Qualification** → **Qualified Hits** → **Hit-to-lead** → **Leads**

- Activity-based
- Affinity-based
- Phenotypic

- Evidence of target binding
- Selectivity vs. undesirable mechanisms

- Potency
- Selectivity
- Structure-activity relationship
- Physical properties

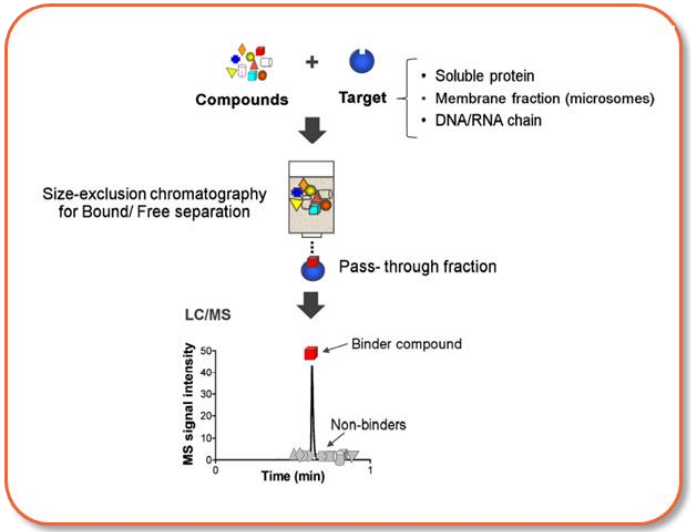
Lead discovery

High through-put screens for lead discovery of small molecules (~100k to billions)

Target Selection | Target Validation | **Lead Discovery** | Lead Opt. | Preclinical Eval. | Phase 1 | Phase 2 | Phase 3

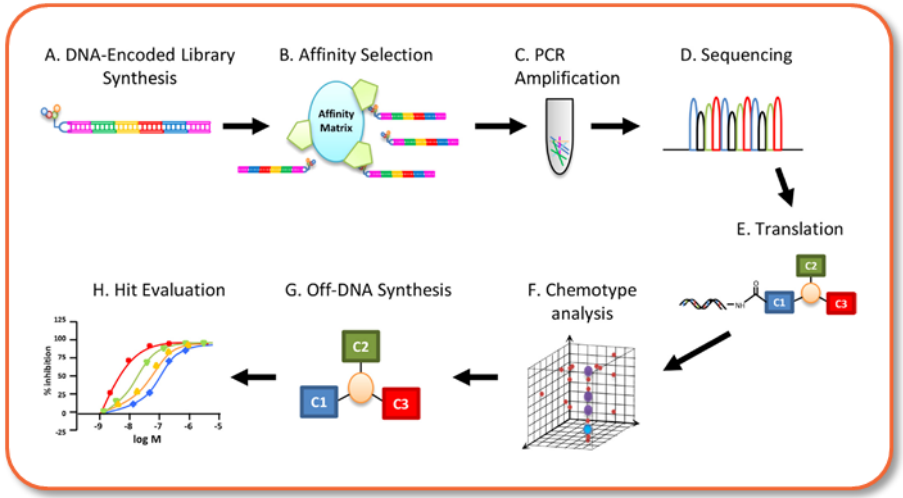
Affinity-first approach

ASMS (affinity selection-mass spectrometry)



Motoyaji (2020) *Chem. Pharm. Bull.*

ELT (encoded library technologies)



Arico-Muendel, *et al.* (2015) *Antimicrob. Agents Chemo.*

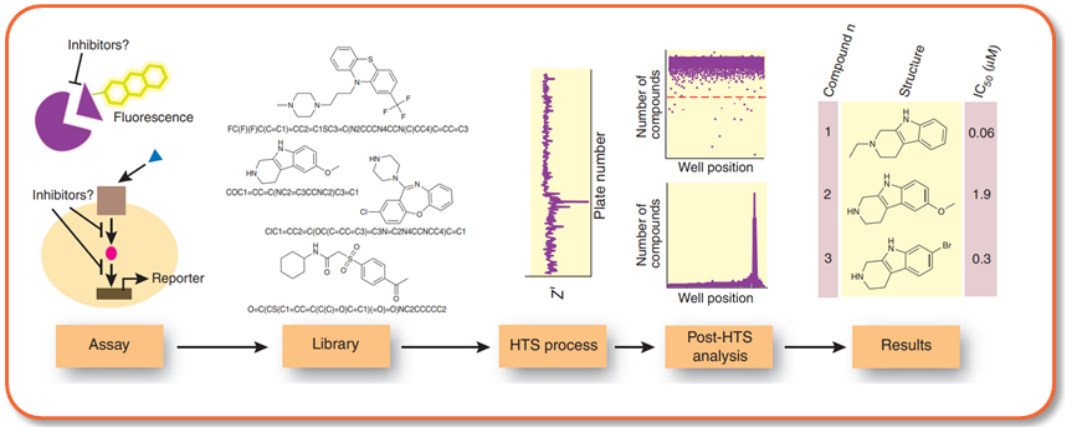
Lead discovery

High through-put screens for lead discovery of small molecules (up to 2m compounds)

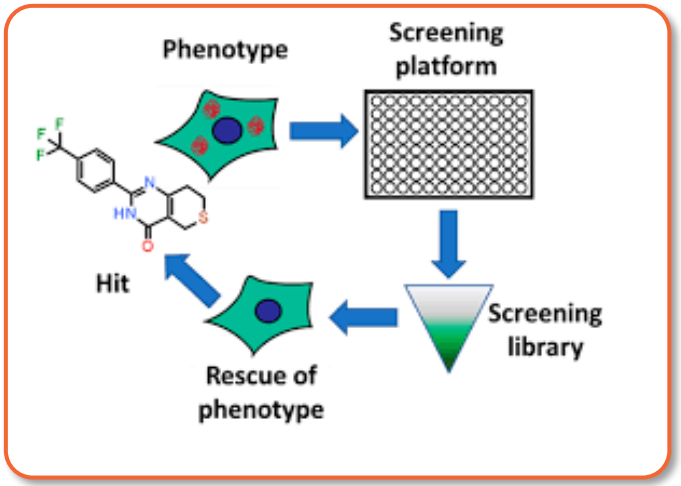
Target Selection | Target Validation | **Lead Discovery** | Lead Opt. | Preclinical Eval. | Phase 1 | Phase 2 | Phase 3

Activity-based screen

Knowledge-based screening



Phenotypic screen



Inglese, *et al.* (2007) *Nat. Chem. Biol.*

Brown & Wobst (2020) *J. Med. Chem.*.

Lead discovery to Lead Optimization (LO)

Example of criteria included in the contractual workplan of a GSK-academic collaboration*

Target Selection → Target Validation → **Lead Discovery** → Lead Opt. → Preclinical Eval. → Phase 1 → Phase 2 → Phase 3

The **Lead identification phase** will be deemed to be completed when

Identification of 3-5 series for progression

A molecule series is defined which

Potency: exemplars show activity with a pIC50 of >6 in the TARGET FLIPR assay (HEK293 cells) with >10 fold selectivity over other GPCRs (negative control) and show similar TARGET antagonist activity using various ligand agonists.

Selectivity: Exemplars show selective antagonist activity against a related endogenous receptor in HEK293 cells, ≥30 fold versus TARGET

Biological Relevant: Exemplars show activity in a relevant mast cell degranulation assay (mast cells) with a pIC50>6 and MoA studies suggest suggests that the effect is TARGET related.

Divergent SAR: show SAR in over >100-fold potency range, and evidence for divergent SAR of any off-target liability identified in cross screening.

PhysChem Properties: have physico-chemical properties consistent with development of an oral drug (Ligand Efficiency >0.3, clogP <3, aqueous solubility >100ug/mL, Property Forcast Index <7).

DMPK: have in vitro DMPK parameters consistent with being able to achieve a low oral dose in the clinic (permeability in a cell membrane permeability assay; P450, especially 3A4, IC^{50} >1uM, no time-dependent decrease in P450 IC^{50}.); demonstration for at least one series that in vivo PK:PD can be achieved

A feasible path has been identified for optimisation of in vivo PK to achieve good oral bioavailability and low-moderate clearance

A "new effort search" does not reveal any substantive findings that would preclude lead optimization

All the reagents required to support early lead optimisation are in place

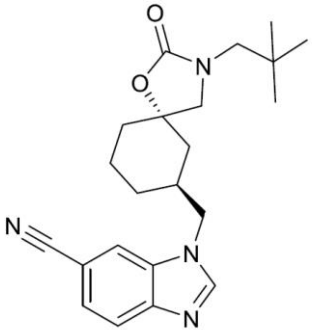
Note: workplan includes criteria and assigns responsibility to each party (not shown)

*slightly modified

Lead optimization

Objective: Identification of a candidate molecule suitable for clinical studies

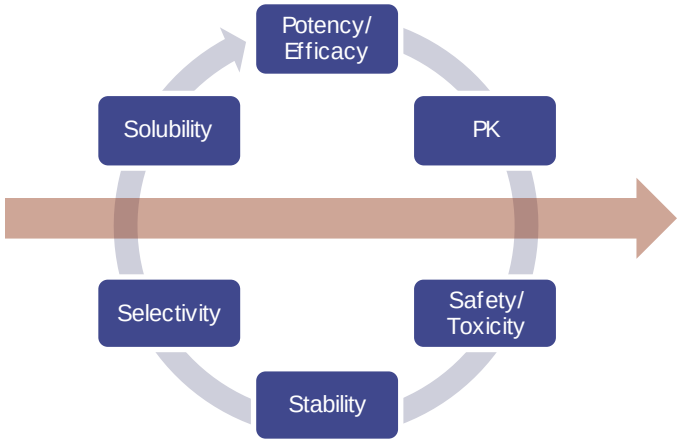
Target Selection | Target Validation | Lead Discovery | **Lead Opt.** | Preclinical Eval. | Phase 1 | Phase 2 | Phase 3

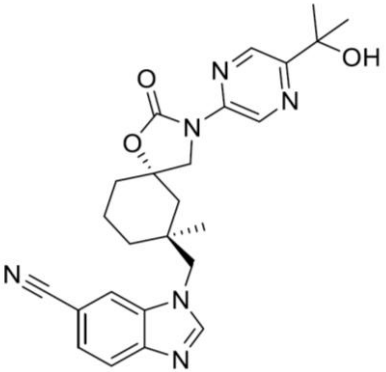


TRPV4 inhibitor: lead

Potent (hTRPV4 IC50 = 16 nM)

Rapidly cleared in rat pharmacokinetics (PK) studies





TRPV4 inhibitor: candidate

Potent (hTRPV4 IC50 = 2 nM)

Improved physicochemical properties

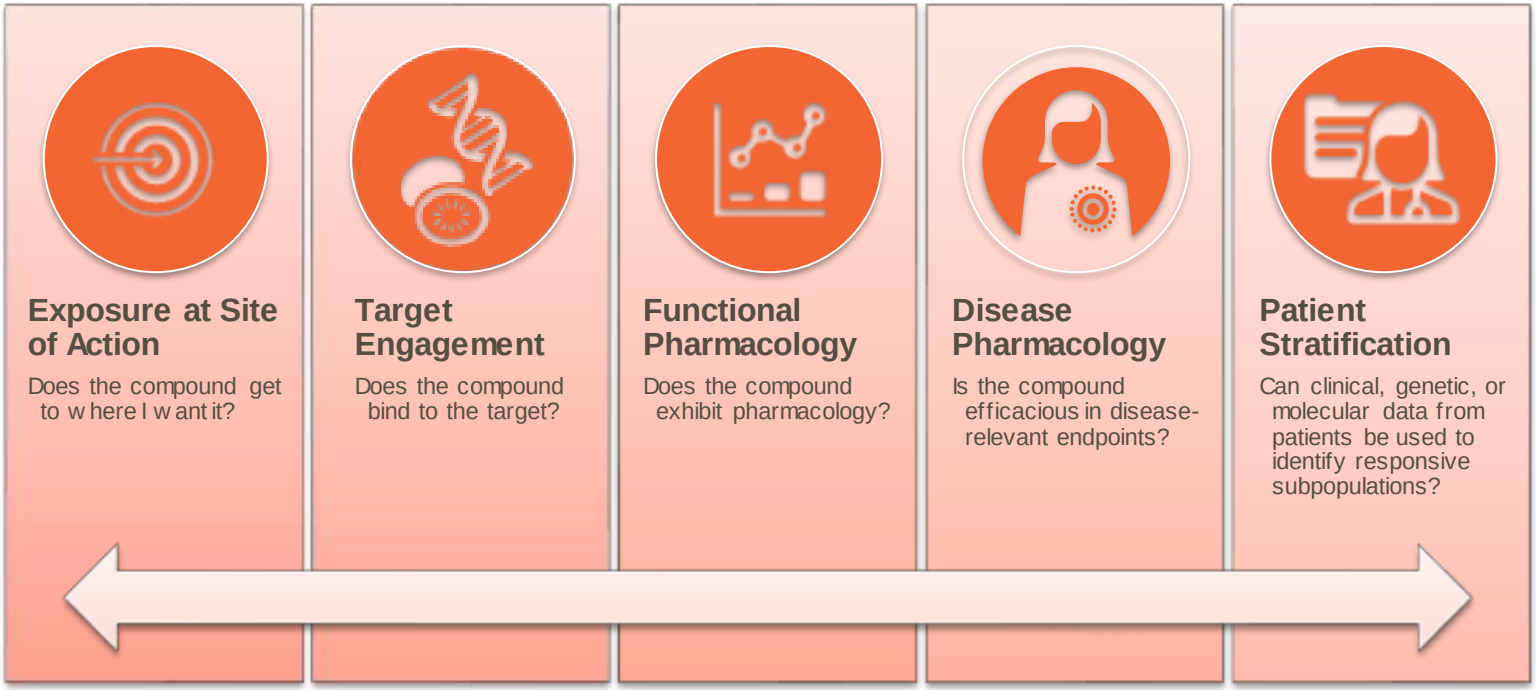
Significantly improved clearance

Brooks, *et al.* (2019) *ACS Med. Chem. Lett.*

Lead Optimization

Objective: Prepare for translation of preclinical data to clinical outcomes

Target Selection | Target Validation | Lead Discovery | **Lead Opt.** | Preclinical Eval. | Phase 1 | Phase 2 | Phase 3



Lead Optimization to Preclinical Evaluation

Example of criteria included in the contractual workplan of a GSK-academic collaboration*

- Declaration by GSK that a specific molecule has been selected to move into full preclinical development in accordance with its usual practices at the relevant time, which is likely to include:
- Pharmacokinetic properties in ≥ 2 species that are consistent with delivery of the desired drug profile (typically, a concentration time profile by the desired route of administration consistent with once or twice-daily dosing in humans, dose dependent exposure, and no indicators of relevant drug-drug interaction);
- Robust efficacy in a relevant in vivo model (or human translational model) with demonstrated concentration – effect relationship consistent with desired clinically differentiated drug profile at a dose of ideally <100 mg in humans;
- A preclinical safety profile in vitro and in vivo consistent with being able to achieve the desired clinically differentiated drug profile (typically a developable overall profile and therapeutic window on repeat dose toxicology and safety pharmacology studies in two species, no hERG related activity, no genotoxicity liability);
- Acceptable pharmaceutical form identified; and
- Patentability (novelty and non-obviousness).

*slightly modified

Note: workplan includes criteria and assigns responsibility to each party (not shown)

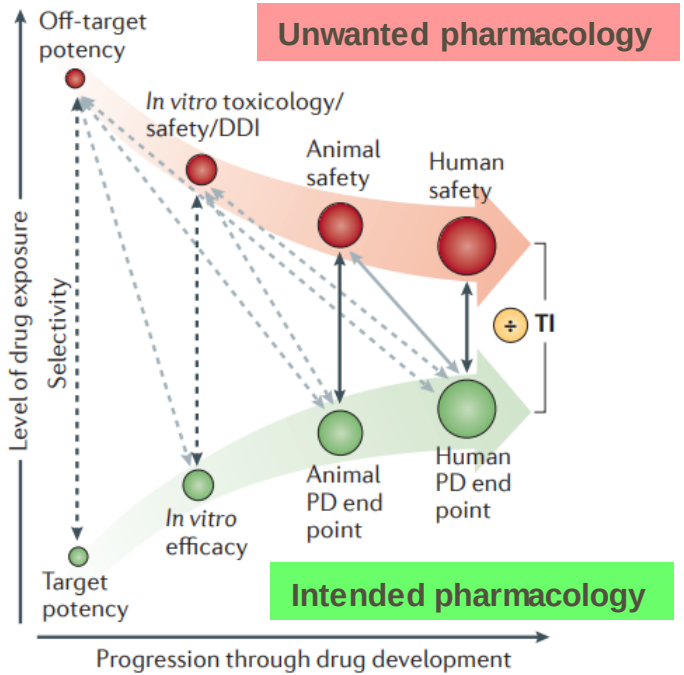
Preclinical Evaluation

Objective: Is the candidate molecule safe to administer to human subjects

Target Selection | Target Validation | Lead Discovery | Lead Opt. | **Preclinical Eval.** | Phase 1 | Phase 2 | Phase 3

- **Determination of target dose:** how much drug should be administered to achieve the desired effect
  - Determined through modeling preclinical exposure (pharmacokinetics) and efficacy (pharmacodynamics)
- **Determination of maximum safe dose:** how much drug can be safely administered
  - Determined from toxicology studies in animals (while upholding the global standards for the replacement, refinement, and reduction of animals in research – NC3Rs)

Therapeutic index: Difference between the target dose and the maximum safe dose



Muller and Milton (2012) *Nature Rev. Drug. Disc.*

Putting it all together …

The 5R Framework from AstraZeneca

Right target

- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

Right tissue

- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug–drug interactions

Right safety

- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity and drug–drug interactions
- Understanding of target liability

Right patient

- Identification of the most responsive patient population
- Definition of risk–benefit for a given population

Right commercial potential

- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized health-care strategy, including diagnostics and biomarkers

Morgan et al. (2018)
Nature Reviews Drug Discovery 17, 167-181

Duration and attrition during preclinical discovery

Objective: Is the candidate molecule safe to administer to human subjects

	12	17	23	20	Duration (mo)
		49%	44%	75%	% Success

Can we decrease cycle time/phase and increase success by

1 + 1 = 3

(academia + pharma/biotech partnerships)

Data from the Centres for Medicines Research (2017-2019)

Drivers for drug discovery academic - pharma partnerships

Incentives for pharma

- Deep biological and disease understanding
- Functional genomics – technology and screens
- Complex in vitro assays and in vivo models to bridge translation
- Clinical expertise
- Access to patients and/or patient tissue

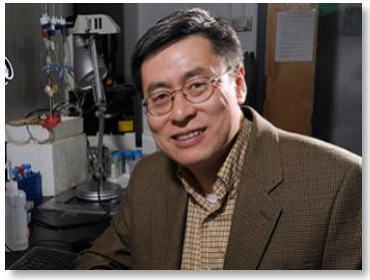
Incentives for academia

- Expertise and platforms to discovery quality molecules to validate therapeutic hypotheses
- Potential to develop initial hypothesis into commercial medicine
- Potential high impact publications
- Additional research funding

JHU-GSK Collaboration on MRGPRX2

GPCR unique to mast cells

Prof. Xinzhong Dong; Johns Hopkins University
HHMI Investigator, School of Medicine



- Discovered the MRGPRX receptor family
- Identified MRGPRX2 as the mast cell receptor responsible for allergic drug reactions
- Demonstrated MRGPRX2 to promote neurogenic inflammation via neuro-immune cross talk

LETTER NATURE | VOL 519 | 12 MARCH 2015

Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions

Report

Neuron [(2019), 101, 412–420]

A Mast-Cell-Specific Receptor Mediates Neurogenic Inflammation and Pain

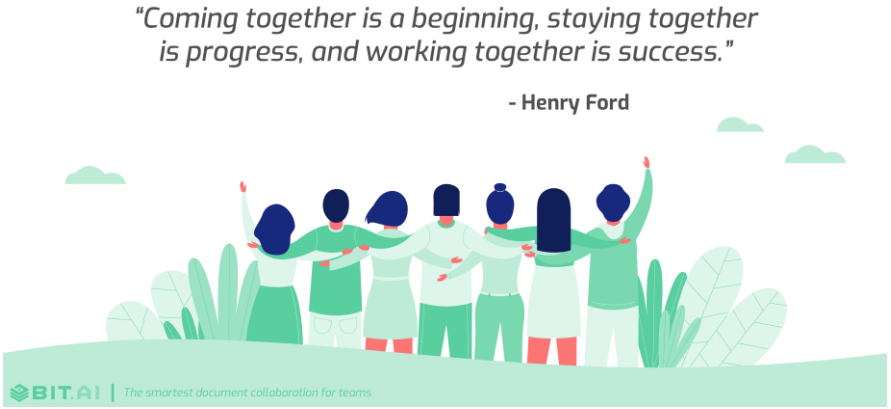
Editorial:

Substance P and Inflammatory Pain: Getting It Wrong and Right Simultaneously

Edita Navratilova[1,*] and Frank Porreca[1,2,*]
[1]Department of Pharmacology, University of Arizona, Tucson, AZ 85718, USA
[2]Mayo Clinic, Scottsdale, AZ 85259, USA

Carolyn's principles of an effective partnership: 1 + 1 = 3

- Share a common goal
- Create clear plans
- Assign accountability
- Compliment one another
- Share data continually
- Communicate transparently
- Provide sufficient resources
- Follow the science
- Outstanding people



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