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4th Annual Collaborative Drug Discovery Community Meeting

21 October 2010, San Francisco, CA

DISTRIBUTED DRUG DISCOVERY FOR NEGLECTED TROPICAL DISEASES.

TRANSLATING PHARMA APPROACHES TO AN ACADEMIC ENVIRONMENT.

Neglected diseases

An abysmal pipeline

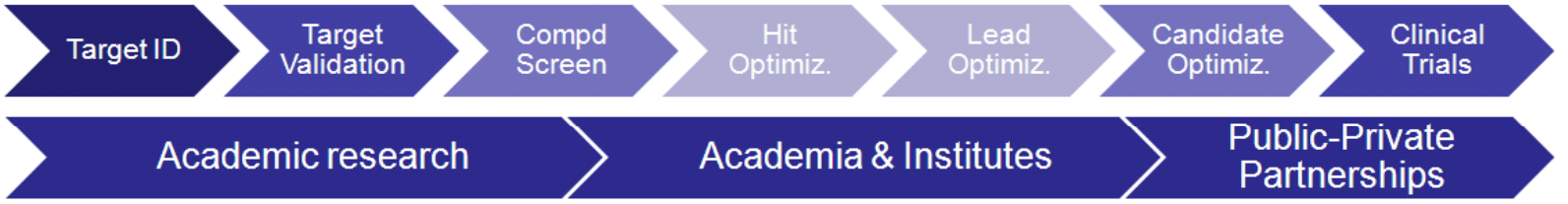
Disease	DALY[1] (millions)
Tuberculosis	34.7
Malaria	34.6
Lung cancer[3]	11.2
Leishmaniasis	2.3
Schistosomiasis	2.1
Prostate cancer[3]	1.6
African trypanosomiasis	1.5
Chagas disease	0.7

Infectious Agent Class	Disease	New Drug needed
Protozoan	Malaria	✓
	African trypanosomiasis	✓
	Viceral leishmaniasis	✓
	Chagas disease	✓
Nemotode	Ascariasis	
	Trichuriasis	
	Hookworm	
	Schistosomiasis	✓
	Lymphatic filariasis	
	River blindness	
	Dracunculiasis	
Bacterial	Leprosy	
	Trachoma	
	Buruli ulcer	✓

1. DALY = Disability-adjusted life years (years of healthy life lost) fr
2. PCD = Preclinical Development 3. Candidate numbers for cancers only include projects with lung or prostate as primary indication

Neglected diseases

- 10/90 disequilibrium in health research spending
- 1975-1999: 1,393 new chemical entities marketed
  - 68.7% registered products represented incremental improvement
  - 13 (1%) registered products for parasitic diseases
- The historical “Blockbuster model” in pharma doesn’t apply to diseases typically found in poor regions.
  - Unique niche for not-for-profit and academic drug discovery efforts



Trouiller *et al* ***2002*** *Lancet 359:2188-2194*

Neglected diseases

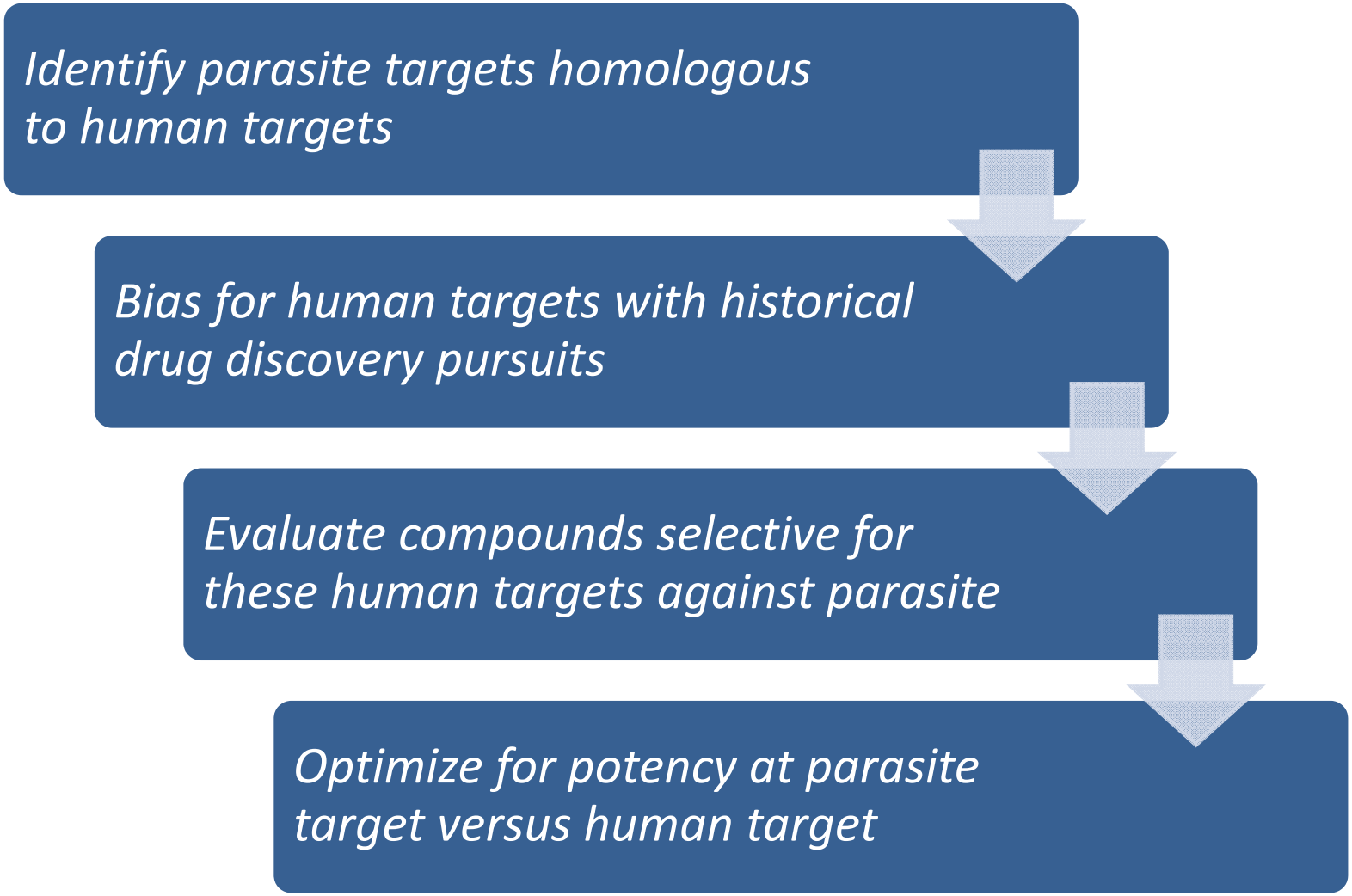
Undermine global health and well-being

- Contribute to extreme poverty and hunger.
- Impede universal primary education.
- Impede gender equality and empower women.
- Major cause of child mortality.
- Diminish maternal health.
- Complicate HIV/AIDS, malaria, & other diseases.
- Impede environmental sustainability.
- Impede beneficial development

Adapted from http://unstats.un.org/unsd/mi/mi_goals.asp Hotez, P.J. 2006 *Brown J. World Affairs*

Repurposing drug discovery

Parachute drug discovery



Advantages of repurposing

- Known to be “druggable” targets
  - Fewer dry holes, potentially more productive discovery efforts
- Lead matter available without HTS
  - Cost: At $0.03 per well, a single point HTS on 1MM compounds in triplicate costs about $90k in supplies alone
  - Consider radio/chemical/consumable waste required for HTS
- A great deal of data can be repurposed
  - Structural biology (enables homology modeling)
  - Structure-activity relationships
- Potential to engage development collaborations

In sum…repurposing should be faster and cheaper.

Industrial drug discovery

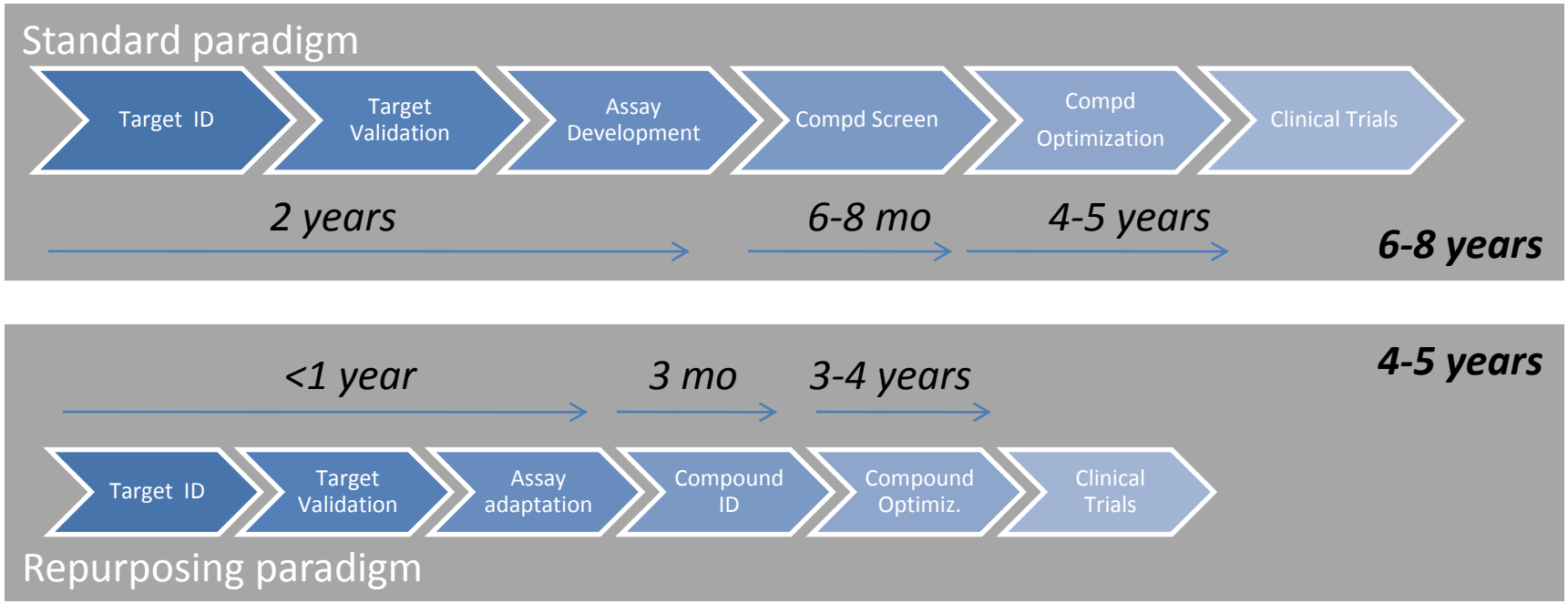
An expensive process

- Resource-intensive:
  - Average of 8 med/synth chemists per project for pursuit of multiple chemotypes
  - Pharmacologists (in vitro, in vivo)
  - Scale-up & formulation chemists
  - Toxicologists
- Expensive
  - $10-20 million USD per project
  - $2-4 million per year in preclinical lead optimization
- Frequent failure
  - < 0.1% of hits can be optimized into drugs

Lowell, J.E. 2007. Closing the Global Health Innovation Gap. BIO Ventures for Global Health. Washington, DC (www.bvgh.org/documents/InnovationMap.pdf)

Conventional versus repurposing

Timeline comparison



Staffing and timeline requirements reduced by repurposing

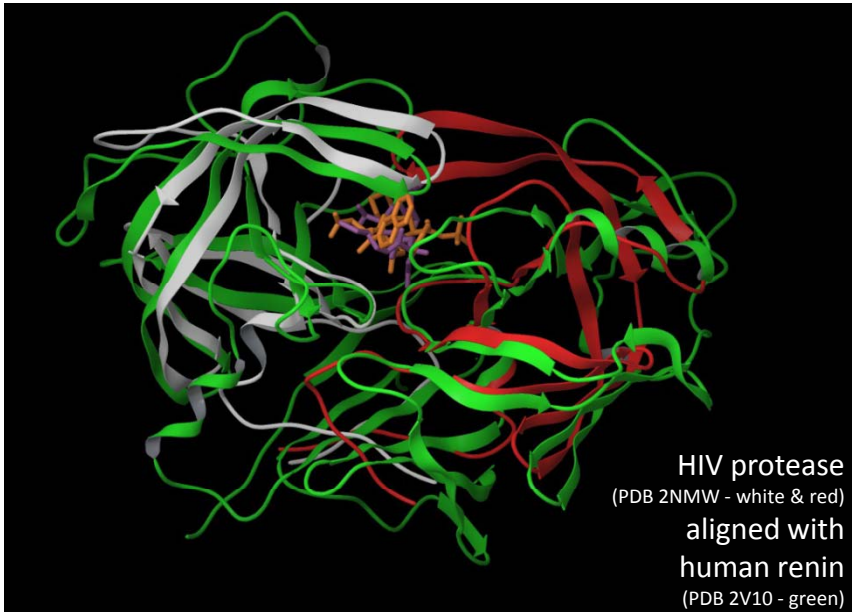
- Assays
  - Can apply parasite growth assays directly
  - Assay protocols can often be readily adapted
- Medicinal chemistry
  - Chemotype behavior well understood for rapid evolution (SAR, solubility, toxicity, etc)
  - Homology models can be based on established crystal structures

Timeline adapted from Fishman, MC & Porter, JA *Nature* **437**, (2005) 491-493

Proof-of concept for repurposing

HIV protease

- Repositioned from renin and other aspartyl proteases
  - 1985 HIV genome sequenced
  - 1988 Protease validated as target
  - 1990 first clinical candidates (and eventual drugs)



Some more recent examples in NTDs:

- N-myristoyl transferase inhibitors for sleeping sickness: *Nature* 2010 **464**, 728-732 (Dundee University: led by Paul Wyatt)
- Lanosterol 14α-Demethylase inhibitors for Chagas' disease: *J. Med. Chem.* 2009, **52**, 3703–3715 (University of Washington: Gelb, Buckner and Hamilton)

Typical project workflow

Bioinformatics

Target ID

Compound procurement

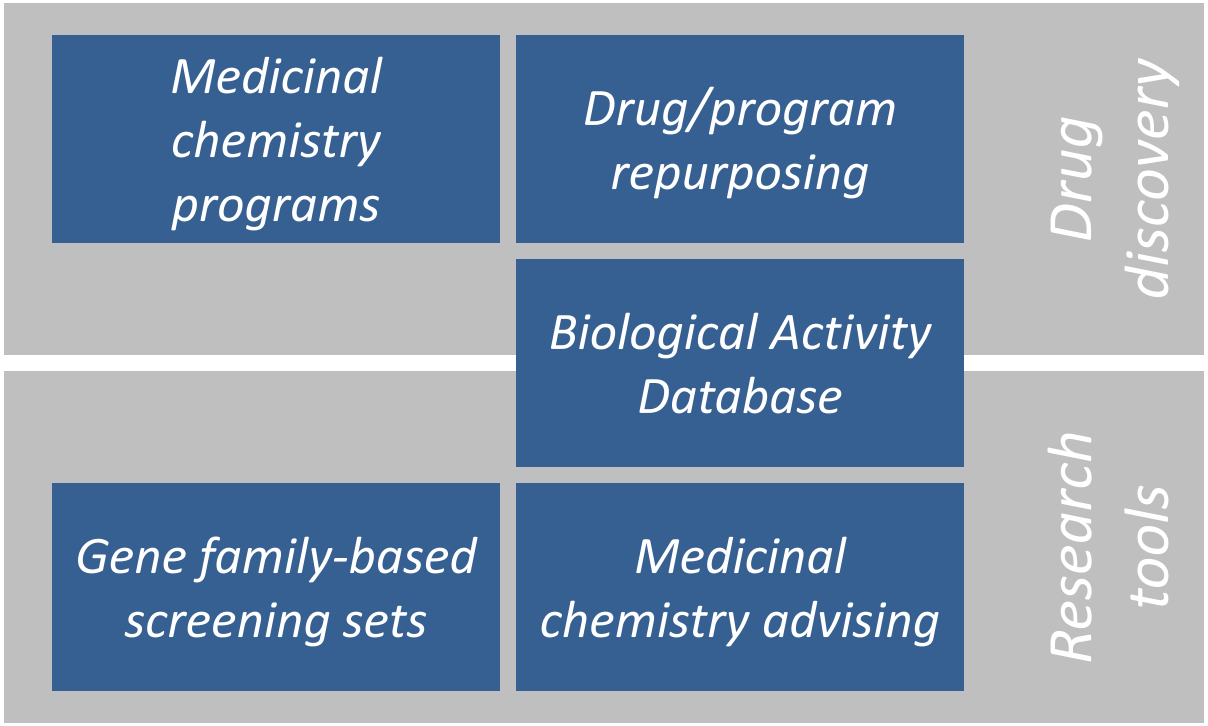
Synthesis, purchase, gift

Compound testing

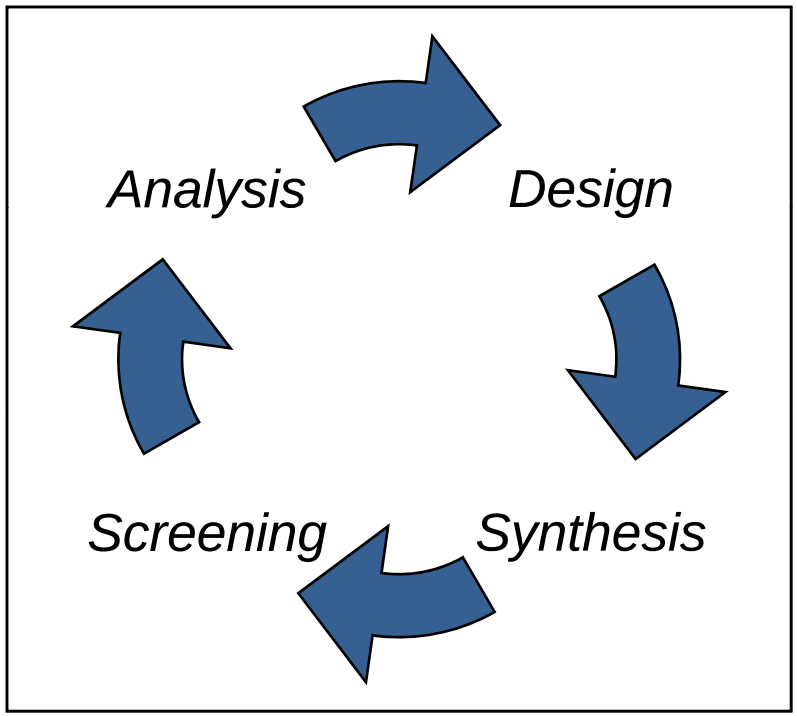
Whole Parasites

Biochemical Assays

Goal: identify targets and pathways that can be repurposed, not just for one parasite, but for multiple pathogens



Iterative optimization process



Design

- Propose next question to test hypothesis

Synthesis

- Prepare, purify & characterize analog

Screening

- Potency/selectivity
- Efficacy
- Physical property/ADME

Analysis

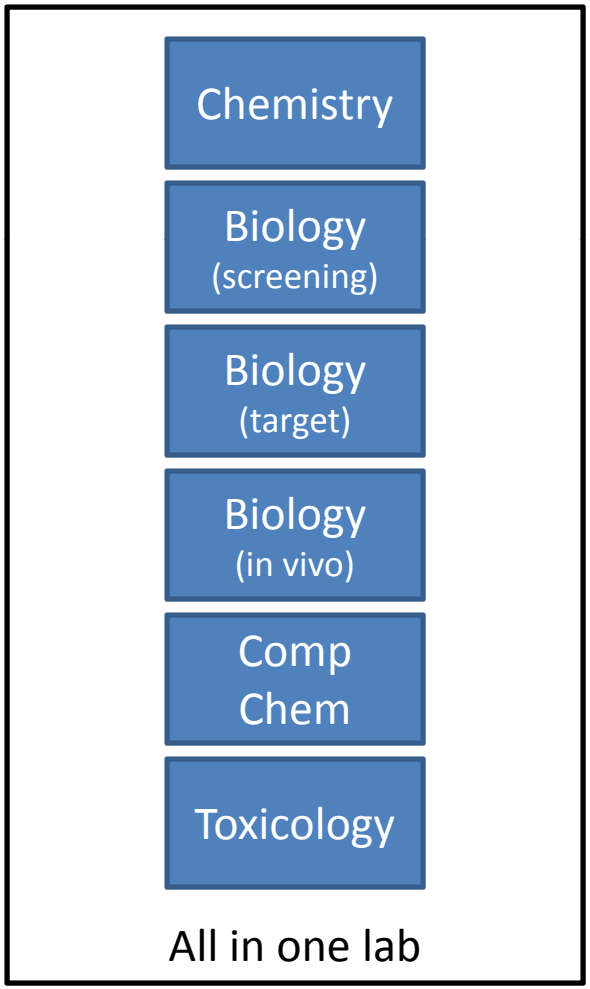
- Form versus function
- Computational experiments
- Inform next design step

Multidisciplinary research

A change in the tide

- Drug discovery is, by definition, multidisciplinary.
- Such efforts are only recently being embraced by the academic world.
  - Multi-PI Proposals to NIH established in 2006, but still frequently perceived as a complication to review
  - Independent investigators rewarded with tenure and large grants for “soup-to-nuts” drug discovery

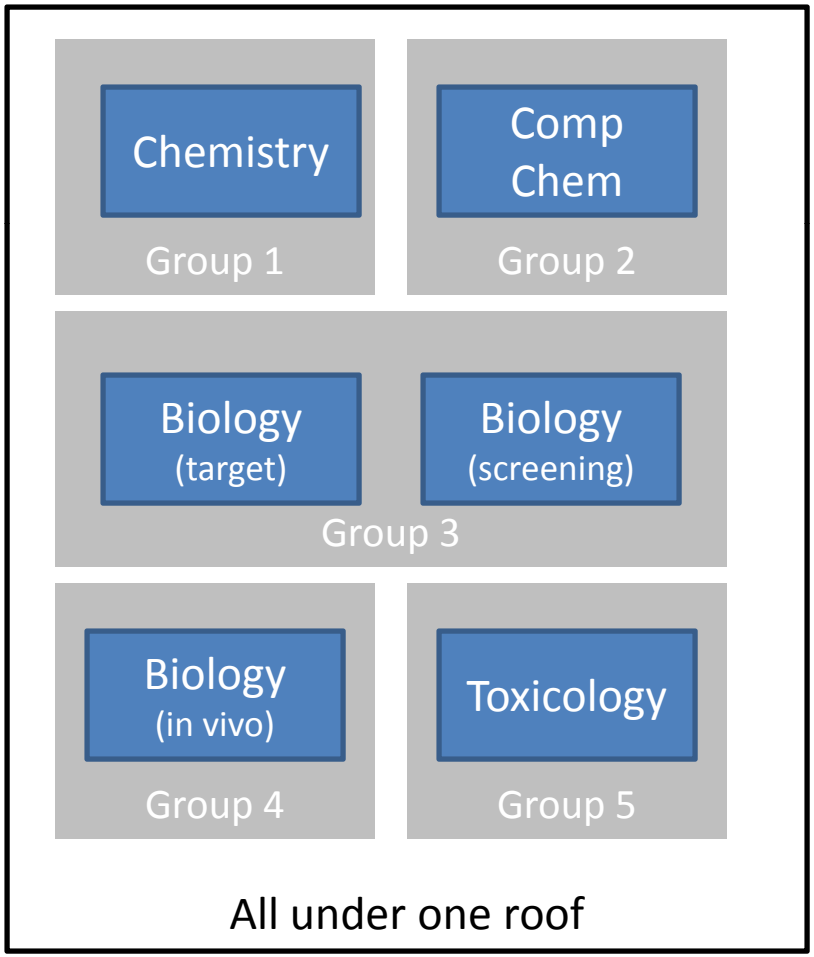
The stereotypical academic model



- **Advantages**
  - Independence
  - High level of recognition upon success
- **Disadvantages**
  - Difficult to have sufficient expertise in all areas
  - Difficult to broadly explore each area (resource limiting)
  - Top-level decision making (by PI) may miss opportunities

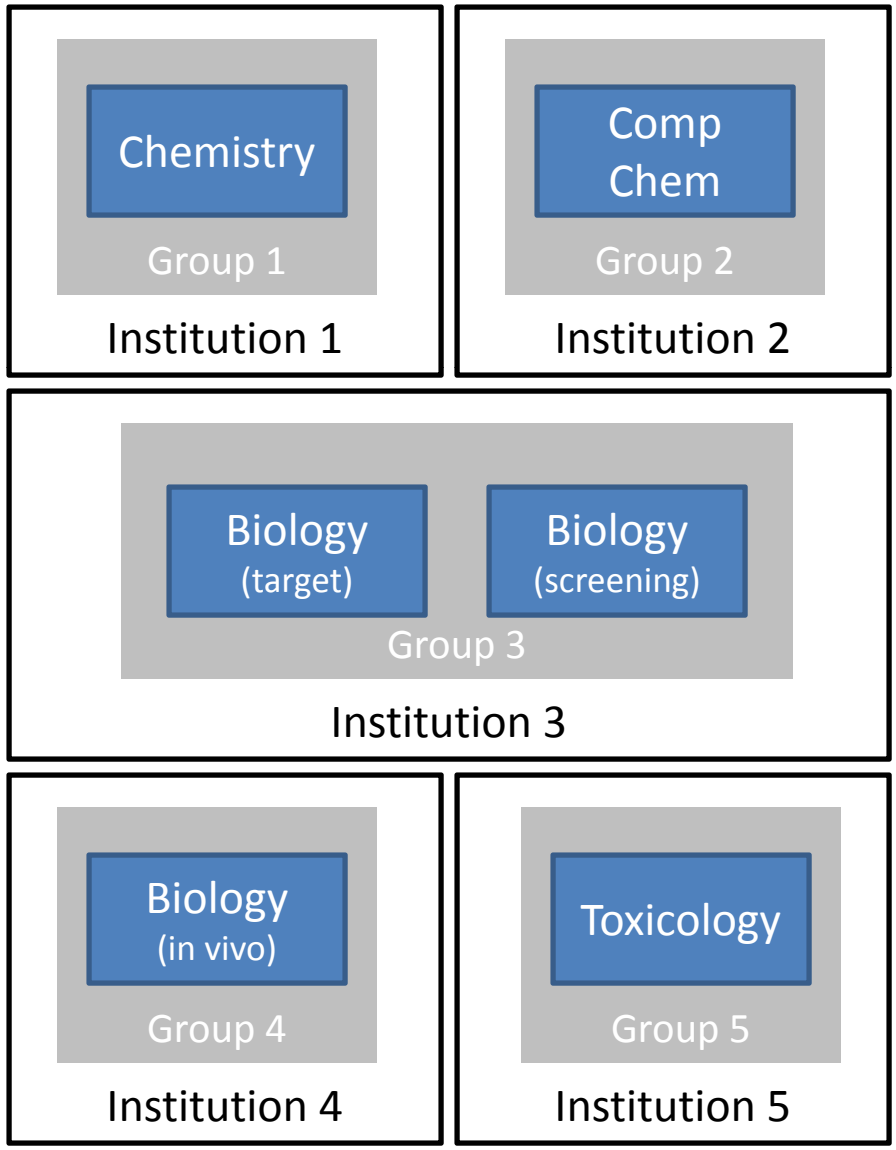
A typical industrial model

- **Advantages**
  - Team approach brings high levels of expertise to each aspect
  - Project workload is scalable and flexible
  - Common goal is clear and singular.
- **Disadvantages**
  - Projects often involve groups in broad, discipline-based org charts
  - Success depends on appropriate skills all being under this one roof.



The distributed model

- **Advantages**
  - Each group within the team selected for specific knowledge
  - Network is expanded far beyond project team.
  - Other opportunities for cross-fertilization become apparent
- **Disadvantages**
  - Project logistics complicated (data, compound, IP)
  - Priorities within different groups may vary



The distributed model in action

Parasite	Target	Molecular Modeling	Target Biology	Parasite Biology	Animal Models
T. brucei	TbrPDEB1/2	M. Ondrechen NEU	R. Campbell MBL	R. Campbell MBL	S. Kunz U. of Bern
	TrypDAC	O. Weist UND	J. Bradner DFCI	D. Horn LSHTM	D. Horn LSHTM
	TbAUK1	M. Ondrechen NEU	L. Ruben SMU	L. Ruben SMU	L. Ruben SMU
	TbrTOR/PI3Ks	M. Ondrechen NEU	Miguel Navarro CSIC-Granada	Miguel Navarro CSIC-Granada	Miguel Navarro CSIC-Granada
T. cruzi	TcrTOR/PI3Ks	M.Ondrechen NEU	A. Rodriguez NYU	A. Rodriguez NYU	A. Rodriguez NYU
L. major	LmPDEC	M. Ondrechen NEU	S. Kunz U. of Bern	S. Kunz U. of Bern	S. Kunz U. of Bern
	LmjTOR/PI3Ks	M.Ondrechen NEU	S. Beverley WUSTL	S. Beverley WUSTL	S. Beverley WUSTL

Trypanosomal phosphodiesterase inhibitors

REPURPOSING CASE STUDY

Outreach components

Proselytizing the "distributed" model

Consulting

- Advice in target prioritization
- Suggestions for project next steps (hit-to-lead, lead optimiz.)

Synthesis

- "Excess capacity" directed to support killer experiments to achieve target validation and proof-of-concept

Collaboration

- Develop programs and proposals for pursuit of new pathogen targets

Products

- Enhanced early stage pipeline for NTDs
- New collaborations
- New proposal opportunities
- Joint publications

This is all ongoing at Northeastern University and we're looking to:

- *Create a consortium of NTD-focused med chemists who are interested in the model,*
- *Attract funding to support these "enabling" efforts.*

Summary

- Target repurposing is a proven approach to streamline drug discovery
- Neglected disease drug discovery is particularly sensitive to speed (ie cost).
- A distributed model of drug discovery has advantages that can further enhance programs
- Further innovation is needed to find the best model(s) for seeding early-stage collaborations

Acknowledgements

TrypPDE

- **Northeastern**
  - Helen Wang, PhD
  - Trent Ashton, PhD
  - Stefan Ochiana
  - Mike Russo
  - Matt Stevenson
  - Craig Tallman
  - Mary Ondrechen, PhD
  - Josie Wang
  - Ritika Kurian
  - Gilmaris Santana
  - Spiro Pavlopoulous
- **MBL, Woods Hole.**
  - Bob Campbell, PhD
  - Nicholas Bland, PhD
  - Alden Gustafson
- **University of Bern**
  - Thomas Seebeck, PhD
  - Stefan Kunz, PhD

TbrAUK

- **Northeastern**
  - Stefan Ochiana
  - Mary Ondrechen
  - Josie Wang
- **Southern Methodist University**
  - Larry Ruben
  - Vidya Pandarinath

TrypTOR

- **Northeastern**
  - Caitlin Hubbard, PhD
  - Mary Ondrechen, PhD
  - Josie Wang
- **CSIC – Granada, Spain**
  - Miguel Navarro
  - Rosario Diaz-Gonzalez
- **Washington U., St. Louis**
  - Stephen Beverly
  - Matt Kuhlmann

TrpDAC

- **Northeastern**
  - Helen Wang, PhD
  - Cheri Snedeker
- **Dana-Farber**
  - James Bradner, MD
  - Jun Qi, PhD
  - Ronald Paranal, PhD
- **London School of Hygeine and Tropical Medicine**
  - David Horn, PhD
  - Qiao PingWang, PhD
- **Notre Dame**
  - Olaf Wiest, PhD
  - Guillermina Estiu

Acknowledgements

Funding

- Northeastern University
- NIH R01AI082577-01
- NIH 3R01GM064700
- Boston University
  - CMLD-BU
  - UROP
  - Ignition Award

Software

- OpenEye
- ChemAxon
- Accelrys
- Collaborative Drug Discovery

Compounds

- Pfizer
- Merck