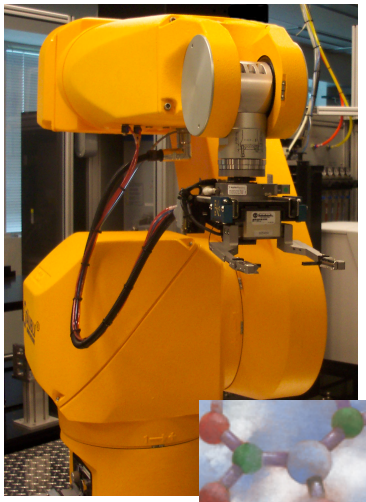
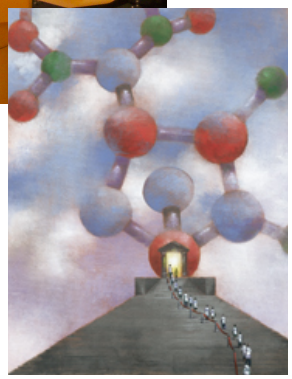


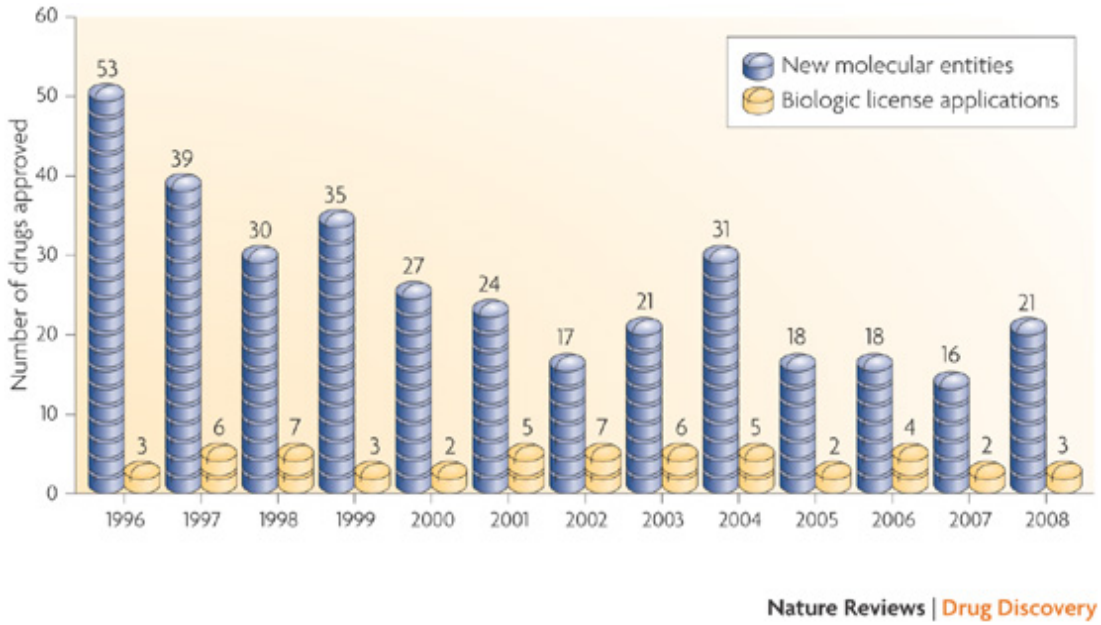


The NIH Translational Therapeutics Pipeline

Christopher P. Austin, M.D.
Director, NIH Chemical Genomics Center
Senior Advisor to the NHGRI Director for Translational Research
National Institutes of Health

NHGRI Science Reporters Workshop
June 7, 2010

The best of times, the worst of times

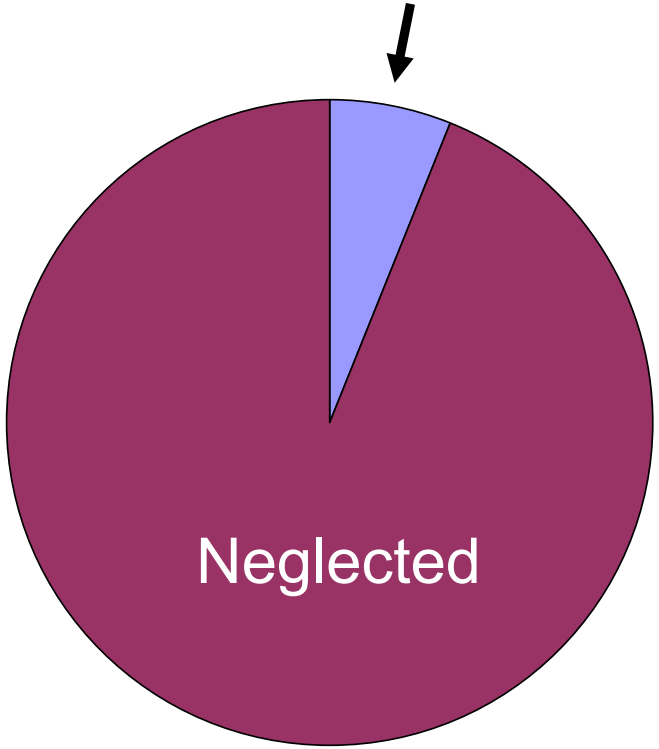


How to translate the genome into biological insights and therapeutics?

Only a small % of diseases and genome-encoded targets are being addressed for drug development

Current drug targets:

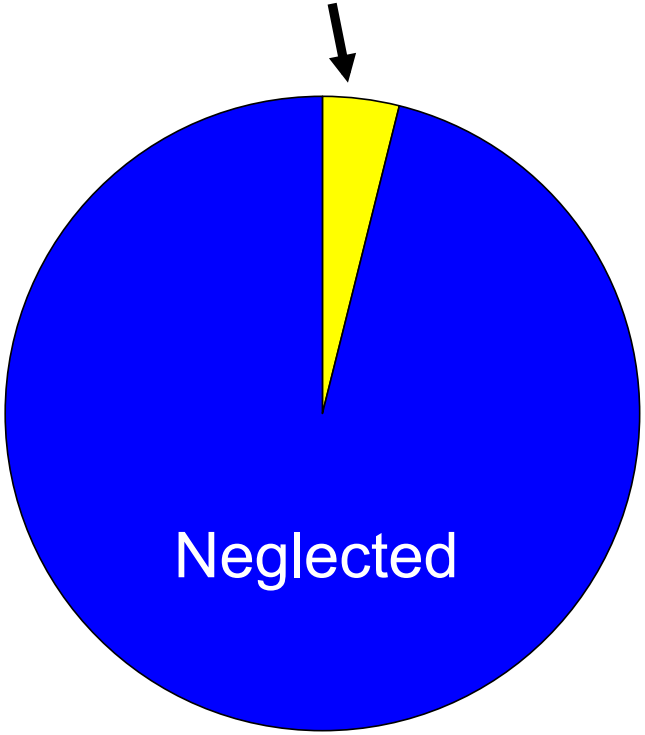
Well understood proteins



Human Genome

Current diseases:

Prevalent diseases that affect developed world



Human Diseases

NCGC

NIH Chemical Genomics Center

Acronyms

- **NCGC**: NIH Chemical Genomics Center
- **MLI**: Molecular Libraries Roadmap Initiative
- **TRND**: Therapeutics for Rare and Neglected Diseases program
- **RAID**: Rapid Access to Intervention Development
- **CAN**: Cures Acceleration Network

Trans-NIH programs to translate genes into drugs

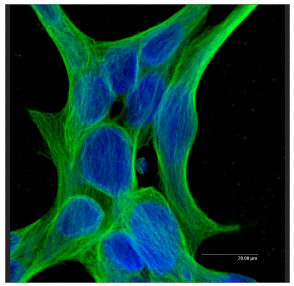
NIH basic research

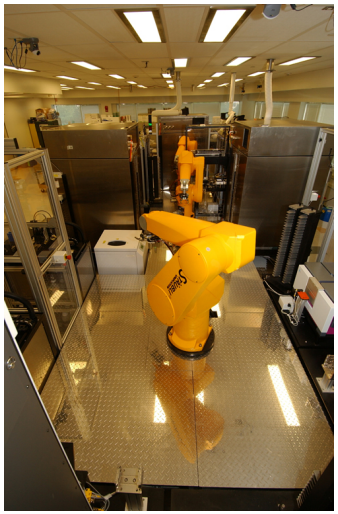
Roadmap Molecular Libraries Program
NIH Chemical Genomics Center (NCGC)

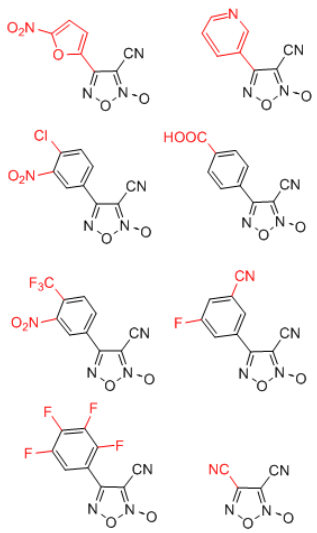
Therapeutics for Rare and Neglected Diseases (TRND) Program

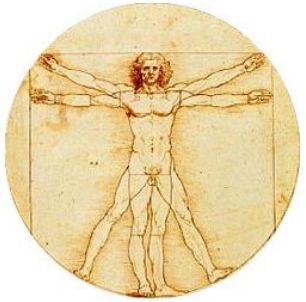
Biotech, Pharma
NIH Clinical Center

Identify target → Create testing system (a.k.a., "assay") → Test >300,000 chemicals for activity on target → Make modifications to active chemicals to make suitable for human use → Test in animals for safety, effectiveness → Test in humans for safety, effectiveness



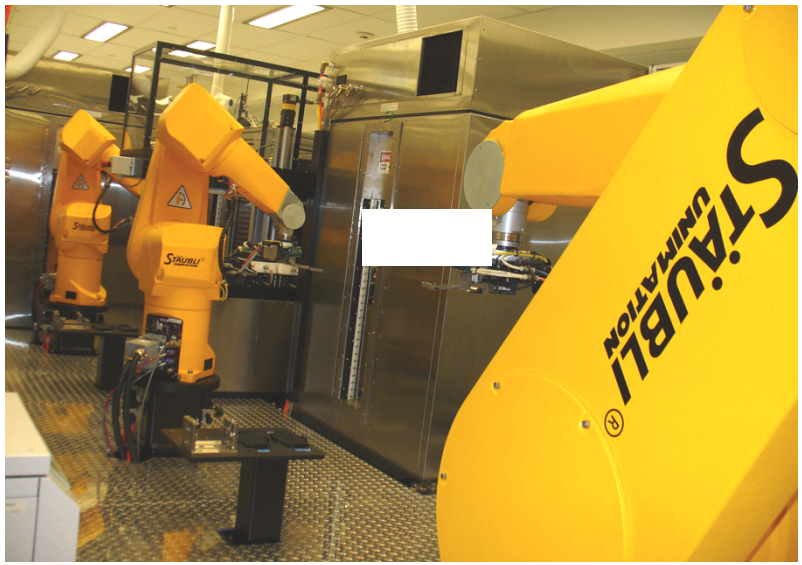




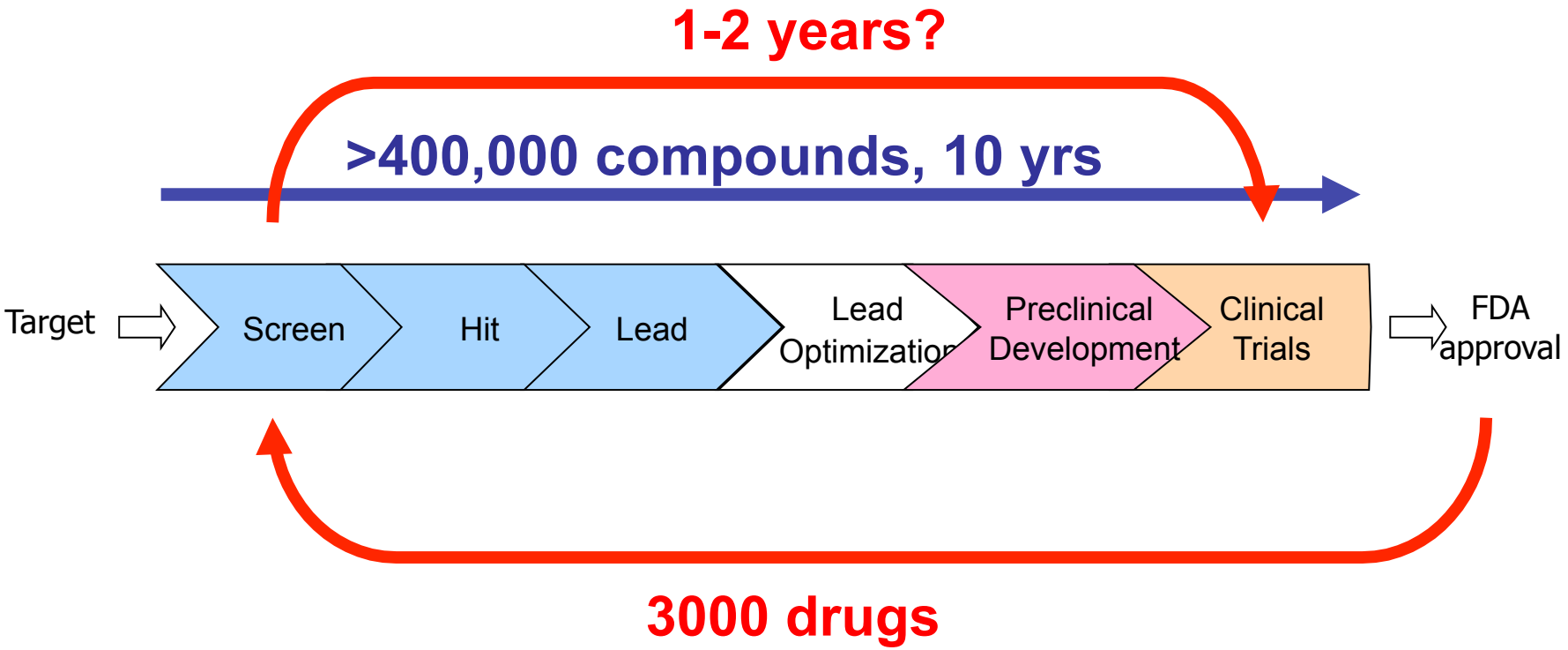


NIH Chemical Genomics Center

- Founded as part of Roadmap
- 75 scientists
- > 100 collaborations with investigators worldwide
  - 75% NIH extramural
  - 15% Foundations, Research Consortia, Pharma/Biotech
  - 10% NIH intramural
- Focus on novel targets, rare/ neglected diseases
- Produces
  - chemical probes/leads
  - new paradigms for assay development, screening, informatics, chemistry



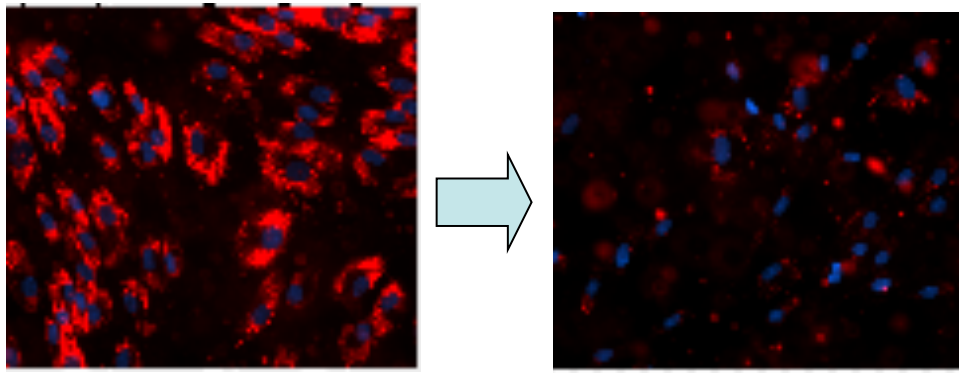
Two approaches to therapeutics for rare and neglected diseases



Repurposing a Drug for Niemann-Pick Disease Type C

NCGC – Dan Ory (Washington Univ) – Steve Walkley (Einstein) – Denny Porter and Bill Pavan (NIH)

- Autosomal recessive
  - Gene ID'ed 1998
- Prevalence: 1:150,000
- Progressive neurodegeneration, death by teens
- NCGC, university investigators, and patient groups are collaborating to repurpose an existing drug for NPC treatment
- Drug identified is entering clinical testing this fall



Developing drugs for Schistosomiasis

- Parasitic disease that affects 250 million people, mostly in Africa
- Dr. David Williams at Rush University identified potential new gene drug target
- NCGC and Dr. Williams worked together to
  - Screen 100,000 chemicals
  - Perform chemistry optimization
  - Successfully identify targeted chemicals that provide proof of principle and a starting point for new drugs

NIH Chemical Genomics Center

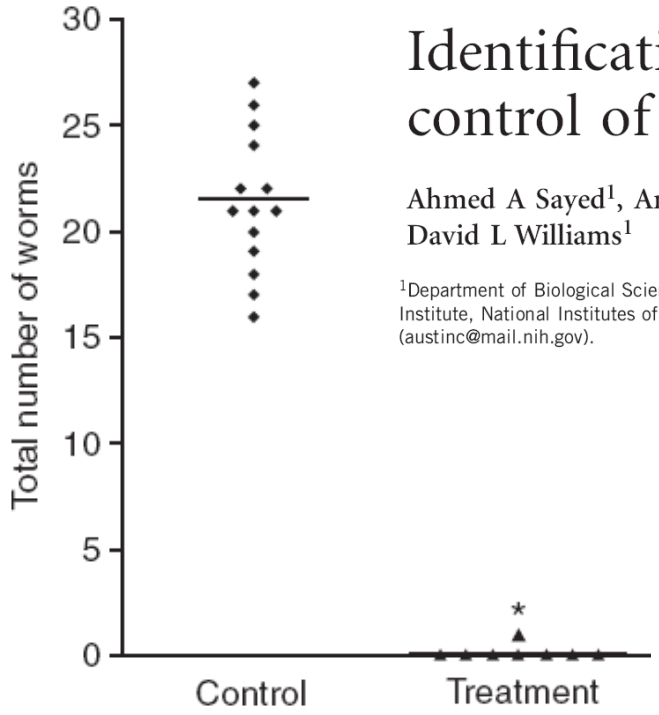
Proof that new medicine works in mice

nature medicine

Identification of oxadiazoles as new drug leads for the control of schistosomiasis

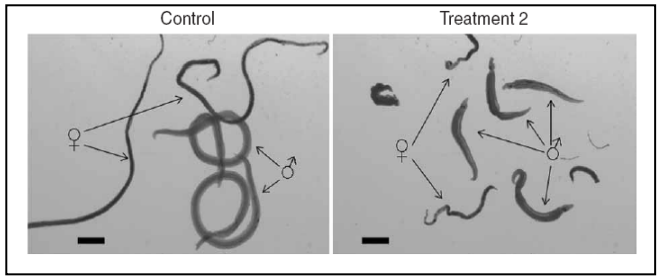
Ahmed A Sayed[1], Anton Simeonov[2], Craig J Thomas[2], James Inglese[2], Christopher P Austin[2] & David L Williams[1]

[1]Department of Biological Sciences, Illinois State University, Normal, Illinois 61790, USA. [2]NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892-3370, USA. Correspondence should be addressed to D.L.W. (dlwilli@ilstu.edu) or C.P.A. (austinc@mail.nih.gov).



Livers of treated mice

S. mansoni-infected mice treated with NCGC1597 @ 10 mg/kg IP for 5 days

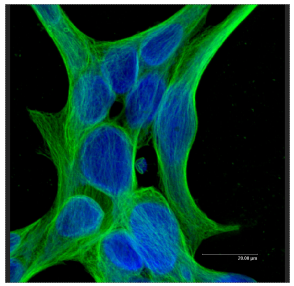


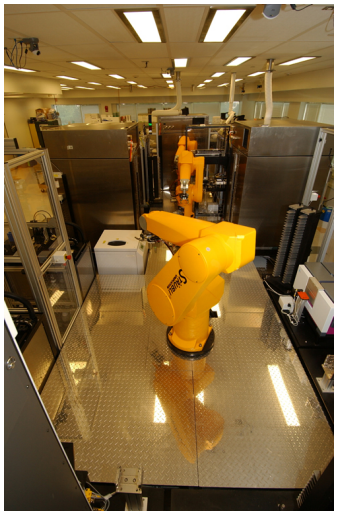
Ex vivo killing of *S. mansoni* worms by NCGC1597

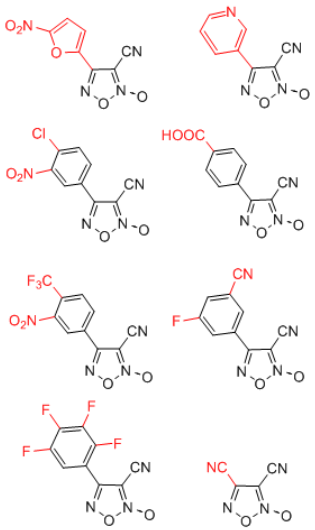
NIH's new programs to translate genes into drugs

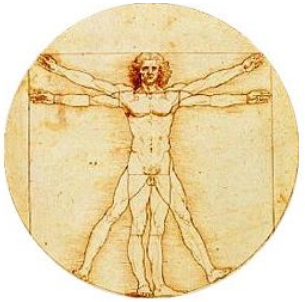
NIH basic research — *Roadmap Molecular Libraries Program, NIH Chemical Genomics Center (NCGC)* — *Therapeutics for Rare and Neglected Diseases (TRND) Program* — *Biotech, Pharma, NIH Clinical Center*

Identify target → Create testing system (a.k.a., "assay") → Test >300,000 chemicals for activity on target → Make modifications to active chemicals to make suitable for human use → Test in animals for safety, effectiveness → Test in humans for safety, effectiveness

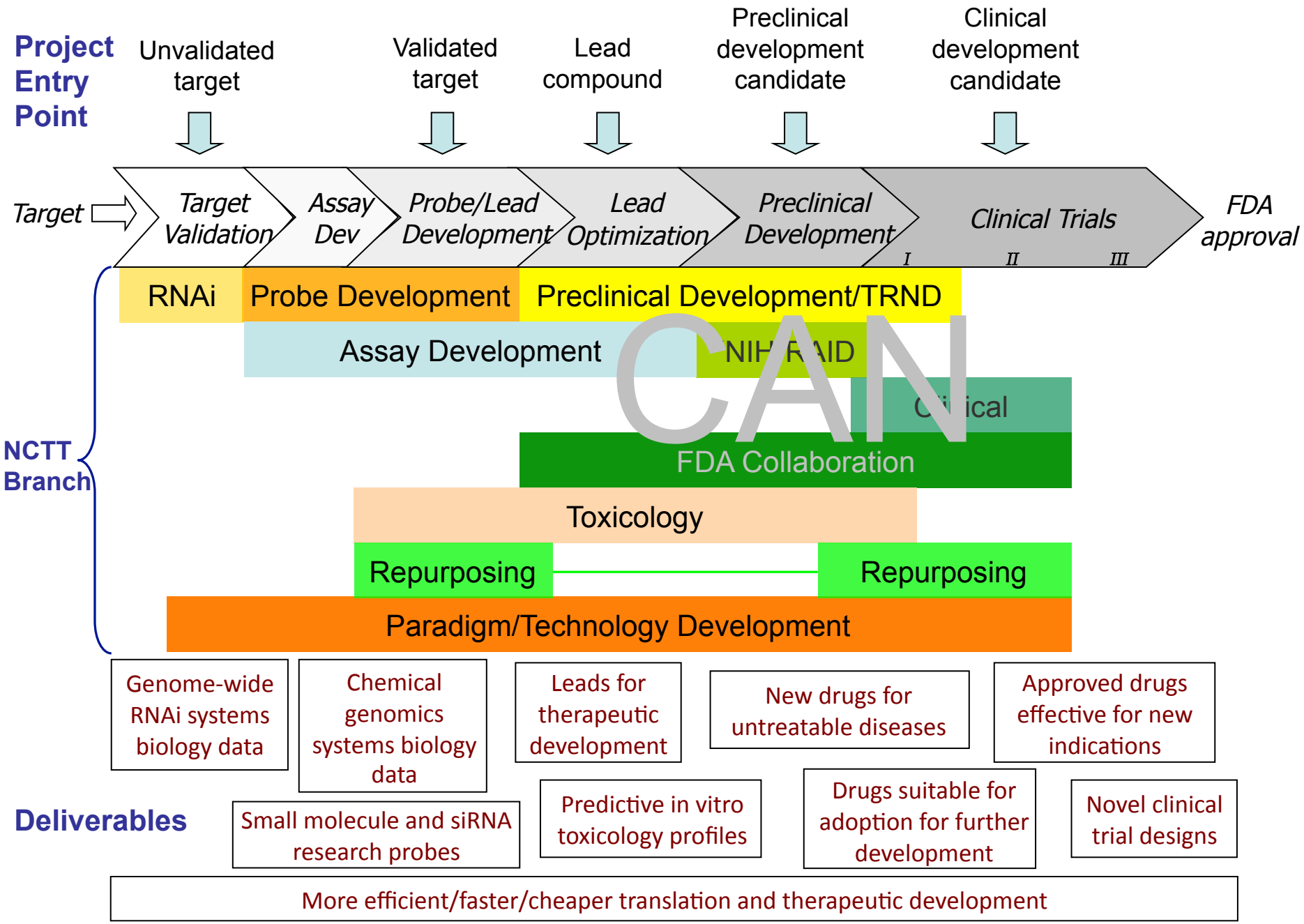








The New NIH Center for Translational Therapeutics: An Integrated Pipeline



BACKUPS

TRND Operational Model

- Analogous to NCGC
- In-house laboratories with expertise in preclinical drug development will collaborate with external laboratories with expertise in disease/target
- Projects will be taken to phase needed for external organization to adopt for clinical development
- Projects will enter TRND at a variety of stages of development
- Distinguishing features
  - Disease agnostic, take advantage of cross-cutting mechanisms
    - "Diseaseome" approach
  - *Science* of preclinical drug development
    - Reasons for successes and failures will be investigated and published
  - Technology Development
    - Efficacy models (iPS), Toxicity models (Tox21), BBB penetration
  - Large-scale systematic repurposing
    - What % of all rare diseases are treatable by entire current pharmacopeia

TRND Pilot Projects Ongoing

- Chosen to establish processes in advance of solicitation, with diversity of project stage, type of disease and collaborators

Disease	Type	Pathology	Collaborators	Compound type	Stage
Schistosomiasis, Hookworm	Neglected	Infectious parasite	Extramural	NME	Early (lead optimization)
NPC	Rare	CNS, liver/ spleen	Disease Fnd, Extramural, Intramural	Repurposed approved drug	Mid-stage
HIBM	Rare	Muscle	Biotech, Intramural	Intermediate replacement	Pre-IND