Accelerating TB Drug Discovery

Ken Duncan
Senior Program Officer

CDD Community Meeting
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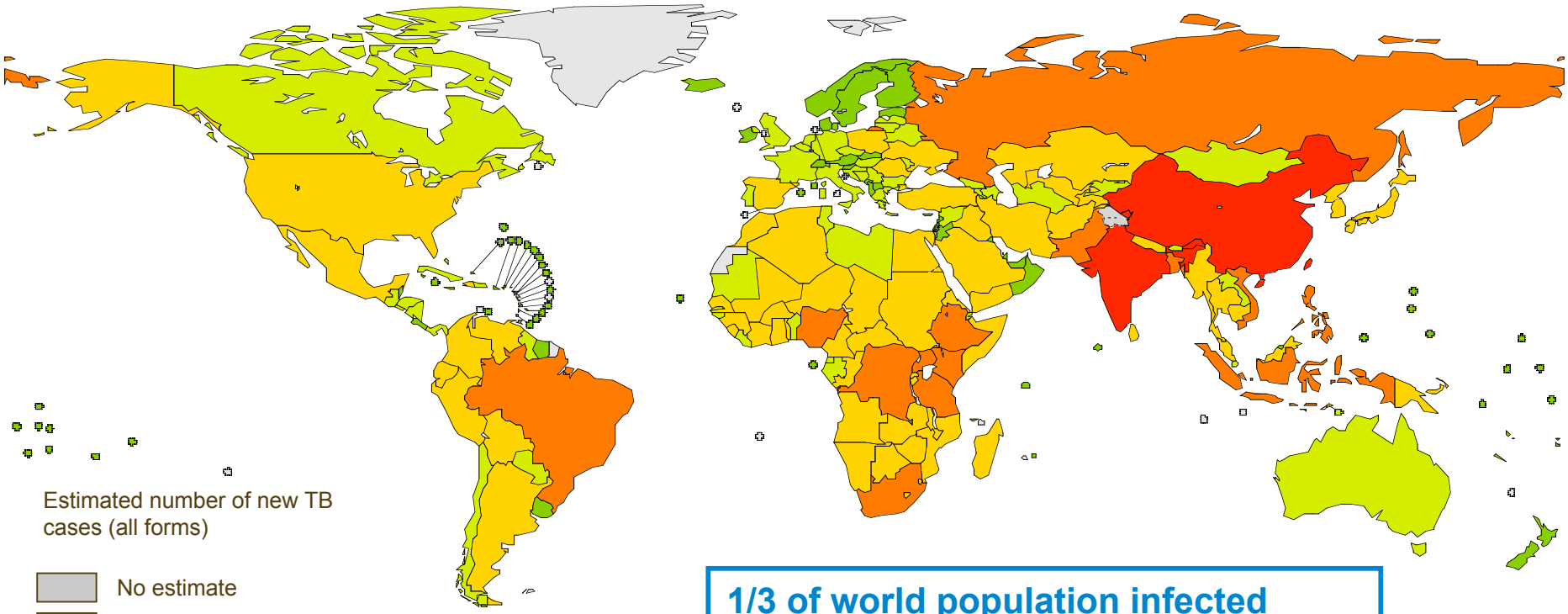
BILL & MELINDA GATES *foundation*

TB in 2005

WHO declared TB a "Global Health Emergency" in 1993

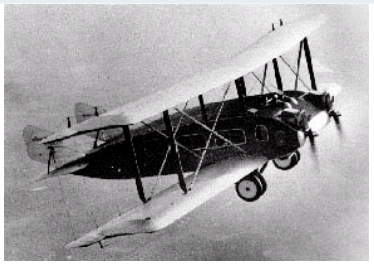


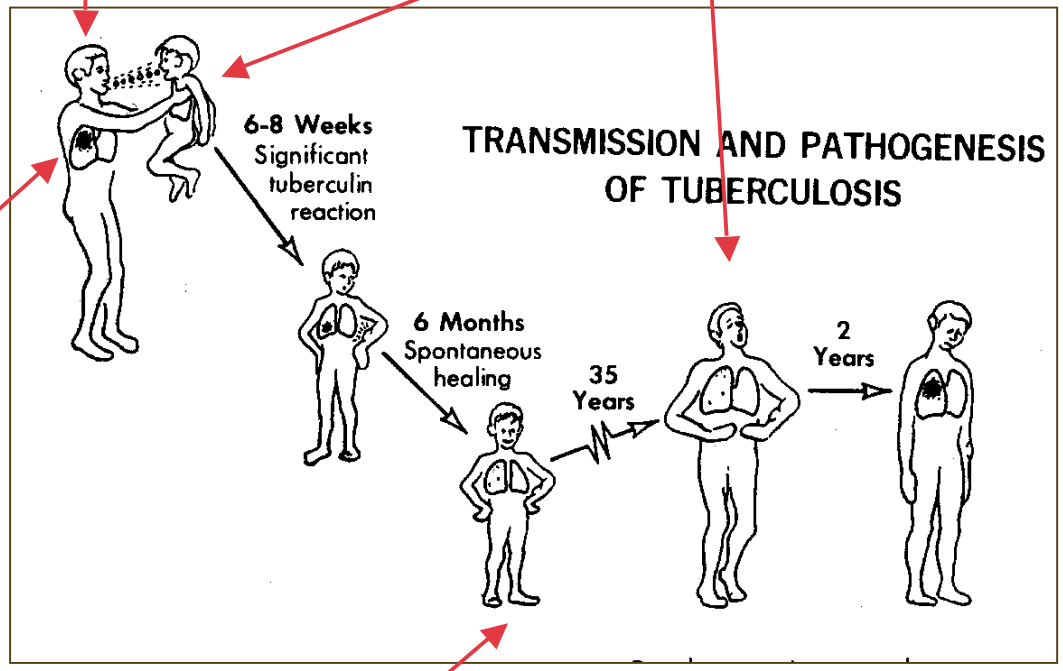
1/3 of world population infected
18 million prevalent cases
8.8 million new cases
1.6 million deaths
700,000 deaths in HIV infected
450,000 MDR cases

Limited Antiquated Interventions

Diagnostics

Vaccination



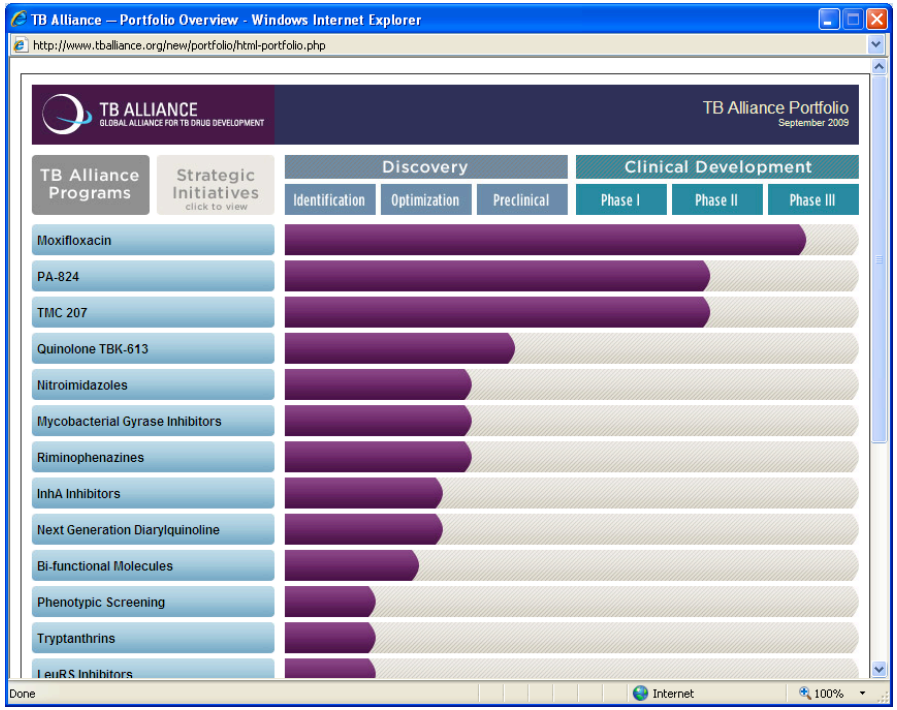


Drugs

Isoniazid Preventive Treatment for Latent TB Infection

TB Drug Discovery

Genesis of the "TB Drug Accelerator" program



Needs

- **Augment pipeline**
- **Treatment shortening**

Impediments

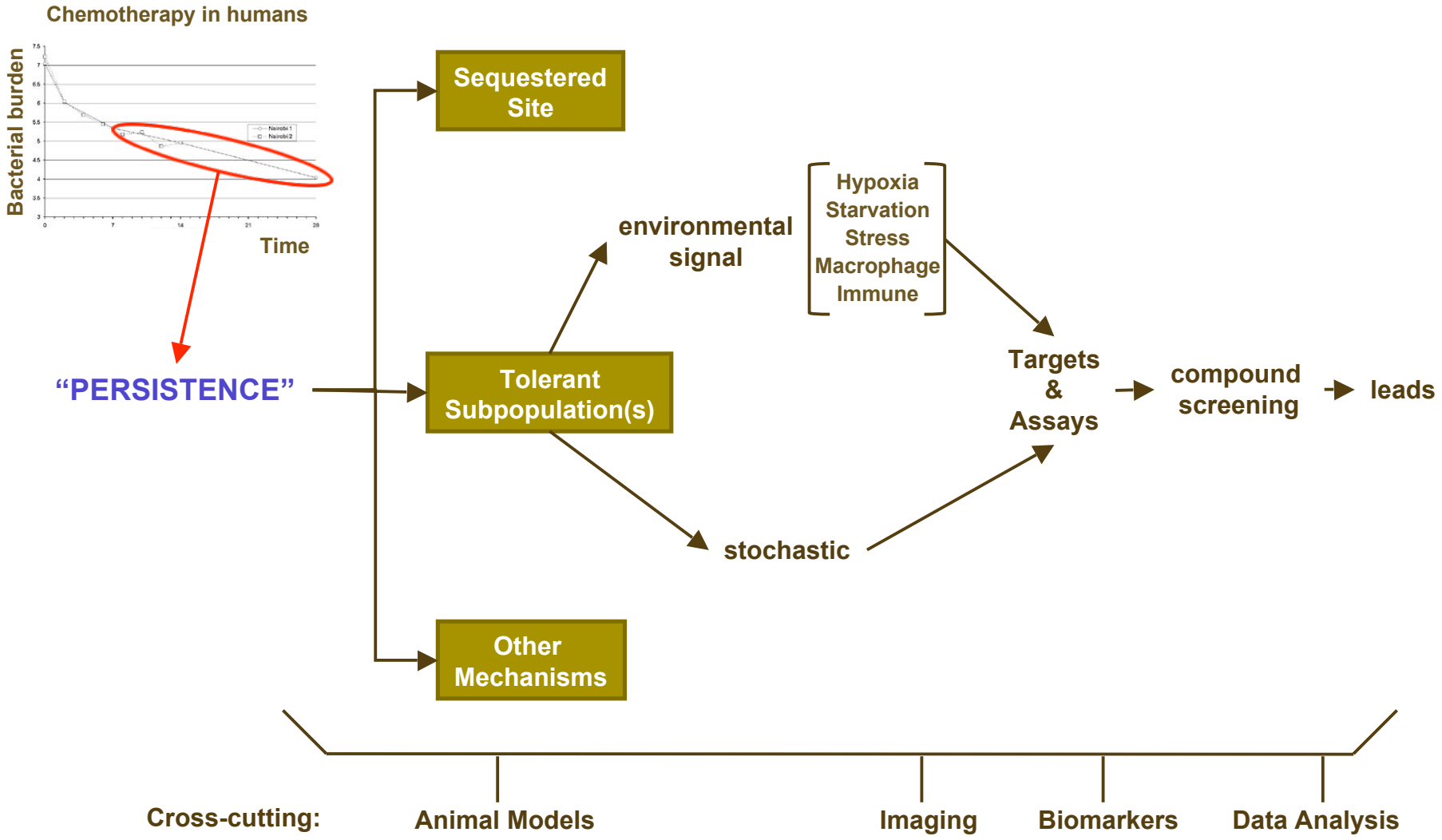
- **No biological understanding**
- **Few well-validated targets**
- **Lack of tools**
- **Poor assays**

Response

- **Develop a path to an ultra-short TB regimen**

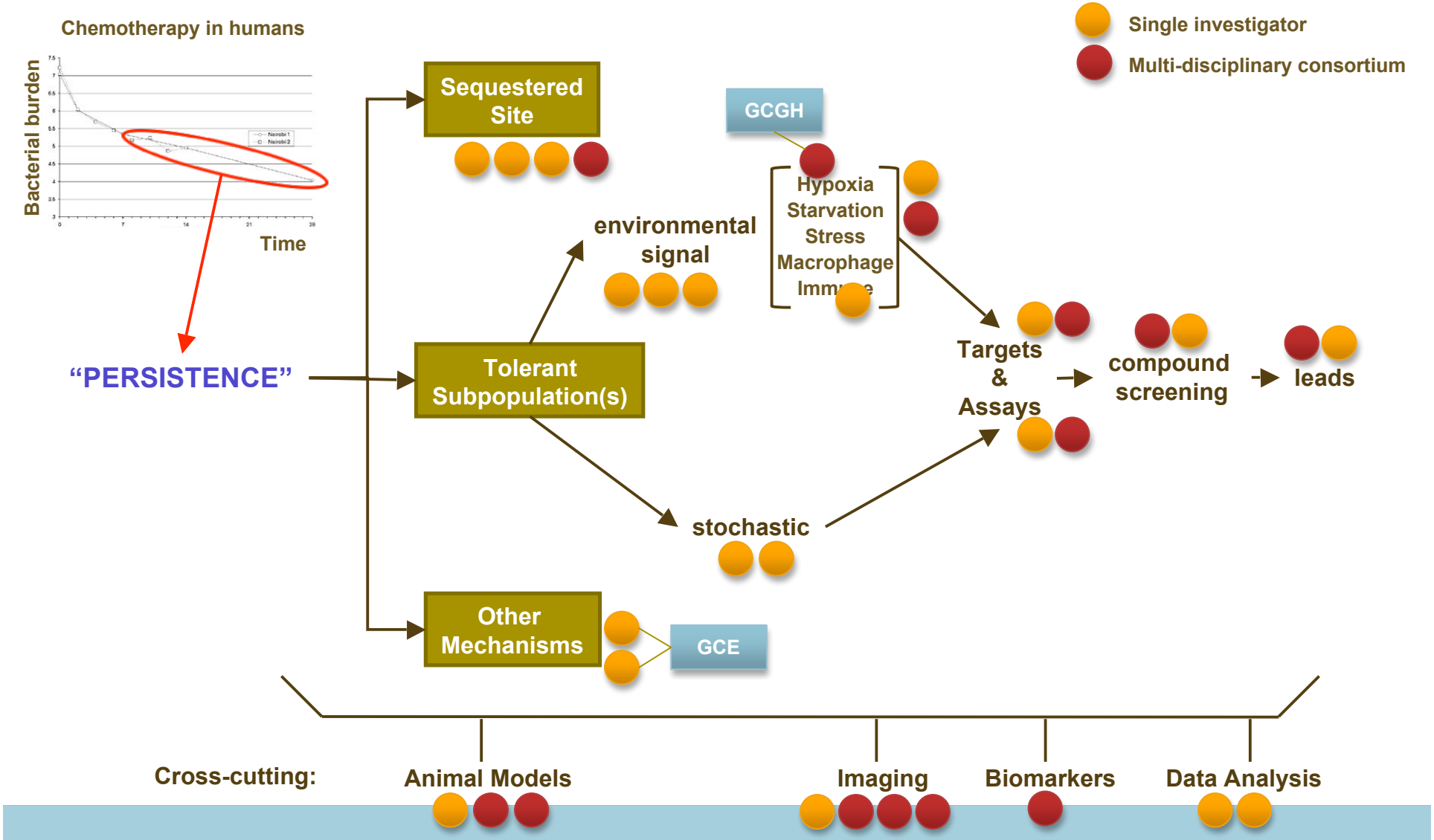
Framework

Develop a strategy for systematically addressing persistence in the face of chemotherapy



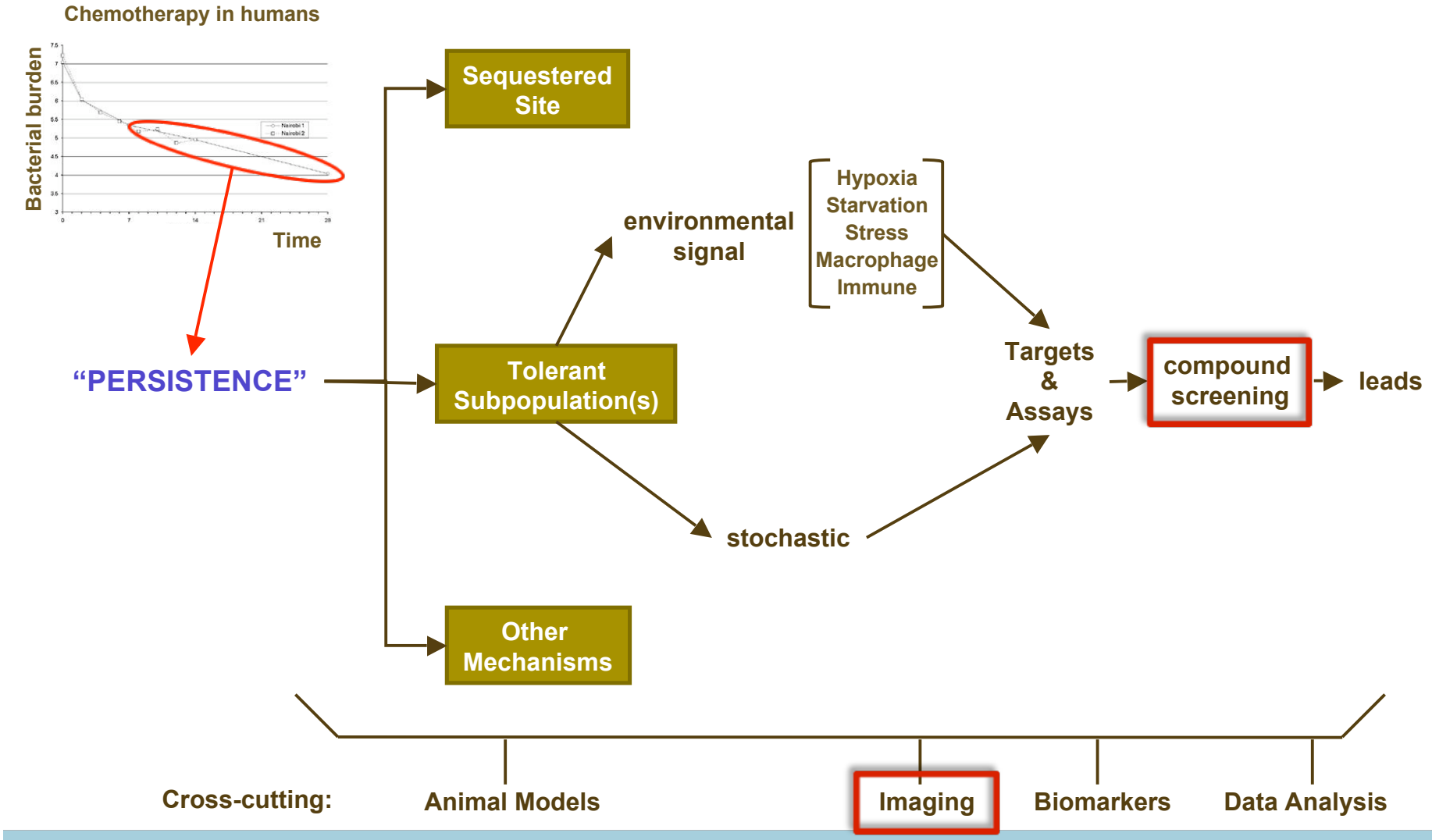
Grantees

A mix of single investigators and multi-disciplinary consortia, all working together



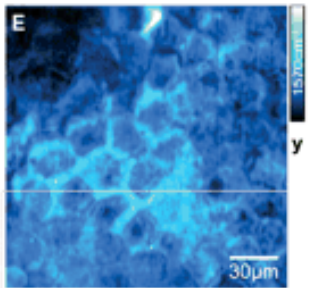
Outputs

Illustrative examples of recent progress

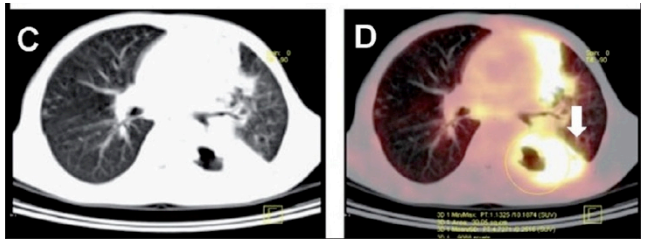


Imaging for TB Drug Discovery

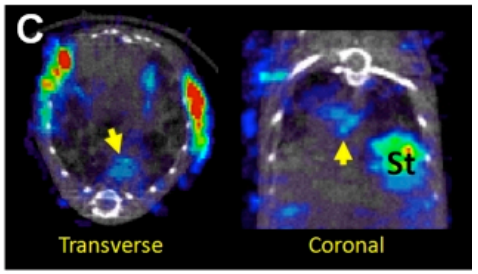
Pre-clinical and clinical imaging technologies being developed



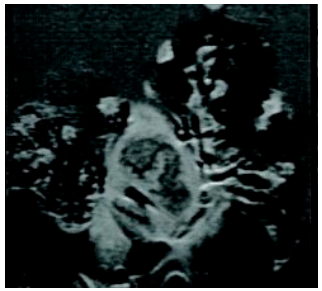
Raman spectroscopy of retinoic acid in tissue



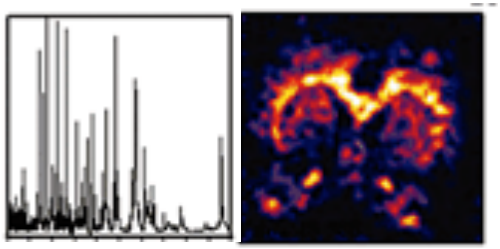
CT/PET imaging of pulmonary TB



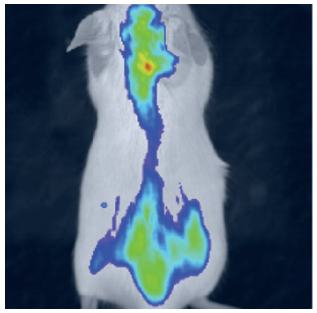
SPECT/CT imaging of TB-infected mice



MRI of infected guinea pigs



Mass spec imaging



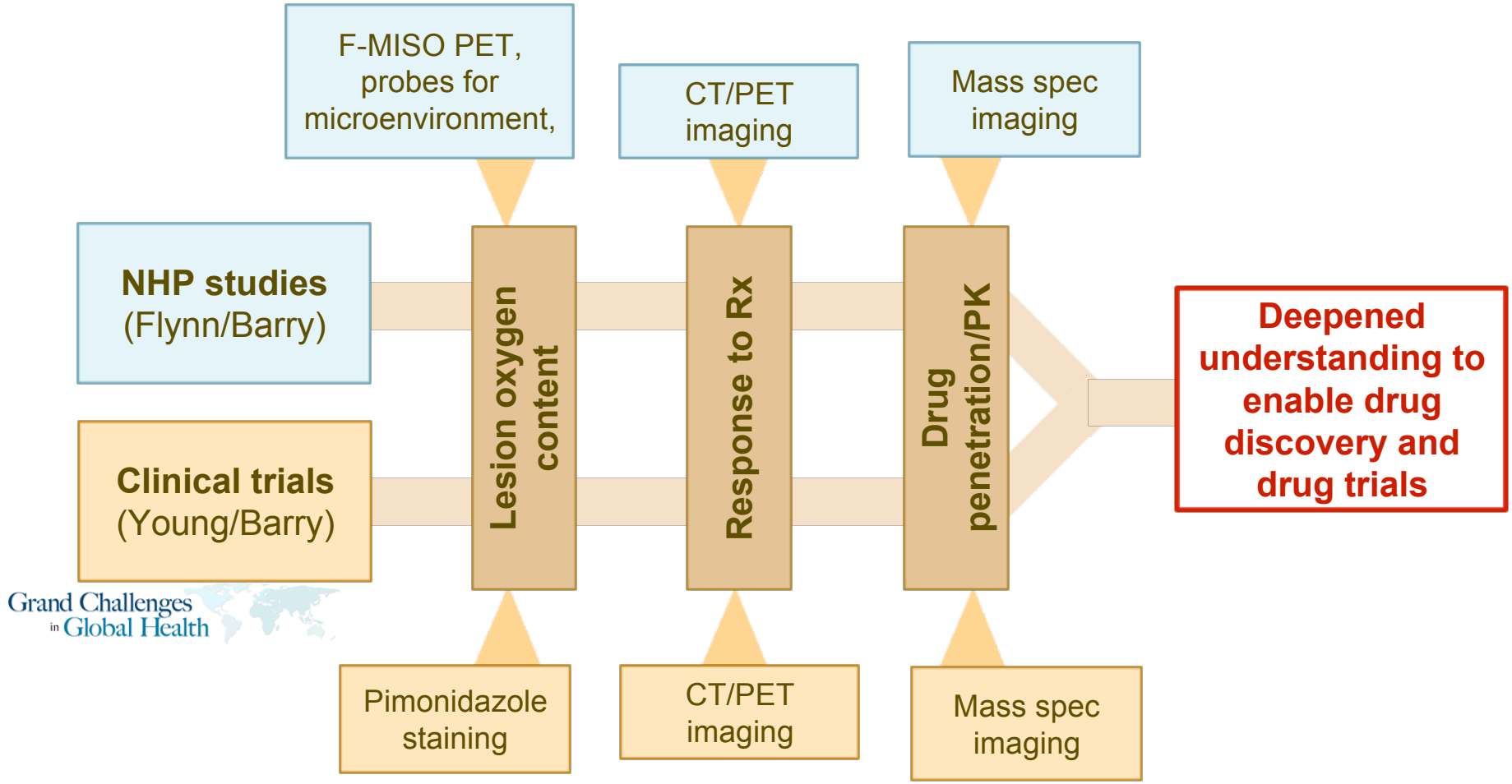
In vivo fluorescent and luminescent imaging

Also: *M. tuberculosis*-specific imaging probes
Bronchoscopic imaging methods

- **Lesion-specific drug response**
- **Drug distribution**
- **Direct visualization of bacteria**
- **Lesion dynamics**
- **Lesion microenvironment**
- **Compare human and animal disease**

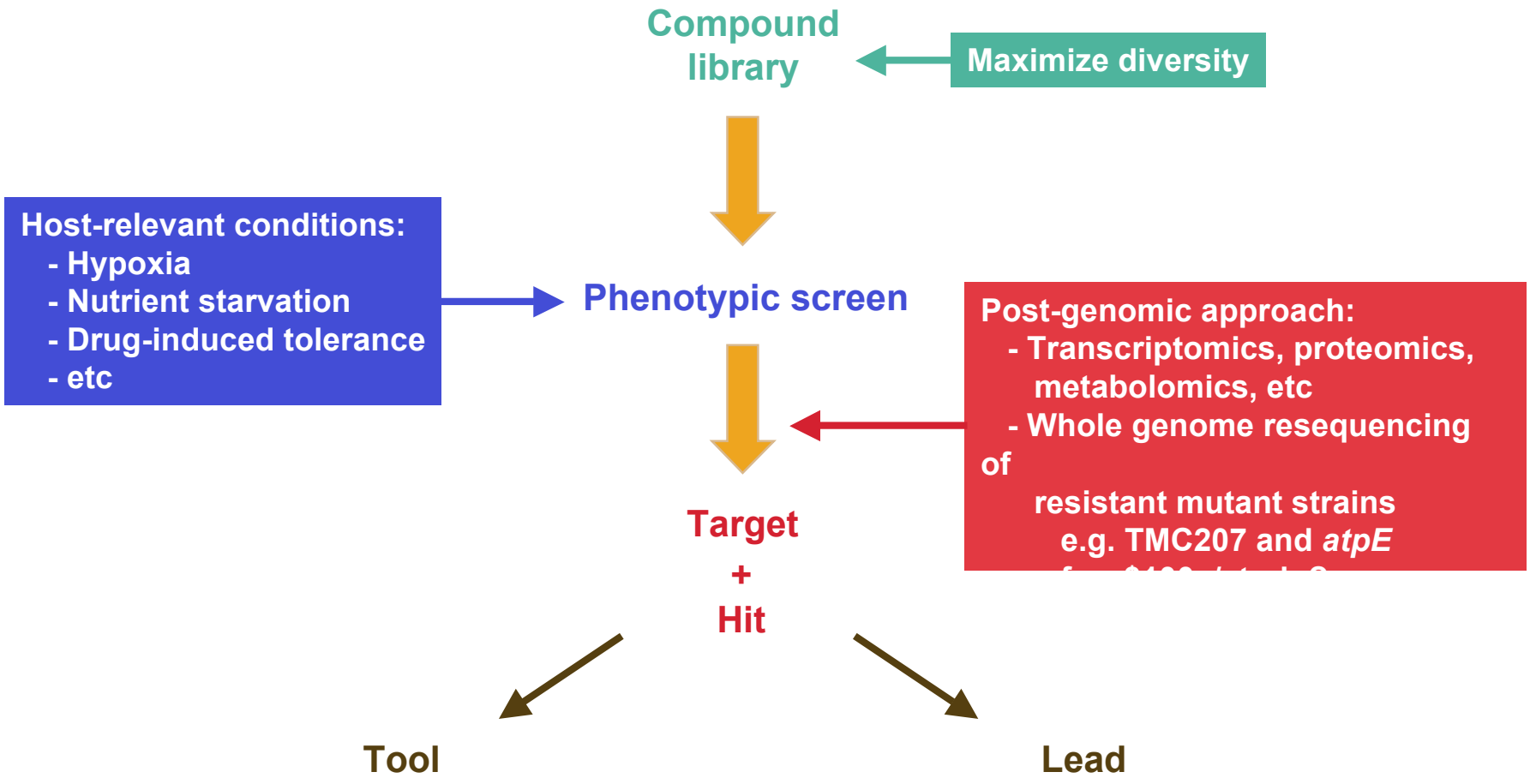
Imaging Studies

Synergy between pre-clinical and clinical imaging studies



Chemical genomics

Targets and leads in one assay



Compound Screening Efforts

Multiple groups engaged from target validation through screening and analysis

Screening & lead identification

- Whole cell screens for *in vivo*-like conditions (hypoxia, carbon starvation, growth on lipids) (Nathan and Sherman)
- Interesting hits emerging from non-replicating persistence screens (Nathan)
- Fragment-based screening (Sherman)

Chemoinformatics

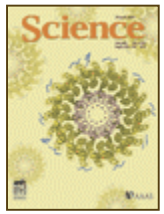
- CDD has engaged multiple screening groups, improving data sharing and screening efficiency

Target identification & validation

- New genetic tools: over- and under-expressing libraries, conditional gene expression (Schnappinger, Sherman)

Evolution of Scientific Communities

Accelerated progress through cooperation and collaboration



A-L Barabási (Science, 29 April 2005)

Isolated nodes: Galileo, Newton, Darwin, Einstein

Small groups: Watson and Crick

Large collaborations: Human Genome Project

Program Outputs

New insight and tools contributing to early stage TB drug discovery

Disease Mechanism
- Metabolism of M.tb within the granuloma
- Contribution of the immune system

Functional Genomics
- Interactome map
- Genes associated with adaptation to persistent cells

Whole-cell/Phenotypic
- Robust, well-validated whole-cell phenotypic screens with SOPs
- Novel target-specific whole-cells screens

Models
- Standardization of in vitro and in vivo models

Imaging
- Imaging tools for pre-clinical development
- Drug penetration

Animal models
- Assessment of the relevance of specific animal models
- Defined Lead PD

Genetic
- New genetics tools for rapid, comprehensive target validation
- List of validated targets

Chemical
- Chemical validation of drug targets

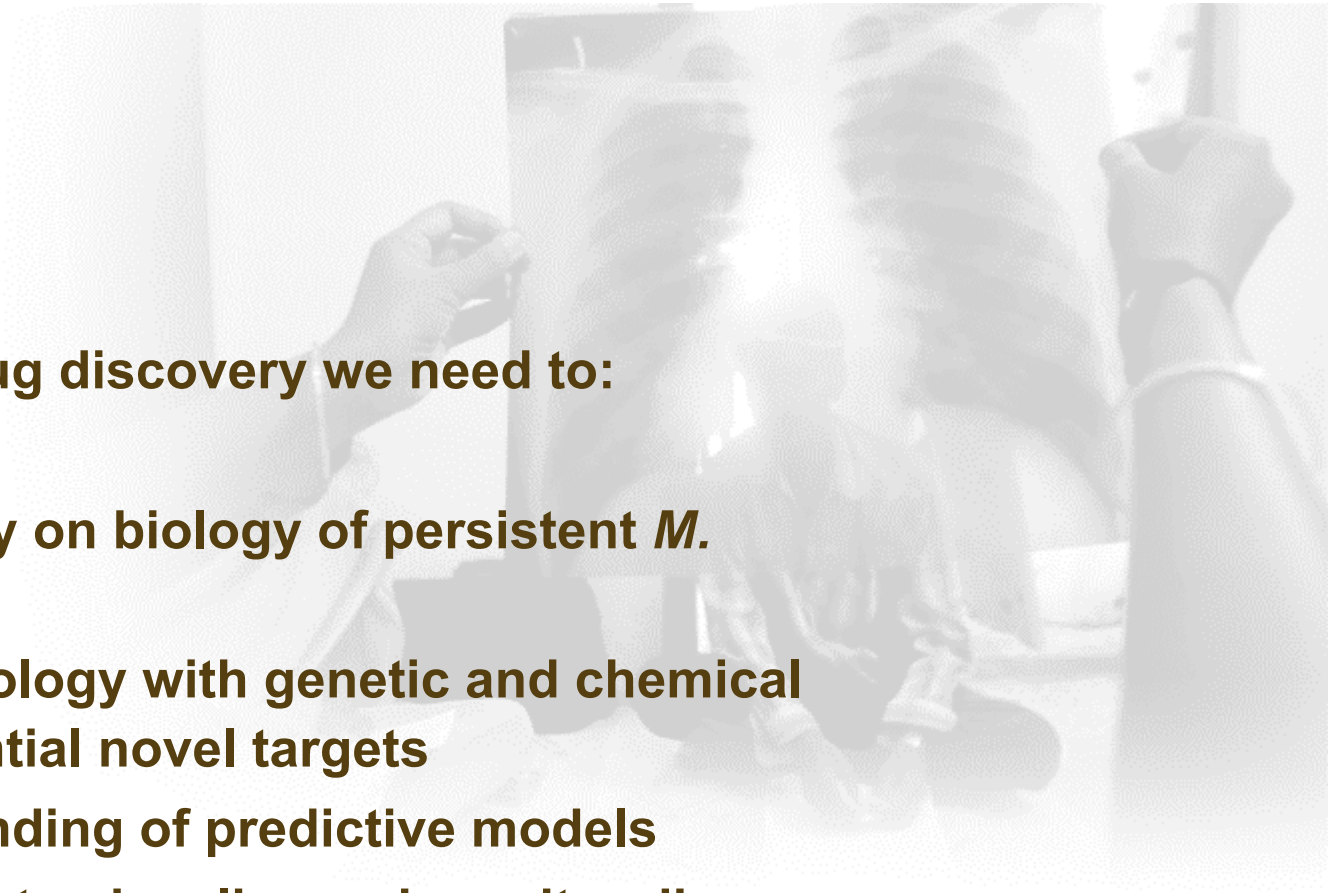
Primary screening
- Screening against diverse compound library

Mechanism of action
- Suite of tools for target identification

Computational/structure-based
- Fragment-based screening

Data analysis
- Database of TB-active compounds
- Data-sharing environment

Summary



To accelerate TB drug discovery we need to:

- **Gain greater clarity on biology of persistent *M. tuberculosis***
- **Exploit the new biology with genetic and chemical validation of potential novel targets**
- **Improve understanding of predictive models**
- **Develop new tools to visualize and monitor disease progression in real time**
- **Co-ordinate and co-operate**

Grand Challenges | Explorations

Because more innovation is needed

- **Recognition that great ideas can come from anywhere**
- **Low burden of entry**
- **Focus on engaging new scientists, new geographies**
- **Champion, not consensus review**
- **Low risk, high reward**

Grand Challenges | Explorations

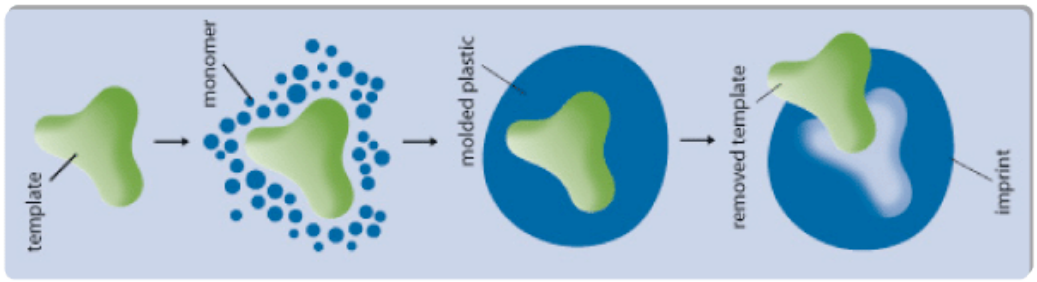
Great response to date

- **Nearly 10,000 applications from scientists in 100+ countries**

- **186 grants ($18.6 M) awarded in 28 countries**
- **Topics and awards announced 2x year**

Grand Challenges | Explorations

Virus Sponge

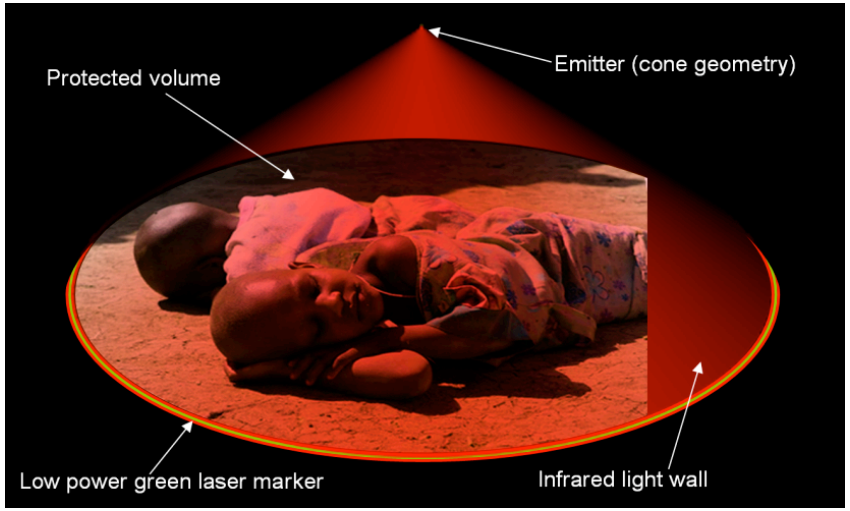


Idea:

- **Molecular imprinting technology, used in chemical industry**
- **Create nanoparticles to "soak-up" circulating virus, rendering them harmless**

Grand Challenges | Explorations

Invisible Mosquito Net

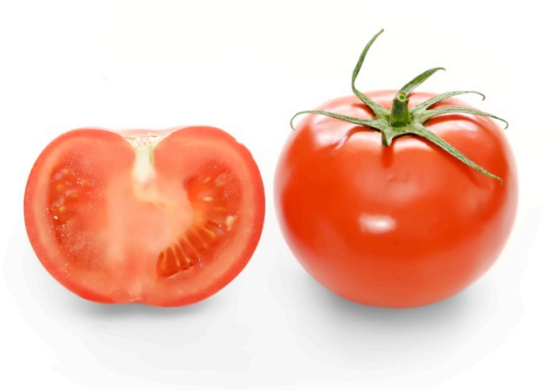


Idea:

- **Mosquitoes use light for short distance range-finding**
- **They may be sensitive to light waves outside of range of human vision**

Grand Challenges | Explorations

An anti-viral Tomato



Idea:

- **Edible foods, containing anti-virals, could provide for more efficient delivery of new medicines**
- **Grow tomatoes that produce compounds which kill virus, but don't damage tomato or people**

Do you have an idea for global health?

- **Round Four open through November 2, 2009**
- **www.grandchallenges.org**