

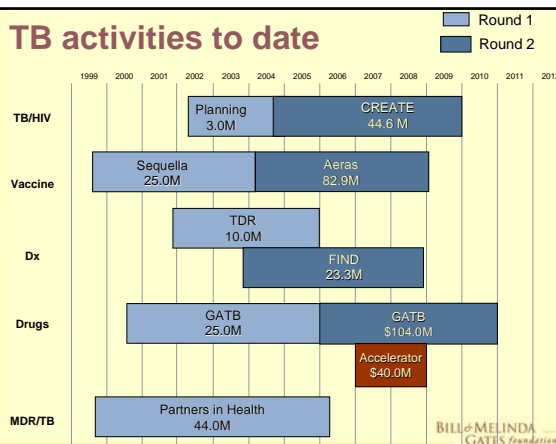
Accelerating TB Drug Discovery

Ken Duncan

MSF Symposium, New York
January, 2007

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TB activities to date



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The challenge

“Today, we have tuberculosis drugs you have to take for 9 months. Why can’t we find one that works in 3 days?”

Bill Gates, 2005 World Health Assembly

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TB drug pipeline

Issues

- Few new chemical entities
- No depth
- Insufficient activity at early stages to fuel pipeline
- No focus on “persistence”

TMC207

- Discovery: whole-cell screen (*M. smegmatis*)
- Pre-clinical data: potential for two month therapy?
- Can we rely on **serendipity** to provide new treatment-shortening drugs in the future?

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What needs to be done?

- Decrease the uncertainty about the biology of persistence to permit rational drug discovery
- Establish a framework for coordinating drug discovery efforts

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Strategic plan for TB drugs



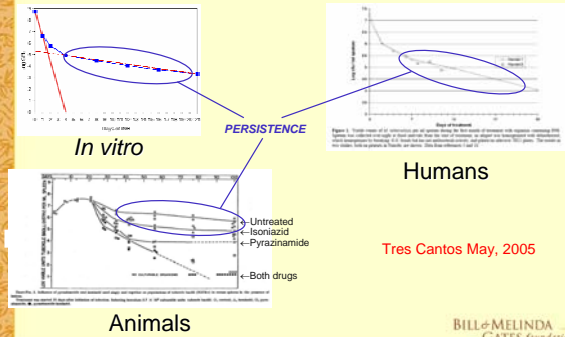
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TB Drug Accelerator: Consultation

- Academic community
- Meetings with Pharma, Biotech
- Focused meetings
 - Academics, drug developers, scientists from other fields
 - "Biology of TB persistence" co-sponsored by GlaxoSmithKline
 - "Biology to drugs" co-sponsored by Novartis
 - "Vetting a plan" co-sponsored by AstraZeneca
- "Request for Comments on a Major Activity"
 - Strategy made available on Foundation web site

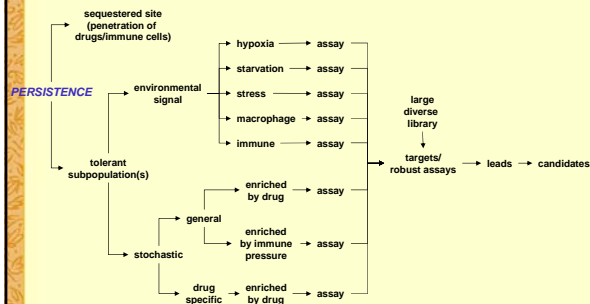
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A common theme - biphasic kinetics of bacterial killing



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A pathway to drug discovery

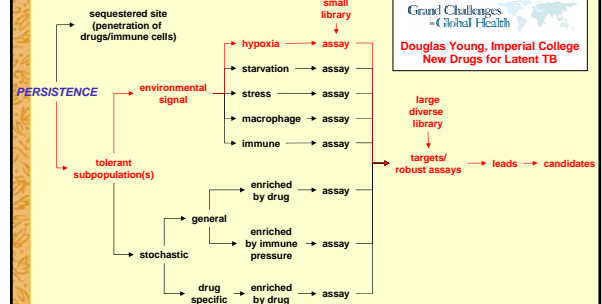


Douglas Young
Tres Cantos May, 2005

Singapore June, 2005

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GCGH provides execution model



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Specific challenges we are facing

- A need to...
1. Reassess what we "know"
 - Action of current drugs
 2. Reduce biological uncertainty
 - Define and characterize the tolerant bacterial sub-population
 3. Ensure adequate drug screening
 - Assays, appropriate libraries, HTS, rational approaches
 4. Create new tools
 - Make it easier to visualize and monitor the disease in real time and *in situ*
 5. Integrate research and drug discovery
 - Link basic research to product development

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Evolution of scientific communities



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Grand Challenges + Global Health
Grand Challenge #11: Create therapies that can cure latent infection

Drugs for treatment of Latent Tuberculosis Infection

Douglas Young, Imperial College London
jointly funded by:

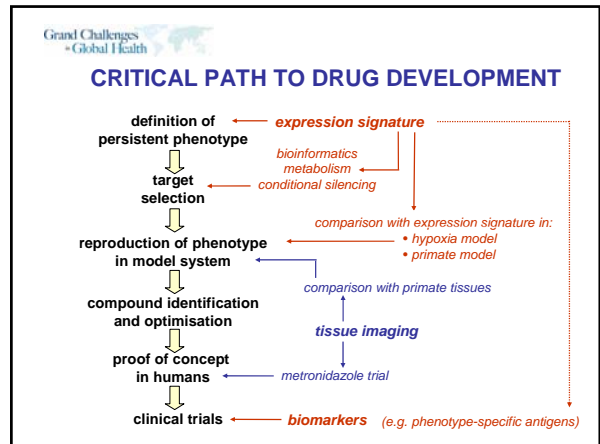
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Hypoxia hypothesis

Histology of "closed" lesions in human tissues suggests a hypoxic environment

Adaptation of *M. tuberculosis* to hypoxic conditions in vitro leads to:

- transcriptional response regulated by two-component signalling
- non-replicating phenotype
- tolerance to front-line TB drugs
- susceptibility to metronidazole



Grand Challenges + Global Health

OUTPUTS

- direct data on *M. tuberculosis* in human tissues
- test of the hypoxia hypothesis
- validation of experimental models
- preclinical development compound active against persistent phenotype



Accelerator status

Posted Request for Proposals

1,387 downloads
128 Letters of Inquiry

Reassess what we "know"	MA1: Fellowship program MA2: PK/PD studies MA3: Drug penetration and sequestration of organisms
Reduce biological uncertainty	MA4: Environmental signals MA5: Stochastic behaviour MA6: Immune pressure MA7: Animal models
Ensure adequate screening	MA8: Genetic methods for target validation MA9: Assay standardisation MA10: Chemical genomics MA11: Lead identification MA12: Data analysis
Create new tools	MA13: Imaging techniques MA14: Biomarkers

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Accelerator status

Posted Request for Proposals

32 Full Proposals
12 Award negotiations

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Accelerator status

Posted Request for Proposals

26 Letters of Inquiry
↓
8 Full Proposals 2Q07

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Looking forward two years

- ✦ Critical milestones related to "proof of principle"
- ✦ Generate data that will inform future investment focused effort on critical questions
- ✦ Build partnerships
- ✦ Link research to product development

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Summary

What we need...

- ✦ A sustainable drug pipeline
 - More candidates
 - Attacking a number of mechanisms
- ✦ New drug combinations
 - Existing agents and approaches: two months
- ✦ New biology: Uncover novel mechanisms
 - An ultra-short regimen: two weeks
- ✦ A new way of working together

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