



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Development of New TB Drugs



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16th Symposium Tuberculose de Muenchenwiler
22 mars 2007



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Outline of this Presentation

- TB treatment: past & present
- Role of the TB Alliance
- New TB drug pipeline



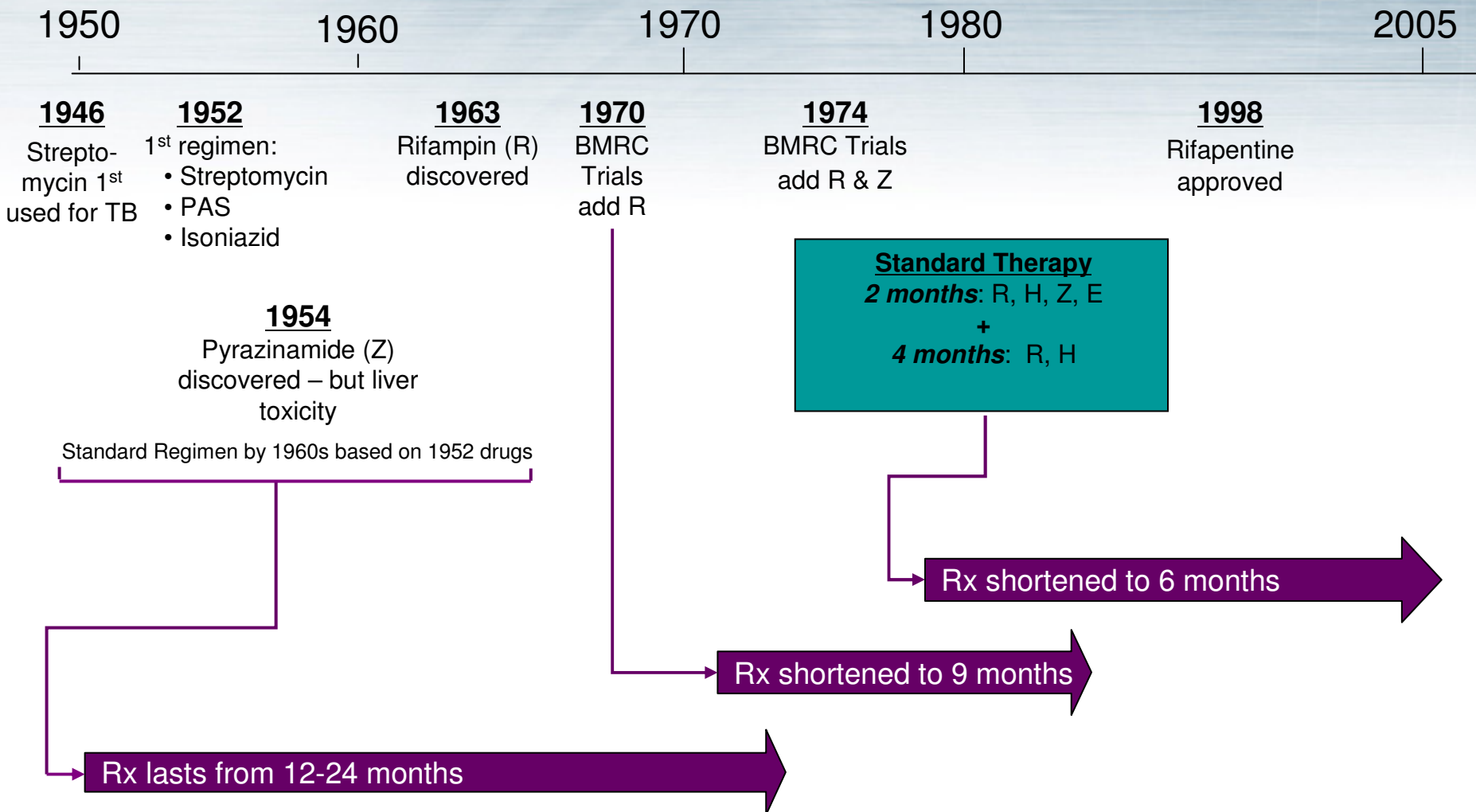
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Developing a faster TB cure.





TB Treatment Evolution





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The Global Alliance for TB Drug Development (The TB Alliance)

- International Public-Private Partnership (PPP)
- Independent, not-for-profit organization
- Based in New York, Brussels and Pretoria
- Entrepreneurial, virtual R&D approach
 - Out-source R&D to public or private partners

The TB Alliance

Mission

- Develop new, better drugs for TB
- Ensure **a**ffordability, **a**ccess and **a**doption (AAA)
- Coordinate and catalyze TB drug development activities worldwide



Affordability, Access and Adoption (AAA)

- Develop cost effective, **affordable** new anti-tuberculosis drugs in a way that is consistent with equitable access for all those who need them most
- Ensure equitable **access** of new TB treatments especially for patients in high-burden countries.
- Working closely with communities, governments and National TB Programme coordinators to ensure the future drugs will be **adopted** into TB Programmes



Developing Leads

- Two-Pronged Strategy
 - Existing Compounds, Analogs, Derivatives
 - Novel Families or Classes
- Worldwide Sourcing
 - Companies, Academia, Compound Libraries, Natural Products
- Obtaining Rights
 - Licensing, Purchase, Donations, Co-development, Co-Investment, etc.



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TB Alliance Priorities

Based on impact and feasibility

- 1. Active disease**
- 2. TB/HIV co-infection/ MDR-TB**
- 3. Latent infection (LTBI)**



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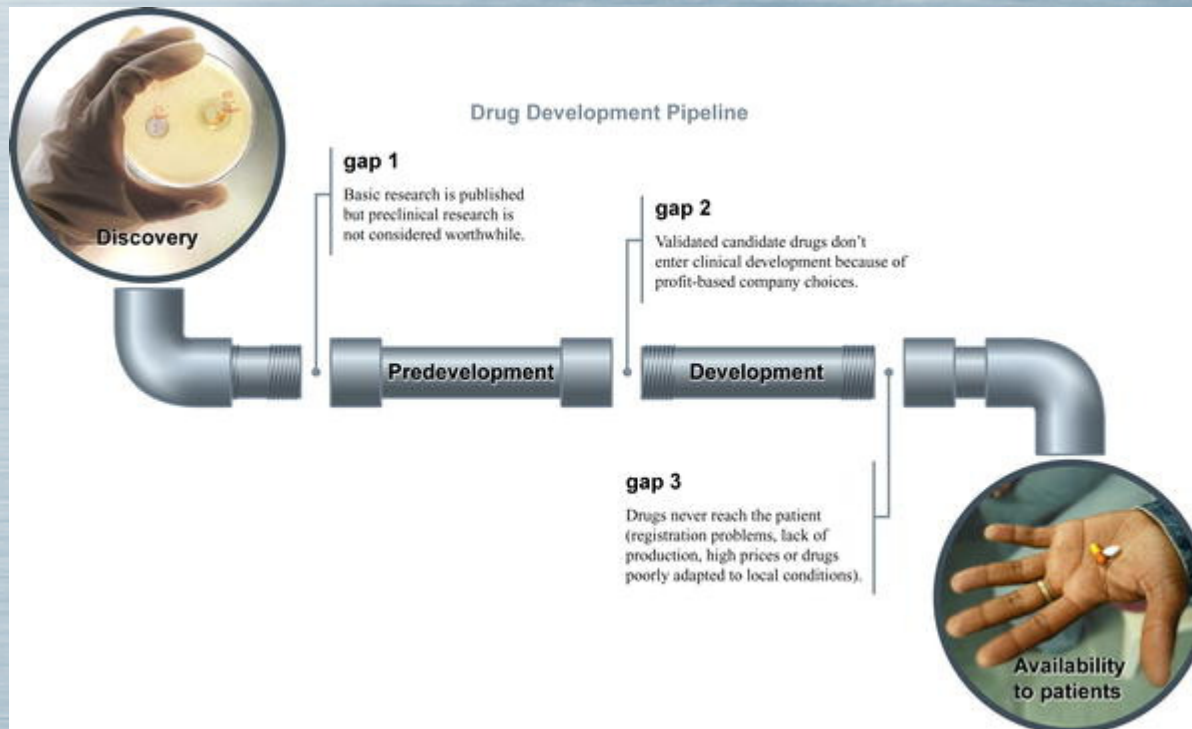
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The Pipeline



Translational Basic Research

Basic research for late
Imperial College London

New targets
University of Pennsylvania

Discovery

Bacterial Topoisomera
GlaxoSmithKline, TB Alliance

Discovery for Latent In
Imperial College London

Identification of comp
tuberculosis in animal

Multi-Functional Molec
Cumbre, TB Alliance

Nitrofuranylamides
NIAID, University of Ten

Novartis Portfolio
Novartis

Proteasome Inhibitors
Cornell University

Riminophenazines
Institute of Materia Medi

Thiolactomycin Analog
NIAID, NIH

Preclinical

Dipiperidine SQ-609
Sequella Inc.

Improved Oxazolidino
Pfizer, Inc.

Clinical

Diamine SQ-109
Sequella Inc.

Gatifloxacin
DMID/NIAID/NIH, Case

Metronidazole for Late
Imperial College London, BMGF/Wellcome Trust

Nitroimidazole PA-824
TB Alliance

SV07 Immune Modulator
SciClone Pharmaceuticals

Identification of gene and biochemical pathway essential for

pantothenate

inhibitors

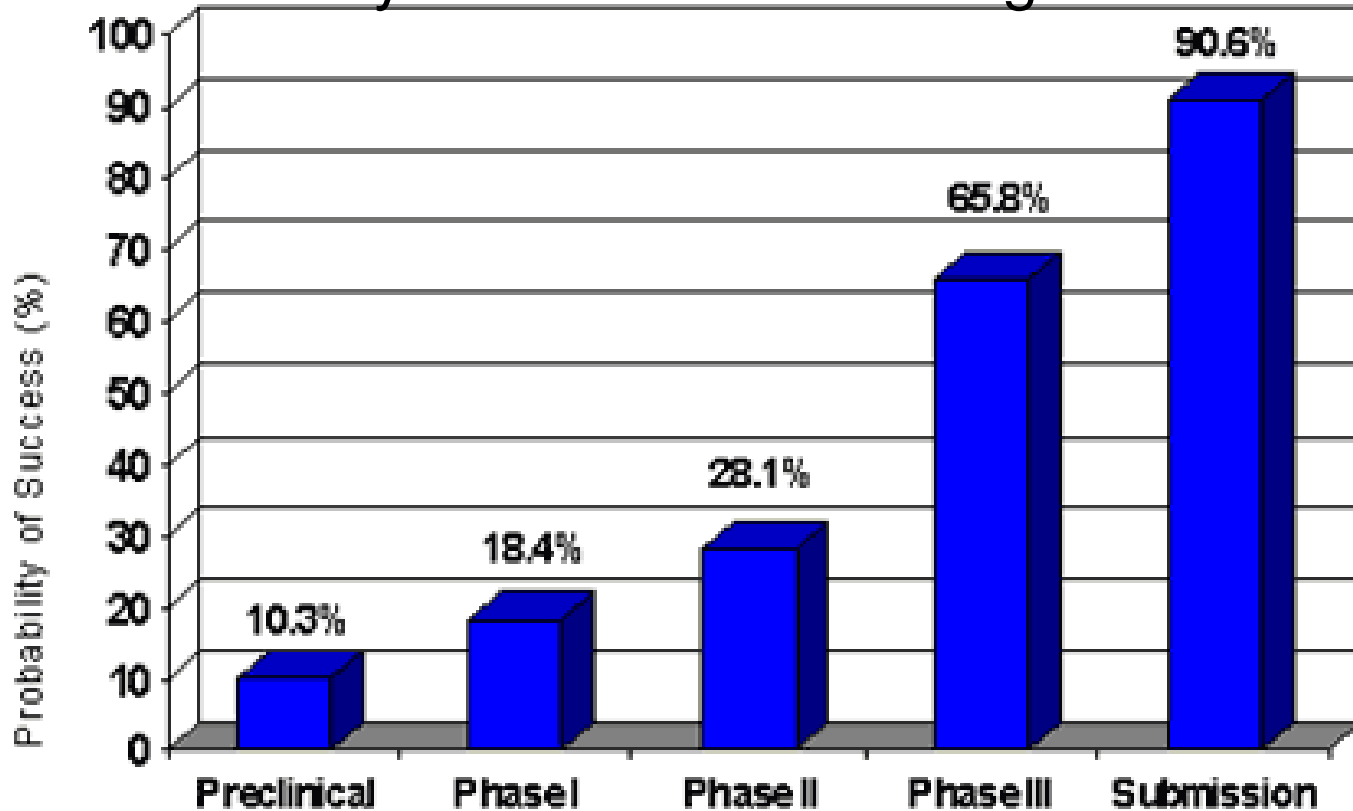
the growth of *M.*

Texas A&M

of Illinois

TBRU, Tuberculosis

Probability of Success for a Drug Candidate



Source: The Pharmaceutical R&D Companion
CMR: International/Scrip's Guide to Trends in R&D 2000

Bayer Pharmaceuticals, CDC TBTC, Johns Hopkins University,
NIAID TBRU, TB Alliance

DMID/NIAID/NIH, Case Western

Nitrodihydro-imidazooxazole Derivative
OPC-67683
Otsuka Pharmaceutical Co.

Pyrrrole LL-3858 (Sudoterb)
Lupin Limited



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Global Clinical Development Pipeline Registration Programs

Compound	Development Stage	Sponsor / Coordinator
Gatifloxacin	Phase III	EC / OFLOTUB Consortium; IRD*; WHO TDR ^o ; Lupin Ltd.
→ Moxifloxacin	Phase II / III	Bayer; TB Alliance; CDC/TBTC [♦] ; University College of London; Johns Hopkins University
TMC 207	Phase II	Johnson & Johnson (Tibotec)
OPC-67683	Early Bactericidal Activity	Otsuka Pharmaceutical Co., Ltd.
→ PA-824	Phase I / IIa	TB Alliance
LL-3858	Phase I	Lupin Ltd.
SQ-109	Phase I	Sequella Inc.

* Institut de Recherche pour le Developement

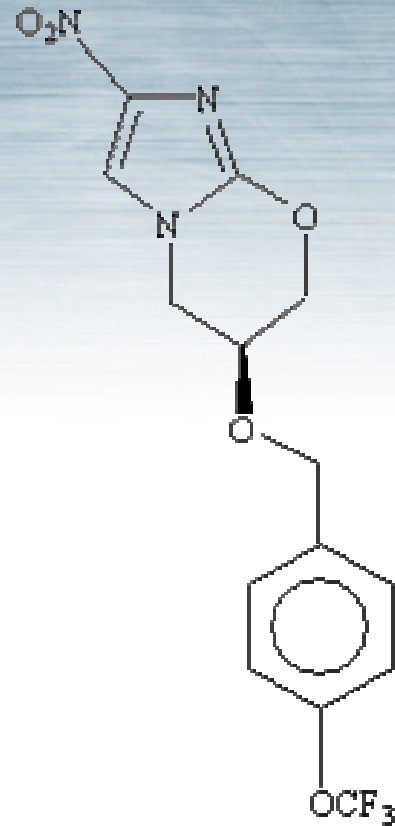
^o World Health Organization, Tropical Disease Research

[♦] Centers for Disease Control and Prevention/ TB Trial Consortium



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PA-824

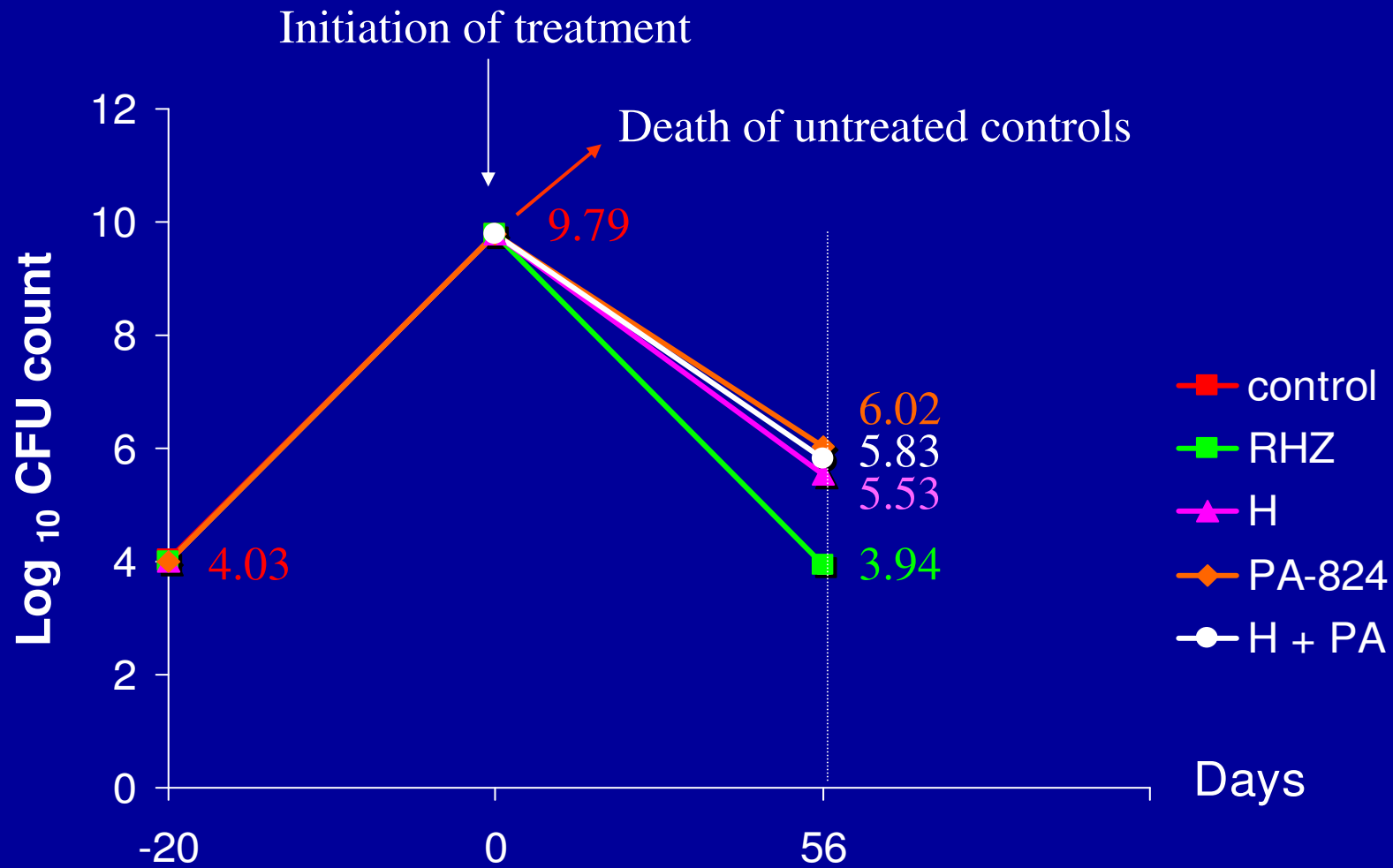




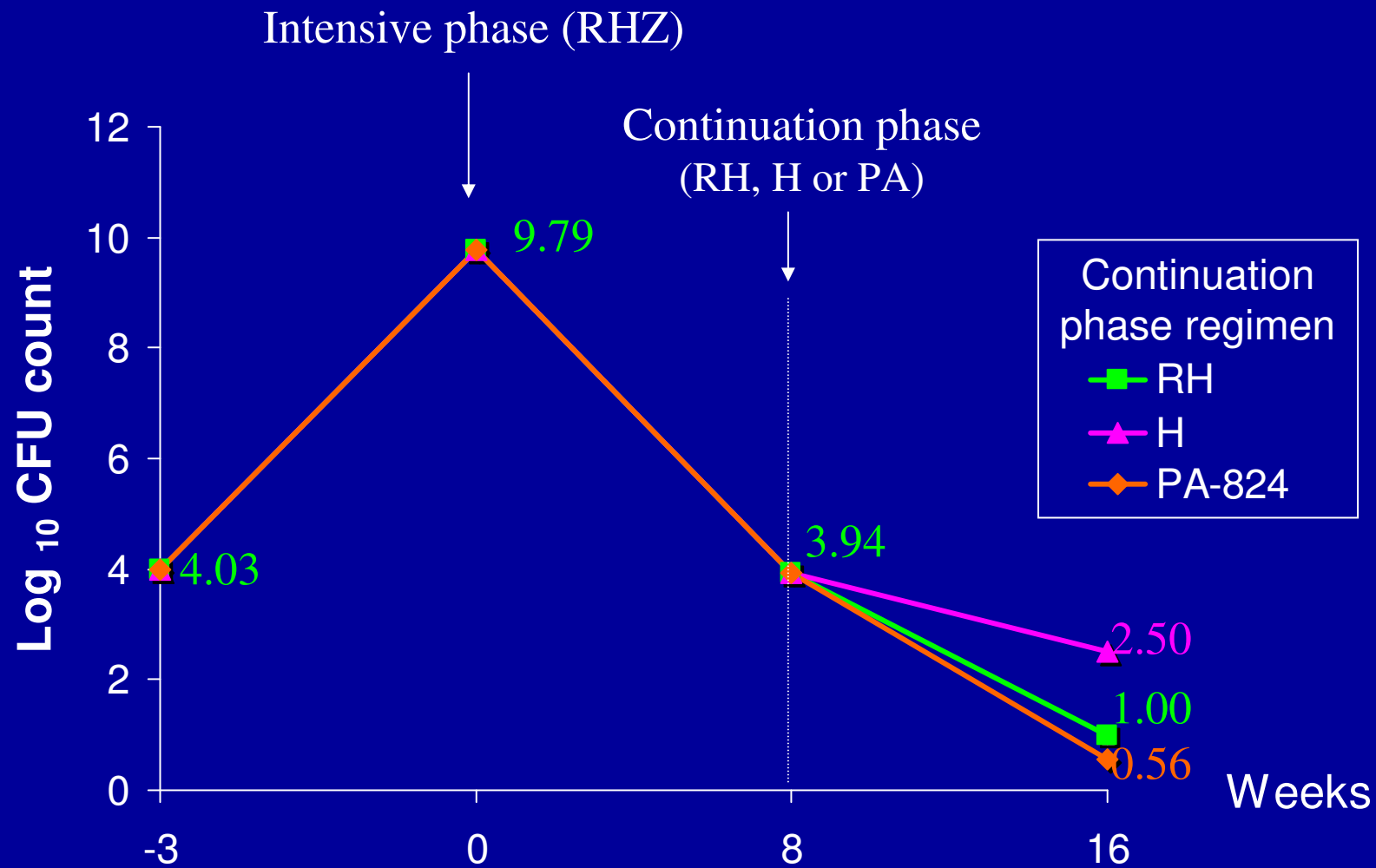
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Rationale for Developing PA-824

- Potent bactericidal activity against replicating and static *M. tb* – *potential for shortening therapy*
- Novel mechanism of action
- Active against drug sensitive and multi-drug resistant (MDR) strains of *M. tb*
- Narrow spectrum of activity



CFU counts in the lungs of mice treated with PA-824 alone or in combination



CFU counts in the lungs of mice treated with PA-824 in the continuation phase



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PA-824 Phase I - Synopsis

Study	CL-001	CL-002	CL-004	CL-005
Design				
Doses				
Population (N)				
Site				
Main Results				



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PA-824 : the next steps

- Food Interaction Study – ongoing
- Extended EBA Study – FPI July 07 (T)
- Drug Interaction Study
- QT Study
- Phase II efficacy trials



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Moxifloxacin



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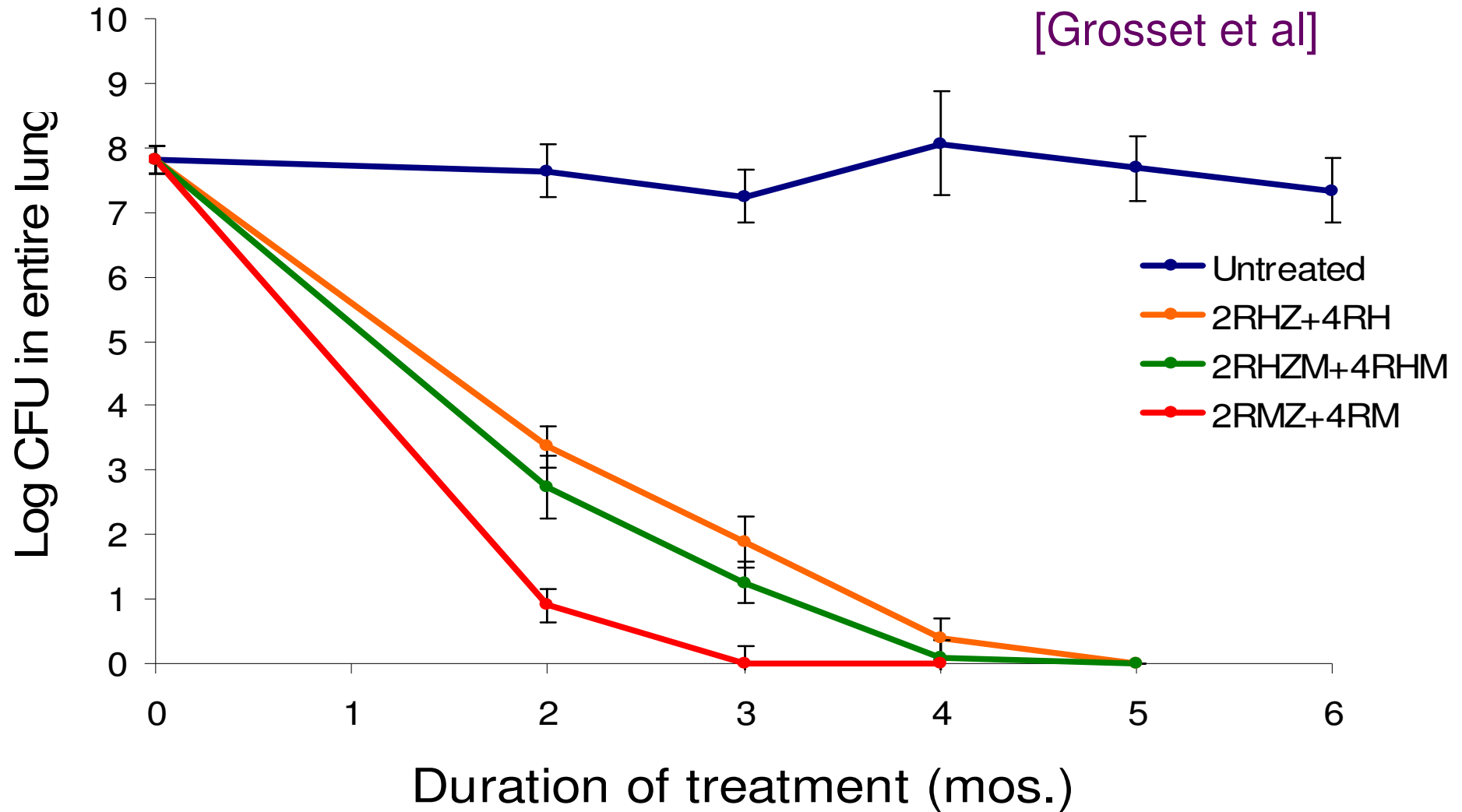
Moxifloxacin

Scientific Rationale

- Fluoroquinolone antibiotic with significant potency against *M. tuberculosis*
- Preclinical data: MRZ-based regimen could potentially shorten therapy to 4 months or less
- Chennai data: fluoroquinolones (ofloxacin) could potentially shorten therapy to 3 months or less
- Novel mechanism of action for TB
- Excellent safety record in humans (>40 million uses)

M = moxifloxacin; R = rifampin; Z = pyrazinamide

Activity of Moxifloxacin in Combination Therapy



M = moxifloxacin; R = rifampin; H = isoniazid; Z = pyrazinamide



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A Novel Development Partnership: Bayer – TB Alliance

- TB Alliance and Bayer signed contract August 2005
- Agreement to conduct joint program for the clinical development and registration of moxifloxacin in TB
 - Other parties (TBTC/CDC, JHU, UCL, BMRC) agreed to coordinated effort under TB Alliance/Bayer umbrella
 - Issue of affordability addressed



Overview of Clinical Development Plan - Initial Studies

Trial (sponsor)	Study Design	Countries	Total # subjects	Status
TBTC #27 (CDC)	Moxi replaces Ethambutol (PII)	USA, Canada, Uganda, South Africa	336	Completed 6/05
JHU	Moxi replaces Ethambutol (PII)	Brazil	170	Enrollment completed 3/07
TBTC #28 (CDC)	Moxi replaces Isoniazid (PII)	USA, Canada, Uganda, South Africa, Brazil, Spain	410	Enrollment completed 3/07
REMOx TB (UCL/MRC)	Moxi replaces Isoniazid (PIII) Moxi replaces Ethambutol (PIII)	Tanzania, South Africa, Zambia, Kenya	1500	Trial initiation planned for 1Q07



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Moxifloxacin *Future Plans*

- Complete Phase II and III clinical evaluation for M for E and M for H based regimens

If data are supportive, ready for filing:

- M for E: 4Q 10
- M for H: 4Q 10



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Clinical Trial Sites – Global Capability Assessments

Dr. Christo van Niekerk a3

Folie 28

a3

No offense to Christo or to ignore his hard work on this project - happy to have you acknowledge his leadership on this verbally, but we do not identify any project with the individuals working on them this way

aginsberg; 07.03.2007



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Global Clinical Trials Capacity

- 7 compounds currently in human testing
- Is global GCP/GLP TB clinical trial capacity sufficient to meet current and future needs?
- No objective assessment available
- Assessment could benefit:
 - sites
 - sponsors of clinical trials
 - resources to build global clinical trial capacity



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Clinical Trial Sites – Assessing and Building Infrastructure

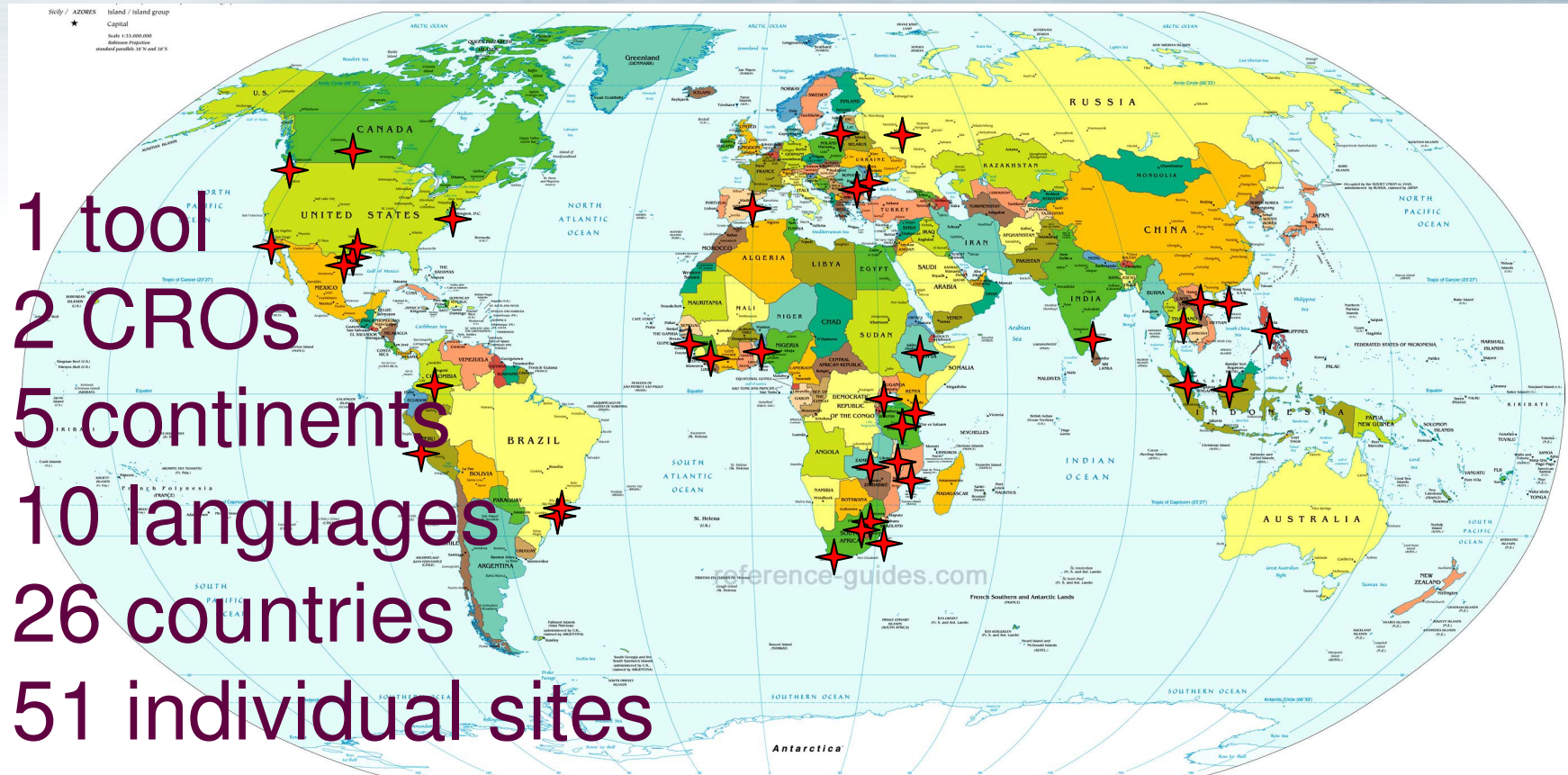
Activities

- 2 CROs hired
 - PPD for S. America
 - Quintiles for Asia, Africa, N. America and Europe
- 2 internationally-recognized *M. tb* lab experts hired to ensure quality of TB lab evaluations
 - Dr. Kathleen Eisenach, Prof. of Pathology and Microbiology and Immunology, University of Arkansas for Medical Sciences, USA
 - Dr Frederick Sirgel, National Tuberculosis Research Programme, MRC, Tygerberg, South Africa



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Sites Assessed



reference-guides.com

CLINICAL SITES: Global Distribution and Time Required to Ready Site for Participation in a Phase III TB Drug Registration Trial

	< 6 months	6 to 12 months	1 to 2 years	>2 years
Africa	11	7	2	0
Asia	1	4	1	0
Latin America	3	3	2	0
North America	7	0	1	0
Europe	1	0	0	0
Former USSR	4	3	1	0
TOTAL	27	17	7	0

LABORATORIES: Global Distribution and Time Required to Ready Lab for Participation in a Phase III TB Drug Registration Trial

	< 6 months	6 to 12 months	1 to 2 years	>2 years
Africa	5	5	6	2
Asia	1	2	1	0
Latin America	3	2	1	0
North America	0	7	0	0
Europe	1	0	0	0
Former USSR	0	0	7	0
TOTAL	10	16	15	2



ABOUT THE ALLIANCE NEED FOR NEW TB DRUGS TB ALLIANCE PROGRAM THE CONTEXT

www.tballiance.org



announces a new

\$104 million grant

from the Bill and Melinda Gates Foundation

[click for more information](#)

- Take Action
- Partner Guidelines
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News & Events

BREAKING NEWS

-TB Alliance Meets with the Indian Minister of Health and Family Welfare

TB ALLIANCE NEWS AND HIGHLIGHTS

-Click here to read the TB Alliance June Newsletter

TB ALLIANCE NEWS AND HIGHLIGHTS

-TB Alliance Announces \$104 Million Gates Foundation Grant

TB ALLIANCE NEWS AND HIGHLIGHTS

-Click Here for Meeting

Portfolio



Slide 30/301

In Depth



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\$104 Million Gates Grant

The TB Alliance has received a generous grant from the Bill and Melinda Gates Foundation. It will advance 11 drug candidates through the pipeline, including two candidates now in clinical trials.





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Accelerating
the development of faster acting and
affordable drug combinations
to fight tuberculosis.

A healthier world is in our reach.





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Thank You !