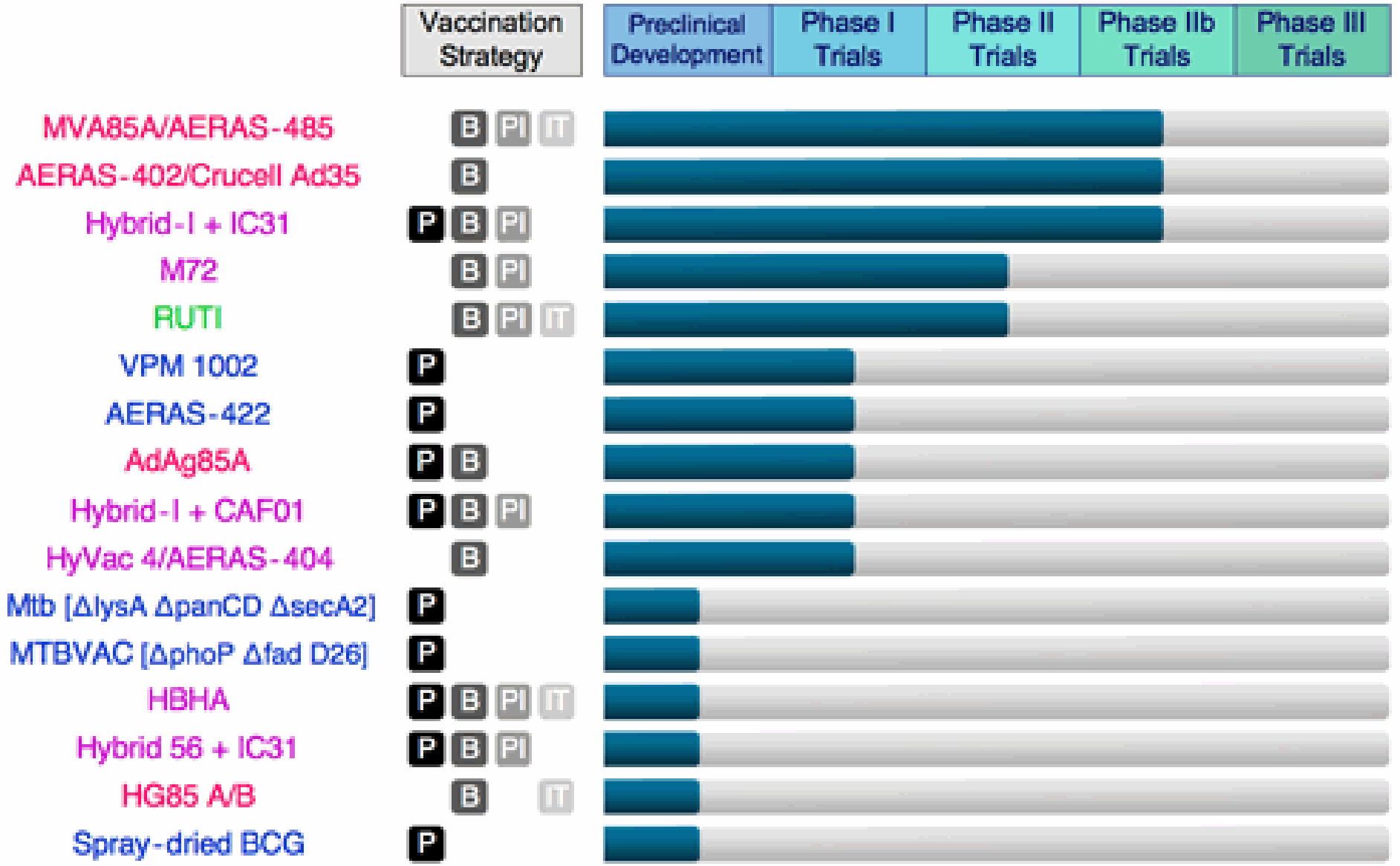
Progress in TB Product Development April 2013

Prasit Palittapongarnpim, M.D.

TB Vaccines



Viral vector vaccines, Recombinant protein vaccines, Inactivated whole cell vaccines, Recombinant live BCG

Immunization Strategies- P: priming vaccine (replace BCG), B: booster vaccine (after P or BCG prime), PI: Post infection booster vaccine, IT: immunotherapy (used in conjunction with drugs)

AERAS Vaccine Portfolio

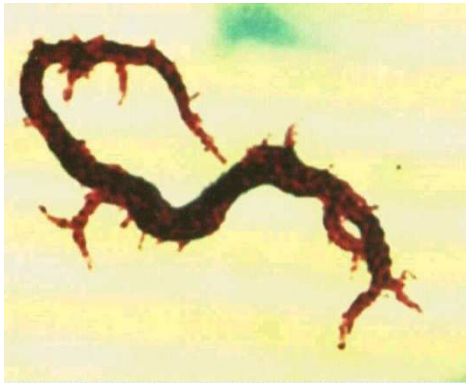
MVA85A/Aeras-485 (Modified Vaccinia Ankara expressing Ag85A)

MVA

- Vaccinia virus passaged >500 times in chicken embryo fibroblasts
- 31 kb deletions (losing host specificity and cytokine induction)
- Not growing in mammalian cells but grow in chicken embryo fibroblasts.
- Used as vaccines for eradication of small pox with excellent safety record.
- Not replicated in immunosuppressed macaques
- MVA-HIV-Nef appear safe in HIV+ve.
- Recombinant MVA in clinical trials include : HIV, HBV and malaria

Ag85A

- A part of Ag85 complex (A,B and C)
- Mycolyl transferases
- Immunodominant major secretory proteins
- Confer some protection in animals
- Relating to cord formation



MVA85A were shown to stimulate CD4+ and CD8+ T cells as well as protections in animal models

- Mice
  - Ag85A DNA-MVA85A prime-boost regimen
  - BCG-MVA85A prime-boost protocol
- Guinea pigs
  - BCG-MVA85A prime-boost protocol
- Macaques
  - BCG-MVA85A-FP85A for immunological response only

MVA85A Phase I studies (MVA85A $5x10^7$ pfu id.)

- To show safety in
  - Naive population:
    - no BCG history and scar,
    - -ve tuberculin test,
    - -ve ex vivo IFN-γ Elispot assay
    - --ve response to ESAT 6, CFP 10 and PPD.
  - BCG-vaccinated populations- (Scriba et. al. Eur J Immunol 2010;40:279-290)
  - *M. tuberculosis* infected populations - checking for the Koch reaction.

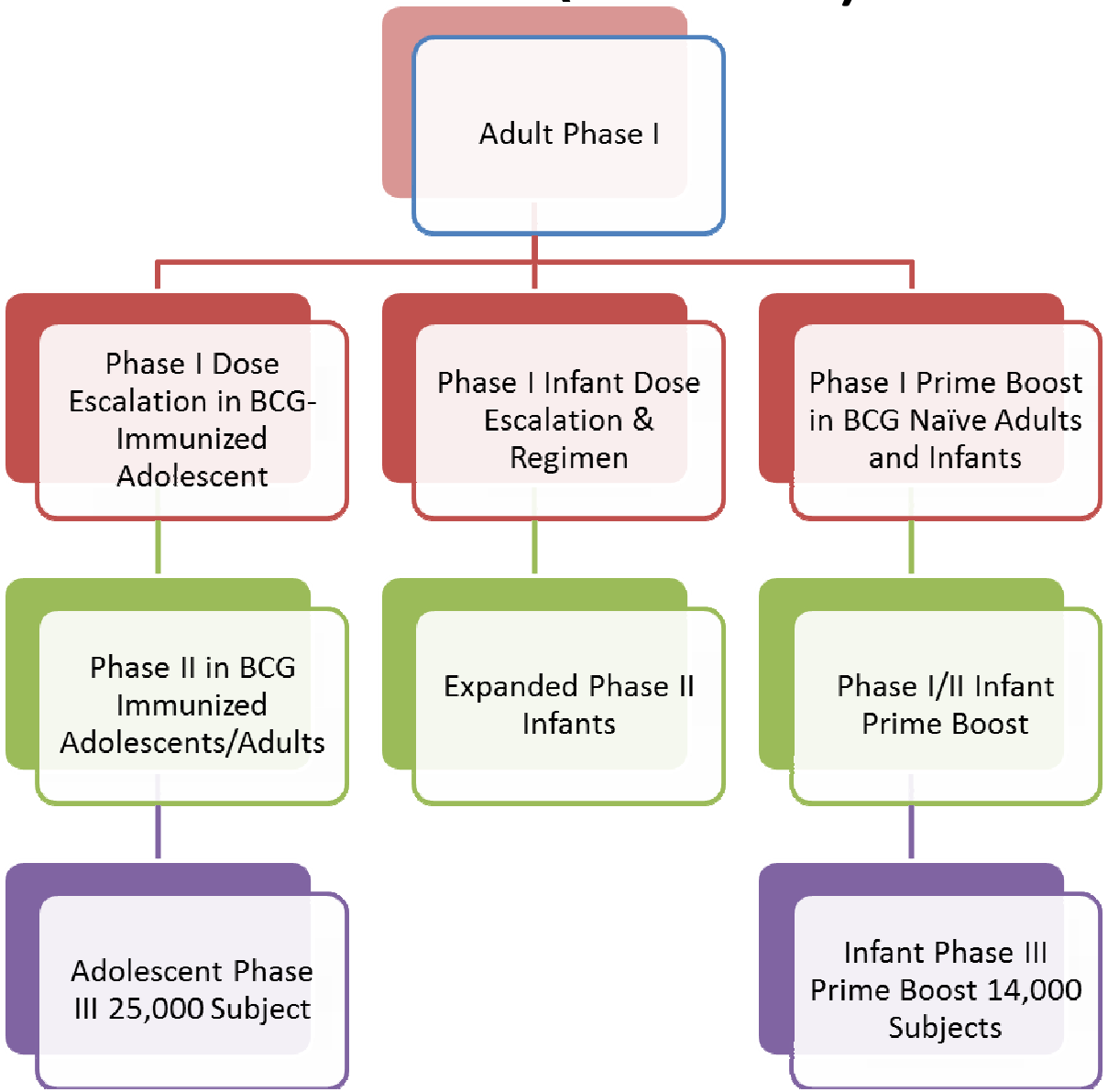
MVA85A/AERAS-485 Phase IIb Proof of Concept Efficacy Trial

- First efficacy trial of a new TB vaccine in infants in more than 80 years (proof of principle)
- 2,800 infants with prior BCG vaccination – 90% power for 60% efficacy compared to BCG
- In collaboration with South African Tuberculosis Vaccine Initiative (SATVI), Oxford-Emergent Tuberculosis Consortium (OETC) and Welcome Trust
- First infant vaccinated 15 July, 2009, by SATVI. The trial ended May 2012.

Lancet 4 Feb 2013

- MVA85A vaccine trial in Cape Western, South Africa, 2797 infants
- Design: Randomized double blind boost vaccine at age 4-6 months for BCG (Denmark strain) vaccinated infants. Control: Candida skin test antigen.
- Protection efficacy for TB = 17% and for M. tuberculosis infection = -3% (both being statistically insignificant). Tolerable side effects.

New TB Vaccines Clinical Trial Protocols (AERAS)



Aeras-402/Crucell Ad35

Adenovirus 35 vector

- Replication deficient (E1-deleted)
- Consistently induce high levels of CD8+ T cell responses
- Efficient manufacturing technology
- Rare serotype in nature

Ag85A-Ag85B-TB10.4 fusion proteins

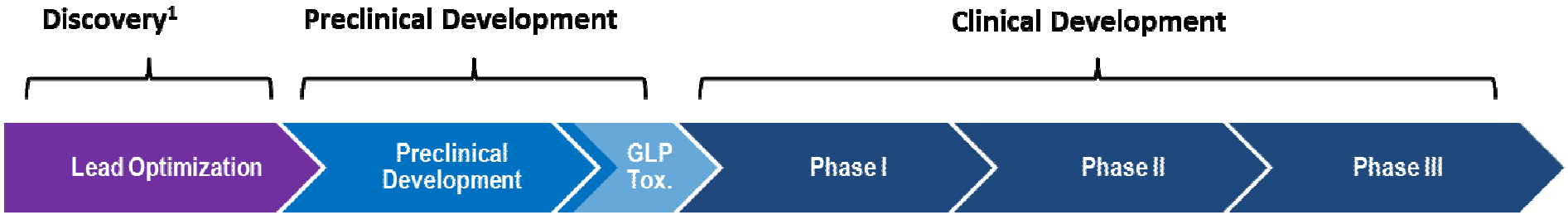
Aeras-402/Crucell Ad35

- Preclinical study
  - Mice (Radosevic et.al. Infect Immun 2007;75:4105-4115.)

Clinical Trials Table
AERAS-402/Crucell Ad35

PROTOCOL NUMBER	DESCRIPTION	LOCATION	STATUS
C-001-402Phase I	Adults, BCG-unvaccinated	USA	Completed
C-003-402Phase I	Adults, BCG-vaccinated	South Africa	Completed
C-008-402Phase I	Adults, BCG unvaccinated Receive BCG Prime	USA	Completed
C-009-402Phase I	Adults, BCG unvaccinated Receive BCG Prime; double-blinded, placebo control	USA	Ongoing
C-010-402Phase II Ongoing	Adults, Previous TB	South Africa	
C-012-402Phase I	Adults, BCG vaccinated	Kenya	Ongoing
C-017-402Phase IIb	Adults, HIV-infected, Latent TB, BCG Vaccinated	South Africa	Ongoing
C-018-402Phase I	Infants, <2 years, BCG vaccinated	South Africa	Ongoing
C-021-402Phase I	Adults, BCG unvaccinated, Receive BCG Prime	USA	Ongoing
C-022-402Phase I	Adults, BCG unvaccinated, Receive BCG Prime	USA	Completed

Global TB Drug Pipeline



Lead Optimization

- Diarylquinolines
- InhA Inhibitors
- LeuRS Inhibitors
- Mycobacterial Gyrase Inhibitors
- Pyrazinamide Analogs
- Riminophenazines
- Ruthenium (II) complexes
- Spectinamides
- Translocase-1 Inhibitors

Preclinical Development

- CPZEN-45
- DC-159a
- Q201
- SPR-10199
- SQ609
- SQ641

GLP Tox.

- BTZ043
- TBA-354

Phase I

- AZD5847
- Bedaquiline (TMC-207)
- Linezolid
- Novel Regimens[2]
- PA-824
- Rifapentine
- SQ-109
- Sutezolid (PNU-100480)

Phase II

- Delamanid (OPC-67683)
- Gatifloxacin
- Moxifloxacin
- Rifapentine

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

[1] Ongoing projects without a lead compound series can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.

[2] Combination regimens: first clinical trial (NC001) of a novel TB drug regimen testing the three drug combination of PA-824, moxifloxacin, and pyrazinamide was initiated November 2010 and completed in 2011 with promising results. The second clinical trial (NC002) of this regimen was launched in March 2012 and will test the efficacy of the regimen in drug-sensitive and multidrug-resistant patients. The third clinical trial (NC003) will evaluate PA-824, TMC-207, pyrazinamide and clofazimine in combinations and is scheduled to begin September 2012.

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org
Updated: November 13, 2012

Global TB Drug Discovery Pipeline [1]

Hit-to-Lead	Lead Optimization
Actinomycete Metabolites (U ILL Chicago, Myongii U)	**Diarylquinoline** (GATB, U Auckland, Janssen)
ATP Synthesis Inhibitors (GATB, Scripps)	**InhA Inhibitor** (GSK, GATB)
DprE Inhibitors (GATB, Scripps)	**LeuRS Inhibitor** (Anacor Pharmaceuticals)
Fungal Metabolites (Mycosynthetix, U ILL Chicago)	**Mycobacterial Gyrase Inhibitors** (GATB, GSK)
Indigoids (U ILL Chicago)	**Pyrazinamide Analogs** (GATB, Yonsei U)
Isoprenoid Biosynthesis Inhibitors (Lilly Ddi)	**Riminophenazines** (GATB, IMM, BRI, U ILL Chicago)
M. tb Energy Metabolism Inhibitors (UPenn, GATB)	**Ruthenium(II)phosphine/picolinate Complexes** (FAPESP/Brazil)
M. tb Protein Kinase Inhibitors (Vertex Pharmaceuticals)	**Spectinamides** (St. Jude, U Tenn, CSU, UZ, Microbiotix)
Malate Synthase Inhibitors (GSK, TAMU, GATB)	**Translocase-1 Inhibitor** (Sequella)
Menaquinone Synthase Inhibitors (CSU, GATB)	
Novel Hit-to-Lead Programs (Lilly DDi)	
Phenotype Hit-to-Lead (AZ; GSK, GATB; Lilly DDi)	

[1] Ongoing projects in clinical development can be viewed at http://www.newtbdrugs.org/pipeline.php

Abbreviations of Developers: **AZ**-AstraZeneca; **BRI**-Beijing Tuberculosis and Thoracic Tumor Research Institute; **CSU**-Colorado State University; **FAPESP**-São Paulo Research Foundation; **GATB**-Global Alliance for TB Drug Development (TB Alliance); **GSK**-GlaxoSmithKline; **IMM**-Institute of Materia Medica; **Lilly DDi**-Lilly TB Drug Discovery Initiative; **RI**-Research Institute; **St. Jude**-St. Jude Children's Research Hospital; **TAMU**-Texas A&M University; **U**-University; **U ILL**-University of Illinois; **UPenn**-University of Pennsylvania; **U Tenn**-University of Tennessee; **UZ**-University of Zurich

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: August 10, 2012

A randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum microscopy smear-positive pulmonary tuberculosis

Antimicrob. Agents Chemother. AAC.02243-12; published ahead of print 4 March 2013,

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 4, 2009 VOL. 360 NO. 23

The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

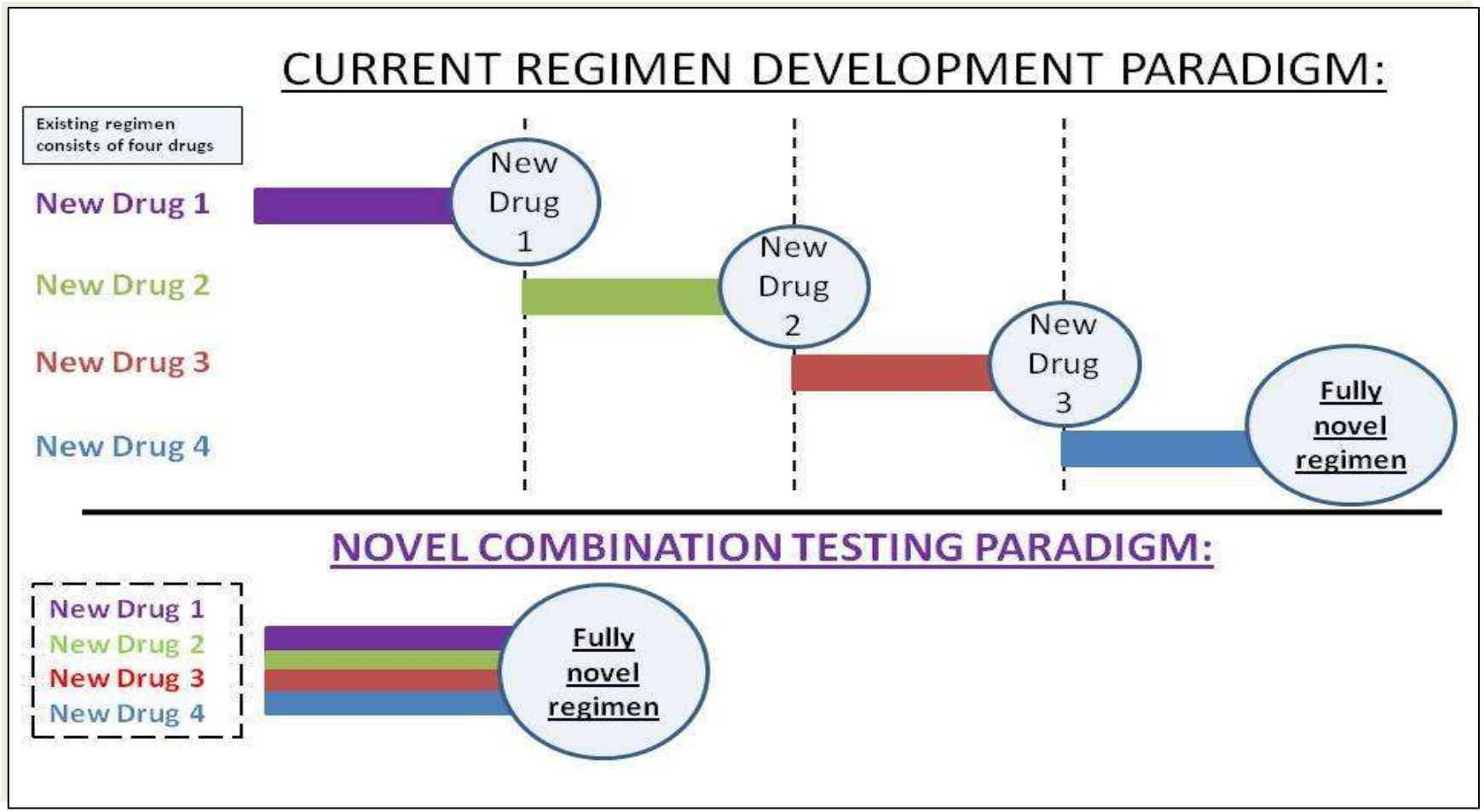
Sirturo (bedaquiline) Janssen

- In December 2012 the FDA gave approval for the drug to be used as part of combination therapy to treat adults with MDR-TB, when no other alternatives are available. The drug does potentially have serious side effects, including affecting the electrical activity of the heart.
- In September 2012 a Marketing Authorization Application was made to the European Medicines Agency, also for the use of bedaquiline as part of combination therapy treatment for MDR TB in adults.
- Two phase 2 studies of the drug have taken place in patients with MDR TB. The results of these trials have already been presented at the Union World TB conferences in 2010 and 2011.
- A phase 3 trial of bedaquiline, TMC207-C210, is due to start in March 2013. It will be a double blind study of 600 patients with sputum smear positive MDR-TB, which will compare TB treatment with bedaquiline and a background regimen, with placebo and a background regimen.
- Compassionate use of bedaquiline is now available in several European countries, and is available in South Africa on a limited basis.

Delamanid (OPC-67683) Otsuka

- Nitroimidazoles, OPC-67683 (Delamanid) and PA-824 are under development as potential TB drugs. Another drug in the same class is TBA-354.
- Delamanid is a member of the nitroimidazo-oxazole family, currently being initially developed by Otsuka as a treatment for MDR-TB.
- In July 2012 the results of a phase 2B trial showed delamanid plus a background regimen resulted in more study subjects becoming non-infectious after two months than a placebo plus a background regimen. The trial was conducted in 17 centres in nine countries. Among patients who received a background regimen plus 100 mg of delamanid twice daily, 45.4% had culture conversion at two months as compared with 29.6% of patients who received background plus placebo.
- Patients who took part in two earlier studies were also then able to take part in a 24 month observational study designed to look at treatment outcomes. This observational study found that favourable outcomes were observed in about ¾ of the patients who received Delamanid for more than 6 months as compared to about ½ of the patients who received Delamanid for less than 2 months.[20]
- Otsuka has started a phase 3 trial of Delamanid. The trial which started in September 2011, is designed to show whether Delamanid is both safe and effective when given as TB drug treatment over a six month period. The completion date for the first tests of effectiveness is August 2013. [21]

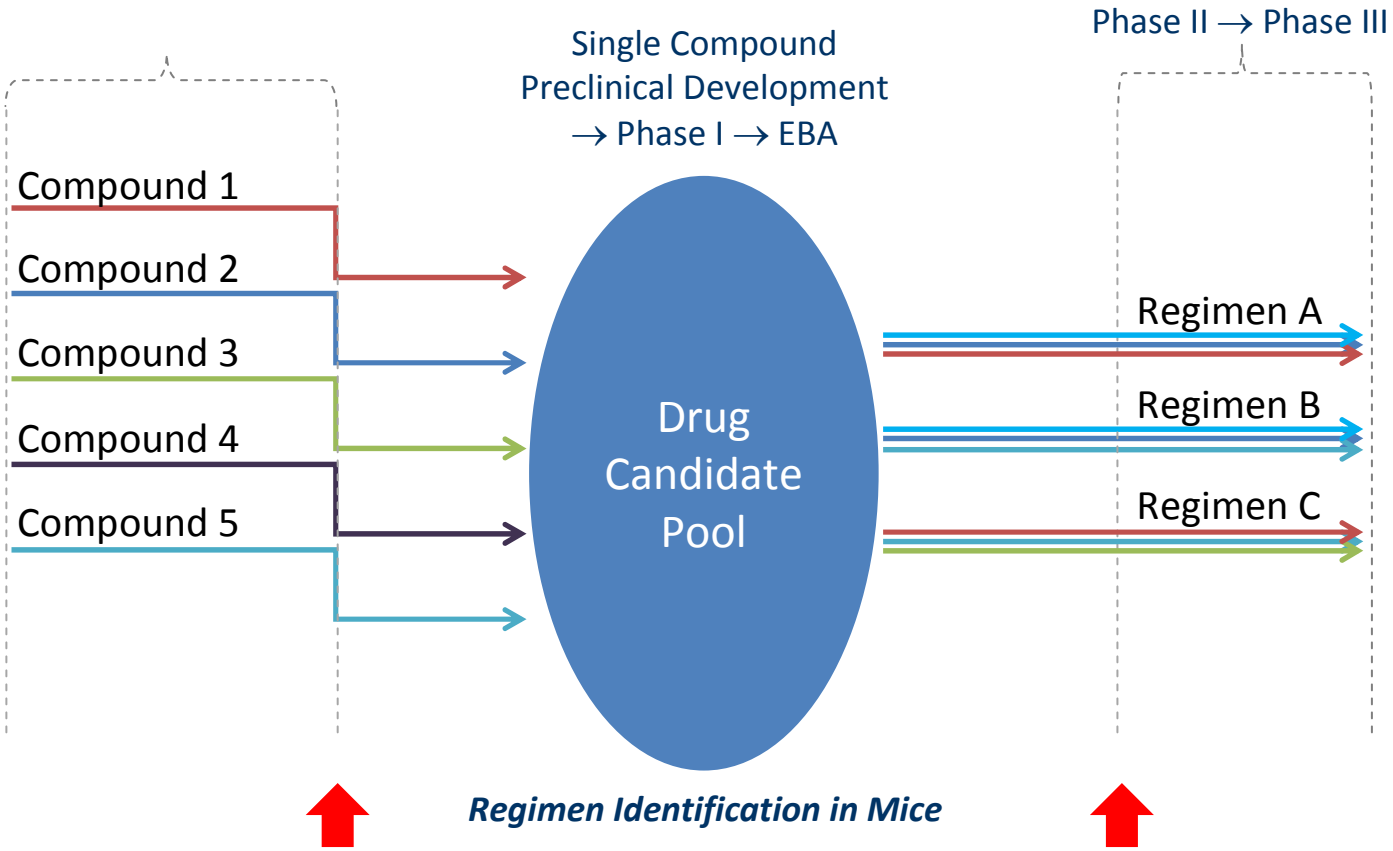
Paradigm Change in TB Drug Development



The Context:

Approach to TB Drug/Regimen Development

Discovery and Development Process



From Drugs to Regimens

- REMOX-TB trial for the treatment of adults with pulmonary tuberculosis.
  - 2 months M, H, R, Z followed by 2 months MHR
  - 2 months M, E, R, Z followed by two months MR
- **Trial** NC001: Evaluation of Early Bactericidal Activity in Pulmonary Tuberculosis With(J-M-Pa-Z)
- **Trial** NC002: Phase II Trial to Evaluate the Efficacy, Safety and Tolerability of the Following: PA-824 Plus Moxifloxacin Plus Pyrazinamide in Drug Sensitive and Multi-Drug Resistant Patients
- **Trial** NC003: Evaluation of Early Bactericidal Activity in Pulmonary Tuberculosis With Clofazimine (C)-TMC207 (J)-PA-824 (Pa)-Pyrazinamide (Z)

TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

TB Alliance Pipeline – Nov '12

New Drug Discovery

TARGET OR CELL-BASED SCREENING	LEAD IDENTIFICATION	LEAD OPTIMIZATION
Topoisomerase I Inhibitors *AZ/NYMC*	Whole-Cell Hit to Lead Program *GSK*	Mycobacterial Gyrase Inhibitors *GSK*
TB Drug Discovery Portfolio *NITD*		THPP Series *GSK*
	Energy Metabolism Inhibitors *AZ/U. Penn*	Pyrazinamide Analogs *Yonsei*
	Folate Biosynthesis Inhibitors *AZ*	Diarylquinolines *Jan/U. of Auck*
	Whole-Cell Hit to Lead Program *AZ*	Riminophenazines *IMM/BTTTRI*
	RNA Polymerase Inhibitors *AZ*	DprE Inhibitors *Scripps*
	Gyrase B Inhibitors *AZ*	Macrolides *Sanofi*
	ATP Synthase Inhibitors *Scripps*	Cyclopeptides *Sanofi*
		Whole-Cell Leads *Sanofi*

Preclinical Development

TBA-354 *U. of Auck/ U. Ill Chi*

Preclinical TB Regimen Testing *JHU/U. Ill Chi*

Clinical Development

CLINICAL PHASE I

Regimen Development

	CLINICAL PHASE II	CLINICAL PHASE III
New Drugs		Moxifloxacin (+ H, R, Z) *Bayer* Enrollment completed
		Moxifloxacin (+ R, Z, E) *Bayer* Enrollment completed
Novel Regimens	PA-824/Moxifloxacin/ Pyrazinamide	
	TMC207/ PA-824/ Pyrazinamide	
	TMC207/PA-824/ Clofazamine	
	TMC207 /Pyrazinamide/ Clofazamine	
	TMC207/PA-824/ Pyrazinamide/ Clofazamine	
Regimen Building Blocks	PA-824/Pyrazinamide	
	TMC207 /Pyrazinamide	

Novel TB regimen development

Our R&D Partners

AZ	AstraZeneca	JHU	Johns Hopkins University	U. of Auck	University of Auckland
Bayer	Bayer Healthcare AG	NITD	Novartis Institute for Tropical Diseases	U. Ill Chi	University of Illinois at Chicago
BTTTRI	Beijing Tuberculosis and Thoracic Tumor Research Institute	Novartis	Novartis Pharmaceutical	U. Penn	University of Pennsylvania School of Medicine
GSK	GlaxoSmithKline	NYMC	New York Medical College	Yonsei	Yonsei University
IMM	Institute of Materia Medica	Sanofi	sanofi-aventis		
Jan	Janssen (of Johnson & Johnson)	Scripps	Scripps Research Institute		

Diagnostics

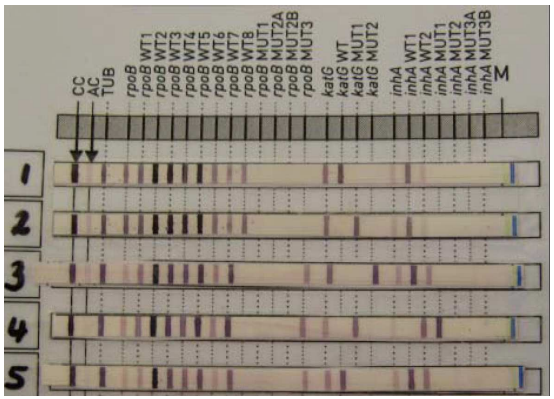
- Approved by
- WHO/STAG

	Concept	Feasibility	Development	Evaluation	Demonstration	Implementation (Approved by WHO/STAG)
Reference laboratory level						Liquid Culture & DST Rapid Speciation Line Probe Assay (1st line drugs)
District / peripheral level		Rapid Colorimetric DST			LAMP TB	LED florescence microscopy Xpert MTB/RIF
Community Level (POC)	LFI sensitivity increase	Antibody detection Antigen detection	β-lactamase detection			

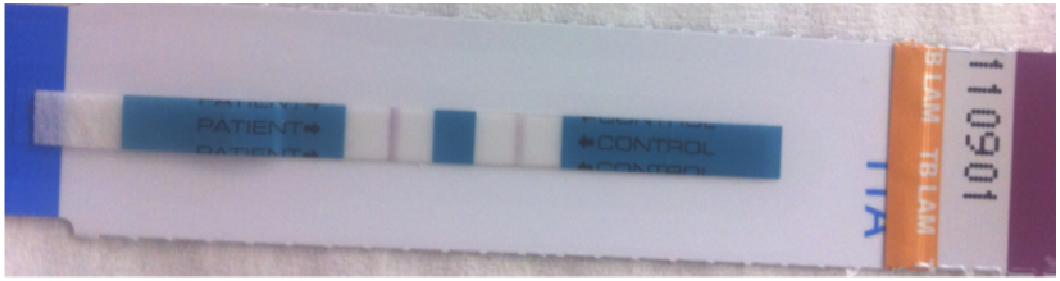
The Rapid March of Diagnostic Technology

- LED Microscopy*

- Line probe assays for MDR



- Urine LAM dipstick**



- GeneXpert TB/RIF*

*BSL-3 not required

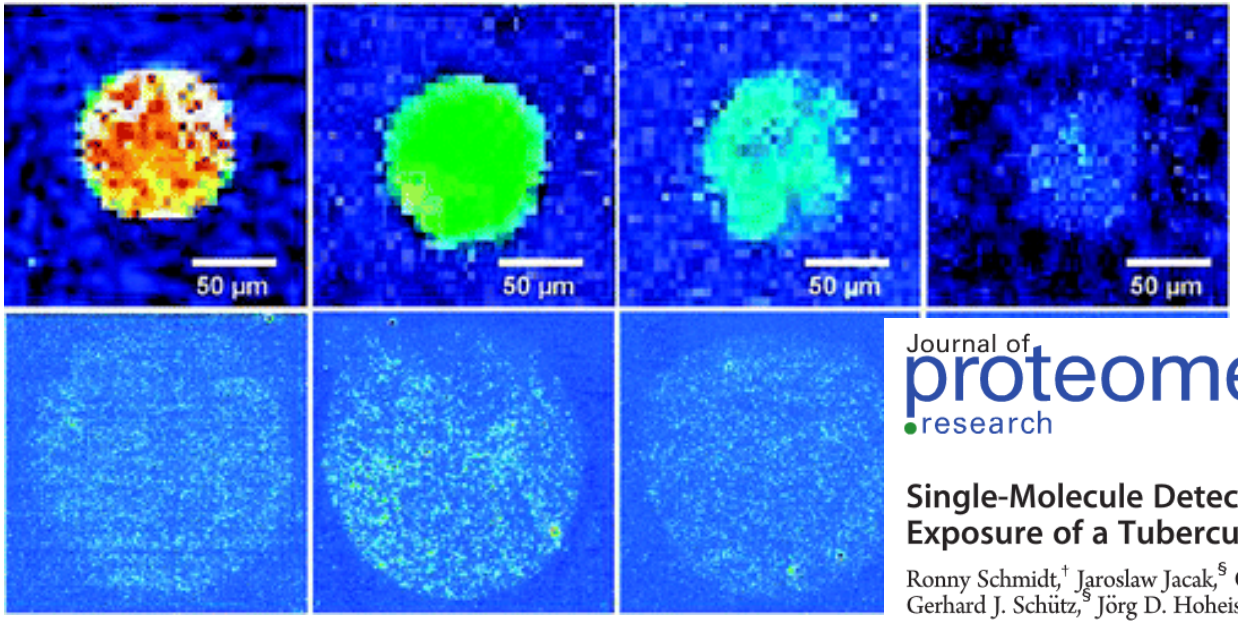
** Point of care test

Diagnostics

- Xpert MTB/RIF assay confirms the high accuracy in a range of settings, including inpatients, HIV coinfection and in children with culture-positive disease. Early experiences with operational implementation are now being reported from South Africa.
- Initial small-scale evaluations suggest that newer versions of line-probe assays have accuracy similar to that of the Xpert MTB/RIF assay.
- LAMP may in the future be more readily implemented at the point of care.
- The first low-cost, lateral-flow (strip-test) assay for lipoarabinomannan (LAM) in urine shows promise as a rapid point-of-care test for TB amongst advanced HIV-infections.

Urine Assay

- **Rationale:** If TB antigens are present in body fluids, these will be present in very low concentrations and will require highly sensitive detection methods. Appropriate point-of-care (POC) platform technologies for highly sensitive analyte detection, as well as an ultrasensitive immunoassay platform are required as reference methods for POC test development.
- **Project description**
- FIND and partners identified and evaluated the most sensitive POC platforms, using LAM antigen detection as a case model. The detection limits of products were compared across various assay formats and types of signal detection, including colorimetric, fluorescent and chemoluminescent. Our data indicates that analyte concentrations in the picomolar to low nanomolar range are detected by at least three of the evaluated POC platforms.
- Moreover, FIND and partners established a reference method able to detect LAM at an unprecedented concentration of several hundred molecules (10^{-14} to 10^{-13} mol/l).



Journal of proteome research

ARTICLE

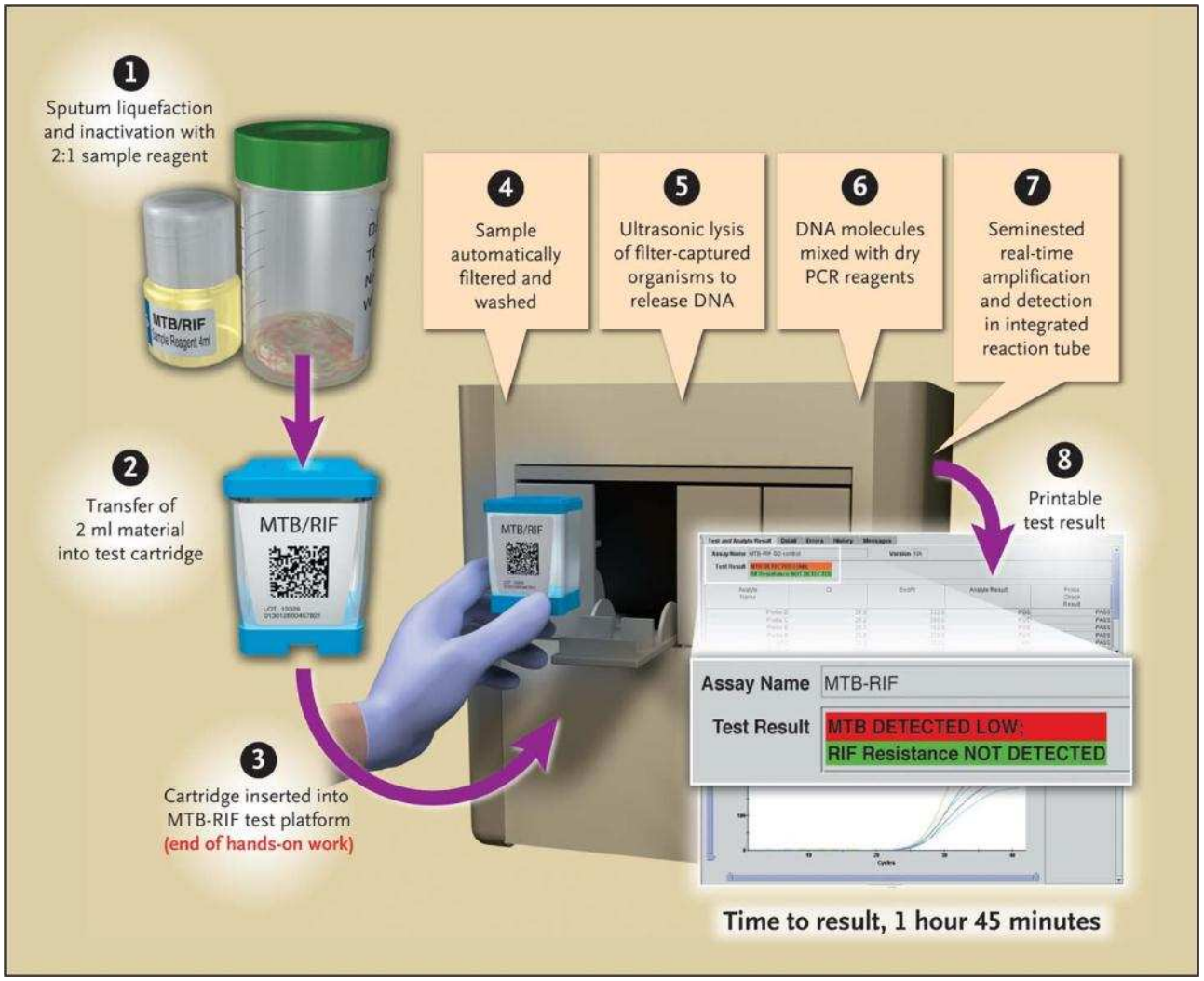
pubs.acs.org/jp

Single-Molecule Detection on a Protein-Array Assay Platform for the Exposure of a Tuberculosis Antigen

Ronny Schmidt,[†] Jaroslaw Jacak,[§] Christopher Schirwitz,[‡] Volker Stadler,[∥] Gerd Michel,[⊥] Nicole Marmé,[◆] Gerhard J. Schütz,[§] Jörg D. Hoheisel,[*,†] and Jens-Peter Knemeyer[†]

- A platform based on a single-molecule sensitive fluorescence-linked immunosorbent assay could detect LAM was with about 3 orders of magnitude more sensitivity than ELISA. No amplification or sample preparation was required. Since individual binding events are detected, true quantification was possible simply by counting individual signals. Utilizing a total internal reflection configuration, unprocessed human urine and plasma to which LAM was added could be analyzed without sample purification or washing steps. **Samples containing about 600 antigen molecules/microliter produced a distinct signal.** The method can be employed for any set of target molecules for which appropriate antibodies exist.
- *J. Proteome Res.*, **2011**, *10* (3), pp 1316–1322

Cepheid GeneXpert MTB/RIF Test



Boehme CC et al. N Engl J Med 2010;363:1005-1015

GeneXpert MTB/RIF Performance Characteristics

No. Sputums Tested	Sensitivity
3 Sputum Samples	
Sensitivity, all	**97.4%**
Smear-positive	**99.8%**
Smear-negative	**90.2%**
1 Sputum Sample	
Sensitivity, all	**92.2%**
Smear-positive	**98.2%**
Smear-negative	**72.5%**

- **Sensitivity HIV+ → 93.9%**
- **Sensitivity HIV- → 98.4%**

Specificity 98.1 – 99.2%
Sensitivity for RIF-resistance 99.1%

Boehme CC et al. N Engl J Med 2010;363:1005-1015

Performance of Xpert MTB/RIF vs. other diagnostic modalities

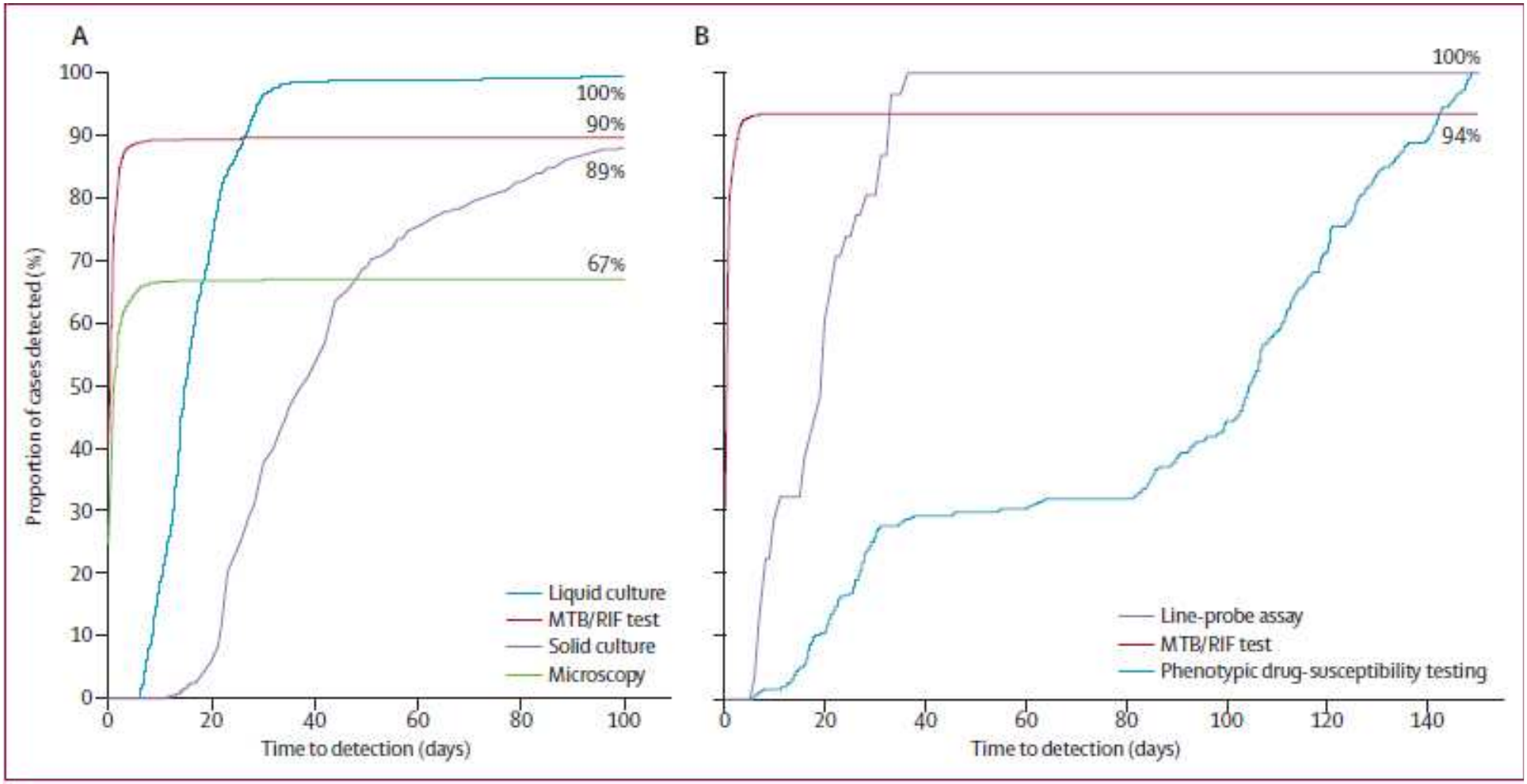
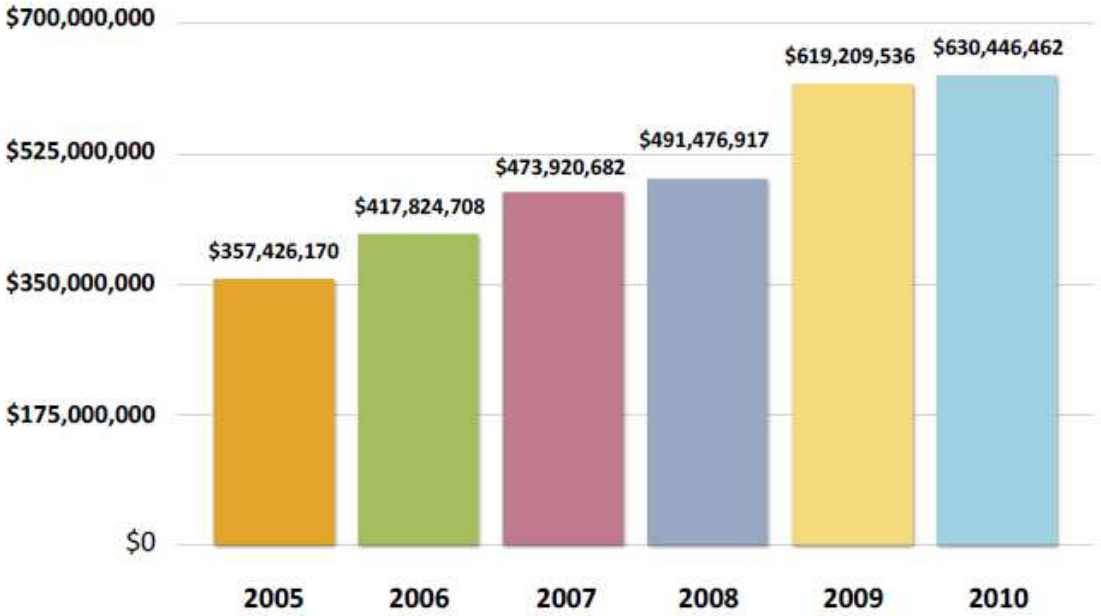


Figure 2: **Proportion of tuberculosis cases detected by each method in culture-positive patients**
Percentages are the maximum proportion of cases detected by every method. (A) Tuberculosis case detection. (B) Detection of rifampicin resistance. Time to detection was defined as time between date of sputum sample collection and date of positive result. MTB–*Mycobacterium tuberculosis*. RIF–rifampcicin.

Boehme et., Lancet 2011

Total TB R&D Funding: 2005-2010



2010 TB R&D investments witnessed a 76% increase over 2005 levels but only 2% growth since 2009.

by Research Category: 2005-2010