

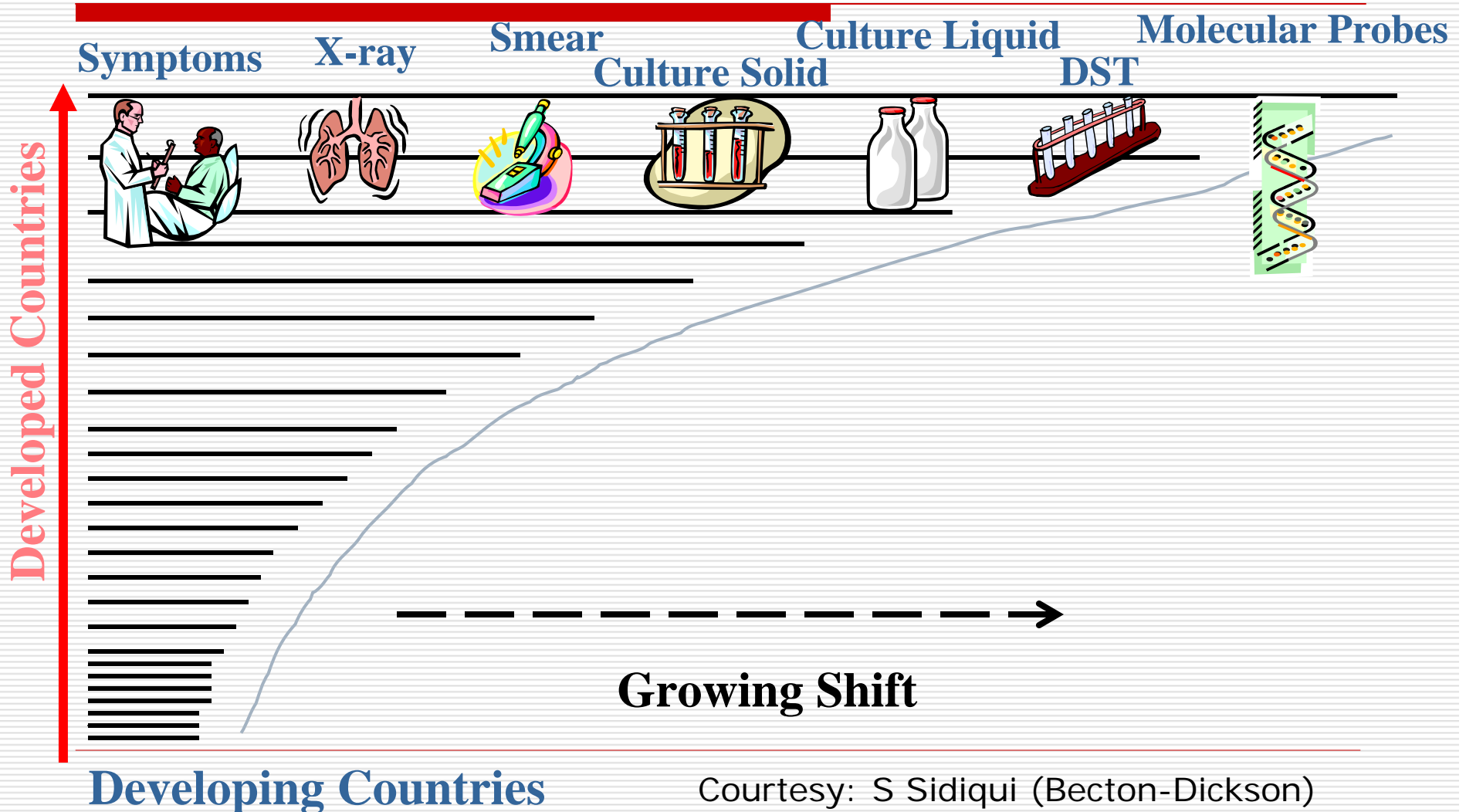
New diagnostics and drugs for TB

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Changing Trends in TB Diagnostics



Courtesy: S Sidiqui (Becton-Dickson)

Bacteriology

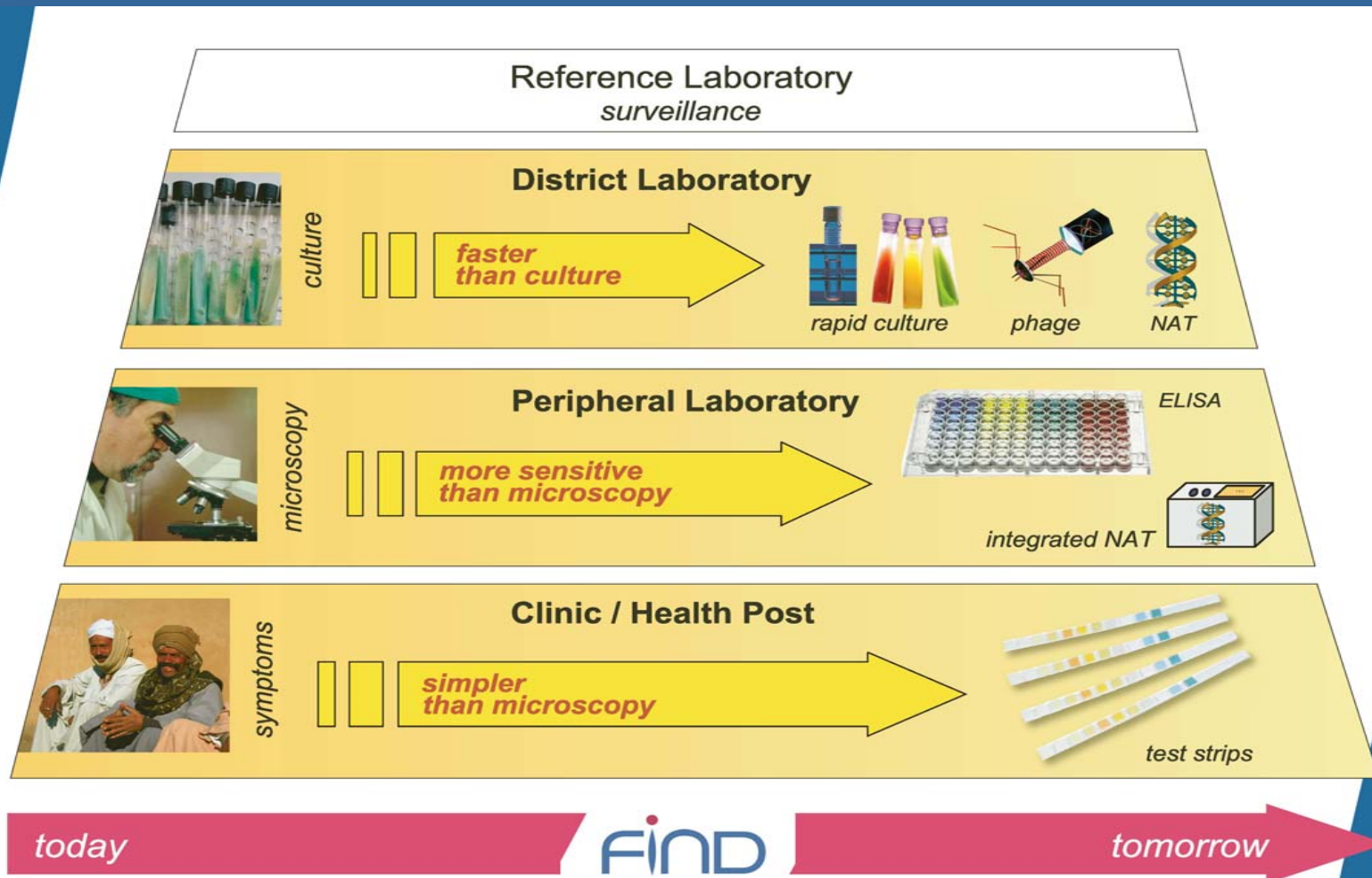
- ❑ Realization that culture is the only definitive diagnosis
- ❑ Culture is necessary for ID and AST
- ❑ Going to remain as a “Gold Standard” for a long time
- ❑ Rapid Turnaround Time is critical
- ❑ More focus on liquid media

CDC Guidelines

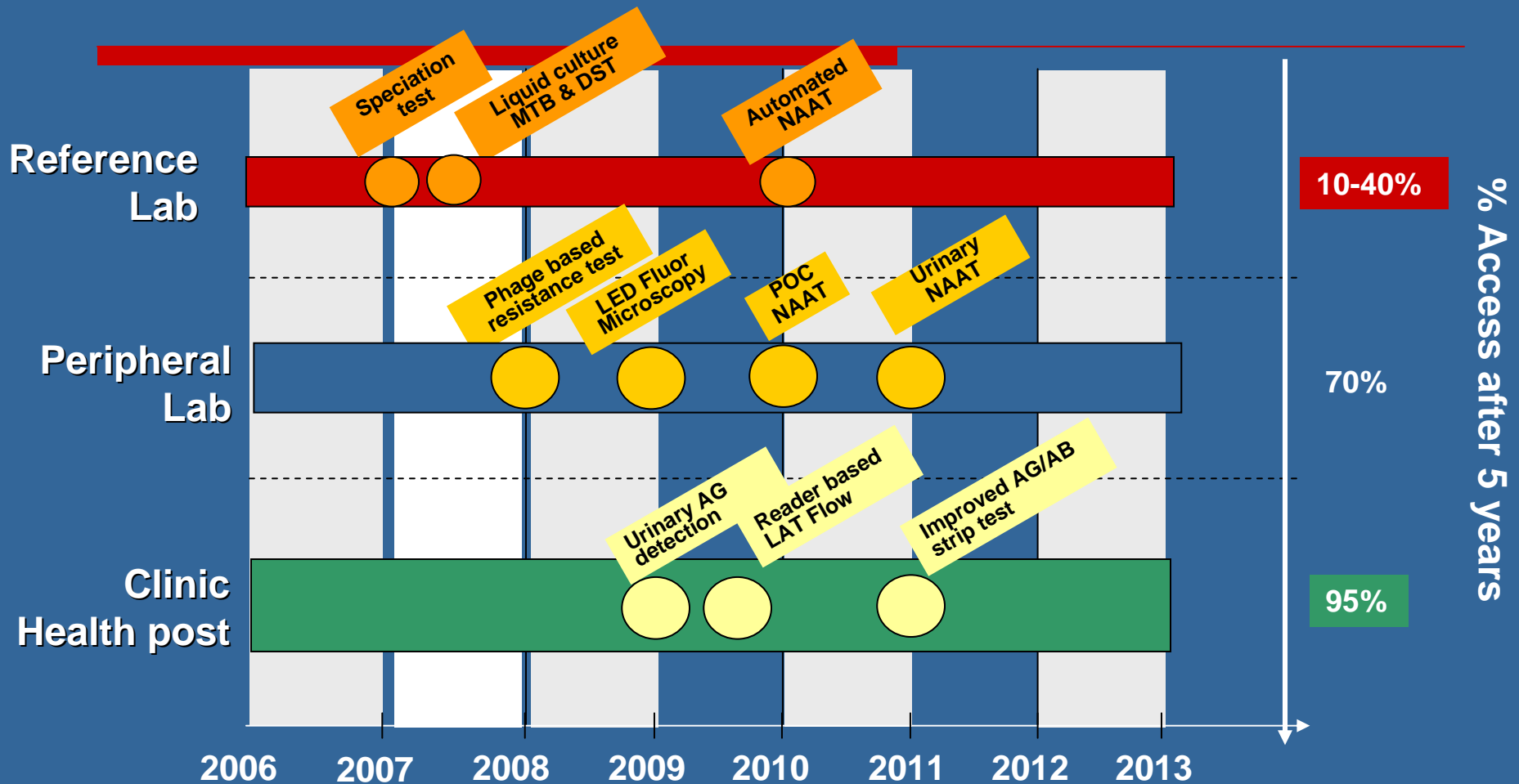
- AFB Smear Results within 24 hours -----
- Culture Results report ave. 2 Weeks ----- Yes*
- Complete culture/Identification 3 Weeks -----Yes*
- Complete Culture/ID/DST in 4 weeks ----- Yes*
- QC, Method, Media and Reagents ----- Yes*

*Role of BACTEC in meeting the guidelines

FIND's Diagnostic Pipeline



FIND Product Deliverables 2006-2013



FIND/TDR Trial in Peru*

- ❑ Comparison of FASTPlaque-Response test, INNO Lipa test, and direct LJ DST
- ❑ Gold standard: indirect DST on LJ medium
- ❑ Costing sub-study
- ❑ Enrolled newly diagnosed and retreatment patients with SS+ PTB
- ❑ Additional 400 SS+ for FP sub-study
- ❑ Discrepant analysis for all RIF-R tests by repeat DST and *rpoB* sequencing

*IMT Cayetano Heredia, Inst Nat Salud, Disa Lima Norte

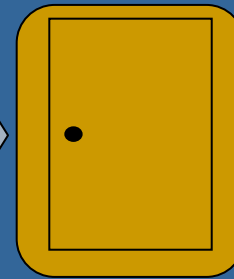
*FAST*Plaque™-Response



Sputum collection

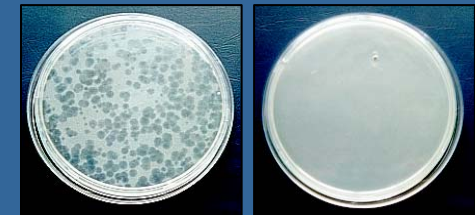


Specimen processing
(NALC-NaOH)



o/n incubation
± rifampicin

*FAST*Plaque-
Response
assay procedure



Interpretation of results

FIND/TDR Trial in Peru Preliminary Results

Performance Characteristics for **RIF-R***

Test	Sens	Spec	PPV	NPV
INNO	93%	99%	93%	99%
FP-1	95%	96%	79%	99%
FP-2 **	94%	100%	100%	99%
D-LJ	95%	99%	95%	99%

*Subject to change pending results of discrepant analysis

**Based on results 135 tests with complete results

FIND/TDR Trial in Peru

Preliminary Results

Performance Characteristics for **MDR TB***

<u>Test</u>	<u>Sens</u>	<u>Spec</u>	<u>PPV</u>	<u>NPV</u>
INNO	94%	97%	84%	99%
FP-1	94%	95%	70%	99%
D-LJ	97%	98%	85%	100%

*Subject to change pending results of discrepant analysis

Species Identification

- ❑ Rapid identification needed for culture-based systems, especially broth culture
- ❑ Current technologies, e.g., DNA probes, PCR, HPLC expensive
- ❑ FIND working with TAUNS/BD to evaluate performance of Capilia TB test in MGIT case finding demonstration projects

Capilia TB Assay

- ❑ Immunochromatic assay based on detection of MPB64, present in M. tb complex but not MOTT or some BCG strains
- ❑ Consists of nitrocellulose membrane with anti-MPB64 mouse antibodies conjugated with colloidal gold
- ❑ With antigen-antibody reaction, see red-purple band within 15 minutes
- ❑ Evaluated for 172 mycobacterial isolates (119 M.tb complex): 92% sensitivity, 100% specificity*
 - 3 false negatives with MPB64 gene mutation

*D. Hilleman, et al. IJTLD 2005;9:1409-11

Molecular Methods

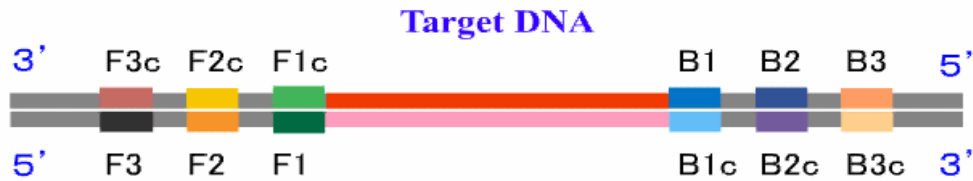
- Good performance characteristics
 - Rapid
 - Sensitive (approaching culture)
 - Specific
- Expensive and requires sophisticated technology
- FIND working with partners with core technology and platform suitable for developing country use

LAMP



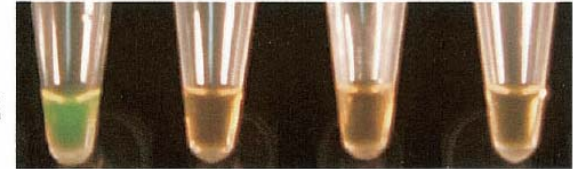
EIKEN CHEMICAL CO.,LTD.

Loop-mediated Isothermal Amplification (LAMP)

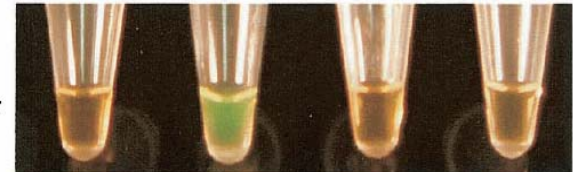


Ver.6.4

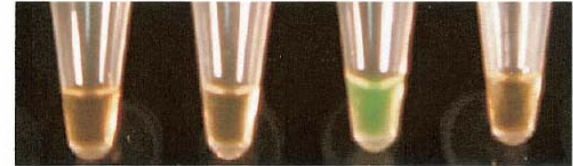
LAMP
w / MTB



LAMP
w / MAV



LAMP
w / MIN



- Closed system
- Isothermal
- Rapid
- Multiprimer
- Visible readout



find
FOUNDATION FOR
INNOVATIVE NEW DIAGNOSTICS



MTB / Rif-resistance test

Workflow

- sputum
- simple 1-step external sample prep. procedure
- time-to-result < 2 h
- throughput: ≥ 16 tests / day / module
- no need for biosafety cabinet
- integrated controls
- true random access

Performance

- specific for MTB
- sensitivity better than smear, similar to culture
- detection of rif-resistance via rpoB gene

Product and system design

- test cartridges for GeneXpert System
- several GeneXpert modules can be combined in 1 workstation
- swap replacement of detection unit
- ~1 day technician training for non-mycobacteriologists

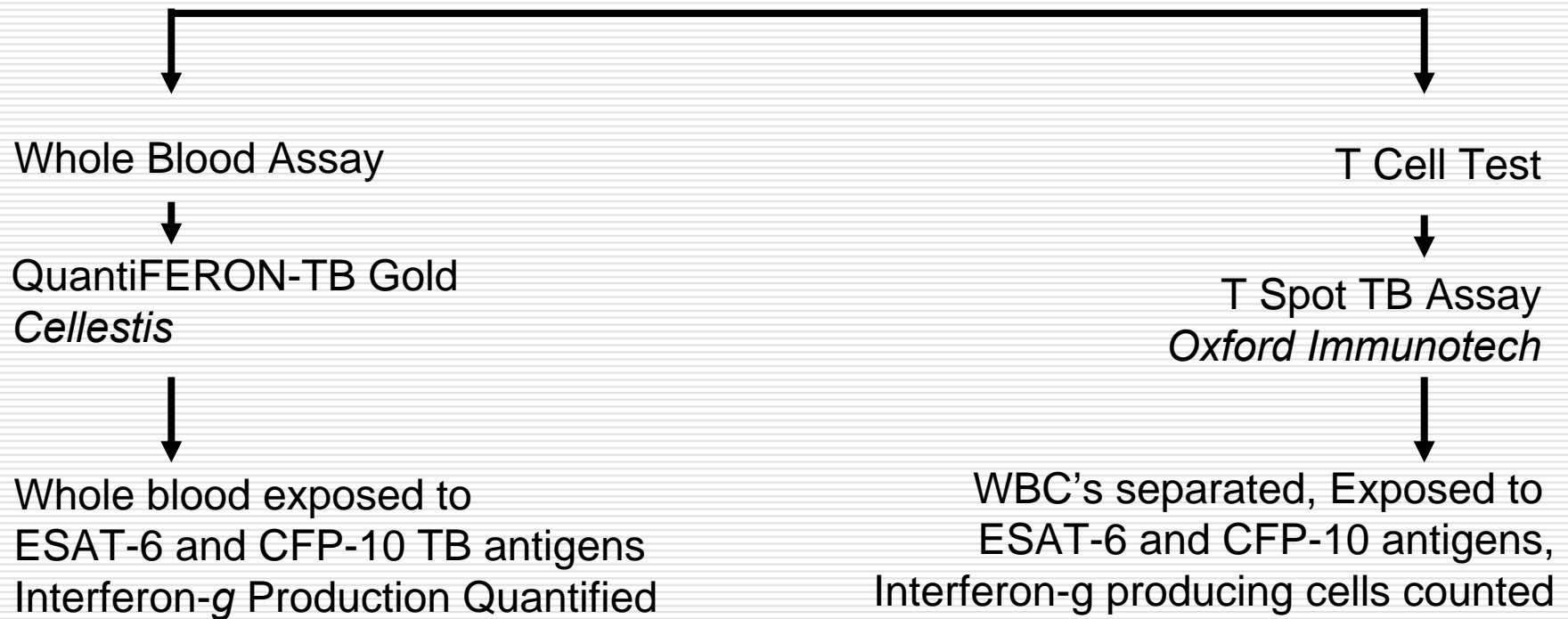


cartridge

FIND Evaluation Studies of Interferon-gamma release assay (IGRA)

- ❑ IGRAs have been shown to be as sensitive and more specific than the TST for diagnosis of latent TB infection (LTBI)
- ❑ Limited data suggest that IGRAs perform well in HIV-infected persons
- ❑ FIND supporting two studies nested in CREATE projects to help define role of IGRAs in diagnosing LTBI in HIV+ persons:
 - THRio: 3000 patients in HIV/AIDS care clinics
 - ZAMSTAR: 10,000 HIV+/- adult TB contacts

Interferon- γ based tests



The Interferon- γ Assays

□ Pro's

- Differentiates TB infection from BCG
- Suitable for repeat. No "booster phenomenon"
- Objective results, in vitro procedure
- Results available in 24 hours
- No patient's second visit
- Specificity (~99%)
Sensitivity (90s%)

□ Con's

- Does not differentiate between latent TB and active disease
- Multiple assays steps
- Blood drawing, transport, test within 12-hours
- Technique dependent
- Equipment requirements (Spec. or reader, incubator, centrifuge, pipetter)
- Refrigerated reagents
- High cost

Useful in low prevalence settings and high-burden HIV

Global TB Drug Portfolio: Sep 2005

Discovery		Preclinical	Clinical Testing
Carboxylates TB Alliance, Wellesley College	Nitrofuranylamides NIAID, University of Tennessee	Diamine SQ-109 Sequella Inc.	Diarylquinoline TMC207 Johnson & Johnson
Cell Wall Inhibitors Colorado State University, NIAID	Nitroimidazole Analogs NIAID, Novartis Institute for Tropical Diseases, TB Alliance	Dipiperidines (SQ-609) Sequella Inc.	Gatifloxacin OFLOTUB Consortium, Lupin, NIAID TBRU, Tuberculosis Research Centre, WHO TDR
Dihydroipoamide Acyltransferase Inhibitors Cornell University, NIAID	Novel Antibiotic Class GlaxoSmithKline, TB Alliance	Non-Fluorinated Quinolone TaiGen	Moxifloxacin Bayer Pharmaceuticals, CDC TBTC, Johns Hopkins University, NIAID TBRU, TB Alliance
InhA Inhibitors GlaxoSmithKline, TB Alliance	Picolinamide Imidazoles NIAID, TAACF	Synthase Inhibitor FAS20013 FASgen Inc.	Nitroimidazole PA-824 Chiron Corporation, TB Alliance
Isocitrate Lyase Inhibitors (ICL) GlaxoSmithKline, TB Alliance	Pleuromutilins GlaxoSmithKline, TB Alliance	Translocase I Inhibitors Sequella Inc., Sankyo	Nitroimidazo-oxazole OPC-67683 Otsuka
Macrolides TB Alliance, University of Illinois at Chicago	Quinolones KRICT/ Yonsei University, NIAID, TAACF, TB Alliance	Nitroimidazo-oxazole Back-up Otsuka	Pyrrrole LL-3858 Lupin Limited
Methyltransferase Inhibitors Anacor Pharmaceuticals	Screening and Target Identification AstraZeneca		
Natural Products Exploration BIOTEC, California State University, ITR, NIAID, TAACF, University of Auckland	Thiolactomycin Analogs NIAID, NIH		

STOP TB New Drugs Working Group

Clinical Development Pipeline

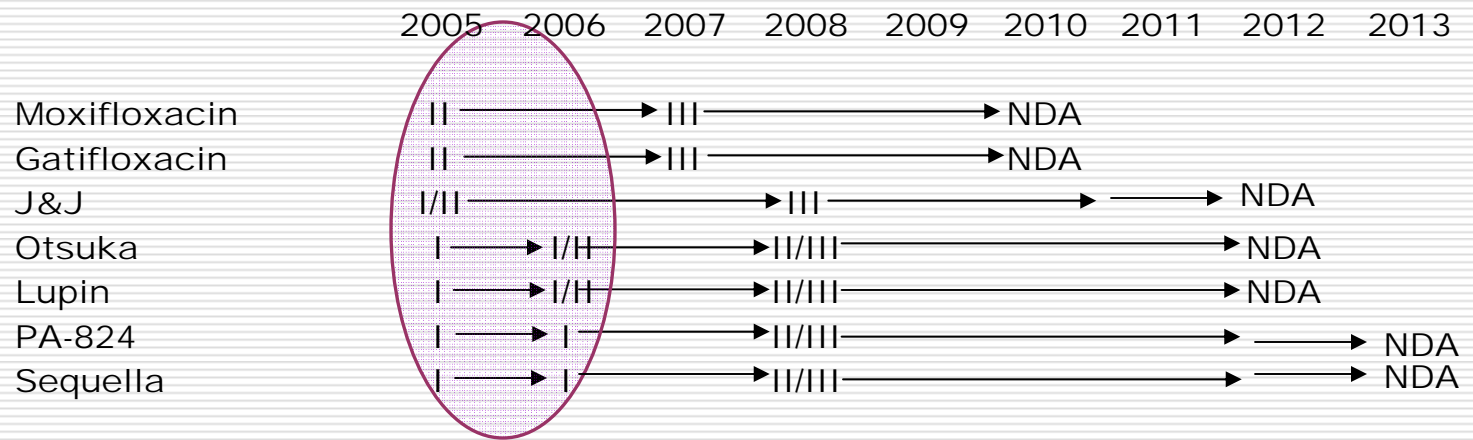
Compound	Development Stage	Sponsor / Coordinator
gatifloxacin	Phase III	EC / OFLOTUB Consortium; IRD [*] ; WHO TDR ^o ; Lupin Ltd.
moxifloxacin	Phase II / III	Bayer; TB Alliance; CDC [◆] ; University College of London; Johns Hopkins University
TMC 207	Early Bactericidal Activity	Johnson & Johnson (Tibotec)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

* Institut de Recherche pour le Developement

o World Health Organization, Tropical Disease Research

◆ Centers for Disease Control and Prevention

Pipeline Compounds



Identify and develop best combination regimen(s)

Short-/Medium-term prospects

- More potent fluoroquinolones
 - Moxifloxacin
 - Gatifloxacin
 - Levofloxacin
 - Capreomycin
 - Injectable
 - (Inhaled dry-powder formulation in advanced development)
 - PAS
 - Tablets
 - Granular with acid-resistant outer coating
 - Clofazimine
 - Capsules
 - (Liposomal)
 - (Other members of class high potency against MDR)
-

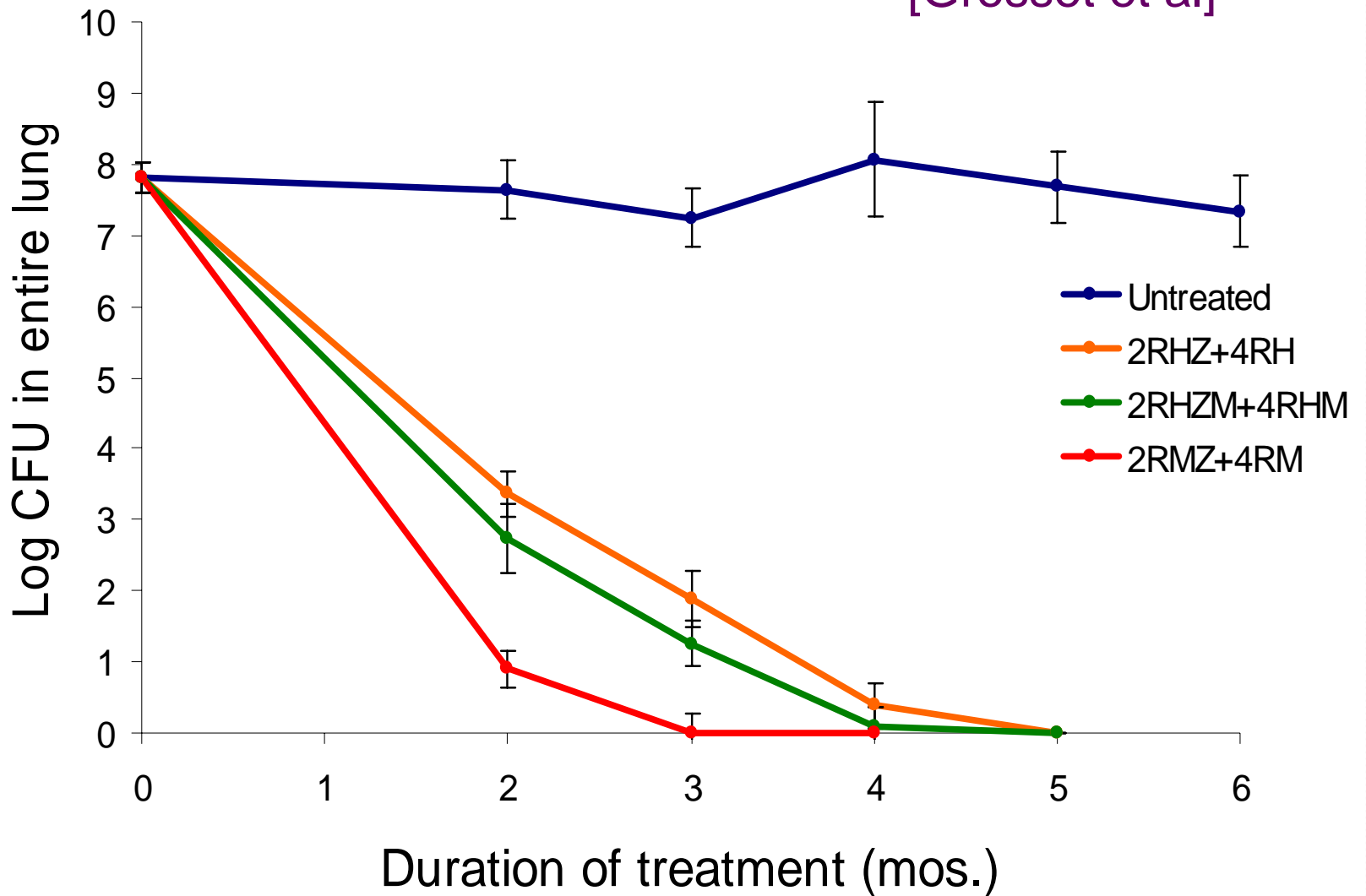
Ratio C_{max} on MIC_{90} of the main fluoroquinolones

Drug (mg)	C_{max} ($\mu\text{g/ml}$)	MIC_{90}	C_{max}/MIC_{90}
Ciprofloxacin 500	1-2	1.0	1-2
Ofloxacin 400	4	2.0	2
Levofloxacin 500	5-7	1.0	5-7
Sparfloxacin 200	1.1	0.5	2
Moxifloxacin 400	4-5	0.5	8-10

Ref. : Hooper et Wolfson AAC 1985 ; 28 : 716-721 ; Hooper Clin. Inf. Dis. 2000 ; 30 : 243-254 ; Lubasch et al., AAC 2000 ; 44 : 2600-2603

Activity of Moxi in Combination Therapy

[Grosset et al]



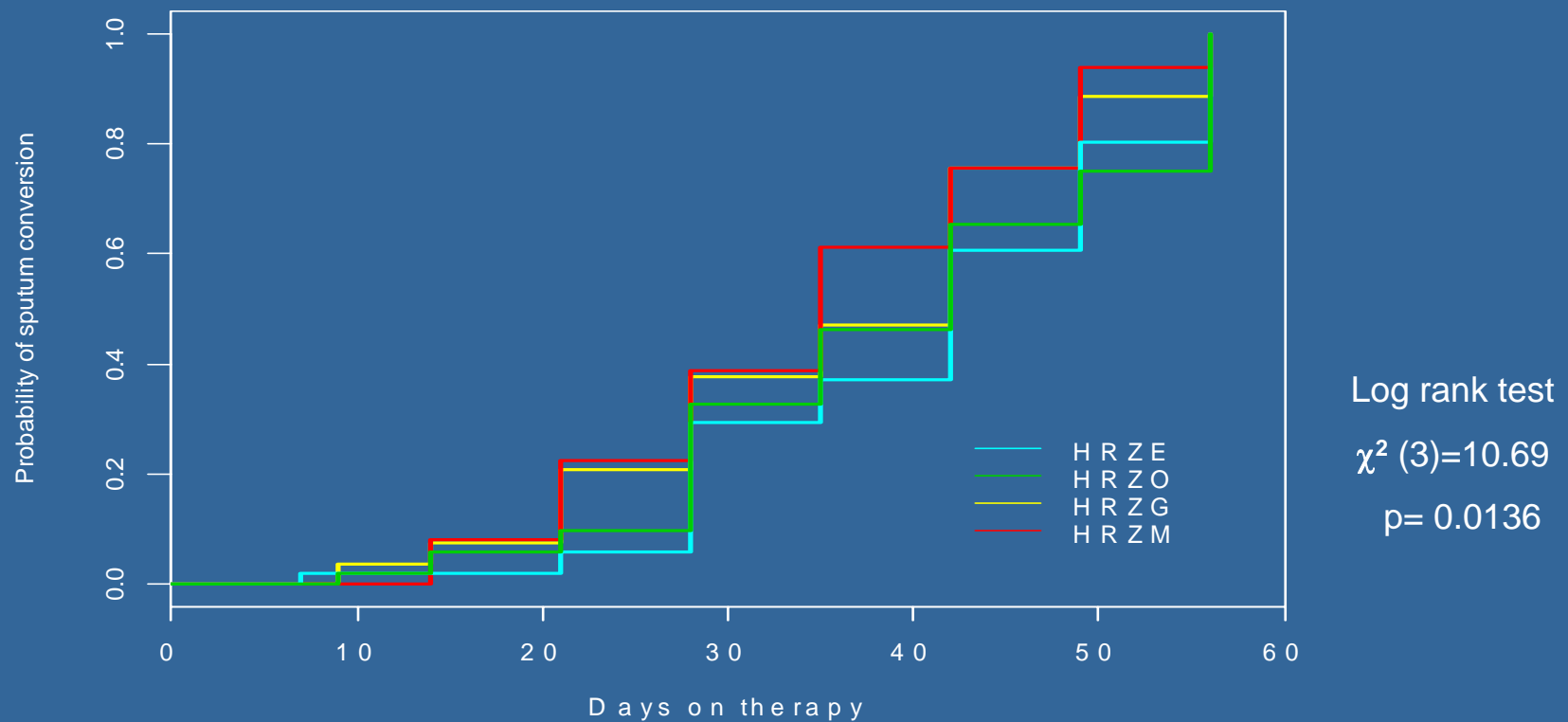
M = moxifloxacin; R = rifampin; H = isoniazid; Z = pyrazinamide

Moxifloxacin in treatment of MDRTB*

- Activity of the OFX-containing third-line regimen against *M. tuberculosis* was rather weak in vivo, whereas when OFX was replaced by MXF, 9 months of treatment with a modified third-line regimen (MXF/AMK/ETH/PZA) displayed bactericidal activity comparable to that of 6 months of treatment with the standard regimen in mice

*Veziris N et al. Antimicrob Agents Chemother. 2003 Oct;47(10):3117-22

Gatifloxacin, moxifloxacin or ofloxacin replacing ethambutol in conventional HRZE regimen – Conversion of sputum during 1st two months*



*Preliminary data presented at IUATLD Conference, Paris 2005
Oflotub Consortium Study supported by EC and WHO/TDR

Survival of HIV-associated MDRTB – NYC Treatment

(Turret, NEJM 1995)

