NIAID TB Therapeutic Clinical Research Priorities

- New drugs and combinations for DS and DR TB:
  - Efficient Phase I and II evaluations → Phase III
  - Killing Persisters – Sterilizing activity is crucial
- Prognostic biomarkers for disease progression, treatment response/relapse
- TB/HIV Therapy – Co-treatment regimens
- Chemoprevention of TB
- Improved diagnostics and DST
- Pathogenesis and translational research

What do we need and how to get it done?

- **Enhance/adapt existing NIAID clinical research resources for TB**
- **Coordination and Collaborations**
- **Develop highly efficient research strategies/agendas and trials designs**
  - **Target persisters**

NIAID Clinical Trials/Research Infrastructure

DAIDS Cooperative Agreements

- ❑ AIDS Clinical Trials Group (ACTG)
- ❑ International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT)
- ❑ International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)
- ❑ HIV Vaccine Trials Networks (HVTN)

DMID Contracts

- ❑ Vaccine and Treatment Evaluation Units (VTEU)
- ❑ Phase I Clinical Trials Units

- ❑ Tuberculosis Research Unit (TBRU)*

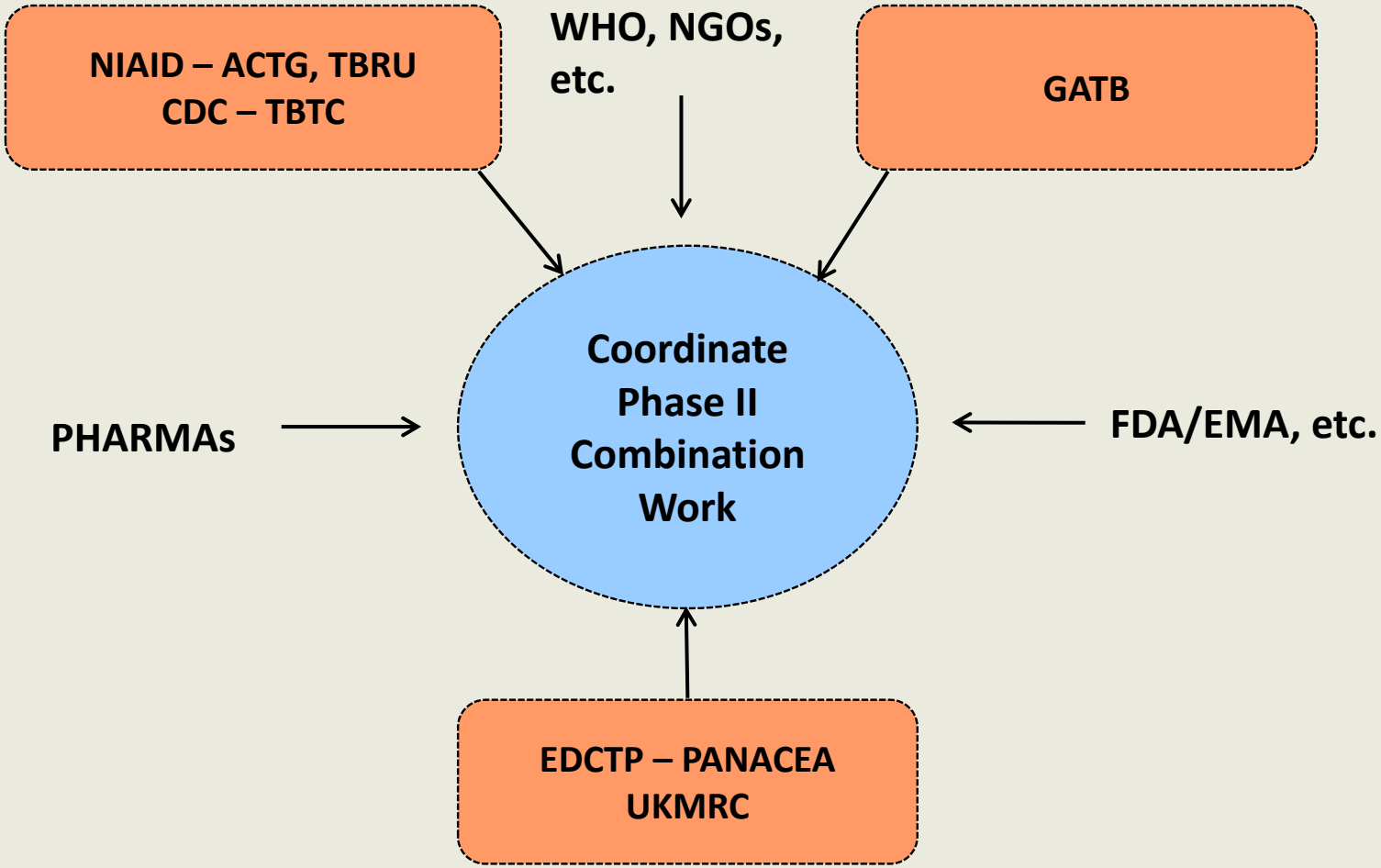
- ❑ Tuberculosis Clinical Diagnostics Research Consortium (CDRC)*

Both Divisions

- ❑ Support for Unsolicited Clinical Research Projects

* TB specific

Coordination of Phase II Combo Trials



Forum to Coordinate Phase II/III Clinical Trials Initial Meeting 10/23/11

- Phase II combination development plan coordination
  - Determine which combinations to be studied - whom/when
  - Efficiently/promptly share new study results
  - Address necessary pre-clinical and clinical data to allow timely study of specific combos
  - Coordination of discussions with Pharmaceutical sponsors
- Establish an ongoing Phase II/III Planning Forum
  - Drafting a proposal for how groups will work to coordinate
  - Proposal for support of future activities (conference calls and meetings)
  - Quarterly discussions with 1-2 meetings/year

Planning for MDR Trials with New Drugs

- **Site surveys**
  - Initial – Completed in ACTG and TBTC
- Initial **Observational** studies to better define local drug susceptibility patterns and feasibility issues
- **EARLY coordination** of planning/drug choices
- **DR TB Trials**
  - Change emphasis to new combos, not single drug additions to OBT
  - **Include MDR/XDR into new combo trials as soon as possible**
- ***Rapid PZA DST*** **will be essential for next generation of MDR trials – Jump-start pncA sequencing capability**

Summary of NIAID Studies for TB – 2

STUDY NUMBER	BRIEF DESCRIPTION
HIV/TB	
A5274	REMEMBER: Empiric TB treatment + ART to reduce early mortality following ART initiation
A5284	RIF + GS-9350 (Cobicistat) PK interaction
A5290	Comparison of LPV/r-based ARV ± RAL with RBT and double dose LPV/r with RIF-based TB RX
LTBI	
A5259	Rifapentine-INH x 3 mos vs SOC for LTBI (TBTC Study 26)
A5279	Ultra-short (1 month) daily course of RPT/INH for LTBI
DMID 07-0083	Phase I Study of Whether Preclearance of LTBI with INH Enhances Specific Immune Responses to MTB following Subsequent BCG Revaccination in Healthy, HIV-uninfected, PPD+ Adults

1

Slide 7

1 really intended to see if pretreatment with INH will improve immune response to BCG
, 10/18/2011

Summary of NIAID Studies for TB – 3

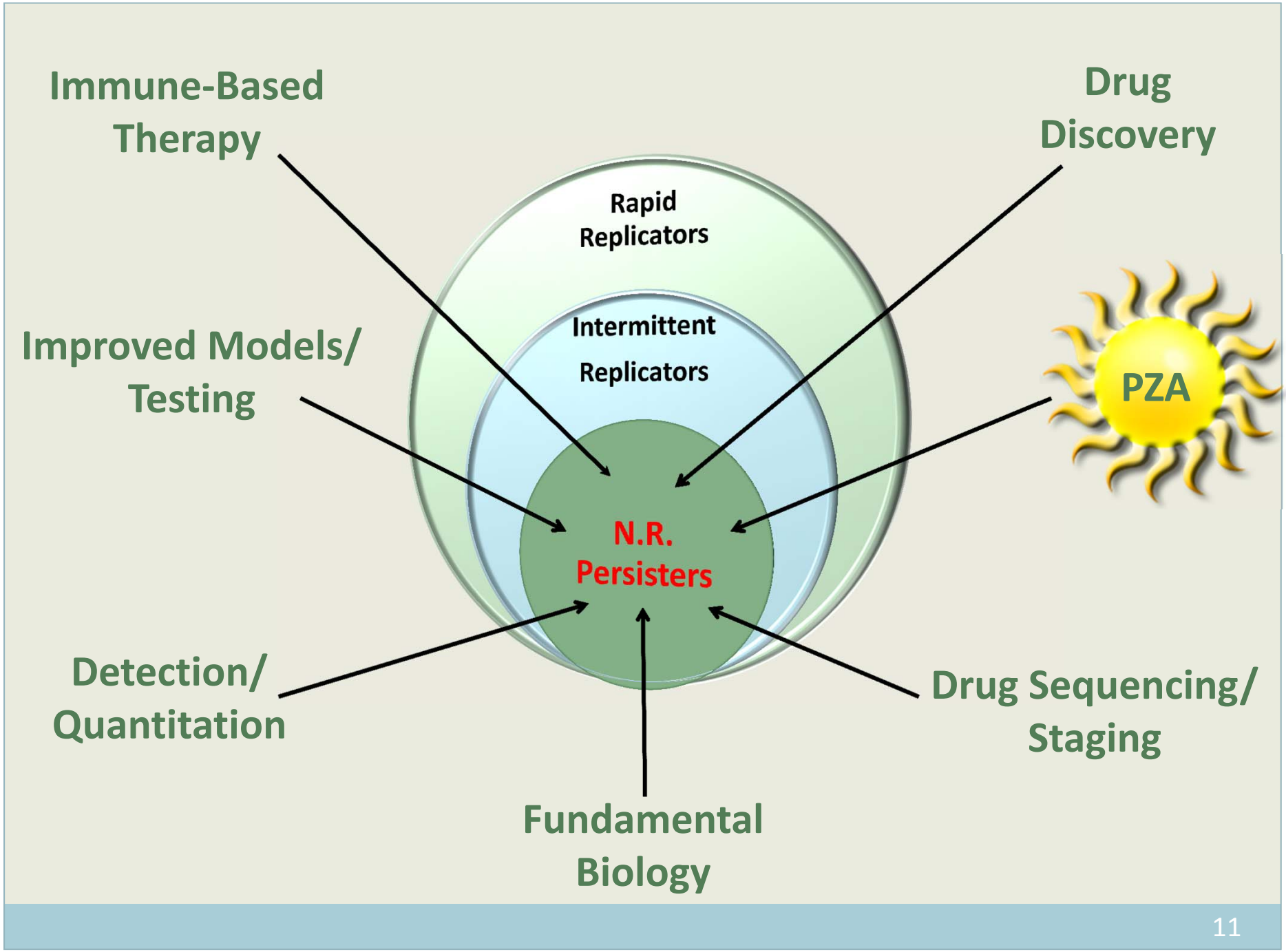
STUDY NUMBER	BRIEF DESCRIPTION
MDR	
A5300	TMC-207 for preventive therapy for MDR/XDR contacts
A5312	The Early Bactericidal Activity of High-Dose Isoniazid among Adult Patients with inhA-related INH-Resistant Tuberculosis
Harvard CFAR	Inhaled Colistin to Decrease XDR TB Infectivity - Nardell
Optimizing Standard Treatment Regimen	
A5307	Essentiality of INH After Two Doses: Randomized 14-day EBA Comparison of Standard RHZE with Only 2d INH + RZE or Substituting Moxifloxacin for INH (RMZE) During Days 3 and 14
A5311	Phase I Clinical Trial of the Pharmacokinetics of High-dose Daily Rifapentine, Given as a Single Dose or in Divided Doses to Healthy Volunteers

Summary of NIAID Studies for TB – 4

STUDY NUMBER	BRIEF DESCRIPTION
Optimizing Standard Treatment Regimen – continued	
DMID 11-0050	Double Blind randomized dose ranging trial of high dose rifampin (10-15-20 mg/day) for safety and improving treatment outcomes
Pediatrics	
P1073	Study of IRIS in children ≤ 5 years of age
P1078	Safety and Efficacy of Antepartum vs. Postpartum INH Preventive Therapy in HIV-infected Women and Infants
IMPAACT CS	TMC-207 with OBT for treatment of MDR TB in children
Other	
TBRU	EBA Feasibility Study with Standard EHRZ Chemotherapy in Kampala/Mulago

Summary of NIAID Studies for TB – 5

STUDY NUMBER	BRIEF DESCRIPTION
New Drug Development	
A5267	PK interaction study of TMC-207 and EFV
A5306	Safety, tolerability, and PKI study of PA-824 together with Efavirenz or Ritonavir-Boosted Lopinavir or Rifampin
DMID 11-0006	Multiple Dose Extended EBA of Oxazolidinone AZD5847
DMID 10-0043	PK interactions of single-dose TMC-207 with steady-state rifabutin or rifampin
New Combo Development	
A5289	TMC-207 substitution of standard drugs for TB treatment
A5304/ REMox	Two Moxifloxacin containing treatment shortening regimens compared with the standard regimen


Immune-Based Therapy
Drug Discovery
Rapid Replicators
Intermittent Replicators
Improved Models/ Testing
PZA
N.R. Persisters
Detection/ Quantitation
Drug Sequencing/ Staging
Fundamental Biology

Dealing with Persisters

- The best targets are NOT necessarily the usual most "vulnerable" or microbe-specific
  - Membrane integrity or critical membrane-function
- More difficult to discover or design agents
- Some potentially sterilizing agents with low activity against active bugs are ignored
- Diagnostics/biomarkers – the TB markers probably differ with changes in subpopulations and disease stage
- Markers for dormant bacilli may be scant to nil at times and change unpredictably as the bugs adapt
- Background NOISE

Efficiency in Combination Development - Focus on Phase II

Problem - Serial trials/amendments are much too inefficient- Delays caused by protocol development (esp. in group setting) and approvals at all levels

Responses

- Innovative, inclusive, new adaptive designs
- Early anticipation and resolution for concerns with new combinations - interactions ad safety
- Improved, real-time quantitative response markers
- Coordination of planning/prompt sharing of data

Efficiency in Combination Development - Focus on Phase II

Desirable Features of Adaptive trials

- Multi-arm and may be *multi-step* (Phase II A → B)
- Frequent ISMC interim reviews (IRs) – *drop* arms early if less active than control – but trial continues
- *Add* new arms as per study criteria
- *Seamless* transitions, step (A → B)
- *Flexibility* of entry into Phase A step or Phase B step, depending on how much is known
- May include arms for both *DS and DR* infections

BACKUPS

NIAID Organizational Structure

Office of the Director

Anthony S. Fauci, M.D.
Director

Hugh Auchincloss, Jr., M.D.
Principal Deputy Director

Gray Handley
Associate Director for International Research Affairs

Deputy Director for Science Management

John J. McGowan, Ph.D.

Deputy Director for Clinical Research and Special Projects

H. Clifford Lane, M.D.

Division of Clinical Research

H. Clifford Lane, M.D.
Director

Division of Extramural Activities

Marvin R. Kalt, Ph.D.
Director

Division of Acquired Immunodeficiency Syndrome

Carl W. Dieffenbach, Ph.D.
Director

Division of Allergy, Immunology, and Transplantation

Daniel Rotrosen, M.D.
Director

Vaccine Research Center

Gary J. Nabel, M.D., Ph.D.
Director

Division of Intramural Research

Kathryn C. Zoon, Ph.D.
Director

Division of Microbiology and Infectious Diseases

Carole A. Heilman, Ph.D.
Director

NIAID TB → DMID
NIAID HIV → DAIDS

NIAID Clinical Team (TB and TB/HIV)

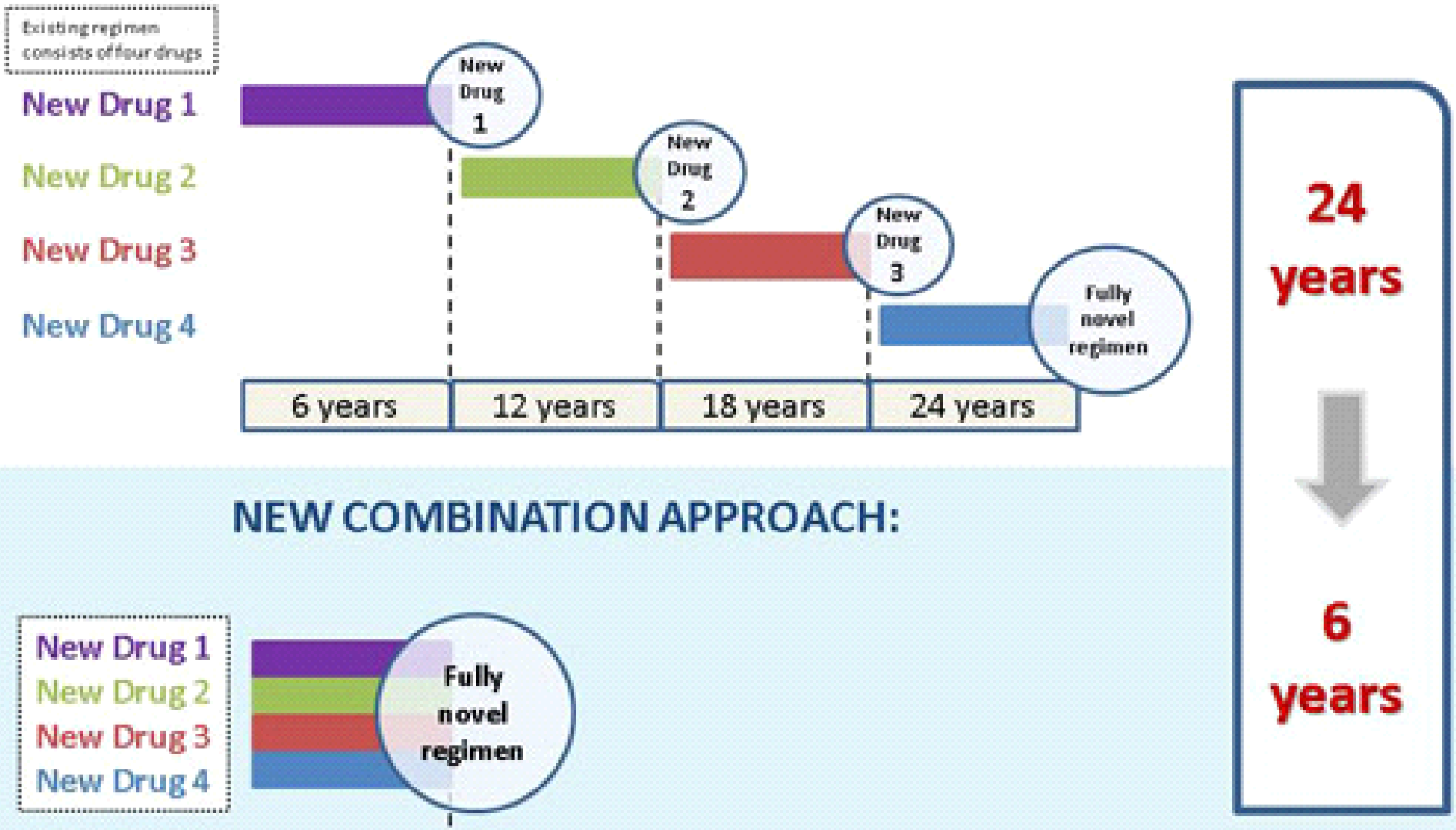
Fundamental | **Non-Clinical** | **Clinical** ***Ph I*** ***Ph IIA*** ***Ph IIB*** ***Ph III-IV***

DMID Resources → DAIDS Resources

- Systems Biology, Biomarker Programs
- Animal Models (Candidate Selection)
- Research Reagents
- "omics" Support Programs
- Preclinical Services, IND-enabling
- Ph I Units
- Clinical Trials Networks
- HIV-TB Basic/Pre-clinical Grants
- *Solicited and Unsolicited Grants - R34/U01/BAA
- Vaccine & Treatment Evaluation Units
- *Tuberculosis Research Unit
- *Clinical Diagnostics Research Consortium

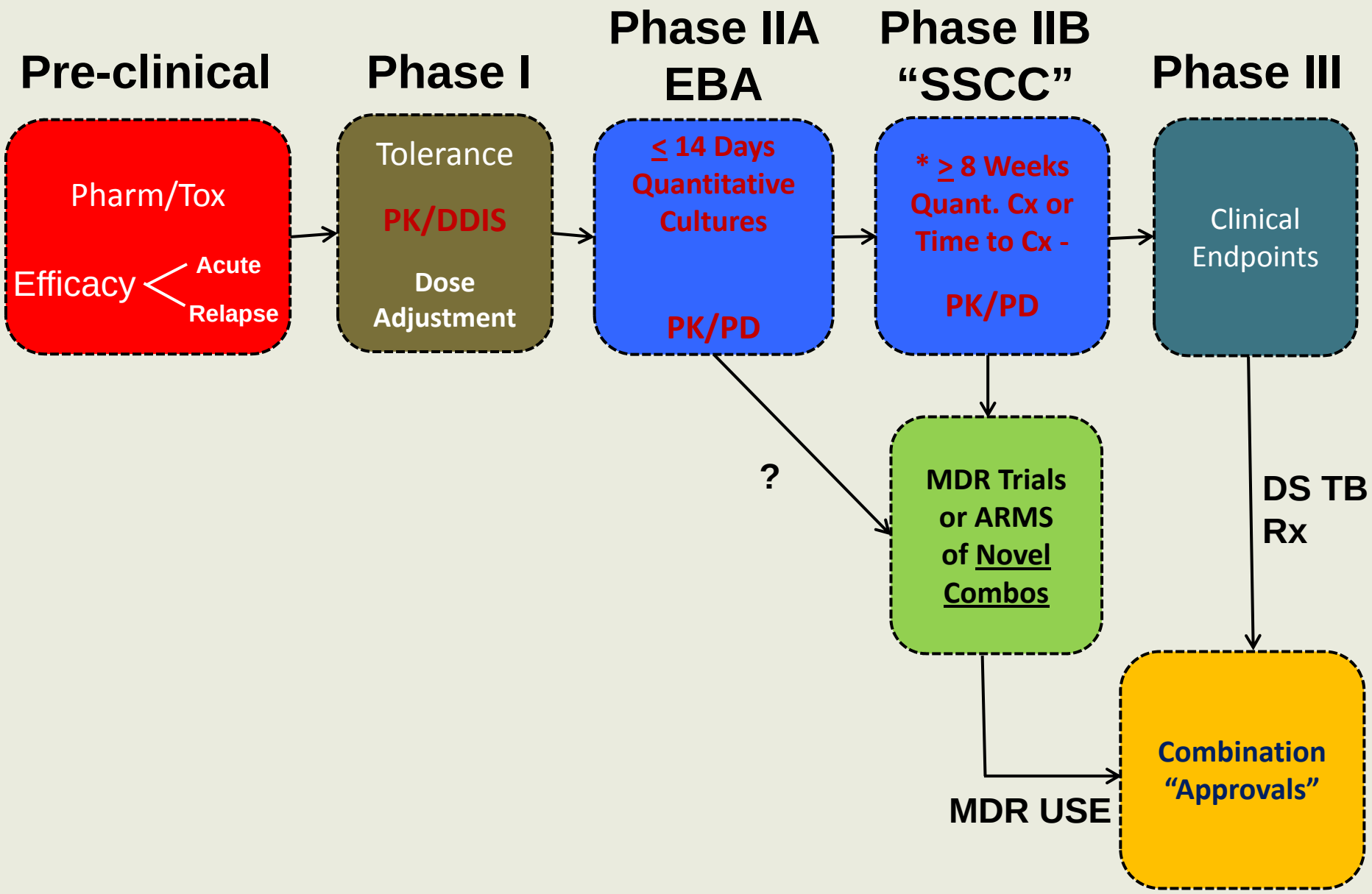
*TB specific

CURRENT REGIMEN DEVELOPMENT PARADIGM:

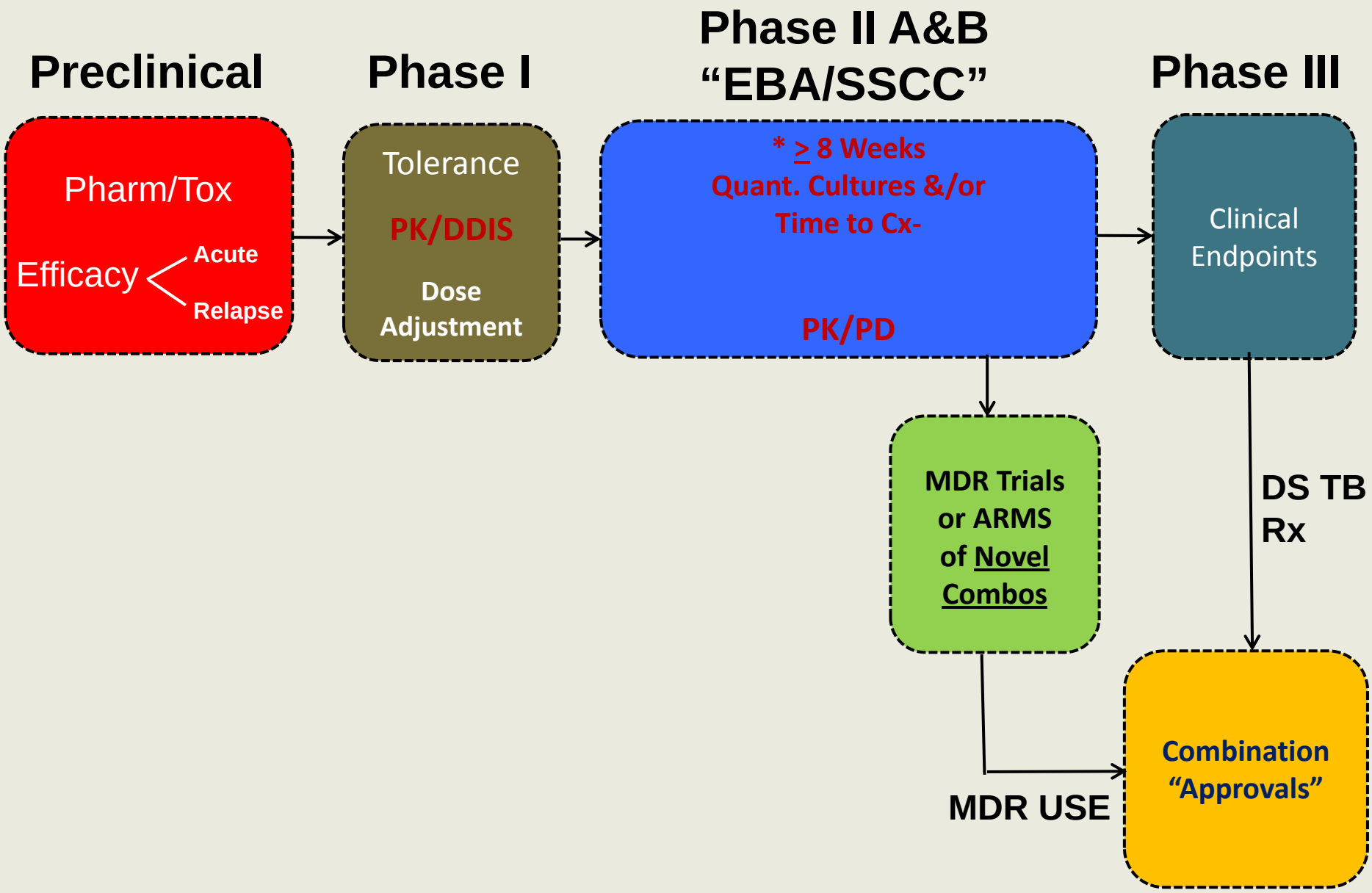


NEW COMBINATION APPROACH:

Combination Drug Development



Combination Drug Development



Possible Combinations

Classes = 8

- **Possible 3 drug combos = 56**
- **Possible 4 drug combos = 70**

Classes = 10

- **Possible 3 drug combos = 120**
- **Possible 4 drug combos = 210**

“Re-purposed “ Drugs

- Beta-lactams and clavulanic acid others
- Antifolates/ sulfas (e.g. sulfamethozazole)
- Nitizoxanide
- Oxyphenbutazone

Initial K-RITH Clinical Studies

- Initial trial, A5307, to open early 2012
- Other Rx concepts (not treatment combo development)
  - Comparison of TB treatment responses among HIV subpopulations vs. non-HIV
  - Efflux pump inhibition
  - Inhaled agents
    - Capreomycin
    - Membrane disrupters - ? Colistin

Substudies to develop:

- Imaging (PET/CT) to evaluate treatment response
- Molecular-based quantitative response assays (rRNA)


Empiric
OBT


SPUTUM

2016 DHHS/WHO Guidelines for Treatment of Tuberculosis in Adults, Adolescents and Children

Antituberculosis Drugs	Approved Agents
DNA-dependent RNA Polymerase Inhibitors – DRPIs	Rifapentine, Rifampin, Rifabutin
Topoisomerase/Gyrase Inhibitors – TGIs	Moxifloxacin, Levofloxacin
ATP Synthase Inhibitors – ASIs	Bedaquiline (TMC), clofazimine?
Protein synthesis Inhibitors – PSIs	Oxazolidinones, amikacin and others
Nitric Oxide Producers/Electron Transport Suppressors – NOPETS	PA-824, Delamanid (OPC)
Mycolic Acid Synthesis Inhibitors – MASIs	INH, Ethionamide
Drugs with Unknown Mechanisms of Bacteriolysis – DUMBs	Pyrazinamide, SQ109

2016 DHHS/WHO Guidelines for Treatment of Tuberculosis in Adults, Adolescents and Children

Preferred regimens for patients with active and latent tuberculosis	
Preferred regimens –all patients	DRPI + ASI + TGI + NOPET for 2 months
Genotypic DRPI resistance	ASI + TGI + NOPET + PSI for 3 months
Genotypic DRPI + TGI resistance	ASI + NOPET + PI + DUMB for 3 months
Multiple resistance	Use TB-Phenosense to customize regimen
Latent TB Infection –DRPI susceptible	Rifapentine/INH for 1 month
Latent TB – DRPI resistant	Bedaquiline for 3 months

Coordination and Collaborations

Trials Capacity

- Phase III trials will be **large** – require collaborations (CPTR is addressing several aspects)
- ***Phase II planning is reaching a critical stage***
  and needs to be efficient and timely
- No one group has enough resources for any aspect
  - Funding -- This is not the 1990's and this is not HIV!!
  - Site and lab capacity, capabilities, training
  - Sufficient potential study populations
- Sufficient study drug supply to include all promising combinations

Coordination and Collaborations

- Communication/Information Sharing

- Coordination/Harmonization

- Collaborative studies

C & C Platforms/Fora

- **Therapeutics (Combination Development)**
  - **Phase II planning forum** and interactions with CPTR
  - Establishment of web site for posting trials in development
- **Diagnostics/DST/Biomarker Research**
  - June workshop → establishment of **C & C Forum** with regular meetings/postings and interactions with CPTR for biomarkers
- **TB Vaccine Research**
  - I) NIAID TB Vaccine Clinical Research **Coordination Committee** including IMPAACT, HVTN, ACTG, NICHD, DMID/VTEU
  - 2) Strategic Coordination Forum with Aeras and TBVI, others

Poster Children for Enhanced Communication

Got Silos?

- ACTG 5274 (REMEMBER)
- PanACEA PROMPT
  - Both are very similar trials that will begin accrual this Summer
- STATIS (SYSTEMATIC EMPIRIC TB TREATMENT IN AIDS PATIENTS TO IMPROVE SURVIVAL)
  - In development until aborted in 12/10 when these other trials became known to proposers