The Critical Path to TB Drug Regimens Initiative

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The new tools that are needed to fight TB are on their way

- **Development of new TB diagnostics, drugs and vaccines are key elements of the WHO's Global Plan to Stop TB and to the Gates Foundation's TB strategy**

- **A transition has occurred from academically focused clinical research to industrial level new TB drug development**
  - » There still are many unknowns in TB and there remains a need for fundamental research
  - » Yet, enough is known to develop new TB products

- **There is an opportunity to develop novel TB drug regimens for drug-sensitive and drug-resistant TB**

- **This has generated a new initiative, Critical Path to Tb drug Regimens**

Current TB drugs have been developed to the standard of their time and have issues

- **Optimal dose and dose regimen not known for some**
- **Individual drug's contribution to effect of the regimen not known**
- **Metabolic interactions, notable with ARV drugs**
- **Tolerability and safety less than ideal**
- **Weak evidence base for 2nd line TB drugs**

Product development partnerships have changed the field

	Product	Process	Research
10 Years Ago	▪ Few credible product candidates	▪ Clinical research approach	▪ Small, active group, academically focused
Premise	***TB-specific PDPs would develop the products and a process, while Grand Challenges and innovations programs would encourage scientific engagement***		
Now	▪ Credible product candidates with development plans	▪ A rational go/no go process exists	▪ Networked group, product focus, industry partners

The foundation chose to invest in new tools through the development of three TB-specific PDPs

- **AERAS**

  The goal of the Aeras Global TB Vaccine Foundation is to develop, test, characterize, license, manufacture and distribute at least one new TB vaccine regimen for infants and another for adolescents and ensure their availability to all who need them.

- **Foundation for Innovative Diagnostics (FIND)**

  Our vision is of a world where everyone will have equitable access to high quality diagnosis. Our mission is to drive the development and implementation of accurate and affordable diagnostic tests that are appropriate to patience care in low-resource settings.

- **Global Alliance for TB Drug Development (GATB)**

  Our mission is to ensure the widespread availability of affordable, faster and better tuberculosis drug regimens that will advance global health and prosperity.

Standard “best practices” have been adopted

- **A programmatic approach**
  - Starting with the end in mind: a target product profile
  - Design a program: a series of studies, in which each informs the next or addresses a particular aspect of the TPP
  - Dose and dose regimen selection on the basis of PKPD
  - Use predefine criteria of success in program decision making
  - Phase IV: think early about data needs beyond licensure requirements
- **Appropriate study designs**
  - Address a single (or very few) questions
  - Limit number of secondary and exploratory endpoints
  - No investigator discretion in particular in phase II
  - Adequately powered
  - Design assumptions based on observation at investigational sites
  - Plan for ITT analysis
- **Rigor in execution**
  - Adherence to protocol
  - Standardized or centralized laboratory assessment
  - Keep methodology stable for the duration of the study
  - Work according to ICH GCP standards
  - Limit use of study execution as opportunity for unrelated studies

Even then, state of the art TB drug development leaves many uncertainties

Limited availability of biomarkers

- (Hinders development of PoC diagnostic)
- (Makes vaccine development empirical, complicates vaccine trial endpoint assessment)
- Not having a biomarker for cure complicates clinical development

Clinical trial endpoints

- An Outcomes endpoint after 1 or 2 years is used in phase III
  - » Failure to cure combined with relapse
  - » Broader unfavorable outcome including lost-to-follow up and death all causes
- Bacterial endpoints like Serial Sputum Colony Counts and Sputum Conversion are used in phase II
- Challenge: can other endpoints be qualified to support approval?
  - » In DR TB?
  - » In DS TB?

Furthermore,

New combination therapy, not just new drugs are needed

- Emergence of Drug Resistant TB
- Current 2nd line treatment regimens are impractical and therefore difficult to scale
- Risk of inducing resistance to a new drug shortly after introduction

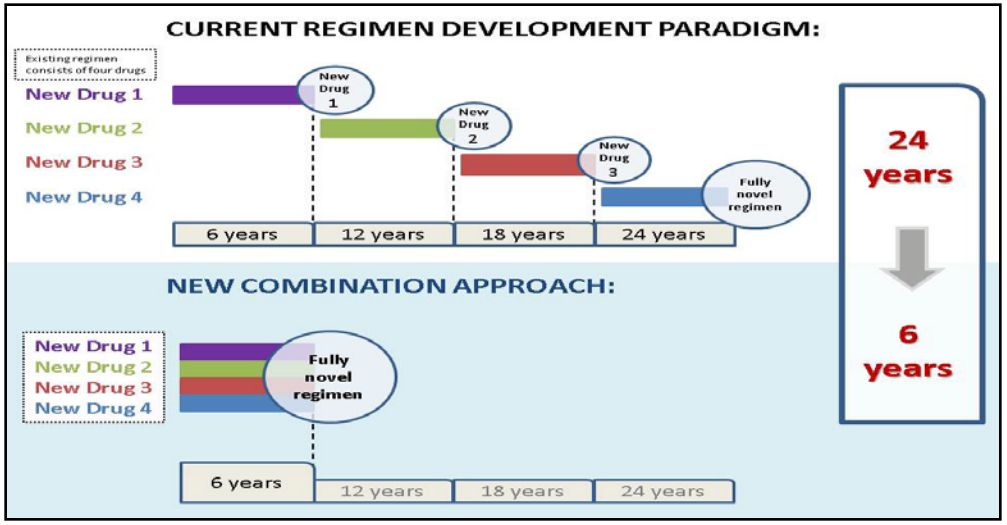
Classical combination development cannot be done

- The current 4-drug regimens were developed empirically to the standard of the seventies
- The individual contribution of each drug to the regimen is not understood.
- Given state of TB clinical trial methodology, sequential development of a new combination would take decades.

Therefore, the CPTR initiative was created

What is the Critical Path to TB drug Regimens – CPTR?

- **Main goal: to accelerate the development of new, safe, highly effective and shorter duration TB regimens through <u>early drug combination testing</u> prior to individual drug approval.**



- **Also: to develop new "regulatory science" to facilitate TB drug development**
  - » Biomarkers
  - » New trial designs
  - » Data Standards
- **A partnership of pharmaceutical companies, the TB Alliance, the Critical Path Institute, a broad group of TB stakeholders, and the regulators**

Launch of the Critical Path to TB Drug Regimens (CPTR)

THE WALL STREET JOURNAL.

A8 Thursday, March 18, 2010 THE WALL STREET JOURNAL.

U.S. NEWS

FDA Is Easing Way for Drug Cocktails

Agency Draws Up Guidelines for Approving Two or More New Drugs Together to Fight Deadly Diseases Such as TB, AIDS

By Mark Schoofs

The Food and Drug Administration is devising guidelines that could accelerate testing and approval of multidrug regimens for some of the world's most deadly diseases.

At least two pharmaceutical consortia are poised to take advantage of the forthcoming policy: a group of 10 drug companies and several nonprofit organizations convened by the Bill and Melinda Gates Foundation to develop medicines to fight tuberculosis; and pharmaceutical giants **Merck** & Co. and **AstraZeneca** PLC, which are jointly testing two anticancer agents.

Many diseases, such as AIDS, tuberculosis and cancer, require multidrug combinations. Such drug cocktails can prevent the development of drug resistance, because the microbe or cancer cell needs to undergo more mutations to escape several drugs than to escape just one. By attacking the disease in different ways, drug combinations pace with the use of products in combination.

Now the FDA is drafting guidelines on how testing and what research would be required in the test tube, animals and humans to determine side effects, proper dosage and each drug's contribution to any cause certain side effects. "Society wouldn't tolerate this degree of uncertainty" except for drugs to treat dire illnesses, she said.

Multidrug-resistant cases—exceeding half a million annually—take two years to treat with drugs that often cause severe side effects but only

executives of 14 drug companies. A representative of **Sanofi-Aventis** SA said the meeting helped catalyze that company's participation in the current tuberculosis collaboration. On Thursday in Washington, D.C., the foundation is expected to unveil the collaboration, in which all partners agree to share data and test new drugs in combination treatments early in the development process.

For companies, sharing the cost of clinical trials and bringing proven combinations to market more quickly might save money. But if a regimen fails, it could give every drug in it a bad reputation, which could be costly to overcome, even for drugs that ultimately prove safe and effective. And there are thorny questions on how competing companies would share data, decide which drugs to combine into regimens, and market their drugs.

The Gates collaboration, known as the Critical Path to TB Regimens, includes drug giants **Pfizer** Inc.,

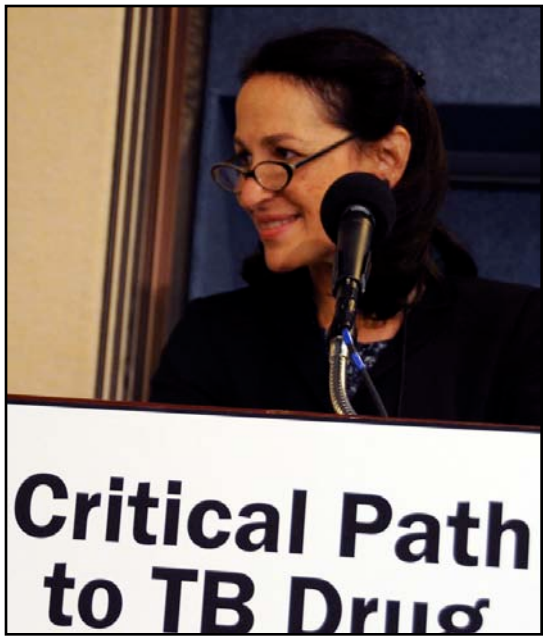
In the Pipeline | Tuberculosis compounds currently in development

Developer	Experimental drug	Class	How it kills the TB bacteria
Tibotec Johnson & Johnson subsidiary; **Global Alliance for TB Drug Development**	TMC-207	Diarylquinolone	Disrupts cellular energy production
Otsuka Pharmaceutical	OPC-67683	Nitroimidazole	Disrupts synthesis of lipids and proteins
Global Alliance for TB Drug Development	PA-824	Nitroimidazole	
Lupin	LL 3858	Pyrrole derivative	Not well understood
Sequella	SQ 109	Ethylenediamines	Affects cell wall, may have other mechanisms

Development of TB drugs and cocktails

- **1952:** First combination therapy using three drugs
- **1960s:** One drug in cocktail replaced
- **1970s:** Fourth drug added to cocktail
- **1980s:** One drug in combination replaced

Sources: Global Alliance for TB Drug Development; Stop TB Partnership's Working Group on New TB Drugs; WSJ reporting; Zhenkun Ma and Christian Lienhardt, article in Clinics in Chest Medicine



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TAG
Treatment Action Group

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NOVARTIS

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CRITICAL PATH INSTITUTE
Improving the Path for Innovative Therapies

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

How will this be done?

- **Identify promising combinations in animal models**
- **Proceed to phase I as usual, study interactions**
- **Proceed to factorial Early Bactericidal Activity studies**
- **Proceed with promising combinations to phase IIB sputum conversion studies**
  - New trial designs?
- **Different phase III pathway for Drug Sensitive and Drug Resistant disease**

…A work in progress…

How is CPTR organized?

CPTR Initiative

BMGF, in association with the TB Alliance and C-Path, will work to accelerate the development of new TB drug regimens

1	2	3
CPTR Consortium "regulatory science"	CPTR Coalition "drug development"	CPTR Infrastructure "key success factors"
Focus		
• **Data Standards/Integration** •**New clinical trial designs** • **Qualified Biomarkers** • **Disease Progression Models**	•**Drug combination testing and development**	• **Clinical trial capacity** • **Regulatory harmonization** • **Funding**
•**C-PATH** •**TB Alliance** •**Pharma companies** •**Regulators** •**TB experts** •**Patient representatives** •**RUF**	•**TB Alliance** •**Pharma companies**	• **BMGF** •**TB Alliance** •**Pharma companies** •**NIH, CDC** •**Regulators** •**Other funders** •**Patient representatives** •**RUF**

CPTR: How will success look?

- **Qualified tools that maximize learning and minimize delay in the testing of new TB drugs in combination and individually**

- **Novel regimens for treatment of DS and MDR TB approved by regulatory agencies, endorsed by the WHO and adopted by high burden countries**

The CPTR approach will become the gold standard for rapid, safe and efficient testing and development of new TB drug combinations

Thank you!