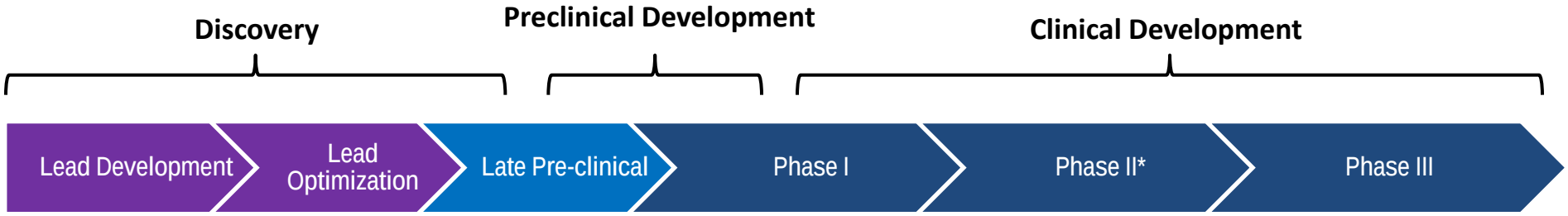
GLOBAL DRUGS PORTFOLIO
INNOVATION IN TB THERAPEUTICS RESEARCH

DAIDS/NIAID

October, 2013

Global TB Drug Pipeline[1]



- Diarylquinolones
- Gyrase Inhibitors
- Cyclopeptides
- Benzimidazoles
- DprE Inhibitors
- ihnA Inhibitors
- LeuRS Inhibitors
- Macrolides
- Ruthenium (II) Complexes
- Spectinamides
- Translocase-1 Inhibitors
- CPZEN-45
- DC-159a
- Q203
- SQ609
- SQ641
- TBI-166
- **BTZ 043**
- **PBTZ 196**
- **TBD 354**
- **Bedaquiline**
- **SQ 109**
- **PA 824**
- **Delamanid**
- **AZD 5847**
- **Sutezolid**
- **Linezolid**
- **Levofloxacin**
- **Moxifloxacin**
- **HD Rifamycins**
- ***Clofazimine***

[1] Projects that have not identified a lead compound series are considered to be in the screening phase of development and are not included. As of publication, there are 11 screening projects in progress as described on http://www.newtbdrugs.org/pipeline.php.

*Initiation of drug combination studies

New Drugs in Clinic

Still a Far Way to Go

Pipeline still not sufficient to assure at least one entirely novel combination with increased potency and tolerance

- Only one of ten candidates entering trials advance to approval

- **"Generating 5 new or repurposed drugs and at least one 1-3 month regimen by 2020 will require an estimated 21 additional new drugs to be in clinical development by 2015."**

Caution with some New Drug Classes

Safety and efficacy concerns

- Very long half-lives and high tissue concentrations
- Consider more extended (not intensive) trial follow-up for safety and efficacy **vs. experience with current drugs**

For combinations

- Additive toxic effects and with **long** half-lives
  - Potentially additive Q-T interval prolongation

  (Bedaquiline + clofazimine)
- Most have important major metabolites - complex

  Difficult to study – when will peak effect occur and how long will increase last?

New Drugs for Combination Studies

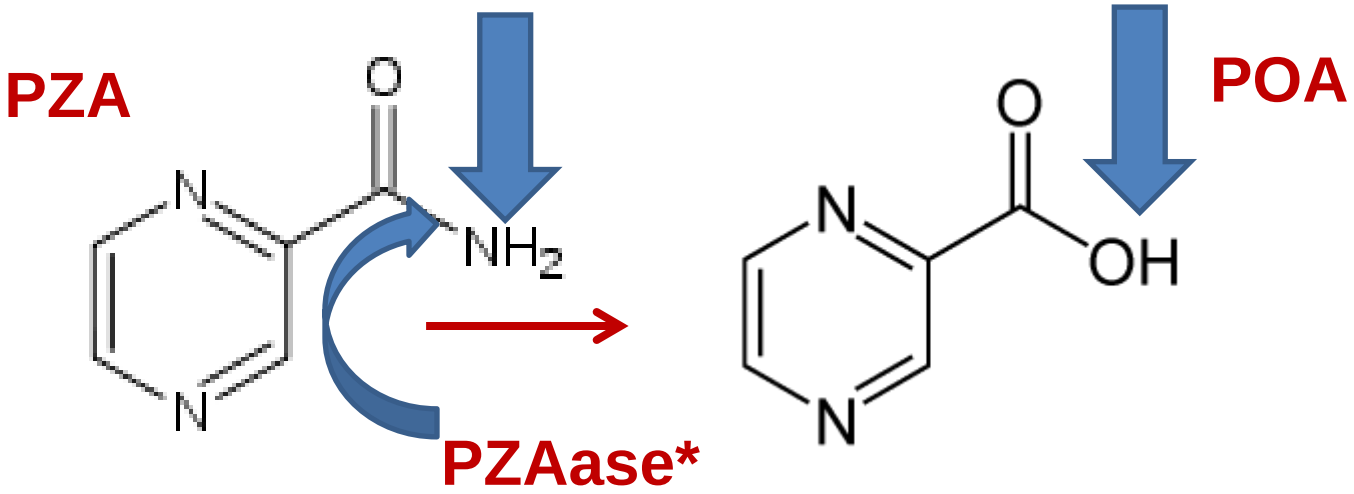
Some new agents for DS/DR combos -

- **Bedaquiline**
  - **Black Box** warning
  - Q-T interval prolongation
  - Drug interactions
- **Oxazolidinones** (sutezolid, AZD-5847, etc.)
  - Possibly serious toxicities with prolonged (> 8 wks) use
- **Nitroimidazoles** (delamanid and Pa-824)
  - Q-T interval prolongation
  - Drug interaction potential (with inducers)

Improving Use of Current Drugs

- **INH** – most cidal drug for active replicators
  - Role in low-level (INH) resistance treatment to be defined
  - **Antagonism with PZA** → best use may be only for **first few days**
- **Rifamycins** (rifampicin/rifapentine/rifabutin)
  - **Dosing being optimized**, PanACEA (RMP) and TBTC (RPT)
- **Quinolones** – (moxifloxacin, levofloxacin)
  - Optimal choice/dosing not clear, less Q-T prolongation with levo
  - **Role in shortening DS TB Rx** - defined soon (Oflotub III, ReMOX)
- **PZA** – Still essential when susceptible = 94% overall
  - Need to develop reliable (+ rapid) PZA DST (pncA mutations)
  - Develop **alternative pro-drug** for POA– overcome resist.

PZA (Pro-drug) Activation



*Mutations to the PZAase gene (pncA) cause “resistance”

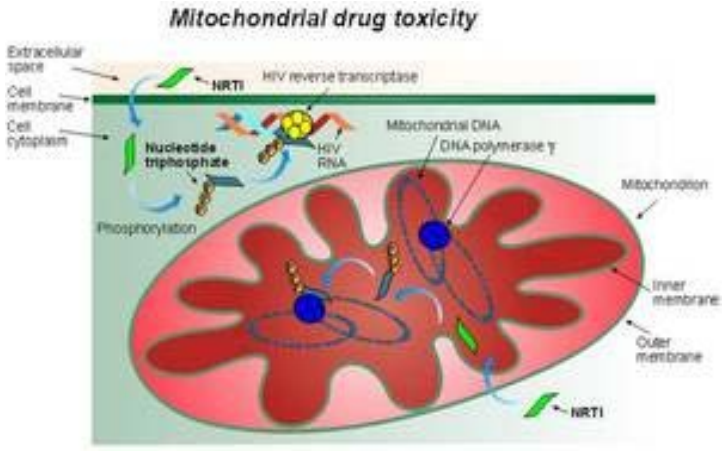
** Changing from amide pro-drug to different pro-drug linkage cleaved by a different enzyme to overcome resistance

Other approach –
Cochleated POA for oral administration

OXAZOLIDINONES

Five possibilities

- Linezolid
- Sutezolid (Sequella)
- AZD-5847 (AstraZeneca)
- Radezolid (Rib-X→Melinta)
- Tedizolid (Trius→Cubist)



Pre-clinical testing – results within a few months

- Efficacy in marmoset model (C. Barry lab)
  – TB lesions mimic human disease
- **Mitochondrial toxicity** (cyt-oxidase synthesis → proteomics) after exposure of target cells to range of drug exposures using hollow fiber system **x 2Mos**

Therapeutics – New Approaches

- **Enhancing** current and new drugs
  - **Efflux pump inhibition**
  - **Inhalation and related formulations**
  - **Optimal drug dosing and duration**

- **Phasing** of drug combinations
- ***Adaptive*** Phase II Combination Trials
  - **Drop less effective arms ASAP and add new arms**
  - **Seamless Phase (IIa - IIb - III) transitions**
  - **Real-time response biomarkers: molecular and imaging (PET/CT)**
- New Frontier - **Host Directed Therapies** (**HDT**)

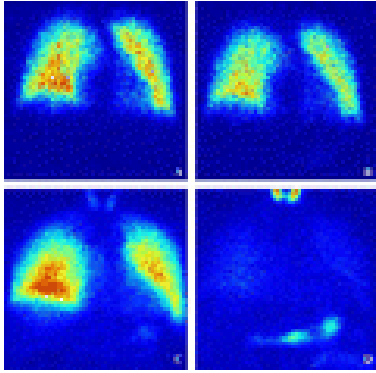
Efflux Pump Inhibition as TB Drug Enhancer

Bacterial efflux pumps remove drugs → lower concentration inside the organism

- **Timcodar** (Vertex 853) – experimental efflux pump inhibitor
- **In vitro - bedaquiline MIC 0.06 → with TIM 0.004 – 15x**
  - **Verapamil has similar effect in vitro**
- In addition – rifampin and H+R activity were clearly enhanced in an mouse model
- The 15-fold potentiation of BDQ is more than could be predicted by efflux inhibition alone
- So what is the mechanism of enhancement?

  Probably not just increase in intra-bacillary concentration

Inhaled Agents/Formulations



Drug	Comment
Pyrazinoic Acid Esters	**NOT PZA (a pro-drug) – for resistance**
Capreomycin	**Also systemic absorption**
Clofazimine	**Reduce systemic absorption**
Metronidazole	
Aminogylcosides	
New drugs with severe toxicities	
Colistin	**Try to decrease XDR transmission**
HDT drugs	**Local immunomodulation**
Arginine	**Increase NO production**
Verapamil	**TB Drug enhancer - Avoid CV effects**

PET scanning to evaluate pulmonary distribution

Optimal Drug/Combination Use

Goals of Optimized Combination Therapy

- Shortest overall **duration** to achieve sterilization
- **Limit toxicities** by using drugs with duration-related toxicities for SHORT TIMES (≤ 8 weeks)
- Avoid **simultaneous** use of:
  - More than 3 drugs
  - Drugs with major PKIs, additive toxicities, or antagonism
  - More than 2 drugs with Q-T interval prolongation
- Prevent **resistance** development despite use of few drugs at the same time
- React to changes in **bacterial populations** during treatment course (increasing NPR predominance)

HOW?

PHASING of drug combinations

Bactericidal and Sterilizing Combination *Phasing*

1. **Initial Cidal & Sterilizing Phase x 4 weeks**

[INH x 3 days*] + Rifamycin + PZA + FQ^

(? or nitroimidazole^)

2. **Secondary sterilizing Phase x 6 weeks**

Bedaquiline #,^ + clofazimine #,^ + oxazolidinone

(? or with a pump inhibitor)

(Would need to compare different durations)

*ACTG 5307 will address in EBA trial

Bedaquline+clofazamine – prolonged tissue levels

^ Q-T interval prolongation

Efficiency in Combination Development - Focus on Phase II

Problem – to study a new combination in Phase II

- **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 first used in cancer chemotherapy Phase II trials
- New biomarkers for rate of reducing total TB burden
  - Enable comparisons with smaller numbers/arm
  - Rapid turn-around to allow real-time decisions for continuing or stopping a study arm

Adaptive Phase IIB - Three Stages

1. **Intensive** safety, PK/PKI, and EBA PD in experimental arms – small numbers – then-
2. Randomize more for comparison to standard arm **with interim review(s)** – drop losers

   (and could add arms with new combination arms OR change duration of therapy)
3. **Extend accrual** into "survivor" arms to compare and pick one or more winners

With a clear winner – (?**4.**) "**seamlessly" transition** into Phase III comparison with standard therapy

MAMS-TB-001

Sites: 2 x Cape Town; 2 x Johannesburg; 3 x Tanzania
Study start: November 2012; End: Sept. 2013
Sponsor: University of Munich (Michael Hoelscher)
Chief Investigator: Martin Boeree

Control (124):	2 months HRZE	+ 4 months HR
Arm 2 (62):	3 months **$HRZQ_{300mg}$**	+ 3 months HR
Arm 3 (62):	3 months **$HR_{20mg}ZQ_{300mg}$**	+ 3 months HR
Arm 4 (62):	3 months **$HR_{20mg}ZM$**	+ 3 months HR
Arm 5 (62):	3 months **$HR_{35mg}ZE$**	+ 3 months HR

+ 6 months subsequent follow-up for all

One planned interim review by IDMC that could result in dropping arms

Challenges - THE CRITICAL GAP

KEY ASPECT FOR IMPROVING TB THERAPY

More Rapid Elimination:

Persisting / Non-replicating / "Dormant" / Inactive / Fat-and-Lazy Bugs*

Biomarkers to measure how quickly they are killed/eliminated for prediction of non-relapsing cure and preferably with rapid-turnaround

– replace cultures and --- sputum

***Need to standardize terminology**

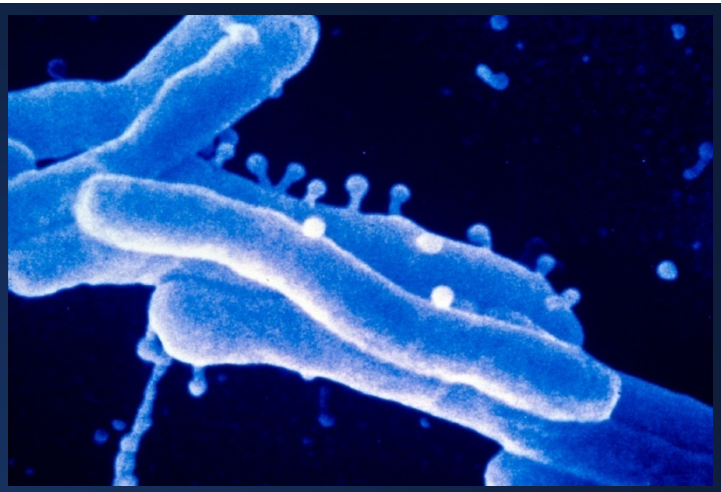
Biomarkers - Quantitating killing of all NON-REPLICATING PERSISTERS (NPRs)

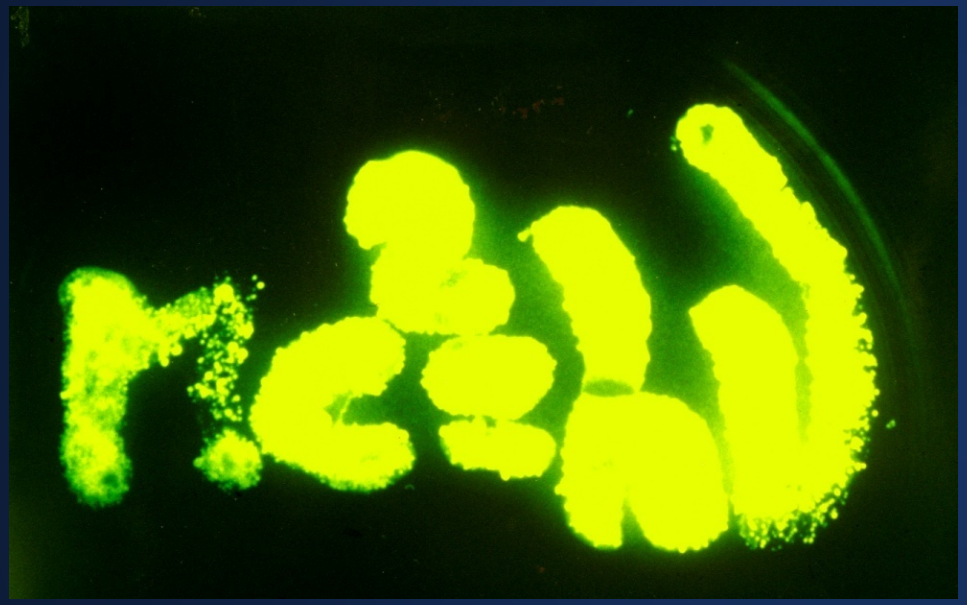
Prognostic Biosignatures for changes in total TB burden, including NPRs to full elimination (cure) vs. following all participants for clinical relapse (12-18 months)

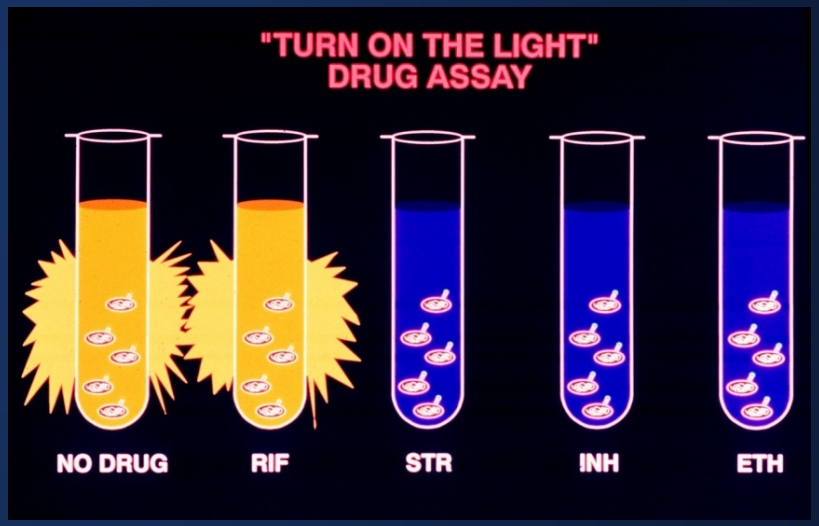
- Detect **bacterial products** correlating with killing
  - Molecular - rRNA, proteomic, metabolomic assays….
- **Immune markers** of bacterial clearance
- **Resuscitation Promoting Factors** – "wake up" NPRs
  - **Stimulate dormant bugs** to grow and be counted
- **Visualize** entire population living bugs
  - In samples -- **Fluorophages** (Jacobs)
  - In lungs or whole body -- **PET scans** with new tracers

Imagination is more important than knowledge.

Albert Einstein







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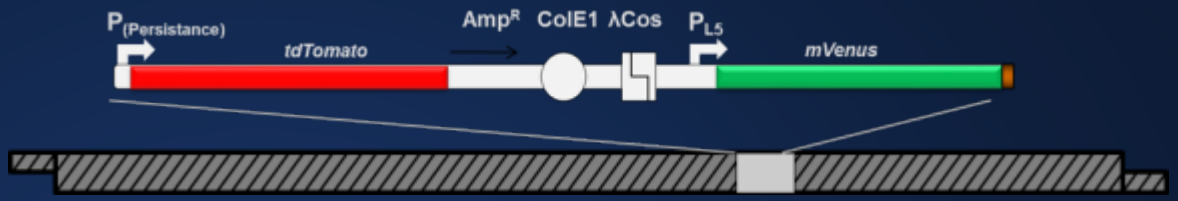
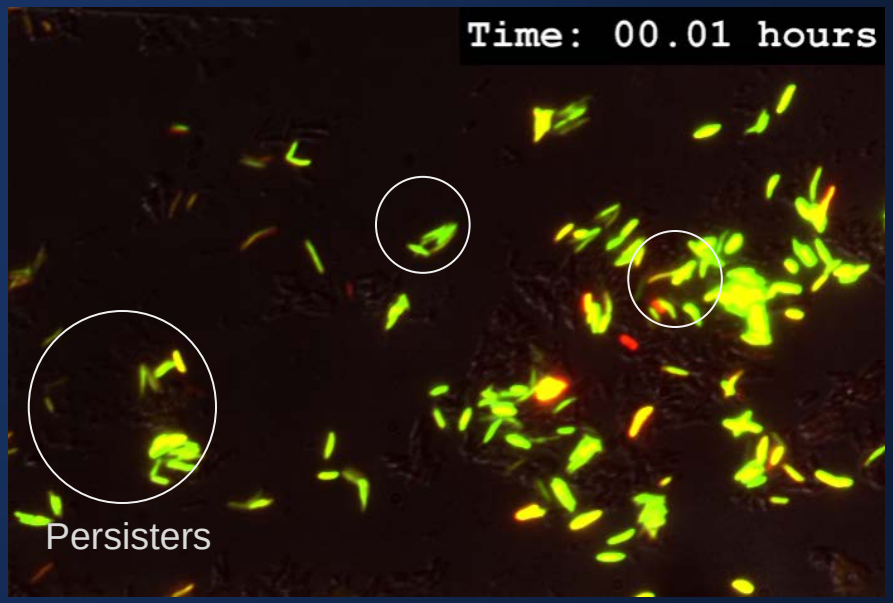
Dual Reporter phage engineered to identify *M. tb* persister cells



Log phase culture incubated
With reporter phage

INH treated culture incubated
with reporter phage



9 different persister specific promoters expressing *tdTomato* were used along with P_{L5} promoter expressing *mVenus*

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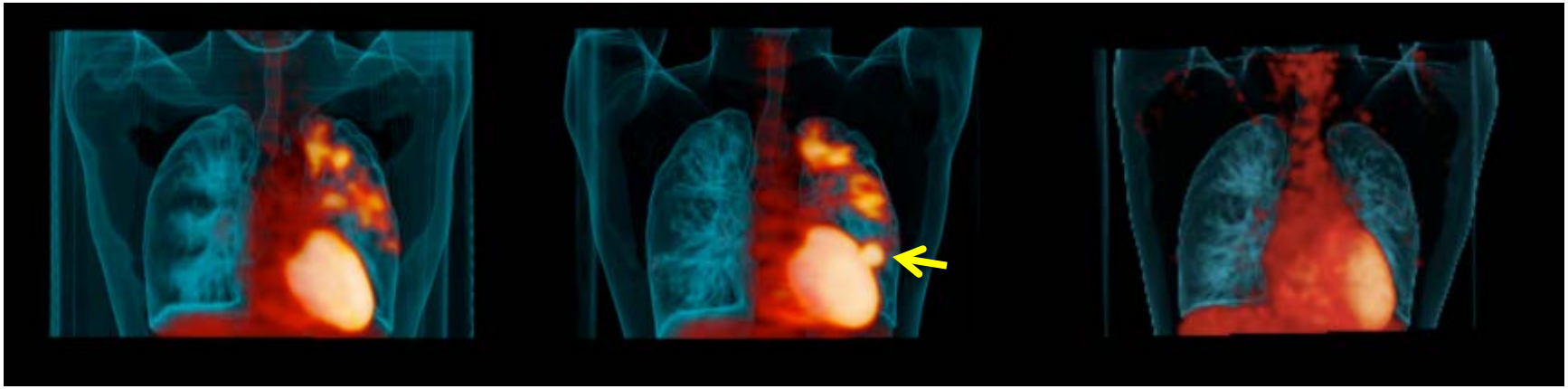
23 year old male enrolled in delayed linezolid arm:

2001	2003	2005	2007	2009
HRZE	PPtOCZ	HZPPtCO	HZKLfRb	HLf
failure	***failure***	***failure***	***failure***	***failure***

2009 DST R:HPSEREtCKORbMCp**, S:**Z(?)

T = -2 months T = 0 months T = 6 months



Sm/C: ++/28 +++/15 -/-

Rationale for Specific, Small Molecule Adjunctive Immunomodulators in TB Rx

- **Improving TB-induced immune defects**
  - Particularly macrophages/innate immunity/autophagy
- **Decreasing tissue pathology/sanctuaries**

(less inflammation, necrosis, caseation, granulomas…➔

Better blood flow/O_2, more permeable local environment, fewer inhibitory molecules)

- Improved immune cell access/function
- Improved anti-TB drug delivery to bacilli

- **Dormant TB may reactivate** and be killed more quickly by anti-TB drugs
- ***Improved TB clearance occurs in animal models***
- ***Several candidate agents also being evaluated for improved HIV therapeutic outcomes***

AUTOPHAGY INTRO

N ENGL J MED 368;7 NEJM.ORG FEBRUARY 14, 2013

REVIEW ARTICLE

MECHANISMS OF DISEASE

Autophagy in Human Health and Disease

Augustine M.K. Choi, M.D., Stefan W. Ryter, Ph.D., and Beth Levine, M.D.

Autophagy: A catabolic pathway involving the degradation of cellular components through the lysosomal machinery, the major subtype of which is macroautophagy.

Xenophagy: A selective form of autophagy in which intracellular pathogens, including **bacteria** and viruses, are degraded through the macroautophagic pathway.

Autophagy's Role in TB

PNAS

Autophagy protects against active tuberculosis by suppressing bacterial burden and inflammation

Eliseo F. Castillo[a,1], Alexander Dekonenko[b,1], John Arko-Mensah[a], Michael A. Mandell[a], Nicolas Dupont[a], Shanya Jiang[a], Monica Delgado-Vargas[a], Graham S. Timmins[c], Dhruva Bhattacharya[a], Hongliang Yang[d], Julie Hutt[e], C. Rick Lyons[b], Karen M. Dobos[d], and Vojo Deretic[a,2]

Departments of [a]Molecular Genetics and Microbiology and [b]Internal Medicine and [c]College of Pharmacy, University of New Mexico Health Sciences Center, Albuquerque, NM 87131; [d]Department of Microbiology, Immunology and Pathology, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 805235; and [e]Experimental Toxicology Division, Lovelace Respiratory Research Institute, Albuquerque, NM 87108

PNAS | Published online October 23, 2012 | E3169

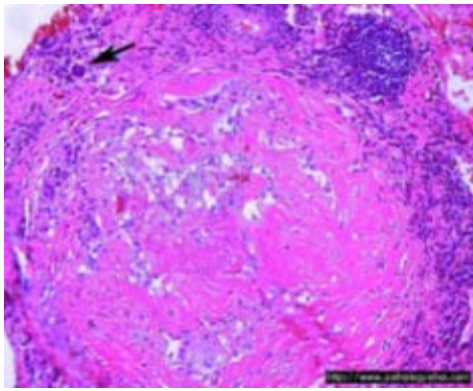
…. Here we show that autophagy plays a dual role against tuberculosis: antibacterial and anti-inflammatory.

Thus, autophagy acts in vivo by suppressing both M. tuberculosis growth and damaging inflammation.

Approved Agents for HDT Study

BOTH enhance immunity/decrease inflammation primarily by enhancing AUTOPHAGY

- Verapamil (+may enhance BDQ, CFZ, PZA, RIF)
- Statins
- Abl/cKIT TKIs – *imatinib*, etc.
- *? Nitazoxinide#*



Decrease inflammation (and IRIS)

- *Ibuprofen#*
- Leukotriene inhibitors
- Phosphodiesterase inhibitors
- Corticosteroids

May also have direct activity against M. Tb

HDT CAVEATS

- **May not work**
  - PK/PD issues - delivery to site of action in active form with sufficient exposure
  - Extrapolation from different disease models/states
  - In vitro and animal model (rodent) data not translating
  - Actions depend on "tissue/cellular context"
  - Complexity of regulation/signaling – counter-reactions
  - ETC.
- **Could cause harm**
  - Worsen TB disease course
  - Increase lung damage
  - Impact on HIV co-infection

Lung Damage and Function Monitoring – Important HDT Trial Secondary Endpoint

- Agents decreasing excess inflammatory damage →

  Decreased pulmonary function loss

- Agents increasing inflammatory damage →

  Increased pulmonary function loss

Pulmonary function monitoring is a necessary evaluation for efficacy and safety of HDT agents (and ? biomarkers for damage or imaging)

Also – Effect on HIV co-infection

– improve or worsen?

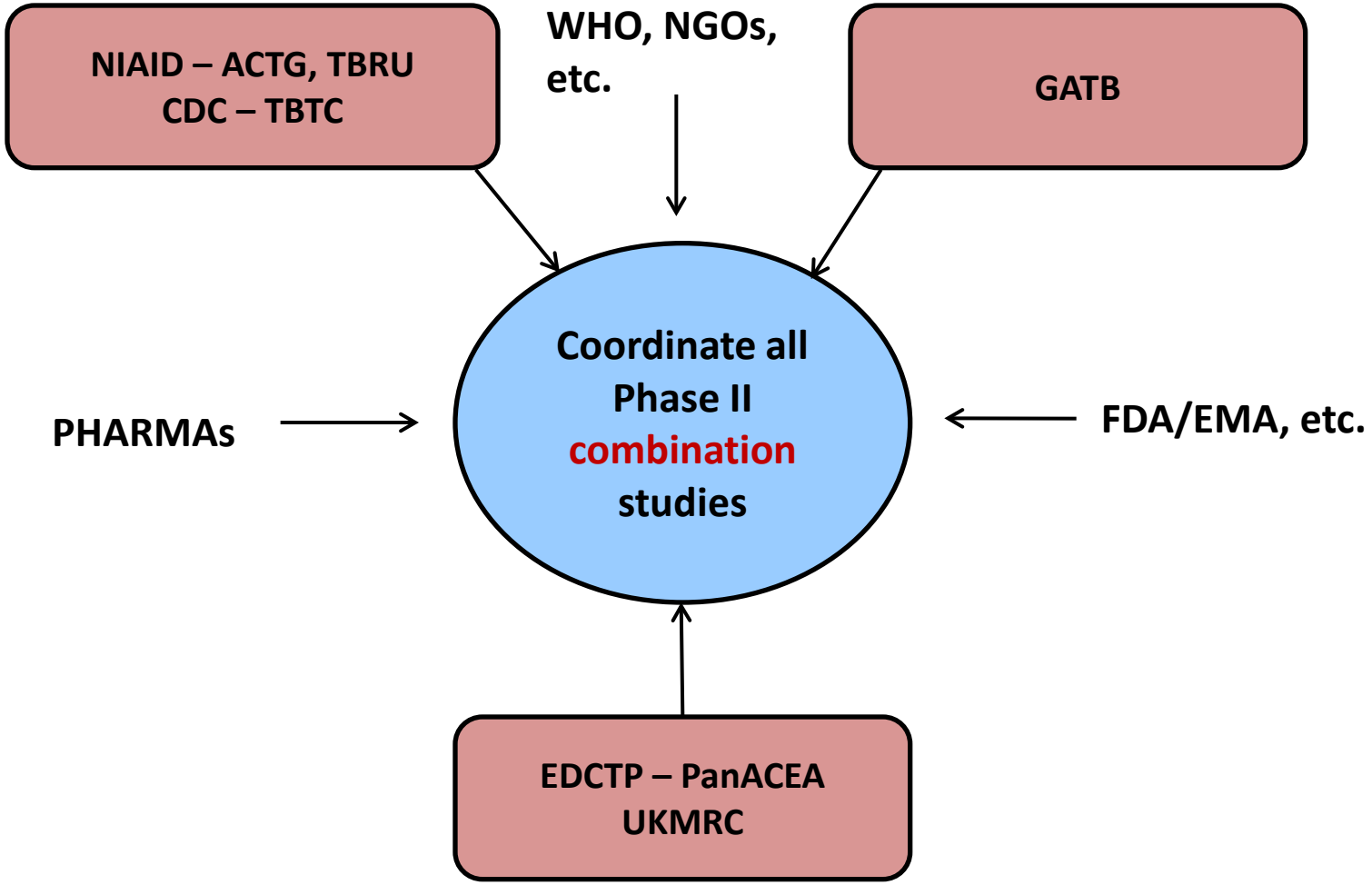
Coordination/Collaboration

Trials Capacity

- **Phase III trials will be large** – will require collaborations among trials groups
- No <u>one</u> group has enough resources
  - **Funding -- This is not the 1990's and this is not HIV!**
  - **Site and lab capacity, capabilities, training**
  - **Sufficient potential study populations**
- ****<u>Phase II planning is reaching a critical stage</u>****

  Coordination – avoid duplication and to be efficient and timely

Therapeutics - Phase II/III Planning
Coordination Forum



International Cooperative Innovation

- Cooperation to achieve large-scale goals – group-collaborative Phase IIIs
- Coordinated division/sharing of different components of projects (e.g., PZA plans)
- Synergy/leveraging of each other's projects
- "Competition" among true colleagues also stimulates advances
- Foster diverse approaches and encourage **innovation – out of the box, challenge dogmas**

Thank You

Further Reading

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2. Dick Menzies and Payam Nahid **Update in Tuberculosis and Nontuberculous Mycobacterial Disease 2012**, American Journal of Respiratory and Critical Care Medicine, Vol. 188, No. 8 (2013), pp. 923-927.
3. Patrick P. J. Phillips, Stephen H. Gillespie, Martin Boeree, Norbert Heinrich, Rob Aarnoutse, Tim McHugh, Michel Pletschette, Christian Lienhardt, Richard Hafner, Charles Mgone, Alimuddin Zumla, Andrew J. Nunn, and Michael Hoelscher **Innovative Trial Designs Are Practical Solutions for Improving the Treatment of Tuberculosis** J Infect Dis. (2012) 205 (suppl 2): S250-S257.
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