Tres Cantos DDW

Medicines Development Campus

Tuberculosis Unit (TB DPU)

David Barros

WGND meeting October 26th, 2011

GSK Tres Cantos: TB Pipeline

Whole Cell Screening (1st (2M)and 2nd (2K)

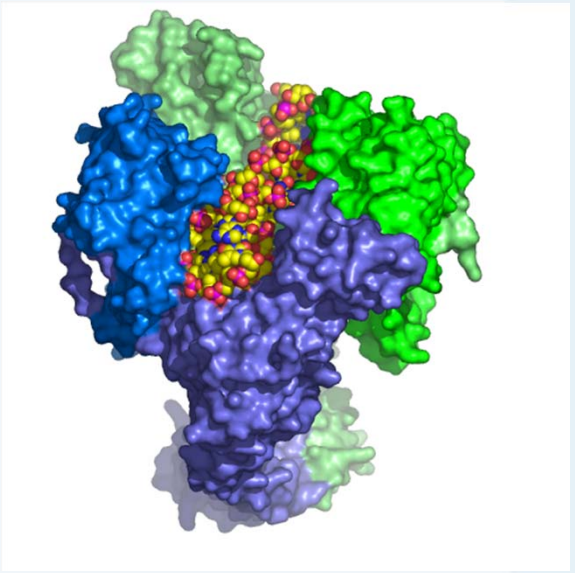
Bacterial DNA gyrase Inhibitors

Whole Cell: THPP series

- First wave: Known AB/TB targets (FABI, PDF, ICL, MS)
- Second Wave: GSK antimicrobials (Pleuromutilins, NBTI)
- Third wave: Phenotypic screen

GSK DNA Gyrase Inhibitors

- GSK discovered in an antibacterial Whole Cell screen a new series of compound that have a new MoA and are no cross resistant with FQ: NBTI's
- GSK's DNA-gyrase antibacterial programs
  - MRSA, RTI, Gram Neg.infection
- Target clinically validated in TB with FQ
- XDR-TB (FQ^R) is a major threat for human beings (85% mortality rate)
- AB leads only marginally active against Mtb



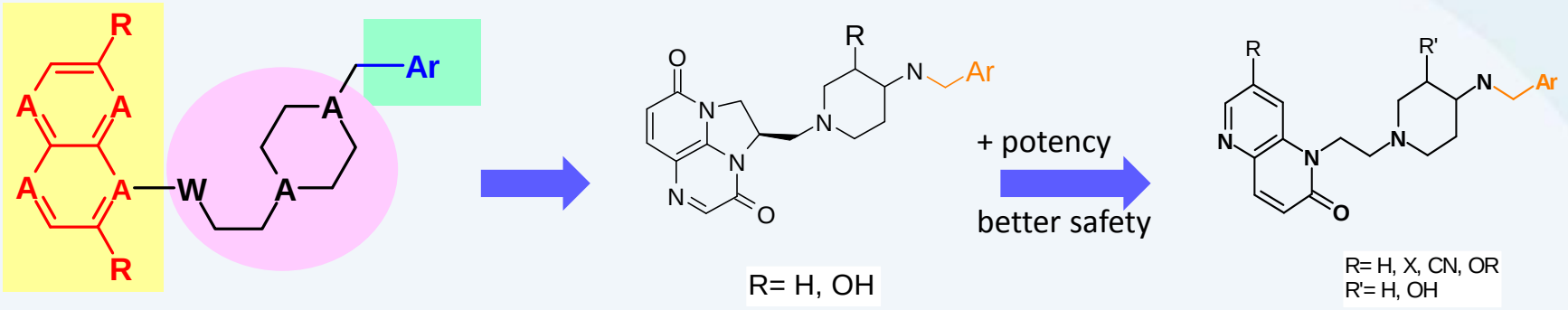
Objective: Tailor NBTI's for the treatment of TB

MIC's of XDR-TB isolates: MGI's and FQ

		MGI Lead Compounds			FQ	
		MGI2195	MGI2120	MGI2197	Moxi	Cipro
	MDR-MIC90	0.60	0.60	0.20	0.30	0.60
XDR-Clinical Isolates	XDR-10492	0.29	0.29	0.02	0.30	1.80
	XDR-11010-B	0.29	0.29	0.07	0.90	5.40
	XDR-12569	0.29	0.29	0.07	2.70	5.40
	XDR-10190	0.29	0.29	0.02	2.70	> 5.40
	XDR-13222	0.86	0.29	0.07	2.70	> 5.40
	XDR-10071	0.86	0.29	0.22	2.70	> 5.40
	XDR-11348	0.86	0.86	0.22	2.70	> 5.40
	XDR-7786	0.86	0.86	0.22	2.70	> 5.40

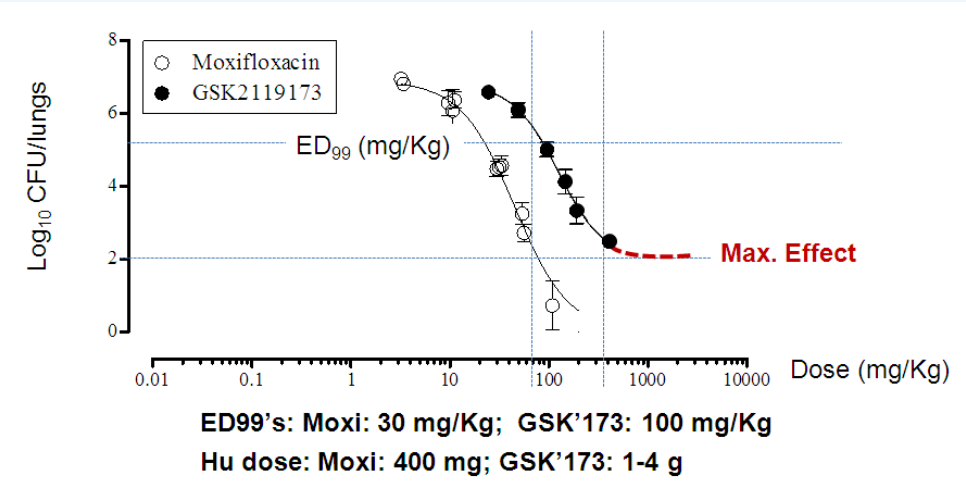
MIC data are expressed in ug/mL.

MGI's Series: 6,6,5 diones and 1,5-naphthyridones



6,6,5-dione: GSK'173 **New 1,5-naphthyridones**

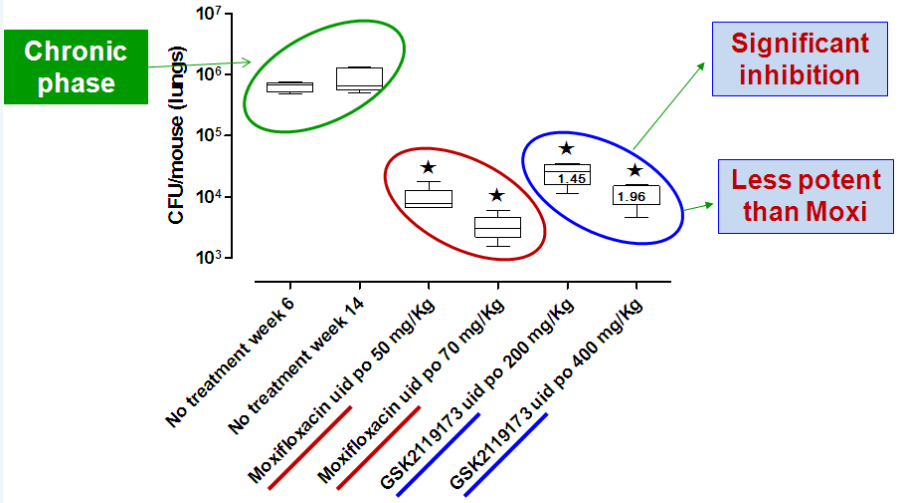
TB **acute** murine model: 1w dosing



ED99's: Moxi: 30 mg/Kg; GSK'173: 100 mg/Kg
Hu dose: Moxi: 400 mg; GSK'173: 1-4 g

TB **chronic** murine model: 8w dosing

- Bacterial burden in lungs after two months of treatment
- MGI lead and Moxi were tested at bioquivalent doses, once a day



MGI's: Current status and next steps

- **1,5-naphthyridone series:**
  - Evaluate efficacy in chronic model of new series
  - Hu dose projection
  - Safety: CV studies (dog)
  - In vivo combination profile (acute and chronic)
  - Chemistry focus on Bup program

- **Expected transition to preclinical phase 1Q2012**

TB Whole Cell- Program background

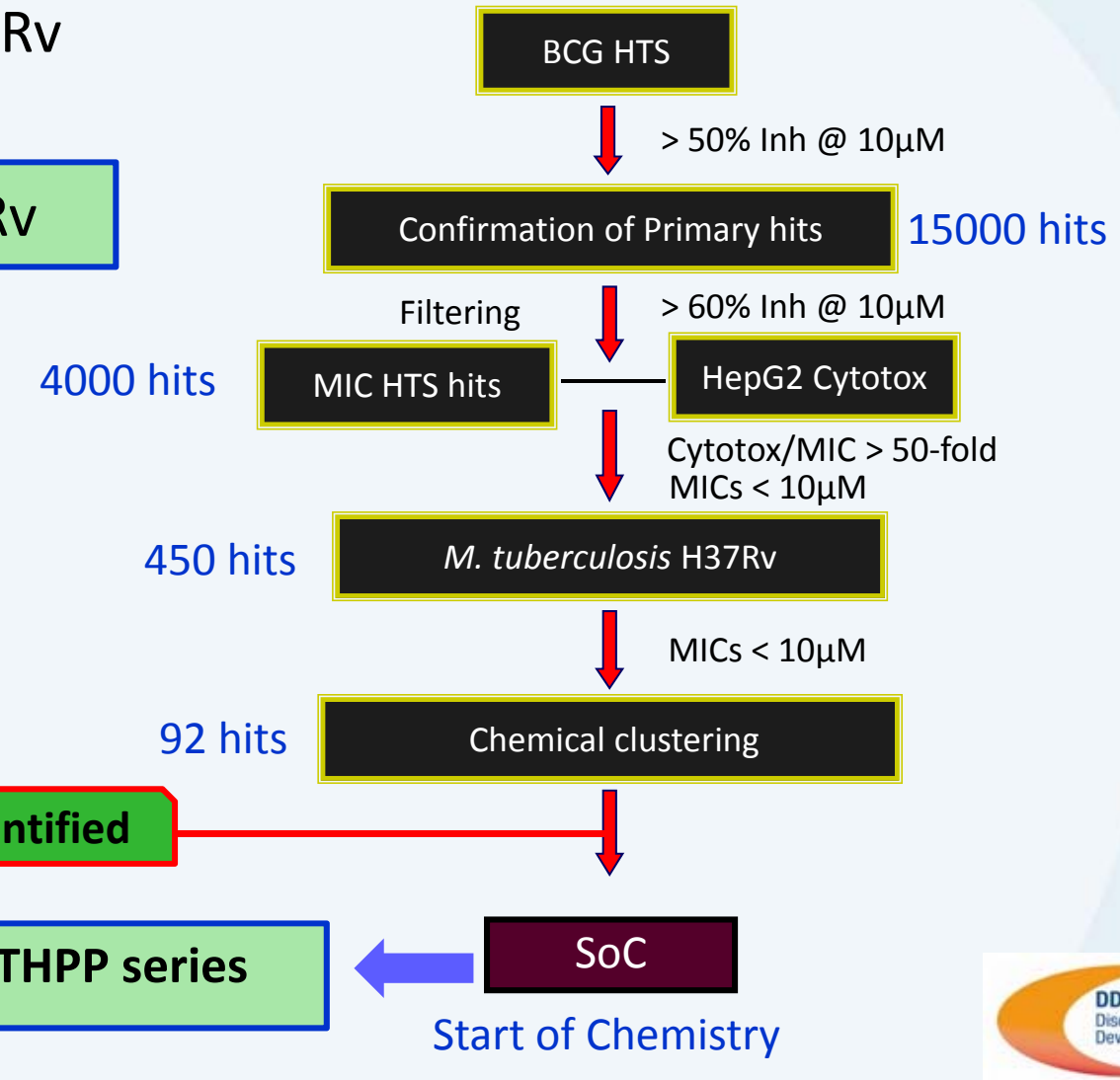
Screening

BCG ⟷ H37Rv

20k compounds

BCG surrogate of H37Rv

2M compounds (GSK collection)



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WC: Current status and next steps

- **Campaign 1: M.bovis BCG Mtb**
  - 7 New chemical series initially identified (TB selective)
  - Work currently focus in two series (in vitro cidality)
  - MoA: GSK + FP-7 program: ORCHID

- **Campaign 2: “top up” 200K new compounds against Mtb**
  - 12 new series identified.
  - Profiling ongoing
  - MoA : GSK+ TB ERAnet pathogenomics and ORCHID

GSK TB Pipeline: Open Innovation approach

TB ALLIANCE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Whole Cell Screening (1st (2M) ; 2nd (2K)

Bacterial DNA gyrase Inhibitors

ERA-NET PathoGenoMics

Whole Cell: THPP series

Direct InhA Inhibitors

ORCHID

SEVENTH FRAMEWORK PROGRAMME

TB LeuRS Inhibitors

ANACOR PHARMACEUTICALS

imi Innovative Medicines Initiative

Open Innovation

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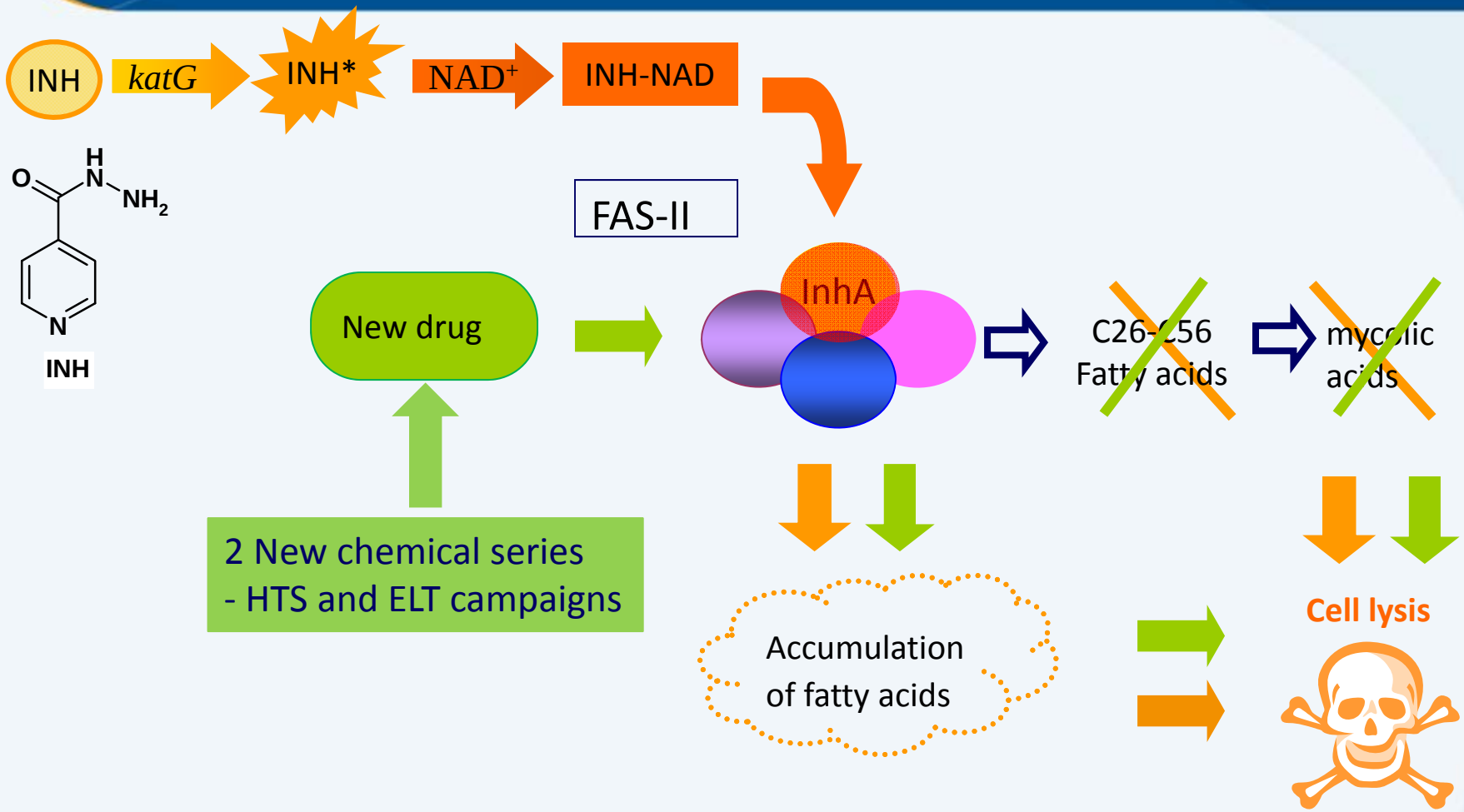
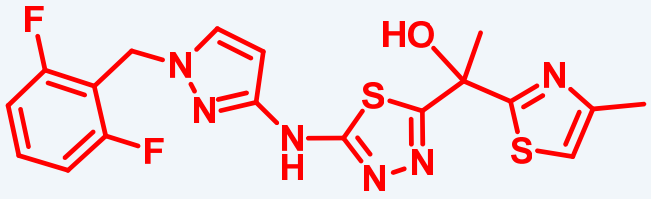
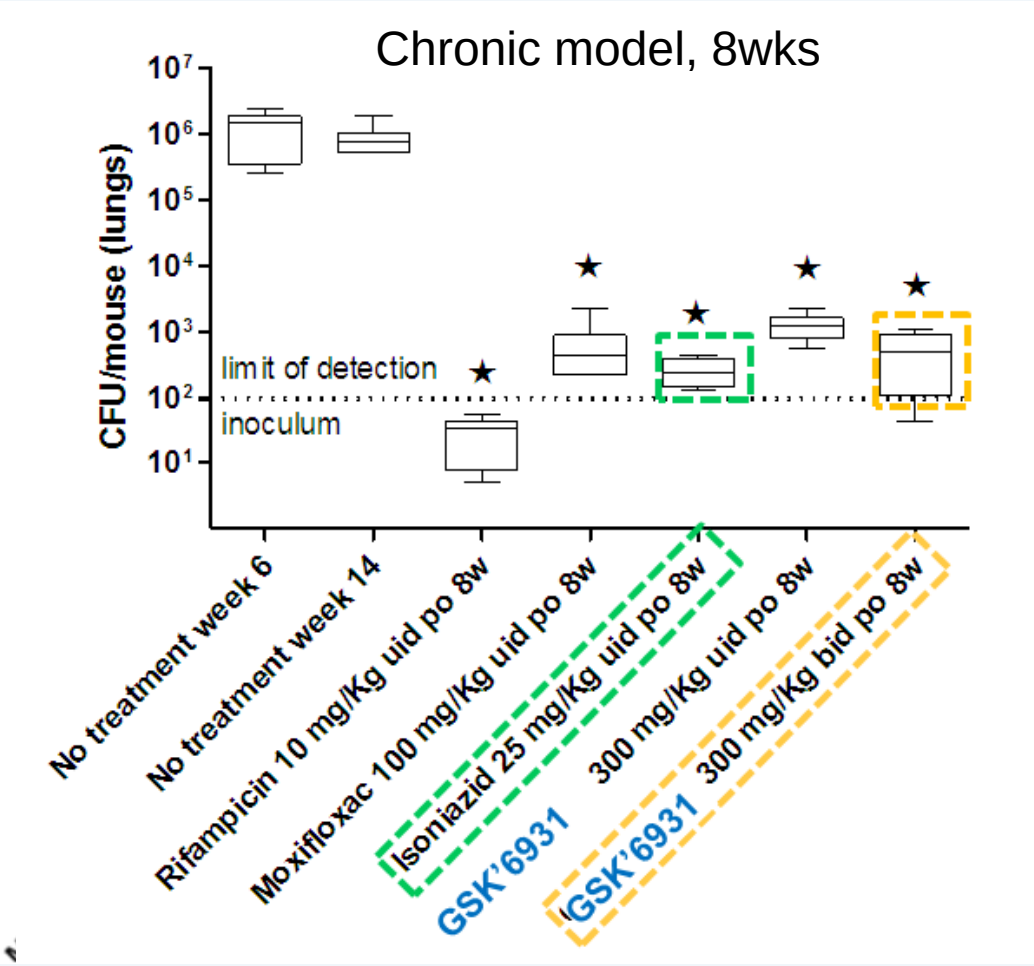
Orchid EU-FP7: Direct InhA inhibitors



Compounds that directly inhibit InhA and do not require activation by *katG* could be promising candidates as TB drugs.

ORCHID EU-FP7: Direct InhA inhibitors





- Nanomolar activity against InhA
- Micromolar antitubercular activity
- Whole-cell activity: InhA inhibition
- Active against drug resistant strains
- Low Spontaneous resistance frequency
- Cidal activity in acute mouse model

First time a competitive, reversible inhibitor of InhA shows efficacy *in vivo*

Direct InhA inhibitos: Current status and next steps

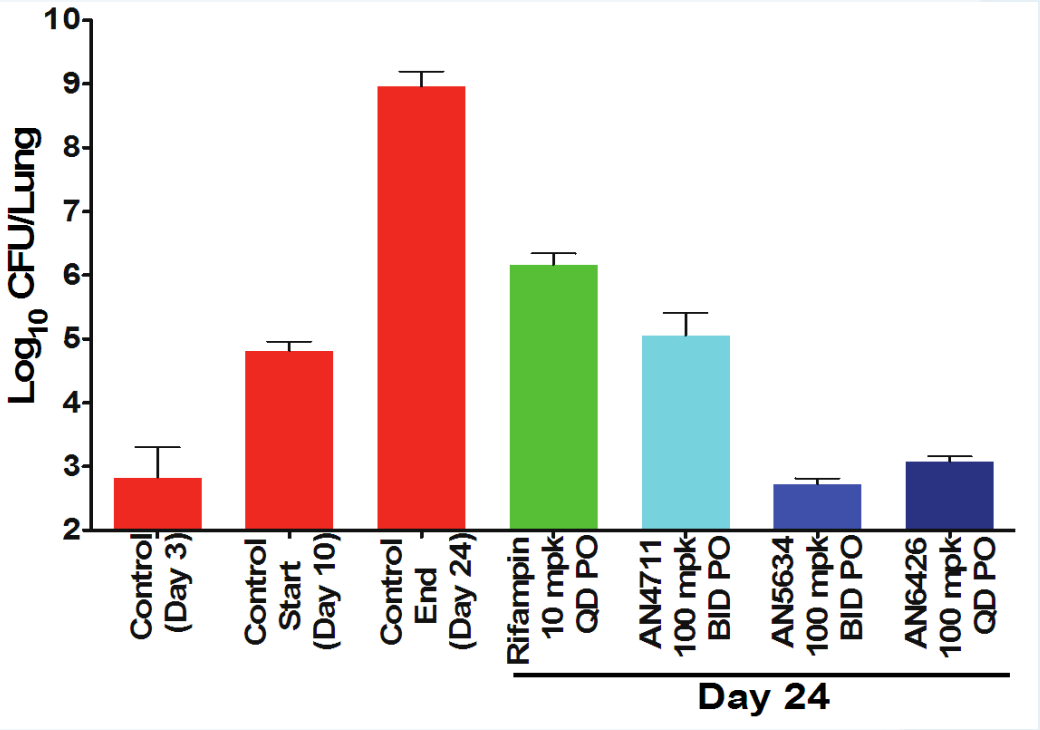
- **Thiadiazole series:**
  - Existing leads:
    - PK/PD short course: better prediction of Hu dose
    - Evaluate combo profile and sterilizing potential
  - Bup Program
    - Improve DDI (achieved)
    - Improve PK profile of current leads (higher species)

- **NCE series**
  - Identify a tool compound for in vivo benchmarking studies (acute and relapse)

Mtb LeuRS inhibitors: LO optimization (DR-TB TPP)

- **Description of current leads**
  - Leads cidal in vivo (acute and chronic murine models)
  - TB selective (only H. flu inhibited). Structural data available

Compound	LeuRS IC_{50} (µM)		*M. tuberculosis* MIC (µg/mL)	
	E. coli	*Mtb*	MABA	LORA
AN4711	0.28	0.128	0.04	0.52
AN6801	NT	0.090	NT	NT
AN6426	0.23	0.020	0.003	0.016
AN5634	0.37	0.066	0.047	0.7



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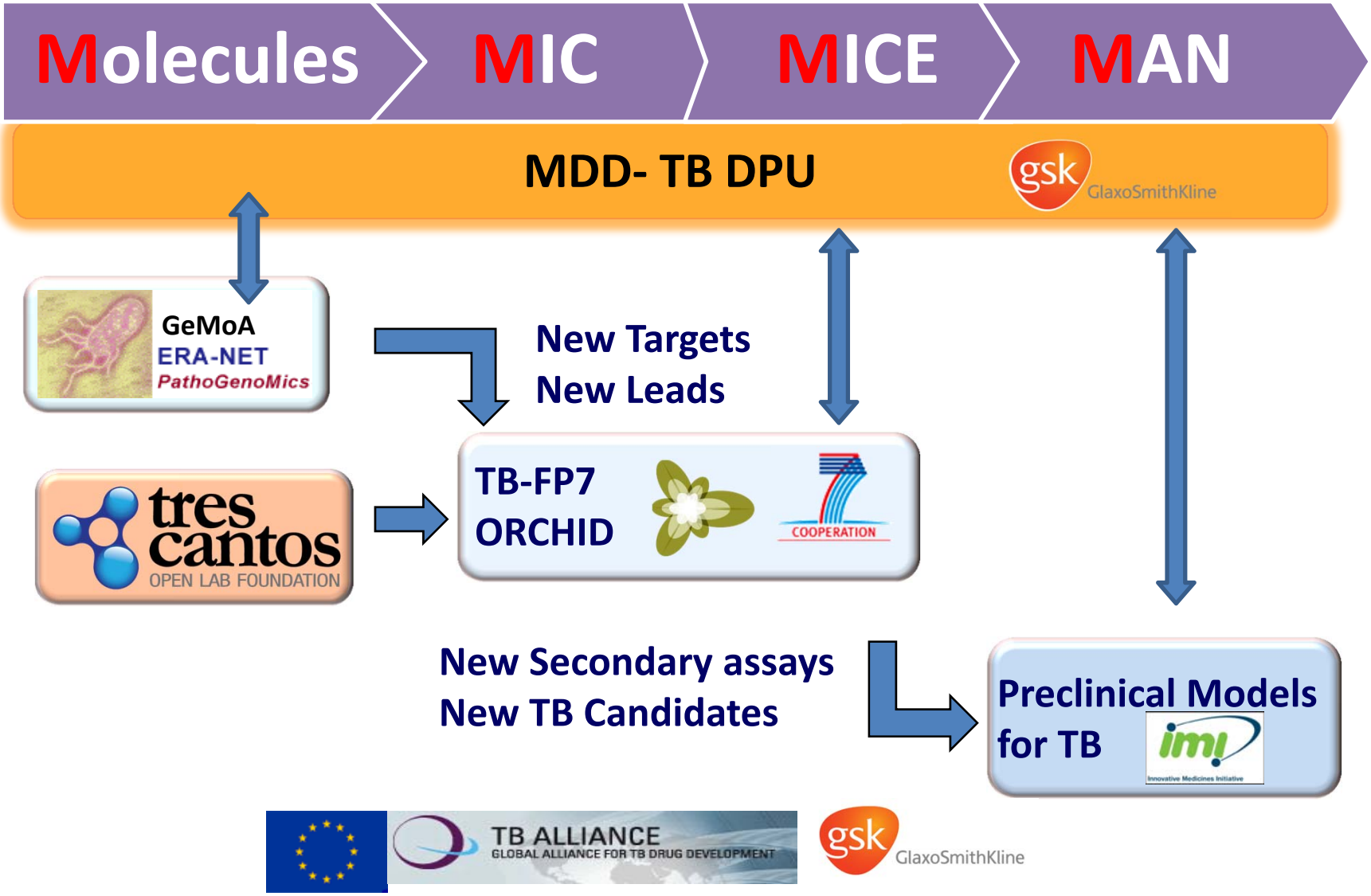
Mtb LeuRS inhibitors: Next steps and Timelines

- **Next steps**
  - Full assessment on safety of current leads
  - Comparison with other Mtb protein synthesis inhibitors
  - PK/PD short course (driver for efficacy)
  - Explore combination profile (acute and relapse)
- **Chemistry**
  - Improve therapeutic window of current leads
- **Expected transition to preclinical phase 4Q2013**

Addressing TB Drug Discovery Gaps

4M disconnection drives attrition



GSK´s open innovation strategy for NTD

- **Sharing data**: Release of 13,500 malaria hits
  - Nature, 465, 2010, 305–310
  - http://www.ebi.ac.uk/chemblntd

- **Sharing intelectual knowledge**
  - http://ntdpool.org/

Pool for Open Innovation against neglected tropical diseases

bvgh BIO Ventures for Global Health

- **Sharing resources:**
  - The Open-Lab initiative

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Thanks!