3P TB R&D Proposal
Push, Pull, Pool.

Dr Grania Brigden

TB Symposium, Yerevan 2015.

New treatments and approaches to Tuberculosis

Tuberculosis Symposium – Eastern Europe and Central Asia
RA Ministry of Health and Médecins Sans Frontières

MDR-TB treatment
The issues

Old – ‘newest’ drug in current regimens was introduced 50 years ago

Long – Treatment takes two years

Complex – different treatment regimens for individual resistance patterns; about 5 different drugs (14,000 pills), including 8 months of painful injections

Toxic – extreme side effects include deafness, psychosis, constant nausea and vomiting, hallucinations, weight loss and more

Expensive – Can cost up to $5000 in drug costs alone

Inadequate – high default rates and low cure rates (~50% for MDR-TB, 13% for XDR-TB) contribute to further resistance; no paediatric formulations

Unproven – No randomized clinical trials conducted or planned for the current regimen

TB drug regimen R&D

Clear case of market failure

Global TB Drug Pipeline [1]

ACCESS CAMPAIGN — MEDECINS SANS FRONTIERES

ТБ Симпозиум Министерство Здравоохранения и ВБГ — TB Symposium Ministry of Health and MSF

Discovery | **Preclinical Development** | **Clinical Development**

Lead Optimization	Early Stage Development	GLP Tox.	Phase I	Phase II	Phase III
Cyclopeptides	CPZEN-45	PBTZ169	AZD5847	Bedaquiline (TMC-207) for DS-TB	Delamanid (OPC-67683)
Diarylquinolines	BTZ043	TBA-354	Bedaquiline (TMC-207) for DS-TB	Linezolid	Gatifloxacin*
DprE Inhibitors	DC-159a	Q203	Linezolid	Novel Regimens[2]	Moxifloxacin*
InhA Inhibitor, Indazoles	SQ609		Novel Regimens[2]	PA-824	Rifapentine for LBTI
LeuRS Inhibitors, Ureas	SQ641		PA-824	Rifapentine for DS-TB	Bedaquiline (TMC-207) for MDR-TB
Macrolides, Azaindoles	TBI-166		Rifapentine for DS-TB	SQ-109	
Mycobacterial Gyrase Inhibitors			SQ-109	Sutezolid (PNU-100480)	
Pyrazinamide Analogs			Sutezolid (PNU-100480)		
Ruthenium(II) Complexes					
Spectinamides SPR-10199					
Translocase-1 Inhibitors					

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

[1] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

[2] Combination regimens: NC-001 -(J-M-Pa-Z), phase 2a, NCT01215851; NC-002-(M-Pa-Z), phase 2b, NCT01498419; NC-003-(C-J-Pa-Z), phase 2a, NCT01691534; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), phase 2b, NCT01785186

*Projects that have been completed

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: August 2014

Healthy Pipeline?

NCEs in Clinical Development:

Hepatitis C

Phase I over 15
Phase II 14
Phase III 11

Total: over 40!

TB

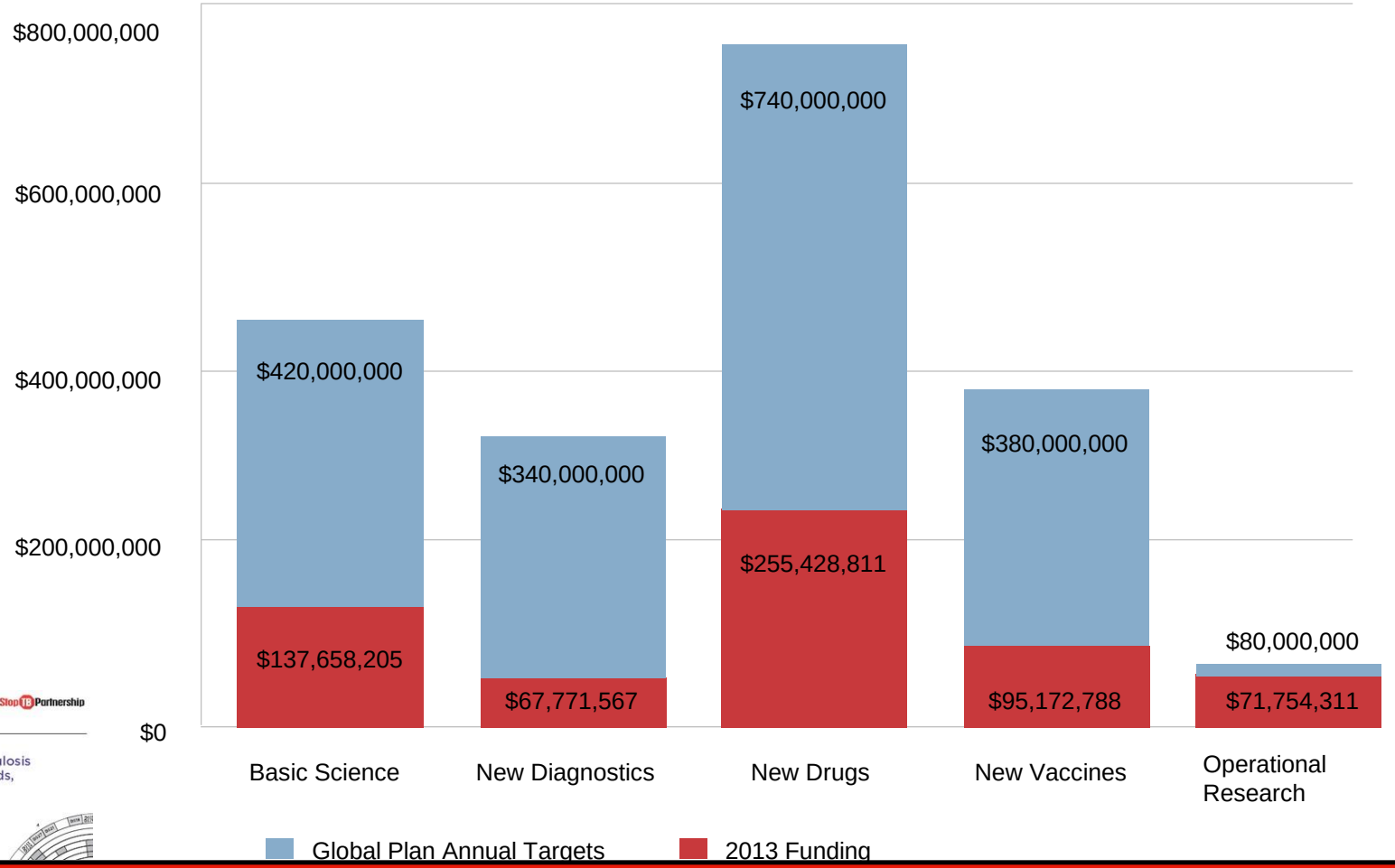
Phase I 0
Phase II 5
Phase III 1

Total: 6

Market Failure leading to…

- Two new drugs...no new regimens. Limited data on how to use them together
- New drugs registered but not available
- High prices; no price transparency
- Chronic under investment in TB R&D
- Likely “famine period” for new TB drugs ahead

Annual *Global Plan* Research Funding Targets versus 2013 Funding

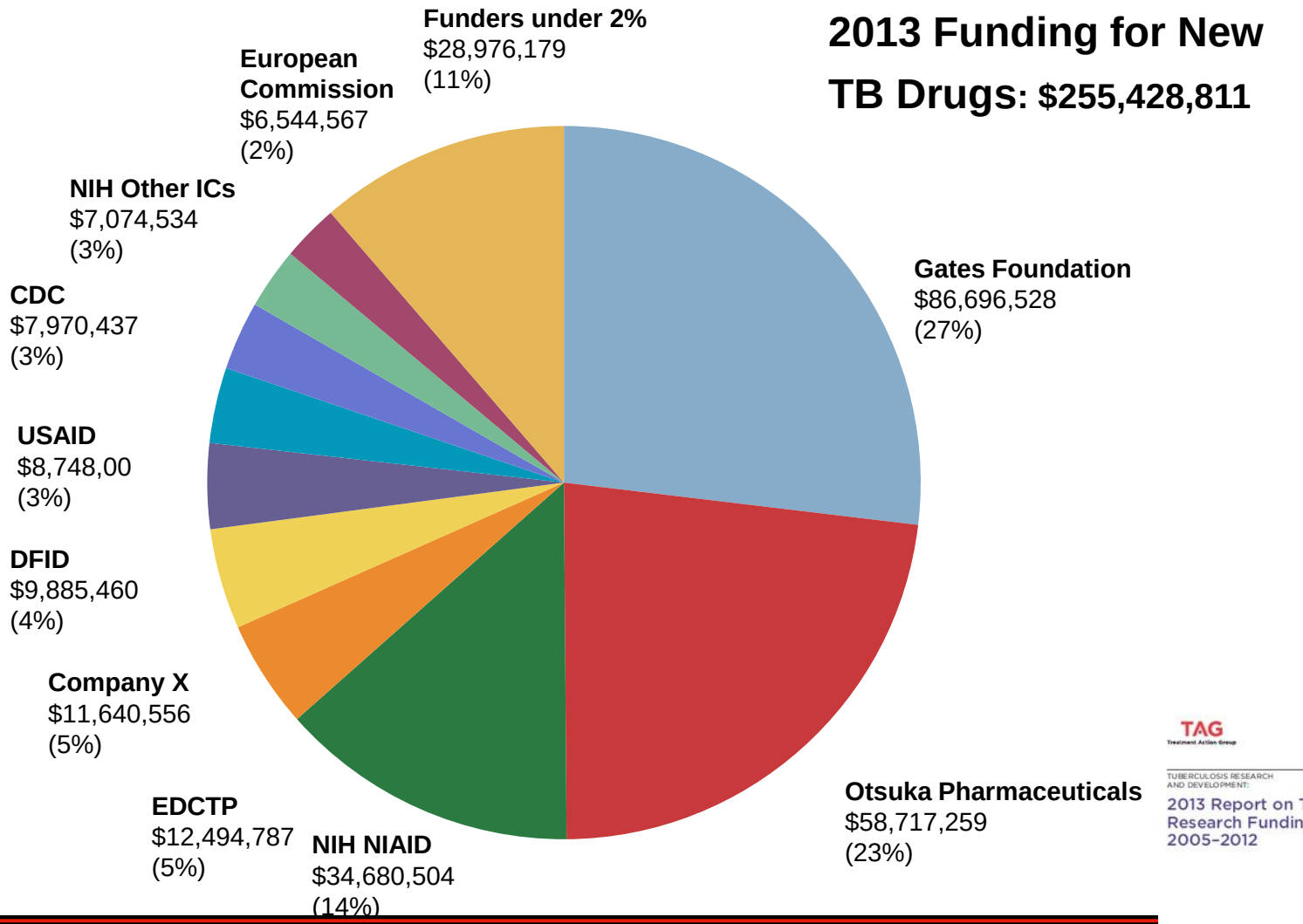


TAG Treatment Action Group

Stop TB Partnership

TUBERCULOSIS RESEARCH AND DEVELOPMENT:
2013 Report on Tuberculosis Research Funding Trends, 2005–2012

TB Drug R&D: a Charitable Endeavor?



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TUBERCULOSIS RESEARCH AND DEVELOPMENT:

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Where is the investment?

- Private sector decreased TB drug R&D from 2012- 2013
- US government funding flat-lining
- Pfizer withdrew from anti-infectives
- AstraZeneca withdrew from NTDs, TB & Malaria
- Otsuka decreased drug discovery efforts, contribution may further decline after development of delaminid is completed
- Similar situation may occur with J&J and bedaquiline
- Pipeline gap in phase I
- Early-stage & preclinical research- public institutions, small companies or PDPs, do they have the capital or capacity for clinical trials?

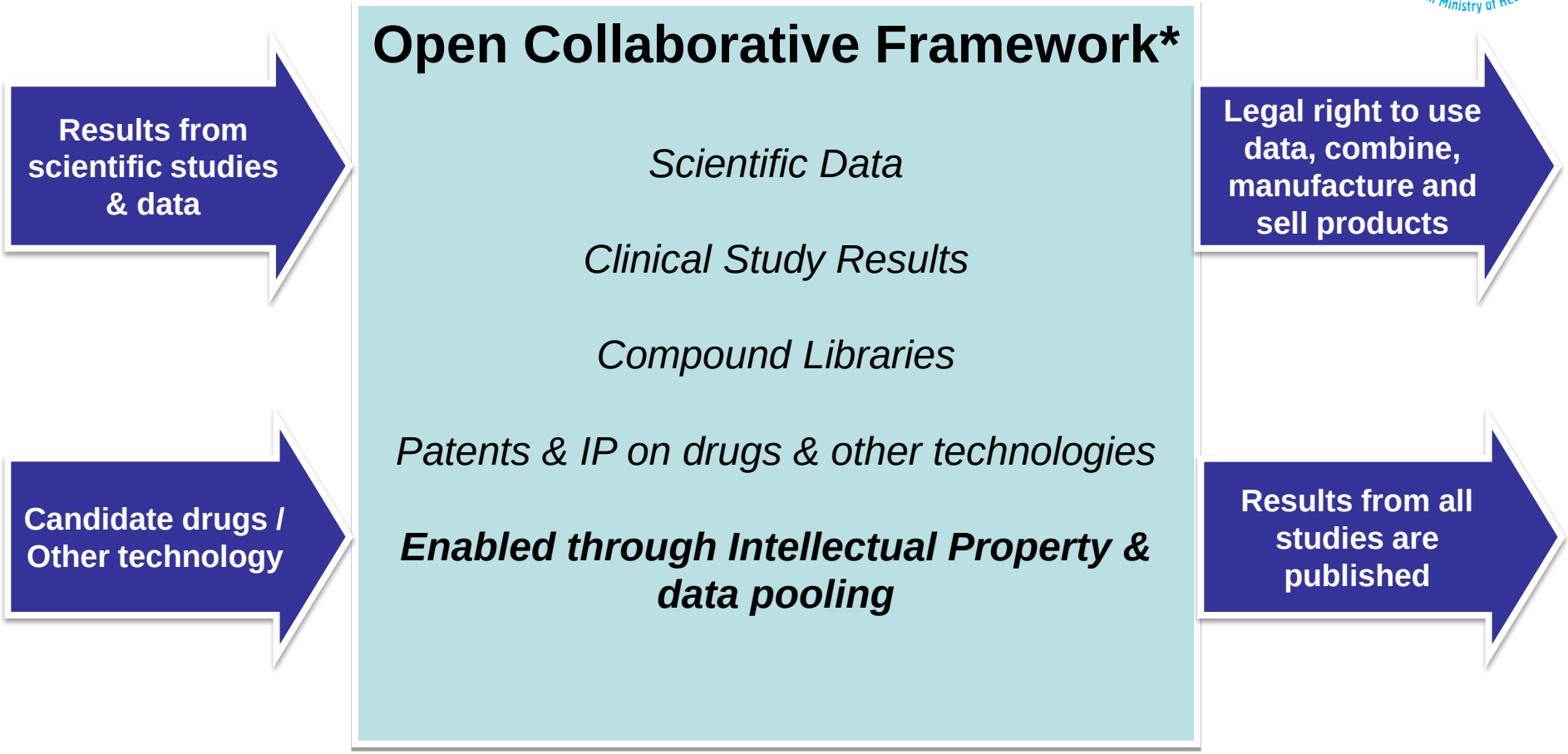
How do we plug the gap in the funding needs and prevent the flight of private sector investment?

3Ps: Push + Pull + Pool

A mix of incentives & the collective management of IP:

- **Push** funding to finance R&D activities upfront (i.e. through grants)
- **Pull** funding to incentivise R&D activities through the promise of financial rewards on the achievement of certain R&D objectives (i.e. through milestone prizes)
- **Pooling** of intellectual property (IP) to ensure open collaborative research and fair licensing for competitive production of the final products

Open collaborative model



* Potentially a virtual model, where different elements are housed in different existing institutions with overall coordination

Open collaborative model – transforms drug pipeline

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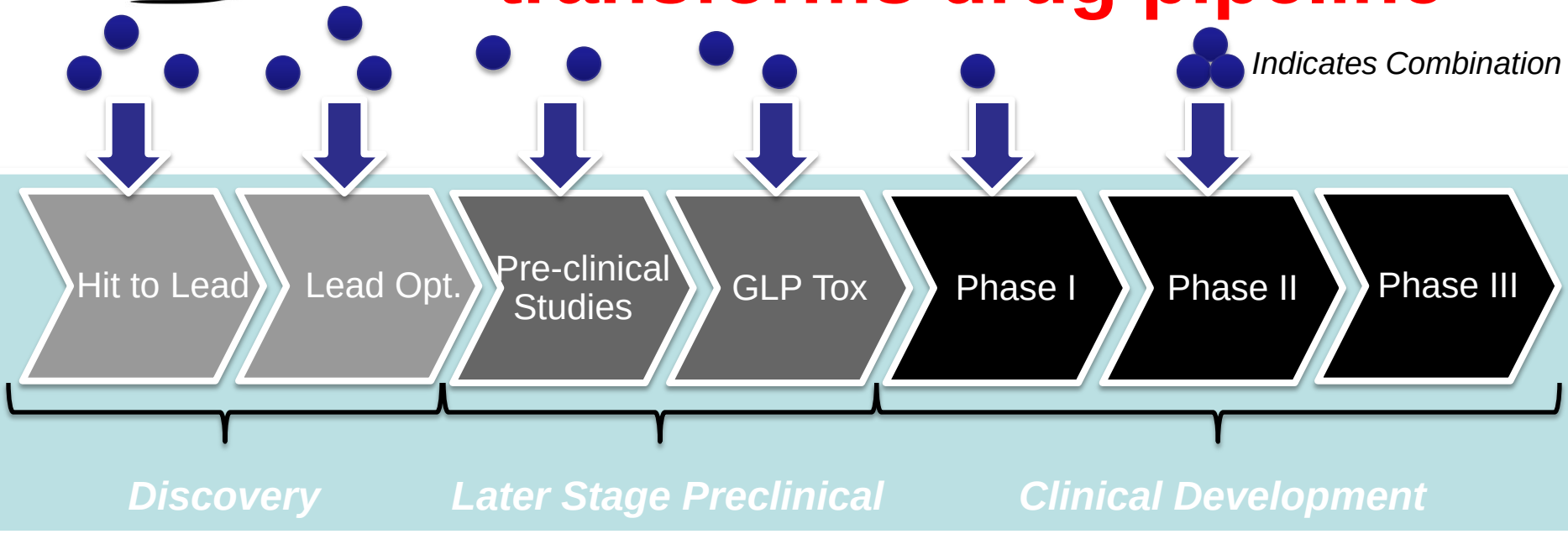

Small, early-stage Milestone Prize (Size 1) mix of small financial and recognition prizes) for licensing the compound to the Open Collaborative Framework

Milestone Prize (Size 2) for entering clinical development (Phase I)

Milestone Prize (Size 3) for combination regimen successfully completing Phase II

Legend

- Various TB Compounds
- Milestone Prizes
- Grant funding

Grant funding for studies from the fund

Grant funding for Phase III from existing and new sources

Benefits of 3P over current model

This framework offers four benefits over the current system:

1) reduces the duplication of research efforts thereby saving time and money

2) "de-risks" potential combinations as early and as affordably as possible

3) accelerates drug combination development

4) reduces the risk of resistance to new compounds

Relevance to Eastern Europe?

- High burden of MDR/XDR TB
- Graduating out of GF/Donor funding
- R&D increasingly on the agenda of high level meetings eg Riga meeting, March 2014 and possibly Eastern Partnership summit
- Widespread political support required; Ministers attending these meetings need to support this initiative.
- Strengthen in-country academic institutes, scientific communities and clinical trial sites.


Thanks!