

# TB Drug Development: *pipeline realities*

Ann M. Ginsberg, M.D., Ph.D.  
Global Alliance for TB Drug Development

**IOM Planning Summit on MDRTB, XDRTB, and Totally Drug Resistant TB**  
Washington D.C.  
November 5, 2008

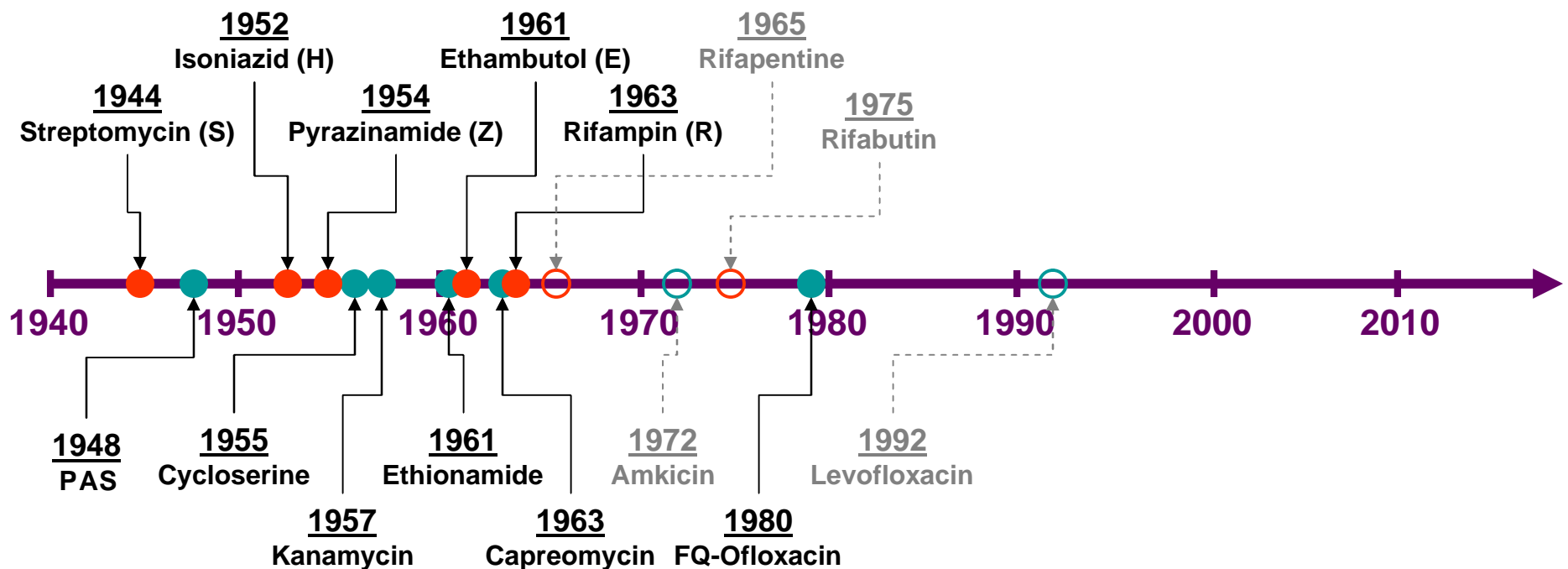


**TB ALLIANCE**  
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

IOM 5 November 2008

# Discovery of Current TB Drugs

## 1<sup>st</sup> line TB drugs (Drug-Sensitive TB)



## 2<sup>nd</sup> line TB drugs (Drug-Resistant TB)



# Current TB Therapy

## § Active, drug-sensitive TB

4 Drugs,  $\geq 6$  months: 2RHZE + 4RH

## § M(X)DR-TB

Individualized therapy for  $\geq 2$  years, few available drugs, poorly tolerated, expensive

## § TB/HIV co-infection

Drug-drug interactions with ARVs - simultaneous therapy difficult

## § Latent TB Infection

9 Month H

Rifampin (R), Isoniazid (H), Pyrazinamide (Z), Ethambutol (E)



**TB ALLIANCE**

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

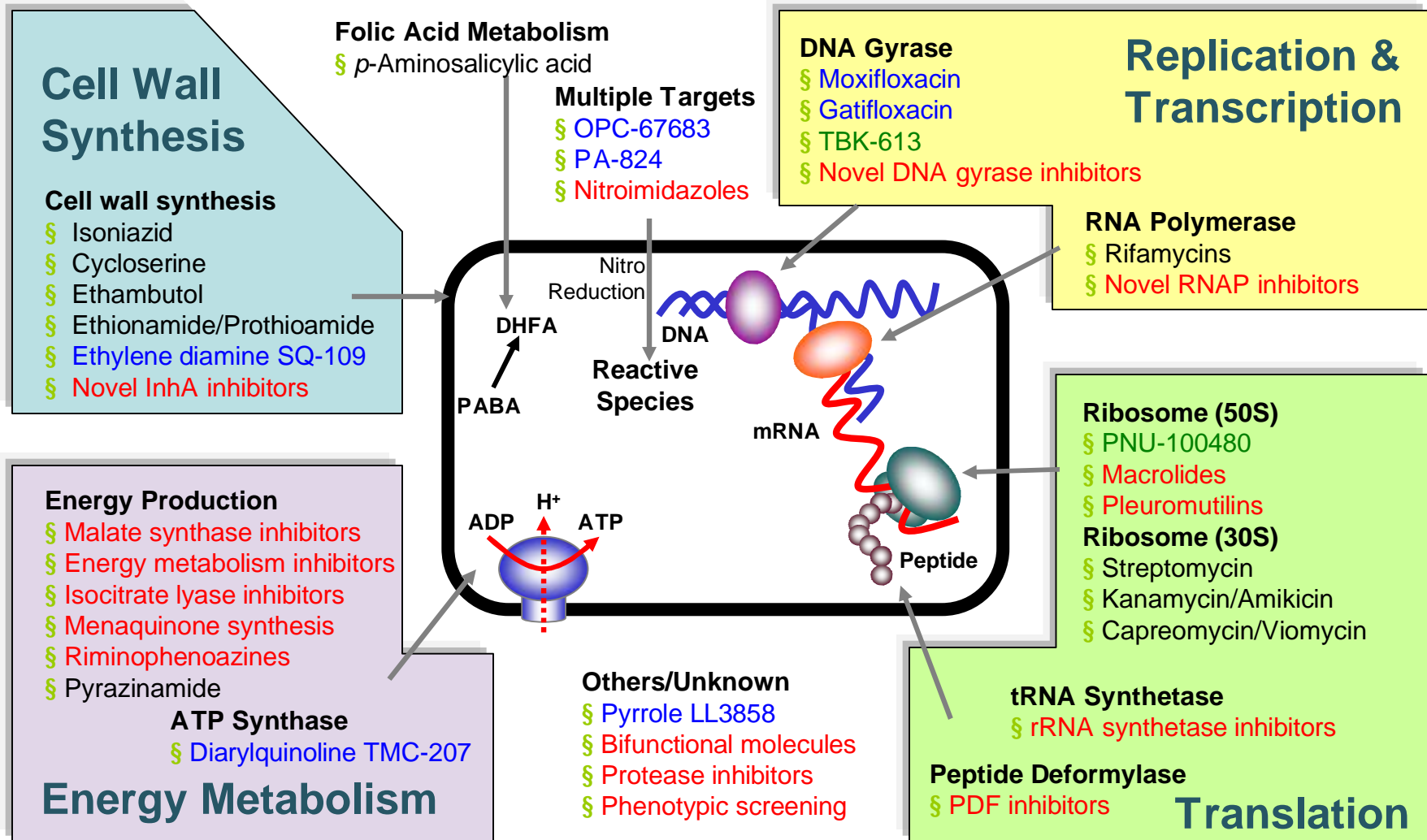
IOM 5 November 2008

# Optimal Target Profile

- § **Shortens and simplifies treatment**  
Active against drug persistent *Mtb* populations
- § **Equally effective against M(X)DR-TB**  
Novel mechanism of action
- § **Easy, safe, co-administration with ARVs**  
No P450 mediated drug-drug interactions
- § **Excellent safety/tolerability**
- § **Oral,  $\leq$  once daily dosing**
- § **Low cost of goods**



# Distribution of TB Drug Targets



Current drugs: Black    Compounds in Clinical: Blue    Compounds in preclinical: Green    Discovery projects: Red

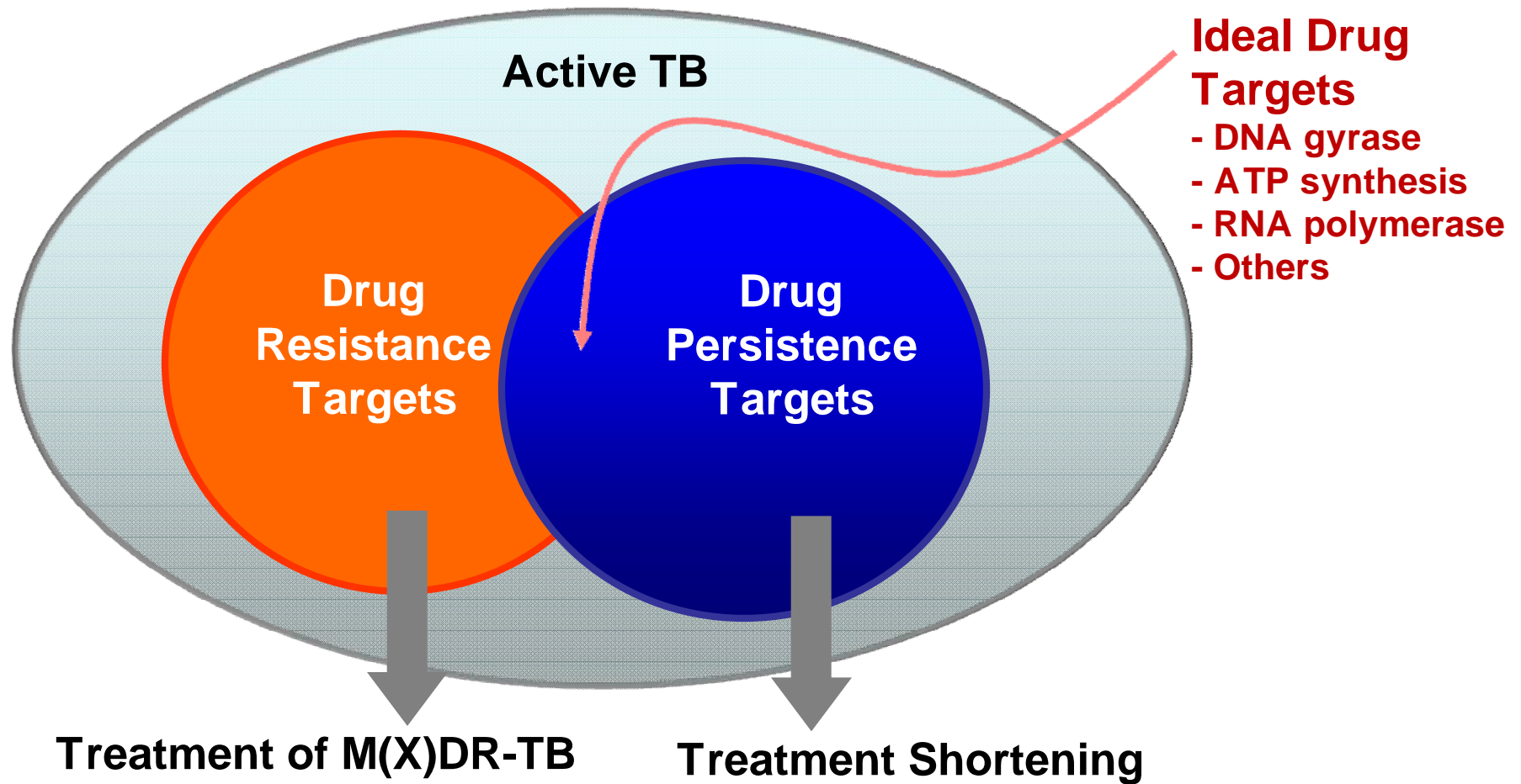


**TB ALLIANCE**

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

IOM 5 November 2008

# New Trends in TB Drug R&D



## Slide 6

---

a3

Why shouldn't malate synthase inhibitors, for example, work on M(X)DR and therefore also belong in the "ideal Drug Targets" list? PDFinhibitors?

aginsberg, 10/15/2008

# TB Drug R&D Process

Drug  
Discovery

Preclinical  
Development

Clinical  
Development

**TOTAL DURATION:  
10 to >15 years**

Identify drug candidates  
that can meet the drug  
target profiles  
*~2-5 Years*

Study safety and  
efficacy in preclinical  
models  
*~1-2 Years*

Demonstrate safety  
and efficacy  
in TB patients  
*~6-10 Years*



**TB ALLIANCE**

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

IOM 5 November 2008

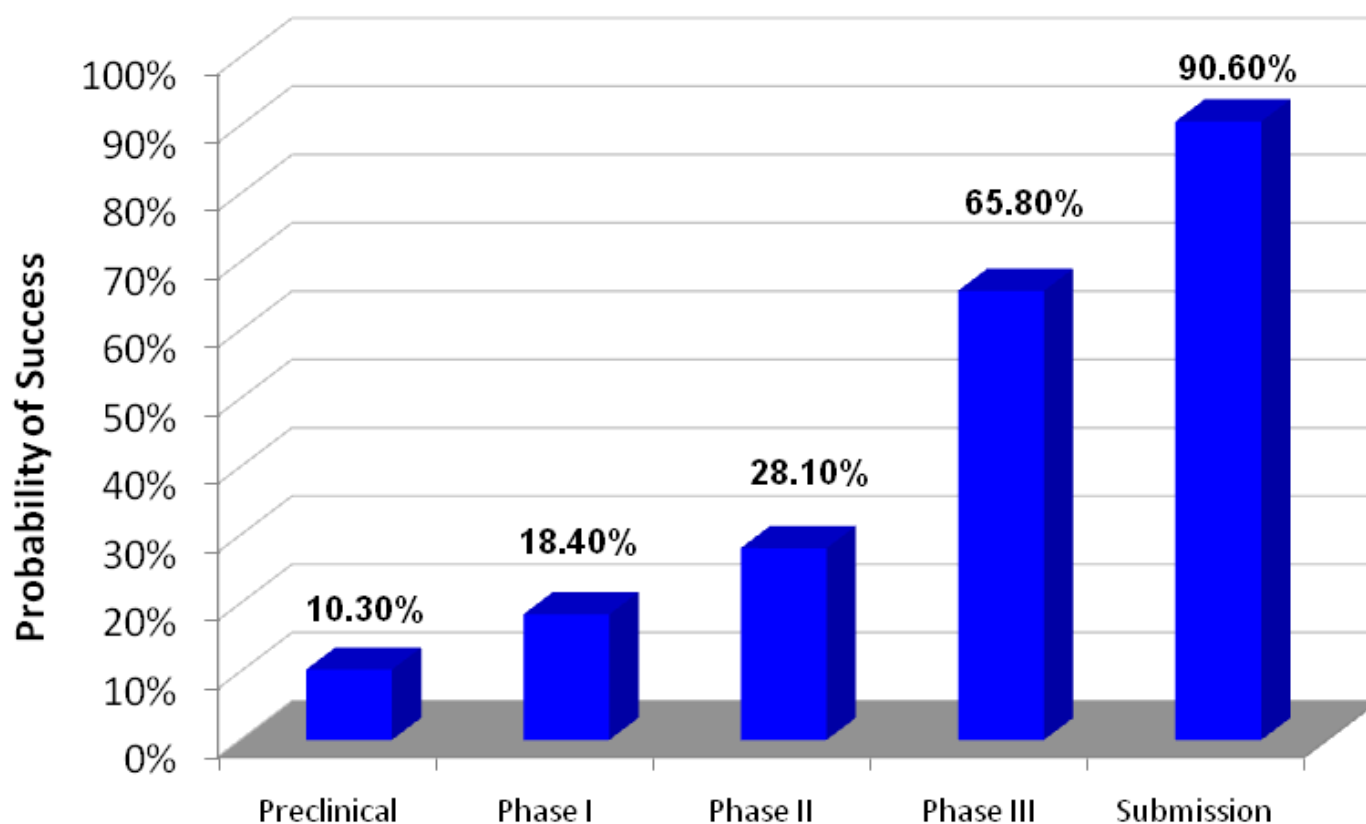
Slide 7

---

a2

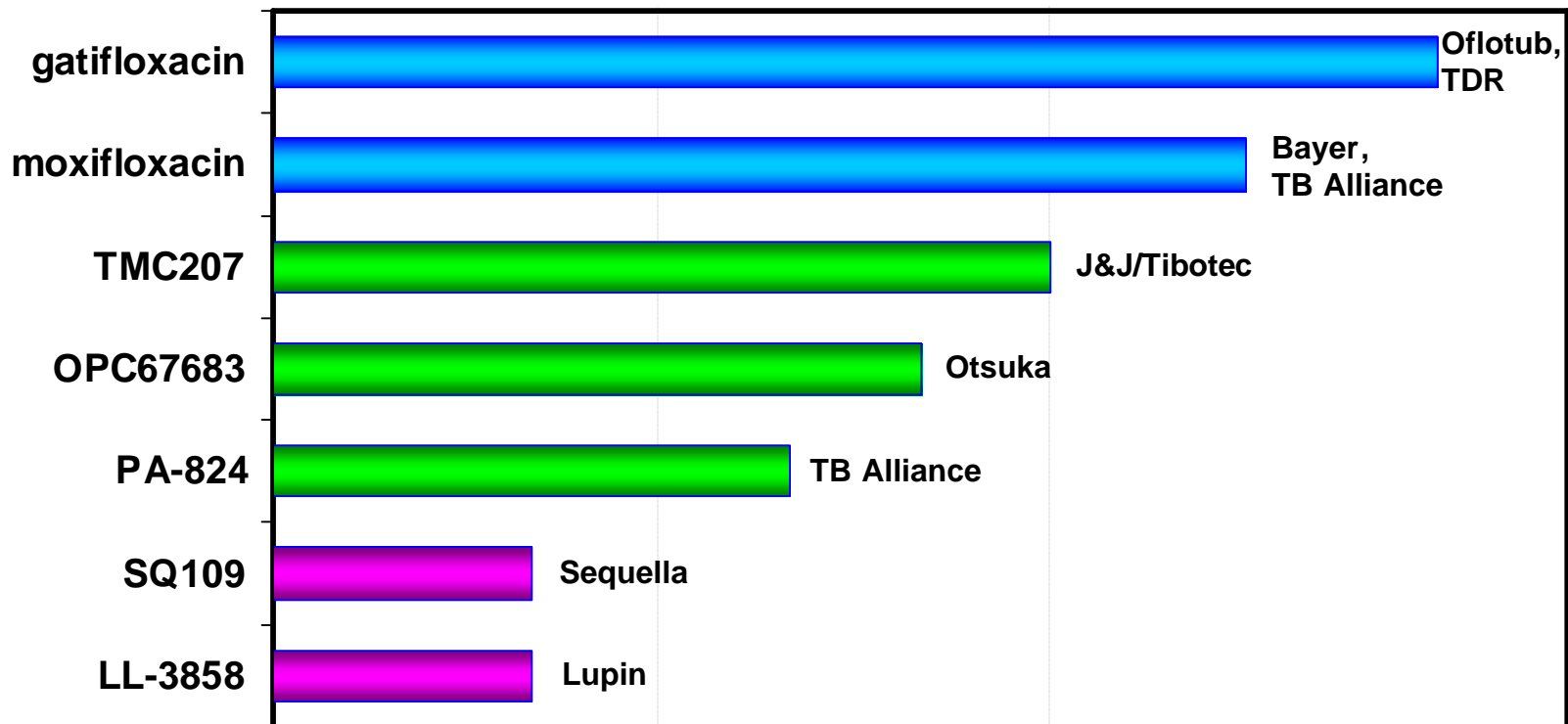
**OFLOTUB** rahter than **OFLUTUB**  
aginsberg, 10/15/2008

# Probability of Success for a Drug Candidate



Source: The Pharmaceutical R&D Companion.  
CMR International/Scrip's Guide to Trends in R&D 2000.

# Global Clinical Portfolio – Registration Programs



Phase I

Phase II

Phase III

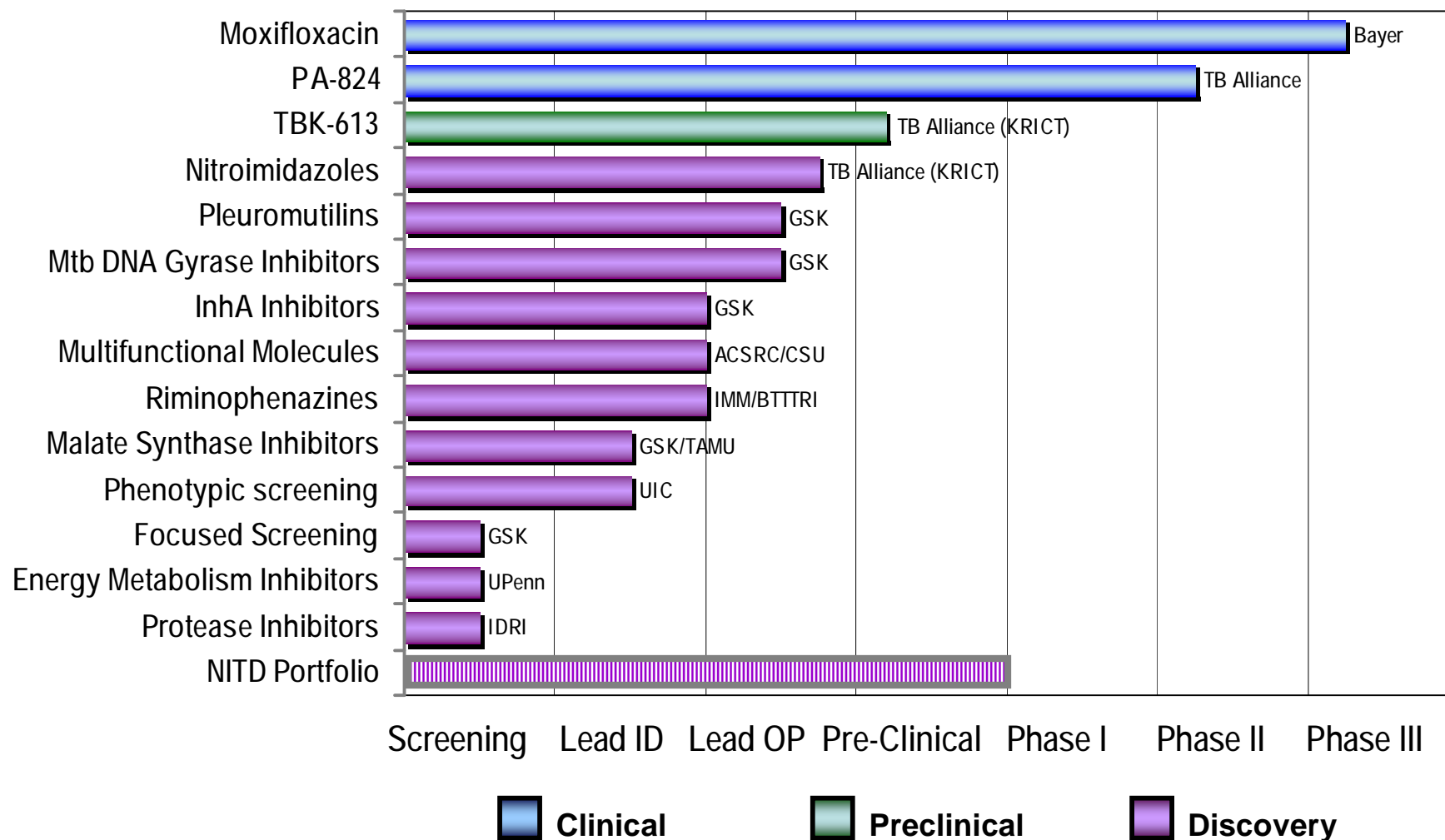


# Key Challenges

- § Multidrug therapy
  - ∅ need *regimens*, not single drugs
  
- § Long clinical development timelines; to streamline, need:
  - ∅ validated biomarkers of drug effect
  - ∅ validated animal model that reliably predicts human dose range and treatment duration
  - ∅ validated “proof of concept” trial design for treatment-shortening
  - ∅ adequate clinical trial capacity (GCP/GLP)
  - ∅ harmonized, TB-specific regulatory guidances



# Current TB Alliance Portfolio



## Key Challenges (2)

§ High costs of clinical development and global registration

∅ parallel programs for DS and M(X)DR

§ Affordability

§ Accessibility

§ Adoption

} NTPs and private sector



# Conclusions

- § Multiple new TB drugs and regimens are needed to address the challenges in TB, including M(X)DR-TB.
- § A resurgence in TB drug R&D is ongoing; 2-3 new drugs may reach registration before 2015.
- § Improved understanding of *M.tb* biology may lead to better, smarter drugs to tackle drug resistance, shorten treatment, and eliminate latent infection.
- § A much more robust pipeline is needed.



Slide 13

---

a4

1st bullet: not sure the challenges are "new"

aginsberg, 10/15/2008

*“TB claims 1.7 million lives each year, and eliminating it will be a global challenge - but it's a challenge we must take on....”*

*- Barack Obama,  
Oct. 3, 2008*



**TB ALLIANCE**  
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

IOM 5 November 2008

*Thank you*



**TB ALLIANCE**

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

IOM 5 November 2008