



# Host-Directed Therapies and their Impact on DM+TB co-epidemic

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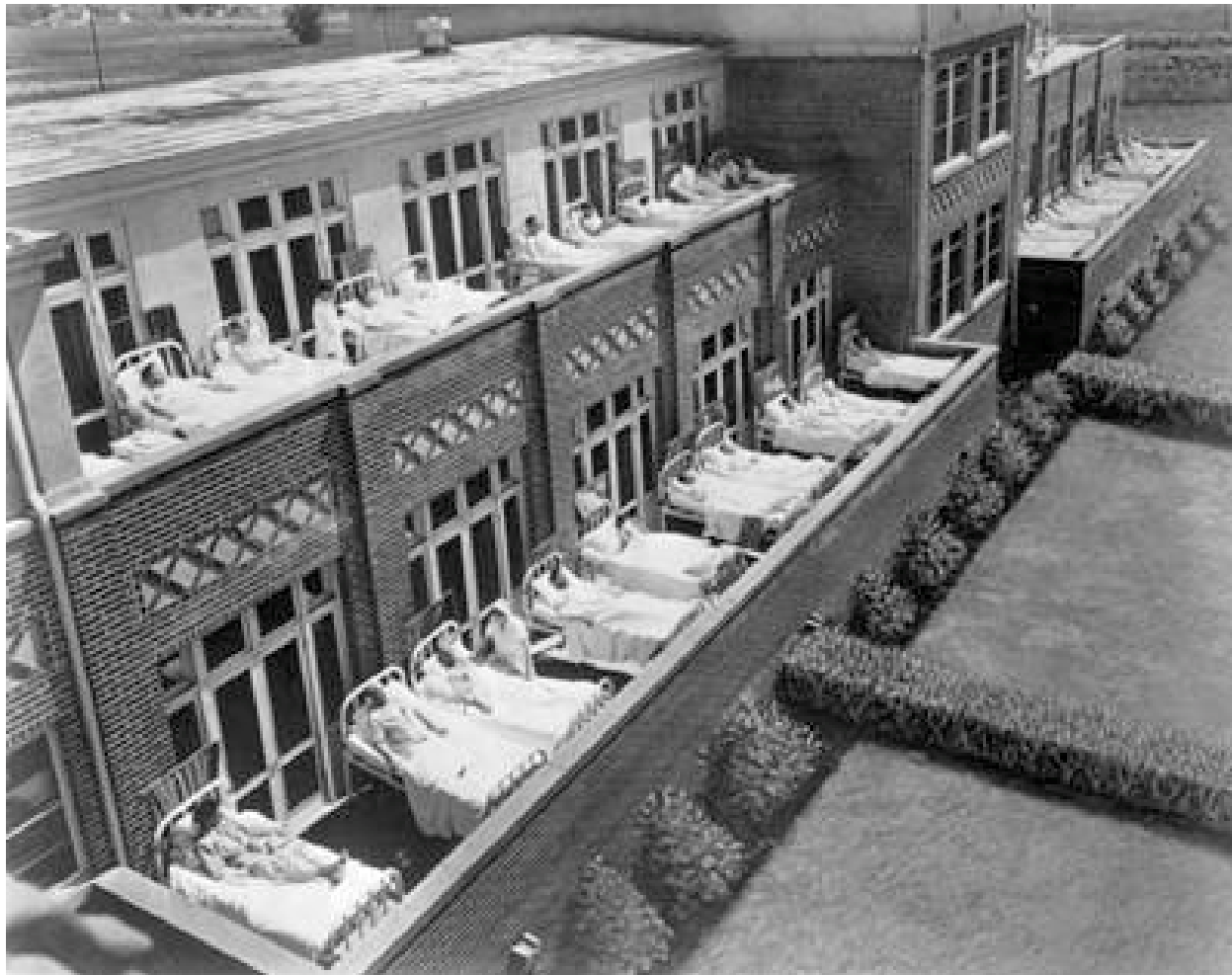
10-11 May 2016, TB+DM Workshop, NIH



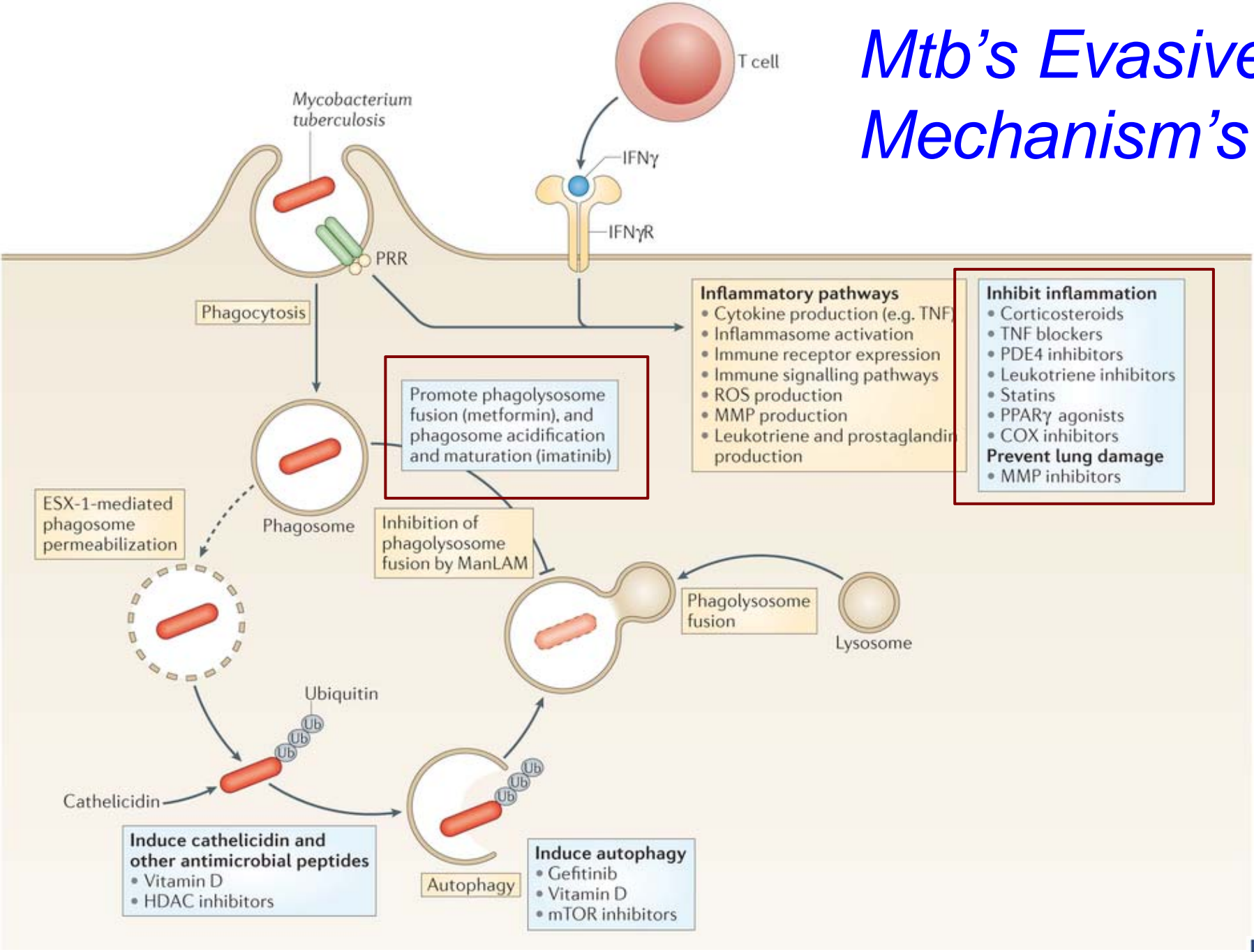
# Why HDTs?

- Conventional pathogen directed approach
  - Do not take into account host immune response
    - ✓ TB pathology
  - Suffer from the serious disadvantage of fostering microbial resistance
    - ✓ MDR on rise
- Toxicity associated with current TB regimen and anti-mycobacterial drugs in pipeline

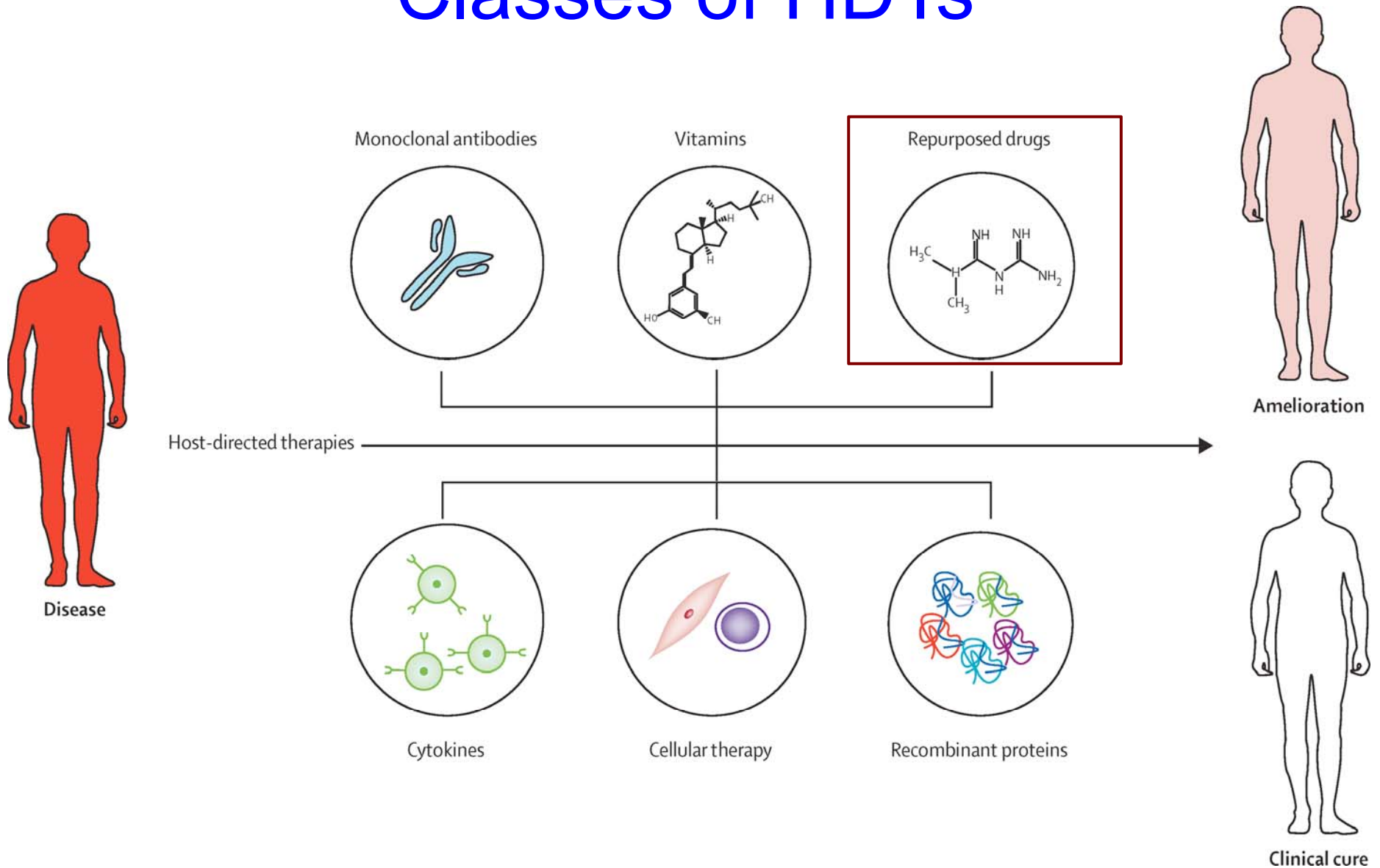
# HDT – not a new paradigm *Existed in pre-antibiotic era*



# Mtb's Evasive Mechanisms

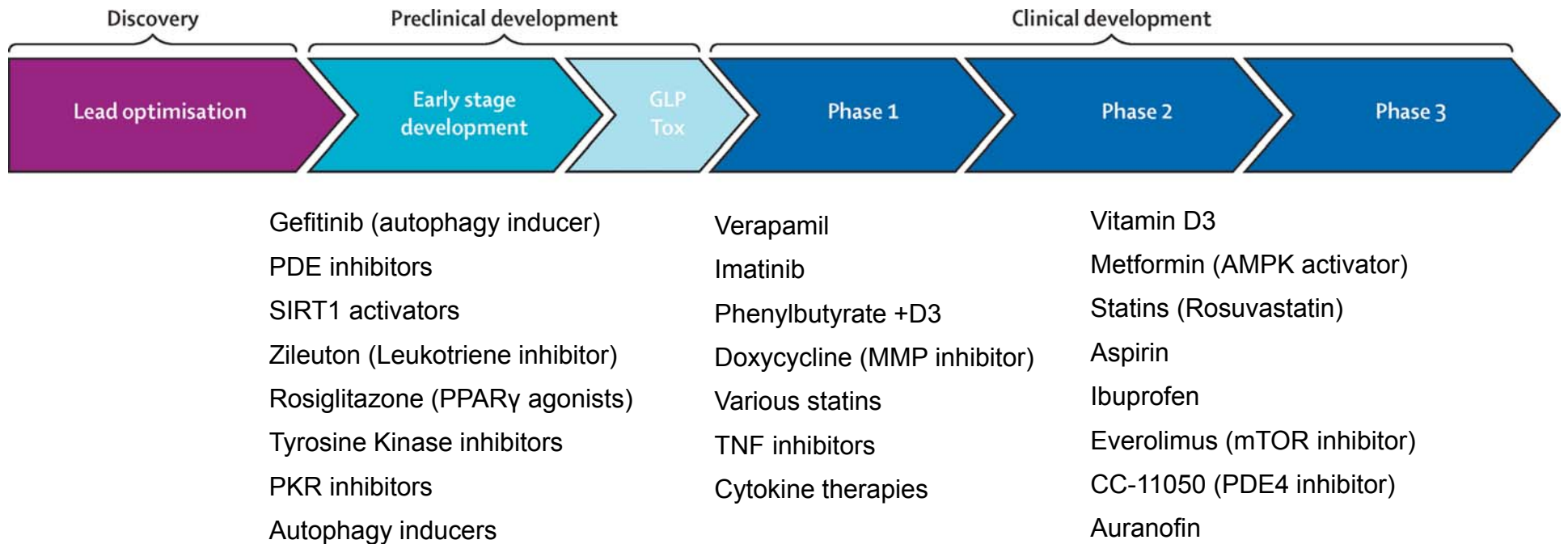


# Classes of HDTs



Zumla et al, Lancet Inf Dis, 2016

# Current pipeline of repurposed drugs



*PDE – Phosphodiesterase*

*SIRT1 – Sirtuin 1; MMP – Matrix Metalloproteinases*

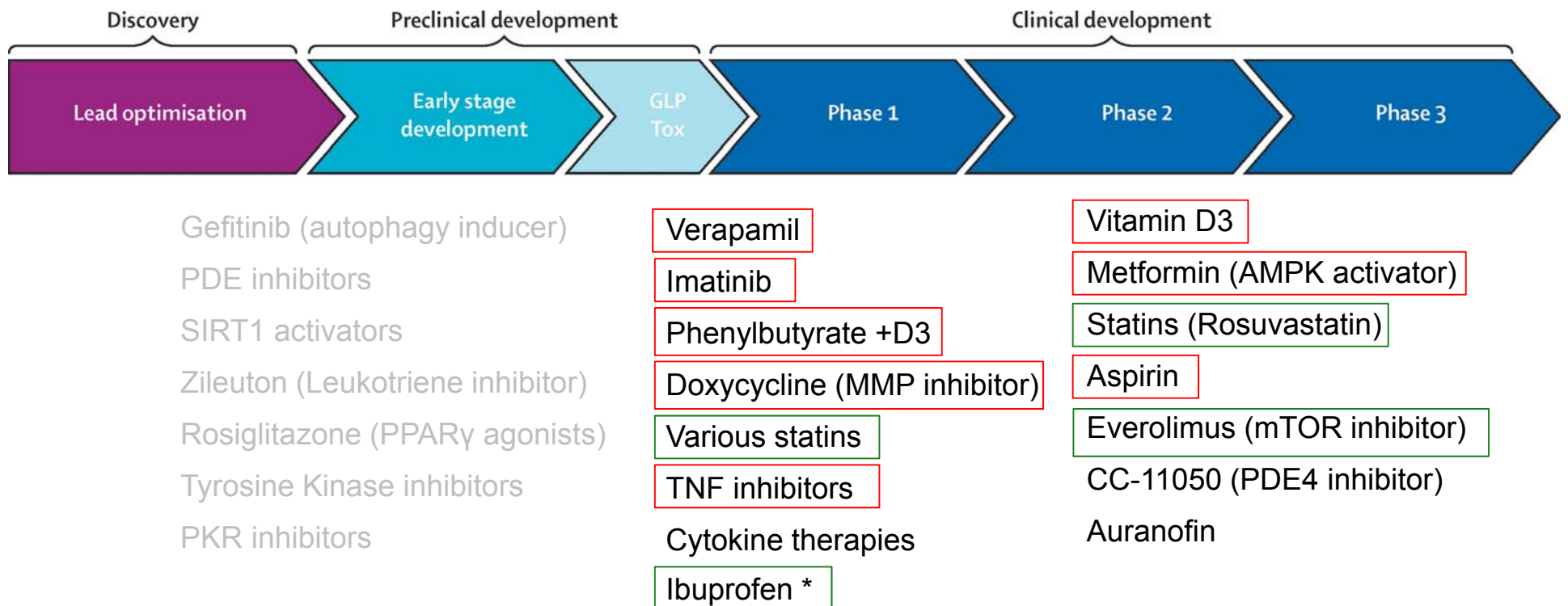
*mTOR – mammalian Target of Rapamycin*

# Possible advantages of Host-Directed Therapy by repurposed drugs

1. Well established safety profiles
2. Shorter therapy duration
3. Lower risk of relapse or re-infection
4. Effective against drug-resistant cases
5. Can be adopted to any chronic infections

*Hawn et al., Microbiol Mol Biol Rev, 2013*  
*Maiga et al., JID, 2013*  
*Zumla et al., Nat Rev Drug Discov, 2013*  
*Wilkinson, Lancet Resp Med, 2014*  
*Wallis & Hafner, Nat Rev Immunol, 2015*

# Interactions of TB-HDTs with DM

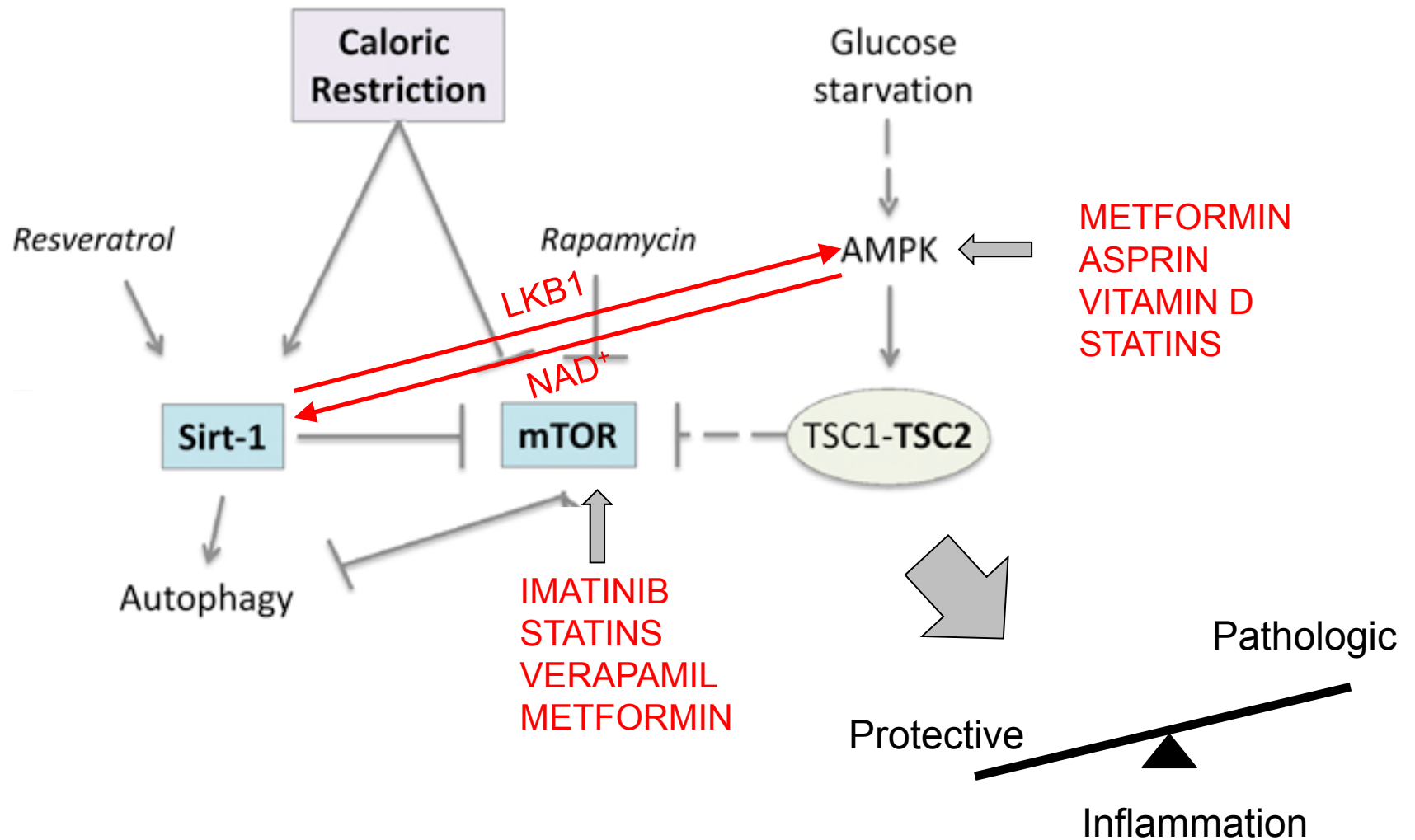


HDTs – reduce risk of DM; improve insulin sensitivity, reduce risk of hyperglycemia

HDTs – increase risk of DM; \* Low risk – 1 in 1000 patient-year (Satter et al., Lancet 2010)



# Repurposed drugs target trilogy of energy / metabolic sensors



Functional connections between immunity and metabolic signaling pathways can be harnessed to treat TB / DM+TB co-epidemic

*Thanks*