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

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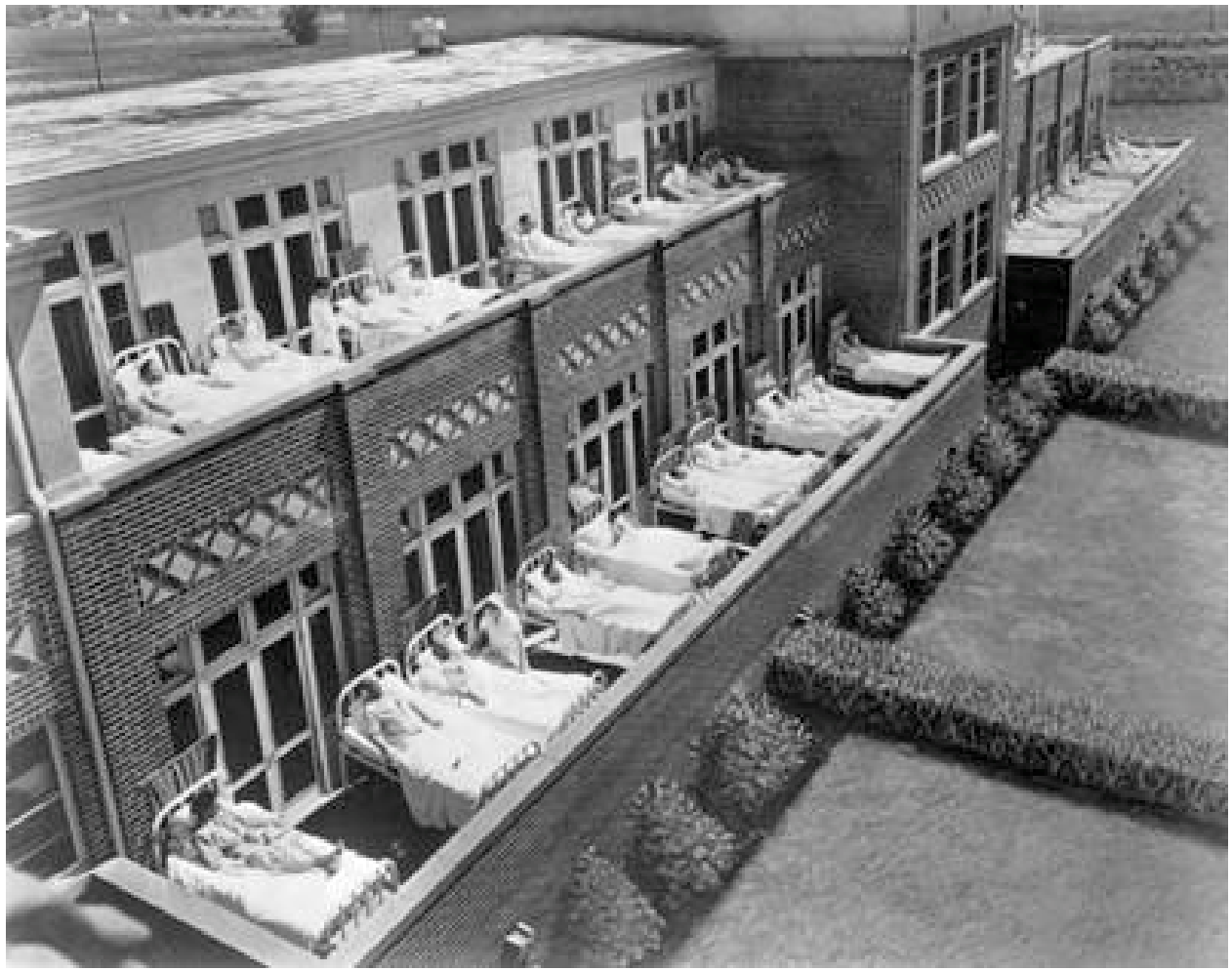
Why HDTs?

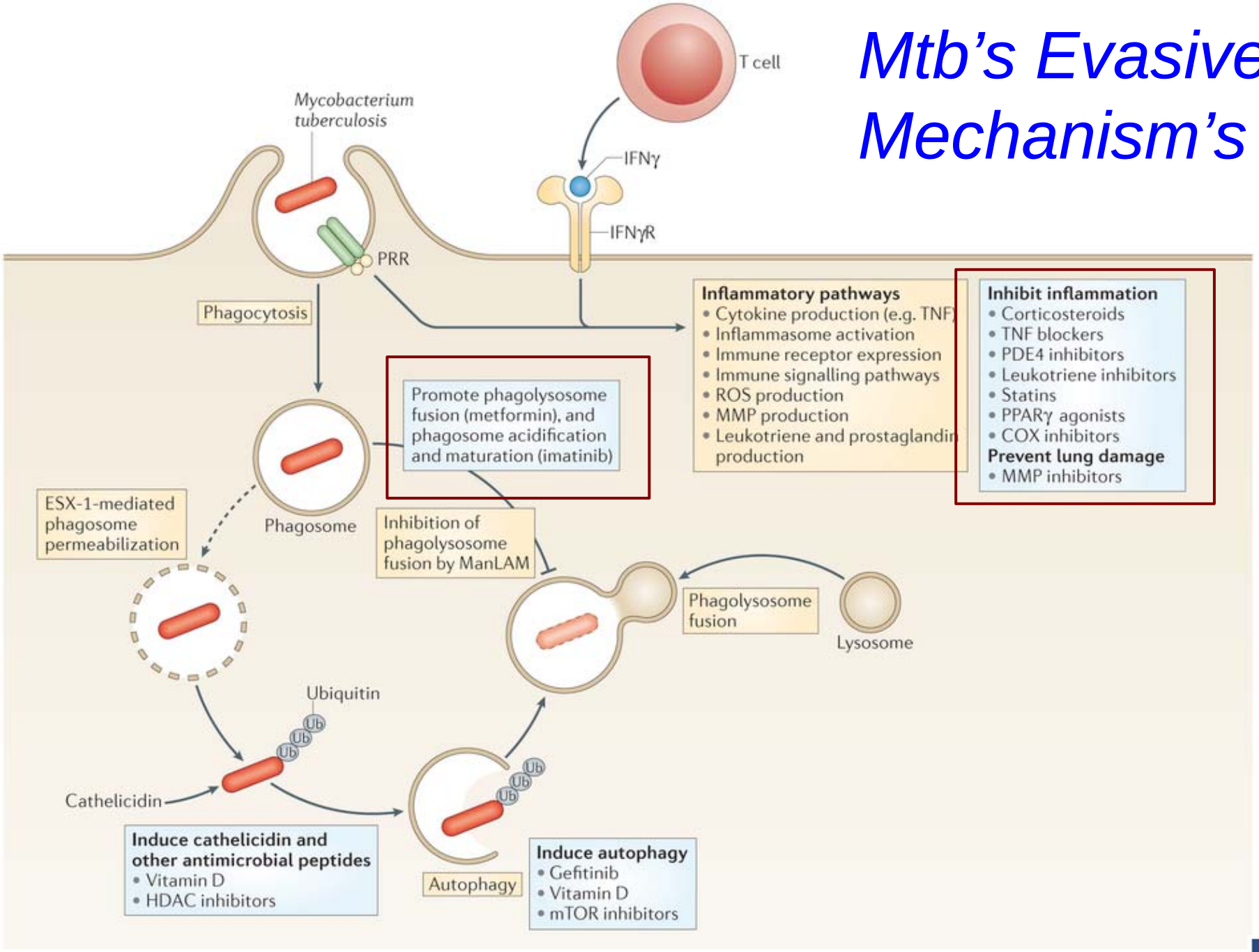
- Conventional pathogen directed approach
  - Do not take into account host immune response
    - ✓ TB pathology
  - Suffer from the serious disadvantage of fostering microbial resistance
    - ✓ MDR on rise
- Toxicity associated with current TB regimen and anti-mycobacterial drugs in pipeline

HDT – not a new paradigm

Existed in pre-antibiotic era

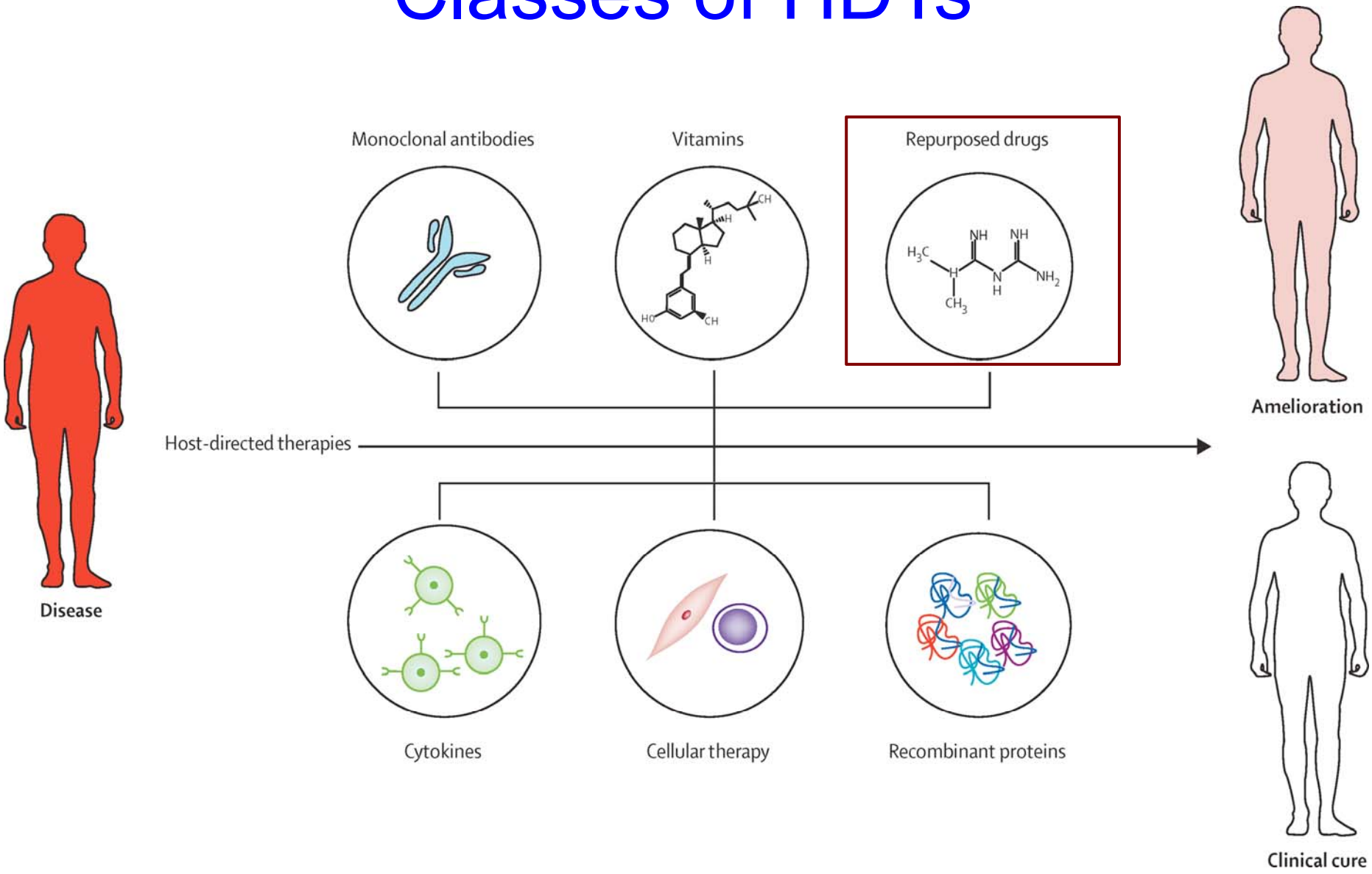


Mtb's Evasive Mechanism's



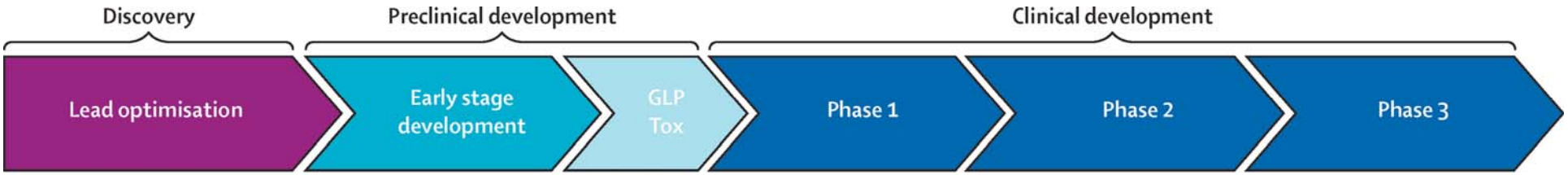
Wallis & Hafner, Nat Rev Immunol, 2015

Classes of HDTs



Zumla et al, Lancet Inf Dis, 2016

Current pipeline of repurposed drugs



Gefitinib (autophagy inducer)
PDE inhibitors
SIRT1 activators
Zileuton (Leukotriene inhibitor)
Rosiglitazone (PPARγ agonists)
Tyrosine Kinase inhibitors
PKR inhibitors
Autophagy inducers

Verapamil
Imatinib
Phenylbutyrate +D3
Doxycycline (MMP inhibitor)
Various statins
TNF inhibitors
Cytokine therapies

Vitamin D3
Metformin (AMPK activator)
Statins (Rosuvastatin)
Aspirin
Ibuprofen
Everolimus (mTOR inhibitor)
CC-11050 (PDE4 inhibitor)
Auranofin

PDE – Phosphodiesterase

SIRT1 – Sirtuin 1; MMP – Matrix Metaloproteinases

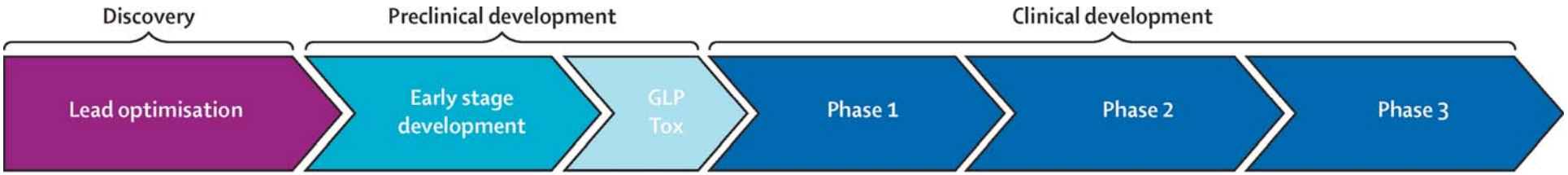
mTOR – mammalian Target of Rapamycin

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



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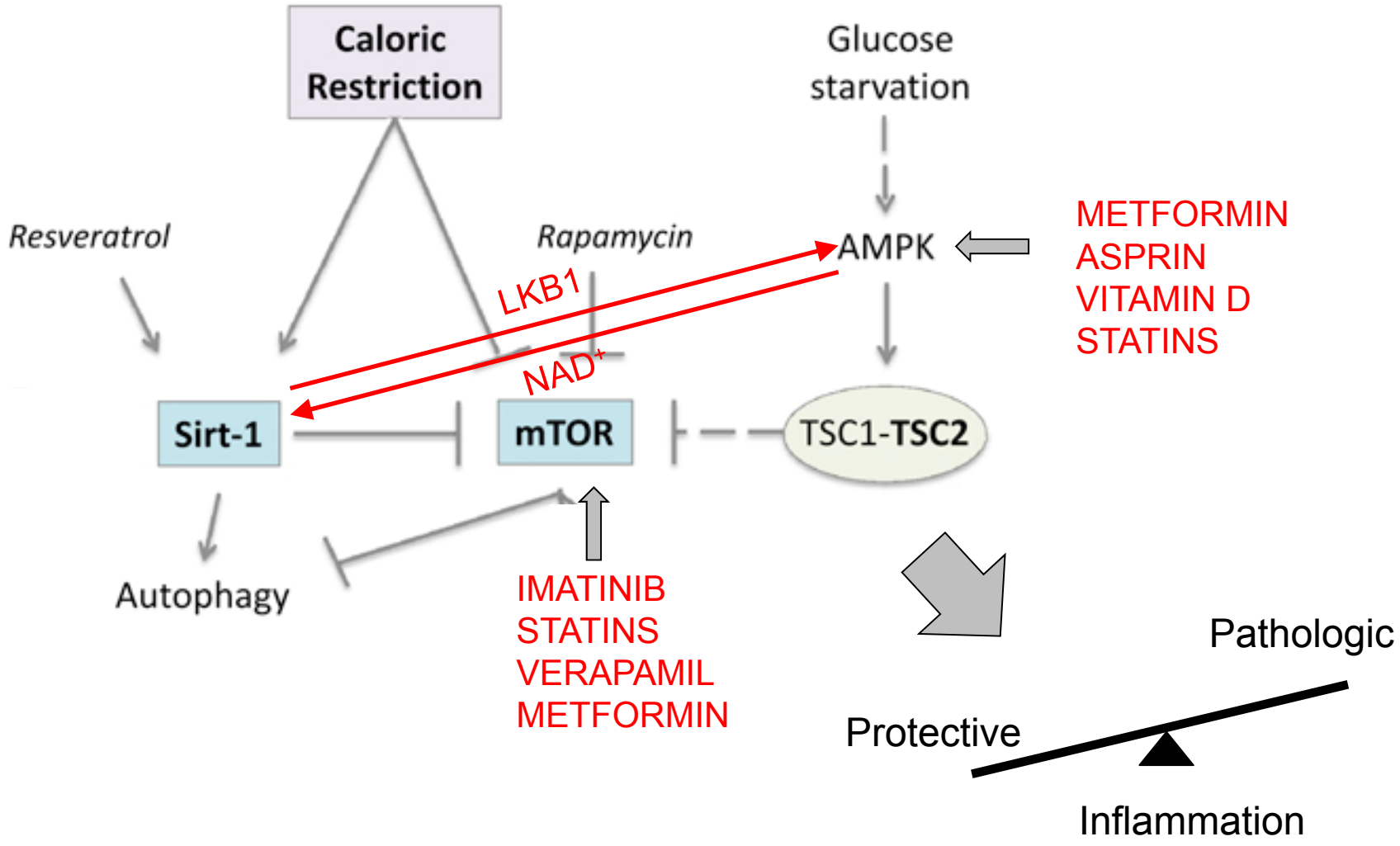
HDTs – reduce risk of DM; improve insulin sensitivity, reduce risk of hyperglycemia

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

Repurposed drugs target trilogue of energy / metabolic sensors



Functional connections between immunity and metabolic signaling pathways can be harnessed

to treat TB / DM+TB co-epidemic

Thanks