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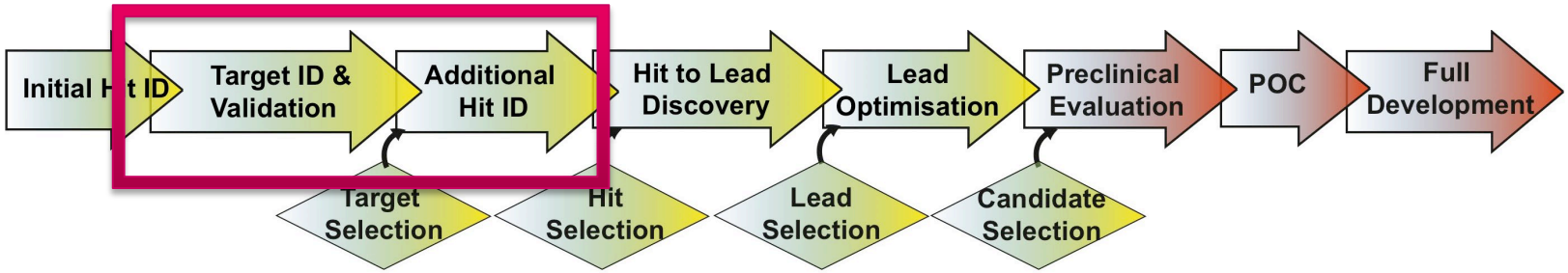
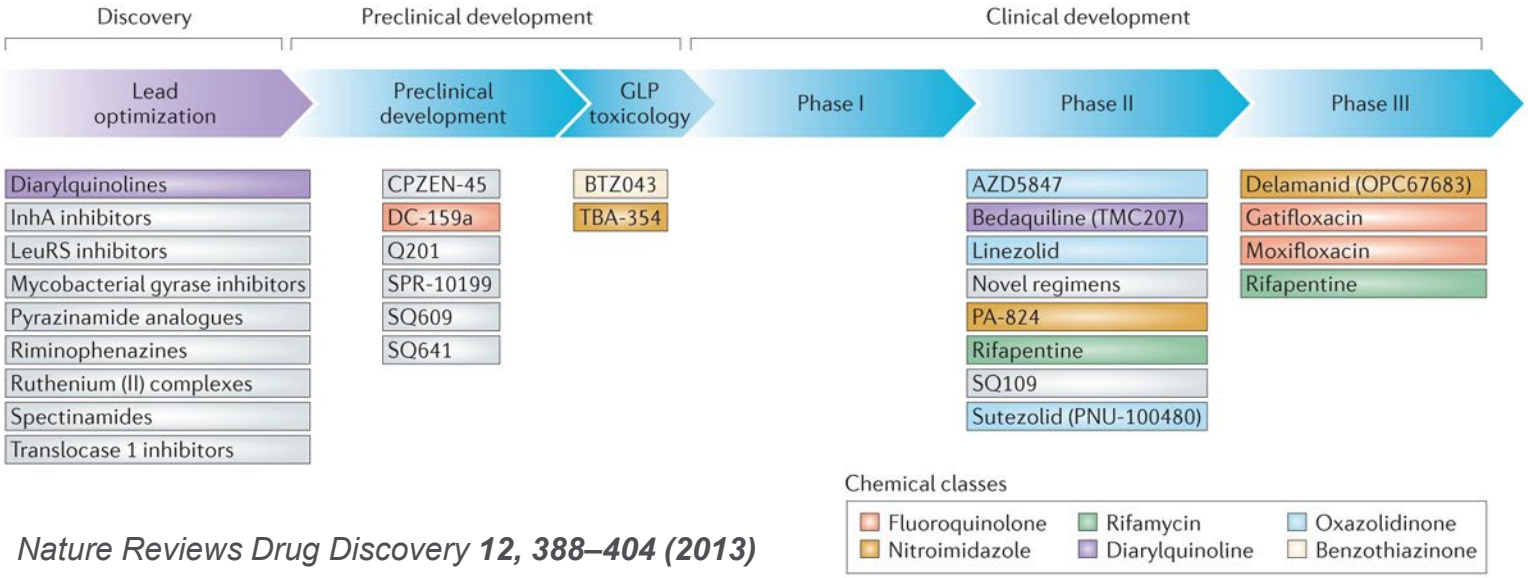
Good drugs for bad bugs:

Finding new antibiotics for tuberculosis

Dr Jonathan Cox
J.A.G.Cox@aston.ac.uk
@DrJonathanCox

TB Drug Discovery Pipeline





Nature Reviews Drug Discovery ***12, 388–404 (2013)***

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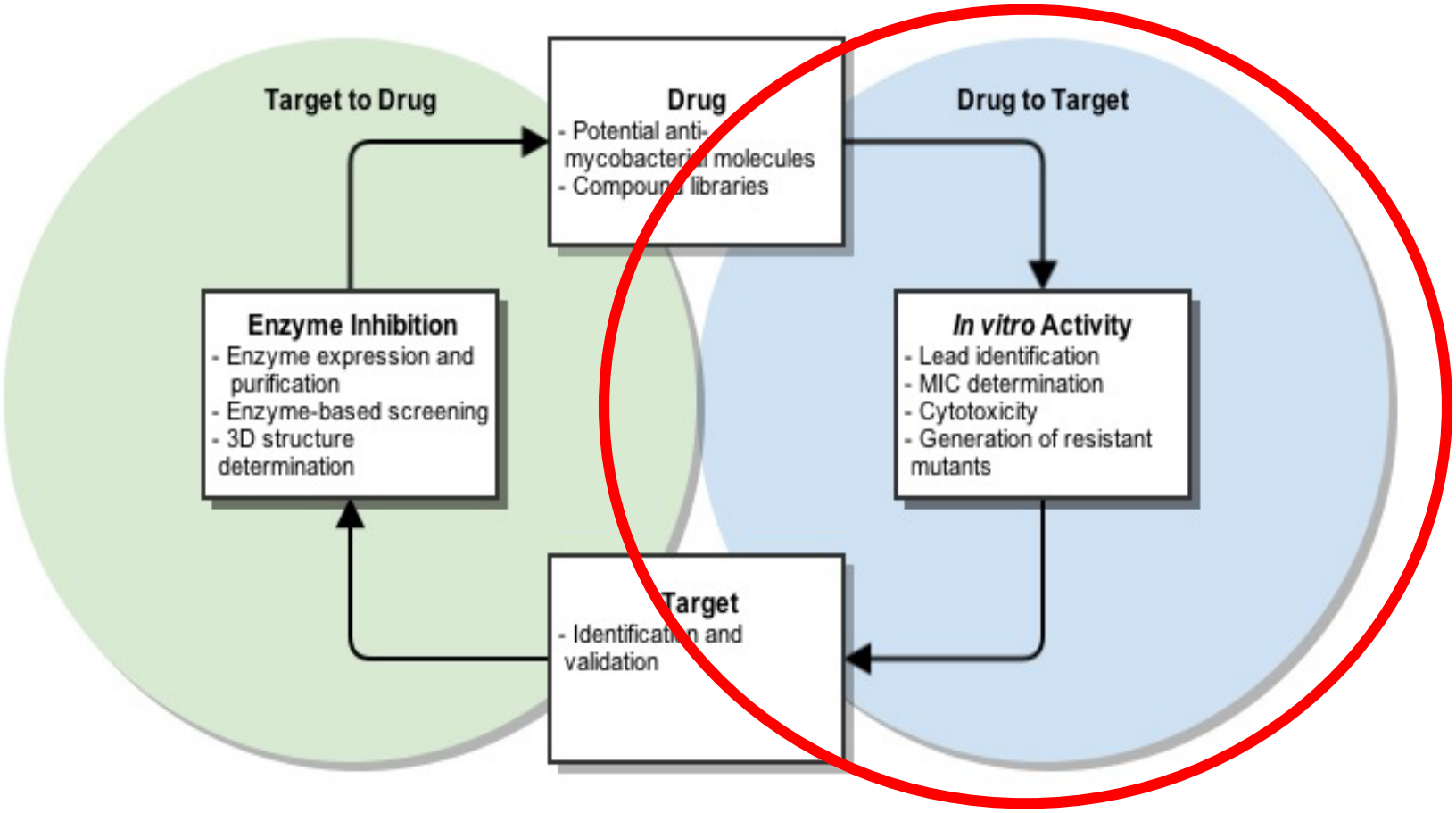
Strategies in AB drug discovery



Drug to target

1) Whole cell phenotypic HTS

2) Generate spontaneous mutants

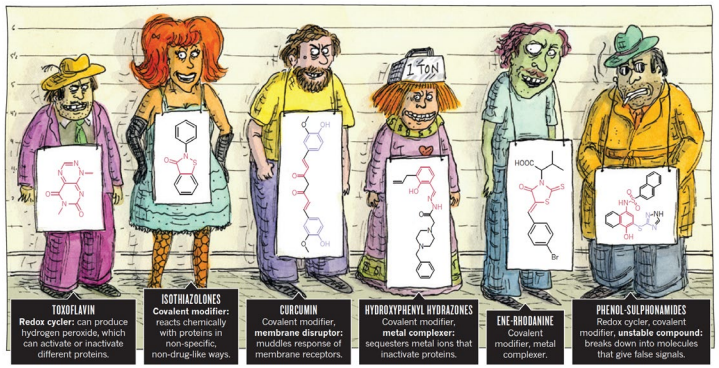
3) Validate resistance phenotype

4) WGS

5) Bioinformatics and SNP identification

6) Genetic validation

7) MOA studies



Pan-assay interference compounds (PAINS)
Baell and Walters *Nature* 2014 (513)

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Chasing your tail… or the wrong target

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PLOS | ONE

Tetrahydropyrazolo[1,5-*a*]Pyrimidine-3-Carboxamide and *N*-Benzyl-6′,7′-Dihydrospiro[Piperidine-4,4′-Thieno[3,2-*c*]Pyran] Analogues with Bactericidal Efficacy against *Mycobacterium tuberculosis* Targeting MmpL3

Modesto J. Remuiñán[1]*, Esther Pérez-Herrán[1], Joaquín Rullás[1], Carlos Alemparte[1], María Martínez-Hoyos[1], David J. Dow[2], Johnson Afari[2], Nalini Mehta[2], Jorge Esquivias[1], Elena Jiménez[1], Fátima Ortega-Muro[1], María Teresa Fraile-Gabaldón[1], Vickey L. Spivey[2], Nicholas J. Loman[3], Mark J. Pallen[3], Chrystala Constantinidou[3], Douglas J. Minick[4], Mónica Cacho[1], María José Rebollo-López[1], Carolina González[1], Verónica Sousa[1], Iñigo Angulo-Barturen[1], Alfonso Mendoza-Losana[1], David Barros[1], Gurdyal S. Besra[3], Lluís Ballell[1], Nicholas Cammack[1]

1 Diseases of the Developing World, GlaxoSmithKline, Tres Cantos, Madrid, Spain, **2** Molecular and Cellular Technologies, GlaxoSmithKline, Stevenage, United Kingdom, **3** School of Biosciences, University of Birmingham, Edgbaston, United Kingdom, **4** Department of Analytical Chemistry, GlaxoSmithKline, Research Triangle Park, North Carolina, United States of America

CHALLENGES:

- WGS has limitations
- It sometimes gives us a hint
- Its not the only strategy
- HTS only as good as the library

nature microbiology

Article | Published: 18 January 2016

THPP target assignment reveals EchA6 as an essential fatty acid shuttle in mycobacteria

Jonathan A. G. Cox, Katherine A. Abrahams, Carlos Alemparte, Sonja Ghidelli-Disse, Joaquín Rullas, Iñigo Angulo-Barturen, Albel Singh, Sudagar S. Gurcha, Vijayashankar Nataraj, Stephen Bethell, Modesto J. Remuiñán, Lourdes Encinas, Peter J. Jervis, Nicholas C. Cammack, Apoorva Bhatt, Ulrich Kruse, Marcus Bantscheff, Klaus Fütterer ✉, David Barros, Lluis Ballell ✉, Gerard Drewes & Gurdyal S. Besra ✉

Nature Microbiology **1**, Article number: 15006 (2016) | Download Citation ⬇

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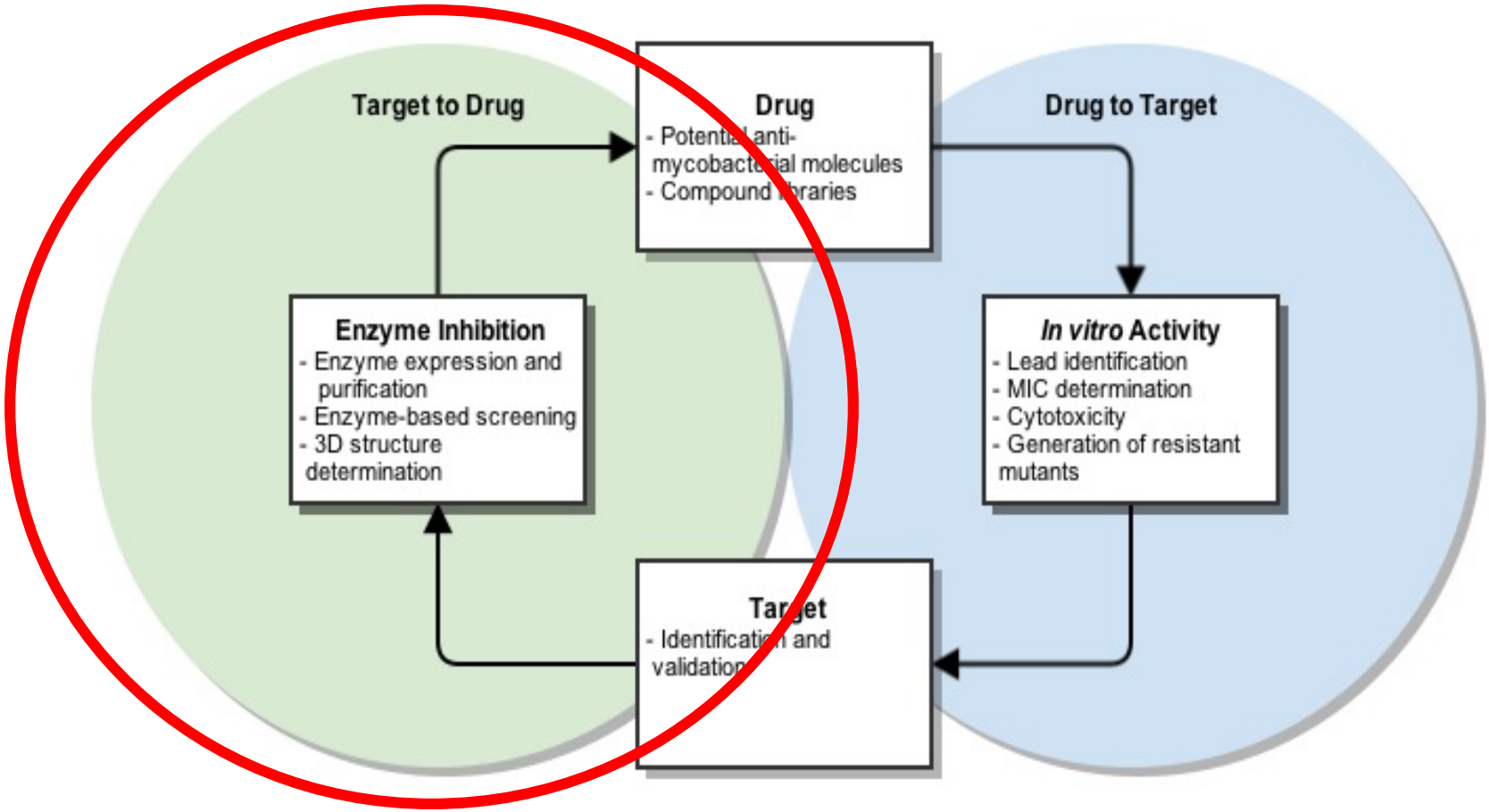
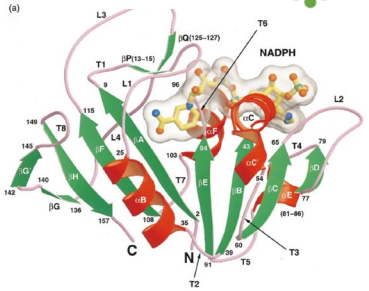
Strategies in AB drug discovery



Target to drug

EMBL European Molecular Biology Laboratory

gsk



Crystal structure of DHFR
(Li *et al.* 2000)

0 x MIC

CHALLENGES:

- Do the drugs get in?
- Are they active?
- Do they engage target?
- You won't discover a new drug target

PLOS ONE

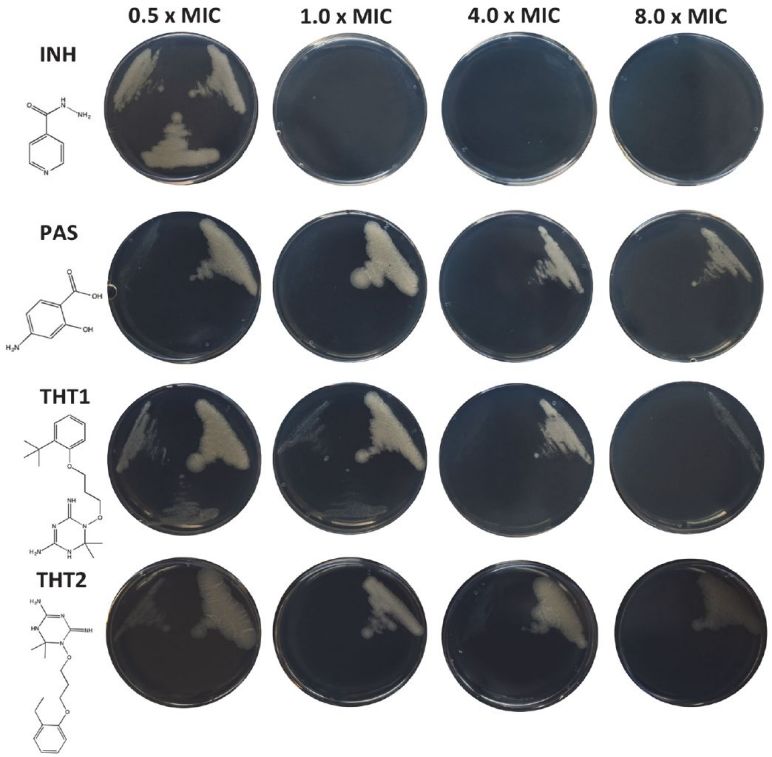
RESEARCH ARTICLE

Mycobacterial Dihydrofolate Reductase Inhibitors Identified Using Chemogenomic Methods and *In Vitro* Validation

Grace Mugumbate[1], Katherine A. Abrahams[3], Jonathan A. G. Cox[2], George Papadatos[1], Gerard van Westen[1], Joël Lelièvre[3], Szymon T. Calus[2], Nicholas J. Loman[2], Lluis Ballell[3], David Barros[3], John P. Overington[1]*, Gurdyal S. Besra[2]*

1 European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Wellcome Trust Genome Campus, Hinxton, Cambridge, United Kingdom, 2 Institute of Microbiology and Infection (IMI), School of Biosciences, University of Birmingham, Edgbaston, Birmingham, United Kingdom, 3 Diseases of the Developing World, GlaxoSmithKline, Severo Ochoa 2, 28760 Tres Cantos, Madrid, Spain

* jpo@ebi.ac.uk (JPO); g.besra@bham.ac.uk (GSB)



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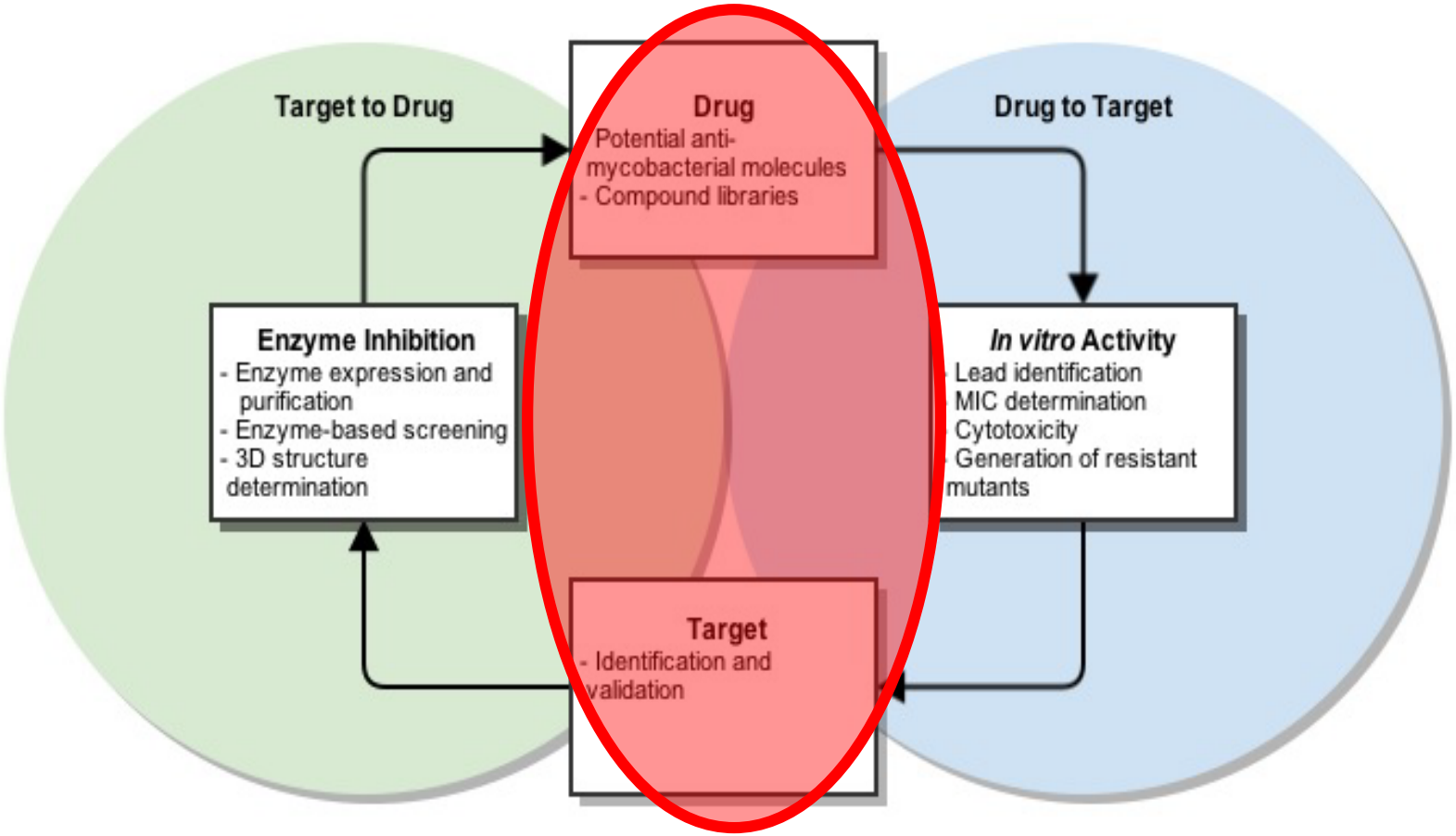
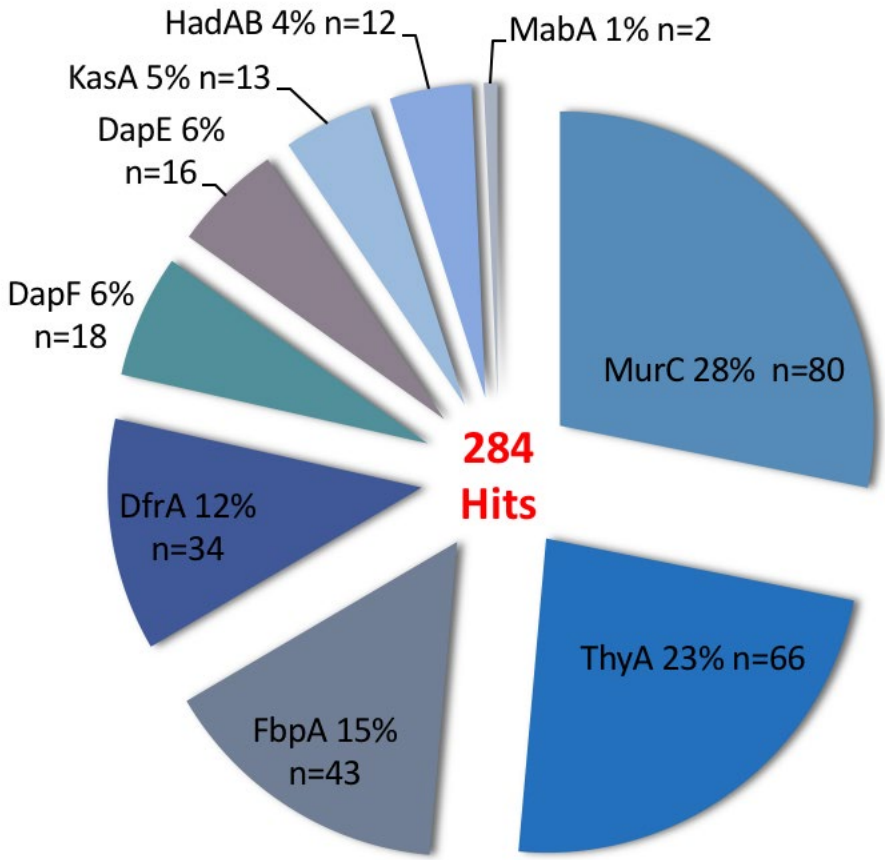
In an ideal world…..



A combined approach…

- Overexpress important genes
- Screen against 10,000 known TB inhibitors
- Look for IC_{50} shift with overexpressing strain

- New targets
- Good inhibitors
- Whole cell activity
- Target engagement



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