



Chemogenomics and *in silico* repurposing as an innovative approach for rapid drug discovery in tuberculosis

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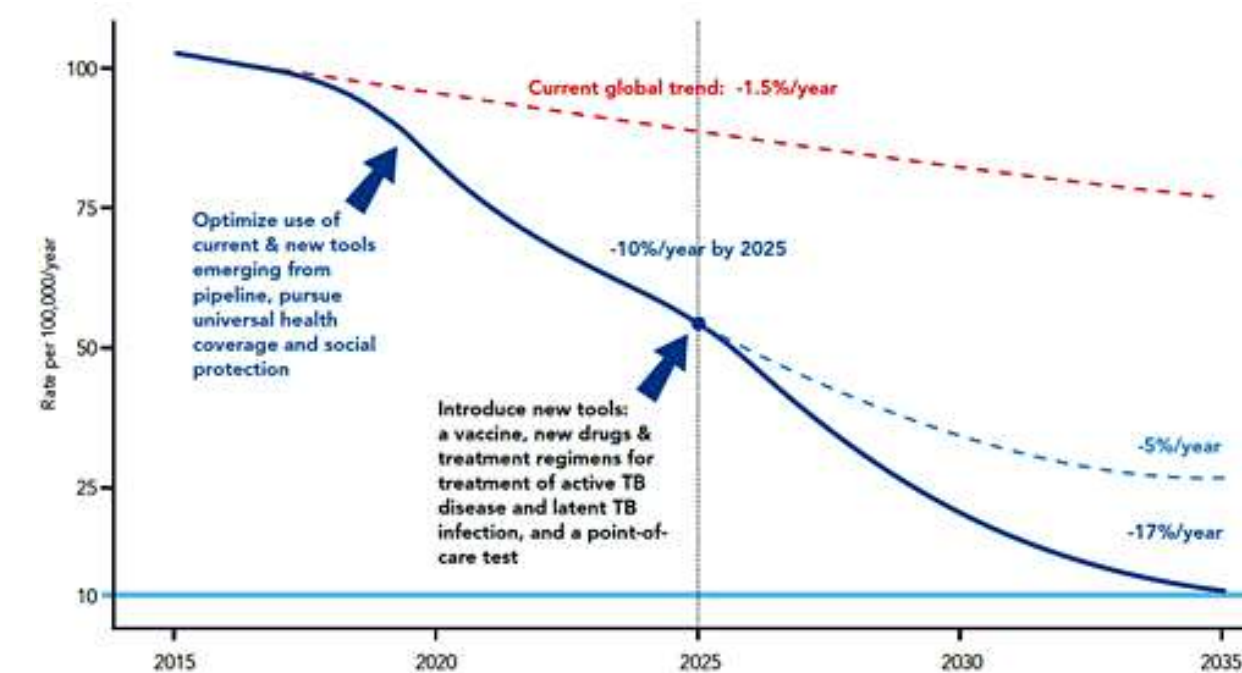
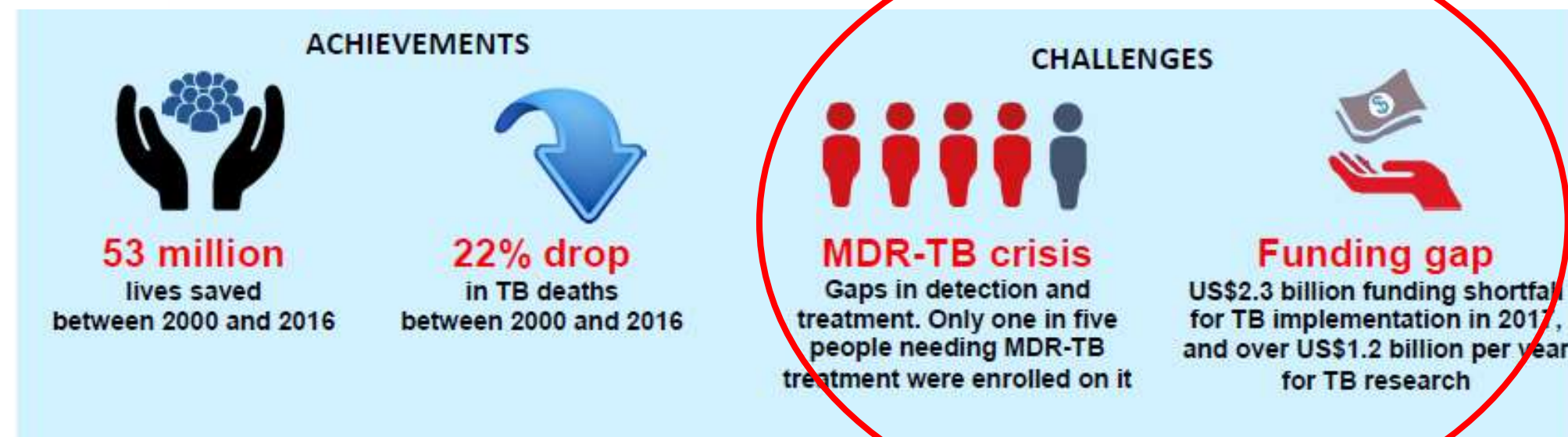
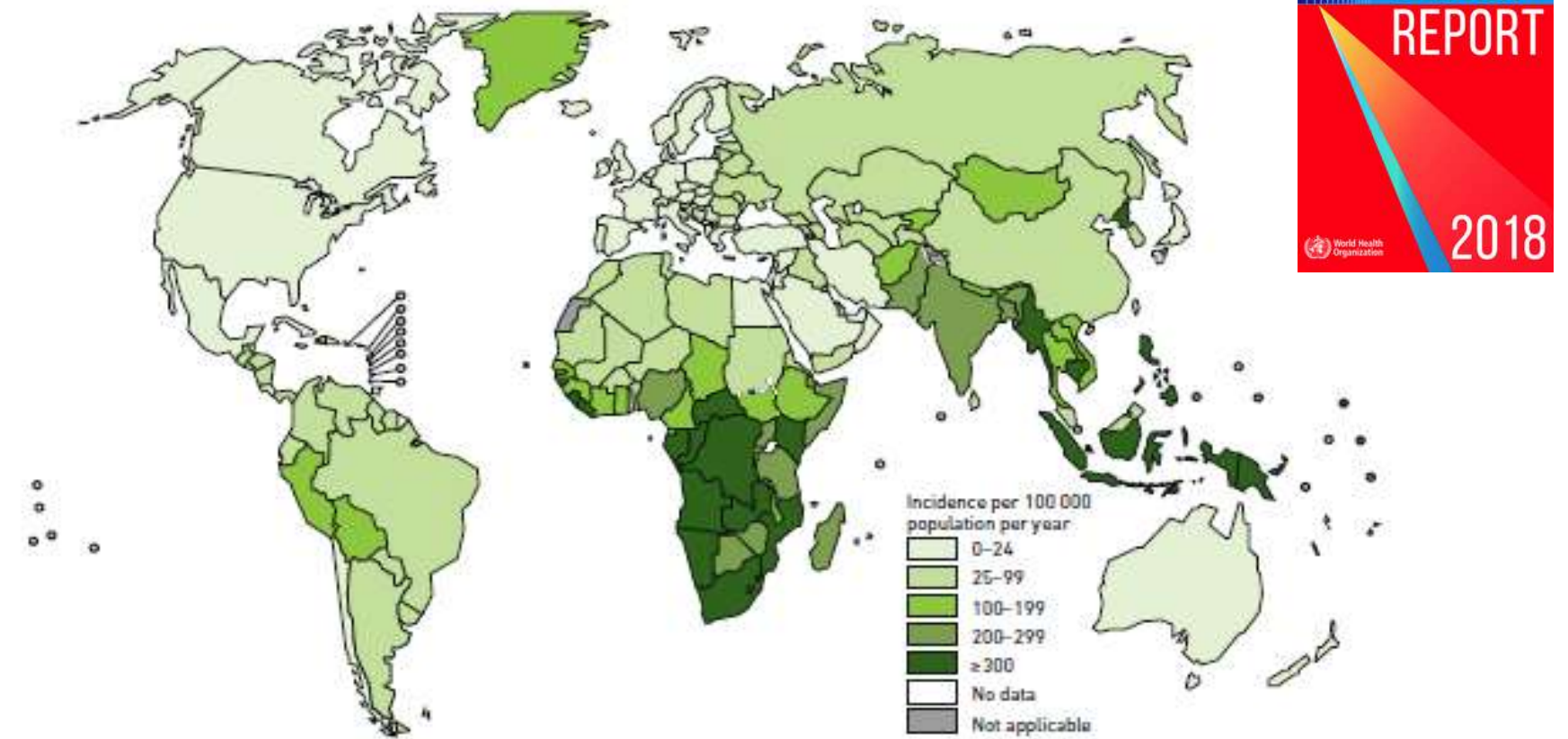


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Tuberculosis in the 21st century

- The world's greatest infectious killer.
- 2017: **10 million** people fell ill with tuberculosis (TB), and **1.6 million died**.
- Leading killer of HIV-positive people.
- **Multidrug-resistant TB** (MDR-TB): **558 000 new cases** with resistance to rifampicin (RIF) of which 82% had MDR-TB (resistance to RIF and isoniazid).



How can we get new drugs faster?
More efficiently and cost effective?



Drug repositioning or repurposing: New use for a previously approved drug

Traditional drug discovery versus repositioning

It is estimated that it takes on average 13.5 years to bring a new molecular entity to market, and the success rate for taking oncology drugs from phase 1 trials to regulatory approval is only about 7%. Drug repositioning builds on previous research and development, allowing compounds to progress through the drug development process more quickly as well as saving on the substantial costs associated with previous attrition.

De novo drug discovery and development

10 to 17 years



Drug repositioning

3 to 12 years



Source: Nature

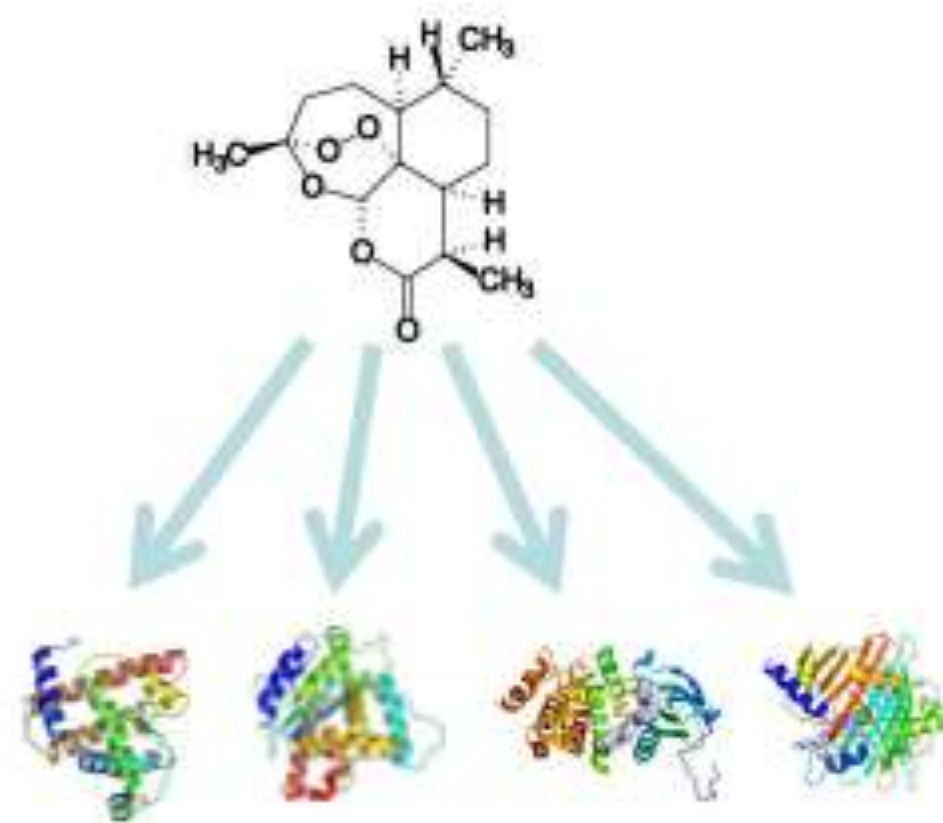


DRUG	ORIGINAL INDICATION	NEW INDICATION
Amphotericin B	Fungal infections	Leishmaniasis
Aspirin	Inflammation, pain	Antiplatelet
Bromocriptine	Parkinson's disease	Diabetes mellitus
Finasteride	Prostate hyperplasia	Hair loss
Gemcitabine	Viral infections	Cancer
Methotrexate	Cancer	Psoriasis, rheumatois arthritis
Minoxidil	Hypertension	Hair loss
Raloxifene	Cancer	Osteoporosis
Thalidomide	Morning sickness	Leprosy, multiple myeloma
Sildenafil	Angina	Erectile dysfunction, pulmonar hypertension

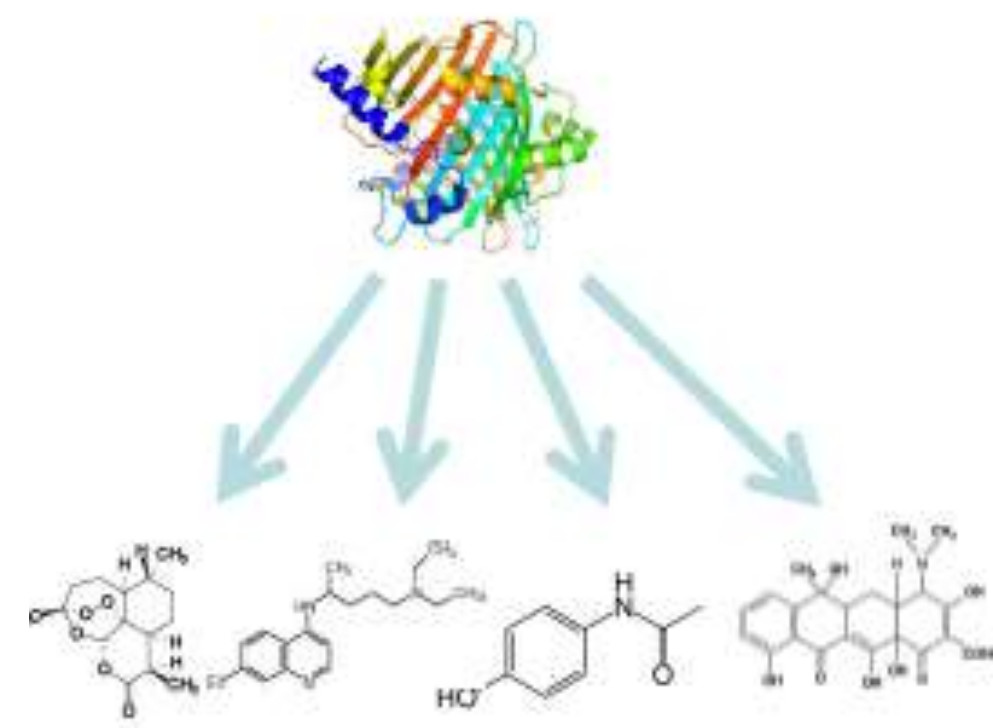


Drug repositioning strategies

Drug-centered



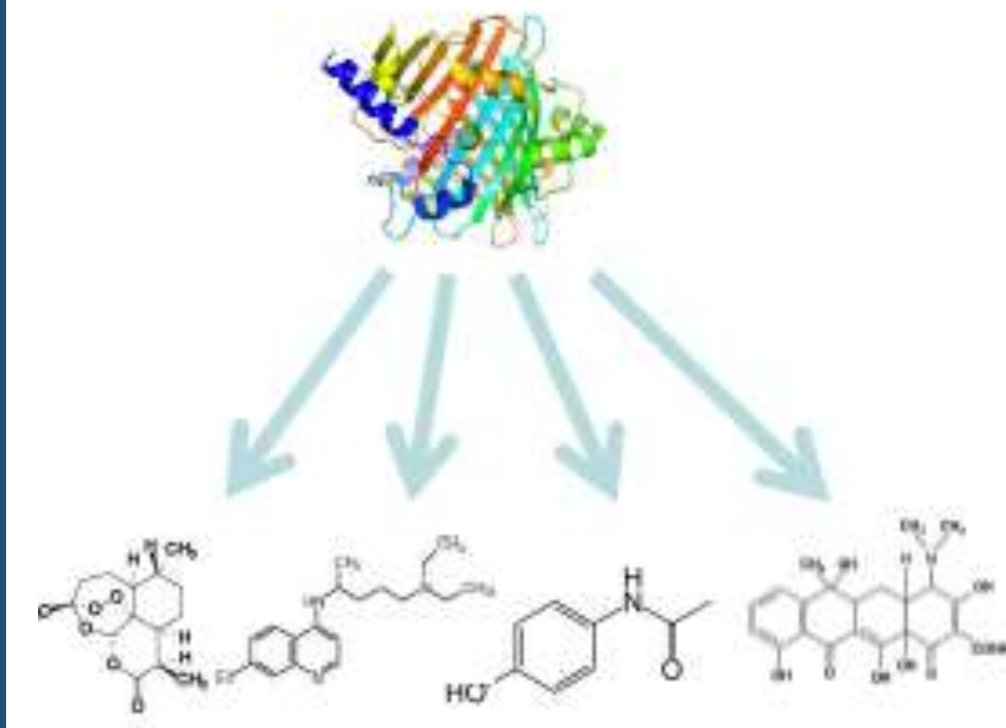
Target-centered





Drug repositioning strategies

Target-centered





Genomics & Bioinformatics are used to repurpose drugs: the principle of “target homology”

OPEN ACCESS Freely available online



A Systematic *In Silico* Search for Target Similarity Identifies Several Approved Drugs with Potential Activity against the *Plasmodium falciparum* Apicoplast

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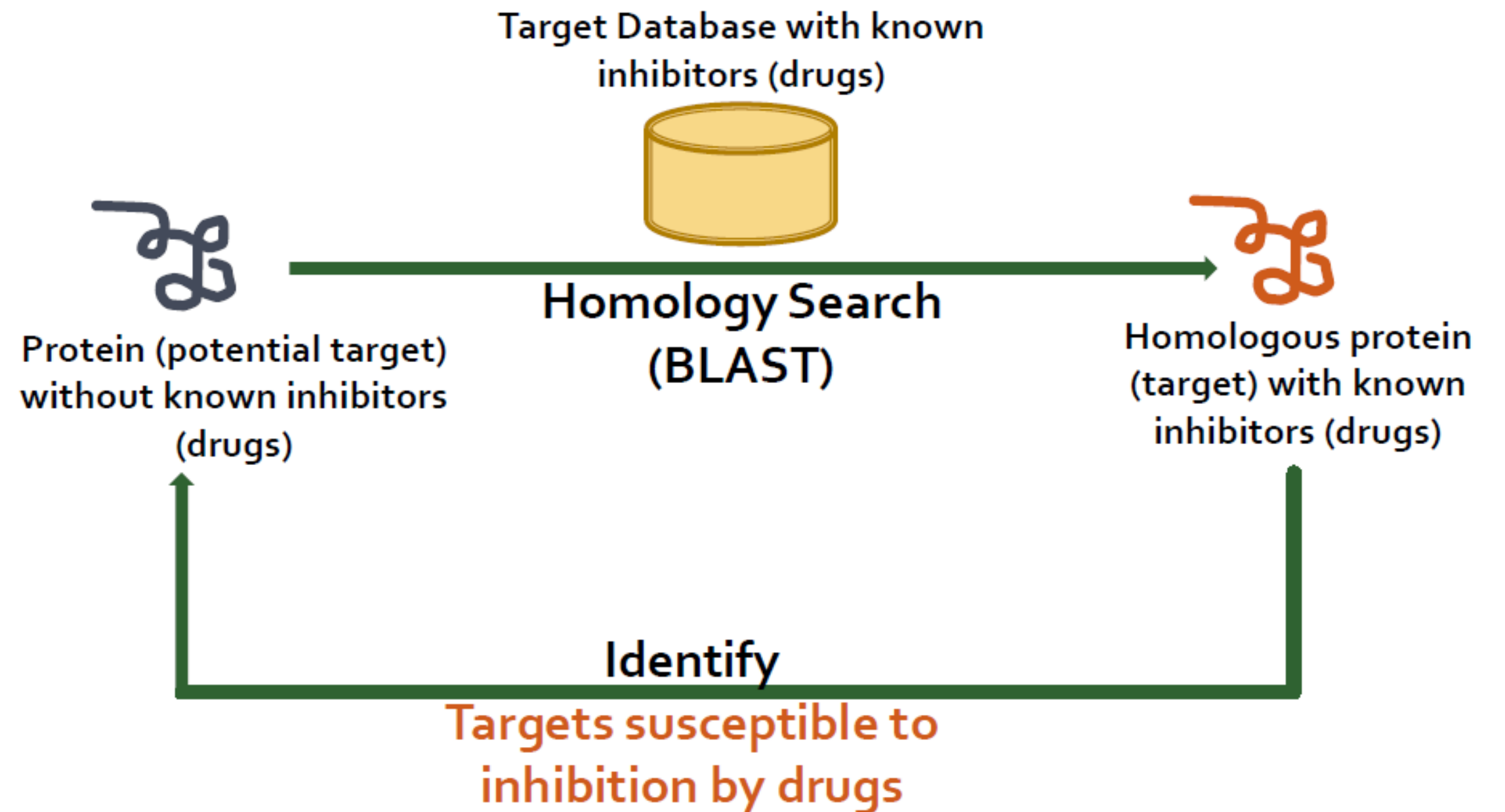
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In Silico Repositioning-Chemogenomics Strategy Identifies New Drugs with Potential Activity against Multiple Life Stages of *Schistosoma mansoni*

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OBJECTIVES

- To use **drug repurposing** and **comparative chemogenomics** to find **new drugs** against **TB**.
- To establish a **new paradigm** for the design of **new drugs** and new therapeutic strategies to be used in the fight against **TB**.



TARGET: Energy Metabolism (Oxidative phosphorylation) in *M. tuberculosis*

in vivo 21: 771-776 (2007)

The Curative Activity of Thioridazine on Mice Infected with *Mycobacterium tuberculosis*

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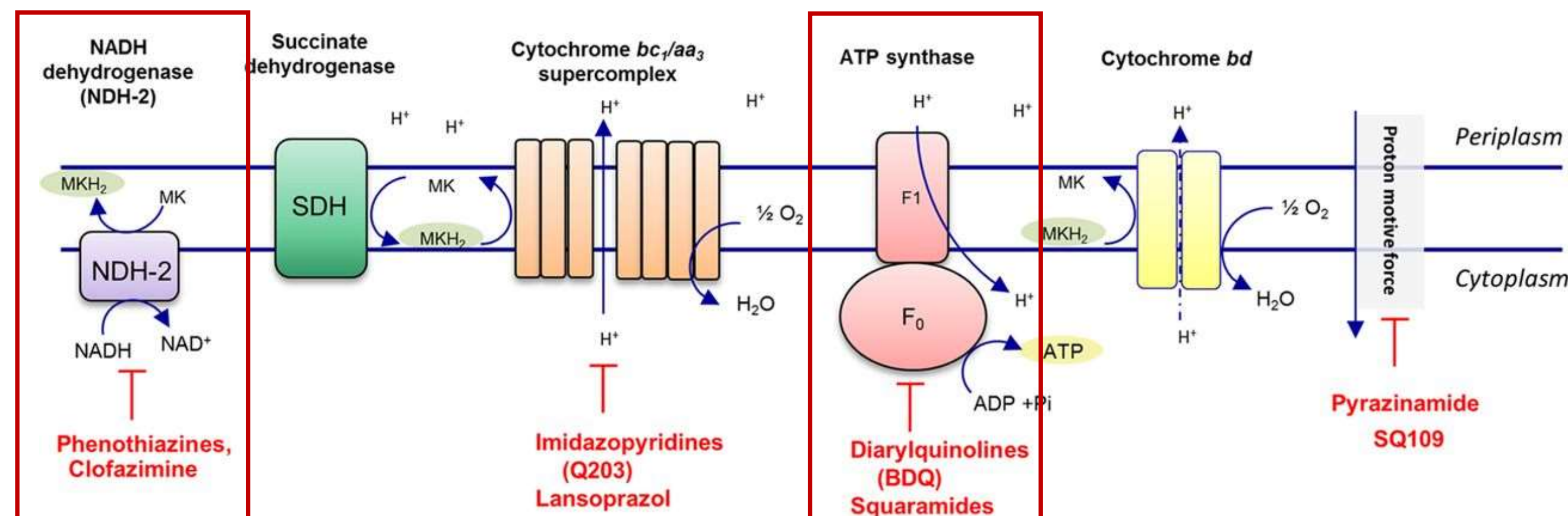
J Antimicrob Chemother 2012; **67**: 473-477
doi:10.1093/jac/dkr500 Advance Access publication 1 December 2011

Journal of
Antimicrobial
Chemotherapy

Successful alternative treatment of extensively drug-resistant tuberculosis in Argentina with a combination of linezolid, moxifloxacin and thioridazine

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Thioridazine

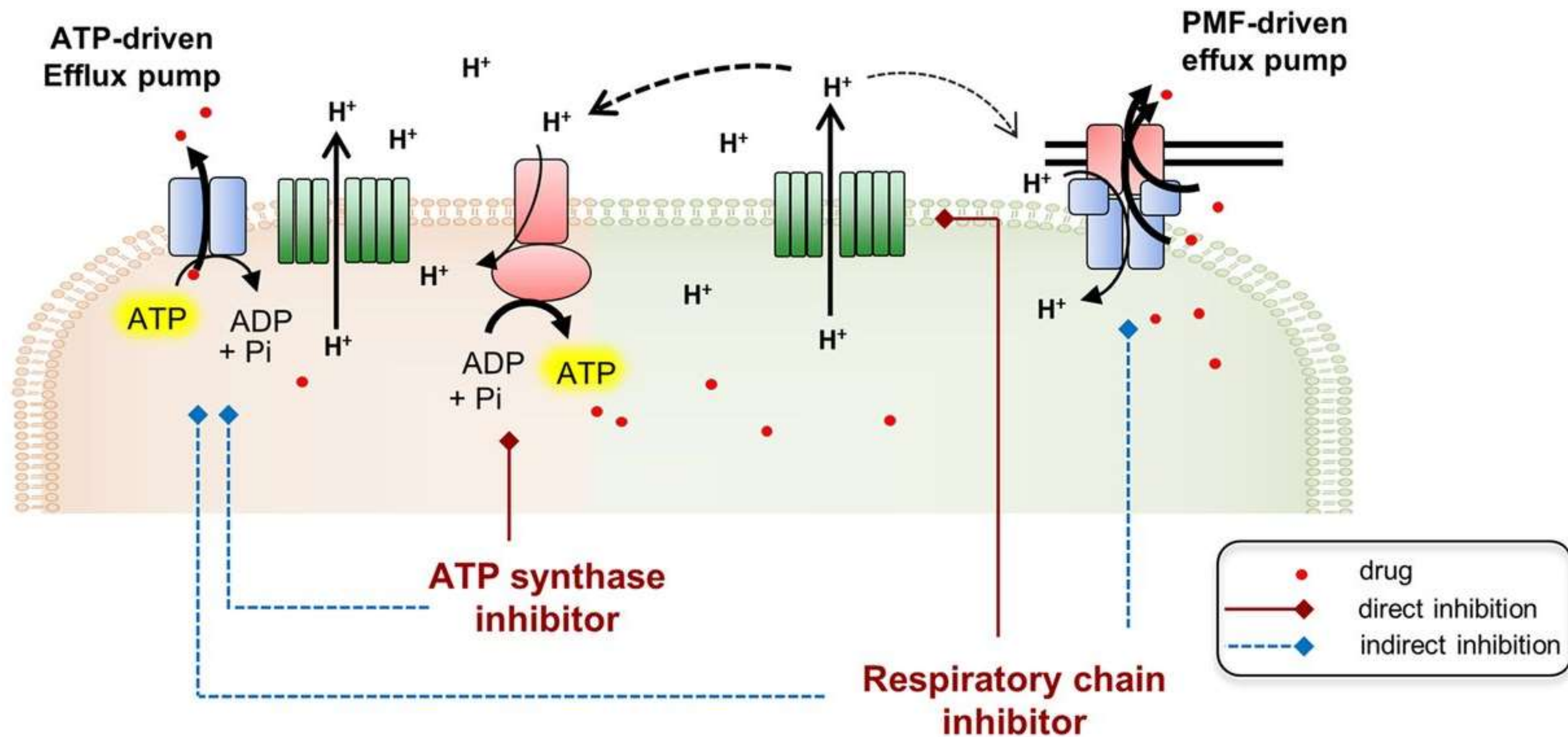
antipsychotic drug,
TB treatment under
consideration

Bedaquiline (BDQ)

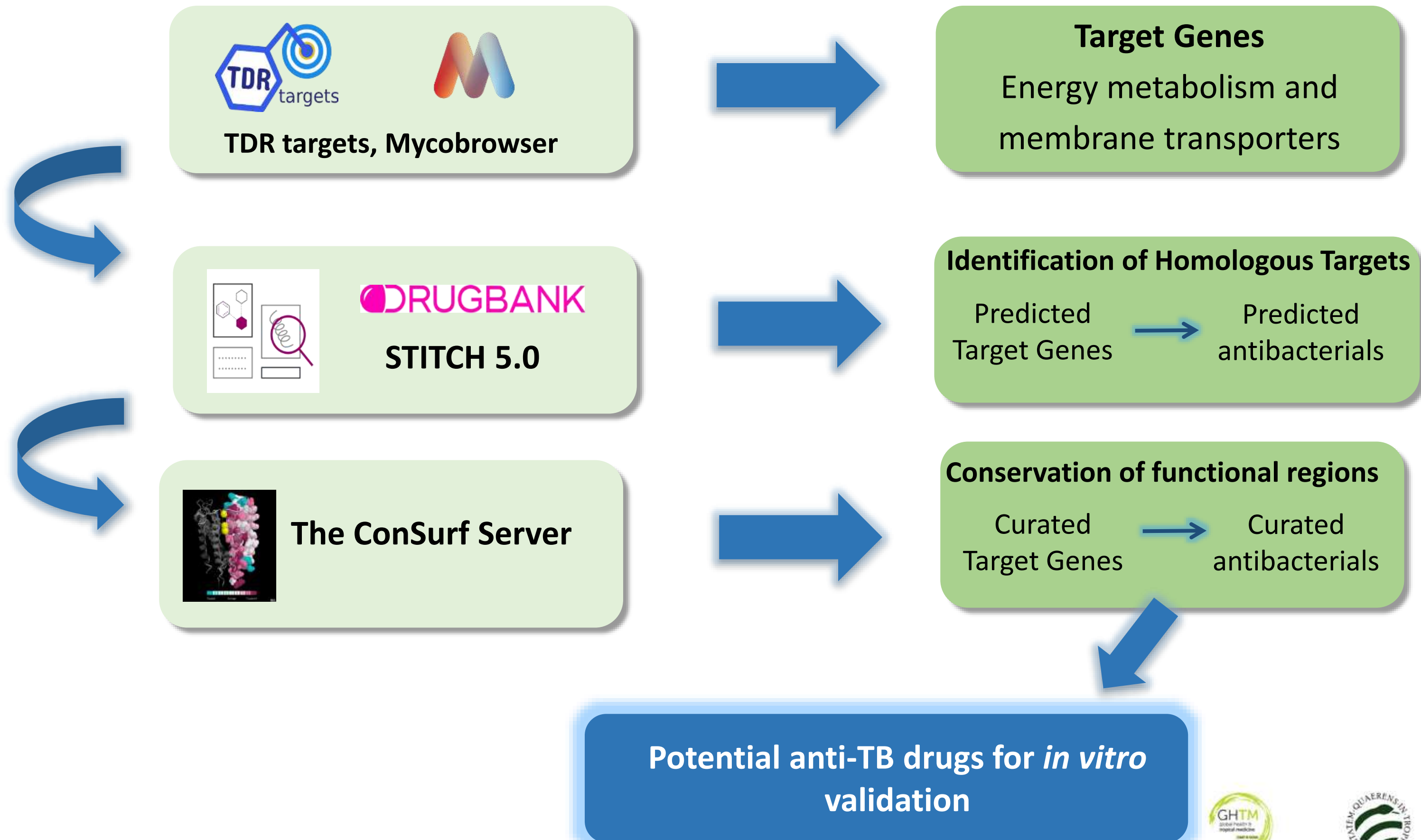
new anti-TB drug
(MDR-TB treatment)



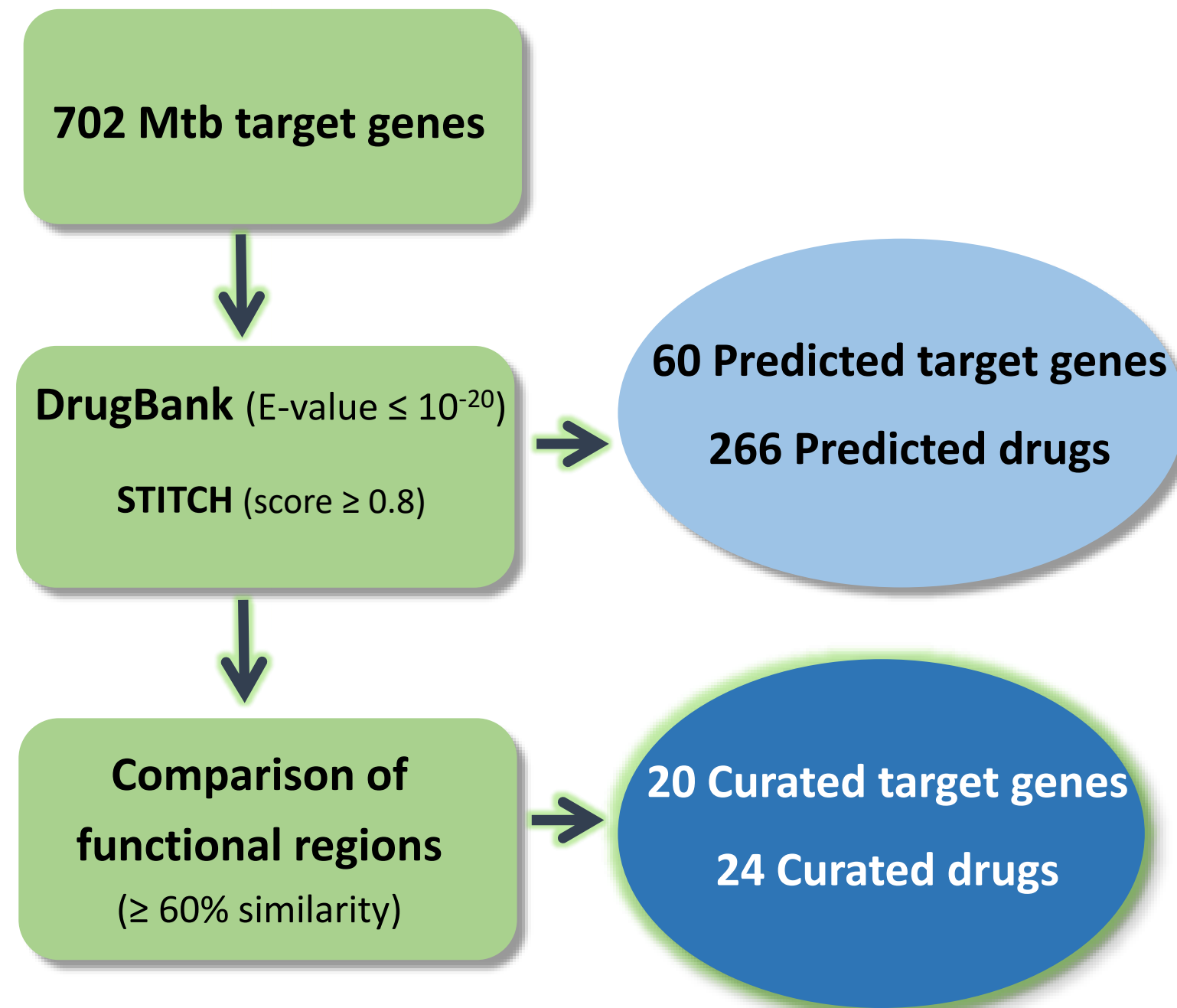
Inhibitors of oxidative phosphorylation can affect membrane transporters (efflux pumps)



In silico Repurposing-Chemogenomics Strategy



Results: *In silico* analysis



Drug	Indication	Predicted Target in Mtb
Thiabendazole	Fungicide, Parasiticide	Succinic dehydrogenase
Deslanoside	Cardiac insufficiency, arrhythmias	Metal cation transporter P-type ATPase A CtpF
Doxorubicin	Cancer	NADH dehydrogenase I
Valproic Acid	Epilepsy	Acyl-CoA dehydrogenase FadE19
Fostamatinib	Chronic immune thrombocytopenia	Transmembrane serine/threonine-protein kinase E

- ✓ Sequence similarity screenings **predicted 60 targets** associated with **266 approved drugs**
- ✓ Functional regions comparison resulted in **20 potential Mtb targets** that could interact with **24 approved drugs**.

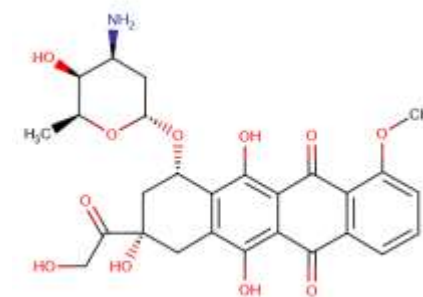


Do these compounds have antibacterial activity?

Preliminary results

Compound	Minimum inhibitory concentration (µg/ml)	
	<i>Escherichia coli</i> AG100	<i>Mycobacterium smegmatis</i>
CPZ/TZ	60 (CPZ)	12.5 (TZ)
Doxorubicin	30	0.78
Deslanoside	>480	>200
Valproic Acid	>480	>200
Thiabendazole	>480	>200
Fostamatinib	>480	>100

CPZ: chlorpromazine; TZ: thioridazine



Doxorubicin is a **anthracycline** antibiotic isolated from the bacterium *Streptomyces peucetius*

Class of drugs used in cancer chemotherapy

Predicted target in *M. tuberculosis*: **NADH**

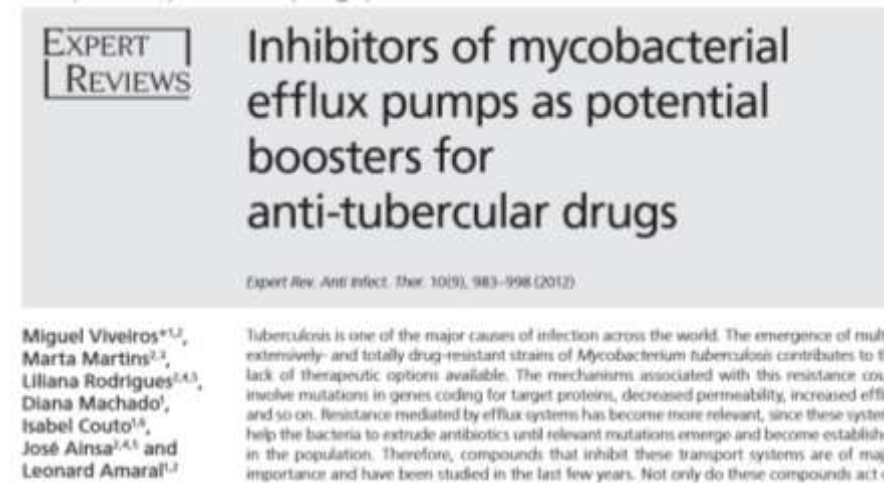
dehydrogenase I (Rv3146, Rv1348)



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What's Next?

- Test synergism with known anti-TB drugs



- Study effect on macrophage killing activity



RESEARCH ARTICLE

Ion Channel Blockers as Antimicrobial Agents, Efflux Inhibitors, and Enhancers of Macrophage Killing Activity against Drug Resistant *Mycobacterium tuberculosis*

Diana Machado^{1,2*}, David Pires^{3,4*}, João Perdigão⁵, Isabel Couto^{1,6}, Isabel Portugal⁶, Marta Martins⁵, Leonard Amaral⁵, Elsa Anes^{3,4,5}, Miguel Viveiros^{1,2,1*}

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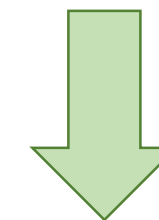


Secondment:



Macrophage studies:

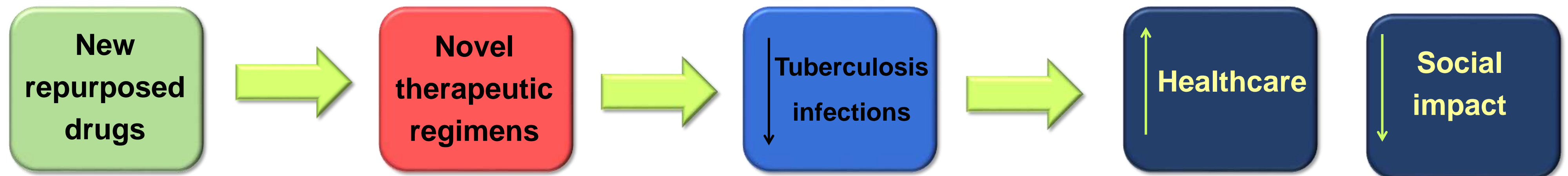
- Compound cytotoxicity
- Infection studies using *Salmonella* as a model



Application to *M. tuberculosis*

CONCLUSIONS

- ✓ We identified **new repurposed drugs** that may target **energy metabolism** and **membrane transporters** in Mtb, using *in silico* **drug repurposing** and **chemogenomics**.
- ✓ These drugs may serve as **lead compounds** for the development of new drugs against TB and MDRTB - **Future projects** and **collaborations**





Chemogenomics and *in silico* repurposing as an innovative approach for rapid drug discovery in tuberculosis

The team



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Global Health and Tropical Medicine (GHTM), IHMT/NOVA



Thank You



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