Understanding the molecular basis of bedaquiline resistance

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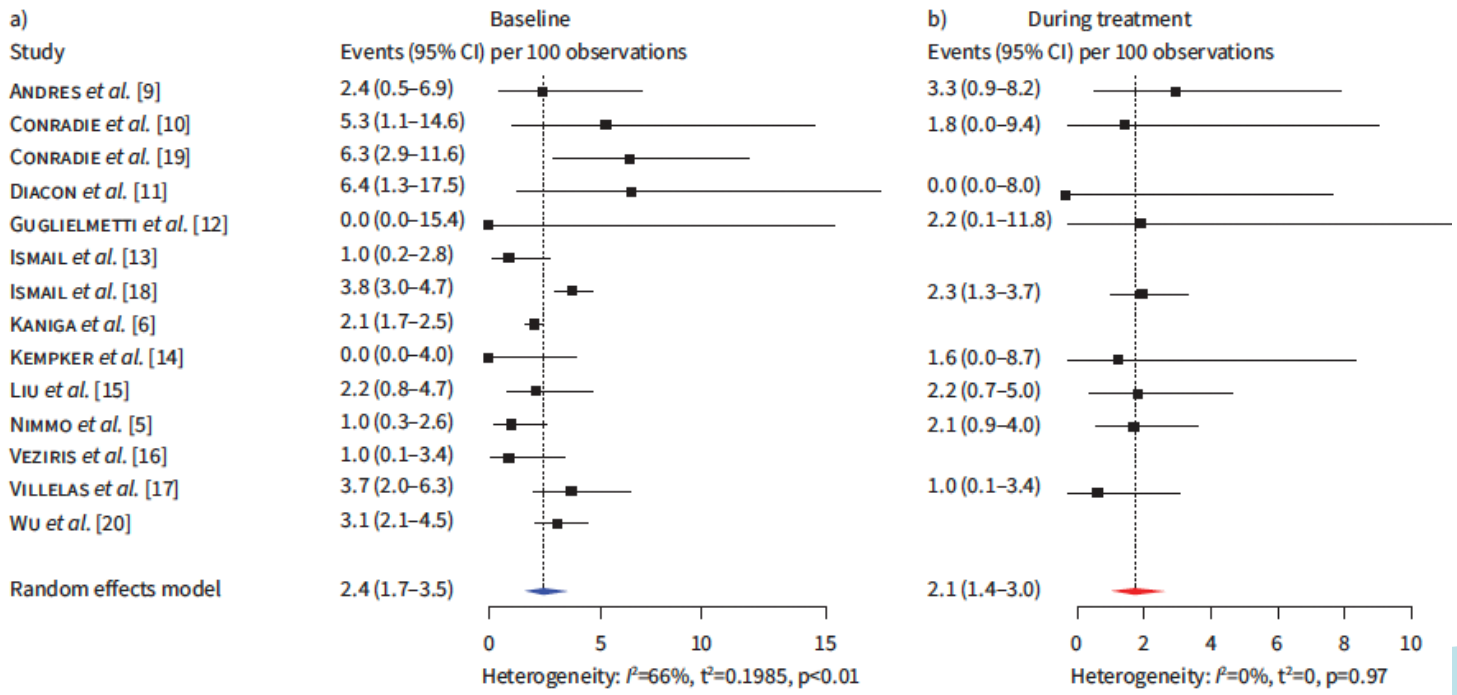
Frequency of bedaquiline resistance

- **Bedaquiline resistance**
- ~2% of MDR-TB is BDQ resistant (= MDR-TB as a proportion of all TB)
- ~2% acquire bedaquiline resistance during treatment (<<1% acquire rifampicin resistance)



Perumal ERJ 2023

Mechanism of bedaquiline resistance

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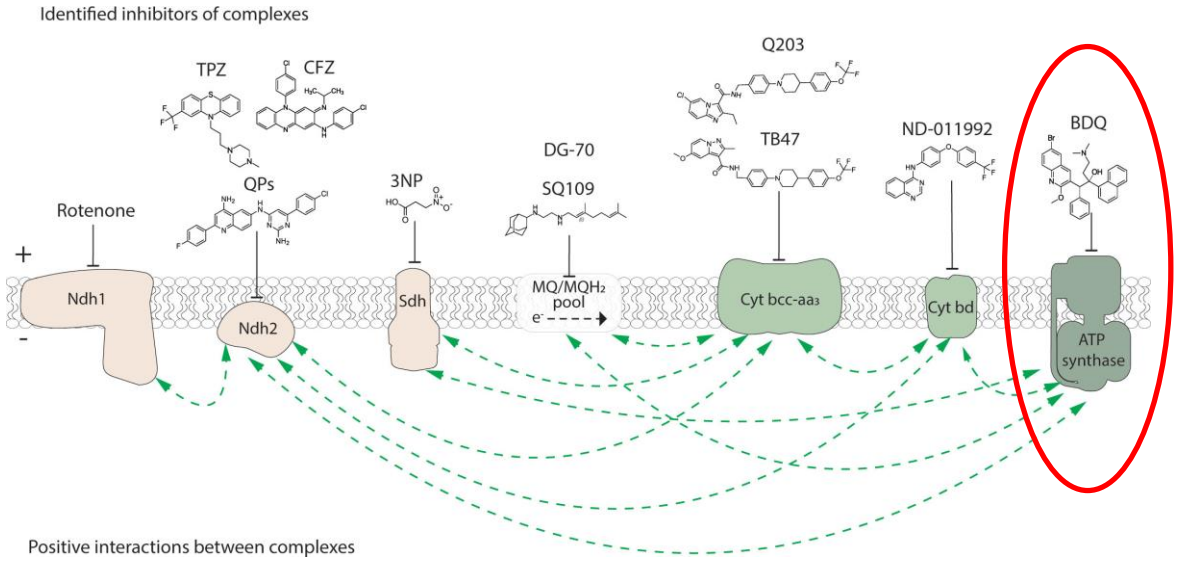
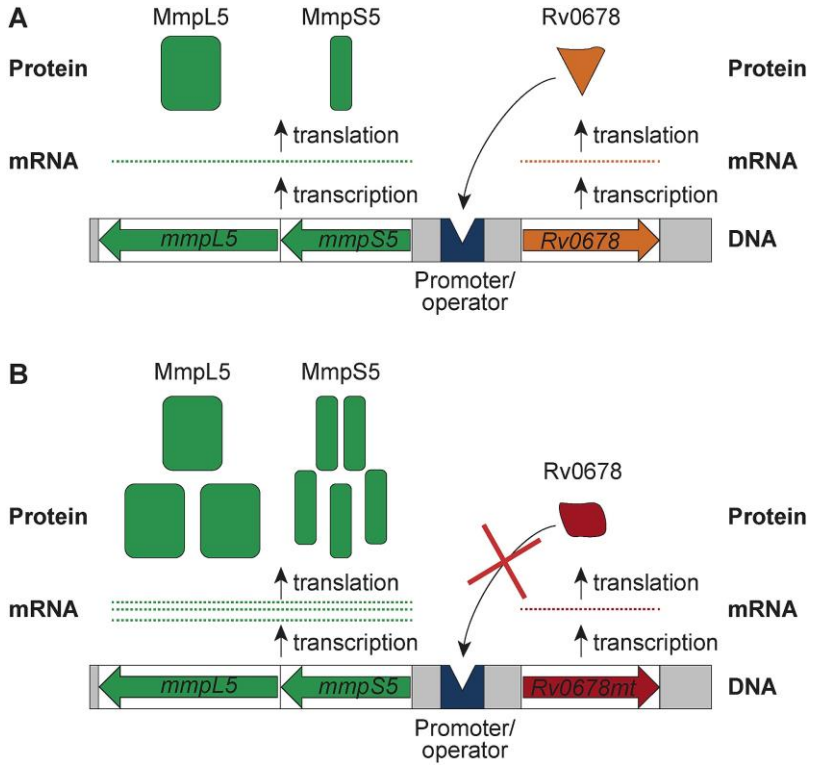
Target-based resistance – ATP synthase



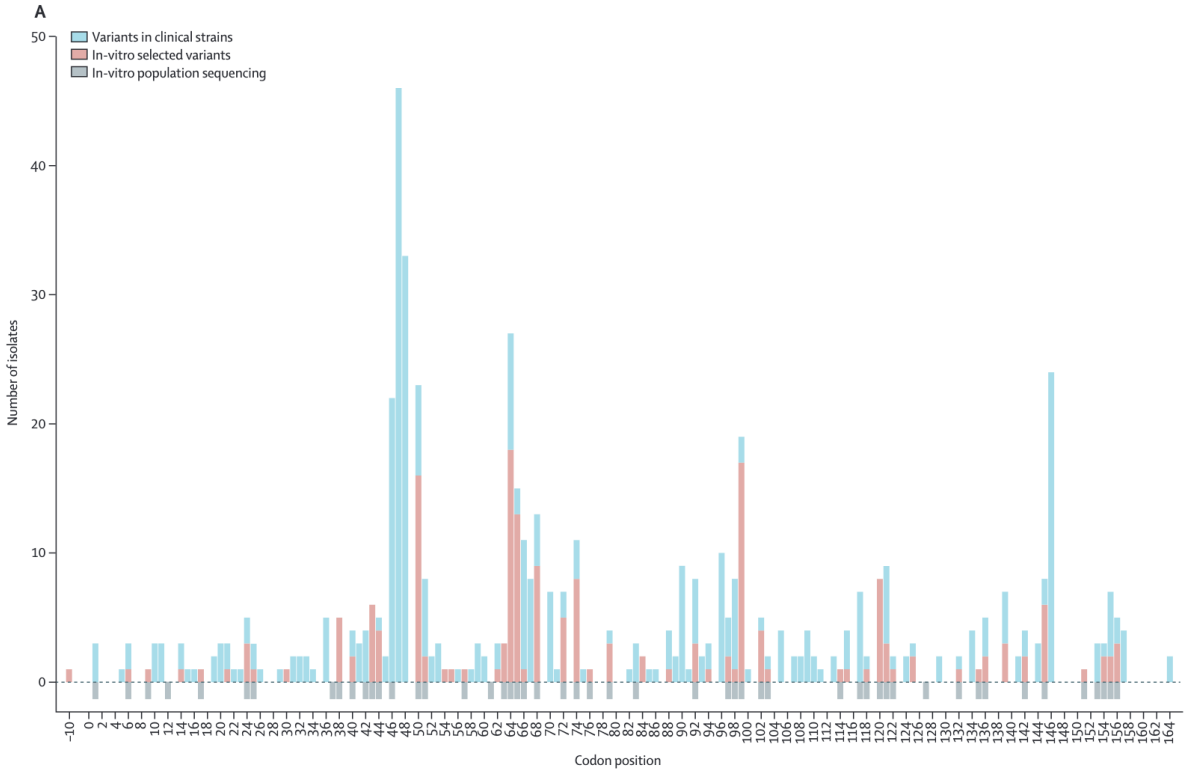
McNeill Front Cell Infect Microbiol 2022

Off-target resistance – efflux pump

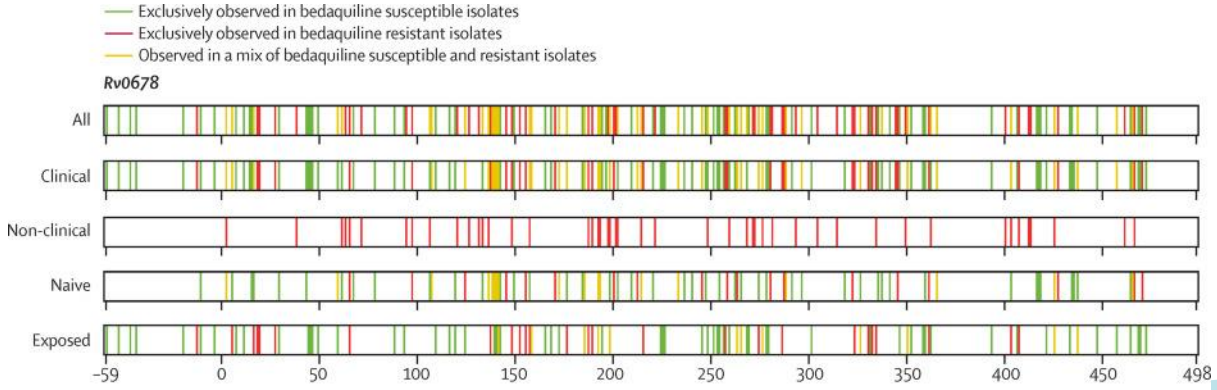


Andries PLoS One 2014

- Most clinically reported resistance mutations in *mmpR5 (Rv0678)*
- Negative repressor of efflux pump
- **Loss of function → pump overexpression → multidrug efflux → resistance**

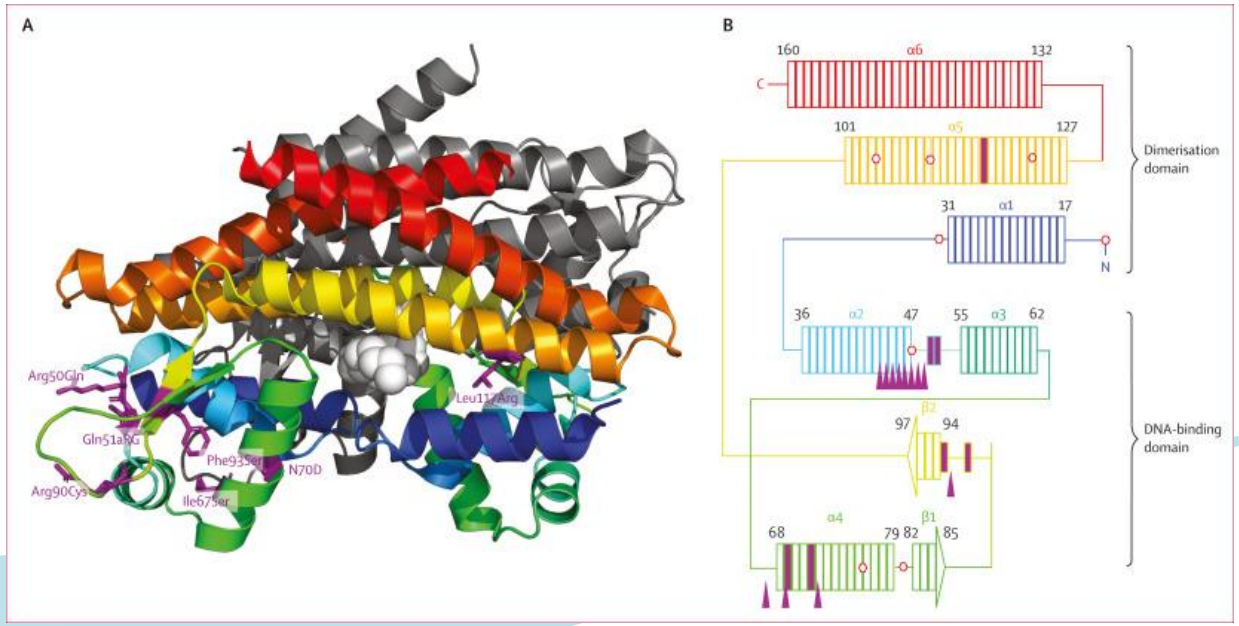


Sonnenkalb Lancet Microbe 2023



Ismail Lancet Microbe 2021

- **Mutations throughout *mmpR5***
- **Some resistance-associated and some not**
- **Most common locations at key locations in DNA binding domain**



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Performance of genetic bedaquiline resistance test

	Intermediate or resistant	Resistant only
Sensitivity		
mmpR5, *atpE*, *atpB*, or *pepQ*	310/591 (52·5%)	190/276 (68·8%)
mmpR5	288/591 (48·7%)	183/276 (66·3%)
Positive predictive value		

	mmpR5				*mmpR5*, *atpB*, *atpE*, or *pepQ*			
	Intermediate or resistant		Resistant		Intermediate or resistant		Resistant	
	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
0·10	68·4%	94·5%	71·8%	96·3%	70·9%	94·9%	54·4%	96·4%
0·25	86·7%	85·1%	88·4%	89·6%	87·9%	86·0%	78·2%	90·8%
0·50	95·1%	65·5%	95·8%	74·2%	95·6%	67·3%	91·5%	75·0%

All mutations are assumed to confer resistance at a selection of population-resistance prevalences. PPV=positive predictive value. NPV=negative predictive value.

Table 2: **Modelled PPV or NPV of *mmpR5* or all candidate genes**

mmpR5	11 542/11 844 (97·5%)	11 753/11 844 (99·2%)

Data are n/N (%).

Table 1: **Sensitivity, positive predictive value, specificity, and negative predictive value of different genomic approaches for determination of bedaquiline intermediate or resistant, or resistant-only isolates**

- **Systematic review/meta-analysis of 18 studies**
- **Sub-optimal sensitivity for bedaquiline resistance assuming any mutation in candidate genes confers resistance (i.e. maximal sensitivity with current knowledge)**
- **Good negative predictive value with low population prevalence**
- **Caveat**
  - much of this relies on isolates from before treatment era
- **Performance in current clinic cohorts still to be determined**
- **Need to explore effects of other genes and genetic background**

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- **How can we systematically evaluate new potential resistance causing mutations?**
- **Challenges**
  - Some do not spontaneously occur in vitro
  - Takes time to generate clinical data, especially when many potential mutations
  - Impact of genetic background (e.g. different lineages)
  - Similar (bigger?) problem for delamanid/pretomanid

CRISPR interference with plasmid complementation

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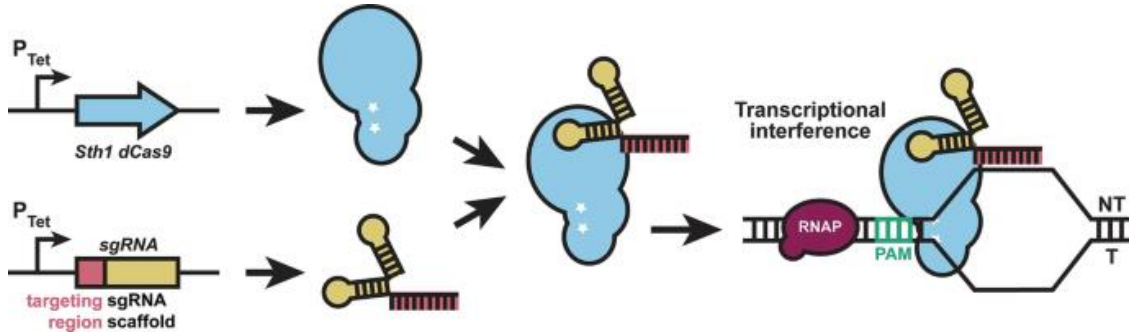
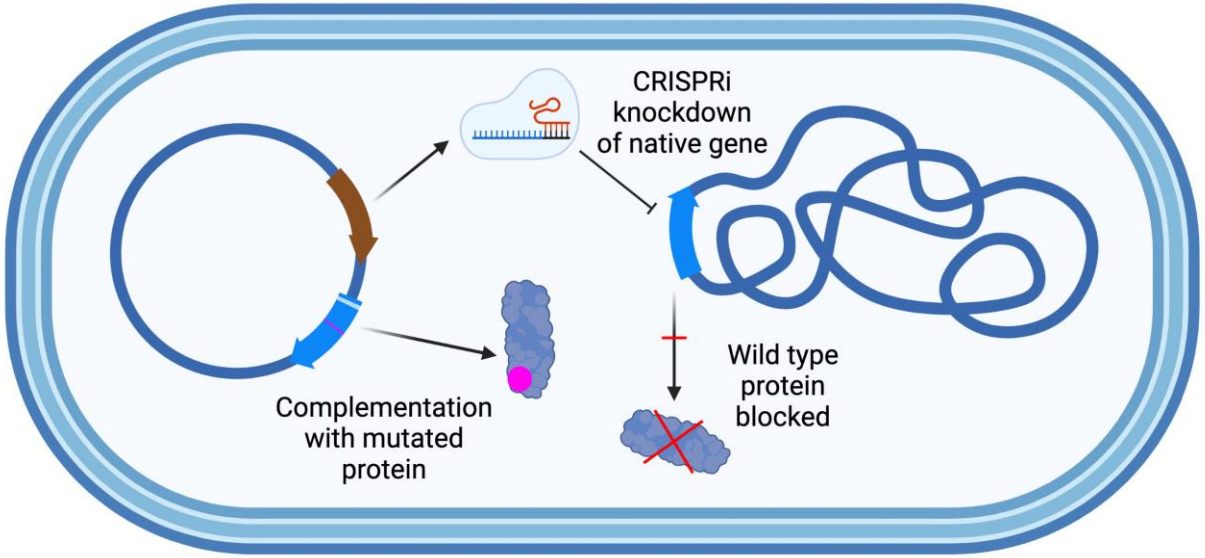
CRISPRi
- CRISPR RNA targets PAM sites (7 nt sequence), guided by adjacent DNA sequence (~20 nt)
- dCas9 binds DNA and causes transcriptional interference



Wong Methods Mol Bio 2021



Plasmid contains CRISPR machinery plus synthetic complementary gene encoding mutation of interest