Molecular underpinnings of resistance to the new drugs

THE FRANCIS CRICK INSTITUTE

Chair:

Michelle Larsen (Albert Einstein College of Medicine)

Panel:

Camus Nimmo (Francis Crick Institute, UK)

James Millard (Imperial College Healthcare NHS Trust, UK)

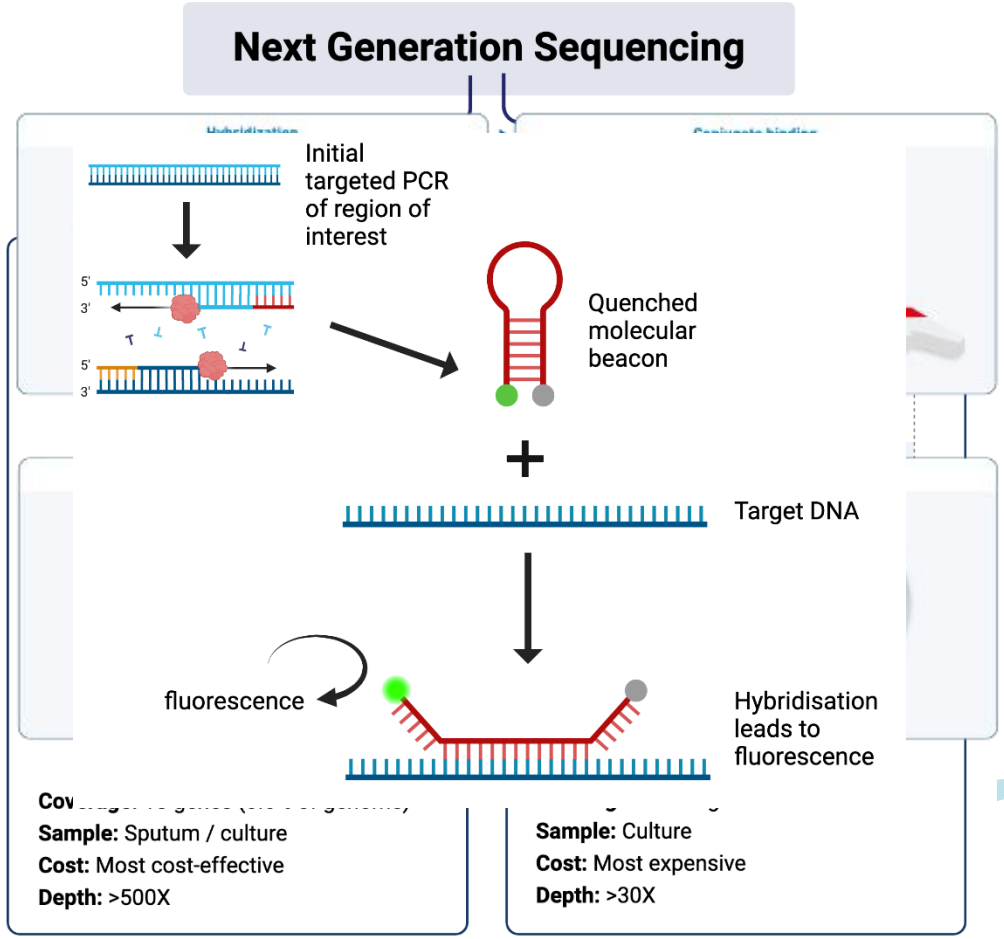
Uma Devi Ramalingam (Head, Department of Bacteriology, National Institute for Research in Tuberculosis, India)

Timothy Walker (University of Oxford, UK)

Molecular diagnostics

- All use *M. tuberculosis* genome sequence to identify drug resistance mutations
- These are associated with phenotypic resistance

- Rapid molecular tests
  - Xpert MTB/RIF
  - Line probe assays
- Targeted (next generation) sequencing
- Whole genome sequencing

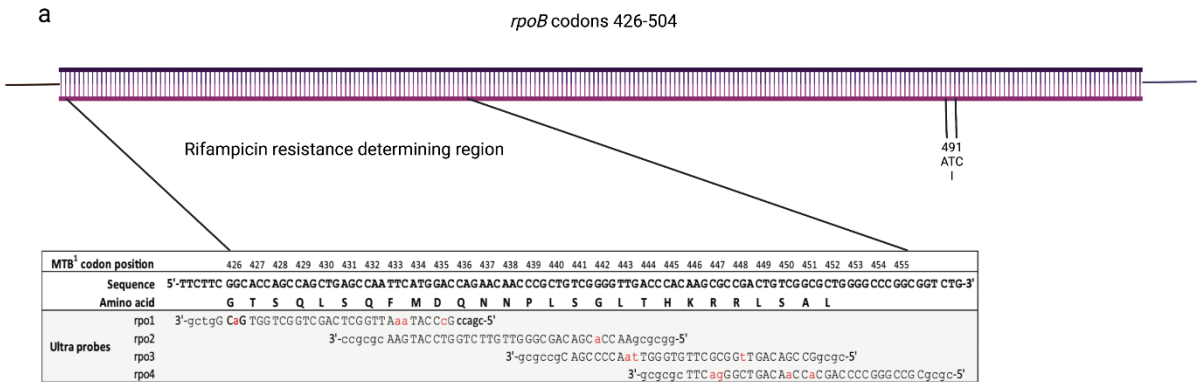


Resistance mechanisms to key drugs pre-2010

THE FRANCIS CRICK INSTITUTE

RIFAMPICIN

- Blocks RNA polymerase – *rpoB* gene
- Essential



Most mutations in 81 base pair region

Image: Nimmo FCIM 2022

FLUOROQUINOLONES

- Block DNA gyrase – *gyrA* and *gyrB* genes
- Essential

gyrA - 18 base pairs

gyrB - 123 base pairs

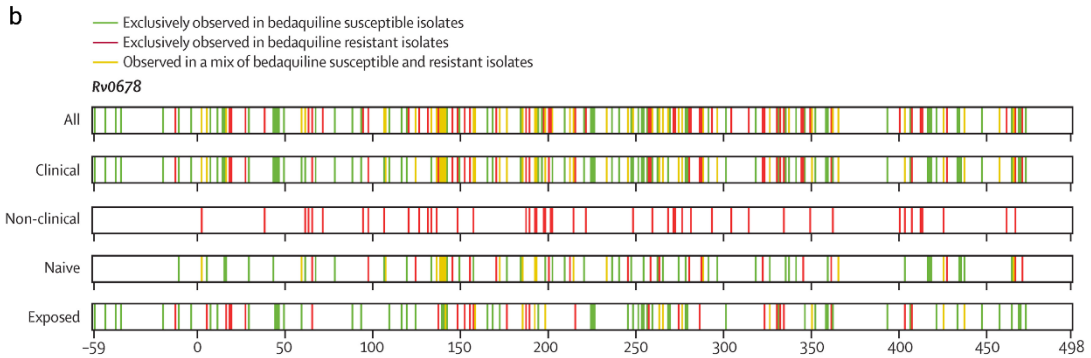
*Xpert MTB/XDR covers 52 base pairs

Resistance mechanisms to newer drugs

BEDAQUILINE

Effluxed by MmpL5 pump, controlled by *mmpR5* regulator

Non-essential, no/minimal fitness cost



Red lines indicate resistance mutations

Mutations throughout 498 base pair gene

Image: Ismail Lancet Microbe 2021

NITRIMADAZOLES (DELAMANID/PRETOMANID)

- **Generates reactive oxygen intermediates and acts against mycolic acid synthesis**
- **Activated by Ddn nitroreductase**
- **Involves Fgd1 co-enzyme**
- **Requires F420 – synthesised by FbiA/B/C/D**
- ***ddn*, *fgd1*, *fbiA/B/C/D* all non-essential**

→ mutations over 7000 base pairs