Tuberculosis research at Warwick

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WARWICK

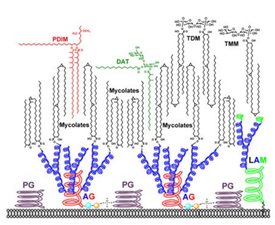
INTEGRATE
ANTIMICROBIAL RESISTANCE

Tuberculosis

Mycobacterium tuberculosis is the etiologic agent of tuberculosis (TB), a disease that is one of the leading causes of death from a single infectious agent worldwide. The World Health Organization currently estimates that 1.8 billion people, approximately one-third of the world's population, are infected with *M. tuberculosis*, and that there are 10.4 million new active cases annually and 2 million deaths each year as a result of infection. There is an urgent need for the identification of novel targets and pathways within *M. tuberculosis* to develop new chemotherapeutic agents and diagnostic tools.

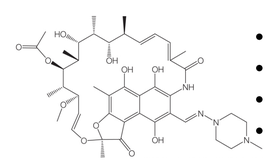
Countries with reported XDR-TB cases

- Drugs taken 6-9 months
- Multi-drug and Extensively-drug resistant strains complicate therapy
- No therapeutic regimens

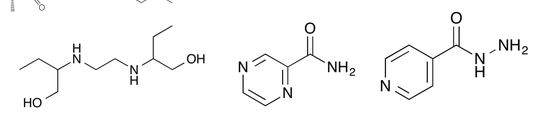


The cell wall of *M. tuberculosis* is unique in its complexity and rich in diverse carbohydrates and lipids that protect the bacterium from environmental stresses and chemotherapeutic agents.

- Plasma envelope, mycolic acids, arabinogalactan, peptidoglycan
- Provides 'waxy' cell coat – difficult for drugs to penetrate
- Unique cell wall structure – biosynthetic steps involved in assembly attractive drug targets



- Front-line drugs for TB
- No new drugs for >40 years
- Need new drugs
- New pathways to target



Can carbohydrate processing pathways be utilised for new anti-tubercular agents/diagnostics?

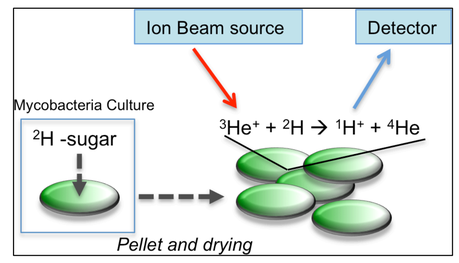
Warwick World TB Day

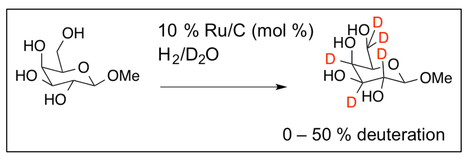
Outreach activity by the Fullam lab at Cannon Park Shopping Centre on World TB Day – 24th March

Label free detection for carbohydrate uptake

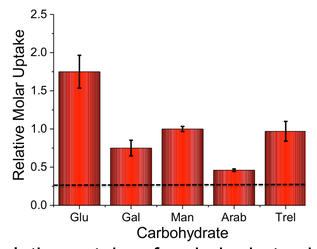
Straight-forward synthesis of deuterated (^{2}H) carbohydrates
Detection of ^{2}H-carbohydrates by ^{3}He Nuclear Reaction Analysis

Chem. Commun. **2015 –**
DOI: 10.1039/C4CC09588J

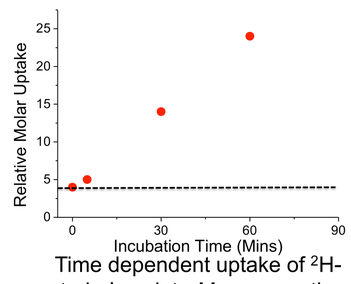




Synthetic scheme for deuterium labelling of carbohydrates

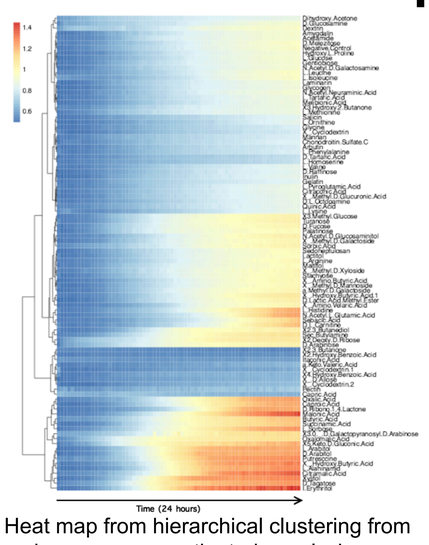


Relative uptake of carbohydrates into *M. smegmatis* by ion beam analysis.

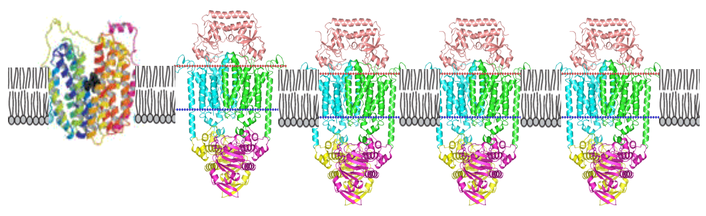


Time dependent uptake of ^{2}H-trehalose into *M. smegmatis*.

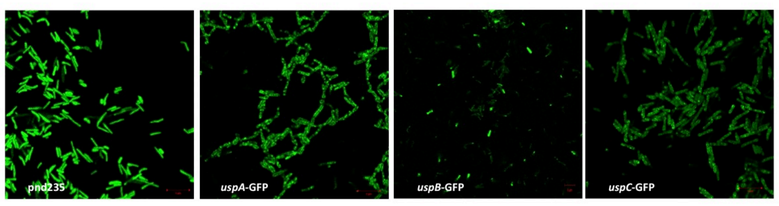
Nutrient requirements of mycobacteria



Heat map from hierarchical clustering from carbon source growth study analysis

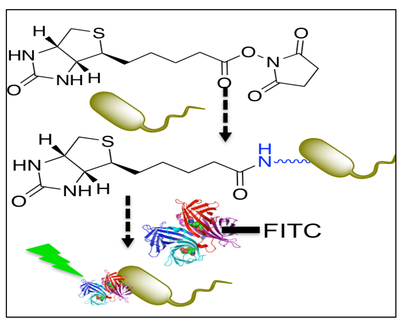


Five putative carbohydrate transporters in *Mycobacterium tuberculosis*

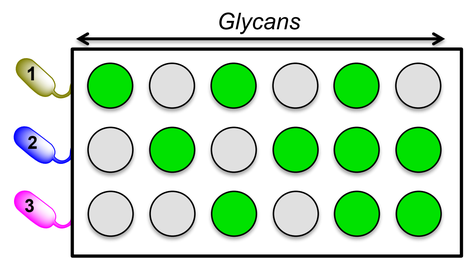


Example of localisation studies of mycobacterial transport systems

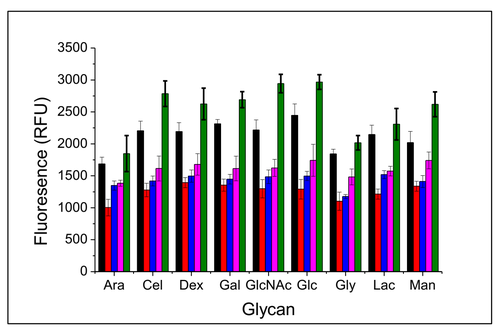
Barcode for bugs – glycans to detect specific mycobacteria



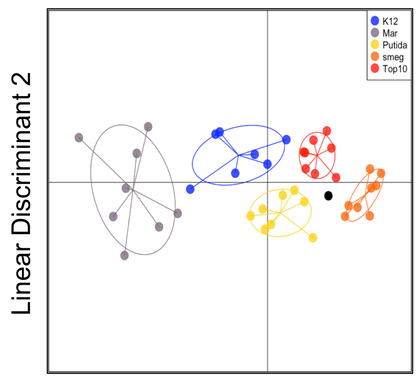
1. Fluorescently label bacteria



2. Add bugs to prepared glycan plate, wash



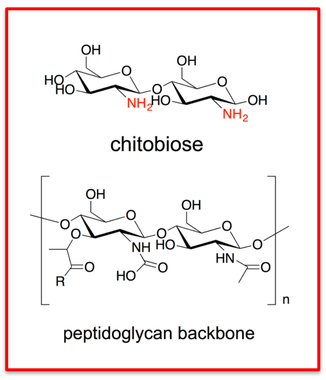
3. Read fluorescence read out

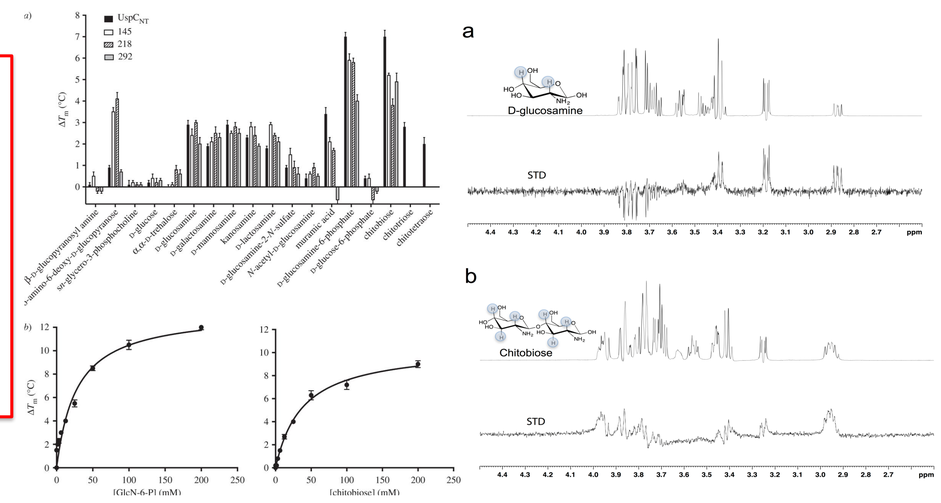


Molecular BioSystems. **2016 –**
DOI: 10.1039/C5MB00720H

Peptidoglycan recycling in mycobacteria

Structure of the UpsC carbohydrate binding domain from *Mycobacterium tuberculosis* at 1.5 Å



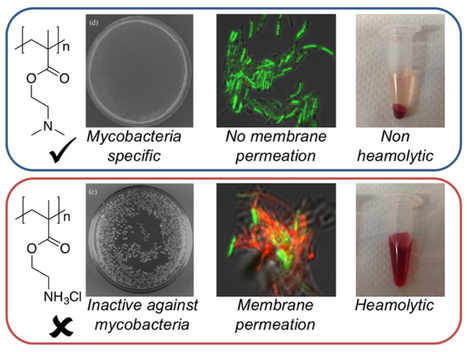


Thermal Shift assay to probe for ligands of UspC

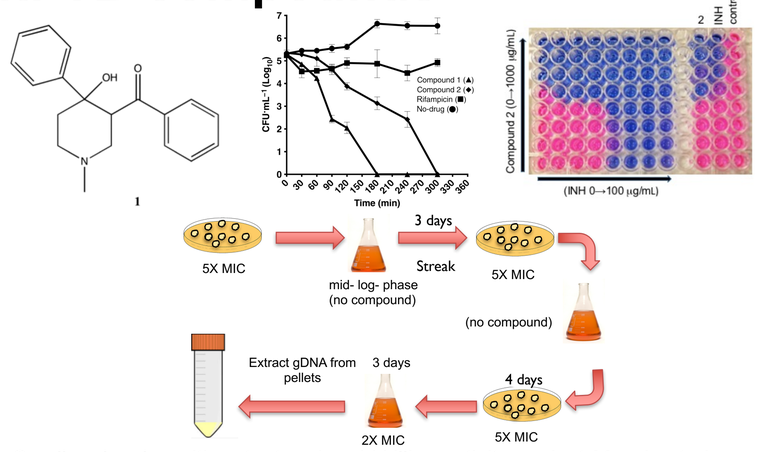
STD-NMR of UspC with two ligands

Open Biology. **2016 –**
DOI: 10.1098/rsob.160105

New anti-TB compounds



Development and synthesis of cationic polymers with selectivity against mycobacteria



Small molecules with potent and rapid killing activity against *Mycobacteria.* Target identified by whole genome sequencing of resistant mutants

Biomacromolecules. **2017 –**
DOI: 10.1021/acs.biomac.7b00210

British Journal of Pharmacology. **2017 –**
DOI: 10.1111/bph.13744

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