Trinity College Dublin
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UNIVERSITY OF PLYMOUTH

ANTIBIOTIC DISCOVERY ABX ACCELERATOR NETWORK

Martha Nash

Old drugs learn new tricks: drug repurposing as a strategy to uncover effective antibacterials

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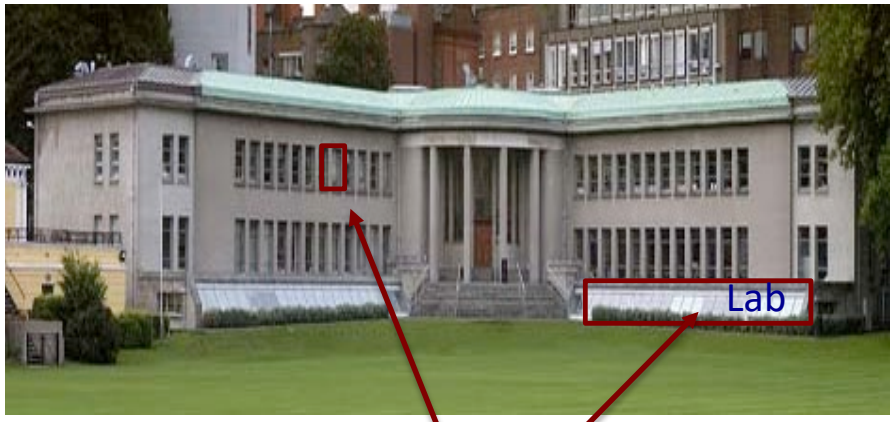
My lab and research area

Department of Microbiology

Moyne Institute of Preventive Medicine

Main areas of Research:

- *In vitro* testing of compounds
- Reversal of antibiotic resistance (EIs)
- Study of antibiotic resistance mechanisms
  - Efflux mediated (and others)
- *Ex-vivo* studies
- Modulation of human macrophages
- Bacterial collection: Clinical isolates (*Salmonella*, *Acinetobacter*, *Klebsiella, etc.*)



Martins Research Group

Antimicrobial Resistance & Host Modulation

Compounds studied

Natural compounds

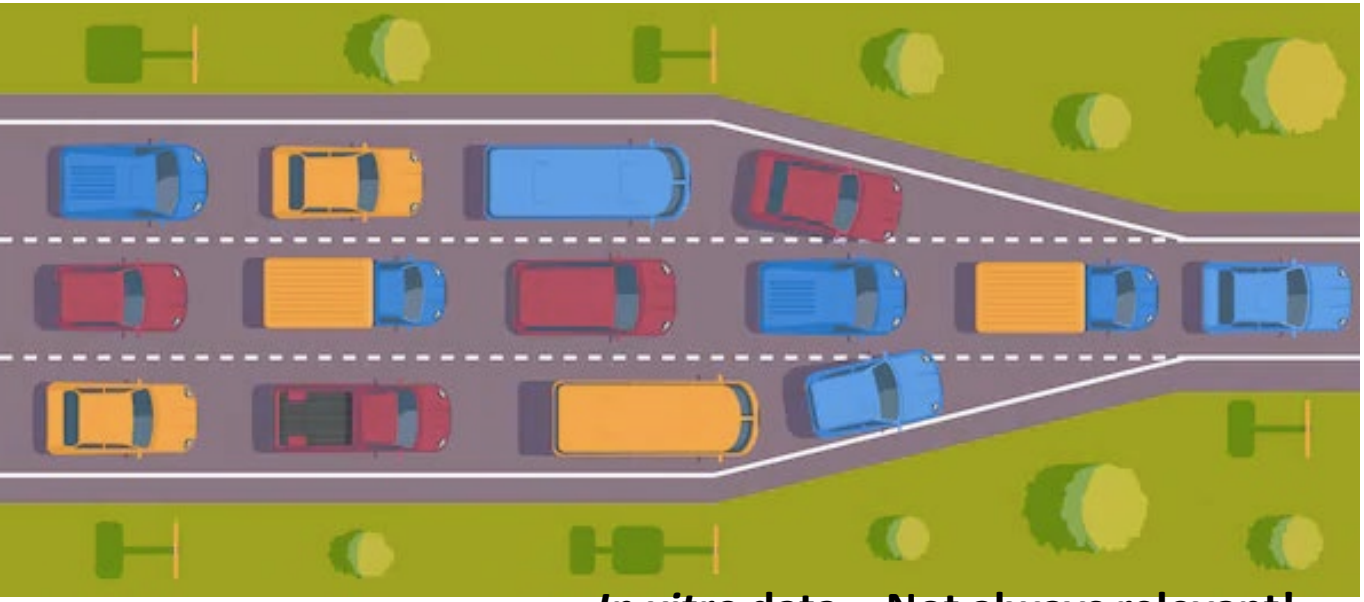
- Antimicrobial peptides (mining using AI)
- Extracted from plants/food sources

Drug repurposing

- Phenothiazines
- Anticancer agents
- Calcium channel blockers

Rational design of known drugs

Bottlenecks…



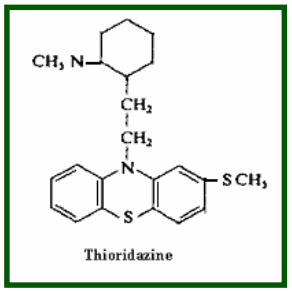
- Solubility of compounds
- Difficult to identify a specific target or mode of action
- Toxicity in human cells
  - *In vitro* data not translated into an *ex-vivo* infection

***In vitro* data….Not always relevant!**

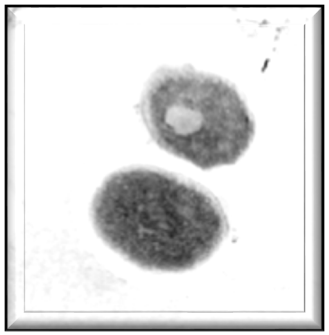
An example…**Thioridazine (TZ)**

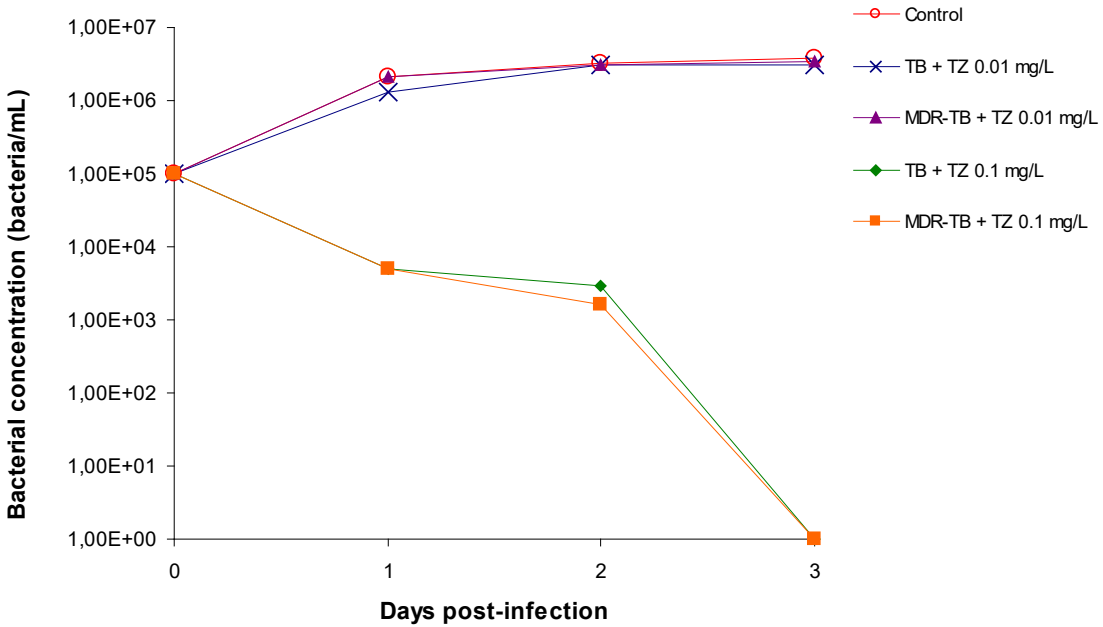
MIC of TZ against several bacterial species

		TZ MIC (mg/L)	TZ MBC (mg/L)
Gram Negative	*E. coli* AG100	200	200
	S. Typhimurium SL1344	>200	>200
	Acinetobacter baumannii 19606	25	25
	Klebsiella pneumoniae ATCC 35218	100	200
	Pseudomonas aeruginosa PAO1	200	>200
	Enterobacter aerogenes ATCC 13048	>200	>200
Gram Positive	MRSA *Staphylococcus aureus* ATCC 43300	50	50
	Mycobacterium tuberculosis H37RV	20	40

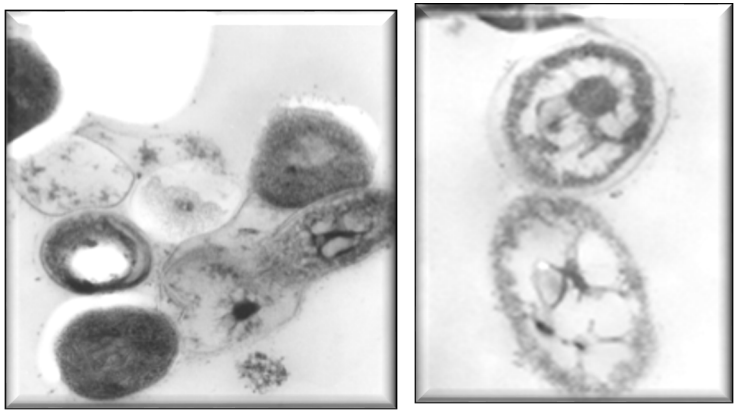


MDR-TB (Control)





Cells treated with 20 mg/L of TZ (24h)



Expertise I can provide

In vitro testing

- Characterization of antibiotic resistance profile (AST)
- Determination of MIC/MBC
- Efflux activity
- Bacterial clinical isolates

Ex-vivo studies

- Toxicity studies
- Infection assays (Macrophages; Epithelial cells)
- Immune response (cytokines; ROS; *etc*)
- Immunomodulation of infected Macrophages

Expertise I am looking for

- New/Novel compounds
- Modification of know compounds (rational design)
- Sequencing capacity of bacterial isolates
- Proteomics
- Bacterial knockouts