Non-Traditional Biomaterial Solutions to Infection. Detect, Neutralize and Kill

The Gibson Group: Chemistry and Medical School

WARWICK
INTEGRATE
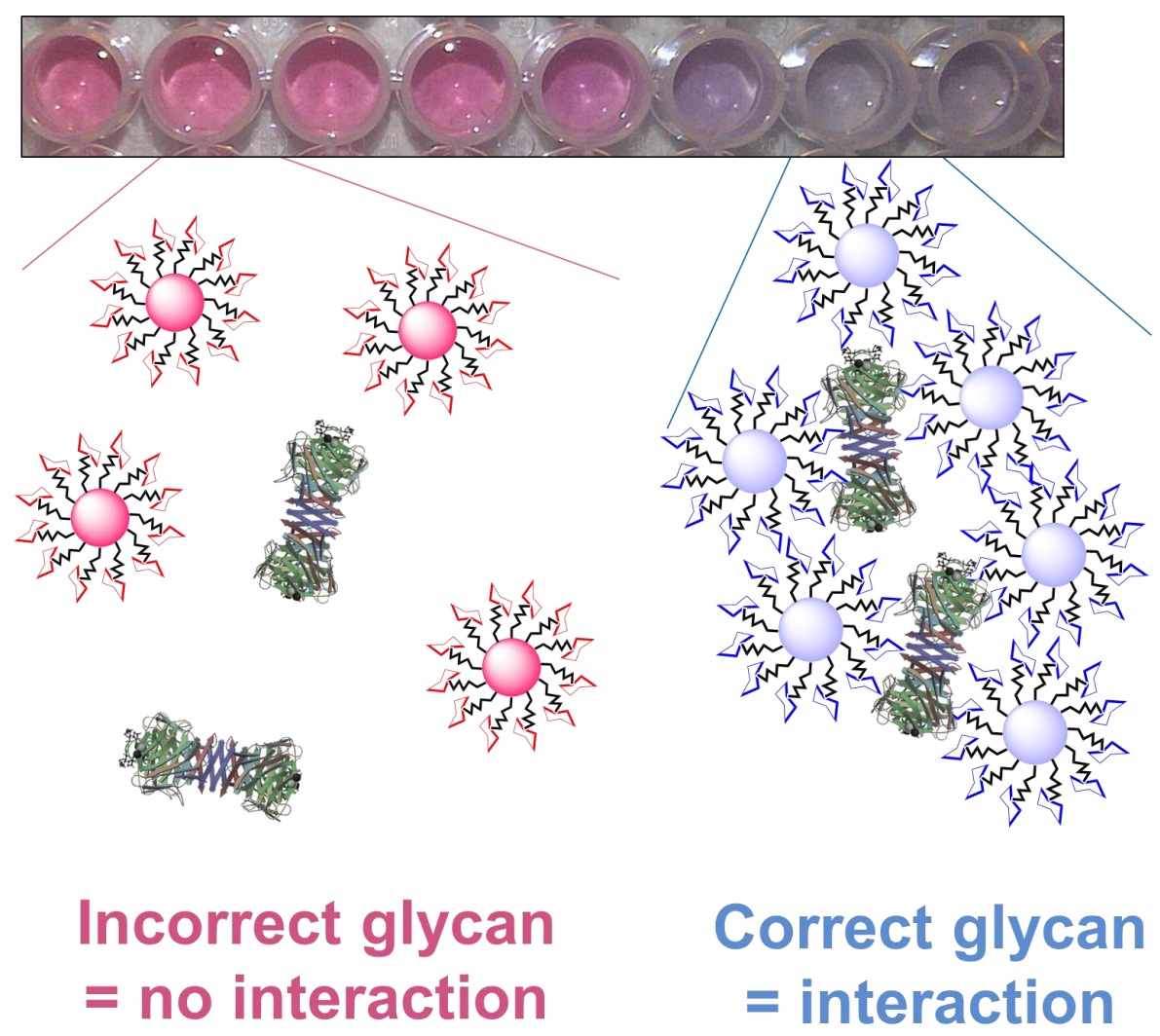ANTIMICROBIAL RESISTANCE
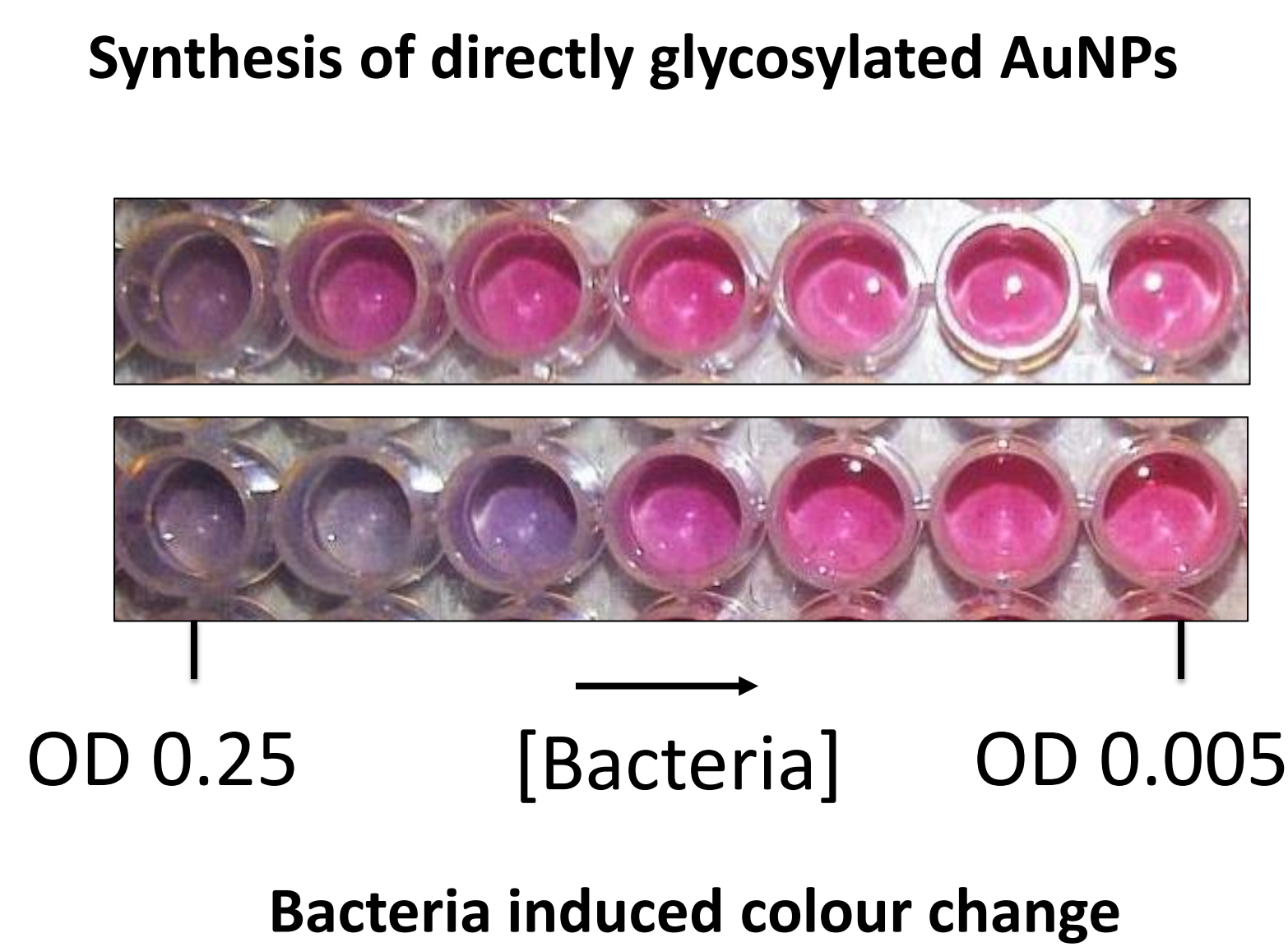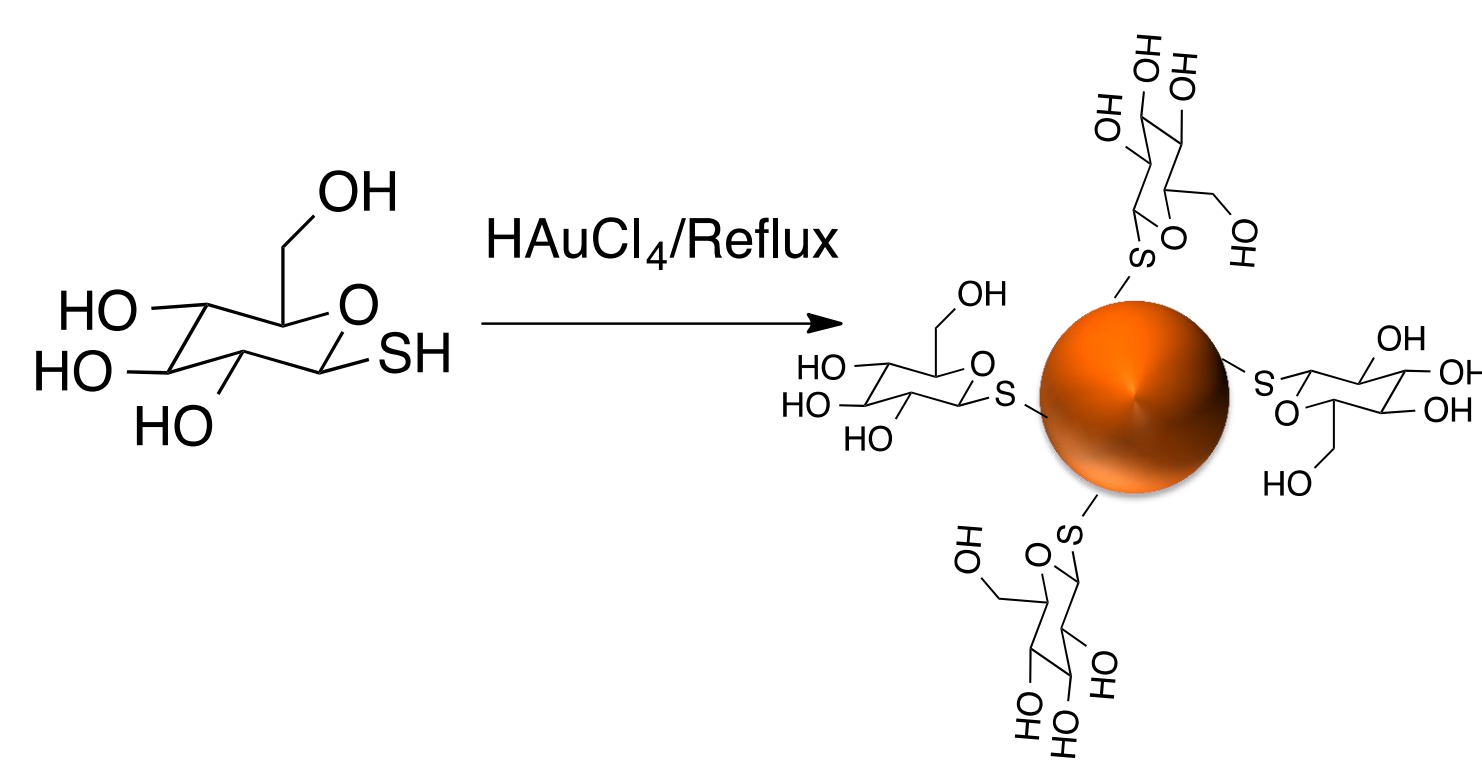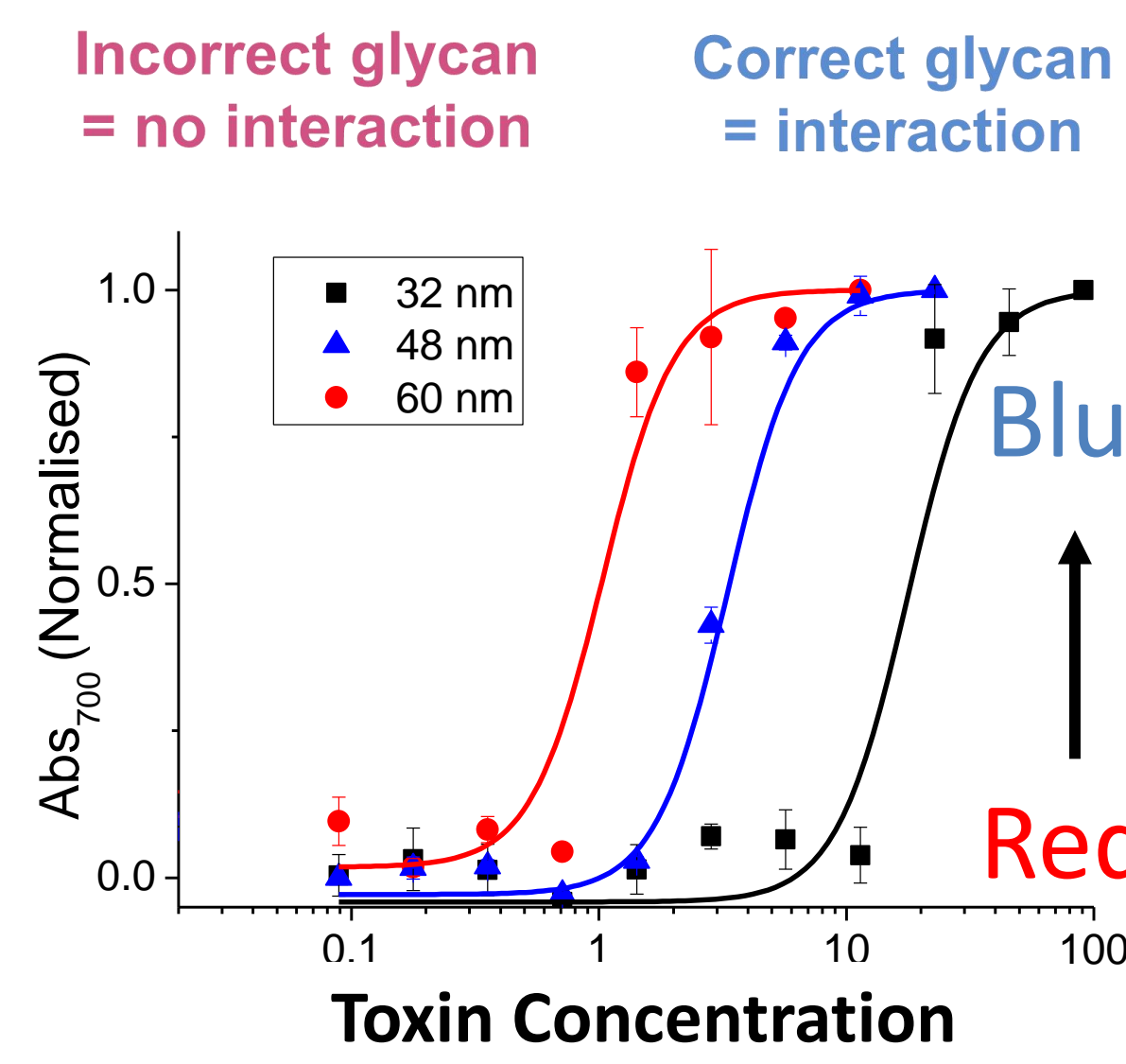
M.I.Gibson@warwick.ac.uk   @LabGibson   www2.warwick.ac.uk/go/gibsongroup

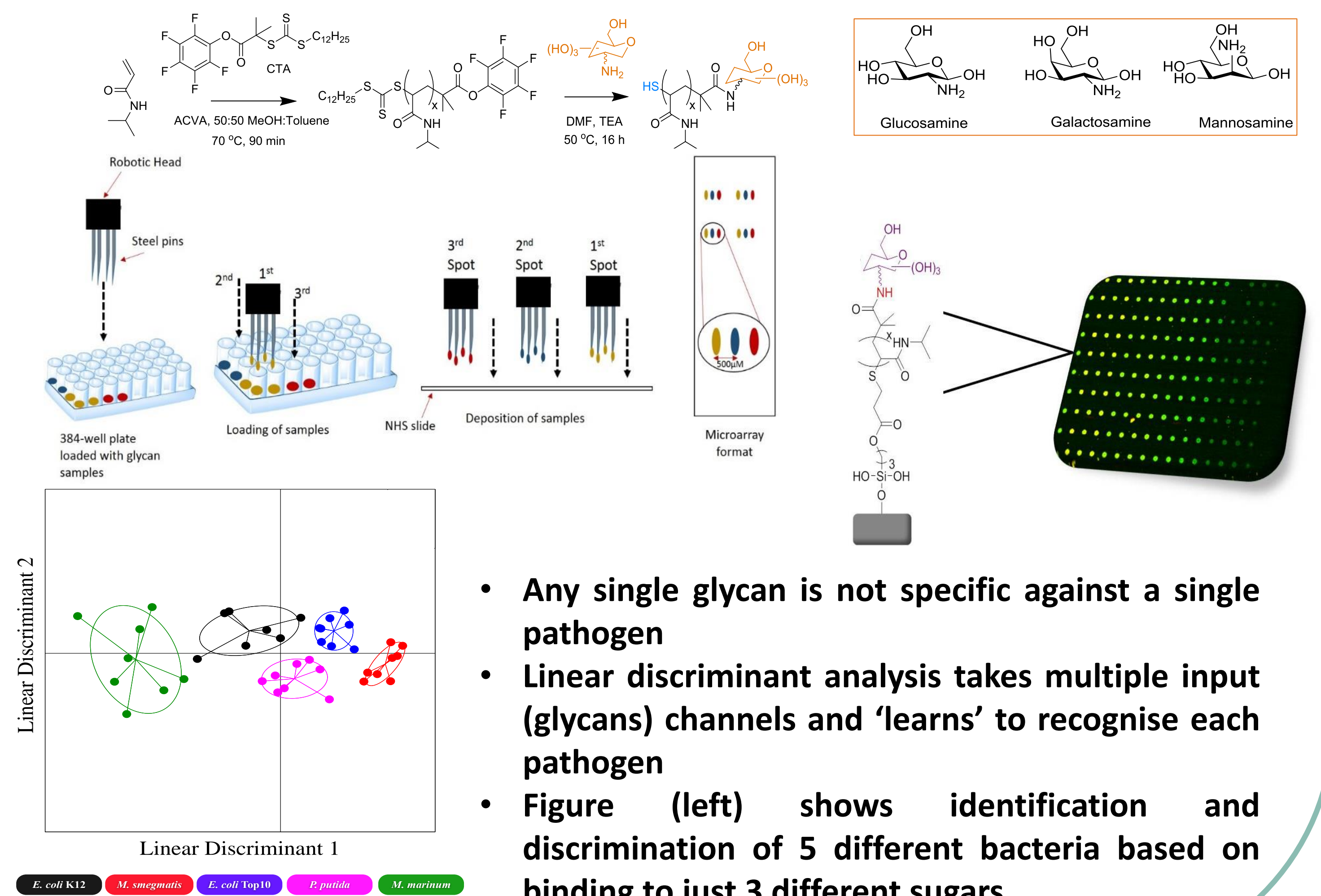# 1. Pathogen Detection

Gold nanoparticles as colorimetric sensors

- Goldnanoparticles (AuNPs) have interesting optical properties. Red in solution → blue upon aggregation.
- Glycosylated AuNPs (glycoAuNPs) could be used to detect bacteria and lectins.

Incorrect glycan = no interaction

Correct glycan = interaction

Abs$_{700}$ (Normalised) vs Toxin Concentration
- ■ 32 nm
- ▲ 48 nm
- ● 60 nm

Blue / Red

HAuCl$_4$/Reflux

Synthesis of directly glycosylated AuNPs

Toxin mediated aggregation

500 nm / 500 nm

OD 0.25   [Bacteria]   OD 0.005

Bacteria induced colour change

J. Mater. Chem. B., **2014**, 2, 1490; *ACS Macro Lett.,* **2014**, 3, 1004;
J. Mater. Chem. B., **2016**, 4, 3046; *Analyst,* **2017**, 141, 4305

High density glycan arrays

- Glycan terminated polymers immobilised onto surface functionalised glass
- *Via* Direct microcontact printing
- Generation of high-density arrays of surface immobilised glycans, with polymer tethers for reduced non-specific binding
- Multiplexing of data enables 'barcoding' of pathogen binding patterns to enable discrimination
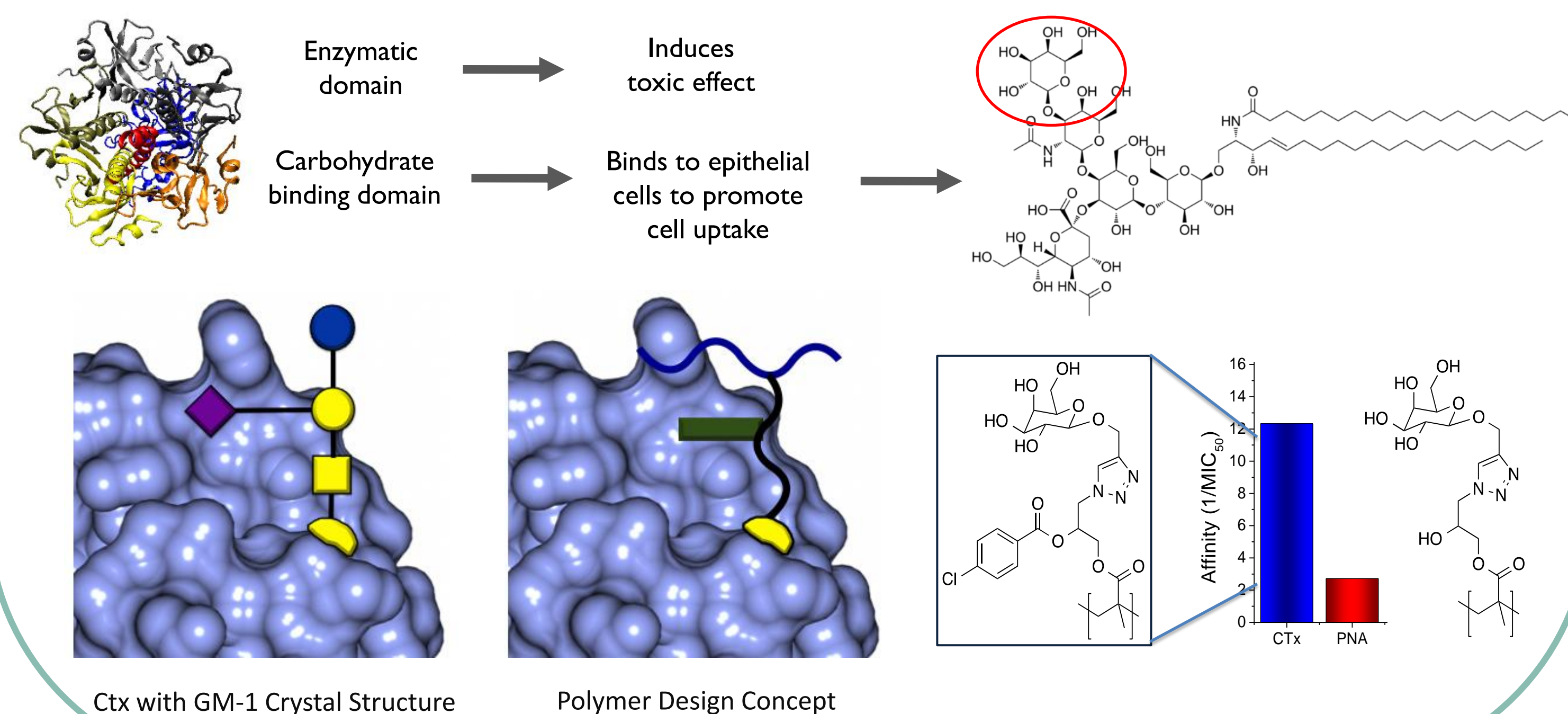

Glucosamine   Galactosamine   Mannosamine

384-well plate loaded with glycan samples | Loading of samples | NHS slide | Deposition of samples | Microarray format

Linear Discriminant 2 vs Linear Discriminant 1

- E. coli K12
- M. smegmatis
- E. coli Top10
- P. putida
- M. marinum

- Any single glycan is not specific against a single pathogen
- Linear discriminant analysis takes multiple input (glycans) channels and 'learns' to recognise each pathogen
- Figure (left) shows identification and discrimination of 5 different bacteria based on binding to just 3 different sugars

Biomater. Sci., **2015**, 3 (1), 175–181; *RSC Adv.,* **2015**, 5, 53911-53914;
Mol. BioSyst., **2016**, 12, 341-344; *Biomacromolecules,* **2016**, 17(8), 2626-2633

2. Neutralize

A — Bacterial adhesion → Infection
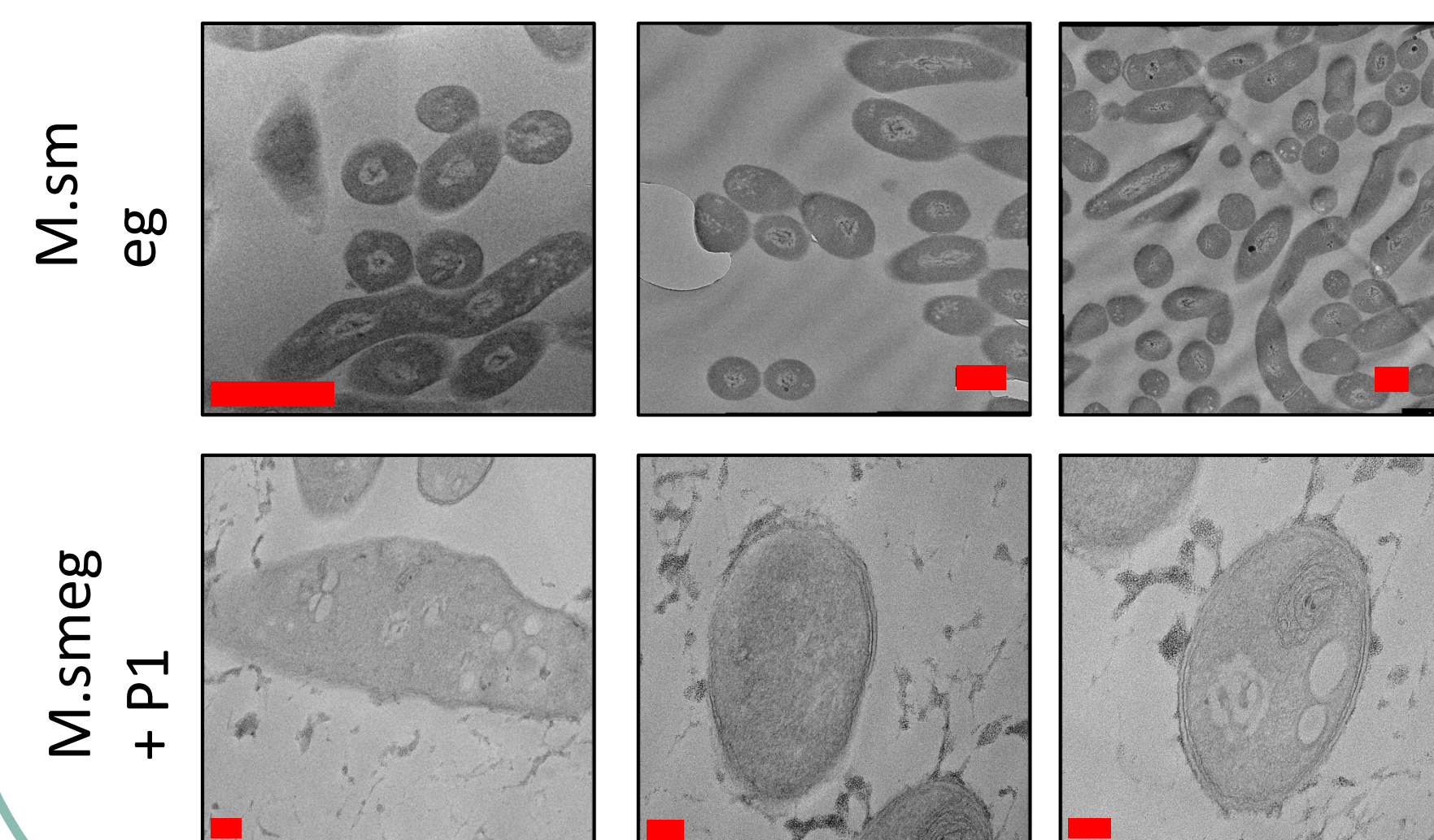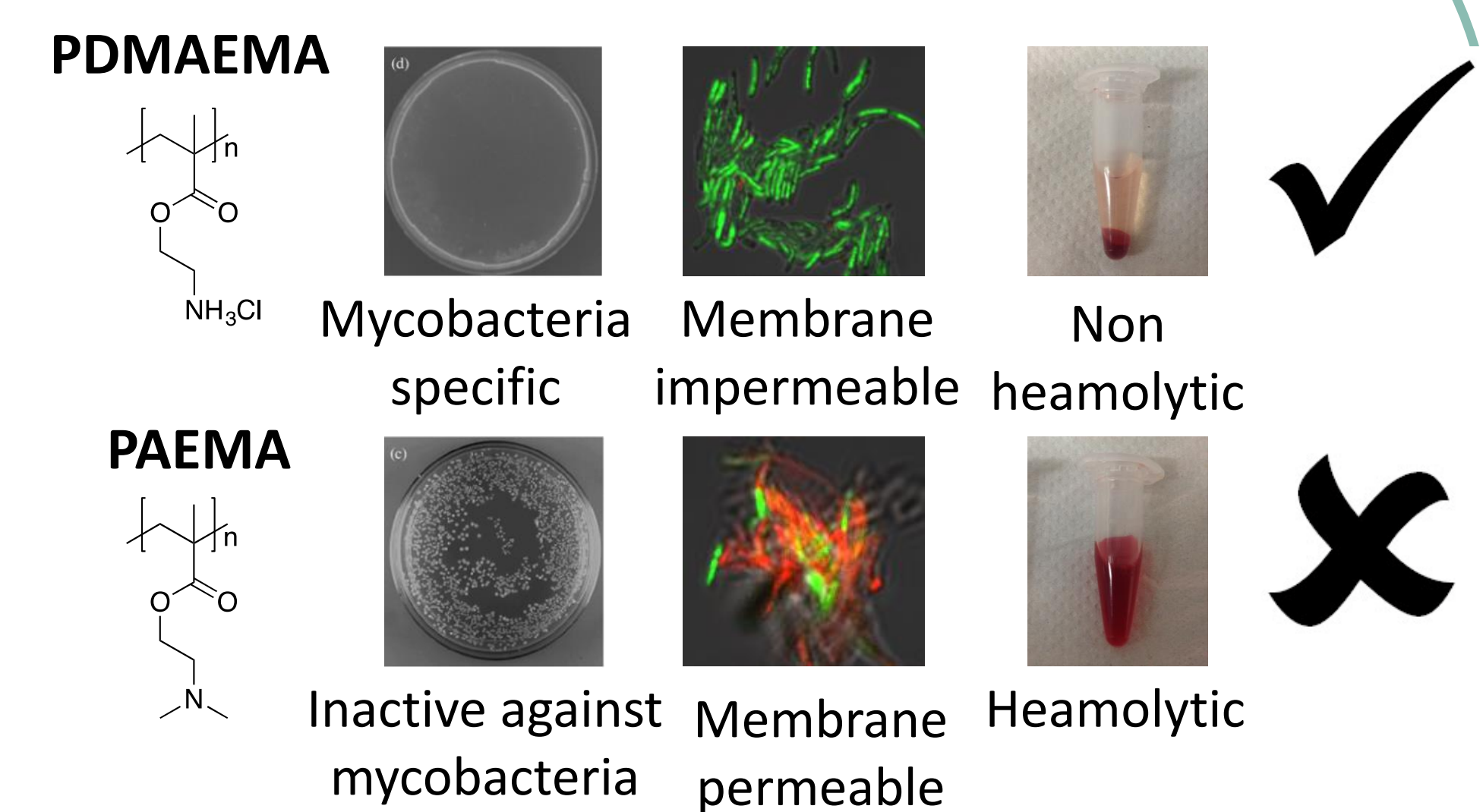B — Prevention of adhesion → Infection (blocked)
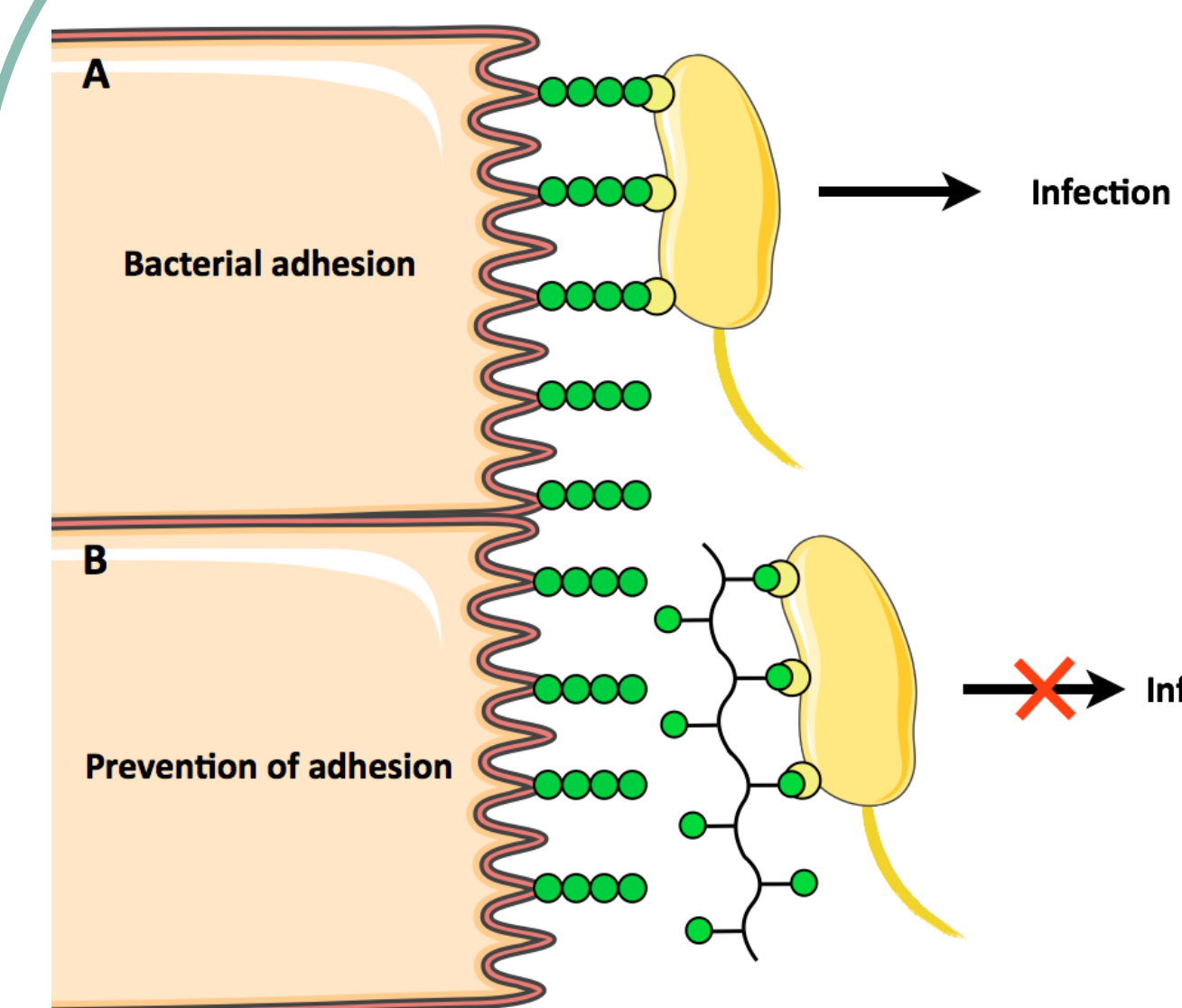
- Anti-adhesion therapy prevents binding of bacteria and toxins to host cells
- Does not target bacteria directly, so less evolutionary stress
- Reduced the need for antibiotics
- Glycopolymers have high affinity due to presentation of 10's of copies of each sugar
- Here we engineer high-affinity binders without total synthesis
- Demosntrated prevent binding of cholera-toxin to GM-1, stopping infection

Enzymatic domain → Induces toxic effect

Carbohydrate binding domain → Binds to epithelial cells to promote cell uptake

Affinity (1/MIC$_{50}$) — CTx / PNA

Ctx with GM-1 Crystal Structure   Polymer Design Concept

Angew. Chem. Int, Ed., **2012**, 51, 7812;
Chem. Sci., **2014**, 5, 1611

3. Kill

- Using cationic polymers as non-traditional antibiotics
- Not previously evaluated against mycobacteria, which includes Tubuculosis
- We found that mycobacteria were killed selectively over gram negative bacteria
- Nature of cationic polymer was crucial for selectivity

PDMAEMA

Mycobacteria specific | Membrane impermeable | Non heamolytic ✓

PAEMA

Inactive against mycobacteria | Membrane permeable | Heamolytic ✗

M.sm eg

M.smeg + P1

1 um / 100 nm

Mechanism of action
- Polymers were found not to lyse the bacterial membrane
- Electron microscopy suggested stress of the cell walls
- Confocal microscopy did not indicate membrane permaion

Biomacromolecules, **2017**, 18, 1592