CHIEF SCIENTIST OFFICE

CODE:TCS/16/24

RESEARCH PROJECT BRIEFING

Accelerating Clinical Introduction of New Antibiotics

AIMS

Strathclyde has developed a family of antibiotics that bind to the minor groove of DNA (S-MGBs); some have antibacterial activity and one (MGB-BP-3) is in clinical trial. Newly-synthesised S-MGBs were screened for antibacterial activity.

The **aims of this work** were to:

- evaluate new members of the S-MGB pipeline made during the CSO grant for antibiotic activity, hopefully to enrich the portfolio of antibacterial S-MGBs
- evaluate other ailing antibiotics for synergy with BP-3 and for synergy with other members of the S-MGB family
- conduct a rigorous experiment to evaluate whether exposure to BP-3 results in the infectious agent becoming resistant, given the observation that clinical strains often become resistant during new antibiotic therapy
- investigate the molecular action of BP-3 as an antibiotic using a next generation sequencing approach for BP-3 on its own and under conditions of synergy with an ailing antibiotic.

KEY FINDINGS

The work funded by CSO has:

- Identified a number of new SMGBs antibiotics that are effective against different bacteria.
- Proof of Concept was established that, for some existing antibiotics such as streptomycin or ceftriaxone to which clinical bacteria have become resistant, SMGBs such as BP-3 or MGB-396 (neither of which is effective on its own against certain bacteria) can be effective in combination.
- Demonstrated that extensive exposure of *S. aureus* (MRSA) to BP-3 has NOT resulted in it becoming resistant.
- Used whole genome sequencing to characterise five vancomycin resistant enterococci (VRE - a type of superbug) isolates from Scottish hospitals. This revealed changes in genes associated with antibiotic resistance.
- Demonstrated the utility of whole genome sequencing in delivering an epidemiological analysis of VRE isolates from a Scottish hospital.

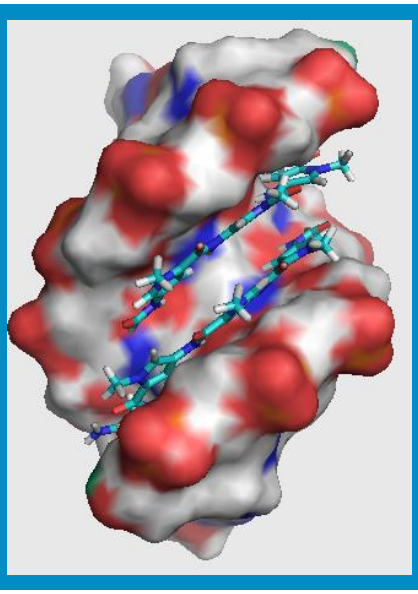
WHAT DID THE STUDY INVOLVE?

- New chemical compounds synthesised at Strathclyde were screened for antibiotic potential using EU approved standard methods.
- Toxicity of these new compounds to human cells (HEK293T) was assayed *in vitro* using a dye that shows if the cells are alive or dead.
- Superbugs were isolated from Scottish hospitals and used for antibiotic screening. Some of these were subjected to whole genome DNA sequencing to identify their antibiotic resistance genes.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

- A key achievement of the project has been to identify two new antibiotics. The new compounds are active against clinical isolates, as well as the laboratory strains. This means that we have discovered new drugs that are urgently needed to treat infection.
- We found an increase in antibiotic activity when we mixed our new compounds with existing drugs. The combination therapy was more effective than each drug alone - this may extend the useful life of antibiotics to which bacteria have become resistant.
- One of our compounds, MGB-BP3 is currently in a phase 2 clinical trial to treat bowel infections. In this project we tried to evolve bacteria to be resistant to our new drug. We found no evidence of evolution of resistance in the MRSA superbug, suggesting that MGB-BP3 will be a vital new form of defence against multidrug resistant infections.
- The CSO project has demonstrated that, for vancomycin-resistant *Enterococcus faecium* (VREfm) infections, MLST is now constrained - specifically due to loss of one MLST locus (*pstS*) which therefore cannot display any variance and contribute to a MLST profile. As whole genome sequencing (WGS) becomes cheaper and more widely-available, clinical practice will likely come to the point where WGS is preferable to MLST because it delivers much more information.

S-MGBs are a novel class of antibiotics developed at Strathclyde. They work by binding to the minor groove of bacterial DNA, pictured right (image credit: Prof. Colin Suckling). The figure shows the three dimensional structure of the DNA double helix with two molecules of MGB antibiotic bound to it.



WHAT IMPACT COULD THE FINDINGS HAVE?

- Successful completion of clinical trials for BP-3 will result in a new antibiotic with a novel mode of action becoming available in the clinic for certain infections.
- Antibiotic resistance is a major global problem and is predicted to kill 10 million people per year by 2050 (more than cancer and diabetes combined). Our new antibiotics will be used to reduce this problem by improving human health.
- Coupled to the reducing cost of whole genome sequencing (WGS), this work adds evidence that may eventually result in WGS become the standard practice for characterising clinical isolates and resolving their epidemiology.
- After this Report was finalised MGB Biopharma announced at £2.78M Biomedical Catalyst grant that, together with existing stakeholder investment, will allow the Phase 2a clinical trial to be undertaken.

HOW WILL THE OUTCOMES BE DISSEMINATED?

- Our findings and details of our new compounds have been widely disseminated online via social media and news organsiations including the BBC.
- Two papers have been written during the course of the CSO grant;
    a) Colin J. Suckling, Iain Hunter, Abedawn Khalaf, Fraser Scott, Nicholas Tucker, Leena Niemenen, Kimon Lemonidis (2017) **Why Antibacterial Minor Groove Binders Are a Good Thing**. 3rd International Electronic Conference on Medicinal Chemistry.

    b) Kimon Lemonidis, Talal S. Salih, Stephanie J. Dancer, Iain S. Hunter, Nick Tucker (2018) Missing *pstS* locus associated with an insertion in *tetM* in vancomycin resistant *Enterococcus faecium.* Submitted to / under review by Journal of Medical Microbiology JMM-D-17-00907. This paper is based exclusively on the genome sequencing of clinical pathogens undertaken during the CSO grant.

CONCLUSION

MGB Antibiotics represent a new approach to treating infections at a time when we urgently need new antibiotics.

RESEARCH TEAM & CONTACT

Prof. Colin Suckling, Dr. Nick Tucker

University of Strathclyde Glasgow.

Nick.tucker@strath.ac.uk

0141 548 2861

Thanks to CSO for funding our research to fight antibiotic resistance.