CHIEF SCIENTIST OFFICE

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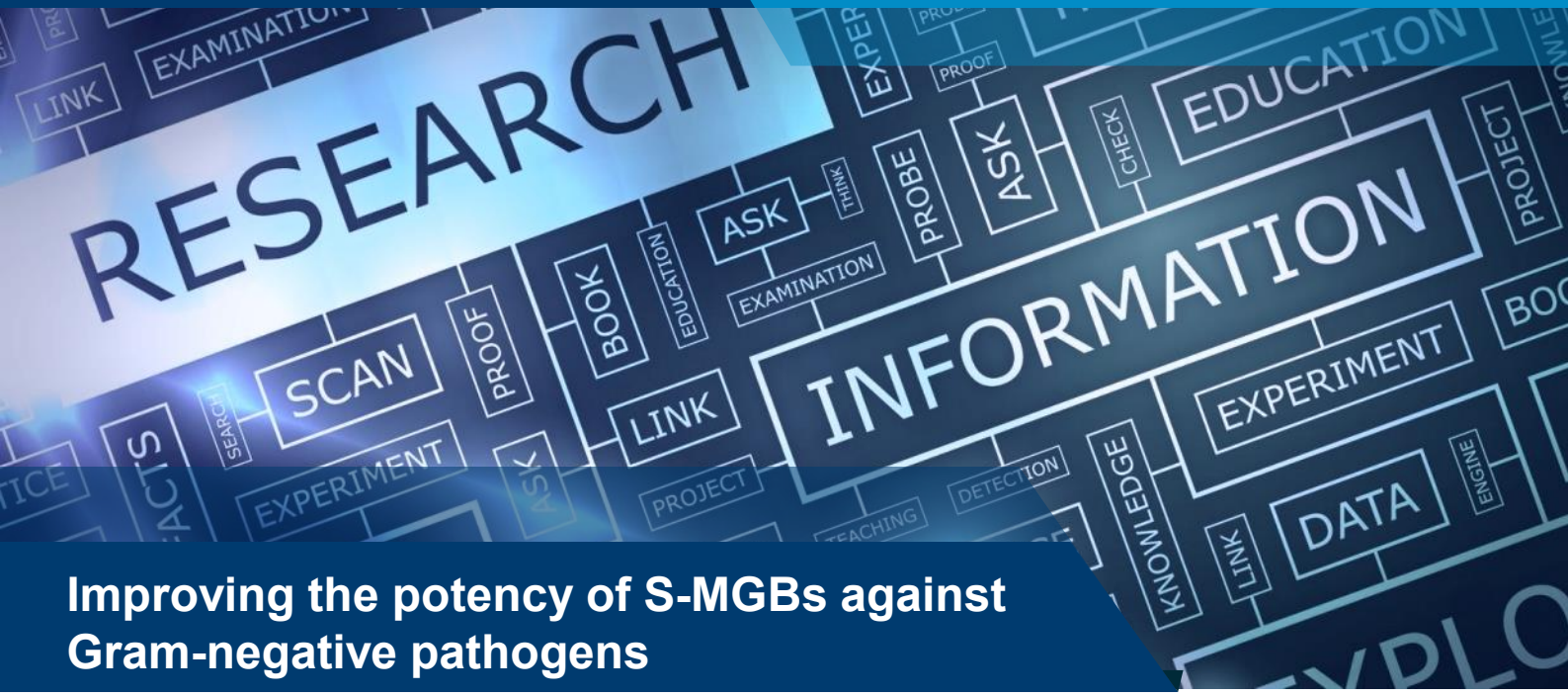
RESEARCH PROJECT BRIEFING



Improving the potency of S-MGBs against Gram-negative pathogens

AIMS

Strathclyde Minor Groove Binders (S-MGBs) are a completely new class of anti-infective agent, developed in Scotland, with one compound, MGB-BP-3, having successfully completed phase IIa clinical trial for the treatment of bacterial infections caused by *Clostridioides difficile*, a Gram-positive bacterial pathogen. This aim of this project was to improve the activity of S-MGBs such that they become active against Gram-negative bacterial pathogens, for which their activity is currently minimal.

KEY FINDINGS

- Existing S-MGBs do not have the correct physicochemical properties, or structural motifs, to be sufficiently potent against the majority of Gram-negative pathogens
- The inclusion of certain structural motifs (undisclosed herein) can significantly improve S-MGB potency against Gram-negative pathogens on the WHO priority pathogen list.
- The investigation of two such structural motifs allowed two ‘hit’ series of molecules to be identified for future drug development programmes, including an assessment of synthesis feasibility and molecular diversification.
- MGB-BP-3, and other unmodified S-MGBs, have been found to have high potency against one Gram-negative pathogen, *Neisseria gonorrhoeae*.
- Another ‘hit’ series has been identified to establish an *N. gonorrhoeae* drug development programme

WHAT DID THE STUDY INVOLVE?

We first explored the reasons behind S-MGBs' low activity against Gram-negative pathogens, using several complementary techniques, including: using S-MGBs in combination with other compounds known to compromise Gram-negative bacterial cells; fluorescence microscopy to observe S-MGBs interacting with Gram-negative and Gram-positive bacterial cells; measuring the strength of binding of S-MGBs to DNA.

The outputs from the above allowed us to design and synthesise better S-MGBs that were able to penetrate into Gram-negative cells. These new compounds have much improved potency against Gram-negative pathogens.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

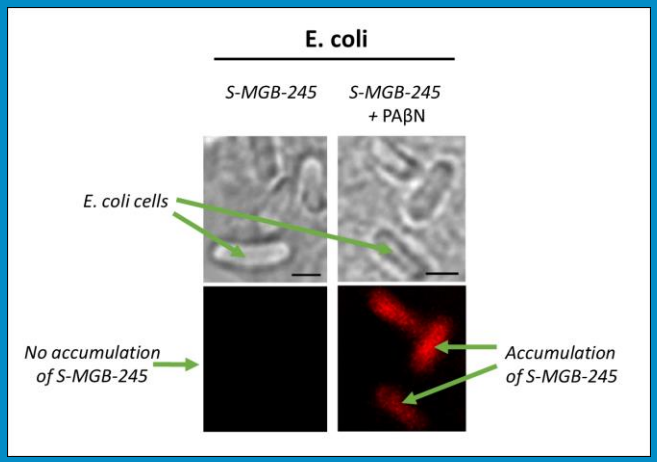
We were able to show that S-MGBs could bind strongly to DNA extracted from both Gram-positive or Gram-negative bacterial, showing that low activity against Gram-negative pathogens is not to do with poor engagement with the target DNA. Importantly, we established that the reason behind the low activity of S-MGBs towards Gram-negative pathogens is due to poor accumulation of S-MGBs within Gram-negative bacterial cells (see figure below).

We were surprised to find that although S-MGBs are not active against most Gram-negative bacteria, they are active against *Neisseria gonorrhoeae* without requiring structural modification. Indeed, several S-MGBs have been identified as 'hits' for further development.

New molecular motifs were incorporated into the S-MGBs to improve accumulation within Gram-negative bacterial cells, and thus improve potency. The specific motifis are not disclosed for reasons related to intellectual property and future patent protection.

The new molecular motifs have enabled two new 'hit' series of S-MGBs to be discovered, which are suitable for follow-on drug development activities.

S-MGB-245 was designed to be a fluorescent probe molecule, to enable tracking of S-MGBs in bacterial cells. Here, S-MGB-245 alone does not enter the Gram-negative bacterial cell of *E. coli*, explaining the lack of activity against *E. coli*. When S-MGB-245 is used in combination with a molecule known to compromise the cell membrane, and prevent molecules being pumped out of the cell, PAβN, S-MGB-245 is able to accumulate within the bacterial cell.



WHAT IMPACT COULD THE FINDINGS HAVE?

- The World Health Organisation (WHO) has identified multiple Gram-negative pathogens as of 'critical' or 'high' priority, recognising their respective urgent health threat, and the need to develop new treatments for these infections.
- This research has laid the foundations for two distinct drug development opportunities going forward: one specifically targeting one specifically targeting *Neisseria gonorrhoeae* and one targeting Gram-negative pathogens more broadly.
- This project has therefore provided significant evidence that S-MGBs have the potential to contribute to answering the WHO's call for more R&D for their priority pathogens.

HOW WILL THE OUTCOMES BE DISSEMINATED?

We are currently preparing a paper for publication that explains our preliminary results in the *N. gonorrhoeae* stand of the project, which will be available for dissemination soon. Following this, we will use the preliminary results to secure further funds to help us translate the outcomes to the drug development phase.

Additionally, the two 'hit' series that are two be developed to target a broad spectrum of Gram-negative pathogens, constitute novel intellectual property. Further work needs to be to be done to better exemplify the molecular space before we can file a patent in this area.

One paper has already been published: https://doi.org/10.1021/acsinfecdis.2c00445

CONCLUSION

S-MGBs may represent a new approach to treating infections caused by Gram-negative pathogens. Specifically, we are now embarking on two separate drug development projects as a consequence of this funding, one specifically targeting *Neisseria gonorrhoeae* and one targeting Gram-negative pathogens more broadly.

RESEARCH TEAM & CONTACT

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Additional Information

Completion Date: 30th April 2023, Project Value: £299,999