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RAPID RESEARCH IN COVID-19 PROGRAMME

Accelerated introduction of a novel class of resistance-proof antiviral drugs: Strathclyde Minor Groove Binders

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 the bacterial pathogen, *Clostridioides difficile*. MGB-BP-3 is now ready to enter the final phase of clinical trials. This aim of this project was to identify S-MGBs that could be developed into new COVID-19 therapeutics, by repurposing MGB-BP-3 or otherwise. This included developing a key partnership with Public Health England to access their expertise in COVID-19 drug discovery.

KEY FINDINGS

- Some S-MGBs have clinically relevant activity against COVID-19 in laboratory tests.
- The lead S-MGB in clinical trials, MGB-BP-3, is not active against COVID-19.
- Certain structural features of S-MGBs can be used to predict activity against COVID-19, and thus allow for future optimisation.
- S-MGBs have been validated as significantly active against bacterial, fungal, parasitic and now viral pathogens.
- S-MGBs can target pathogens that use RNA (rather than DNA) as their store of genetic information.
- S-MGBs have shown positive effects in preliminary animal experiments against COVID-19 and thus are now under further study to optimise their activity.

WHAT DID THE STUDY INVOLVE?

The activity of a library of existing S-MGBs was evaluated against COVID-19, in partnership with the expertise at Public Health England (PHE). This was achieved by determining activity in a laboratory test by measuring the number of viruses that had been replicated within a cell, using a clinical isolate of COVID-19.

Through other resources, we had already completed toxicity studies in animals. Thus, were we able to immediately assess the efficacy of the lead S-MGBs in an animal model of COVID-19 at PHE. This assessment included measuring the presence of the virus throughout the animal and also monitored the clinical signs of damage from the virus, such as lung tissue health. All of these evaluations of activity were supported by synthesis of large amounts of compounds at the University of Strathclyde.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Chemists at the University of Strathclyde were able to devise a new synthetic route to S-MGBs of interest that afforded us access to a large amount of compound that was of suitable purity for biological experiments. Moreover, this was achieved in a very short amount of time. These new routes are applicable for further work in our project relating to COVID-19, but are also applicable to our wider interests of anti-infective drug design.

Preliminary laboratory studies revealed that for S-MGBs to be active against COVID-19, certain structural features had to be present within the molecule. Specifically, by comparing compounds where only one structural feature was different, it was found that compounds with 'amidine' groups within their structure were consistently more active than those with 'morpholine' groups. This helps to identify which compounds should be made in future studies.

The laboratory test assessment of efficacy of S-MGBs against COVID-19 resulted in 3 'hit' compounds with activities acceptable for progression to animal studies. Of these, one compound was chosen based on existing data that demonstrated that it was well-tolerated in animal experiments, and that it localised substantially in lung tissue when administered by injection.

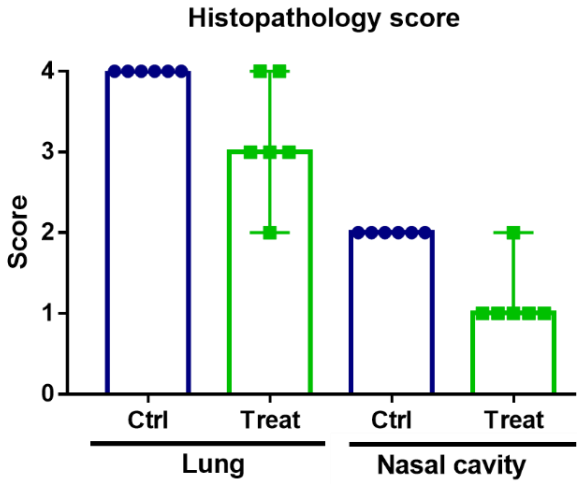


Figure 1. Data from animal model of COVID-19 using most active S-MGB. Histopathology score is a measure of tissue damage (greater 'score' number means more damage).

Ctrl means control group (given no treatment intervention) and Treat means treatment group (given the S-MGB).

Each circle or square represents an observation made on the tissue from one rodent. The score is made by visual inspection of the tissue damage under the microscope with higher scores indicating more damage.

The S-MGB was able to reduce the amount of virus detected in the animal, and also able to reduce the damage that the virus caused to the lungs and nasal cavity (figure 1). However, for this compound, the dose was not curative. None-the-less, this experiment validates the potential of S-MGBs as treatments for COVID-19, and potentially other coronaviruses. Consequently, we have begun to optimise the structure of S-MGBs to improve their efficacy, and have future animal models planned.

Identifying S-MGBs that are active against COVID-19 is very significant. S-MGBs have previously only been found to be active against pathogens that use the nucleic acid molecule, DNA as their store of genetic information; however, the virus that causes COVID-19 uses a slightly different nucleic acid molecule to store its genetic information, RNA. Consequently, this project has significantly expanded the potential therapeutic scope of S-MGBs to include RNA viruses.

WHAT IMPACT COULD THE FINDINGS HAVE?

- If COVID-19 continues to linger into the near future, we may have identified a novel class of therapeutic that could contribute to treatment options, with further clinical development.
- Outbreaks and pandemics caused by coronaviruses will likely continue to be a significant cause for concern for global heath. Our new class of anti-viral agent, S-MGBs, could contribute to managing future coronavirus threats, after suitable clinical development.
- This project has provided significant evidence that S-MGBs have potential against infectious organisms from the bacterial, fungal, parasitic, and now viral context. Consequently, S-MGBs could be positioned in the future to be agents to secure our future global biosecurity.

HOW WILL THE OUTCOMES BE DISSEMINATED?

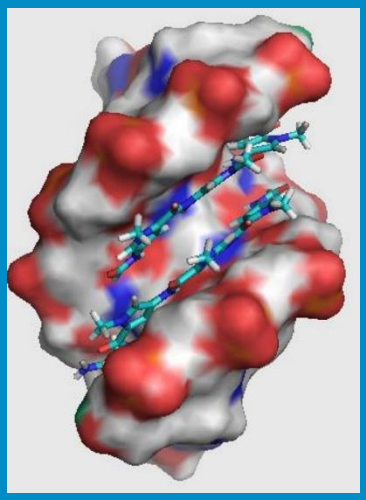
We are currently preparing a paper for publication that explains our preliminary results, which will be published in a peer-reviewed journal, thus informing other scientists of our findings. Following this, we will use the preliminary results to secure further funds to help us translate the outcomes to the clinical development phase.

We have already embarked on a series of follow on investigations, with new collaborators, based on the outcomes of this CSO project.

CONCLUSION

S-MGBs may represent a new approach to treating viral infections at a time when we urgently need new therapeutic options. Specifically, we are now seriously pursuing S-MGBs as options for treating COVID-19 and future coronavirus pandemics.

S-MGBs are a novel class of Anti-infective agent developed at the University of Strathclyde. They work by binding to nucleic acids in the infectious organism, pictured right (image credit: Prof. Colin Suckling). The figure shows the 3D structure of a segment of a DNA double helix with two molecules of S-MGB bound within it.



RESEARCH TEAM & CONTACT

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ADDITIONAL INFORMATION

Project completion date: 30th November 2020, Project value: £294,897