PROJECT PARTNERS: Mark Skidmore and Marcelo Andrade de Lima, Keele University; Ruth Yates, Anglo-Italian Chemometrics

POCE3B015 BB/S009787/1

GLYCOVID-19: Investigating the modulatory effect of metal ions on the interaction of polyanionic heparin with the SARS-CoV-2 spike protein

"This project fostered a strong link between academia and a UK-based SME. Significant outputs resulted from this collaboration and the data generated from this project will underpin ongoing and future research directions."
Anglo-Italian Chemometrics

PROJECT AIMS: The anticoagulant heparin interacts with SARS-CoV-2 and can protect host cells from viral infection. Furthermore, heparin alleviates inflammation and prevents blood clotting - two processes that are linked to COVID-19 mortality. The activity of heparin can be modulated by metal ions, but the precise effects of individual metal cations on heparin bioactivity is not fully understood. The aim of this project was to establish how cation–heparin formulations influence the bioactivity of heparin regarding COVID-19.

OUTCOMES & NEXT STEPS

- The inhibitory potential of metal cation forms is being investigated in pseudotyped and live-viral inhibitory assays together with Oxford University and the UK Health Security Agency
- Results from this study are being prepared for publication
- Data has been presented at the International Symposium on Glycosaminoglycans, September 2021
- New collaborations with Queensland University of Technology, The University of Queensland, University of Copenhagen, Oxford University, Zucero Therapeutics, The Ronzoni Institute, National Institute of Biological Standards and Control, and the UK Health Security Agency
- The PI interacted with Science Media Centre and was quoted in several news stories globally.

PUBLICATIONS: Davies, S.P. et al. (2021). The hyperlipidaemic drug fenofibrate significantly reduces infection by SARS-CoV-2 in cell culture models. *Frontiers in Pharmacology* doi:10.1101/2021.01.10.426114 | Lima, M. A. *et al.* (2021). Development of a nano-luciferase based assay to measure the binding of SARS-CoV-2 spike receptor binding domain to ACE-2. *Biochemical and Biophysical Research Communications* doi:10.1016/j.bbrc.2020.11.055 | Mycroft-West, C. J. *et al.* (2020). Heparin inhibits cellular invasion by SARS-CoV-2: structural dependence of the interaction of the spike S1 receptor-binding domain with heparin. *Thrombosis and Haemostasis* doi: 10.1055/s-0040-1721319

OUTCOMES: Pharmaceutical-grade, porcine mucosal heparin was ion-paired with cations of each of the following: Na, Ca, Ag, Fe, Li, K, Co, Mn, NH_4, Mg, Zn, Ba, Cu, Al. The anti-anticoagulation potential of these cation heparin forms was determined.

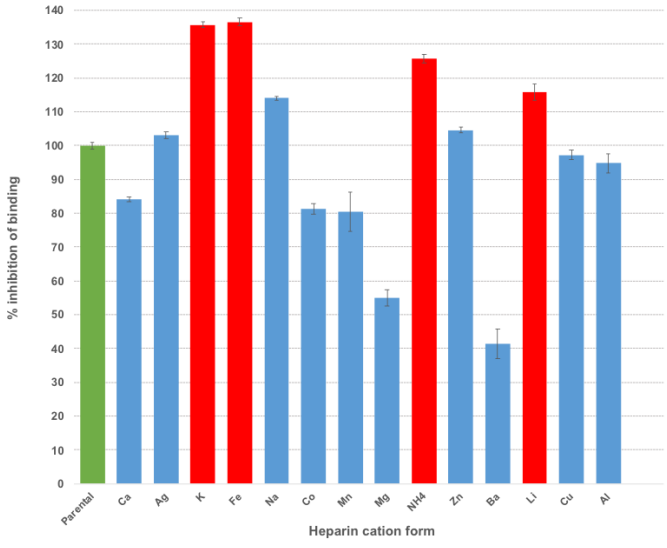
Next, the metal cation forms of heparin were screened for their ability to disrupt the interaction between the SARS-CoV-2 spike receptor-binding domain (RBD) and angiotensin converting enzyme 2 (ACE2). Distinct cation forms of heparin either augmented or diminished the potential of heparin to perturb this interaction (see Figure).

Conditions for differential scanning fluorimetry were established and this technique was utilised to investigate changes to the thermal stability of the spike RBD. Heparin metal cation forms that augmented the interaction between the RBD and ACE2 were found to destabilise the spike RBD.

Finally, the researchers showed that the cations associated with heparin may influence the enzymatic fragmentation of heparin.

KEY MESSAGE: Metal cations modulate the potency of heparin to inhibit the binding of the SARS-CoV-2 spike protein to human ACE2.

Change in technology readiness level: 1 to 2



Results from an enzyme-linked immunosorbent assay of SARS-CoV-2 spike S1 RBD–ACE2 binding in the presence of distinct heparin–metal cation forms compared with parental heparin (100% inhibition).