Applying novel multi-omic approaches to investigate the impact of training on airway immunity and molecular pathways underpinning MMEA and EIPH
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This project will use state-of-the-art investigative approaches to improve understanding of the cause and mechanisms underpinning two highly prevalent, performance-limiting disorders of racehorses; namely, mild to moderate equine asthma (MMEA) and exercise induced pulmonary haemorrhage (EIPH). This is a necessary step in the development of more targeted preventative and treatment options for these disorders. Although a number of factors have been associated with MMEA, incomplete understanding of the precise cause and course of events underpinning this syndrome means that our current treatment options are limited. Similarly, while EIPH is associated with progressive narrowing of the veins draining the lungs leading to an increase in blood pressure within the microscopic blood vessels surrounding the air sacs, the additional and potentially pivotal contribution of inflammation at this site has received little attention. Further understanding of the mechanisms underpinning MMEA and EIPH offers potential to identify specific targets for treatment and preventative interventions.

We have demonstrated that training per se can alter the immune status of cells within the airway, with the potential to result in airway inflammation and/or susceptibility to infections. This was evidenced by changes in the genetic coding for (transcriptomics), or levels of a vast array of specific cell messenger proteins (proteomics) within samples derived from the airways of racehorses in training. As genetic coding for protein production does not always align with "end stage" protein production, this combined approach enables a more holistic assessment of the immune status of the lower airways and is more sensitive and specific than current methods used to "measure" inflammation (i.e. counting inflammatory cells). It also facilitates the "mapping" of specific immune and inflammatory pathways; effectively "joining the dots" between detected changes in groups of proteins and the processes which they control (e.g. inflammation, remodelling), potentially revealing appropriate interventional targets.

We hypothesise that:
1)   race training results in an altered immune status of the lower airways, characterised by changes in genetic coding for, and/or production of, messenger proteins and that this combined approach will have superior sensitivity in detecting inflammation and greater specificity in identifying potential treatment targets than the currently adopted method of inflammatory cell counting;

2)   this combined approach will reveal the key inflammatory pathways specific to different MMEA "types" (currently based on the predominant inflammatory cell), with the potential to inform more "MMEA type"-specific therapies;

3)   application of a state-of-the-art methodological approach (spatial transcriptomics) to lung tissue samples derived from EIPH cases (post mortem) will allow identification of the specific cells responsible for encoding the production of messenger proteins at the site of bleeding. This will help to elucidate the relative role of both specific cell types (e.g. blood vessels, lung cells) and specific pathways (e.g. remodelling, inflammation) in this complex disease and further scrutinise the link between airway inflammation and bleeding.

The methodologies applied to address the above hypotheses will provide a greater understanding of the mechanisms underpinning MMEA and EIPH and help to inform the development of more targeted treatment and prevention strategies.