**Funding Source: Self-funded / own sponsor**

**Proposed start date: to be confirmed/negotiable**

**Closing date for applications: open until filled**

**Eligibility: UK/International**

***International Tuition fee: £29,300 per annum (2024/5 entry).***

***Standard UK PhD tuition fees for Home students:*** *full-time £4,786, part-time £2,393 (2024/5 rates). Please note that depending on your area of research there may be additional costs to allow for such as attendance at conferences, travel, training and consumables etc.*

**Department/School: Healthcare**

**Supervisors:** Lesley McBride lm555@leicester.ac.uk, Seth O’Neill Seth.oneill@leicester.ac.uk, Dr. Mary Collier, University of Leicester, Professor Flaviano Giorgini, University of Leicester, Dr. Patrick O’Halloran University of Birmingham

**Project Title:** Biomarkers Associated with motor Neurone Disease and Dementia development after concussion in Females and Males: BANDD.

**Application link:**

[**https://le.ac.uk/study/research-degrees/research-subjects/school-of-healthcare**](https://le.ac.uk/study/research-degrees/research-subjects/school-of-healthcare)

**Project Description:**

## Highlights:

|  |  |
| --- | --- |
| 1. | This will be an exciting opportunity to explore the differences between male and female brains responses to trauma in sport |
| 2. | This will be the first time that links to existing neurodegenerative diseases in retired players will be explored in relation to their sport |
| 3. | This project is highly likely to generate important REF returnable papers and further large NIHR grant applications with a high chance of success |

## AIMS

## Identify the impact concussion (Rugby) or low-grade brain injury associated with heading the ball (Football) has on biomarkers (micro-RNA’s) found in the Saliva and Blood and determine whether gender influences this. We will then determine how these biomarkers influence neural cellular activity invitro and whether these biomarkers are involved in the longer-term health consequences associated with concussion induced dementia or motor neurone disease.

**Hypotheses**

**Work Package 1**

***Female players will have different levels of concussion biomarkers compared with Males.***

***Female Players will recover differently post-concussion or Ball heading compared with Males***

**Work Package 2**

***The impact of micro RNA molecules on peripheral and central nervous system cells will differ.***

**Work Package 3**

***Retired players with early onset dementia or Motor Neurone Disease will express unique Salivary and Blood markers for neural function.***

**Work package 1a**: An observational prospective multi-squad cohort study recruiting subjects in the 2024-2025 season from the two highest tiers of Female and Male Rugby in English, Irish and Scottish Rugby and relevant national squads. During the season any match or training related concussion will be recorded by the medical teams and a saliva sample taken. A smaller number of blood samples will also be taken for analysis of novel biomarkers.

**1b:** A 2nd cohort of players, this time from Football will be recruited, this group will undergo repeated bouts of heading to replicate in game demands, following previously published protocols. The recruits will be from professional football clubs with equal weighting for Female and Male recruitment.

All samples will be stored as per published protocols. The concussed player samples will be matched with one other player who played the same position and participated for similar amount of minutes. Storage and analysis of the samples will follow previously published protocols.

**Work package 2:** Laboratory based analysis of the impact on identified biomarkers on human peripheral and central nervous system cells.

Extracellular vesicles (EVs) will be isolated from saliva samples by precipitation with ExoQuick-TC technology followed by size exclusion chromatography. Total EVs will be analysed directly and neuronally enriched EVs will be isolated using immuno-capture beads, as a window into CNS alterations. EVs will be lysed and micro RNAs (miRNAs) isolated. RNA-sequencing will then be used to identify miRNAs that are differentially expressed between groups and significantly different miRNAs will be validated by qPCR. miRNA databases will be used to identify potential gene targets of miRNAs that are significantly different between groups. Based on these analyses, we will then test the effects of key miRNAs on the health of neurons using the SH-SY5Y human neuronal cell line and the NSC-34 mouse motor neuron-like cell line. These cells will be transfected with miRNA mimics corresponding to miRNAs of interest and outcomes on target gene expression, cell viability, mitochondrial function and reactive oxygen species production (ROS) will be examined. In parallel, we will utilise these outcomes to test the effects of direct treatment of the neuronal lines with isolated EVs from the experimental groups.

**Work package 3**

An observational study examining the biomarkers of early onset Dementia or MND in retired players who attribute these disorders to their playing careers. This study will utilise both saliva and blood samples. Recruitment will be supported by the governing bodies and the professional footballers association and the professional players federation. Salivary and blood analysis will follow published protocols.

**Data analysis**

Data analysis will be completed by a biostatistician. Primary analysis will compare concussed with non-concussed counterparts and Male and Female comparisons. Testing will use appropriate between group analysis.

**Experimental methods and research plan**

Player and stakeholder representatives have been involved with the planning of this study, specifically around the importance of understanding the role of concussion in motor neurone disease development and the pace research needs to examine this. This work has informed the proposed methodology.

## Background

## Traumatic brain injury can be diagnosed from saliva and blood samples, however current literature has focussed predominantly on concussion in males despite evidence Female players suffer more frequent concussions with higher severity, possibly linked to fall mechanics. This may result in different quantities of MicroRNAs (Biomarkers of Concussion) in the saliva or blood of a female who is concussed. Concussion (or mild traumatic brain injury) has also been identified to occur with heading of the ball in football. Female participation has rapidly expanded in both Rugby and football but recent data has shown a significant increased risk of Motor neurone disease (MND), increased by 15 times in retired rugby players and an increased risk of Dementia in both Rugby and Football, alongside other sports. How concussion/mild traumatic brain injury increases the risk of neurodegenerative disorders is currently unknown and un-explored.

**Entry requirements:**

Applicants are required to hold/or expect to obtain a Bachelor Degree 2:1 in a relevant subject area.

The University of Leicester English language requirements apply where applicable: <https://le.ac.uk/study/research-degrees/entry-reqs/eng-lang-reqs/ielts-70>

**Application advice:**

To apply please refer to: <https://le.ac.uk/study/research-degrees/research-subjects/school-of-healthcare>

With your application, please include:

* CV
* Personal statement explaining your interest in the project, your experience, why we should consider you in addition to confirmation of how you will pay your fees.
* Degree Certificates and Transcripts of study already completed and if possible transcript to date of study currently being undertaken
* Evidence of English language proficiency if applicable
* In the reference section please enter the contact details of your two academic referees in the boxes provided or upload letters of reference if already available.

*In the proposal section please provide the name of the supervisors and project title (a proposal is not required)*

Application and project queries to soh-pgr@le.ac.uk