Arthritis Australia 2024 Lay Project Grant Report (May 1, 2025)

Grant Title: ***Does mild joint injury and how its managed, increase risk of catastrophic injury and post-traumatic osteoarthritis?***

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Australia is at the forefront of a global increase in knee joint anterior cruciate ligament (ACL) ruptures, with the highest incidence per head of population in the world. These injuries have an enormous negative impact on quality of life, physical activity, work, and in children education outcomes. The impact is compounded by ACL tears markedly increasing the risk of developing osteoarthritis (OA) within 15 years. However, there can be very different outcomes for patients with the "same" apparent injury, with ~50% of patients with anterior cruciate ligament (ACL) tears in the knee progressing to OA irrespective of treatment. What factors drive this difference in outcome and whether these are modifiable is unclear. In the current study we used our novel mild joint injury model in mice (developed through prior Arthritis Australia grants) to address for the first time in a controlled laboratory study, knowledge gaps regarding the role of mild joint injury and its common treatment with ibuprofen, on the risk of subsequent ACL rupture and osteoarthritis if such a rupture does occur.

We confirmed our previous findings that a mild knee injury that in itself does not disrupt the ACL nor result persistent pain or OA, causes remodeling and weakening of the ACL and changes to nerve function that increase risk of future ACL rupture. We showed for the first time that this mild injury also leads to worse and more progressive OA if a major joint destabilizing injury subsequently occurs. Importantly, we found that a 1 week course of ibuprofen started immediately after a mild joint injury led to restoration of ACL strength, partial resolution of nerve changes, and modulation of specific inflammation and molecular changes in the joint that at least partially ameliorated the worse OA when a subsequent critical injury occurred. Critically, these beneficial effects were delayed taking up to 8-12 weeks after ibuprofen treatment for maximum effect.

These findings highlight the importance of prior mild joint injuries, that in the absence of any joint instability or persistent pain are considered resolved and largely ignored. These mild injuries represent a significant and currently under appreciated risk for ACL rupture and OA. Importantly we now show that this risk is modifiable, but that restoration of normal joint tissue strength may take up to 14 weeks. Future studies will determine the therapeutic window for risk modulation and the potential effect of other agents. This work highlights the need to better monitor and treat mild injuries to reduce critical injury and ptOA risk.