John Stocker Postdoctoral Fellowship

Bioengineering novel biomaterial based cellular therapies for the prevention of childbirth induced pelvic organ prolapse

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Pelvic Organ prolapse (POP) is a debilitating gynaecological condition that affects **~25% of all women, ~50% aged 50+ years and ~65% aged 68+ years** who have given birth. While obstetric trauma associated with vaginal childbirth is the major risk factor, other factors such as age, ethnicity, parity, obesity, and family genetics are also known to be associated with POP. POP occurs when the pelvic floor muscles and connective tissue are overstretched and/or damaged during childbirth. This ultimately causes pelvic floor biomechanical failure leading to the herniation of organs such as the uterus, bladder or bowel into the vagina and sometimes out of the body (through the vagina). Symptoms of POP include difficulty in defecation and urination, sexual dysfunction and sometimes bowel and urinary incontinence, and frequently requires surgery as a treatment. This condition profoundly impairs women's quality of life, abilities to perform at their work place, mental health, social anxiety and increases their dependence on care at old age. Untreated POP symptoms account for high medical expenses for families and the healthcare system. Incontinence alone accounts for >$200 million annually in Australia, and >$20 billion in the US.

Until recently, **non-degradable** polypropylene (PP) transvaginal meshes were commonly used for reconstructive surgery to mitigate native tissue repair failures. However, regulatory body reports and growing evidence indicated that the risks of additional complications such as mesh erosion, exposure and pain out-weigh the benefits of these meshes [3]. This has collectively led to the **ban on transvaginal meshes** in Australia, UK and more recently is the USA. ***There are no alternative treatments on the horizon, nor are there any preventative therapies for POP.*** Delayed diagnosis and poor biocompatibility of mesh materials are the major hurdles to quality gynecological care. In ***this project, we have merged parallel technologies of mesenchymal stem cell biology, materials chemistry and nanotechnology to bioengineer new t*****herapies for *(*a) treatment of chronic POP and (b) minimally *invasive therapy to PREVENT the progression of POP after childbirth.***

Outcomes and Impact: The inability of current POP materials to mimic the tissue microenvironment may be critical to its failure in the long term. This prevents integration and healing at the site of implantation. In order to overcome the impediment of mesh integration it is desirable to design biomaterials that mimic some mechanical and biochemical properties of the native tissues. Endometrial Mesenchymal stem/stromal cell (e**MSCs)** have the potential to promote vaginal tissue repair. ***Hence, injection of reparative eMSCs using*** *nanostructured* ***biomaterials that can protect the cells long term is an attractive strategy for POP management.***

We have made significant progress in understanding the immunobiology of tissue engineered constructs using eMSCs and nanobiomaterials in a urogynecological application. We have identified

- Impact of material design and mesh composition on the foreign body response and mesh integration

- Impact of fabrication method of biomaterials on the macrophage mediated innate response using immunocompromised and immunocompetent models.
- The role of eMSCs play on healing following birth injury
- Impact of eMSCs in driving neo-matrix formation, angiogenesis and immunomodulation

Based on this we have developed novel animal models and methods of assessing birth trauma as well as eMSC based therapeutics to promote vaginal healing. These preclinical studies and novel research outputs have formed the foundation for future clinical trials to overcome a significant women's health problem. Ultimately, this project brings us closer to improving the quality of life for millions of women who currently suffer in silence and await a treatment for this debilitating condition.