It is estimated that 17.8 million people live with a musculoskeletal (MSK) condition in the UK, accounting for the 28.9% of the total population. These conditions represent the leading cause of years lived with disability (YLDs) and the third largest cause of disability-adjusted life years (DALYs) (Global Burden of Disease Network, 2017). MSK conditions represent a major burden on the NHS, and are growing in parallel with an increasingly old and sedentary population, whilst being often associated with severe comorbidities, including: cardiovascular diseases, lung problems, cancer, diabetes and mental health issues (Arthritis Research UK, 2018).

A very prevalent MSK disease is osteoarthritis (OA), which affects 8.75 million people in the UK and is associated to severe joint pain, synovitis, deformity and disability, particularly in the elderly (Arthritis Research UK, 2018). Synovial fibroblasts (SFs) contribute to establishing joint inflammation and tissue degeneration processes in OA (Mathiessen and Conaghan, 2017; Scanzello and Goldring, 2012; Ongaro et al., 2011; Varani et al., 2010 a and b; De Mattei et al., 2009). Although the detailed biology of SFs is still partly unknown, the investigation of SFs characteristics is critical step in understanding their full contribution to profile, severity and progression of OA, with possibility to inform new clinical approaches. Interestingly, these cells share several characteristics of Mesenchymal Stem Cells (MSCs) (Masieri et al., 2015; Ongaro et al., 2015) and are suggested as a useful tool in MSK regenerative medicine (Kim et al., 2015; Bilgen et al., 2009; Jones et al. 2004).

Induced Pluripotent Stem Cells (iPSCs) have emerged as a “game-changer” in the field of regenerative medicine (Park et al., 2008; Takahashi and Yamanaka, 2006). These cells are an amenable tool to help studying complex diseases and find new therapeutic targets. iPSCs are produced by delivering key ‘Yamanaka reprogramming factors’ (Oct3/4, Sox-2, Klf4, CMyc) via biotechnological approaches, with the capability to ‘reset’ virtually any type of somatic cell to a pluripotent, undifferentiated status, resembling the one of embryonic stem cells (ESCs).

Despite coming with a fraction of the ethical complexity associated to ESCs, iPSCs safety is, amongst other factors, strictly connected to the biotechnological approaches applied for their reprogramming (Hu et al., 2016). Traditional lentiviral-based, integrative methods have been associated to issues of high genetic instability in the derived cells and teratocarcinoma formation when these are introduced in animal models, therefore compromising potential clinical applications of these cells. In recent years, Sendai virus-based, non-integrative methods of reprogramming have been offering a safer and relatively efficient way of delivering the ‘Yamanaka factors’ to obtain good quality iPSCs (Buthani et al., 2016).

This project aims at deriving iPSCs from synovial fibroblasts of patients suffering from OA, using a Sendai virus-based approach of reprogramming. The resulting OA-iPSCs may be used in the future as a tool for better understanding the development of OA, the molecular and cellular pathways underlined and therefore finding new avenues for personalised medicine. If successful, this study will represent the first to date at deriving OA disease-specific iPSCs with the use of non-integrative reprogramming techniques, therefore delivering a safer proof-of-concept cell product for potential future applications in the clinical setting.

1. References


