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Stem cell treatment for musculoskeletal disease

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Musculoskeletal disease is prevalent in society and with an ageing population, the incidence and impact on public health are set to rise. Severe long-term pain and mobility restriction impair the welfare and quality of life of patients with musculoskeletal disease. Current treatments are often restricted to the management of symptoms or temporary replacement with inert materials, rather than targeting prevention and cure. There is an urgent need for alternative biological approaches to musculoskeletal disease therapy. The rapid emergence of stem cell technologies, primarily using 'mesenchymal stem cells' (MSCs), has resulted in a number of pre-clinical and clinical studies in an effort to provide more effective treatment options. Challenges exist in bench-to-bedside translation, but they are not insurmountable.

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Introduction

Our understanding of stem cells has accelerated in recent years, and with it their potential use in regenerative medicine to treat a spectrum of human disorders. The World Health Organisation has described musculoskeletal disease as the most common cause of severe long-term pain and physical disability [1]. The classification of musculoskeletal disease is broad including both acute and chronic conditions; they can affect any part of the musculoskeletal system, namely bones, muscle, cartilage, tendons, ligaments, joints and nerves. With an increasingly ageing population, the incidence of musculoskeletal disease is rising and predicted to be a significant socio-economic burden on society, yet the complex nature of these diseases generally means that treatment options are limited to managing symptoms rather than prevention and cure [2]. This unmet need is driving rapid advances in stem cell technology with the potential of using regeneration therapy to aid these conditions.

Stem cells — embryonic stem cells and induced pluripotent stem cells

Stem cells are defined by their ability to undergo asymmetric cell division to self-renew, maintaining a stem cell pool, and give rise to differentiated progeny. This inherent trait makes stem cells a very attractive choice for regenerative therapies. Stem cells can be broadly characterised into two groups; embryonic stem cells (ESCs) and adult stem cells. ESCs are derived from the inner cell mass of blastocyst-stage embryos and possess the ability to differentiate into all cell derivatives from the three primary germ layers, ectoderm, endoderm and mesoderm (from which skeletal tissues arise). The plasticity of ESCs makes them attractive therapeutic cells for many clinical applications including the treatment of musculoskeletal disease [3,4]. Despite this potential, the use of ESCs in regeneration therapy does require a number of issues to be resolved. The implantation of ESCs has been reported to result in hyperproliferation giving rise to teratomas; cancerous tumours possessing cells/tissue from the three primary germ layers [5]. Additionally, the incompatibility of the host cells with the newly implanted ESCs can lead to immune rejection [6]. Finally, most reported protocols require ESCs to be partially differentiated before implantation in order to ensure their progression down the correct lineage. This typically uses animal products in culture medium generating a risk of xenobiotic transfer, which will need to be addressed before ESC technology can be used in a clinical setting.

Induced pluripotent stem cells (iPSCs) can be generated by introducing factors (such as Oct4, Sox2, Klf4 and cMyc) into somatic cells to initiate reprogramming to an ESC-like state [7]. Consequently, iPSCs provide a primitive, patient-specific cell source for directed differentiation to new tissues in degenerative disorders, including musculoskeletal disease. Recent work has shown that iPSCs can be produced from osteoarthritic synovial cells [8] and chondrocytes [9] with subsequent re-differentiation to cartilage tissue, and improved outcome for the homogeneity and quality of chondrogenic differentiation [10]. iPSC technology could transform regenerative medicine strategy, but concerns associated with teratoma risk, use of (viral) gene delivery and low reprogramming efficiency remain. The technical challenges associated with the use of pluripotent stem cells in therapy are likely to be addressed in time; however, the current lead therapeutic cell for musculoskeletal disease is the 'MSC', which will be main focus of this review.

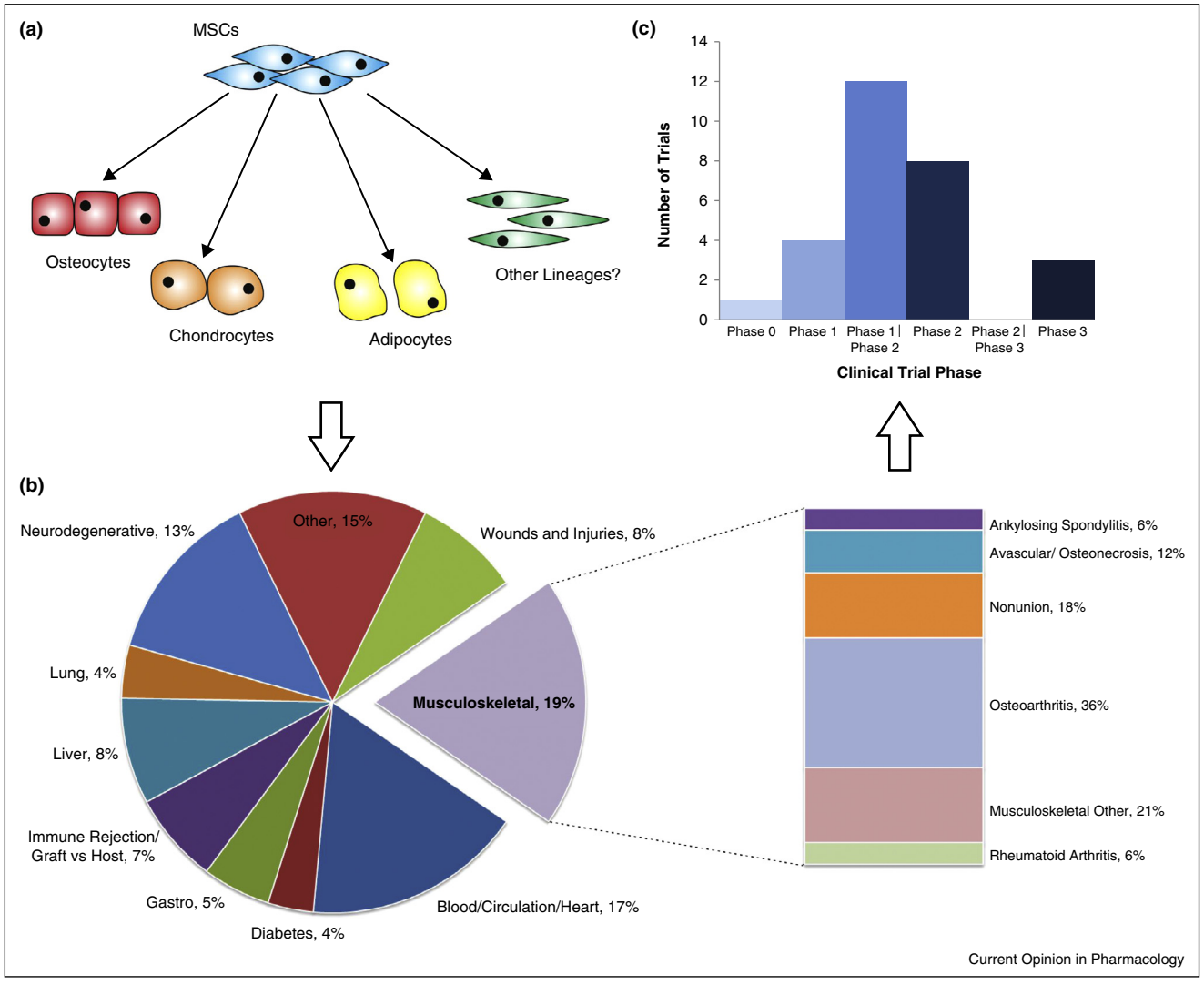
Stem cells — 'MSCs'

The term 'MSC' has been given to mesenchymal stem cells, mesenchymal stromal cells and bone marrow stromal cells (as well as other related cell populations). In

truth, very few studies have employed authentic *mesenchymal stem cells* (i.e. that are homogenous, identifiable self-renewing cells capable of differentiation into all mesenchymal tissues) and the vast majority of work is performed using heterogeneous stromal cultures. Still, the 'MSC' abbreviation has been widely adopted and will be used here with this caveat in mind. MSCs provide an attractive option for cell-based therapy as they remove some of the technical constraints (and ethical issues) associated with ESCs and iPSCs. MSCs hold great promise for musculoskeletal disease in particular, as they can be isolated from various tissues and induced to differentiate into relevant cell types such as osteoblasts (bone), adipocytes (fat) and chondrocytes (cartilage) (Figure 1a) [11,12]. The pathways governing lineage specification are not entirely clear; however, there are two additional intrinsic properties of MSCs that aid tissue regeneration. First is their ability to secrete a wide range of growth factors, which have trophic effects on surrounding host cells [13,14]. Second, once administered these cells can coordinate differentiation in tandem with differentiated and undifferentiated resident host cells [15]. Combined with the relative ease of expanding these cells in culture, a partially differentiated start point and possible immunomodulatory properties [16], MSCs are an attractive source for clinical usage.

There have been many clinical trials using MSCs, particularly targeting musculoskeletal diseases such as fracture nonunions, avascular/osteonecrosis and osteoarthritis.

Figure 1



The value of MSCs in musculoskeletal disease therapy. **(a)** Schematic summary of the differentiation potential of MSCs. **(b)** Analysis of clinical trials by disease type registered at clinicaltrials.gov using MSCs. The database was searched using the search criteria 'mesenchymal stem cells' OR 'mesenchymal stromal cells' to find all relevant clinical trials. The clinical trials here have been registered since January 2011 and have a known status. **(c)** Clinical trials relevant to musculoskeletal conditions using MSCs listed by phase. Data accessed: 14th November 2013.