COMMENTARY

Transforming healthcare through regenerative medicine

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Abstract

Regenerative medicine therapies, underpinned by the core principles of rejuvenation, regeneration and replacement, are shifting the paradigm in healthcare from symptomatic treatment in the 20th century to curative treatment in the 21st century. By addressing the reasons behind the rapid expansion of regenerative medicine research and presenting an overview of current clinical trials, we explore the potential of regenerative medicine to reshape modern healthcare.

Keywords: Regenerative medicine, Cell therapy, Tissue engineering, Stem cells, Clinical translation

Background

The current dilemmas for modern day healthcare, such as an aging population and the increasing prevalence of chronic diseases, require solutions that limit organ dysfunction and tissue degeneration and which potentially offer replacement. This was first addressed through transplantation, a field that advanced rapidly in the 1950s through a combination of surgical innovations and fundamental scientific breakthroughs in immunosuppression [1]. In contrast to the allogenic replacement of transplantation, regenerative medicine seeks to apply stem cell research with developmental biology principles to regenerate cells, tissues and organs de novo [2].

The regenerative medicine research field resulted from the convergence of multiple scientific avenues, such as successful culture of cells in the laboratory [3], identification, characterization and differentiation of stem cells [4–7], and an improved understanding of developmental and molecular biology [8], to conceivably allow control of the intracellular and extracellular environment to promote tissue and organ formation in the laboratory (Fig. 1).

Regenerative medicine has been recognized worldwide as a developing research field that offers the potential to revolutionize patient care in the 21st century [9]. The prospect of addressing massive healthcare markets, such as cardiovascular disease, neurological conditions or chronic metabolic diseases (e.g. end-stage renal disease or diabetes), means that there has been sustained scientific, public and commercial interest despite early setbacks and slow progress.

Expansion and potential impact of regenerative medicine

Demand for regenerative medicine products has been driven by an increase in degenerative and chronic diseases which place cost pressures on healthcare providers, combined with advances in new technologies such as nanotechnology, bioengineering and stem cell therapy [10]. Long-term cell, tissue and organ replacement will not only provide an alternative to transplantation [11], but will also provide therapeutic options for degenerative conditions (e.g. neurodegenerative conditions (Parkinson’s), stroke and heart failure), which are currently only managed through palliation [12, 13].

According to the World Regenerative Medicines Market forecast for 2013–2020 [14], the global regenerative medicines market for small molecules and biologics, gene therapy and cell therapy is expected to reach $67.5 billion by 2020, which is an increase of $51.1 billion from 2013, thus reflecting its commercial potential. Governments across Europe and the US, as well as their medical research councils, have identified tissue engineering and regenerative medicine at the top of their research priorities [9]. Removal of previous restrictions in embryonic stem
Fig. 1 Regenerative medicine origins

2014
First human clinical trials using stem cells to treat macular degeneration, ALS, diabetes & heart disease

2013
Researchers convert human skin cells into neurons that arrange themselves into structures resembling the anatomy of the foetal brain

2012
Human embryonic stem cells show medical promise to treat blindness

2008
iPS reprogrammed into neurons to improve Parkinson's symptoms in animal model

2006
Professor Shimya Yamanaka shows that differentiated adult cells can be reprogrammed by inserting four key genes, giving rise to the term 'induced pluripotent stem cells' (iPS)

1999
Researchers discover that stem cells can be made to differentiate into different cell types

1998
First human embryonic stem cell line derived by Dr. James Thomson

1995
Researchers derive first embryonic stem cells from non human primates

1981
Sir Martin Evans discovers mouse embryonic stem cells (ESCs) in the inner cell mass of blastocysts

1978
Hematopoietic stem cells were isolated in human umbilical cord blood

1961
Till and McCulloch identify the existence of hematopoietic stem cells

1956
First successful bone marrow transplant

330BC
Aristotle observes that a lizard can regenerate its tail

1712
Réaumur publishes work on crayfish limb regeneration

2010
A person with spinal injury becomes the first to receive medical treatment derived from human embryonic stem cells
cell research in 2009 by the Obama organization is predicted to contribute to further considerable growth within the field as well as improved potential for clinical translation [15].

**Clinical trials in regenerative medicine**

The expansion of regenerative medicine as a scientific discipline, with its core principles of rejuvenation, regeneration and replacement (the 3Rs), is shifting the

| Medical Specialty | Pathology | Cell/Tissue Therapy | Clinical Trial Phase | Patient numbers | Clinical Trial Study |
|-------------------|-----------|---------------------|----------------------|-----------------|---------------------|
| Neurology         | Parkinson's | Fetal porcine cells Transplantation of embryonic dopamine neurons | I, II | 34 | Fink 2001; Freed 2001 |
|                   | Paraplegia, Spinal cord injuries | MSCs transplanted directly into injured spinal cord. Bone marrow nucleated cells injected intrathecally and intravenously coupled with MSC infusion by lumbar puncture | I, II | 80 | Park 2012; Jarocha 2015 |
|                   | Multiple Sclerosis | IV infusion of MSCs Haemopoietic stem cell transplants | I, II | 30 | Connick 2012 |
| Cardiology        | Ischaemic cardiomyopathy, heart failure | Transendocardial injection of MSC derived from BM or adipose tissue Intracoronary injection of cardiac stem cells IV infusion of MSC | I, II | 104 | Heldman 2014; Hare 2014; Chugh 2014; Perin 2014 |
| Respiratory       | Idiopathic pulmonary fibrosis | IV infusion of placental- Chambers derived MSC | I | 8 | Chambers 2014 |
|                   | Chronic lung disease | IV infusion of HLA-matched allogeneic MSCs derived from BM/umbilical cord | I,II | 62 | Weiss 2013 |
| Rheumatology      | Osteoarthritis | Intra-articular injection of autologous or allogeneic MSC | I, II, III | 104 | Orozco 2013; Jo 2014 |
|                   | Osteogenesis Imperfecta | Allogeneic bone marrow derived MSC Haemopoietic stem cell transplant plus MSC infusion | I | 8 | Horwitz 2002; Horwitz 2002 |
| Orthopaedics      | Fracture healing; Joint resurfacing; Osteoporosis | MSC combined with/without calcium sulphate Allogeneic bone graft containing stem cells G-CSF-mobilised Haemopoietic stem cells with collagen scaffold for non-union fracture healing | I,II | 96 | Kuorroma 2014; Jones 2015; Bajada 2007 |
| Haematology       | Hematopoietic stem cell transplant (H SCT); Graft versus Host Disease (GvHD) | Prochymal (MSC) for severe refractory acute GvHD MSC infused with or following hematopoietic stem cell transplant | I, II, III | 240 | Prasad 2011; Ringden 2006; Perez-Simon 2011 |
| Ophthalmology     | Macular degeneration | ESC-derived retinal pigment epithelium | I | 2 | Schwartz 2012 |
| Gastroenterology  | Liver cirrhosis; Decompensated liver disease | MSC injected into peripheral or portal vein Autologous bone marrow mononuclear cells infused IV for liver cirrhosis UC-MSC IV in fusion in decompensated liver disease | I,II | 45 | Kharaziha 2009; terai 2006; Zhang 2012 |
|                   | Crohn's disease | Autologous hematopoietic stem cell transplantation for refractory Crohn's disease | I, II, III | 98 | Oyama 2005 |
| Endocrinology     | Diabetes (type 1 & 2) | Stem cell educator therapy with cord blood derived stem cells for insulin resistant type II diabetes Hematopoietic stem cell transplantation for new onset type 1 diabetes | I, II | 65 | Zhao 2013, D’Addio 2014 |
| Nephrology/Urology | Kidney transplant rejection | MSC based therapy to prevent rejection in living-related kidney transplants | I, II | 159 | Tan 2012 |

**MSC** mesenchymal stem cells, **BM** Bone marrow, **ESC** Embryonic Stem cells, **iPSC** induced Pluripotent stem cells, **IV** intravenous, **G-CSF** granulocyte-colony stimulating factor, **3D** 3-dimensional, **UC** umbilical cord
paradigm in healthcare from symptomatic treatment in the 20th century to curative treatment in the 21st century [13]. This is evidenced by the rapid increase in regenerative medicine clinical trials in each specialty [16, 17], which can be broadly classified as using either cell- or tissue-based products (Table 1). The Food and Drug Administration in the US and the European Medicines Agency have more complex classification systems of regenerative medicine products, including cellular therapy, gene therapy, stimulators of endogenous repair, biologic-device combination products, and human tissue and xenotransplantation [18]. Broadly, the regulatory requirements can be based on the pillars of sterility, stability and potency, and these need to be addressed prior to successful clinical translation in the future (Table 2).

Cell-based therapies work either via stimulation of endogenous repair through extracellular factors or differentiation and functional replacement of endogenous cell types [17]; they include stem cell implantation or infusion to treat hematopoietic diseases, cardiac conditions and Parkinson’s disease. Most of the pioneering work has been performed using haematopoietic stem cells due to the early bone marrow transplant work, making them the most well-studied stem cell type [19]. In particular, adult mesenchymal stem cells have gained interest as they avoid the ethical concerns of using embryonic stem cells, can be rapidly expanded in vitro and avoid immunogenicity. Studies have shown contradictory results on the efficacy of the transplanted cells, with patient variability with regards to response (Table 1); further work is needed to elucidate cell identity and health to ensure patient safety (Table 2).

The tissue engineering strand of regenerative medicine incorporates cells with biodegradable scaffolds to engineer replacement tissues like dermis or cartilage [20] and whole organs such as trachea and bladder [21, 22]. Limitations of synthetic polymer scaffolds, such as infection, extrusion and degradation product toxicity, have encouraged interest in decellularised matrices as well biologics for use as scaffolds as one of the more effective ways of replicating native tissue anisotropy [21, 22]. Decellularised matrices provide durability, enhanced integration and biocompatibility whilst avoiding allosensitization [21]. This may explain why many of the significant breakthroughs and first-in-man studies have utilized this technique combined with autologous cell-seeding with some success [21–23], and even showed promise in vitro for more complex structures such as pulmonary and aortic valves as well as whole organs such as heart and liver [24, 25]. However, despite early interest and investment in tissue engineering research, with annual R&D spending estimated at US$580 million, initial clinically applicable product release has been slow but steady [26].

### Controversies in the field

The regenerative medicine field has been shrouded in controversy. Significant potential gains have led to several high profile allegations of research misconduct [27, 28]. There is also a growing stem cell tourism industry based on unproven treatments that aims to capitalize on stem cell hype [29, 30]. Desperate patients would rather approach private clinics offering experimental stem cell treatments, with unproven safety and efficacy profiles, than wait for outcomes of clinical trials [30]. Media coverage and direct advertising of stem cell therapies as well as the political, ethical and religious controversies surrounding human embryonic stem cells, can contribute not only to increased public awareness but also inflated expectations of regenerative medicine products, and there continues to be a significant gap between the perceived and realistic benefits [31]. A concerted effort from the scientific community as well as robust outcome data from clinical trials will be needed to temper unrealistic claims [16, 17].

### Conclusion

Medical breakthroughs often require the convergence of multiple scientific advances for which interdisciplinary collaboration is fundamental. Similar to transplant medicine, regenerative medicine requires the convergence of a number of scientific disciplines, including stem cell biology, developmental and molecular biology, engineering

### Table 2 Overview of testing of regenerative medicine products to validate sterility, stability and potency

| Pillar | Obstacles | Method | Reference |
|--------|-----------|--------|-----------|
| Sterility | Sterility testing | Direct inoculation test in aerobic and anaerobic media | [32] |
| Stability | Chromosomal stability | Karyotyping | [33] |
| Cell metabolism | Mitochondrial bioenergetics | [34] |
| Safety | Animal testing to investigate interactions between native tissue and product | [35] |
| Potency | Cell identity | Flow cytometry and immunohistochemical analysis | [36] |
| Reproducibility | Purity and viability of cell population | [37] |
| Cell tracking | Fluorescent/superparamagnetic iron oxide cell labeling prior to animal implantation | [35] |
and biomaterials. Despite media hype, scientific overclaim and unrealistic expectations, which have been previously witnessed for a number of healthcare technologies, regenerative medicine continues to make steady progress reflected by the increasing number of clinical trials [16, 17]. Significant potential has been demonstrated in the cell therapy field to treat haematological, neurological and rheumatological conditions. The tissue engineering field, although holding great promise, still has some way to develop before the excitement surrounding novel biofabrication strategies, such as 3D bioprinting, is translated to patient care. The fast moving and versatile field of regenerative medicine is at the cutting edge of translational research and could shift the paradigm in healthcare from symptomatic to curative treatment. *BMC Medicine* is very interested in breakthroughs in regenerative medicine/stem cell therapy and submission of such relevant articles is encouraged.

Acknowledgements

Mr. Steve Atherton RMP, MIMI, Medical Illustrator, ABMU Health Board for Fig. 1.

Authors’ contributions

ZMJ, AA and WF undertook a literature review, collated data and wrote the final manuscript. ISW conceived the manuscript, contributed content and provided a critical overview. All authors read and approved the final manuscript.

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Competing interests

There are no sources of financial or other support, or any financial or professional relationships that might pose a competing interest for any of the authors.

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Received: 8 July 2016 Accepted: 5 August 2016 Published online: 10 August 2016

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