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Research review paper

Review: Development of clinically relevant scaffolds for vascularised bone tissue engineering

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ABSTRACT

Clinical translation of scaffold-based bone tissue engineering (BTE) therapy still faces many challenges despite intense investigations and advancement over the years. To address these clinical barriers, it is important to analyse the current technical challenges in constructing a clinically relevant scaffold and subsequent clinical issues relating to bone repair. This review highlights the key challenges hampering widespread clinical translation of scaffold-based vascularised BTE, with a focus on the repair of large non-union defects. The main limitations of current scaffolds include the lack of sufficient vascularisation, insufficient mechanical strength as well as issues relating to the osseointegration of the bioresorbable scaffold and bone infection management. Critical insights on the current trends of scaffold technologies and future directions for advancing next-generation BTE scaffolds into the clinical realm are discussed. Considerations concerning regulatory approval and the route towards commercialisation of the scaffolds for widespread clinical utility will also be introduced.

Contents

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1. Introduction

1.1. Bone tissue engineering

Organ shortage has been a growing problem all over the world due to the increasing incidences of organ failure and inadequacy of organ donors to meet the existing demands for organ transplantation. There has been an alarming increase in the number of patients on the waiting list in the past decade. In the United States, one patient is added on to the national organ waiting list every 10 minutes, while an average of 18 deaths per day were due to organ donor shortage. In 2011, it was reported to have a total of 28,535 organ transplants, with 79% of the transplants from deceased donors and a declining number of living organ donors (New York Organ Donor Network I, 2012). To overcome the dire shortage and long patient wait time for organ transplantation, tissue engineering strategies have emerged as an alternative over the years to replace, repair, restore diseased tissues and improve the quality of lives of patients.

Currently, the United States contributes 48.6% of the global market revenue to tissue engineering solutions and is the leading country dedicating 60% of the global tissue engineering expenditure to research and development (R&D) (Frost&Sullivan, 2012) (Fig. 1). With the increasingly active lifestyles, accidents, obesity and ageing population, orthopaedic solutions encompassing joint and bone repair, fractures, oral and maxillofacial treatment, osteoporosis and bone tumours remain to be in the greatest demand. Bone is the second most transplanted tissue in the world and the immense need for bone grafts and substitutes have been forecasted to reach $3.3 billion of revenues by 2013, with a compound annual growth rate of 13.8% from 2006 to 2013 in the United States (Frost&Sullivan, 2007). Globally, the statistics have reported an annual incidence of approximately 15 million fracture cases (O'Keefe and Mao, 2011), of which up to 10% are complicated by non-unions (Praemer et al., 1992; Salgado et al., 2004).

1.2. Non-unions

In addressing the challenges faced during BTE therapies, it is important to understand the underlying cause resulting in non-union repair and then tailor these BTE strategies accordingly. Typically, non-union fractures that fail to heal after 3–6 months and can be caused by various factors including surgical technique, pathological conditions and/or fracture types that vary between patients. These fractures can be broadly categorised as hypertrophic, oligotrophic and atrophic non-unions which are caused mainly by insufficient mechanical stabilisation, poor fracture apposition and poor vascularity respectively (Tseng et al., 2008). Table 1 compares the differences between the various non-union fractures.

1.3. Current strategies

A common characteristic of non-union fractures is the substantial gap between the fractured bone ends. To bridge this distance, a platform is necessary and to also serve as a temporary support at the defect zone, (Hutmacher, 2000; Langer and Vacanti, 1993). Current strategies for bone grafts include the use of autografts, allografts and synthetic grafts. Briefly, autografts are bone harvested from the own patient which remains to be the gold standard because of its osteoconductive and osteoinductive environment and non-immunogenicity (Rose and Oreffo, 2002; Schroeder and Mosheiff, 2011). However, there are disadvantages associated with limited quantities for harvest and donor morbidity (Laurie et al., 1984) which has resulted in alternative solutions. While allografts and synthetic grafts overcome these problems, they do not provide the necessary osteoinductive signals and vascularity, hence poorer bone healing compared to autografts (Damien and Parsons, 1991; Lane et al., 1999; Salgado et al., 2004). In addition, allografts may also suffer a possibility of graft rejection by the host immune system and disease transmission from donor to host (Rose and Oreffo, 2002), while synthetic grafts are subjected to fatigue and wear over time (Salgado et al., 2004).

Currently, most grafts still suffer a lack of integration with bone substitution often only at the ends of grafts, leading to non-unions (Muramatsu et al., 2003; Soucacos et al., 2006) with late graft fracture occurring as high as 60% at 10 years (Wheeler and Enneking, 2005). BTE has since emerged as an alternative for fracture repair to satisfy the current unmet need for BTE strategies. This review will focus on the scaffold aspect in BTE and will discuss in greater detail its design and current unmet needs for successful utility in the repair of large bone defects in the clinics.

2. Scaffolds

2.1. Scaffolds in bone tissue engineering

There has been increased interest in scaffold-based strategies for BTE as represented by the exponential rise in the number of publications over the past decade (Fig. 2A). Various scaffolds used in conjunction with stem cells and gene therapy strategies have demonstrated promising results of new bone formation and repair of segmental defects in both small and large animal studies (Tseng et al., 2008). The clinical trial using autologous bone marrow stromal cells showed a

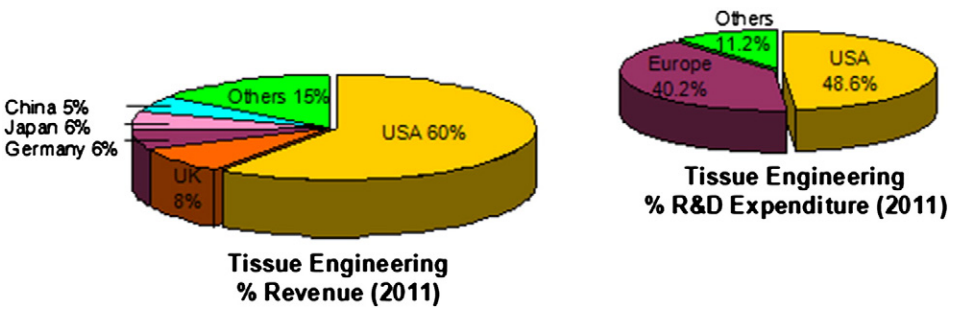

Fig. 1. Leading countries in the area of tissue engineering, as represented by their revenue and R&D expenditure (Frost&Sullivan, 2012).