A medical device for prefabrication of large bone grafts in modern medicine

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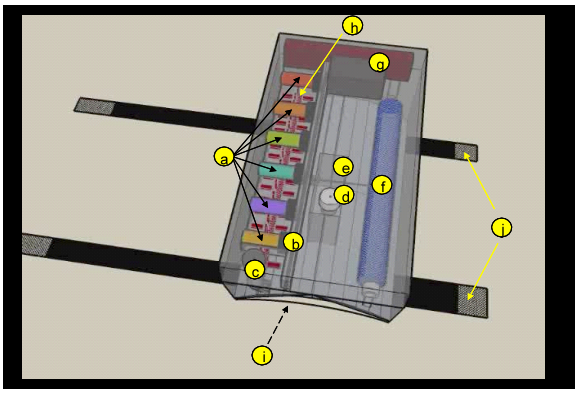
Introduction: Restoring the normal physiology of a part of the body damaged by physical, chemical or ischemic insult, or as a consequence of infections or genetic disease, is the essential aim of regenerative medicine. Translating advances in the laboratory into sound clinical practice presents series of formidable conceptual and technical challenges [1]. A critical issue in tissue engineering is the inability to maintain large grafts of living cells upon transfer from *in vitro* to *in vivo* conditions. This involves different parameters including scaffold. Thus the art of tissue bioengineering is: *How to place cells within the heart of the scaffold*? The design of the scaffold prior to exposure to cells is of vital importance. The scaffold must present a structure that promotes cell attachment, growth and differentiation, while providing a porous network for tissue ingrowths. Therefore, we think that integrating stem cells and vascular elements along a highly original blend of silk/collagen/hydroxyapatite knitted fibered scaffold in an (automated) unwinding fashion is an innovative process of constructing an "organised" and "layer-by-layer 3D construct" suitable for bone tissue engineering. Stem cells and growth factors play important role in tissue engineering. A stem cell is one that, through asymmetric mitotic cell division, is able to differentiate into several specialised lineages (multipotency), while retaining the potential for self-renewal [2]. The progression of cells from immature phenotypes to the highly specialised phenotypes present in tissues is a complex process governed by many factors. At present, combination therapies of stem cells and growth factor- release scaffolds tailored to promote angiogenesis and osteogenesis are under evaluation and development for the active stimulation of bone regeneration. Interaction between specialized cell and its environment is achieved through an array of receptor systems that are found on its outer membrane [3]. **Automated "biocreators":** Communication between the cell and ECM molecules influences various cellular processes, such as adhesion, proliferation, differentiation, migration, as well as growth factor and cytokine modulators [4]. The timing of these events critically affects tissue formation and remodelling, processes that are crucial for the integration of a tissue engineering scaffold into the surrounding environment including the short half life of growth factor (60-240 minutes). Finally, Vascular tissue engineering is one of the Holy Grails of tissue engineering. Still, the development of other novel, bioreactor-free methods of bone tissue growth, including vascular tissue assembly and rapid vascular biofabrication, represent probably the most important breakthroughs. **Presentation of our hypothesis.** The "Diamond Concept" in bone tissue regeneration includes four key factors. Based on the understanding of basic elements of tissue engineering construction, prefabrication and conditioning techniques and the nano- vascularisation of the scaffold, we hypothesise that a combination of cells, a solid multipolymeric scaffold as the "core element", that works like the ECM, and growth factors and a nano- vascularisation setting may eventually generate a large, ready-to-use *in vitro* and *in vivo* graft within a short period of time (16-20 weeks). Growth factors will provide step-by-step organisation of the bone tissue engineered construct (BTEC). The medical device, IV2B2TEC (Figure 1), will be automated and able to deliver GF via appropriate pumps under continuous flow and in physiological medium (under controlled pH, O_2, nutrients uptake and body temperature). As compared with conventional reconstructive methods, the strategy has the four following advantages. First, the volume and shape of TEC would be customised, and the osteogenic cells would be integrated inside the scaffold within less than 150-200 μm from newly formed capillaries by endothelial cells, as suggested in the literature. Secondly, grafting TEC to the bone defect would become a typical technique in surgery. Thirdly, it would promote bone healing in sites with poor blood circulation, particularly in post-radiated bone. Fourthly, it would be a novel armamentarium for regenerative medicine.

Figure 1. The prototype of the IV2B2TEC. **A**. Growth factors in recipients. **B**. Micropumps (black squares). **C**. Endothelial cells-seeding site (dark grey). **D**. Stem cells-seeding site (light grey). **E**. Stem cells chamber. **F**. Electrospinning fibers (blue). **G**. Electronics and motors. **H**. Hydroxyapatite scaffold (red). **I**. Intravenous connectors (under). **J**. "Velcro" forearm straps.



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