Quo Vadis Breast Tissue Engineering?

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Tissue engineering and regenerative medicine emerged at the end of the 20th century and early 21st century, aiming to augment the healing processes of the body to repair and/or regenerate injured or missing tissue. The idea of using tissue engineering approach for breast regeneration is not a new one — Langer, Vacanti and Atala some of the pioneers — yet never pursued such a project reviewing the current literature (Vacanti et al., 1998; Chhaya et al., 2015a; Chhaya et al., 2015b). There have been only a small number of teams truly investigating breast tissue engineering (Chhaya et al., 2015a), with many more teams researching scaffold and/or hydrogel based adipose tissue engineering more generally. Despite this, surprisingly little progress has been made towards viable clinical application, with as of yet only one human case study and only a few teams producing clinically relevant volumes of tissue. A key problem limiting tissue engineering is the regeneration of a vascular supply into a large volume 3D construct, which is necessary to supply nutrients for tissue growth (Chhaya et al., 2015a). This is especially important in adipose tissue engineering, with fat cells being highly metabolically active and undergoing necrosis when not adequately supplied with nutrients (Kakagia and Pallua, 2014). Morrison’s group then changed the concept and used a porous chamber and/or a scaffold. This concept was ultimately studied in a large preclinical animal model. In the results published in Plastic and Reconstructive Surgery, they demonstrated the production of 80 ml of soft tissue by encasing an AV loop (alone, with a muscle flap, or with a fat flap) and a biodegradable sponge-like scaffold in a hard plastic chamber, and implanting it subcutaneously in a pig model (Findlay et al., 2011). In a reply in the same journal, Yuan suggests that the success of this approach was due to the modulation of physical forces promoting adipogenesis (Yuan and Ogawa, 2015). In other work Yuan has shown that adipogenesis is inhibited by mechanical forces in contrast to musculoskeletal tissues that are known to proliferate in response to physical stress — this is consistent with the observation of volume loss in lipofilling (Yuan and Ogawa, 2015). And the encouraging results have been used by the group to generate a clinically relevant volume of adipose tissue, which they herald as paving the way to human trials presented in this issue of EBioMedicine (Morrison et al., 2016). Although we aim for regeneration as an ultimate result, this is very hard to accomplish.

While the work of Morrison et al. (2016) in EBioMedicine is significant as the first group to engineer clinically relevant volumes of adipose tissue in humans, its widespread clinical application of the current technique is questionable. This approach requires the implantation of what could be defined as a hard casing that may not be comfortable for the patient, as well as an additional operation for removal. The mixed clinical results may be related to that the authors changed their original chamber concept, which was studied in the pig model to a dome shaped porous sheet, which was completely open towards the chest wall of the patient. Furthermore, the authors did decide against using a scaffold even so the pig results were better in the scaffold group. One might get the impression that the authors are admitted contrarians to the current knowledge in scaffold design and fabrication. A well-designed fully interconnected large pore network allows the formation of a blood clot inside the scaffold architecture (Holzapfel et al., 2013). The clot consists of platelets embedded in a mesh of cross-linked fibrin fibers, together with a growth-factor rich cocktail of fibronectin, fibrinectin and thrombospondin. It is well known in the literature that the fibrin network and the associated growth-factor cocktail stimulates a strong angiogenic response and induce highly organized connective tissue to penetrate into the affected region. As seen by the others in previous animal studies and well known by another concept called guided bone regeneration (GBR) in which space maintain concept has been used clinically with high success for decades (Nyman, 1991). GBR uses biodegradable or originally non-resorbable membrane that acts as a barrier to prevent soft-tissue invasion into the defect and forms a chamber to

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guide the bone regeneration process. In a landmark study (Buser et al., 1990) it was shown that in large bone defects, bone formation occurs only to the marginal stable zone with a central zone of disorganized loose connective tissue, and, therefore, additional use of bone-graft materials is required in these cases, with the bone graft acting as a scaffold for the formation of blood clot in combination with a stable fibrin network which is a condition sine qua non to allow mesenchymal precursor cells to migrate into the defect and develop the microenvironment for osteoinductive extracellular matrix which ultimately lead to large volume bone formation (Nyman, 1991). The regeneration of any large volume mesenchymal tissue is based on certain biological principles, which should be taken into account for any tissue engineering strategy, which aims at clinical translation (Yannas, 2013).

In the past decades, a series of transformations have changed the way in which researchers decipher diseases and develop new treatments. Among other significant shifts in biomedical research, scientists, educators as well as funding agencies are more mindful of the necessity of aligning highly qualified interdisciplinary teams, encouraging people with very different expertise and technical skills, such as biologist, engineers, chemists, physicists, mathematicians, medical doctors and veterinary surgeons, to work together towards advancing our knowledge in medicine. This becomes particularly important when aiming to develop patient-specific platforms for personalized medicine. As seen in the current study, the challenges that arise when working in such interdisciplinary teams are not trivial, and among other tasks a lot of work still needs to be done in order to bridge more effectively the existing gap created by the different technical terminologies and methodologies specific to each discipline.

The future of tissue engineering and specifically the clinical companion regenerative medicine relies upon the investment in continuing to make it the pinnacle of biomedical research. Rapid advances of translational research into the development of tissue engineering technology platforms have the potential to start a new era in personalized medicine. Regenerative medicine will thus grow in conjunction with the realization of individualized medicine paradigms to create predictive, personalized, and preemptive solutions for tailored delivery of patient-specific health care. In closing, the authors concluded rightly that the first steps are completed yet ongoing research is required aiming to establish an ideal chamber concept for breast/adipose tissue regeneration with optimized characteristics in terms of biocompatibility, space-making, tissue integration and clinical manageability for maximum clinical efficacy and safety.

Disclosure

The author declares to have an active research program on breast tissue engineering and that he is a founder of the spin off company Bella Seno.

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