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Tissue Engineering: Then, Now, and the Future

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Impact Statement

This ''invited submission'' concisely reviews the author's involvement in the early era of tissue engineering and summarizes his perspective. He points out the journal was present in this early era and that it functions as a viewing chamber for seeing the last 25 years of progress and that it stands ready to provide viewing of the next 25 years.

As an undergraduate, I started doing research in 1958. These intervening 60 years have brought enormous changes to our approach and delivery of scientific data, discovery, and understanding of the biologic world. The engineered recreation of a tissue has been an experimentalist's goal since the dawn of time where fixing broken bones or providing a leg amputee with a peg leg is now superseded with motorized jointed creations. In this regard, the Capua leg is the oldest artificial limb constructed of bronze and dating back to 300 BC although the Egyptians certainly used crutches and crude forms of prosthesis.[1] I see the current crop of metal hip implants with their pseudo femoral heads and long intramedullary stems as merely a miniaturized refinement of the Capua leg. The long-term challenge is to put some meat (muscle, tendon, and ligament) on these prosthesis that have neural connections. Indeed, such prosthesis now have small servomotors that serve as contractors instead of live innervated muscle tissue.[2,3] Yet no tissue-engineered muscle is available to replace excised or inoperative tissue. Why is there no muscle product on the market?

The history of tissue engineering is complicated and the early days are reviewed by Charles Vacanti in 2006 in JCCM[4] with the first published article by JP Vacanti in 1988.[5] The first tissue engineered products that I was involved with were ''skin equivalents'' brought forth by Burk, Yannos, Green, and/or Bell.[6–8] In fact, in the early 1990s while I was trying to commercialize human mesenchymal stem cells (hMSCs), Eugene Bell, the founder of Organogenesis, Inc, brought me to Boston and tried to hire me as the VP for Research and Development. The very clever skin equivalent produced by Organogenesis was culture-expanded foreskin keratinocytes on top of a collagen gel into which foreskin dermal fibroblasts had been seeded.[9] This product eventually was provided for several tens-of-thousands patients in the United States and Europe and through the 1990s was refined and thrived. Eventually, the cost of manufacturing exceeded the reimbursement, which, as you might expect, caused a business dilemma.

The other skin-like equivalent was introduced by the La Jolla, CA, company Advanced Tissue Sciences (ATS) that designed and developed the world's first upscaled manufacturing facility for tissue-engineered products in collaborations with Smith & Nephew, Ltd. In 2003, after raising >$300 million, ATS closed its doors.[10]

There are many lessons to be learned from all of the pioneering tissue engineering companies. The two prominent pressures are the ''market,'' which always wants a large return on their investment and high profitability, and the concept of ''scale-up.'' In this context, Anthony Atala and his colleagues worked long and hard to show how to tissue engineer unique organs such as a bladder or a uterus and the company Tengion, Inc. was founded in 2003 and declared Chapter 7 bankruptcy in December 2014.[11,12] Several patients have successfully received organs,[13] but the ''market'' pressure was too intense to sustain this effort.

In the context of the 1990s when the journal *Tissue Engineering* was born, my colleagues and I started Osiris Therapeutics, Inc. in December of 1992 as a bio-orthopedic tissue engineering company. We imagined that we could obtain massive numbers of autologous MSCs from a donor and through cell culture expansion of these cells they could be used to tissue engineering replacement of skeletal tissues[14–16] and to provide support for bone marrow transplantations because MSCs were shown to support hematopoietic cell expansion and engraftment.[17] We erroneously thought that MSCs would differentiate into bone marrow support tissue *in vivo* and, thus, the first-in-man use of MSCs by us was to support and enhance bone marrow transplantation.[18] When MSCs were added to the hematopoietic progenitors of a bone marrow transplantation, they did, indeed, enhance engraftment and recovery. We now know that MSCs have a powerful immunomodulatory and tissue regeneration support capacity and that allogeneic cells function similarly to autologous

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MSCs.[19] It is now known that MSCs are derived from perivascular cells on capillaries and sinusoids in marrow and all other vascularized tissues.[20] Interestingly, MSCs can be derived from any vascularized tissue with fat providing 300- to 500-fold more MSCs per milliliter of tissue than bone marrow.[21] Others have shown that MSCs are not multipotent *in vivo*.[22]

We have reported how to expose marrow MSCs to different culture conditions to cause their *in vitro* differentiation into cartilage, bone, tendon, fat, and other mesenchymal tissues.[15,16] The MSCs are so phenotypically plastic in culture that others have reported that marrow MSCs can differentiate into neural cells.[23] We have described a pellet culture system that can be optimized to differentiate MSCs from marrow into a cartilage lineage pathway.[24] This cartilage is not suitable for implantation into knees since the cells will become hypertrophic and be replaced by bone *in situ*; recently, we have determined that exposure to fibroblast growth factor-9 or -18 will inhibit this lineage hypertrophy.[25]

One of the technical issues with tissue engineering is to have an assay to determine when the tissue is suitable (phenotypically and mechanically) for implantation. To develop nondestructive interrogation of cultured cartilage tissue starting with MSCs,[26] we started the Center for Multimodal Evaluation of Engineered Cartilage (CMEEC) as supported by NIBIB. The technology for evaluation of an *in vitro* maturing tissue focuses on quantitating chemical, biochemical, and mechanical parameters to predict when the intact tissue is suitable for implantation. We have used 1-month-old neonatal cartilage as our molecular standard to help redirect MSCs in culture into the appropriate articular cartilage lineage and have reasoned that this neonatal cartilage has all of the instructional capability to cover the joint of a 5- to 10-year old. In this case, we have identified both transcription factors and proteins that are expressed as transcripts in neonatal cartilage that are not found in pellet-cultured marrow MSCs.[27] These molecules have become the active agents and targets to obtain in the successful tissue engineered construct (in progress).

Based on the aforementioned, I can say that we, as an industry, have slowly and painfully made our way through the 1990s and the 2000–2010s. We have made great technical strides to produce engineered tissues that are quite useful medically (e.g., bladders and skin equivalents) but are not market sustainable. The journal, *Tissue Engineering*, has been the viewing chamber for cataloguing all of these scientific and technical achievements for the past 25 years. No doubt, the next 25 years will bring currently unimagined progress.

Disclosure Statement

No competing financial interests exist.

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