Tissue Engineering

Is the Allure Only Skin Deep?

The field of tissue engineering had a remarkable run in the 1990s but has been confronted with serious challenges in more recent times. This overview frames the issues likely to determine the long-term success of the field.

The strategic vision of tissue engineering is to combine the ready availability of contemporary man-made devices for organ replacement with the biologic function of living cells. Early attempts to implement this approach in animal models or in "one-off" human experiments were highly successful, perhaps too much so. For example:

- As early as 1978, Chick demonstrated excellent short-term secretory dynamics with an artificial pancreas in diabetic rats. By the early 90s, several groups had advanced the approach to 3 month survival and normoglycemia in diabetic rodent models.
- In the late 70s and early 80s, Bell, Yannas, and other MIT scientists developed the concept of living skin equivalents and demonstrated successful in vivo application in rodent models.
- By the 90s, the Vacanti brothers and Langer implanted chondrocyte-loaded matrices into human recipients, replacing part of a rib cage and the phalynx of the thumb. The latter operation was performed live on "Good Morning America."

Coming as it did in the roaring 90s, the combination of a highly appealing rationale with success in high-profile "proof of principle" experiments was grist for the investor mill. Tissue engineering became fundable and bankable, and start-ups proliferated and prospered.

Over 60 companies were formed and financed. A dozen of these went public, and in the year 2000, the net capital value of these 12 firms exceeded $2 billion. At its peak, total employment in the field approached 3000 scientists and support staff.

Cumulative investment between 1990 and 2000 exceeded $3.5 billion. This was largely, though not entirely, a private sector enterprise; government spending never reached 10% of the total. The United States dominated the field.

Comparison with the dot.com bubble of the late 90s is tempting but misleading. The day-to-day business approach of tissue engineering companies was quite different from the now discredited behaviour of the dot.com's.

Most tissue engineering firms were managed by seasoned biopharmaceutical executives. There was accountability, peer review, achieved milestones, and credible bookkeeping, and in many cases, operating costs for the startups were offset by revenue from corporate partnerships. Most importantly, the industry made considerable progress in moving technology from concept into successful preclinical products.

However, as clinical trials progressed, performance became less sanguine, and today the industry faces three serious challenges: (1) early products have fared poorly in the market, (2) several high-profile devices have failed to win FDA approval after clinical trials, and (3) tissue engineering's product niche is being compressed by advances in first-generation organ replacement and by the "new new biology" based on stem cells and therapeutic cloning.

The accompanying table lists details of the seven tissue-engineered products that are currently commercially available. Four of these are FDA approved; the remaining three are being sold in Europe. Five of the seven are for skin replacement or repair in patients with burns or non-healing skin ulcers. These living skin equivalents (LSEs) are planar and avascular and thus avoid some difficulties encountered with more complex tissue-engineered products. The relative lack of complexity in skin products, and their predominance in the commercial market, have lead to the observation that "tissue engineering is only skin deep."

The first tissue engineered product to be approved was Carticel® cartilage replacement. Carticel is based on autologous chondrocytes proliferated in vivo after harvest by arthroscopic biopsy from the patient's femoral condyles. Its primary indication is repairing cartilage in knees damaged by injury or trauma in relatively young recipients; expansion to the larger rheumatoid arthritis population was an unrealized possibility.

In 1998, Apligraf® gained FDA approval and is still the only LSE product with enough post-approval history to assess its commercial performance. Apligraf is targeted at diabetic and venous stasis ulcers. It consists of living fibroblasts suspended in a collagen film with an overcoating of keratinocytes. Both the fibroblasts and keratinocytes are harvested from neonatal foreskins.

Although these two products are technically innovative, their market performance has been disappointing. Their combined annual

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COMMERCIALLY AVAILABLE TISSUE ENGINEERED PRODUCTS

Product	Manufacturer	Introduction	Indications	Cells	Biomaterials
Cartilage					
Carticel®	Genzyme Biosurgery Cambridge, MA www.carticel.com	1996	Acute cartilage trauma in young adults	Autologous cultured chondrocytes	None
MACI® *	Verigen Leverkusen, Germany www.vtsi.de	1999	Cartilage repair	Autologous chondrocytes	Collagen
Living Skin Equivalent					
Apligraf®	Organogenesis Canton, MA www.organogenesis.com	1998	Diabetic and venous stasis ulcers	Allogeneic fibroblasts and keratinocytes	Bovine collagen
EpiDex™*	Modex Therapeutics Lausanne, Switz. www.epidex.com	1999	Alternative to split-thickness skin graft	Autologous keratinocytes	None
Dermagraft®	Advanced Tissue Sciences, La Jolla, CA www.advancedtissue.com	2001	Diabetic and venous stasis ulcers	Allogeneic fibroblasts	PLGA degradable polymer
OrCel™	Ortec New York City www.ortecinternational.com	2001	Donor site wounds in burn patients	Allogeneic keratinocytes and fibroblasts	Bovine collagen
Epibase®*	Laboratoire Genevrier Sophia Antipolis, France www.laboratoires-genevrier.com	—	Wound healing	Autologous keratinocytes	None

* Not available in the U.S.

sales in 2001 was less than $40 million. Neither is profitable. Genzyme Tissue Engineering, which introduced Carticel, was merged with Genzyme Surgical Research. Organogenesis, the manufacturer of Apligraf, has been forced to restructure and is operating under a "going concern" warning from its auditors.

Two LSE products have received approval within the last 6 months: OrCel™ from Ortec and Dermagraft® from Advanced Tissue Sciences. Sales figures are not yet available, but Ortec is also operating under a "going concern" warning, and ATS has announced that it is diversifying into the cosmetics business, attracted by the potential for short-term revenues and fewer regulatory barriers.

Three tissue-engineered products are available in Europe, one cartilage replacement product and two LSEs. All are based on autologous approaches, where the recipient's own cells are harvested, proliferated in vivo, and re-implanted.

European firms can bring products to market quickly because regulatory barriers are minimal. However, routine reimbursement often depends on controlled trials. The European firms combined sales in 2001 were almost certainly under $1 million.

In aggregate, then, the total sales of all tissue-engineered products in 2001 was about $40 million, and all seven firms marketing products in the field were operating at a loss.

Why such lackluster performance? Were the approved indications too narrow? Are the products ineffective or perhaps simply not cost effective? Did firms ignore reimbursement considerations in designing the clinical trials? Is the upfront cost of FDA approval (roughly $100 million) simply too high to be recovered by products with the slow growth curve of medical devices? Does the problem lie with ineffective efforts in sales and marketing?

Such questions lack a clear answer, and it is still possible that one of the new products will find its wings and soar. What is clear, however, is that sales in the low tens of millions of dollars simply cannot continue to support and justify annual development expenses and cumulative burn rates that are at least an order of magnitude higher. Tissue engineering very much needs a success story.

A view of the pipeline of future products, and recent dropouts from the pipeline, is equally disconcerting. Two promising devices recently failed to win approval after completing phase III clinical trials. CereCRIB®, which is an encapsulated bovine chromaffin implant for treating chronic pain, and HepatAssist®, a bioartificial liver using an extracorporeal membrane containing porcine hepatocytes as a bridge to transplantation, both showed efficacy in subsets of patients but not enough to meet phase III statistical end points. Also, Diacrin's NeuroCell® neuro-

logical implants were placed on hold in the midst of phase II/III trials.

Two bladder valve repair products from Curis, based on chondrocytes suspended in alginate, completed phase I or II trials and were simply abandoned because the firm did not believe that it could recover the cost of further clinical trials from product sales. Some of the LSE products are undergoing trials to expand their indications, but no new tissue-engineered product is currently in phase III trials.

The average cost for clinical and preclinical trials for tissue-engineered products is approximately $100 million. This is considerably less than the $400 to $800 million spent to bring a pharmaceutical product to market, and some believe that larger budgets for clinical trials for tissue-engineered products would translate into a higher success rate.

Certain tissue engineered products are treated as devices, and others as biologics, which then follow the phase I-II-III cycle for drugs. The FDA is aware of the procrustean nature of this regulatory scheme but lacks the ability to custom-tailor new approval procedures for new technologies.

Some argue that the regulatory process is doing what it should (*"protecting the public from devices which are unsafe or not proven effective"*), while others hold that the regulatory process is itself the greatest barrier to tissue engineering (*"delaying worthwhile products at enormous expense and keeping other worthwhile products off the market for procedural rather than substantive reasons"*). The truth most likely lies between these extremes.

From one vantage point, the current difficulties of tissue engineering may simply be "going in" problems, which will be quickly forgotten once the field achieves commercial success. In this context, it is unwise to fixate on short-term, transient issues.

A different perspective is that tissue engineering, like any new technology, has a finite window of opportunity, and the field must succeed while that window is open or not at all. And, in the case of tissue engineering, progress in two related therapies appears to be pushing the window shut: first-generation organ replacement technology and therapeutic cloning.

Consider Parkinson's disease, an area viewed as promising for tissue engineering because numerous animal studies have demonstrated symptomatic relief with approaches based on implantation of dopaminergic neurons. Despite these promising results, no tissue-engineered implant has moved beyond phase I human trials. In contrast, deep brain stimulation using a modified pacemaker (which does not involve tissue engineering) recently won FDA approval for treating Parkinson's tremor and is quickly moving toward other parkinsonian indications.

Or consider the tissue-engineered vascular graft for coronary artery disease. Despite excellent progress in animal models, these grafts are still in the preclinical stage and have yet to be tried in humans. Meanwhile, stents with anti-inflammatory coatings are near clinical introduction. If coated stents perform as well in practice as early reports suggest, the need for a tissue-engineered vascular graft may be much diminished.

And still other groups are focusing on pharmacologic approaches for coronary artery disease, including the application of cholesterol-lowering drugs to stents and the experimental use of angiogenic factors to grow new vessels rather than surgically bypass clogged arteries. It will do tissue engineers little good to develop a coronary vascular graft if bypass surgery becomes a progressively marginalized intervention.

Stem cells and therapeutic cloning represent the final unknown in an assessment of the prospects of tissue engineering. Will the promise of these biological technologies be part of tissue engineering, or is it a powerful competitor?

The issue is more than semantic. Only a handful of established tissue engineering firms appear to have shifted their focus to this new technology. Similarly, startups founded to exploit the therapeutic applications of stem cells are solidly positioned in the domain of "applied developmental biology." Most employ no biomedical engineers; the culture and personalities of tissue engineering have not merged with those of stem cell biology.

As an historical analogy, not one of the top five producers of vacuum tubes in the 1960s successfully made the transition to become a leading transistor or integrated circuit company. This should be a sobering thought for tissue engineers.

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