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# The first stem cell-based tissue-engineered organ replacement: implications for regenerative medicine and society

*“In June 2008, a young woman with end-stage bronchial disease received a decellularized donor tracheal graft that had been repopulated with autologous cells, many of which ... were derived from mesenchymal stem cells; 6 months later, she is well and actively caring for her two young children.”*

In June 2008, a young woman with end-stage bronchial disease received a decellularized donor tracheal graft that had been repopulated with autologous cells, many of which (chondrocytes) were derived from mesenchymal stem cells; 6 months later, she is well and actively caring for her two young children. She has no signs of stenosis or rejection and is on no immunosuppressive medication [1]. This success has been hailed as a breakthrough in some quarters, but what are the real implications for regenerative medicine and for society?

Total, functional organ replacement has represented an elusive nirvana for surgeons for decades. Clinical allografting has led to new life for millions of recipients, but in exchange, immunosuppressant medication has many side effects, including a reduction in life expectancy of 10 years on average. The possibility of using autologous cells, whether embryonic or adult stem cells or, alternatively, mature cultured cells to repopulate organ grafts has now become a reality. This presents a future in which conventional transplantation will become, if not obsolete, either complimentary or even second choice to customized, tissue-engineered replacements. Whilst the trachea may be viewed as a relatively simple organ, solutions to engineering the muscles and nerves to drive bowel, bladder and larynx replacements are also close to the clinic [2,3]. Never has there been a more exciting time to be involved in surgical science.

The experience also has major implications for stem cell biology. The realistic prospect of clinical translation gives new impetus to the myriad of cutting edge groups who aim to generate a deeper understanding of the way in which stem cells of all types interact with the human environment in which they are inserted. By close scrutiny of the biological outcomes of our patient's graft and of those implanted in her successors, hypotheses

of true clinical relevance may be generated and tested to feedback into the clinic. Thus, the modus operandi of the 'human bioreactor' may become clear and harnessed for technological refinements to the transplant process.

This first stem cell-based tissue-engineered organ replacement was still based on a donor tracheal graft. Nevertheless, the clinical success might be an important step to a future practice of fully tissue-engineered organ replacements not depending on donor grafts anymore. The implications of such a practice for society would be twofold.

First, such a practice might provide solutions for many of the problems of conventional organ transplantation. In the last few decades enormous progress has been made in the field of conventional transplantation. This has led to an enormous increase in the demand for transplantable organs. However, the supply of transplantable organs has not grown with the same speed [10]. The shortage of donor tissue and organs is becoming more and more acute with each passing year. This poses a huge problem to patients, the transplantation community and society as a whole. In addition, conventional organ transplantation has triggered a lot of difficult ethical problems. For example, there are issues around the definition of human death, questions about our obligation to donate organs and problems of distributive justice. Clearly, a successful practice of fully tissue-engineered organ replacements might more effectively deal with the problem of organ and tissue shortage and would not pose the same ethical problems.

Second, populations are aging, not only in the West but worldwide. At first sight, this seems to be a good thing. Aging populations, however, show an increasing incidence of damaged and lost tissues and organs. This problem can be considered as one of our biggest future health

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challenges. Tissue-engineered organ replacements would be a highly valuable asset in tackling this problem. However, there are still important open questions.

Our successful use of decellularized cadaver tracheal tissue as the scaffold for our tissue engineering raises some fundamentally important questions: Did the donor scaffold contribute only shape or did it also contribute functional proteins such as sequestered growth and angiogenic factors? Did the micro- and nano-scale organization of the decellularized trachea play a role in the tissue-engineering process? If the scaffold did indeed supply rather more than a macro-scale template, then we must ask if it will ever be possible to engineer a scaffold from synthetic materials or natural molecules that can play the same role. If we cannot reproduce the sophistication of the natural material in an artificial scaffold then we may have to rely on cadaver material for the foreseeable future.

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Success for this one recipient has also led to unintended spin-offs for the public perception of stem cell science, and for the ethical framework within which translational scientists and clinicians work. The positive publicity that surrounded this experience permitted the difference between adult and embryonic stem cells to be understood by a wide audience, whilst the debate in internet chat rooms between those for and against embryonic stem cell applications became slightly less based on fear and preconception and slightly more on the evidential base. The courage and perseverance required to battle through the regulatory and clinical barriers to performing such innovative surgery may also pay-off by encouraging other groups hovering on the brink of tissue-engineered organ replacements to step over the threshold. Furthermore, it may assist their respective regulators and funding bodies to look at their plans in a more positive way. Thus, a cohort of such technologies may appear in a shorter space of time than might otherwise have been the case.

For the broad field of regenerative medicine, the sights have been raised; raised from the bench-tops to the faces of the patients in the clinic next door. There remains a necessary, but comfortable, home in cell biology and early-phase animal experimentation for stem cell science, but from somewhere funding and regulatory support needs to be found to help others negotiate the overgrown path between the two arenas, via preclinical studies and scale-up/automation facilities. Those countries that have seen this reality early may steal a march on other nations who rest on their laboratory laurels. President Obama's position on stem cell treatments is likely to permit the USA to gear up in this field [102]. However, such competition is healthy and if it helps to generate appropriately commercialized functional tissue-engineered organ replacements to clinics more quickly, then it is the patients who will benefit the most.

Meanwhile, for one young woman from Colombia and her children, the implications of the first stem cell-based organ transplant are quite clear.

#### Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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