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Tracheal bioengineering: the next steps. Proceeds of an International Society of Cell Therapy Pulmonary Cellular Therapy Signature Series Workshop, Paris, France, April 22, 2014

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Abstract

There has been significant and exciting recent progress in the development of bioengineering approaches for generating tracheal tissue that can be used for congenital and acquired tracheal diseases. This includes a growing clinical experience in both pediatric and adult patients with life-threatening tracheal diseases. However, not all of these attempts have been successful, and there is ongoing discussion and debate about the optimal approaches to be used. These include considerations of optimal materials, particularly use of synthetic versus biologic scaffolds, appropriate cellularization of the scaffolds, optimal surgical approaches and optimal measure of both clinical and biologic outcomes. To address these issues, the International Society of Cell Therapy convened a first-ever meeting of the leading clinicians and tracheal biologists, along with experts in regulatory and ethical affairs, to discuss and debate the issues. A series of recommendations are presented for how to best move the field ahead.

Key Words: *consensus, trachea, tissue-engineering*

Introduction

End-stage tracheal disease necessitating replacement of diseased or damaged tissue is a rare but devastating situation. Despite recent advances in surgical techniques and *ex vivo* tracheal engineering, replacement continues to present major scientific and technical challenges [1–4]. As such, bioengineering this seemingly uncomplicated yet enigmatic organ has become emblematic of progress and also the challenges in regenerative medicine. Reasons for this include the alluringly straightforward demands of replacing a "simple" tube, the fact that pioneers have emerged from specialties focusing on the airway and cardiothoracic surgery, but most importantly because end-stage disease presents the most serious and sometimes acute threat to life. Thus, tracheal bioengineering has leant itself to compassionate use applications in a way that would be hard to justify for many other potential organ replacement targets. This has led not only to important leaps but also exposed important gaps in both scientific and clinical understanding [1–3]. Thus, progress in this "niche" area remains of high interest to the world's regenerative medicine community (Figures 1–4).

One of the corollaries of this path has been that a number of groups in Europe and North America have taken different routes to the clinic. The various approaches have included the use of allografts, preserved homografts and of *ex vivo* tissue-engineered tracheas that are based on both biologic (decellularized) and

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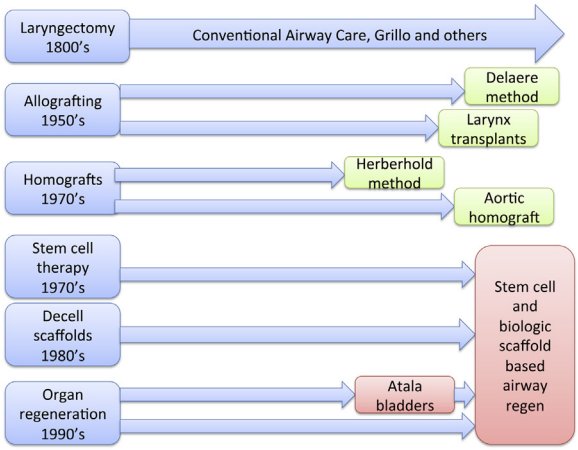

Figure 1. Evolution of technologies leading to present options for tracheal bioengineering and transplantation.

synthetic scaffolds populated with a range of different cell types [1–4]. These approaches have yielded varying degrees of success, but, as yet, there is no clear optimal technique, and each has pros and cons for use. In particular, whether any one approach can result in an implanted graft with the full range of appropriate cellular and physiologic functions remains unclear and has provoked significant, sometimes acrimonious, debate and discussion [5,6]. A variety of growth factors and other agents have been used as adjunct treatments along with surgical implantation. These include both treatment of the graft either before or during implantation as well as systemic administration to the recipient. However, the utility, and in some instances the rationale, of these approaches is not clear and may be based on only limited pre-clinical data. Furthermore, clinical reports are sometimes lacking in

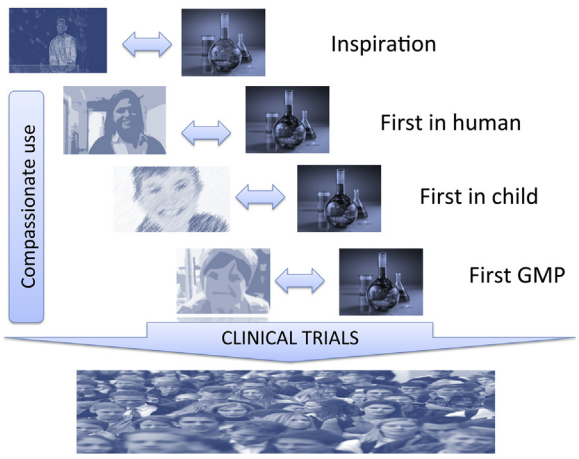

Figure 2. Pathway to clinical trials for biologic scaffold-based tissue-engineered tracheal replacements (Karolinska and London groups). At each stage, observations of implanted patients led back to the laboratory for further hypothesis testing and refinement of technology. The return of scientific information from future clinical trials of all bioengineering technologies is critical for a better mechanistic understanding ("reverse translation"). GMP, Good Manufacturing Practice.

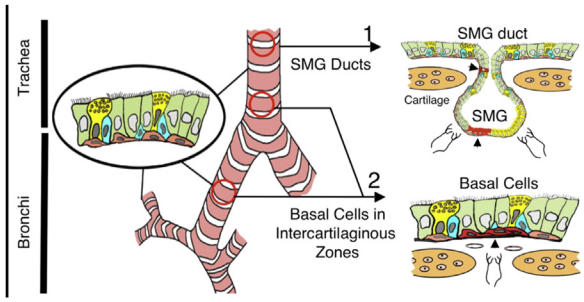

Figure 3. Schematic of the trachea shows representative proposed stem/progenitor niches. The identity and function of the range of cells that can participate in upper-airway repair and regeneration is the subject of ongoing research. SMG, submucosal gland.

key data that can help gauge the success or highlight the problems with current implantation approaches.

In parallel, discovery and translational scientists and the emerging regenerative medicine industry have made important recent breakthroughs that will significantly improve the underlying science. This is especially true of tracheal epithelial and stromal biology and upper-airway progenitor cells and will have implications for the design and application of bioengineered tracheas over the next decade [7–9]. These are rapidly progressing "cutting edge" areas of research favorably looked on by the National Institutes of Health and other relevant funding agencies.

To date, most of these international efforts have occurred in relative isolation, with little sharing of ideas and methodologies between the basic/translational scientific communities and the clinical and commercial efforts. Furthermore, more extensive communication must occur between the different clinical and commercial efforts. For example, clinical inclusion criteria, techniques used and reported outcome measures, particularly assessments of graft recellularization and optimal physiologic functions, vary widely. Some of this may have been necessary, given the nature of compassionate applications of tracheal grafts and the extraordinary speed of change in regenerative medicine science. Nonetheless, this confounds comparative assessments of the different approaches used, impedes more rapid coordinated progress and promotes unconstructive argument.

Thus, the Pulmonary Committee of the International Society for Cell Therapy convened a meeting to bring together the leading experts in clinical applications of bioengineered tracheas, leading scientists studying tracheal biology and industry leaders. The specific goal was to discuss and debate the current state of knowledge and to devise effective means of combining efforts to most effectively move the field of tracheal repair forward. These discussions were accompanied by presentations on regulatory and ethical issues with the goal of contributing to