Invited Commentary

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Re: Dua et al. In-vivo Oesophageal Regeneration in Human Subject with Four-year Follow-up. Manuscript Number: THELANCET-D-15-05316R2

Dua and colleagues present a timely paper describing a novel approach to oesophageal reconstruction with a surprising result. The subject is a man who required anterior spinal plating following a car accident. Some years' later, the plates became infected, and this resulted in a large upper oesophageal and pharyngeal defect. Whilst it was possible to treat the infection and repair some of the pharynx, the remaining oesophageal defect made eating impossible and (potentially fatal) mediastinitis likely. The authors fashioned a repair composed of an expandable stent wrapped in a commercial extra-cellular matrix preparation (AlloDerm®, LifeCell Corporation, NJ) and coated with platelet-rich plasma gel. The stent was removed at two years, and four years' later the underlying oesophageal tissue appeared to have regenerated in all its layers, as measured by ultrasound. Oesophageal manometry and impedence was approaching normal in the repaired zone when swallowing liquids and at the time of reporting he was maintaining his weight through oral feeding alone[1].

A key to understanding the contribution of the implanted graft material, and an interesting approach, lies in the endoscopic ultrasound data. This appears to confirm complete regeneration of all layers of the oesophagus using a cell-free engineered construct, which is remarkable given the presumed complexity of this organ. Previous authors have used AlloDerm® to repair muscle defects in congenital diaphragmatic hernia with very high recurrence rate[2]. Based on the ultrasonic images presented here, it is not possible to completely exclude that the engineered construct may have led to a fibrotic residuum, rather than a normal 5-layer wall throughout. The ultrasound data is not presented at multiple levels and this limits the conclusions somewhat, as readers may have liked to assess the appearance of the whole oesophagus and not just that segment assumed to the 'regenerated' section. However, if the images are truly representative and backed in larger numbers by physiological data, then a technically straightforward, though protracted, new tissue-engineering treatment could become available.

The ethics of compassionate use implantation of tissue-engineered organs has come under intense, but necessary scrutiny[3]. Proponents argue that the early use of new technologies in patients, where those patients have no suitable conventional treatment, provides safety and potential efficacy data for formal clinical trials in a far more relevant way than that delivered by animal and bench-top (e.g. 'organotypic') models[4]; that results from 'one successful human (as here) is worth more than that of ten thousand mice'. However, such seriously ill patients are generally not 'typical', with highly disordered physiology and, in the case of surgical disorders, anatomy. Thus, sceptics argue that you cannot

understand the underlying mechanisms for success or failure in such patients, and that well-designed animal studies are the most appropriate precedents to early phase clinical trials[3].

Schwartz described three categories of surgical innovation: practice variation (minor changes to technique covered by routine consent forms), experimental research (formal trials), but also a Transition Zone in between these two positions[5]. She outlines the ETHICAL (Expertise, Technical skill, Hazard awareness, Informed consent, Conflict of interest avoidance, Analysis of results, Literature publication) model for the appropriate conduct of such studies, which seeks to protect both patient and surgeon, as well as maximise learning, and scientific hypothesis generation, from the experience.

The present case falls into this Transition Zone. The authors used local compassionate use guidance to apply technology that might otherwise have taken years to go through formal, and funded, clinical trials[4]. Both the FDA and the local IRB appear to have been consulted and content for the implant to go ahead, and dedicated consent was obtained. The surgeons were technically expert and had no obvious conflict of interest. Importantly, they have analysed their results and published them.

Despite this success, however, testing in preclinical models remains essential, although individual components of the technology are reflected in other groups' experiments as reviewed in the paper's discussion section (References 13, 19, 49, 53[1]). Both ECM and platelet-rich plasma have regenerative potentials that are

related to their angiogenic[5] and immunomodulatory[6] properties. Reverse translation should drive this group and others to test the hypothesis generated by this clinical success. If an accelerated treatment process, backed by well-designed animal studies and based on the learning points herein, successfully replicates the observations reported in this paper in formal phase 1/2 clinical trials, then the method could have a significant impact on oesophageal surgery for both benign and malignant conditions.

1. Dua et al. In-vivo Oesophageal Regeneration in Human Subject with Four-year Follow-up. (Lancet to insert full reference please)
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