Institution: University College London

Unit of Assessment: 15 – General Engineering

Title of case study: Development and transplant of human organs using nanocomposite materials

1. Summary of the impact

Researchers in UCL's Centre for Nanotechnology and Regenerative Medicine have pioneered a transformative therapy using their platform technology of next-generation nanocomposite biomaterials to create wholly synthetic human organs for transplant, including the world's first synthetic trachea, lacrimal (tear) ducts and bypass grafts. These products improve patient outcomes in situations where conventional therapies have not worked. Because the organs are functionalised with peptides and antibodies, as well as seeded with the patients' own stem cells, patients do not require immunosuppression. A university spinout company has been set up to commercialise the use of UCL's patented nanomaterial for cardiovascular devices as well as other organs.

2. Underpinning research

Biomimetics involves the extraction and exploitation of biological design principles found in nature. There is a close relationship between nano-, micro- and macroscale structures and their chemical function in biological systems. Macro-scale architectural mimicry attempts to replicate biophysical properties such as 3D structure, and mechanical (elasticity, strength) and surface (roughness) properties. At the micro- and nano-scale, however, the focus of biomimicry is the biochemical and nanotopographical replication of materials, enabling precise matching to the structure and function of complex natural materials.

Since 2004, Alexander Seifalian (Professor of Nanotechnology and Regenerative Medicine, UCL 1998-present) has led a multidisciplinary team of physicists, materials scientists, engineers, biologists and clinicians in work on biomimicry at UCL. The research team has used the approach outlined above to generate a range of technologies for the development of human organs. Taking its inspiration from natural structures such as butterfly wings, the team seeks to mimic covalent nanostructures within a polymer matrix. The *Morpho* butterfly's wings, for example, are superhydrophobic due to nanoscale surface roughness; replicating this quality in a biomaterial can help inhibit infection after surgery.

In 2005, Seifalian developed and patented two novel non-biodegradable and bioabsorbable nanocomposite polymers based on the integration of the nanocage, polyhedral oligomeric silsesquioxane (POSS) (core structure 1.5 nm), into a backbone of poly(carbonate-urea)urethane (PCU) [1]. In further extensive studies conducted (under good laboratory practice [GLP] and god manufacturing practice [GMP]) between 2007 and 2011, Seifalian performed *in vivo* toxicology and biocompatibility testing with these POSS-PCU nanocomposite materials. The research showed that the incorporation of POSS with polyurethane protects the structure's flexibility and elasticity from oxidative and hydrolytic degradation. Indeed, POSS-PCU was shown to exhibit a range of properties making it a desirable material for organ regeneration scaffolds: it is non-toxic, exceptionally biocompatible, biostable, and supportive of the attachment and proliferation of various cell types. POSS-PCU is particularly suited for cardiovascular applications due to its oxidative and hydrolytic stability and inherent ability to prevent blood clot formation. The concept of incorporating POSS-PCU was subsequently used in synthesising 'smart' scaffolds to regenerate a multitude of organs and tissues, including for use in paediatric patients.

The potential to deliver 'smart' organ development scaffolds was expanded further by the research team's production of the second polymer, POSS-PCL (poly(caprolactone urea-urethane) [2]. A different member of the POSS nanocomposite family, POSS-PCL is the bioabsorbable version of POSS-PCU. Further research conducted at UCL demonstrated that, whilst POSS-PCL shares POSS-PCU's inherent versatility, its better able to be fine-tuned in terms of its stability: more specifically, it showed that the degradation of POSS-PCL could be controlled using either hydrophilic groups in the soft segment (polyester groups), or amino acids in the hard segment of the polymer backbone. This finding allowed the research team to control the rate of POSS-PCL degradation from 8 weeks to 12 months. The implications of this discovery for organ development were significant, since it meant that POSS-PCL could both be used to provide an initial 3D scaffold to support cells, and would then degrade at the same pace as new tissue formed. Different organs require varying levels of bioabsorbtion – for example, skin needs 8 weeks while a nerve conduit slowly biodegrades over 12 months. In children, this means that as the biological matrix grows, the synthetic scaffolding materials can be gradually bioabsorbed and replaced by biological material.

Using the nanocomposite polymer to create organs required Seifalian's team to manufacture 3D scaffolds from it, functionalised with proteins and peptides and/or seeded with stem cells. To this end, Seifalian conceived a number of extrusion methods, including coagulation phase inversion [3], casting, electrospinning, and 3D organ printing (bioprinting). His research team used a series of bioreactors to study cell/tissue development using stem cell technology. Further research into nanoparticles, such as fume silica, quantum dots, and gold and silver nanoparticles, allowed them to attach peptides and antibodies to the scaffold, as well as to track stem cells and their differentiation [4]. Together, these developments enabled the manufacture of synthetic organs specifically tailored for individual patients based on CT scans of their native organs. Development focused on the production of synthetic trachea, bypass graft, oesophagus and membrane patches.

Using these platform technologies, Seifalian's team implanted the world's first synthetic trachea in 2011 [5]. They have also implanted the first synthetic tear duct with silver-coated nanoparticle; vascular bypass graft; and (as compassionate cases) nose and ear, which Seifalian plans to take to clinical trial. *In vitro* and *in vivo* tests conducted under GLP in 2012 showed that the grafts developed by the UCL team performed much better than control grafts, made of PTFE (polytetrafluoroethylene). Whilst all of the control bypass grafts became blocked within the first 14 days after implantation, just 15% of the UCL grafts suffered blockages over the nine-month period of the trials. Other organs under development include a transcatheter heart valve and stents for both for paediatric and adult patients (both at preclinical stage under GLP) [6], as well as urethra bladder cardiac patch and bone, all of which are still at R&D stages.

3. References to the research

1. Kannan RY, Salacinski HJ, Butler PE, Seifalian AM. Polyhedral oligomeric silsesquioxane nanocomposites: the next generation material for biomedical applications. Acc Chem Res 2005; 38(11):879-884. http://doi.org/b9xgnm
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3. Ahmed M, Ghanbari H, Cousins BG, Hamilton G, Seifalian AM. Small calibre polyhedral oligomeric silsesquioxane nanocomposite cardiovascular grafts: influence of porosity on the structure, haemocompatibility and mechanical properties. Acta Biomater 2011; 7(11):3857-3867. http://doi.org/cz9spg
4. de MA, Oh JT, Ramesh B, Seifalian AM. Biofunctionalized quantum dots for live monitoring of stem cells: applications in regenerative medicine. Regen Med 2012; 7(3):335-347. http://doi.org/pwk
5. Jungebluth P, Alici E, Baiguera S, Le BK, Blomberg P, Bozoky B et al. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. Lancet 2011; 378(9808):1997-2004. http://doi.org/c9fxk5
6. Tan A, Goh D, Farhatnia Y, G N, Lim J, Teoh SH, Rajadas J, Alavijeh MS, Seifalian AM. An Anti-CD34 Antibody-Functionalized Clinical-Grade POSS-PCU Nanocomposite Polymer for Cardiovascular Stent Coating Applications: A Preliminary Assessment of Endothelial Progenitor Cell Capture and Hemocompatibility. PLoS One. 2013 Oct 8;8(10):e77112. http://doi.org/pwj

References [2], [3] and [6] best demonstrate the quality of the research.

Grant funding: Since 2006, the research conducted by Prof Seifalian and his group has been supported by more than £6 million of research grants from bodies included the EPSRC, Wellcome Trust, TSB, NIHR and Department of Health.

4. Details of the impact

Its work on next-generation biomaterials and development of the patented POSS nanocomposite polymers allowed the UCL research team to bring the first fully synthetic organ into the clinical setting. This has had a transformative effect on organ development and replacement therapies and, in turn, the outcomes for and wellbeing of patients around the world.

Introduction of new therapy: Although it is possible to surgically resect tracheal tumours, most are already of an inoperable size by the time of diagnosis. As such, the synthetic trachea addressed a pressing clinical requirement for alternative therapeutic options. In 2011, a patient with advanced tracheal cancer who had exhausted all existing treatment options was referred to cardiothoracic surgeon Professor Macchiarini at the Karolinska Institutet, Stockholm. In turn, Macchiarini approached Seifalian for help. Seifalian used his POSS-PCU polymer [output 1] and knowledge of developing and seeding 3D scaffolds [output 4] to manufacture the synthetic trachea implant, which consisted of a 12cm trachea along with two bronchi – the largest such implant ever attempted and the **world's first wholly tissue-engineered synthetic organ transplant** [a,b]. By using the patient's CT scans, Seifalian was able to model the implant on the exact dimensions of the patient's own trachea, making implantation significantly easier. Mechanically, the synthetic trachea had similar properties to a native organ, including ring-like cartilage structures, with porous materials between them allowing 15% stretchability. UCL's researchers developed a bioreactor for the organ's development, which dripped the patient's own stem cells onto the porous scaffold under physiological conditions in an incubator. Because it used his own stem cells, there was no need for the patient to take the immunosuppressive drugs required after donor transplants. The trachea and bronchi were implanted in June 2011; more than two years on, the patient has a functioning organ and is doing very well. Describing the implantation and its effects, Professor of Laryngology at the Royal National Throat, Nose and Ear Hospital said: "This is the first time that a trachea made from a synthetic scaffold (here repopulated using stem cells), has preserved life and quality of life for longer than a few months…follow up is now 2.5 years" [c].

This was the first instance in which doctors had ever been able to manufacture human organs using synthetic scaffolds, and then incorporate autologous stem cells. As such, the work not only saved the life of the patient in whom the synthetic trachea was implanted, but **revolutionised the development of organs** more broadly. The success of previous lab-generated transplants, which lined a decellularised donor trachea with the patient's stem cells, had been limited by a number of problems that Seifalian's trachea was able to overcome. These included the very real difficulties of obtaining the necessary donor organs; even assuming that these could be found, moreover, the decellularising is suitable only for small sections of trachea, rather than an entire organ, and risks damaging their underlying structure, leading to their collapse once they are implanted in the patient. The danger of donor cells not being completely removed produces a further, significant risk of prompting a potentially serious immune system response in the organ recipient [c]. The considerable comparative benefits of Seifalian's synthetic organ development are explained by a Professor of Plastic Surgery at the Royal Free Hospital, who explains that the POSS nanocomposite: "provides a platform to create innovative solutions to reconstructive problems facing military and civilian casualties. It has applications in many regions of the body… It has the advantage of being a material that can be modified to allow tissue integration or to reduce adhesion as well as being biodegradable and non biodegradable" [g]. The global significance of the contribution made by the synthetic trachea to organ development and replacement was acknowledged by Seifalian's receipt of the "most innovative new product" award at the 2012 Life Science Awards in Germany [f].

The research has, moreover, been used to develop organs other than the synthetic trachea. These include **lacrimal (tear) ducts**, which have been implanted into five patients since September 2010. Without treatment, patients whose tear ducts have had to be removed because of cancer or trauma, would have constantly watering eyes, making effective replacement imperative for those affected. The UCL tear duct conduit, which is made from nanocomposite polymer and coated with silver nanoparticle, replaces the previous standard therapeutic use of a glass tube to direct tears into the nasal cavity, a practice with generally poor clinical outcomes and a high risk of breakage. The surgeon who performed the surgery in several patients reports that complications have been almost non-existent and tear flow well-regulated [d]. The conduit was filed for patent in 2011 [h].

The UCL team has also developed the **world's first bypass graft capable of in-situ**

endothelialisation from the patient's own endothelial progenitor stem cells in circulating blood. Bypass grafts can be manufactured using a specially designed and developed automated extrusion system, which produces grafts up to 100cm in length with a diameter ranging from 1-16mm, suitable for replacing even long blood vessels in legs. Vascular bypass grafts were carried out in two patients in 2010 and 2011; both patients are doing well. POSS-PCU is a particularly suitable material for cardiovascular devices because of its anti-thrombogenicity and viscoelastic properties. In October 2013, clinical trials of the use of this graft for coronary artery bypass began at Heart Hospital London, and of vascular access at Royal Free Hospital. [e]

Commercial impacts: UCL has used the research to develop more than 10 patents**,** with the POSS polymer granted a US patent in 2010 [j]. A number of other patents have been filed since 2008, including a heart valve prosthesis made from POSS-PCU, and synthetic scaffolds and organ and tissue transplantation [j]. Seifalian's POSS materials have also begun to produce commercial benefits, with new businesses established to commercialise the technology. These include SmartTech, set up in 2013 as a joint venture with Pharmidex and Flexicare Medical, which is commercialising the use of POSS-PCL for nerve regeneration and stents. Another spinout business, Belsize Polymer, was also established in May 2013 in order to take organs including trachea, facial organs and breast filler to clinical trial and commercialisation [j].

5. Sources to corroborate the impact

[a] For corroboration of the success of the trachea implant, see: Jungebluth P, Alici E, Baiguera S, Le Blanc K, Blomberg P, Bozóky B, Crowley C, Einarsson O, Grinnemo KH, Gudbjartsson T, Le Guyader S, Henriksson G, Hermanson O, Juto JE, Leidner B, Lilja T, Liska J, Luedde T, Lundin V, Moll G, Nilsson B, Roderburg C, Strömblad S, Sutlu T, Teixeira AI, Watz E, Seifalian A, Macchiarini P. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. *Lancet.* 2011; 378 (9808): 1997-2004. http://doi.org/c9fxk5

[b] There were over 3,000 media reports of the news that a lab-made organ had been implanted for first time. The story was twice on front page of Wall Street Journal as well as other main newspapers. E.g.: CNN, 8 July 2011, http://bit.ly/18KPIZh; BBC, 2011, http://bbc.in/1c0W3D4; WSJ, 2011, http://on.wsj.com/151dmzq; WSJ, 2013, http://on.wsj.com/1g0BQ0d;

[c] The superiority of the tracheal implant over other types of tracheal transplant is evidenced by the statement from a Professor of Laryngology at the Royal National Ear, Nose and Throat Hospital. Available on request.

[d] "Nanotechnology meets lacrimal duct system", corroborates the use of POSS-PCU in synthetic lacrimal duct surgery and the benefits to patients. http://www.congress-info.ch/medidays/upload/File/handouts-2012/Mittwoch_Plenar_Nano_Chaloupka.pdf

[e] A statement from a Consultant Vascular Surgeon at the Royal Free Hospital Trust corroborates the suitability of POSS-PCU for cardiovascular devices and its use in vascular grafts. Available on request.

[f] For Seifalian's receipt of the "most innovative new product" Life Science Award for his synthetic trachea: http://www.lifescienceawards.com/award-categories.aspx

[g] A copy of the statement from a Professor of Plastic Surgery at the Royal Free Hospital about the revolutionary effect of the POSS material on the development of organs is available on request.

[h] Implantable small diameter drainage conduit patent, WO/2013/005004: http://patentscope.wipo.int/search/en/WO2013005004

[i] Patents: Polymer for use in conduits and medical devices, US7820769 B2: http://assignments.uspto.gov/assignments/q?db=pat&pat=7820769; heart valve prosthesis, US20120165929 A1, http://assignments.uspto.gov/assignments/q?db=pat&pub=20120165929; synthetic scaffolds and organ and tissue transplantation, WO/2013/005110, http://patentscope.wipo.int/search/en/WO2013005110;

[j] Belsize Polymer, Company No. 08547328, Companies House.