BAPRAS PATON MASSER AWARD RESEARCH UPDATE

Optimisation of Nanocellulose-based Bioinks for 3D Printing Facial Cartilage

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Lay Summary

This research project aims to revolutionise how we offer facial reconstruction surgery for patients with absent or injured facial cartilage tissue (ears and noses) through the design of a new ink for 3D printing cartilage tissue.

We had previously identified a novel biological material called nanocellulose which held promise as a material for biological 3D printing. By combining this with varying amounts of hyaluronic acid: commonly used as an injectable filler in cosmetic practices, we were able to significantly strengthen the material allowing it to be easily printed into 3D shapes, even holding its shape as a human ear. Furthermore, these materials support the growth and development of new cartilage tissue. This is all contributing to building an extremely promising case for the future of 3D printing cartilage tissue with this novel material combination. Ultimately, this would mean that 3D printed facial structures could be produced containing living cartilage tissue, for those affected by visible differences.

COVID-19

The last 12 months has been an unpredictable and unusual year for everyone but has had a particular impact on clinicians, researchers.

Although the pandemic meant a return to clinical duties I was fortunate in that along with peers in my research group, we were able to use some of the 3D printing technology we have been optimising for this project to help with the global pandemic by turning our attention to 3D printing visors and venturi valves for use in the hospital.

In line with government restrictions access to university laboratories was suspended during the first wave. As such, I managed to initiate an epidemiology/big data project through a collaboration with the SAIL databank at Swansea University to look at the epidemiology of microtia in Wales, its impact on affective disorders and school performance and access to surgical intervention which offers greater insight into this patient demographic and further justification for pursuing 3D printed tissue options for microtia patients.

The pandemic notwithstanding, research has now resumed to normality as part of this research project on 3D printing facial cartilage.

Laboratory Progress

In brief, progress has not been significantly hindered since the resumption of lab activity with tissue samples now becoming available more frequently for this research project which has been broadly focussing on characterising the cartilage cells for tissue engineering, developing and optimising the novel biological ink, determining its ability to encourage cartilage formation and verifying its biocompatibility. The data generated so far is novel, promising and helping to build a foundation for clinical translation – I have acquired an extensive dataset that will form the basis of several publications and which I hope I will be able to continue to present nationally, internationally and online wherever the opportunities arise.

This project has demonstrated that our novel biological ink composed of hyaluronic acid and nanocellulose appears to be highly effective at producing cartilage, and possesses properties that enable it to be extruded through a 3D printer and retains it shape post-printing in the form of a human ear.

Figure 1: 3D printed auricle using nanocellulose-based bioink

Personal & Professional Implications

The Paton Masser Award has helped to realise my ambitions of developing independent thought processes, designing my own research questions and developing the skillset needed to approach and answer those questions. Through collaborations both within and outside Swansea University, I have been able to develop experience in numerous techniques from molecular biology (PCR and protein analysis) to imaging (histology, confocal and atomic force microscopy) and engineering (mechanical compression testing). The collaborations and techniques will be instrumental in enabling me to engage in multidisciplinary basic science research for the rest of my career.

Personally I have found it extremely rewarding, challenging and intellectually stimulating and despite the hurdles, obstacles and difficulties lab research presents I remain as determined as ever to retain a career that integrates clinical work and academia, to ultimately yield superior treatment options for patients.

Research Impact & Future Directions

This research project has generated pilot data that has helped to secure a grant from the Scar Free Foundation to establish a Centre for 3D Bioprinting for Facial Reconstruction in Swansea University (>£1million). The research specifically demonstrates that the biological ink I have developed has suitable mechanical properties to be 3D printed and hold its shape as an ear, that it supports the growth of cartilage cells and tissue and that the material is non-toxic to the cells within it. The next stages of the research will be further in-depth toxicology and immunology experiments and animal studies to help push this research along a trajectory to clinical translation.

As a clinical-academic trainee I will have 20% protected academic time for the remainder of my plastic surgery training and I hope to use this time to progress my skills as an independent clinician researcher, apply for intermediate research fellowships and drive this research towards clinical translation.

Clinical Implications

Through my clinical work I have exposure to children affected by craniofacial abnormalities such as cleft and microtia and the impact of these diagnoses for the patient, their self-perception, psychosocial integration and their families is profound. More recently having been involved with big data projects investigating the associations between ear anomalies and affective disorders has highlighted the effects of ear anomalies on school performance and mental wellbeing. Our current interventions: surgery and prosthetics – go a long way to helping restore form and function in these patients, but prostheses discolour, displace and degrade and surgery requires long and complex surgery with the use of tissue borrowed from other bodily sites. Better options could exist for these patients, and 3D bioprinting technology is one such approach that could transform how we restore form function and psychological wellbeing to these patients without the need for extensive surgery.

However, a novel technology such as 3D printing, combines stem cell biology, material science and bioengineering expertise to render a suitable living tissue replacement. This in turn demands significant investment from scientists, clinicians, engineers and funders to ensure robust laboratory-based research is undertaken and a convincing evidence base is built for developing this novel technology into a meaningful, clinically viable option for patients. Every funded research project in the field helps add to this evidence base and pushes us closer to this technology being a possibility for children affected by visible differences.

Outputs during Paton Masser Award period

Publications:

1. Tarassoli, S.P., Jessop, Z.M., Jovic, T.H, Hawkins, K., Whitaker, I.S. **Candidate bioinks for extrusion 3D bioprinting – A systematic review of the literature.** *Frontiers in Bioengineering & Biotechnology* (accepted; in press)
2. Thomson, R. M., Jovic, T., Drake, D., & O'Neill, T. 2021. Nasolabial appearance of bilateral cleft lip repair at 5 years of age, comparing techniques of Modified Advancement-Rotation (Delaire) with Manchester repair: a retrospective cohort study. *British Journal of Oral and Maxillofacial Surgery*.
3. Ibrahim, N., Jovic, T., Jessop, Z. M., & Whitaker, I. S. 2021. Innovation in a Time of Crisis: A Systematic Review of Three-Dimensional Printing in the COVID-19 Pandemic. *3D Printing and Additive Manufacturing*.
4. Jovic, T.H., Gibson, J.A.G., Griffiths, R., Akbari, A., Costello, R., Key, S., Evans, P., Lyons, R., Whitaker, I.S. 2021. **Microtia: A data linkage study of epidemiology and implications for service delivery.** *Frontiers in Paediatrics*, 9, pp. 218
5. Browne, R., Jovic, T.H., Walker, L., Delveccio, D. and Whitaker, I.S. 2021. **Botched Botox Injections: A Transatlantic Epidemic**. *Plastic & Reconstructive Surgery*, 147 (2), pp.362-363.
6. Jovic, T.H., Combellack, E.J., Jessop, Z.M., Whitaker, I.S. 2020. **3D Bioprinting and the Future of Surgery.** *Frontiers in Surgery*, 7; pp.129
7. Holford, P., Carr, A., Jovic, T. H., Ali, S.R, Whitaker, I.S., Marik, P., Smith, D. **Vitamin C - An Adjunctive Therapy for Respiratory Infection, Sepsis and COVID-19**. *Nutrients*, 12 (12); pp. 3760
8. Jovic, T.H., Ali, S.R., Ibrahim, N., Jessop, Z.M., Tarassoli, S.P., Dobbs, T.D., Holford, P., Thornton, C.A. and Whitaker, I.S., 2020. **Could Vitamins Help in the Fight Against COVID-19?**. *Nutrients*, *12*(9), p.2550.
9. Jovic, T.H., Combellack, E.J., Jessop, Z.M. and Whitaker, I.S., 2020. **Using 3D Printing Technology to Teach Cartilage Framework Carving for Ear Reconstruction.** *Frontiers in Surgery*, *7*, pp.44-44.
10. Ali, S.R., Jovic, T., Gibson, J.A., Rich, H., Jessop, Z.M. and Whitaker, I.S., 2020. **Evolution of Plastic Surgery Provision due to COVID-19–The Role of the 'Pandemic Pack'.** *Journal of Plastic, Reconstructive & Aesthetic Surgery*.
11. Jessop, Z.M., Dobbs, T.D., Ali, S.R., Combellack, E., Clancy, R., Ibrahim, N., Jovic, T.H., Kaur, A.J., Nijran, A., O'Neill, T.B. and Whitaker, I.S., 2020. **Personal Protective Equipment (PPE) for Surgeons during COVID-19 Pandemic: A Systematic Review of Availability, Usage, and Rationing.** *British Journal of Surgery*.
12. Jovic, T.H., Stewart, K., Kon, M. and Whitaker, I.S., 2020. **Auricular Reconstruction: A Sociocultural, Surgical and Scientific Perspective.** *Journal of Plastic, Reconstructive & Aesthetic Surgery*.
13. Grinsell, D., Jovic, T.H., Saravolac, V. and Whitaker, I.S., 2020. **Authorship in surgical articles.** *Journal of Plastic, Reconstructive & Aesthetic Surgery*, *73*(5), pp.983-1007.

Presentations:

Meeting	Title	Date	Format

BAPRAS Winter Scientific Meeting	Using 3D Printing Technology to Teach Cartilage Framework Carving for Ear Reconstruction	Dec 2020	Oral
BAPRAS Winter Scientific Meeting	Hyaluronic acid: Nanocellulose composite bioinks for 3D bioprinting facial cartilage	Dec 2020	Oral