**Lay Abstract**

**Prostate cancer: Now showing in 3D**

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Currently we do not know the underlying biology that increases cancer risk. One key factor in the progression of advanced prostate cancer is a high level of vascularisation (connection with blood vessels) that is associated with it. However, there is still much to learn about the role of vascularisation in cancer progression, and what mechanisms are involved that could become potential prognostic markers for patients. Studies have shown that the standard culture of cancer cells on two dimensional surfaces for research, is not accurately mimicking natural cancer progression, and therefore is hindering the development of new research technologies. This study seeks to uncover the cellular interactions in prostate cancer that control its vascularisation and metastasis through the development of more relevant and sophisticated three dimensional culture technologies. Using these, we have the potential to provide novel therapeutic intervention points, streamline the testing of new drugs and individualise patient treatment strategies.

**Scientific Abstract**

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Prostate cancer (PC) is a leading cause of death in Australian males.The prognosis for PC patients worsens rapidly upon cancer progression to advanced and metastatic disease. Therefore, it is imperative that we gain a greater understanding of the progression from localised to advanced cancer using relevant physiological systems. The culture of cells on rigid two-dimensional (2D) substrates, such as tissue culture plastic, does not recreate the dynamic and highly complex tissue microenvironment, but rather distorts cell-integrin and cell-cell interactions, affecting gene expression, signal transduction, cell proliferation and differentiation. Hydrogels prepared from star-shaped poly(ethylene glycol) (starPEG) and maleimide-functionalised heparin provide a potential matrix for use in developing three-dimensional (3D) culture models. We have previously demonstrated that these hydrogels support the cultivation of human umbilical vein endothelial cells (HUVECs). We extended this body of work to study the ability to create an extracellular matrix (ECM)-like model to study PC cell growth in 3D. Also, we investigated the ability to produce a tri-culture mimicking tumour angiogenesis with cancer spheroids, HUVECs and mesenchymal stem cells (MSC), or normal or cancer-associated fibroblasts. Cultures prepared in starPEG-heparin hydrogels displayed spheroid formation in contrast to adherent growth on tissue culture plastic. Differing phenotypes were observed in the PC cells when ECM-functionalisations were incorporated into the 3D microenvironment, demonstrating our ability to manipulate and tailor the 3D culture model. Interactions were visualised between PC tumours and the surrounding capillary network. Our results confirm the suitability of starPEG-heparin hydrogels for the co-cultivation of primary patient-derived tissue-specific cells to study cell-cell and cell-matrix interactions in a 3D microenvironment. These findings provide a significant basis for more mechanistic studies to advance our understanding of how the ECM modulates cancer cell invasion and how to interfere with this process, and highlights the potential application of our models for personalised medicine.

**Short CV**

**Laura J. Bray, PhD**

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**Short Biography**

Dr Bray is a Biomedical Engineer with expertise in 3D *in vitro* models for cancer research. She was awarded her PhD from QUT in 2012 and as recognition for her work she received an Outstanding Alumni Award from the University of the Sunshine Coast for the year 2012. In 2013, she was awarded the inaugural Prime Minister’s Queen Elizabeth II Diamond Jubilee fellowship and undertook 3 years of postdoctoral research at the Leibniz Institute for Polymer Research Dresden, Germany under the mentorship of Prof Carsten Werner. In 2015, she was awarded the Lush Prize UK in the young researcher category for her work on *in vitro* cancer models as a replacement for animals in research. In 2016, Dr Bray moved her research to QUT upon receipt of a Cure Cancer Australia Foundation grant and a fellowship from the National Breast Cancer Foundation. She has 7 years of teaching experience as a guest lecturer and sessional academic. Her publication track record proves the high-impact quality of her research, publishing in top journals such as Biomaterials, Stem Cells, and Advanced Drug Delivery Reviews. She has received >400 citations. She is currently acting as Primary Supervisor of 2 PhD students and 2 Bachelor students, and Associate Supervisor of 2 PhD students and 2 Masters students at QUT. 2 Undergraduate Thesis Projects and 4 Masters Thesis Projects have been completed successfully under her supervision. Most recently in 2017, Dr Bray was made Deputy Director of the Centre for Regenerative Medicine at QUT.

**Qualifications**

**2012 Doctor of Philosophy (PhD) by Publication**

*Queensland University of Technology, Gardens Point, Brisbane, QLD, Australia*

**2008 B. App. Sc. (Honours, First Class)**

*Queensland University of Technology, Gardens Point, Brisbane, QLD, Australia*

**2004-2006 B.Sc. (Biomedical)**

*University of the Sunshine Coast, Buderim, Sunshine Coast, QLD, Australia*

**Current Positions:** National Breast Cancer Foundation Research Fellow, School of Chemistry, Physics and Mechanical Engineering, QUT; Deputy Director, 3D Cancer Models, Centre for Regenerative Medicine, Institute of Health and Biomedical Innovation, QUT; Honorary Associate Lecturer, Mater Medical Institute, UQ.

**Employment History and Appointments**

Feb 2013 – Feb 2016: **Postdoctoral Research Fellow**, Leibniz Institute of Polymer Research, Dresden, Germany.

Jan 2012 – Jan 2013: **Postdoctoral Research Fellow**, Queensland Eye Institute, Brisbane.

Jan 2009 – Jan 2013: **Guest Lecturer/Sessional Academic**, QUT, Brisbane.

Feb 2007 – Feb 2008: **Research Assistant**, Mater Medical Research Institute, Brisbane.

**Honours:** University of the Sunshine Coast Outstanding Alumni Award 2012 **•** Dickson Community Award for Academic Achievement – Australia Day 2013 **•** Lush Prize – Young Researcher Category 2015.

**Recent Career Summary and Contribution to the Field of Medical Research:** My research over the past 5 years has focused primarily on the two broad medical research areas of 3D culture models and tissue engineering. My research, through the use of state of the art matrix engineering techniques and innovative parameters, has led to a number of significant advances in knowledge in the area of 3D tissue engineering and culture techniques. My work has helped to clarify the potential role of the matrix environment in 3D epithelial cell cultivation and has provided new insights into mimicking the natural tissue environment *in vitro*. Most recently, I established for the first time, a 3D culture model of breast and prostate cancer incorporating tumour cell lines as well as surrounding vascular and supporting cell types. I have been exploiting hydrogel matrices for the study of tumour angiogenesis for the last 4 years. My research work from my entire career has led to 25 publications consisting of 19 research articles (9 first/last author; 3 second author), 3 reviews and 3 book chapters, with the majority in leading biomaterials journals.

**National and International Profile:** I have been invited to give presentations and chair sessions at national and international conferences. Additionally I have been involved in conference organisation (IHBI Inspires, QUT 2010-2011) and chaired a session in 3D Cancer Models at the 2016 Brisbane Cancer Conference. I have given presentations at 24 conferences in total. In the last 5 years I have presented at a number of national and international conferences including the 9th International Conference of Anti-cancer Research (2014) as an invited speaker and Goodbye Flat Biology: 3D Models and the Tumour Microenvironment (2014). I also attended the Tissue Engineering and Regenerative Medicine Annual Meetings in Genoa (2014), Vienna (2012) and Granada (2011), and the NC3Rs Workshop: Understanding Target to Function Biology in Nonclinical Oncology Research in London 2015. In Dresden, Germany, I was an invited main speaker for the Centre of Regenerative Therapies Symposiums on Biomaterials (2014) and Haematology/Immunology (2015). My research has had significant impact outside of the academic sphere as well. News articles have appeared about my research in the local and international press, including ‘The Courier Mail’ in Brisbane and a segment on ABC National News.

**Research Support:** As an early career researcher, I have a substantial track record in obtaining research funding relative to opportunity. My PhD was funded by an ANZ Trustees Medical Research in Queensland PhD Scholarship from 2010 until the award of my PhD in 2012. I have gained over $700K in fellowship/grant funding as chief investigator to fund my research. These include a Cancer Australia PdCCRs Young Investigator Grant funded by Cure Cancer Australia, a National Breast Cancer Foundation Postdoctoral Fellowship and the Lush Prize UK Young Investigator Prize. I was also the inaugural recipient of the Queen Elizabeth II Diamond Jubilee Postdoctoral Award (presented by former Governor General Her Excellency the Honourable, Quentin Bryce).

**Community Engagement and Participation:** As an NBCF-funded researcher, I participate in regular fundraising events such as the Mother’s Day Classic. At these events, I am often asked to speak about my research to the general public. I also have attended the Australian-German Science Circles at the Australian Embassy in Berlin, networking with German researchers regarding exchange with Australia. I am a long-term fundraising volunteer for PCFA, NBCF and Cancer Council QLD. I also participate as a volunteer in the Cybermentor,de mentor program for female school students in Germany interested in the STEM fields.

**Supervision and Mentoring:** Since 2012, I have supervised/co-supervised 4 PhD students, 7 Masters students (5 completed), and 3 undergraduate students (1 completed).

**Professional and NHMRC peer review involvement:** Professional Memberships –Tissue Engineering and Regenerative Medicine International Society (TERMIS), Women in Technology (WIT), European Association for Cancer Research (EACR) and American Association for Cancer Research (AACR). Editorial Responsibilities –Dr Bray regularly acts as a reviewer for a number of highly regarded cell and biomaterials journals including: ‘Advanced Drug Delivery Reviews’, ‘Biomaterials’, ‘Acta Biomaterialia’, ‘Stem Cell Reviews and Reports’, ‘Cytotherapy’ and ‘International Journal of Nanomedicine’. Grant Review Experience – Cure Cancer Australia Grant Reviewer (2016), Genesis Oncology Grant Reviewer (2015).

**Publications**

Please note that my maiden name was Sinfield

*Peer-reviewed Journal Articles*

19. Bas O, De-Juan-Pardo EM, Meinert C, D’Angela D, Baldwin J, **Bray LJ**, Wellard RM, Kollmannsberger S, Rank E, Werner C, Klein TJ, Catelas I, Hutmacher DW. Biofabricated soft network composites for cartilage tissue engineering. Biofabrication 2017. *Accepted for publication 06/04/2017.*

 (Impact factor 2015: **4.702**; Citations: **0**; **Q1** journal)

18. **Bray LJ**, Binner M, Körner Y, von Bonin M, Bornhäuser M, Werner C. A three-dimensional tri-culture model for the *ex vivo* study of acute myeloid leukaemia. Haematologica 2017. *Accepted for publication 15/03/2017.*

 (Impact factor 2015: **6.671**; Citations: **0**; **Q1** journal)

17. Binner M, **Bray LJ**, Friedrichs J, Freudenberg U, Tsurkan M, Werner C. Cell-instructive starPEG-heparin-collagen composite matrices. Acta Biomater 2017;53:70-80.

 (Impact factor 2015: **6.008**; Citations: **0**; **Q1** journal)

16. Hogerheyde TA, Suzuki S, Walsh J, **Bray LJ**, Stephenson S, Harkin DG, Richardson NA. Optimization of corneal epithelial progenitor cell growth on *Bombyx mori* silk fibroin membranes. Stem Cells Int 2016;8310127.

(Impact factor 2015: **3.687**; Citations: **0**; **Q2** journal)

15. Dhawan A, v. Bonin M, **Bray LJ**, Freudenberg U, Bejestani EP, Werner C, Hofbauer L, Wobus M, Bornhäuser M. Functional interference in the bone marrow microenvironment by disseminated breast cancer cells. Stem Cells 2016;34(8):2224-2235.

 (Impact factor 2015: **5.902**; Citations: **1**; **Q1** journal)

14. Taubenberger A\*, **Bray LJ\***, Haller B, Shaposhnykov A, Binner M, Tsurkan M, Friedrichs J, Freudenberg U, Werner C, Guck, J. 3D extracellular matrix interactions modulate tumour cell growth, invasion and angiogenesis in engineered tumour microenvironments. Acta Biomater 2016;36:73-85. \*These authors contributed equally to this work.

(Impact factor 2015: **6.008**; Citations: **11**; **Q1** journal)

13. **Bray LJ**, Binner M, Holzheu A, Friedrichs J, Freudenberg U, Hutmacher DW, Werner C. Multi-parametric hydrogels support 3D in vitro bioengineered microenvironment models of tumour angiogenesis. Biomaterials 2015;53:609-620.

 (Impact factor 2015: **8.387**; Citations: **36**; **Q1** journal)

12. Gillies P, **Bray LJ**, Richardson NA, Chirila TV, Harkin DG. Isolation of microvascular endothelial cells from cadaveric corneal limbus. Exp Eye Res 2014;131:20-28.

(Impact factor 2015: **2.998**; Citations: **2**; **Q1** journal)

11. Hogerheyde TA, Suzuki S, Stephenson S, Richardson NA, Chirila TV, Harkin DG, **Bray LJ**. Assessment of freestanding membranes prepared from Antheraea pernyi silk fibroin as a potential vehicle for corneal epithelial cell transplantation. Biomed Mater 2014;9:025016.

(Impact factor 2015: **3.361**; Citations: **10**; **Q2** journal)

10. **Bray LJ**, Heazlewood CF, Munster DJ, Hutmacher DW, Atkinson K, Harkin DG. Immunosuppressive properties of mesenchymal stromal cell cultures derived from the limbus of human and rabbit corneas. Cytotherapy 2014;16(1):64-73.

 (Impact factor 2015: **3.625**; Citations: **21**; **Q2** journal)

9. Chirila TV, Suzuki S, **Bray LJ,** Barnett NL, Harkin DG. Evaluation of silk sericin as a biomaterial: In vitro growth of human corneal limbal epithelial cells on *Bombyx mori* sericin membranes. Prog Biomater 2013;2:14.

 (Impact factor not yet assigned; Citations: **16**; quartile not yet ranked)

8. **Bray LJ**, Suzuki S, Harkin DG, Chirila TV. Incorporation of exogenous RGD peptide and inter-species blending as strategies for enhancing human corneal limbal epithelial cell growth on *Bombyx mori* silk fibroin membranes. J Funct Biomater 2013;4:74-88.

 (Impact factor not yet assigned; Citations: **17**; quartile not yet ranked)

7. Hogerheyde TA, Stephenson SA, Harkin DG, **Bray LJ**, Madden PW, Woolf MI, Richardson NA. Evaluation of Eph receptor and ephrin distribution and expression in cells of the human cornea and limbus. Exp Eye Res 2013;107:110-120.

 (Impact factor 2015: **2.998**; Citations: **6**; **Q1** journal)

6. **Bray LJ**, Heazlewood CF, Atkinson K, Hutmacher DW, Harkin DG. Evaluation of methods for cultivating limbal mesenchymal stromal cells. Cytotherapy2012;14(8):936-947.

 (Impact factor 2015: **3.625**; Citations: **29**; **Q2** journal)

5. **Bray LJ**, George KA, Hutmacher DW, Chirila TV, Harkin DG. A dual-layer silk fibroin scaffold for reconstructing the human corneal limbus. Biomaterials2012;33(13):3529-3538.

 (Impact factor 2015: **8.387**; Citations: **55**; **Q1** journal)

4. **Bray LJ**, George KA, Ainscough SL, Hutmacher DW, Chirila TV, Harkin DG. Human corneal epithelial equivalents constructed on Bombyx mori silk fibroin membranes. Biomaterials. 2011;32(22):5086-5091.

(Impact factor 2015: **8.387**; Citations: **86**; **Q1** journal)

3. Christensen ME, **Sinfield LJ**, Cullup H, Waterhouse NJ, Atkinson K, Rice AM. Environmental conditions are important for establishing and evaluating pre-clinical models of GVHD. Bone Marrow Transplant 2012;47(4):607-609.

 (Impact factor 2015: **3.636**; Citations: **1**; **Q1** journal)

2. Christensen ME, Turner BE, **Sinfield LJ**, Kollar K, Cullup H, Waterhouse NJ, Hart DNJ, Atkinson K, Rice AM. Mesenchymal stromal cells transiently alter the inflammatory milieu post-transplant to delay graft-versus-host disease. Haematologica 2010;95(12):2102-2110.

(Impact factor 2015: **6.671**; Citations: **40**; **Q1** journal)

1. Turner BE, Kambouris ME, **Sinfield LJ**, Lange J, Burns AM, Lourie R, Atkinson K, Hart DNJ, Munster DJ, Rice AM. Reduced intensity conditioning for allogeneic hematopoietic stem cell transplant determines the kinetics of acute GVHD. Transplantation 2008;86(7):968-976.

(Impact factor 2015: **3.690**; Citations: **27**; **Q1** journal)

*Review Articles:*

3. **Bray LJ**, Werner C. Evaluation of three dimensional in vitro models to study tumour angiogenesis. ACS Biomaterials Science & Engineering 2017. *Accepted for publication 01/05/2017.*

 (Impact factor not yet assigned; Citations: **0**; quartile not yet ranked)

2. Harkin DG, Foyn L, **Bray LJ**, Sutherland A, Li FJ, Cronin B. Can Mesenchymal stromal cells differentiate into corneal cells? A systematic review of the published evidence. Stem Cells 2015;33(3):785-791.

 (Impact factor 2015: **5.902**; Citations: **16**; **Q1** journal)

1. Chwalek K, **Bray LJ**, Werner C. Tissue-engineered 3D tumor angiogenesis models: Potential technologies for anti-cancer drug discovery. Adv Drug Deliv Rev 2014;79-80:30-39.

 (Impact factor 2015: **15.606**; Citations: **29**; **Q1** journal)

*Book Chapters:*

3. **Bray LJ**, Binner M, Werner C. 3D Models of Tumour Angiogenesis. In *3D Cell Culture: Methods and Protocols*, Z Koledova, Editor. Methods Mol Biol 2017. Springer, New York.

2. Harkin DG, Foyn L, **Bray LJ**, Sutherland A, Li FJ, Cronin B. Mesenchymal stromal cells for corneal tissue regeneration. In *The Biology and Therapeutic Application of Mesenchymal Cells*, K Atkinson, Editor. 2016. John Wiley and Sons, Inc., New York.

1. **Bray LJ**, George KA, Suzuki S, Harkin DG, Chirila TV. Fabrication of a corneal-limbal tissue substitute using silk fibroin. In *Corneal Regenerative Medicine: Methods and Protocols*, B Wright and C Connon, Editors. Methods Mol Biol 2013;1014:165-178. Humana Press Ltd, New York.

 (Citations: **9**)