23rd NSW Stem Cell Network Workshop

Stem Cells and the Gastrointestinal System

Darlington Centre
City Rd, Sydney
Wednesday, October 7th, 2015

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WELCOME

Welcome to the 23rd Workshop of the NSW Stem Cell Network

The gut is a unique, complex system responsible for the breakdown of food in order to supply cells with nutrients to sustain life. Food begins its journey through the GI tract in the oral cavity where it is mechanically broken down. It then leaves the mouth and transits through a 7-meter long tube consisting of the stomach, small and large intestines and colon. Feeding into the system are the accessory organs, pancreas and liver, which assist in the digestion of food; secrete hormones to control metabolism of carbohydrate, fat and protein; and assist in detoxification. A poorly functioning gastrointestinal (GI) system has major impacts on health.

GI research is a continuously advancing field with numerous groups across Australia working on treating the different pathologies that arise from the various organs that contribute to the GI system. In recent years, stem cell research has broadened our understanding of the biology and pathophysiology of GI development and disease. However, despite this, we are still faced with the dilemma of a large number of untreatable, and often fatal conditions that continue to threaten the patients' health and quality of life. In fact, Australia has amongst the highest incidence of inflammatory bowel disease worldwide; liver disease is the most rapidly growing condition worldwide, affecting over 2 million Australians; periodontal conditions are the fifth most common condition affecting Australians.

In order to understand how these conditions arise, and therefore be able to manage and treat them accordingly, it is important to bring together the expertise from scientists and clinicians across the fields of GI research. This workshop*, "Stem cells and the gastrointestinal system*" aims to do just that.

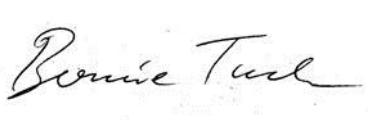
Starting with the application of dental stem cells, and followed by the role of stem cells in the hepatic, pancreatic, intestinal and colonic systems, you will hear from researchers and clinicians from across the country who will discuss their advances in GI stem cell research. You will hear the latest findings from the lab and from the clinic, with the aim of promoting cross-disciplinary and innovative solutions to a variety of conditions that span the GI tract and play havoc on the daily lives of patients world-wide.

Our thanks go to our sponsors and supporters, which, without their help, it would not have been possible to run this event. Their names and crests appear on the opposite page.

We hope you enjoy the workshop.

Rachel Shparberg
NSW Stem Cell Network
Manager

Bernie Tuch
NSW Stem Cell Network
Director



PROGRAM

8:30 am	Registration opens/ Light refreshments
9:15 am	**Prof. Bernie Tuch - NSW Stem Cell Network** *Welcoming*
9.20 am	**The Hon. Jillian Skinner - NSW Minister for Health** *Opening Address*
Session 1	**Dental** **Chair: A/Prof Luke Henderson (University of Sydney, NSW)**
9:30am	**Dr. Russell Vickers (Sydney Oral & Maxillofacial Surgery and University of Sydney, NSW)** *Dental, Oral and Facial Applications of Stem Cells*
9:50 am	**Prof. Yin Xiao (Queensland University of Technology, QLD)** *Dental Pulp Derived Stem Cells and the Application for Regenerative Medicine*
10:10 am	**Dr. Agnes Arthur (University of Adelaide, SA)** *Isolation, Characterisation and Application of Dental Stem Cells*
10:30 am	Morning tea
Session 2	**Liver and Pancreas** **Chair: Dr Lionel Hebbard (James Cook University, QLD)**
11:00 am	**Prof. Grant Ramm (QIMR Berghofer Medical Research Institute, QLD)** *Liver Progenitor Cell-Hepatic Stellate Cell Interaction in Driving Fibrogenesis and Liver Regeneration*
11:20 am	**A/Prof. Nick Shackel (University of Sydney, NSW)** *Stem Cells and Progenitor Responses in Liver Injury: Friend or Foe?*
11:40 pm	**Dr. Liang Qiao (Storr Liver Centre, Westmead Millennium Institute, NSW)** *Using Aptamers to Target Cancer Stem Cells in Liver Cancer*
12:00 pm	**Dr. Andreia Pinho (Garvan Institute, NSW)** *Embryonic Progenitor Signalling Pathway Reactivation in Pancreatitis and Pancreatic Cancer*
12:20 pm	**Prof. Minoti Apte, OAM (University of NSW)** *Stem Cell Niche in Pancreatic Cancer – Influenced by the Tumour Microenvironment?*

PROGRAM

12:40 pm	Lunch/ Poster session
Session 3	**Bowel** **Chair: Dr Michael O'Connor (University of Western Sydney, NSW)**
1:40 pm	**Prof. Robert Ramsay (Peter MacCallum Cancer Centre, VIC)** *Transcriptional Networks Co-operate to Orchestrate the Stem Cell Compartment in the GI Crypt*
2:00 pm	**A/Prof. Helen Abud (Monash University, VIC)** *Snail Proteins as Master Regulators of Stem Cell Fate in the Intestinal Epithelium*
2:20 pm	**Dr. Lincon Stamp (University of Melbourne, VIC)** *Neural Stem Cell Therapy for Gut Motility Disorders*
2:40 pm	**Prof. Rupert Leong (Concord Hospital, University of Sydney, University of NSW)** *Mesenchymal Stem Cells in Inflammatory Bowel Disease*
3.00 pm	Afternoon tea / Networking

Dr E. Russell Vickers PhD, MDSc, MMSc, MArt (Hons, Painting), BDS, FFPMANZCA, DipHerbalMed.

Dr Russell Vickers is an Oral & Maxillofacial Surgeon and Pain Specialist. In addition, he is qualified in herbal medicine and is an analytical and peptide chemist. Dr Vickers holds an appointment as Clinical Senior Lecturer at Sydney Medical School, University of Sydney. He was appointed as the Balthasar Research Scholar in Anaesthesia at the University of Sydney and has published approximately 35 book chapters, research articles and clinical case reports. He is a reviewer for four international journals. Dr Vickers completed his training in stem cells in 2010 at the Australian Government Stemcore Facility, University of Queensland. In his spare time he is a professional artist in painting and printmaking focussing on figurative and abstract art.

Dental, Oral and Facial Applications of Stem Cells

Stem cells have been identified in several dental tissue types including the periodontal ligament, dental follicle, apical papilla, exfoliating deciduous teeth and two subpopulations of the adult dental pulp. Sourcing dental stem cells is relatively simple and ethical – children's deciduous exfoliate naturally, and impacted adult wisdom teeth. Teeth represent an autologous supply and act as a robust and protective casing for long-term cryostorage of cells. The dental pulp is an enriched neurovascular tissue with potential clinical applications of stem cells in treating neurodegenerative disease. Animal studies have shown excellent recovery of stroke injury using dental pulp cells. The author has recently demonstrated the administration of autologous adipose stem cells to the oral and facial regions is safe and efficacious for human neurological pain (Vickers et al. J Pain Res 2014) and regeneration of human facial atrophy (Vickers, Modern Medicine 2015 in press).

Prof Yin Xiao—Queensland University of Technology

Professor Yin Xiao is currently a group leader of the Bone and Tissue Engineering research program at Queensland University of Technology (QUT). He obtained his BDSc and MDSc from Wuhan University, China, and has 10 years clinical experience. In 2000, he graduated with a PhD from the School of Dentistry at the University of Queensland (UQ), Australia. He is currently the Director of Australia-China Centre for Tissue Engineering and Regenerative Medicine (ACCTERM). Professor Xiao's work has predominantly focused on the fields of bone biology, biomaterials, stem cells, dentistry, osteoarthritis, and tissue regeneration/engineering. He has published 2 edited books, 10 invited book chapters and more than 170 journal papers. In the last five years, Professor Xiao's citation index (h-index: 36) has risen significantly with more than 3400 citations.

Dental Pulp-Derived Stem Cells and the Application for Regenerative Medicine

Dental pulp-derived stem cells (DPSCs) have shown promising potential in tissue repair and regeneration. However, during *in vitro* culture, these cells undergo replicative senescence and result in significant alterations in cell proliferation and differentiation. For the first time we demonstrated that reprogramming markers Oct-4, Sox2 and c-Myc were spatially and temporally expressed in the early culture of dental pulp derived cells. The expression pattern and sequential loss of these markers in DPSC cultures may be related to the cell fate of dental pulp-derived cells during the long-term *in vitro* cultivation under current culture conditions. It is noted that microenvironment can manipulate these key molecular pathways controlling the potential stem cell application in regenerative medicine.

Dr Agnes Arthur—University of Adelaide

Dr Agnes Arthur is a Mary Overton Research Fellow employed by The Royal Adelaide Hospital, located at the South Australian Health and Medical Research Institute (SAHMRI) working with Prof. Stan Gronthos in the Mesenchymal Stem Cell Laboratory. She completed a Bachelor of Science at the University of Adelaide in 1999, with honours in the Department of Surgery (2000), investigating the involvement of the Eph/ephrin molecules in sciatic nerve injury and repair. She then worked as a research assistant for two years before commencing her PhD in 2003 through the University of Adelaide under the guidance of Prof. Simon Koblar and Prof. Stan Gronthos. During her PhD and thereafter, she investigated the role of the Eph/ephrin molecules during dental pulp stem cell (DPSC) migration and differentiation. Secondly; she investigated the neural potential of DPSC, establishing novel (patented) techniques using an *in ovo* avian embryo model to investigate the neuroplasticity of DPSC and their therapeutic potential to treat the effects of stroke. Furthermore, with the support of the Mary Overton Research Fellowship, ADRF and NHMRC grants, she has continued to investigate the function of the Eph receptor tyrosine kinase family during mesenchymal stem cells migration and endochondral differentiation and their importance during skeletal development and repair following trauma induced by tooth injury, fracture or osteoporosis. She has also investigated the supportive role of bone marrow derived MSC in lymphocyte function and haematopoietic support. This work has utilised both human samples, transgenic and conditional knockout mouse models.

Isolation, Characterisation and Application of Dental Stem Cells

Stem cell research has highlighted the importance of mesenchymal stem cells (MSC) for tissue regeneration. Mesenchymal stem cells, were initially identified in bone marrow aspirates, then later from various other tissues such as adult dental pulp (DPSC: dental pulp stem cells), primary teeth (SHED: stem cells from human exfoliated deciduous teeth) and periodontal ligament (PDLSC: periodontal ligament stem cells). These MSC-like cell populations can be identified, isolated and purified from their respective tissues with specific markers such as STRO-1 and CD146. The different tissue specific MSC populations are ideal candidates to investigate tissue regeneration due to their ability to extensively proliferate in culture and their self-renewal capacity following serial transplantation *in vivo*. In addition, their "plasticity" allows them to differentiate into a variety of stromal cell types including bone, fat and cartilage, and other lineages such as muscle cells and neural cells. Furthermore, xenogeneic transplantation studies demonstrate that cultured human DPSC and SHED when implanted with hydroxyapatite-tricalcium phosphate ceramic granules subcutaneously into immune-compromised mice were able to recapitulate a donor-derived dentin-pulp-like tissue containing a distinct odontoblast layer which lined mineralised dentin surfaces. A unique and important attribute of MSC, including DPSC and SHED is their immunomodulatory properties, including their ability to augment immune responses and escape immune cell surveillance. Collectively, these observations demonstrate the presence of multipotential MSC-like populations derived from specific dental tissues with the potential to regenerate living human dental *in vivo*. Their characteristics make DPSC and SHED potential candidates for allogeneic based cell therapies. However, advancement in the field requires a greater understanding of the properties of these MSC, to help elucidate the essential conditions necessary to maintain and expand primitive cell populations *ex vivo*, in order to effectively direct and enhance their developmental potential for a range of tissue engineering and gene therapy strategies.

Prof Grant Ramm—QIMR Berghofer Medical Research Institute

Professor Grant A. Ramm is Head of Department - Cell and Molecular Biology, Group Leader - Hepatic Fibrosis and Principal Research Fellow at QIMR Berghofer. He is funded by a NHMRC Senior Research Fellowship. His research is focussed on the mechanisms associated with hepatic stellate cell transdifferentiation into fibrosis-causing myofibroblasts and their interaction with liver progenitor cells driving wound healing, inflammation, fibrogenesis and liver regeneration. In addition, translation of mechanistic observations into clinical application for the differential diagnosis, monitoring progression, and predicting disease outcome in chronic liver disease associated with Haemochromatosis, Biliary Atresia and Cystic Fibrosis-associated liver disease.

Liver Progenitor Cell-Hepatic Stellate Cell Interaction in Driving Fibrogenesis and Liver Regeneration

Despite advances made in understanding the mechanisms of liver injury, liver disease continues to be one of the most rapidly growing cause of death in subjects aged <65yrs and will remain a top 10 cause of global mortality until at least 2030. Recent data from Deloitte Access Economics proposes that the total economic burden of chronic liver disease in Australia in 2012 was >$50 billion, representing a cost to the nation ~40% higher than the economic costs associated with type 2 diabetes and chronic kidney disease combined. Mortality and morbidity are the results of uncontrolled and inappropriate hepatic wound healing and regeneration, which ultimately results in cirrhosis and hepatocellular carcinoma. Recent studies have demonstrated that a specific type of liver injury response known as the “ductular reaction”, (including proliferation and expansion of the liver stem cells, the bipotential liver progenitor cell), may be a driver of wound healing. My research investigates the interaction between hepatic stellate cells (myofibroblasts) and liver progenitor cells in driving both the ductular reaction and fibrogenesis. We propose that the activation and differentiation status of both cell types, as well as their beneficial vs. pathological contributions, are controlled by cellular cross-talk involving molecules of the TNF superfamily, signalling mediators such as notch/jagged1, along with miRNAs, chemokines and growth factors which direct cellular differentiation and activation. *Strategies to reduce the impact of liver disease in the future will have to rely on new treatments targeting such regulatory pathways, irrespective of the inciting aetiology.*

A/Prof Nicholas Shackel – University of Sydney

Associate Professor Nick Shackel is a clinical scientist with an established tract record in academia. He is the recipient of multiple awards including a NHMRC Gustav-Nossal Scholarship and a NHMRC C. J. Martin Fellowship and has authored 78 publications. A/Prof. Shackel pioneered the use of functional genomics methods to study human liver and his academic output to-date has resulted in a number of significant novel findings including:

1. Identification of a Th1 immune phenotype in HCV liver injury
2. Identification of increased WNT pathway gene expression in biliary liver disease
3. Identification of the collagen receptor DDR1 on human hepatocytes and its increased expression in human cirrhosis
4. Identification of increased RERE expression and trans-alternate splicing in HCV cirrhosis
5. Identification of EMMPRIN in human cirrhosis
6. The initial description of the Hh pathway in human liver disease

A/Prof. Shackel has been awarded a number of prizes overseas for research excellence including the 1st Poster Prize at the 2002 Basel Liver Week, an American Australian Association Keith Murdoch Award in 2002, an American Liver Foundation Post-Doctoral Fellowship in 2003 and poster prize at the 2007 Australian Gastroenterology Week. Dr Shackel is a Staff Specialist in Gastroenterology Royal Prince Alfred Hospital Camperdown, Sydney, Head of Genomic Medicine and Research Officer, Centenary Institute, Sydney, a Senior Lecturer at The University of Sydney (Department of Medicine, University of Sydney and supervises research students and staff.

Stem Cells and Progenitor Responses in Liver Injury: Friend or Foe?

The contribution of bone marrow stem cell responses to liver homeostasis, injury and malignancy will be discussed. Pluripotent stem cells or their more committed progenitor progeny are essential to tissue development, regeneration and repair and are widely implicated in the pathogenesis of malignancy. Stem cell responses to injury are the focus of intense research efforts in the hope of future therapeutic manipulation. Stem cells occur within tissues, such as the liver, or arise from extrahepatic sites, in particular, the bone marrow. As the largest reservoir of stem cells in the adult, the bone marrow has been implicated in the stem cell response associated with liver injury. However, in liver injury, the relative contribution of bone marrow stem cells and intrahepatic progenitor responses is poorly characterized. In this presentation, a summary of liver-specific extrahepatic stem cell and intrahepatic progenitor responses will be presented. The physiological relevance of bone marrow stem cell and progenitor responses to adult liver homeostasis, injury and malignancy is discussed with emphasis on mechanisms of bone marrow stem cell or progenitor cell recruitment to sites of liver injury and its contribution to intrahepatic malignancy.

A/Prof. Liang Qiao—Storr Liver Unit, Westmead Millennium Institute

Associate Professor Liang Qiao is currently the Group Leader of the Cancer Biology at the Storr Liver Centre at the Westmead Millennium Institute, the University of Sydney. His research projects are funded by NHMRC and NSW Cancer Council. A/Prof Qiao's research interests include inflammation-related gastrointestinal and liver cancers, with a particular focus on the role of cancer stem cells in inflammation related cancers. He is currently working on several projects, including role of IL-6 and Notch signaling in liver cancer and targeting cancer stem cells as a novel approach in liver cancer therapy. A/Prof Qiao serves as an assessor for NHMRC project grants and several other overseas funding bodies (Wellcome Trust, The Israel Science Foundation, National Research Foundation of UAE College of Science). He is on the editorial board for several international journals in the field of cancer and gastroenterology/hepatology (Cancer Letters, Current Gene Therapy, etc). He reviews manuscripts for several international journals (Oncotarget, Int J Nanomed, J Hepatol, Stem Cell Dev, J Gastroenterol Hepatol, Liver International). He is a member of the European Association for the Study of the Liver (EASL), a member of the Australian Society for Stem Cell Research (ASSCR), and a member of the Cell Reprogramming Australia (CRA).

A/Prof Qiao has published in Hepatology, J Hepatol, Mol Cell Biol, Mol Biol Cell, Hum Gene Ther, Cancer Res, Mol Cancer Ther, Int J Cancer, Oncotarget, Carcinogenesis, BBA-Mol Cell Res, Cancer Lett, and Cancer Stem Cell Dev).

Using Aptamers to Target Cancer Stem Cells in Liver Cancer

Hepatocellular carcinoma (HCC) is the sine qua non inflammation-associated malignancy, with hepatitis B virus (HBV) and hepatitis C virus (HCV) the major etiological factors. Globally, HCC is the 6th most common cancer the 3rd most common cause of cancer-related death. Only 20% of cases are suitable for curative surgery, leaving the majority with non-curative options and a 5-year survival <30%. Liver cancer is highly resistant to chemotherapy and not responsive to radiotherapy. The multikinase inhibitor Sorafenib increases median survival by just 3 months and adaptive resistance is common. Thus, there is an urgent unmet clinical need to develop novel approaches to treat this disease, predicated on a better understanding of the molecular mechanisms driving tumor growth and treatment resistance. In this regard, HCC is in part a stem cell disease wherein liver cancer stem cells (LCSCs) are involved in tumor initiation, recurrence and drug resistance. We hypothesize that resistance of HCC to current treatments is due to their inability to eradicate LCSCs. Hence, selective eradication by high-affinity, high-specificity RNA aptamers against stem cell surface markers, coupled with conventional chemotherapeutic agents will greatly enhance cure rates.

Dr Andreia Pinho—Garvan Institute

Dr. Andreia Pinho was a fellow of the Portuguese Doctoral Program GABBA and carried out her PhD research in the Spanish National Cancer Research Centre in Madrid, Spain, under the supervision of Dr Francisco Real. Her doctoral research project focused on understanding the mechanisms of pancreatic cell differentiation involved in pancreatitis and pancreatic cancer. In 2011, Dr. Pinho joined the Pancreatic Tumourigenesis Group at the Garvan Institute in Sydney, where she is engaged in providing further insights into the molecular mechanisms implicated in the development of pancreatic cancer. Her project's aim is to uncover the function of novel signalling pathways altered in pancreatic cancer patients, with the aim of discovering new pancreatic cancer biomarkers and therapeutic targets. Dr Pinho is a Cancer Institute NSW Early Career Fellow and a Conjoint Lecturer at St. Vincent's Clinical School, UNSW Australia. She has authored numerous papers published in journals such as Nature, Gut, JCO, Cancer Research and Cancer Letters and has been attributed several awards and honours, including the Young Garvan Award in 2012.

Reactivation of Embryonic Signalling Pathways During Pancreatitis and Pancreatic Cancer

The pancreas is a glandular organ composed of two distinct compartments, exocrine and endocrine. The exocrine compartment is constituted by acinar and ductal cells, being responsible for the production and delivery of enzymes essential for digestion of food, while the endocrine islets of Langerhans regulate glucose homeostasis. The presence of a defined stem cell compartment in the adult pancreas has been debated for many years and genetic lineage tracing studies have failed to identify true pancreatic stem cells. Nevertheless, during stress conditions, pancreatic acinar cells are able to dedifferentiate and function as facultative progenitors in the adult pancreas, retaining the capacity for self-renewal, as well as to transdifferentiate into ductal and endocrine cells. The ability of acinar cells to undergo acinar to ductal transdifferentiation has been shown to be a trigger event in the development of diseases that affect the exocrine pancreas such as chronic pancreatitis and pancreatic ductal adenocarcinoma (PDAC). We have shown that during pancreatitis, murine acinar cells reactivate characteristics of embryonic pancreatic progenitors but yet, are unable to proliferate due to the activation of a p53-dependent senescence program. Activation of KRas oncogene, the most common mutation in pancreatic cancer patients, is able to overcome this growth arrest leading to the development of PDAC. Several transcription factors that specify embryonic pancreatic progenitor cells and the subsequent acinar and duct cell lineage have recently been found to play a role in tumourigenesis. We and others have shown that reactivation of Sox9 expression in adult acinar cells is required for the occurrence of acinar to ductal transdifferentiation and consequent initiation of PDAC. We found that Sox9 acted through the activation of the oncogenic EGFR/ERBB signalling pathway. In summary, acinar cells can function as facultative progenitor cells in the adult pancreas, being responsible for pancreatic cell regeneration following stress conditions and injury. Nevertheless, the ability of acinar cells to transdifferentiate into ductal cells can also lead to pathologies such as chronic pancreatitis and pancreatic cancer. It is essential to understand the mechanisms that regulate acinar cell plasticity in the pancreas to improve detection and therapeutic approaches.

Prof Minoti Apte—University of New South Wales

Professor Minoti Apte OAM, is a Professor of Medicine at UNSW and Director of the Pancreatic Research Group in the SWS Clinical School, based at the Ingham Institute, Liverpool Hospital. She is internationally recognised for her pioneering work in pancreatic fibrogenesis. Her group was the first in the world to isolate and characterise pancreatic stellate cells, now known to play critical roles in the progression of pancreatitis and pancreatic cancer. Professor Apte has held more than $11 million in competitive research grants and her work has received over 4000 citations. She is currently the Editor-in-Chief of Pancreatology, one of the two leading journals in the field.

Professor Apte has served as Presiding Member of the Faculty of Medicine (2008-2011), and as Chair of the Faculty Board, Faculty Standing Committee and the Faculty Higher Degree Committee. She has been the Postgraduate Coordinator for the South Western Sydney Clinical School since 2001. Professor Apte was awarded a Medal of the Order of Australia in 2014 and has received the 2015 NSW Premier's Award for Woman of the Year in recognition of her contribution to medical research, tertiary education and the Indian community.

Stem Cell Niche in Pancreatic Cancer – Influenced by the Tumour Microenvironment?

Pancreatic cancer stem cells have received increasing attention over the past 8 years or so, starting with the first report published in 2007 of a subpopulation of cancer cells exhibiting upregulated expression of stem cell markers such as CD24, CD44 and epithelial-specific antigen (ESA) and importantly, displaying a high potential for tumorigenicity. Several studies have subsequently reported additional markers for pancreatic cancer stem cells including nestin, ABCG2, c-Met and ALDH-1. The challenge in the field is i) to determine whether all these markers are uniformly expressed by all cancer stem cells or whether subsets of stem cells are differentially enriched for one or more of the above markers; and ii) to identify the mechanisms that facilitate the maintenance of stemness. Accumulating evidence supporting a key role of the tumour microenvironment (stroma) in pancreatic cancer progression has led to studies assessing the effects of stromal cells on cancer stem cells. It has been reported that pancreatic stellate cells (PSCs, the key cells responsible for the production of the collagenous stroma in pancreatic cancer) induce the expression of the stem cell markers nestin, ABCG2 and LIN28 in pancreatic cancer cells and stimulate spheroid formation and invasiveness of pancreatic cancer cells in vitro. These findings suggest that PSCs may facilitate the formation of a stem cell niche in pancreatic cancer that may be responsible for tumour recurrence, a well-known feature of pancreatic cancer. Therefore, it is now increasingly acknowledged that effective therapy of pancreatic cancer requires a two-pronged approach that targets not only cancer cells but also interrupts stromal- tumour interactions.

Prof Robert Ramsay—Peter MacCallum Cancer Centre

Professor Robert Ramsay is the Group Leader of the Differentiation and Transcription Laboratory (since 1995) and Head of the Cancer Cell Biology Program at Peter MacCallum Cancer Centre. His PhD in Biochemistry was gained at the Queensland Institute for Medical Research. He did post-doctoral training at Memorial Sloan Kettering, New York and the Ludwig Institute, Melbourne and currently holds a NHMRC Senior Research Fellowship. He is President of the National Association of Research Fellows.

His research group's interests span from stem cells and colorectal (CRC) and breast cancer to neurogenesis, radiotherapy and genome instability.

Transcriptional Networks Co-operate to Orchestrate the Stem Cell Compartment in the GI Crypt

The intestinal crypt stem cell (ISC) population is cast with the life-long role of replenishing the gastrointestinal tract (GIT) mucosa every 3-4 days. If this was not enough of a responsibility there is also the task of responding to extrinsic damage following mucosal damage as a result of cytotoxic insults associated with infection, inflammation and chemo and radiotherapy. Central to this capacity is the network of transcription factors which co-ordinate the transcriptome underpinning both homeostasis and emergency responses. In an attempt to understand these networks we have employed *in vitro* and *in vivo* mouse model systems in reference to these transcription pathways noting those that are commonly activated in GI cancer. Importantly, we have deliberately examined these pathways together rather than in singularity, and also not simply *in absentia* (ie. by knockout studies). Five transcription factors will be considered; NFkB, STAT3, MYB, b-catenin/TCF4 and NOTCH1. Although not an exhaustive list we have found that these factors are substantially responsible for the dynamic responses of ISC to the life-long demands of the normal GI mucosa. In addition, from these studies we have a greater insight into the hierarchy and interplay between the signalling pathways that activate these transcriptional networks.

A/Prof Helen Abud—Monash University

Associate Professor Helen Abud is a Senior Lecturer in Developmental Biology and Head of the Epithelial Regeneration Laboratory in the Department of Anatomy and Developmental Biology within the School of Biomedical Sciences at Monash University. Following her undergraduate degree at Melbourne University, she initially trained at the Walter and Eliza Hall Institute before undertaking her doctorate at Oxford University in cell and developmental biology. This was followed by postdoctoral training in the Department of Anatomy (Oxford), Peter MacCallum Cancer Centre (Melbourne) and the Ludwig Institute for Cancer Research (Melbourne). A/Prof Abud's current research is centred on understanding the molecular mechanisms and environmental influences that regulate stem cells within tissues. A/Prof Abud has a particular interest in molecules that promote intestinal epithelial development and regeneration following damage and how these factors may be altered in degenerative diseases and colon cancer.

Snail Proteins as Master Regulators of Stem Cell Fate in the Intestinal Epithelium

Gastrointestinal diseases, infections and pathologies that arise in the epithelial layer are very common clinical problems. The intestinal epithelium is constantly renewed via a population of stem cells that reside in crypts. Understanding the mechanisms that regulate the maintenance of intestinal stem cells and their differentiation into specific cell types may provide insight into how to effectively manage intestinal disease. We are investigating the role of the Snail family of transcriptional regulators in regulating intestinal stem cell fate. Snail transcriptional regulators are well known for their role in mediating epithelial to mesenchymal transitions during cancer metastasis and embryonic development. Snail proteins have also been implicated in regulating stem cell populations in several adult organs. Our studies have revealed that Snai1 is localised in intestinal crypts and is required for survival and function of intestinal stem cells. Comparison of phenotypes where Snai1 is either conditionally deleted or ectopically expressed in the intestinal epithelium of mice demonstrates another key role for Snai1 in lineage specific differentiation of mature cell types. The specific function of Snail proteins in regulating regeneration of the intestinal lining following damage and in colorectal cancer is being examined using mouse models, organoid culture and analysis of primary tissue from patients with bowel cancer.

Dr Lincon Stamp—Melbourne University

Dr Lincon Stamp's research has focused on the derivation, isolation, characterisation and transplantation of stem cells from a variety of sources. Dr Stamp did his doctoral studies under the supervision of Professor Martin Pera at Monash University. The research involved investigation of the early differentiation of human ES cells toward the endodermal lineage, with a focus on hepatopancreatic development. This work led to 2 co-first author publications in *Stem Cells* journal (IF: 7.133), as well as the granting of an international patent on which Dr Stamp is a co-inventor (#WO2005/033126). Dr Stamp then joined the lab of Professor Heather Young as a Postdoctoral researcher at the University of Melbourne Department of Anatomy and Neuroscience, where he is working to develop a stem cell therapy to treat enteric neuropathies. Here the focus is on the development of neural crest and the enteric nervous system, and development of a small animal model of neural crest stem cell transplantation to treat enteric neuropathies. In particular, the research has aimed to develop a stem cell therapy to treat the paediatric enteric neuropathy, Hirschsprung disease. This work has led to a co-first author publication in the high-ranking journal, *Journal of Clinical Investigation* (IF: 13.765). In this world first study, Dr Stamp and colleagues showed that neural stem cells transplanted into the postnatal colon of mice can generate functional neurons of the appropriate neurochemical and electrophysiological phenotype. Dr Stamp's continued work in a broad range of stem cell populations has made a significant contribution to the field, especially the recent work on neural stem cell transplantation in small animal models of Hirschsprung disease.

Neural Stem Cell Therapy for Gut Motility Disorders

The enteric nervous system (ENS) plays important roles in controlling blood flow, secretion and motility in the gastrointestinal tract. Absence, loss or damage to the ENS, "*enteric neuropathies*", results in gut motility disorders. Cell therapy offers the potential to generate neurons in the bowel of patients with enteric neuropathies. We examined whether transplanted enteric neural progenitors can migrate and generate functional neurons in the colon of post-natal mice *in vivo*. Enteric neural progenitors were isolated from the gut of E14.5 or P4 transgenic mice and neurospheres were generated. Neurospheres were transplanted *in vivo* into the external muscle layers of the distal colon of 2-3 week old wild-type mice. The grafted cells migrated extensively and many of the graft-derived cells formed ganglion-like clusters containing glia and different subtypes of neurons, some of which projected fibres to the circular muscle of the recipients. Intracellular electrophysiological recordings demonstrated that the graft-derived neurons received synaptic inputs and could fire action potentials. To examine whether transplanted progenitors generate neurons that functionally innervate the gut musculature, enteric neural progenitor cells that express the light-gated ion channel, channelrhodopsin 2 (ChR2), were transplanted into the colon of 2-3 week old wildtype mice, and several weeks later, intracellular recordings were made from circular muscle cells near the transplant site. Light stimulation of transplant-derived ChR2-expressing neurons evoked inhibitory junction potentials (IJPs) in the muscle mediated by ATP and nitric oxide, and excitatory junction potentials mediated by acetylcholine. Our data also suggest that the transplanted progenitors generate both interneurons and motor neurons. In conclusion, using optogenetics to selectively stimulate transplant-derived neurons, our data show that enteric neural progenitors can generate neurons with appropriate phenotypes that functionally innervate the colonic circular smooth muscle in recipient mice.

Prof Rupert Leong—Concord Hospital

Professor Rupert Leong MBBS, FRACP, MD, AGAF is a Senior Staff Specialist gastroenterologist, Director of Endoscopy and Head of the Inflammatory Bowel Disease Service at Concord Hospital, Clinical Professor of Medicine at University of Sydney and UNSW, and founding director of IBD Sydney, Australia. He has an international reputation for the management of inflammatory bowel diseases and was involved in the Phase 2 study of mesenchymal stem cells in the treatment of refractory Crohn's disease. Professor Leong has made a substantial contribution to research with over 120 high quality scientific journals publications. Amongst these are senior authorship of national and international consensus guidelines in both Australia and in Asia. His service includes executive positions in the Research Committee of the Gastroenterological Society of Australia and section editor of the *Journal of Gastroenterology and Hepatology*. He is an executive member of a number of government bodies including the Agency for Clinical Innovation of NSW Health nominated for expertise in IBD and the Cancer Council of Australia Working Party on the revision of the clinical practice guidelines for the prevention, early detection and management of colorectal cancer. Professor Leong was awarded the American Gastroenterological Association Fellowship by invitation on the basis of research excellence in 2012.

Mesenchymal Stem Cells in Inflammatory Bowel Diseases

Despite the advent of biologic therapy for Crohn's disease (CD), about one quarter of patients still need major abdominal surgery within 5 years after their diagnosis. To avoid surgery, cellular therapy by bone marrow or peripheral blood stem cell transplantation, either allogeneic or autologous, has been used successfully in small numbers of patients, but requires prior myeloablative therapy or hematopoietic stem cell mobilization.

By contrast, mesenchymal stromal cells (MSCs) are multipotent adult stem cells that are considered to lack immunogenicity. They have low level HLA class I expression, lack HLA class II antigen, and do not express co-stimulatory molecules. Accordingly, in allogeneic administration, donor to recipient matching is not required, nor chemotherapeutic marrow conditioning. The immunomodulatory properties of MSC have been applied successfully to steroid-refractory graft-versus-host disease (GVHD) and are under evaluation in other diseases. Prior experience demonstrated efficacy of MSC in the treatment of fistulising CD.

We investigated the efficacy of allogeneic MSCs in patients with luminal CD in a phase 2 study. Among the 15 patients who completed the study, the mean Crohn's disease activity index (CDAI) score was reduced from 370 (median, 327; range, 256–603) to 203 (median, 129) at day 42 ($P < .0001$). The mean CDAI scores decreased after each MSC infusion (370 before administration, 269 on day 7, 240 on day 14, 209 on day 21, 182 on day 28, and 203 on day 42). Twelve patients had a clinical response (80%; 95% confidence interval, \ 72%–88%; mean reduction in CDAI, 211; range 102– 367), 8 had clinical remission (53%; range, 43%–64%; mean CDAI at day 42, 94; range, 44–130). Seven patients had endoscopic improvement (47%), for whom the mean CDEIS scores decreased from 21.5 (range, 3.3–33) to 11.0 (range, 0.3–18.5). One patient had a serious adverse event (2 dysplasia-associated lesions), but this probably was not caused by MSCs.

We concluded that administration of allogeneic MSCs was well-tolerated, reduced CDAI and CDEIS scores in patients with luminal CD refractory to biologic therapy.

Posters

1. **Investigation of the tongue myogenic mechanisms during embryonic development and adult satellite cell differentiation**

   Neha Pandey, Sanjeev Julka, Munira Xaymardan

   Bioengineering Laboratory, University of Sydney

2. **GCTM-5 a marker of Endodermal progenitors and a possible biomarker for pancreatic cancer and other disease states**

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