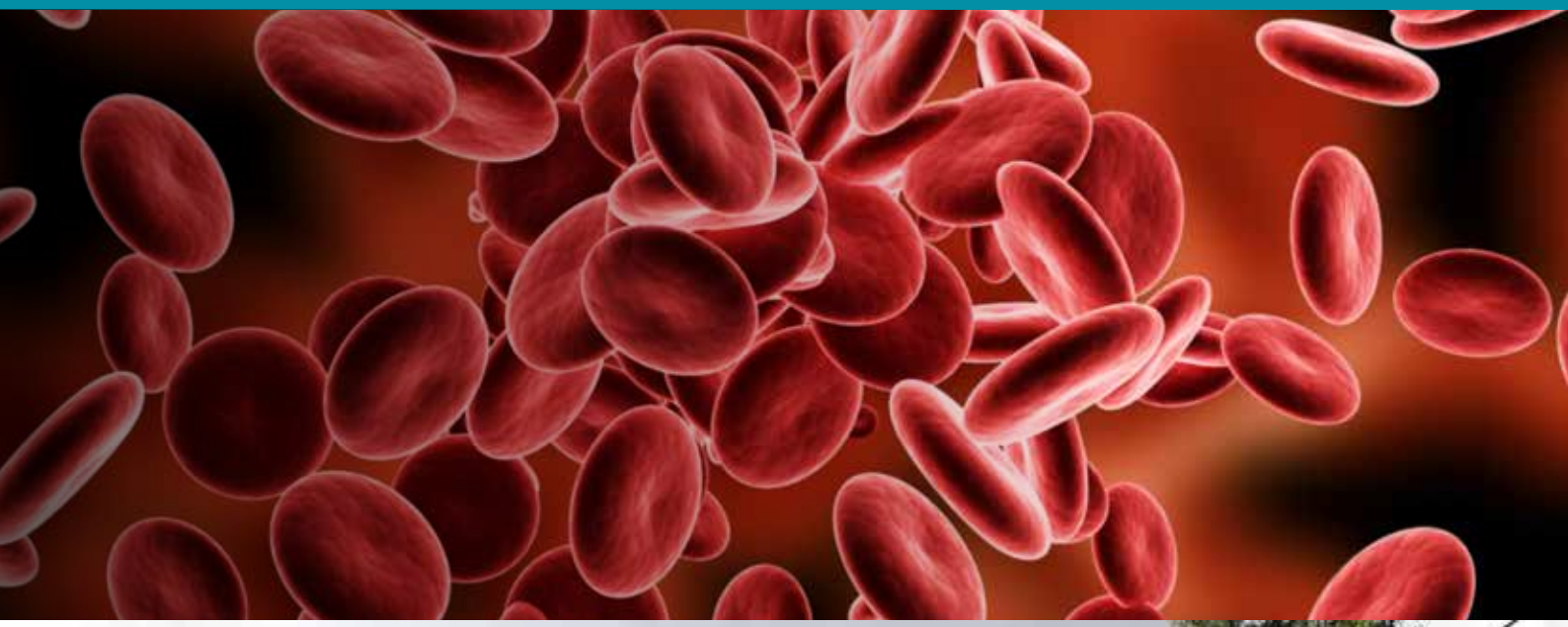
# MMR

Medical and Molecular Research (MMR) Strategic Research Centre

DEAKIN
UNIVERSITY AUSTRALIA



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# OVERVIEW

The Molecular and Medical Research (MMR) SRC represents a critical mass of world-class medical researchers investigating the molecular basis of health and disease. It combines biomedical, pre-clinical and clinical research programs consisting of over 100 staff and research students. The MMR-SRC attracts extensive funding from National Competitive Grant schemes, including multiple prestigious Fellowships. There is an emphasis on high quality research that makes a difference, reflected in highly cited, high impact publications.

Research within the MMR SRC encompasses the following core Themes:

- Metabolic Research
- Musculoskeletal Medicine
- Cancer
- Infection & Immunity
- Neuro/Vision Science
- Cell and Organism Biology
- EnviroHealth

An innovative feature of the MMR SRC is its strong inter-disciplinary approach, which includes significant expertise in the use of sophisticated animal models, including mouse, rat and zebrafish, buttressed with cellular, molecular and clinical studies. This work is supported by cutting-edge technological approaches, including phenomic, metabolic and genomic analysis, as well as advanced imaging and cell analysis, extending to clinical trials.

This research is performed at the following leading-edge research facilities across Deakin and its partners:

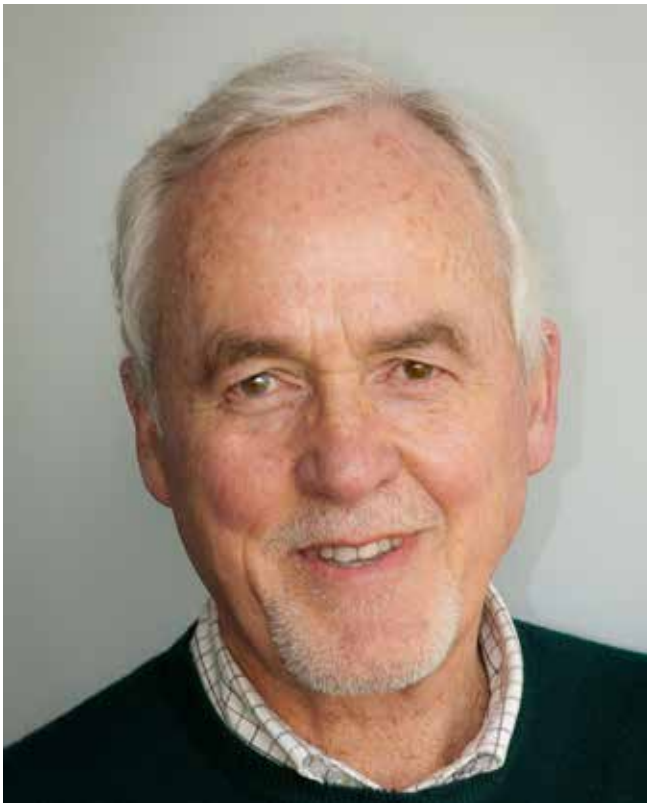
- Metabolic Research Unit
- Molecular Medicine Research Facility
- Centre for Cellular and Molecular Biology
- Barwon Biomedical Research Laboratories/ Andrew Love Cancer Centre
- CSIRO(AAHL)/Deakin Collaborative Laboratories

# RESEARCH HIGHLIGHT: LIFETIME ACHIEVEMENT AWARD TO PROF ANDREW SINCLAIR

A lifetime devoted to the study of fatty acids and lipids has been honoured with an "Alexander Leaf Distinguished Scientist Award for Lifetime Achievement 2014", awarded to Professor Andrew Sinclair by the International Society for the Study of Fatty Acids and Lipids (ISSFAL), the world's premier lipids and fatty acids research organisation. The award named in honour of ground-breaking nutritionist Dr Alexander Leaf, and to recognise and reward international research excellence in this field, will be presented at ISSFAL's Biennial Congress, to be held in Stockholm in June this year.

Professor Andrew Sinclair is Chair in Nutrition Science within the School of Medicine, and is located in the Metabolic Research Unit. He is known as one of Australia's leading nutritionists, with much of his 46 year career devoted to the study of the role of lipids and fatty acids in human health, functional foods, saturated and trans fatty acids and long chain omega 3 fatty acids. He has played a key role in raising awareness of the importance of omega 3 fatty acids for a range of health benefits, as well as some key research findings on the essential nature of different fatty acids including the first report of essential fatty acid deficiency in an adult human, the first report of linolenic acid deficiency in a primate, the discovery that domestic cats had abberant fatty acid metabolism, and characterising the unique polyunsaturated fatty acid fingerprint of the mammalian brain. Professor Sinclair's current research program focusses on the bioavailability of omega 3 fatty acids from different food sources in humans and animals. Omega 3s are contained within polyunsaturated fat, particularly in oily fish, and play a major role in the prevention and management of cardiovascular disease, reducing inflammation resulting from rheumatoid arthritis, as well as helping to maintain eyesight, weight, cognition and mental health.

Professor Sinclair is the immediate past Chairperson of the Nutrition Committee of the Australian Academy of Science and has long been very active in the Nutrition Society of Australia, with whom he is a Fellow. Within this Society, he has held several positions including Editor, Secretary and President. He is also an Associate Editor of the "British Journal of Nutrition", and sits on the



Editorial Board of "Prostaglandins, Leukotrienes and Essential Fatty Acids" and "Asia Pacific Journal of Clinical Nutrition."

Professor Sinclair has also made a significant contribution to the Deakin research community, establishing links with researchers from all campuses in the area of omega 3 research, along with colleagues Professor Leigh Ackland, Assoc Prof Giovanni Turchini and Professor Colin Barrow. In addition, Professor Sinclair, along with Dr Laura Gray, has established the Deakin Neural Network – a network for brain researchers across all Deakin campuses. Both of these research networks are involved in mentoring younger researchers and trying to establish collaborations across the University.

# RESEARCH HIGHLIGHT: FELLOWSHIP TO DR CHRISTIN GASCH

*Members of the Mellick Lab. Dr Christin Gasch, Dr Albert Mellick, Dr Prue Plummer.*

Dr Christin Gasch was awarded her doctorate in 2012 from the University of Hamburg, University Medical Centre Hamburg-Eppendorf for work in identifying genetic heterogeneity in single tumour cells isolated from the blood of colorectal cancer patients. Dr Gasch was subsequently awarded a prestigious German Research Foundation Fellowship which she has recently transferred to Deakin University, commencing in the Molecular Medicine Research Facility of the Deakin Medical School in 2014. This forms part of a collaboration with Dr Albert Mellick and Prof Pantel at the Institute for Tumour Biology (University Hospital Hamburg-Eppendorf).

Despite many decades of research, colon cancer remains an important cause of mortality. However, cancer-related deaths are rarely a direct result of growth of the tumour in the colon. Instead colon cancer cells shed from the tumour often metastasise to important organs and tissues, such as the brain, lung and liver. There is an inverse correlation between the number of circulating tumour cells (CTCs) in the peripheral blood and prognosis for patients with colorectal cancer. However, not all CTCs will be founders of secondary metastatic lesions, and only those CTCs with the predisposition to form metastases are clinically significant. As CTCs are rare (as few as 1 CTC in 106-108 blood cells) the detection and characterization of these cells remains technically challenging. However, Dr Gasch has shown in previous work that these cells are genetically and phenotypically heterogeneous (Gasch et al., Clinical Chemistry & Cancer Research 2013), which only partly reflects the heterogeneity observed in the primary tumour, and likely to be clinically important. For instance, mutations present in CTCs that cannot be detected in the primary tumour may explain why the application of certain drugs (anti-EGFR inhibitors), leads to resistance through the selection of a resistant CTC subpopulation. Therefore, identifying clinically significant CTCs in the peripheral blood of cancer patients is essential for the development of future therapies.

Dr Gasch's Fellowship will study clinically important circulating tumour and circulating endothelial progenitor cell (CTCs and CEPs) in the peripheral blood as a diagnostic marker of clinical course and outcome. Dr Gasch will apply novel techniques in single cell analysis, and cell based diagnosis, as well as genetic marker identification, to breast and colon cancer patients.

# RESEARCH FOCUS: DR BERNHARD DICHTL

## Background

Dr Dichtl's research revolves around the function of complex molecular machines that are involved in the processing of RNA and the modification of chromatin. He performed his PhD studies at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany and at the University of Edinburgh, Scotland working on the molecular toxicity of lithium and the processing of ribosomal RNA and transfer RNA precursors. Supported by a prestigious EMBO Long-term Fellowship he then took up post-doctoral work at the Biocenter, Basel, Switzerland where he studied the mechanisms of pre-mRNA polyadenylation and transcription termination. The awarding of a highly competitive Foerderprofessur grant from the Swiss National Science Foundation (SNF) allowed him to establish his own research group at the Institute of Molecular Life Sciences, University of Zurich, Switzerland. There he expanded his research activities to the analyses of chromatin modifying enzymes and the assembly of multi-protein complexes. In November 2010, Dr Dichtl's laboratory relocated to the Centre for Cellular & Molecular Biology in the School of Life & Environmental Sciences, Deakin University. In 2014 he was awarded an ARC Discovery Project grant to study the 'mechanisms of protein complex formation'.

## Research interests

1. The role and regulation of alternative polyadenylation in health and disease.

Pre-mRNA 3' end formation is an essential RNA maturation step that impacts on virtually all aspects of mRNA function. The process adds a tail of approximately 250 adenosines to the 3' end of mRNA and determines the length of the 3' un-translated region (3'UTR), which is targeted by a large number of regulatory factors. Control of 3'UTR length via alternative polyadenylation (APA) is an important mechanism to control gene expression. Research is focused on the regulation of APA and how it is integrated with cellular signaling pathways.

2. The function and regulation of Set1C histone methyltransferase.

Histone modifying enzymes regulate diverse processes that occur in association with chromatin. Extensive yeast two-hybrid screening in the Dichtl laboratory identified novel cellular roles for the Set1C chromatin-modifying enzyme. This resulted in a recent publication in Science (Acquaviva et al., 2013) describing the molecular mechanisms linking chromatin modification of histone H3 lysine 4 to the formation of double strand DNA breaks, which initiates the process of meiotic recombination.

3. Co-translational protein complex formation.

Multi-protein complexes constitute some of the most relevant molecular units of cellular function. Despite their important role it remains mysterious how eukaryotic cells manage to assemble with precision hundreds of different complexes in the crowded cytoplasmic compartment that produces thousands of nascent proteins at the same time. Work from the Dichtl laboratory has demonstrated that assembly of protein complexes can be initiated on nascent proteins as they emerge from the ribosome (Halbach et al, 2009). Current projects are investigating the functional significance of co-translational protein interactions.

## Key publications:

*1. Acquaviva L, Székvölgyi L, Dichtl B, Dichtl BS, de La Roche Saint André C, Nicolas A, Géli V. (2013) "The COMPASS subunit Spp1 links histone methylation to initiation of meiotic recombination.", Science 339, 215-218.*

*2. Holbein S, Scola S, Loll B, Dichtl BS, Hübner W, Meinhart A, Dichtl B. (2011) "The P-loop domain of yeast Clp1 mediates interactions between CF IA and CPF factors in pre-mRNA 3' end formation.", PLoS ONE 6, e29139.*

*3. Halbach A., Zhang H., Wengi A., Jablonska Z., Gruber I. M., Halbeisen R., Dehé P.M., Kemmeren P., Holstege F., Geli V., Gerber A. and Dichtl B. (2009) "Cotranslational assembly of the yeast SET1C histone methyltransferase complex." EMBO J. 19, 2959-2970.*

# RESEARCH FOCUS: DR MUSTAFA KHASRAW

## Background

Dr Khasraw's research is focused on the development of novel therapies that improve outcomes in cancer patients. He is engaged in numerous collaborative research projects across different tumour streams including breast cancer, gastrointestianal and neuroendocrine tumours and in neuro-oncology, including primary brain tumours, brain metastasis and the neurological complications of cancer.

Dr Khasraw completed his medical oncology training in Sydney, and subsequently undertook an oncology fellowship in the United States at Memorial Sloan-Kettering Cancer Center in New York. His fellowship encompassed both neuro-oncology and breast cancer, where he participated in design and conduct of clinical and translational studies. He is the author of numerous manuscripts and book chapters and acts regularly as a reviewer for a number of scientific journals. Dr Khasraw was a panel member of the Priority-driven Collaborative Cancer Research Scheme, and invited reviewer for a number of grant schemes and scientific journals.

Dr Khasraw is the clinical lead of the Haematology-Oncology clinical trials unit at the Andrew Love Cancer Centre in Geelong, and a consultant medical oncologist at Geelong and Royal Melbourne Hospitals in Victoria. He is also a Senior Clinical Lecturer at Deakin University, School of Medicine and a Clinical Research Fellow for the NHMRC Clinical Trials Centre at The University of Sydney.

## Research interests

1. Systemic therapy for breast cancer.

Neoadjuvant or primary systemic therapy is commonly used when tumours are relatively large and shrinking them is desirable to make surgical removal possible or to have a wide local excision rather than mastectomy. Chemotherapy in the neo-adjuvant setting can shrink breast tumours and sometimes complete pathologic response defined as absence of invasive tumour in the excised surgical sample.

Dr Khasrasw is conducting the NEONAB clinical trial which offers women with early breast cancers larger than 2 cm the option of undergoing neoadjuvant chemotherapy if their tumour is highly likely to respond to cytotoxic agents. This enriched population includes triple negative, HER2 positive breast cancers and hormone receptor-positive tumours with an Oncotype DX score > 25. Oncotype DX is a gene test that has been shown to predict which patient is likely to benefit from chemotherapy after surgical removal of the tumour, so that

women who are unlikely to have a good response are spared the side effects of chemotherapy. In addition to assessing how well the treatment works, a set of translational endpoints will also be measured to increase our understanding and improve future therapies of breast cancer. Dr. Khasraw has also developed a clinical trial program in collaboration with national and international collaborators to offer the testing of novel therapies to breast cancer patients in the Geelong region.

2. Novel therapies for high grade gliomas.

Dr Khasraw works for the The Australian Cooperative Trials Group for Neuro-Oncology (COGNO) to develop and conduct innovatine clinical trials in patients with brain tumours. He has also led the completion of the ExCentric clinical trial of Radiotherapy (RT), temozolomide (TMZ), procarbazine (PCB), and the integrin inhibitor cilengitide in patients with glioblastoma (GBM) without methylation of the MGMT gene promoter. This multicentre study was conducted across 4 Australian sites and the results are being analysed. Dr Khasraw is working closely with COGNO for the development of several new clinical trials in this field.

3. Strategies to treat and prevent neurocognitive impairment in cancer patients.

Dr Khasraw is conducting a study using lithium as a neuroprotective agent in patients undergoing cranial irradiation (TULIP). Neurocognitive impairment is a serious consequence of brain radiotherapy evident in long-term survivors of cancer. Prevention and treatment strategies are urgently needed. There is preclinical evidence that lithium induces neuronal and glial growth after radiation, and a recent small phase 1 study in cranial irradiation patients has been reported. As a first step toward large randomised studies, Dr Khasraw is conducting a feasibility study where patients will receive a short course of lithium after cranial irradiation. The study will demonstrate the feasibility of the treatment approach as a prelude to a larger randomised multi-institutional trial.

4. Neuroendocrine neoplasms.

Neuroendocrine tumours (NETs) are cancers that develop from cells found throughout the body but which are found most commonly in the gastrointestinal system. The term neuroendocrine implies that these cells have received nervous connections (neuro-) and are able to secrete hormones (endocrine). Neuroendocrine carcinomas (NEC) are the rapidly growing form of NETs that tend to respond to chemotherapy but relapse quickly in most patients within months after diagnosis. Few studies have focused on chemotherapy, which is the most important treatment modality currently. Dr Khasraw is working with the Australian Gastrointestinal Trials Group (AGITG) to lead the conduct of a clinical trial to test a novel chemotherapy (NAB paclitaxel) in combination with carboplatin in NECs. In addition the study will explore diagnostic, prognostic and predictive markers in neuroendocrine tumours treated as part of this study.

*Key publications:*

*1. Davis J, Ahlberg F, Berk M, Ashley D and Khasraw M; Emerging pharmacotherapy for cancer patients with cognitive dysfunction; BMC Neurol. 2013 Oct 24;13(1):153.*

*2. Khasraw M, Ashley D, Wheeler G, Berk M. Using lithium as a neuroprotective agent in cancer patients; BMC Med. 2012 Nov 2;10(1):131.*

*3. Khasraw M, Goldlust S, Lassman A, DeAngelis L; Intracranial hemorrhage (ICH) in cancer patients treated with bevacizumab; the Memorial Sloan-Kettering (MSK) experience. Ann Oncol. (2012) 23 (2): 458-463.*

*4. Khasraw M., Posner, J.: Neurological complication of systemic cancer; Lancet Neurol. 2010 Dec; 9(12): 1214-27.*

*5. Khasraw, M; Lassman, A.B.: Neuro-oncology: late neurocognitive decline after radiotherapy for low-grade glioma; Nature Rev Neurol. 2009; 5(12): 646-7.*

**MMR Contact Details**

Medical and Molecular Research (MMR)
Strategic Research Centre
School of Medicine
Deakin University
Pigdons Rd, Waurn Ponds, VIC, 3216

alister.ward@deakin.edu.au
deakin.edu.au/mmr
Cricos Provider Code: 00113B

**Our mission**

A world-class medical research grouping with a unique research profile that will enhance Deakin's reputation nationally and internationally