SAiGENCI
SOUTH AUSTRALIAN iMMUNOGENOMICS CANCER INSTITUTE

an alliance of

THE UNIVERSITY of ADELAIDE

Government of South Australia Health Central Adelaide Local Health Network

EMBL Australia

SAiGENCI EMBL Australia Group Leader Symposium

Wednesday 17 May, 12.30pm – 5pm
AHMS Building, Ground Floor, Room G030

Candidate Profiles

Dr Stefano Mangiola

Stefano Mangiola is a VCA fellow in computational cancer immunology. He has a background in biotechnology, biostatistics and cancer biology (PhD, Unimelb/WEHI 2019). During his PhD, he elucidated the role of monocytes in prostate cancer progression and discovered the detrimental impact of adipocyte inflammation surrounding the prostate.

His recent research in Professor Papenfuss's laboratory (WEHI) focuses on the immunodiagnosis of metastatic breast cancer and the study of its microenvironment. Recent efforts also include modelling the immune system tissue map across demographic groups and ageing for precision medicine.

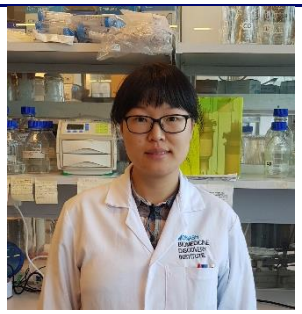
He also focuses on developing bioinformatics and statistical tools for large-scale single-cell data analysis. He has developed an innovative statistical model for differential tissue composition analyses for single-cell data and outlier identification. He introduced the analysis paradigm of tidy transcriptomics.

Creating a precision medicine whole-body immune map.

Immunotherapies use the patient's immune system to fight diseases, including cancer. However, the immune system is complex and diverse across people, which makes it challenging to develop effective treatments for everyone. To overcome this challenge, we need a better understanding of the immune response across tissues and demographics.

We harmonised 29 million cells from 12,981 samples to create the CuratedAtlasQuery resource and map the healthy immune system across 45 anatomical sites. The resource was used to analyse the evolution of the immune system through ageing and diversity across demographic groups. Our analysis, based on a novel Bayesian compositional method, shows tissue-specific inflammation and loss of plasticity through ageing and differences across ethnicities.

This presentation will include a brief introduction of Stefano’s other research streams and major collaborations.



Dr Qi Zhang

Dr Qi Zhang is an NHMRC EL1 Investigator and a former ARC DECRA fellow. As a group leader at the Monash Biomedicine Discovery Institute, she seeks to understand the fundamental mechanisms governing the regulation of chromatin modifiers in gene repression. Previously, during her postdoctoral fellowship at Monash University, Dr Zhang conducted mechanistic studies of the histone methyltransferase polycomb repressive complex 2 (PRC2). Prior to this, she was a postdoctoral fellow at the Structure Genomics Consortium at the University of Toronto, where she studied the structure and function of ubiquitination complexes involved in stress response and gene regulation. Qi completed her PhD in 2013 at China Agricultural University, investigating the molecular mechanism of the regulation of a histone demethylase. Her work resulted in publications in high-quality journals, including in Nature Structural & Molecular Biology, Proceedings of the National Academy of Sciences of the USA, Nature communications, Genes & Development, Cell Research, and Nucleic Acids Research, and also led to the determination of 22 high-resolution protein structures.

Molecular mechanisms for the regulation of histone modifiers in development and in cancer.

The maintenance of cell identity relies on the repression of lineage-specific genes, which is largely regulated by the histone modifier polycomb repressive complex 2 (PRC2). Dysregulation of PRC2 contributes to human diseases, including cancer. PRC2 maintains gene repression by depositing repressive histone marks (H3K27me3), and its enzymatic activity and recruitment to chromatin are regulated by cofactors such as DNA, RNA and accessory subunits. In this seminar, Dr Zhang will demonstrate how PRC2 is mechanistically regulated by its cofactors through a combination of approaches, including biochemistry, structural biology, cell biology and genomics. The generalization of this mechanistic investigation into other histone modifiers will be discussed.

Dr Fuyi Li

Fuyi is a Professor at the College of Information Engineering, Northwest A&F University, China, and an Honorary Research Fellow at the Peter Doherty Institute for Infection and Immunity, the University of Melbourne. With a background in software engineering and expertise in bioinformatics, Fuyi has developed a series of data-driven machine learning-based algorithms and tools to address open complex biological problems. His research interests focus on the development of machine learning-based bioinformatics approaches to functionally interpret massive heterogeneous biology datasets involving genomics, proteomics, and 3D structural data.

Leveraging AI and big data in bioinformatics: exploring opportunities, tackling challenges, and driving innovation.

Advancements in high-throughput technologies have enabled the collection of vast amounts of biological data, providing an opportunity for data-driven discoveries in biology. However, the complexity and scale of these data present significant challenges for traditional data analysis methods. The field of bioinformatics aims to address these challenges by developing computational tools and algorithms to analyse biological data. In recent years, the application of artificial intelligence (AI) has revolutionized the field of bioinformatics, enabling new approaches for data analysis and interpretation. In this presentation, I will discuss the opportunities and challenges of using AI-driven bioinformatics approaches to analyse large and complex biological datasets. I will showcase examples of AI-driven bioinformatics research, including our work on developing machine learning-based approaches for understanding open biological questions. I will also discuss the potential applications of AI-driven bioinformatics in drug discovery, personalized medicine, and agriculture. Finally, I will highlight future directions in the field and the importance of interdisciplinary collaborations between computer scientists and biologists to tackle the challenges of the era of big data in biology.

Dr Merav Shmueli

Merav D Shmueli, PhD is a biotechnologist, biochemist, and proteomics researcher. She is a Research Associate at the Department of System Immunology, Weizmann Institute of Science, Israel. Merav is a driven and accomplished researcher with a passion for cancer, immunity and Epi-proteomics. During her time with the WIS, she developed expertise in a unique proteomics approach called proteasomal profiling, which allows the analysis of cellular protein degradation products. This technology led to a groundbreaking discovery in lung cancer research, uncovering altered degradation patterns in NSCLC and the upregulation of the regulatory subunit, PSME4. This finding ultimately demonstrated the attenuated T cell-mediated anti-tumor immunity associated with PSME4 upregulation and lack of response to immunotherapy in several cancer types.

Her insights are now leading efforts, with a research team, to identify small molecules that prohibit the binding of PSME4 to the proteasome and block its deleterious effects. These efforts should provide novel means to sensitize responses to immunotherapies.

Merav is dedicated to advancing our understanding of proteasome biology and its implications for human diseases.

Proteasomal profiling: novel view of degradation in cancer.

Immunotherapy has revolutionized treatment options for cancer patients. Yet, most patients do not respond to therapy, response rates vary greatly between cancer types, and the underlying mechanisms remain poorly understood. Cellular proteasomes have been implicated in promoting anti-tumor immunity by regulating antigen processing and presentation, inflammatory signaling and promoting immune cell activation. A systematic examination of whether and how proteasome complex heterogeneity may affect tumor growth and the response to immunotherapy has not been examined to date. In this presentation you will see that proteasome complex composition which varies significantly across cancer types and can be used to stratify patients' response to immunotherapy. Specifically, we found that the proteasome regulator PSME4 is upregulated in NSCLC and associated with poor prognosis. Through proteasome profiling of patient-derived NSCLC samples and immunopeptidomics, we show that tumor-intrinsic PSME4 alters proteasome activity and antigen processing, attenuates presented antigenic diversity and associates with lack of response to immunotherapy across cancer types. Using scRNA-seq, we uncovered that PSME4 plays an anti-inflammatory role in cancer, abrogating anti-tumor immunity and promoting an immunosuppressive tumor microenvironment. Collectively, our approach may be adapted to other cancer types and pathological settings and affords a novel paradigm by which proteasome composition heterogeneity and function should be examined and targeted in the context of precision oncology.

Dr Piyushkumar Mundra

Dr Piyushkumar Mundra is a Senior Research Officer at the Garvan Institute of Medical Research in Sydney, Australia. He holds a PhD in Computer Engineering, which he earned from Nanyang Technological University in Singapore. His PhD thesis was highly impactful, resulting in three publications in leading computational journals. After his PhD and short stint as a research fellow at NTU, Dr Mundra went on to work in the Metabolomics lab at Baker Institute in Melbourne, Australia. There, he conducted advanced lipidomics research on clinical trial samples, which led to numerous publications, including in the prestigious journal *Circulation*. To expand his experience in genomics, he moved to the Molecular oncology lab at Cancer Research UK Manchester Institute. During his tenure there, he worked on several melanoma studies using both preclinical and clinical samples. His research resulted in publications of ten manuscripts, with the first or joint-first author papers in highly respected journals such as *Nature Medicine* and *Nature Communications*. Through his research, he was able to gain a fundamental understanding of the impact of ultraviolet radiation on melanomagenesis and developed a novel signature for immunotherapy response. Since 2020, Dr Mundra has returned to Australia, where he is currently working on developing a genetic compendium of germline mutations in sarcomas. He recently co-authored a manuscript in *Science*, describing two novel pathways implicated in sarcomas. Dr Mundra specializes in bioinformatics analysis of various -omics datasets and his expertise has enabled him to make significant contributions to the field of computational biology through several high-impact publications (Google h-index :26).

Deciphering oncogenesis through genomic biomarker discovery.

High-throughput -omics technologies such as genomics, transcriptomics, proteomics, and metabolomics have revolutionised the way we study cancer biology and make treatment decisions. Genomic biomarker discovery approaches can help identify key genetic changes that are associated with cancer development, progression and therapy response. In this presentation, multiple case-studies will be presented discussing how biomarkers could be identified from tumour as well as blood samples to decipher cancer evolution. Using genomics and transcriptomics approaches on a *BRAF* induced melanoma preclinical model, melanoma tumours were classified into groups by mutation signatures, and ten recurrently mutated UVR signature genes were identified that predict patient survival. In response to anti-PD-1 treatment, stromal and proliferation signatures were associated with prolonged response. Both of these studies are corroborated in multiple independent melanoma patient cohorts. In rare disease such as sarcomas, whole-genome sequencing on blood samples could play a pivotal role in discovering novel biology. Two distinct biological pathways were identified where mutations increase the inherited risk for developing sarcoma through alterations of telomere biology and mitotic function. This presentation will highlight how analysing -omics data could lead to uncover novel biology and biomarkers of direct clinical relevance that could accelerate personalised treatments.