CRT 2017 Collaborative Cancer Research Grant

Enabling advanced single cell cancer genomics in Western Australia

Lay summary

To fight cancer we need to understand how it develops at the single cell level, which is now possible courtesy of major advances in technology. In this project, a collaborative team of scientists and medical doctors from all of the major institutions in WA will build a unique single cell molecular atlas of hundreds of cancer samples donated by patients. Knowing which genes are on and off, in every cell within a tumour will help us better understand, earlier detect and ultimately kill cancer cells.

Highlights

Funding from the CRT has given a major boost to cancer genomics funding within Western Australia. Since being awarded the funding in 2017 we have leveraged over $10.7 million in additional funding with major highlights being:

- Being awarded an Australian Cancer Research Foundation grant to establish the ACRF Centre for Advanced Cancer Genomics (https://www.acrf.com.au/support-cancer-research/cancer-research-projects-and-grants/acrf-centre-advanced-cancer-genomics/)
- Successfully bidding to host the 2020 Human Genome Meeting in Perth (http://hugo-hgm2020.org/)
- Establishment of Genomics WA (more news to come).

Synopsis of the grant proposal

Cancer genomics has revolutionized our understanding of the myriad genetic lesions that cause cancer, and for some cancers such as melanoma, a single mutation can be translated directly into a therapeutic choice and improved outcome. But, for most tumors the situation is much more complex. Interrogation of large genomic surveys across multiple cancer types (e.g. Cancer Genome Atlas and the International Cancer Genome Consortium) has provided a greater understanding of the diversity of cancer subtypes and the active molecular targets. However, almost all of this data has been generated from tumor samples containing a mixture of cell types, making it difficult to understand the relative contributions of each cell type to the cancer. Disruptive new single cell genomics technology have the potential to overcome this hurdle. We have a once in a decade opportunity to invest in technology and the people that run it to revolutionize our understanding of cancer and give WA researchers new opportunities and a competitive advantage.

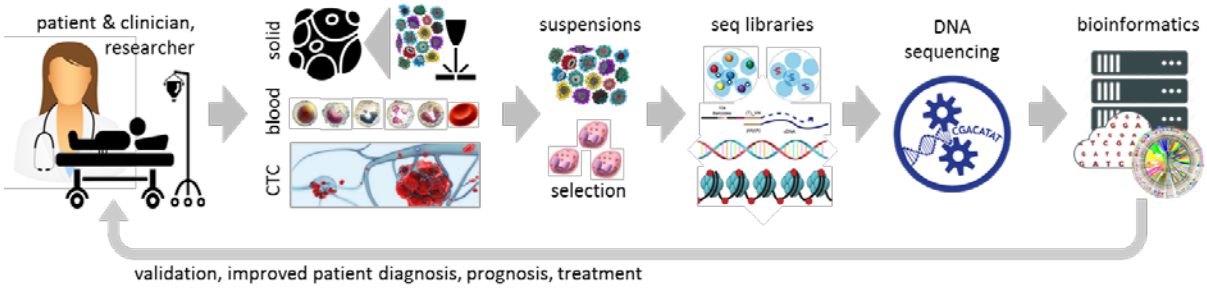
Our multidisciplinary team of surgeons, oncologists and pathologists, cancer biologists and immunologists, genomic scientists and computational biologists from all of the major universities, hospitals and medical research institutes across Perth has come together to establish high throughput single cell profiling of cancers. In a flagship project, we will profile

thousands of individual cells from each patient's cancer, survey the genes active in single cells then build a unique molecular atlas of hundreds of cancer samples. These single cell profiles will allow us to better study the tumour microenvironment, tumour heterogeneity, identify new biomarkers including circulating tumour cells and better predict response to therapy and relapse. In short, establishment of cancer single cell profiling in WA will have a transformational impact on cancer research in this state and position WA researchers at the forefront of translational genomics in cancer.

Significance to cancer research and health outcomes

Single cell characterization of tumours will revolutionize our understanding of cancer providing fundamental insights into tumour heterogeneity, the tumour microenvironment, cancer stem cells, metastasis, development of resistance and recurrence and help to identify novel diagnostic and prognostic markers. Ultimately understanding of these fundamental aspects of tumour biology will lead to new approaches for therapeutics, earlier diagnosis and better targeting of personalised therapies that take into account the specific cellular make up of a patient's tumour. These technologies are the next wave of genomics and we have a once in a decade opportunity to establish them and remain at the leading edge.

The technology is cutting edge and our multidisciplinary team (surgeons, oncologists, pathologists, cancer cell biologists, genomic and computational scientists) has an opportunity to lead Australia now rather than attempting to catch up in the future. Together our highly collaborative network is committed to create the pipeline below.



An advanced tumour profiling pipeline

Investigators

Chief Investigator: Prof Alistair Forrest

Associate Investigators: Prof Peter Leedman, Prof Ryan Lister, Prof Christobel Saunders, Prof Anna Nowak, Prof Terrance Johns, Prof Mel Ziman, Prof Camile Farah, Prof Bruce Robinson, Prof Ruth Ganss, Prof George Yeoh, Prof Charles S Bond, Prof Simon A. Mallal, Prof Arlene Chan, Prof Peter Friedland, Prof Ursula Kees, Prof Mariapia Degli-Esposti, Prof Wendy Erber, Prof Michael Millward, Prof Cameron Platell, Prof Richard Lake, Assoc Prof Timo Lassmann, Assoc Prof Andrew Redfern, Assoc Prof Benhur Amanuel, Assoc Prof Pritinder Kaur, Assoc Prof Fiona Pixley, Dr Katie Meehan, Dr Elin Gray, Dr Paul Cohen, Dr Willem Joost Lesterhuis, Dr Louise Winteringham, Dr Andrew Currie, Dr Carolyn Grove, Dr Annette Lim, Dr Carlos Aya-Bonilla, Dr Andrea Lisa Holme, Dr Raelene Endersby, Dr Anthony Bosco, Dr Jason Waithman, Dr Mark Cruickshank, Dr Shane Herbert, Dr David Chandler

Financial summary

CRT funding:
$750,000 per annum for 5 years (up to 9 years subject to performance)

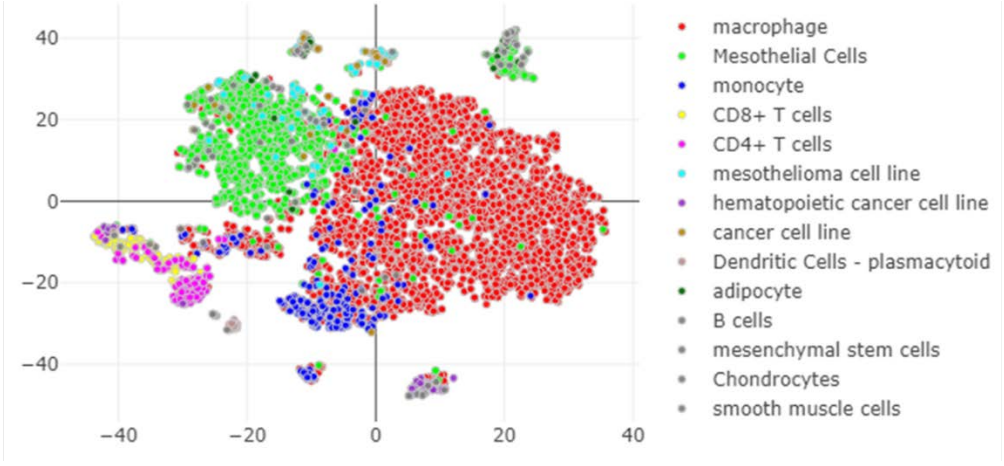
Co-funding:
$50,000 per annum – Cancer Council WA.
$50,000 per annum – Harry Perkins Institute.
$50,000 per annum – Telethon Kids Institute.
$50,000 per annum – University of Western Australia.
$50,000 per annum – Edith Cowan University.

Additional leveraged funding:
Total funding leveraged thus far: **$10,775,131**

Scientific summary

Since the project started we have generated single cell (and single nuclei) expression data from 164 samples. This includes human tumour samples, mouse models of tumour development and treatment, and normal matching tissues. To work with the data we have developed several computational tools and pipelines. Of note we developed a tool for automatically annotating single cells based on comparison to reference expression profiles. An example output is shown below.

Annotation of cell types present in pleural effusion of a mesothelioma patient using scMatch. Samples from J. Creaney, G.Lee, B. Robinson.

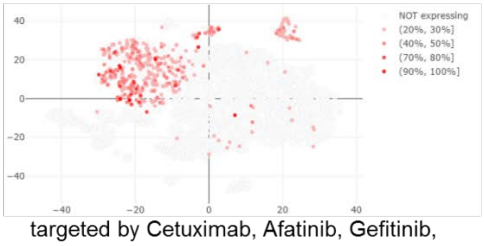


We have also made progress on predicting cell-to-cell communication between cell types based on their ligand and receptor expression profiles. This is critical to studying tumours as a cellular ecosystem.

Moving forward we are also exploring the use of single cell expression profiles to predict response to targeted therapeutics. Through reanalysis of published bulk cell line expression profiles and sensitivity to hundreds of drugs we have identified a subset of drugs where expression profile is predictive of response to a drug. Below we highlight the expression of four of these drug targets in single cell data from mesothelioma patients to predict what drugs they may respond to. We are hoping to test these *in vitro*.

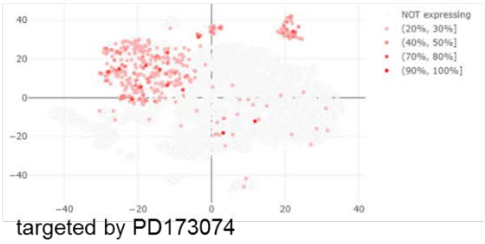
Drug target expression in a mesothelioma cells. Samples from J. Creaney, G.Lee, B. Robinson.

EGFR



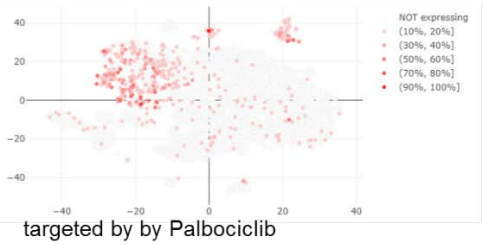
targeted by Cetuximab, Afatinib, Gefitinib, Lapatinib, Erlotinib, vandetanib, pd 153035

FGFR



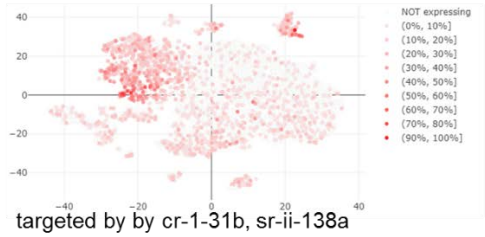
targeted by PD173074

CDK6



targeted by by Palbociclib

EIFA42



targeted by by cr-1-31b, sr-ii-138a

Cancer types profiled to date

- mesothelioma
- non-small cell Lung Cancer
- oral squamous cell carcinoma
- pre-B acute lymphoblastic leukemia
- myelodysplastic syndrome
- ovarian cancer
- melanoma

Mouse models profiled to date

- pancreatic cancer
- liver cancer
- mesothelioma
- breast cancer

Publications acknowledging the grant

Roy R *et al.* Expression levels of therapeutic targets as indicators of sensitivity to targeted therapeutics. ***Molecular Cancer Therapeutics*** https://doi.org/10.1158/1535-7163.MCT-19-0273 (2019)

Rou R, Denisenko E, Forrest A. scMatch: a single-cell gene expression profile annotation tool using reference datasets. ***Bioinformatics*** https://doi.org/10.1093/bioinformatics/btz292 (2019)

Zemek RM *et al.* Sensitization to immune checkpoint blockade through activation of a STAT1/NK axis in the tumor microenvironment ***Science Translational Medicine*** https://doi.org/10.1126/scitranslmed.aav7816 (2019)