# MDHS Graduate Research Conference 2020

## Cancer Booklet

https://mdhs.unimelb.edu.au/mdhs-graduate-research-conference-2020

mdhs-grconference@unimelb.edu.au

# MESSAGE FROM THE CHAIRS

Dear Delegates,

Welcome to the virtual inaugural Medicine, Dentistry and Health Science Graduate Research Conference 2020 (MDHS GR Conference), a student conference for all biomedical graduate research students that are part of the MDHS Faculty of the University of Melbourne. The organising committee is made up of members from 11 different student society across the MDHS faculty campus. The conference schedule consists out of 12 parallel session covering a variety of interesting topics and accommodating our student talks as well as national and international keynote speakers, Science Communication workshop and a Career Panel Discussion. This event was only possible due to the generous support of the University of Melbourne and the Graduate Student Association (GSA).

We hope that MDHS GR Conference will provide you with opportunities to listen to national and international leaders talking about their ground-breaking research in different biomedical fields and communicate your research to a broad scientific audience. Despite the fact that this conference will be virtually it will give you a unique chance to meet and network with peers from different research fields engage in discussions. We hope that the MDHS GR Conference will inspire you with new possibilities for your future career by listening to our invited speakers from academia and industry.

We wish you all the best for your presentation and hope you enjoy the event and get novel project ideas, career opportunities and new connections out of it.

Martha Blank & Alexander Anderson

*(Chair & Deputy-Chair of the Medicine, Dentistry and Health Science Graduate Research Conference 2020)*

# GENERAL PROGRAM

**08.00 - 08.15 Conference Opening & Welcoming Address**
Professor Alex Boussioutas and Martha Blank

**08.15 - 10.00 Session 1**

**10.00 - 10.30 Break**

**10.30 - 12.30 Session 2**

**12.30 - 13.00 Break**
Virtual Socialise

**13.00 - 14.30 Science Communication Workshop**
Dr. Shane Huntington

**14.30 - 16.00 Break**
Virtual Socialise | Networking | Games

**16.00 - 17.00 Careers Panel Discussion**
A/Prof. Nicholas Opie | Dr. Danijela Mirosa | Dr. Ashish Sethi
Dr. Maryam Hussain | Dr. Simranpreet Kaur

**17.00 - 19.00 Session 3**

**19.00 - 20.00 Award Ceremony & Conference Closing**
Martha Blank and Alexander Anderson

# SCIENCE COMMUNICATION WORKSHOP

## Dr. Shane Huntington

Dr. Shane Huntington has been providing consulting services in communication and strategy for over 20 years. As a successful broadcaster, business owner, academic and strategist he draws together experience from multiple sectors, offering clients a more detailed and analytical approach than competitors. Shane has trained thousands of people to communicate more effectively, especially in fields of research. His unique and engaging style has led to him delivering programs to some of Australia's most prestigious institutions.

# CAREERS PANEL DISCUSSION

## A/Professor Nicholas Opie

Synchron Founding Director and CTO
Co-Lab Head of the Vascular Bionics Laboratory, The University of Melbourne

## Dr. Danijela Mirosa

Franchise Director of Oncology for the Oceanic Cluster
Takeda Pharmaceuticals

## Dr. Ashish Sethi

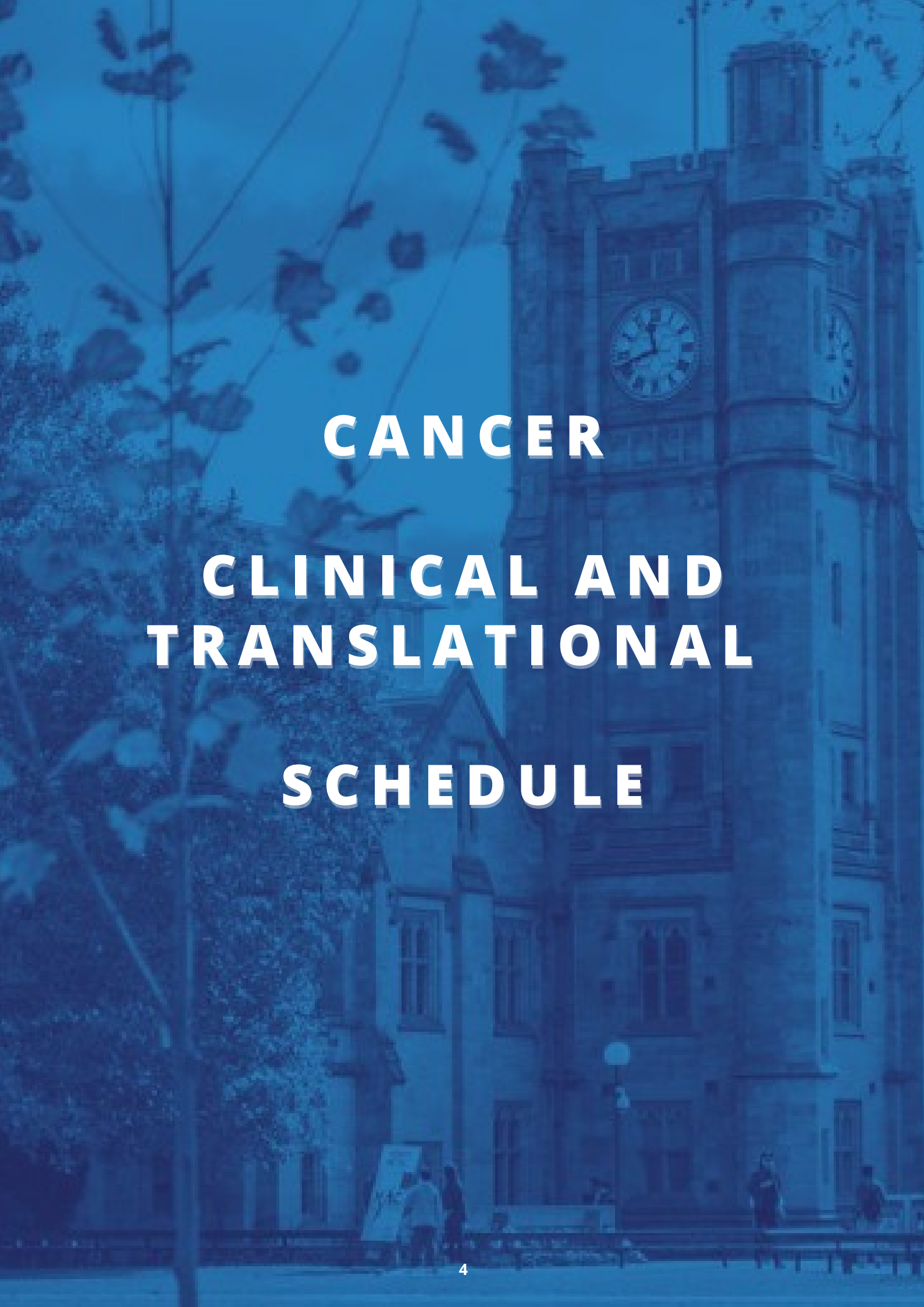
Postdoctoral Research Fellow
Department of Biochemistry & Molecular Biology, TheUniversity of Melbourne

## Dr. Maryam Hussain

Medical Science Liaison
Boehringer Ingelheim

## Dr. Simranpreet Kaur

Postdoctoral Researcher
MitoBrain Murdoch Children's Research Institute



# CANCER

# CLINICAL AND TRANSLATIONAL

# SCHEDULE

# CANCER
# Clinical and Translational

## SCHEDULE

### SESSION 1

| | | |
|---|---|---|
| 08.15 – 08.45 | **Harnessing the intracellular bacterium Listeria monocytogenes as a cancer vaccine**<br>**Keynote Speaker:** Prof. Yvonne J. Paterson | |
| 08.45 – 09.00 | **Serum microRNA is a prognostic and post-operative monitoring biomarker in glioma**<br>Jordan Jones | 9 |
| 09.00 – 09.15 | **Investigating the contribution of cysteine protease legumain to oral carcinogenesis**<br>Bethany Anderson | 10 |
| 09.15 – 09.30 | **Living with MPN fatigue**<br>Ashleigh Bradford | 11 |

### SESSION 2

| | | |
|---|---|---|
| 10.30 – 11.00 | **Liquid Biopsies in Cancer**<br>**Keynote Speaker:** Prof. Sarah Jane Dawson | |
| 11.00 – 11.15 | **Towards automated detection of invasive fungal infection using data linkage in patients with haematological malignancy**<br>Jake Valentine | 12 |
| 10.15 – 11.30 | **CDK4/6 inhibition reprograms the breast cancer enhancer landscape by stimulating AP-1 transcriptional activity**<br>April Watt | 13 |
| 11.30 – 12.00 | **Blending the old with the new – Translating new drugs into the clinic for childhood brain cancer**<br>**Keynote Speaker:** Dr. Raelene Endersby | |

### SESSION 3

| | | |
|---|---|---|
| 17.00 - 17.30 | **Altered gastric bacterial composition in intestinal metaplasia and its association in gastric cancer progression**<br>**Keynote Speaker:** A/Prof. Zhang Yongliang | |
| 17.30 – 17.45 | **Interleukin 11 signalling promotes glioblastoma progression**<br>Sarah Stuart | 14 |
| 17.45 – 18.00 | **Inactivation and deletion of adoptively transferred CTL encountering a high number of antigen presenting lymphoma cells**<br>Christina Scheffler | 15 |
| 18.00 – 18.15 | **Cancer-associated fibroblasts: Master inducers of breast cancer progression by secretion of exosomal TGF-beta**<br>Adilson Teixeira | 16 |
| 18.15 – 18.30 | **Utilising murine pancreatic cancer organoids to understand epithelial-mesenchymal transition in cancer**<br>Ronnie Ren Jie Low | 17 |

# Cancer

## *Clinical and Translational*

## Keynote Speakers

**Professor Yvonne Paterson**
**Perelman School of Medicine**
**University of Pennsylvania**

**Session 1 08.15 - 8.45 am**

Yvonne Paterson Ph.D. is professor of microbiology at the University of Pennsylvania. Her research is in the field of cancer immunotherapy. She is the inventor of a vaccine approach that harnesses the abilities of a bacterium, Listeria monocytogenes, and its products, to induce potent immunity. This approach has won many awards including the World Vaccine Congress' Best Therapeutic Vaccine in 2012, the Medical Visionary Award from the Farrah Fawcett Foundation in 2015, and the Vision of Hope award from the Sarcoma Foundation of America in 2016. Dr. Paterson has over 40 U.S. patents, and numerous international patents, licensed to Advaxis Immunotherapies Inc., which she founded in 2002. In 2017 she was named "Inventor of the Year" by the Penn Center for Innovation. She has 185 research publications and has edited two books. Dr. Paterson is a fellow of the National Academy of Inventors, the American Academy of Microbiology, the American Association of Arts and Sciences and she was selected in 2014 for inclusion in PharmaVoice's 100 Most Inspiring People in the Life-Sciences Industry.

A recombinant Listeria monocytogenes vaccine expressing a model tumour antigen protects mice against lethal tumour challenge and causes regression of established tumours.
Pan, Z-K, Ikonomidis, G., Lazenby, A., Pardoll, D., and **Y. Paterson.** *Nature Medicine* 1:471-477. 1995

**Professor Sarah-Jane Dawson**
**Peter MacCallum Cancer Centre**
**University of Melbourne**

**Session 2 10.30 - 11.00 am**

Professor Sarah-Jane Dawson is a clinician-scientist. She obtained her medical degree from the University of Melbourne in 1998, and trained as a medical oncologist in Melbourne, Australia. She completed her PhD at the University of Cambridge, UK. Following postdoctoral studies at the Cancer Research UK Cambridge Institute, she returned to Melbourne in 2014 to head the Molecular Biomarkers and Translational Genomics Laboratory at the Peter MacCallum Cancer Centre. She also holds a joint appointment with the Centre of Cancer Research at The University of Melbourne (since 2016) and currently holds a CSL Centenary Fellowship (2018-2022). She is a fellow of the Australian Academy of Health and Medical Sciences and was recipient of the Jian Zhou Medal in recognition of translational medical science in 2020. Her current research interests are focused on the development of noninvasive blood-based biomarkers ('liquid biopsies') for clinical application, including early detection, risk stratification and disease monitoring in cancer management.

Analysis of circulating tumor DNA to monitor metastatic breast cancer
**SJ. Dawson***, D.W.Y. Tsui*, M. Murtaza, H. Biggs, O. Rueda, SF. Chin, M. Dunning, D. Gale, T. Forshew, B. Mahler-Araujo, S. Rajan, S. Humphray, J. Becq, D. Halsall, M. Wallis, D. Bentley, C. Caldas and N. Rosenfeld. *New England Journal of Medicine*. 2013 March 28; 368(13):1199-209

# Cancer

## *Clinical and Translational*

## Keynote Speakers

**Dr. Raelene Endersby**
**Telethon Kids Institute**
**University of**
**Western Australia**

**Session 2 11.30 am - 12.00 pm**

Dr. Raelene Endersby completed a Bachelor of Science with first-class Honours in Molecular Genetics from Curtin University. Inspired to make a difference in medical research, she completed a PhD focused on the characterisation of a previously unknown leukaemia-associated gene. Raelene then undertook postdoctoral training in childhood brain cancers and developmental neurobiology at St Jude Children's Research Hospital, USA. In 2011, she was awarded a fellowship to return to Australia and join the Telethon Kids Institute. In 2016, Raelene was awarded the Brainchild Fellowship and appointed Joint Head of Brain Tumour Research within the Telethon Kids Cancer Centre.

Dr Endersby has made significant contributions to her field of research having published numerous manuscripts and supervised 24 post-graduate student research projects in cancer. The impact that she has made can be evidenced by having been awarded an international patent for work stemming from her PhD, but perhaps most importantly research performed in her laboratory has led to the approval and implementation of a new clinical trial for children with incurable medulloblastoma called SJ-ELIOT (Clinicaltrials.gov NCT04023669), which began recruiting patients in 2019.

Cooperativity within and among Pten, p53 and Rb pathways induces high-grade astrocytoma in adult brain. Chow LM, **Endersby R**, Zhu X, Rankin S, Qu C, Zhang J, Broiscer A,Ellison DW, Baker SJ.*Cancer Cell.* 2011. 19(3):305-16.

**A/Professor Zhang Yongliang**
**Yong Loo Lin School of Medicine**
**National University of Singapore**

**Session 3 5.00 - 5.30 pm**

A/Professor Zhang Yongliang obtained his BSc in Biology from Zhejiang Normal University, China in 1992, his MS in Microbiology from Wuhan University, China in 1995, and his PhD in Molecular Microbiology in 2002 from the National University of Singapore (NUS), Singapore. He performed his postdoctoral research in the Department of Immunology, University of Washington, USA, and the Department of Immunology, the University of Texas M. D. Anderson Cancer Center, USA. He was an Instructor in the Department of Immunology, M. D. Anderson Cancer Center before he joined the Department of Microbiology and the LSI Immunology Programme, NUS, as an Assistant Professor in 2009. He was promoted to Associate Professor with Tenure in 2017. Research in his laboratory focuses on deciphering the physiological and pathophysiological functions of signalling molecules, mainly a group of proteins known as MAPK phosphatases (MKPs) or dual-specificity phosphatases (DUSPs). He utilizes multiple animal models including chemical-induced and genetic mutation-mediated cancer models, obesity and obesity-associated disease models, and microbial infection models, as well as clinical sample analysis to address the function of these key molecules in cell signalling. Findings made by his group unveiled novel and important roles played by MKPs/DUSPs in diseases. Targeting MKPs/DUSPs for the development of novel therapeutic methods to improve patient outcomes is one of his major research interests currently and in the future. He has published research articles in top international journals including Nature, Nature Immunology, Immunity, EMBO J, PNAS, Oncogene and Cell Reports.

Gut microbiota and immunology of the gastrointestinal tract. Manley G. C. A., Lee Y. K., and **Zhang Y**. 2019. *Clinical & Basic Neurogastroenterology & Motility*. Elsevier Science Publishing Co Inc

# ABSTRACTS

## CANCER
## Clinical and Translational

### Serum microRNA is a prognostic and post-operative monitoring biomarker in glioma

Jordan Jones[1,2], Kate Drummond[1,2] & Andrew Morokoff[1,2]

[1] Department of Surgery, University of Melbourne.
[2] Department of Neurosurgery, Royal Melbourne Hospital

**Introduction:** Gliomas are the most common primary brain tumour affecting adults and its most aggressive form, glioblastoma, is rapidly uniformly lethal. Although magnetic resonance imaging (MRI) provides accurate anatomical and spatial details regarding gliomas, it is not reliable at predicting biological behaviour and is confounded by problems such as pseudo-progression. A circulating biomarker has the potential to improve predictions of glioma outcome and identify tumour progression post treatment, however no such biomarker is currently available. We aimed to discover a microRNA (miRNA) serum biomarker for longitudinal monitoring of glioma patients as well as identify miRNAs that are predictive of survival outcomes.

**Methods:** A prospectively collected cohort of 91 gliomas and 17 healthy controls underwent pre and post-operative serum miRNA profiling using the next-generation sequencing platform Nanostring®. Differentially expressed miRNAs were discovered using a machine learning random forest analysis. Candidate miRNAs were then assessed by droplet digital PCR in 10 patients with multiple follow-up samples and compared to tumour volume based on MRI. A lasso-regression model was used to identify candidate miRNAs from pre-operative serum that were associated with both progression-free and overall survival.

**Results:** We identified a 9-gene miRNA signature that could distinguish between glioma and healthy controls with 99.8% accuracy. From the signature two miRNAs; miR-223 and miR-320e, best demonstrated dynamic changes that correlated closely with tumour volume on MRI in LGG and GBM respectively. Importantly, miRNA levels did not increase in two cases of pseudo-progression, indicating the potential utility of this test in guiding treatment decisions. Additionally, altered expressions of 6 miRNAs were found to be associated with overall and progression-free survival.

**Conclusion:** We have identified a highly accurate 9-miRNA signature associated with glioma serum and observed specific miRNAs that both correlated with tumour volume over long-term follow up and were predictive of survival. A validated circulating biomarker would significantly improve the care of patients with brain tumours and as such these results support a large prospective validation
study of serum miRNA biomarkers in glioma.

## CANCER
## Clinical and Translational

### Investigating the contribution of cysteine protease legumain to oral carcinogenesis

Bethany M. Anderson[1], Brian L. Schmidt[3] & Laura E. Edgington-Mitchell[1,2,3]

[1] Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Parkville, Victoria, Australia
[2] Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia
[3] College of Dentistry, New York University, New York, New York, USA

**Introduction:** Oral cancer is the 6th most common form of cancer worldwide. The mechanism behind oral carcinogenesis is poorly understood and predicting which cancers will go on to metastasise is currently not possible. Thus, the mechanisms behind oral carcinogenesis need to be further studied to prevent many patients undergoing unnecessary precautionary invasive surgery. Legumain is a cysteine protease that has previously been reported to contribute to the carcinogenesis of several cancers. A recent study has revealed that legumain contributes to severe orofacial pain suffered by oral cancer patients via cleavage of protease-activated receptor 2 (PAR2). We therefore sought to investigate whether legumain contributes to the features of oral carcinogenesis.

**Methods:** The activity-based probe LE28 was used to measure legumain activity in human oral squamous cell carcinomas (OSCC) and patient-matched normal oral mucosa. Tumour samples from murine models of oral cancer were used to identify the localisation of legumain within the tumour microenvironment. We also examined legumain levels in a panel of human OSCC cell lines as well as in macrophages primed by conditioned media from these cells. Finally, we examined the contribution of legumain to cell proliferation and invasion using a legumain inhibitor and legumain-deficient cells generated by CRISPR-Cas9.

**Results:** We found that legumain activity was strongly upregulated in tumours of all patients examined compared to normal oral mucosa. We validated this finding in two murine models of oral cancer: HSC-3 orthotopic xenografts and 4NQO carcinogen-induced SCC. Immunohistological analysis of murine tumours revealed that legumain is expressed predominantly at the invasive edge of tumours. This suggests a role for legumain in oral carcinogenesis. Compared to normal oral keratinocytes, cultured human oral cancer cells express higher levels of active legumain, as do macrophages exposed to tumour-derived factors. Preliminary results reveal that legumain does not promote proliferation in oral cancer cells although it may contribute to tumour cell invasion.

**Conclusion:** Collectively, these results reveal that legumain is highly active in the oral cancer tumour microenvironment and may be contributing to carcinogenesis. Future studies aim to distinguish the proteolytic or non-proteolytic mechanisms behind the contribution of legumain by re-introducing legumain containing various mutations. Additionally, murine models are underway to further delve into the mechanisms by which legumain contributes to oral carcinogenesis.



## Living with MPN fatigue

Ashleigh Bradford[1] & Elizabeth Pearson[2]

[1] The University of Melbourne, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[2] Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

**Background:** Myeloproliferative neoplasms (MPNs) are a group of rare, chronic haematological cancers. Several studies report fatigue as the most common, persistent and severe symptom which contributes to a reduction in overall quality of life (QoL) and life expectancy. In-depth knowledge about how fatigue impacts the lives of people with an MPN is needed to drive better symptom management.

**Aims:** This study was hypothesis generating and aimed to gain insight into the lived experience of fatigue in MPN.

**Methods:** People diagnosed with MPN were invited to complete an online survey and if eligible, express interest in further participation. Then, online qualitative semi-structured interviews and focus groups explored participant's experience of fatigue, the impact of their fatigue and the advice/self-help they received or were implementing. Thematic analysis of the eleven verbatim focus group and interview transcripts was conducted by two researchers and themes about the lived experience of fatigue were developed.

**Results:** Twenty-three of the 82 survey respondents (PV =14, ET=3, MF=6) between the ages of 31-76, participated in seven interviews and four focus groups. Results provide in-depth knowledge into how fatigue can dramatically affect the functional, social/family, emotional, cognitive/mental and physical wellbeing of those diagnosed with an MPN, to the ultimate detriment of quality of life. Four qualitative themes describing the experience of fatigue in MPN were developed: (1) Life with an MPN, (2) "It's not being tired, it's completely different. It's fatigue", (3) "It changes your life completely" and (4) Strategies to manage MPN fatigue. These themes encompass the lived experience surrounding the diagnosis of an MPN, the description of fatigue, the daily life of people with fatigue, how people manage their fatigue and the significant emotional burden associated with the effects of fatigue. A striking finding was that of participants inability to recognise fatigue as a symptom, and friends/family and particularly health professional's lack of awareness of the symptom of fatigue. These findings highlight the multifactorial nature of fatigue and the absence of information surrounding the experience of it.

**Conclusions:** Fatigue in MPN is all-encompassing and can affect all aspects of health, wellbeing and general life, yet is seldom addressed by health professionals. This raises issues of awareness, interest and capacity to respond. An increased recognition of the full disease burden associated with MPNs will help identify patients with unmet needs who may benefit from a change in management.



## Towards automated detection of invasive fungal infection using data linkage in patients with haematological malignancy

Jake Valentine[1,2], Lisa Hall[1,3], Karin Verspoor[1,4], Michelle Yong[1,2,5], Tim Spelman[1,6], Lynette Chee[7], Monica Slavin[1,2,5], Karin Thursky[1,2,5,8] & Leon Worth[1,2,5,9]

1 National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
2 Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia
3 School of Public Health, University of Queensland, Brisbane, Queensland, Australia
4 School of Computing and Information Systems, University of Melbourne, Parkville, Victoria Australia
5 Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
6 Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
7 Department of Haematology, Peter MacCallum Cancer Centre and Melbourne Health, Melbourne, Victoria, Australia
8 Health Services Research and Implementation Science, Peter MacCallum Cancer Centre, Melbourne Victoria, Australia
9 Victorian Healthcare Association Infection Surveillance System Coordinating Centre, Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia

**Introduction:** The manual, time-consuming and costly nature of current surveillance for invasive fungal infection (IFI) in haematological malignancy patients has motivated the need for electronic methods. Determining the combination of data elements which yield highest classification performance for IFI case ascertainment is a critical step in developing semi-automated electronic surveillance systems. This was a proof of concept study whose objectives were to use historic linked data to identify the set of data elements yielding greatest improvement for case detection of IFI and to inform future development of customised IFI surveillance systems at the Parkville Precinct.

**Methods:** Deterministic linkage was performed by BioGrid Australia Ltd. to link episode-level deidentified administrative coding (ICD-10-AM + ACHI codes), pathology, antimicrobial-dispensing, histology and gold standard IFI diagnostic data for all haematology admissions spanning 01/01/2007-31/12/2017 at the Peter MacCallum Cancer Centre. Unique combinations of each data element were developed and sensitivity (Sn), specificity (Sp), positive (PPV) and negative predictive values (NPV), F1 scores and 95% confidence intervals [95% CI] were calculated. Each algorithm was run twice using two Boolean rules, either as a union (Pr(A∪B), "or") or an intersect (Pr(A∩B), "and") of data elements.

**Results:** Of 36,530 linked hospitalisations, 3,446 occurred during periods of retrospective IFI case detection, of which 39 (1.13%) were complicated by IFI according to gold standard criteria. Of 309 algorithms, or outperformed and Boolean rules across all performance measures and was highest for combination of ICD-10-AM IFI codes ∪ antifungal-dispensing ∪ pathology (any) ∪ histology (any) data (Sn=90% [76-97]; Sp=55% [53-56]; PPV=2.00% [2.00-3.00]; NPV=99% [99-99]; F1=3.90%). Refinement of pathology data to include only fungal case finding indicators marginally improved algorithm performance (Sn=90% [76-97]; Sp=66% [64-67]; PPV=3.00% [2.00-4.00]; NPV=99% [99-99]; F1=5.80%). Replacing fungal pathology data with ACHI codes denoting bronchoscopy/BAL decreased Sn, but increased Sp and PPV (Sn=85% [69-94]; Sp=80% [79-82]; PPV=5.00% [3.00-7.00]; NPV=99%; F1=9.40%). Overall, the addition of increasing sets of data elements increased sensitivity at the expense of decreased specificity and PPV. PPV and Sn were highest and lowest, respectively, for and Boolean algorithms comprising ICD-10-AM IFI codes ∩ antifungal-dispensing ∩ pathology (fungal) ∩ any ACHI procedural code (Sn=8.00% [2.00-21]; Sp=99% [99-99]; PPV=60% [15-95]; NPV=99% [99-99]; F1=14.1%).

**Conclusion:** Algorithms including combined sets of ICD-10-AM IFI codes, antifungal-dispensing, histology with fungal pathology or bronchoscopy/BAL procedural codes yield highest overall classification performance for IFI case detection. Efforts are required to reduce false positive cases in order to maximise PPV and safeguard high Sn.

## CANCER
## Clinical and Translational

### CDK4/6 inhibition reprograms the breast cancer enhancer landscape by stimulating AP-1 transcriptional activity

April C. Watt[1,2*], Paloma Cejas[3,4,5*], Molly J. DeCristo [6*], Otto Metzger-Filho[7], Enid Lam[1,2], Haley BrinJones[6], Rhiannon Coulson[1], Niko Kesten[3], Xintao Qiu[3], Veerle W. Daniels[7], Omer Gilan[1,2], Anthony Letai[7], Myles Brown[3,7], Mark Dawson[1,2], Henry Long [3,7], Jean J. Zhao [6,8,9] & Shom Goel[1,2]

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[6] Department of Cancer Biology, Dana-Farber Cancer Institute, Boston MA 02215, USA
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[*] These authors have contributed equally

**Introduction:** Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors are a class of small molecule inhibitors that has led to a profound change in the treatment of breast cancer. The CDK4/6-cyclin D-RB axis mediates cancer cell proliferation and is often dysregulated in breast cancer. CDK4/6 inhibitors are designed to effectively prevent RB phosphorylation and induce cancer cell cycle arrest. Recent reports have suggested that CDK4/6 inhibition can also have other effects in cancer cells, modulating their immunogenicity, apoptotic responses, and differentiation. However, the mechanism behind these biological effects is unclear.

**Method:** Using human breast cancer cell lines, mouse models, and paired patient biopsies, we profiled the chromatin landscape using ATAC-seq and ChIP-seq and examined the chromatin 3D conformation using HiChIP to show that CDK4/6 inhibition induces dramatic remodelling of cancer cell chromatin. We performed RNA-seq and functional studies to demonstrate the effects of CDK4/6 inhibition on luminal differentiation, apoptotic evasion, and immunogenicity. Using gene expression and protein analyses, as well as ChIP-seq, we investigated the role of Activator Protein-1 (AP-1) factors.

**Results:** In addition to promoter inactivation of cell cycle related genes, CDK4/6 inhibition causes an unexpected activation of many enhancers and superenhancers at genes involved in apoptotic evasion, tumour cell differentiation, and immunogenicity. We show that CDK4/6 inhibition's effect on chromatin remodelling is RB-dependent, as RB knockdown prevented the formation of new active enhancers. Importantly, CDK4/6 inhibition increases the expression and activity of AP-1 factors, and CDK4/6 inhibition-induced enhancers show increased binding of these factors. Pharmacological transrepression of AP-1 activity reverses the luminal differentiation and immunogenicity caused by CDK4/6 inhibition.

**Conclusion:** Our results demonstrate that CDK4/6 inhibition causes chromatin architecture remodelling and widespread enhancer activation in breast cancer. These are previously unreported consequences of CDK4/6 inhibitors and may explain some of the effects of these drugs. Our findings shed new insights into CDK4/6 pathway biology, and have implications for the future development of CDK4/6 inhibitors.

## CANCER
## Clinical and Translational

### Interleukin 11 signalling promotes glioblastoma progression

Sarah Stuart[1] & Rodney Luwor[1]

[1] Department of Surgery, The University of Melbourne, The Royal Melbourne Hospital, Parkville, Victoria 3050, Australia

**Introduction:** Glioblastoma is the most common and lethal brain tumour in adults with a mean survival rate of only 12-15 months with current treatment. The microenvironment of a tumour is considered to be essential to tumour pathogenesis. This includes the critical growth factors and cytokines that activate signalling pathways controlling many pro-oncogenic cellular functions. The IL-11 cytokine has become increasingly more important in the pathogenesis of a wide range of cancers, however, very little is known regarding its role in glioblastoma.

**Method:** To study the role of IL-11 in glioblastoma, we first evaluated IL-11 and IL-11R expression in the TCGA database. We also stably transfected IL-11R into 2 patient derived primary glioblastoma cell lines (#20 and #28) to examine the effect of over-expression of IL-11R on Glioblastoma cell proliferation, migration, invasion and survival in glucose and glutamine-depleted conditions.

**Results:** Analysis of TCGA data identified that IL-11 and IL-11Ra expression correlates with tumour grade and glioblastoma patient survival. Expression of IL-11R also led to an increase in cell proliferation compared to matched control/un-transfected cells. Wound healing and transwell migration assays also demonstrated that IL-11R transfected cell displayed significantly greater migratory ability than control/un-transfected cells. Finally, we demonstrated that cells transfected with the IL-11R could survival in media starved of either glucose or glutamine significantly better than control cells and this enhanced survival was due to reduced activation of cell apoptosis.

**Conclusion:** In conclusion, the data collected suggests interleukin-11 signalling plays a major role in glioblastoma proliferation, migration and survival in sub-optimal conditions.

## CANCER
## Clinical and Translational

### Inactivation and deletion of adoptively transferred CTL encountering a high number of antigen presenting lymphoma cells

Christina Scheffler[1], Justine Mintern[2] & Jose Villadangos[1,2]

[1] Peter Doherty Institute, Microbiology and Immunology, University of Melbourne, Melbourne, VIC, Australia
[2] Bio21 Institute, Biochemistry and Molecular Biology, University of Melbourne, Melbourne, VIC, Australia

**Introduction:** Adoptive T cell therapy (ACT) is a promising immunotherapeutic approach to fight cancer by transferring cytotoxic T lymphocytes (CTL), which specifically target and eradicate tumour cells. However, one major limitation of this therapy is the ability of tumours to interfere with the CTL through immune escape mechanisms, which may lead to poor CTL persistence and effector function.

**Methods:** In a mouse model of B-cell lymphoma and ACT, we investigate the mechanisms underlying this failure. We inject mice with tumour cells expressing an antigen, which can be targeted with antigen-specific CTL and analyse CTL survival and effector functions.

**Results:** We found that tumour-antigen-specific CTL, upon transfer into a mouse with low tumour burden successfully eradicate lymphoma cells, while upon encounter with a large tumour burden most of the CTL fail to survive and those that survive lose their effector functions. CTL death and loss of effector functions are not induced by long-term persistence of antigen but were observed as early as 24-48 h after the adoptive transfer. Furthermore, CTL survival as well as killing ability and cytokine production were found to be dependent on the number of antigen expressing tumour cells rather than the total tumour burden.

**Conclusion:** Our results describe a rapid deletion and inactivation mechanism of adoptively transferred CTL induced by encounter with a high number of antigen-expressing tumour targets. Further analysis of this mechanism may enable us to develop ways to improve adoptive T cell therapy by preventing CTL inactivation and deletion.

## CANCER
## Clinical and Translational

### Cancer-associated fibroblasts: Master inducers of breast cancer progression by secretion of exosomal TGF-beta

Adilson Teixeira[1], Yanhong Wang[1], Josephine Iaria[1], Peter ten Dijke[2], and Hong-Jian Zhu[1]

[1] The University of Melbourne, Parkville, Victoria, Australia.
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**Introduction:** Metastasis is the leading cause of cancer fatality. Cancer cell migration and invasion are essential steps of metastasis and they are facilitated by the epithelial-mesenchymal transition (EMT). Transforming growth factor-beta (TGF-beta) is a master inducer regulating the EMT-related processes. Despite overwhelm success in preclinical animal tumour models, outcomes of TGF-beta targeted therapies in clinical trials are disappointing, highlighting gaps in our understanding about TGF-beta biology. Of particular importance are the dynamic nature of TGF-beta signalling, the opposing effects on EMT and mesenchymal-epithelial transition (required for metastasis seeding), TGF-beta in exosomal form, as well as tumor microenvironment. Little is known about non-cancer cells-secreted TGF-beta and how the absence of cancer-associated fibroblasts (CAFs) in preclinical models limits its applicability in real patient metastasis. Further complicating is that TGF-beta, particularly in the cancerous environment, may exist largely in exosomes, which can disable the efficacy of anti-TGF-beta agents. As such, we evaluated the role played by CAFs-secreted exosomal TGF-beta in cancer cells.

**Methods:** Exosomes isolated from 19TT breast CAFs-conditioned medium were used to treat MCF7 (poorly invasive; hormone responsive) and MDA231 (highly invasive; triple negative) breast cancer cells. TGF-beta signaling pathway activation was investigated by the levels of SMAD3 transcriptional activity (luciferase assay) and SMAD2 phosphorylation/nuclear translocation (western blot and immunofluorescence/IF staining). EMT was confirmed by assessing the localization of the epithelial markers E-cadherin and ZO-1 (IF staining). Then, cancer cells proliferation (luciferase assay) and migration (wound healing assay) were analyzed. Additionally, cancer cells were co-cultured with CAFs to further evaluate these effects.

**Results:** Compared with the recombinant human TGF-beta (rhTGF-beta), CAFs-secreted exosomes amplified TGF-beta signaling activity in breast cancer cells, resulting in changes in MCF7 cells morphology and loss of epithelial markers, and enhancing cancer cells migration without impacting their proliferation. Because exosomes transport different cargoes, the inhibitory SMAD7 was overexpressed in cancer cells to investigate the contribution of exosomal TGF-beta. SMAD7 inhibited the effects triggered by exosomes to levels similar to those exhibited by untreated controls, confirming a major role for TGF-beta among exosomes cargo. Compared with mono-cultures, MCF7 cells co-cultured with CAFs showed higher SMAD3 activity and EMT-related alterations. Moreover, CAFs increased cancer cells proliferation and migration. On the other hand, interrupting exosome trafficking in the highly invasive MDA231 cells decreased TGF-beta signaling activation and consequently reduced EMT-related functions.

**Conclusion:** Exosomes secreted by CAFs amplify TGF-beta signaling pathway activation and increase tumorigenicity. Targeting exosome trafficking may improve the efficacy of anti-TGF-beta therapies.

## CANCER
## Clinical and Translational

### Utilising murine pancreatic cancer organoids to understand epithelial-mesenchymal transition in cancer

Ronnie Ren Jie Low[1,2,3,4], Ka Yee Fung[1,2] , Adele Preaudet[1], Gemma van Duijneveldt[1,2] , Frederic Hollande[3,4] , Sean M. Grimmond[3,4] & Tracy Putoczki[1,2]

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**Introduction:** Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers of all solid malignancies. Most patients succumb to the disease within 6 months, with the average 5-year survival of 9%. PDAC patients are often diagnosed with advanced stage disease where the cancer has metastasised. Epithelial-mesenchymal transition (EMT) is strongly implicated in tumour cell invasion, metastasis and drug resistance. There is an urgent need to better understand the progression of pancreatic cancer, including the role of EMT, so that novel treatment options can be identified.

**Methods:** A pipeline has been optimised for the growth of murine organoids. YFP+ ductal epithelial cells were isolated from the pancreata of PdxCre; RosaYFP mice to generate normal pancreatic organoids, whereas tumour organoids were generated from YFP+ cells isolated from the primary tumours and matched metastases (liver, peritoneum or lung) of the PdxCre; KrasG12V; p53R172H; RosaYFP mouse model of PDAC. Immunofluorescent staining for Epcam was performed on the primary tumour to further divide the YFP+ tumour population into cells in epithelial state (Epcam positive) and tumour epithelial cells that underwent EMT (Epcam negative). The EMT states of the organoids were further studied using quantitative polymerase chain reaction, western blot, immunohistochemistry and allograft generation to determine if the EMT state is retained in the organoid ex vivo.

**Results:** There were 100% success rate of both normal and tumour organoid generation resulting in a biobank of 5 normal ductal organoids, 9 primary tumour organoids and 8 metastatic organoids. Epithelial state and EMT state organoids were successfully generated from all 9 primary tumours. The molecular and histological analyses confirmed that the organoids retain the characteristics ex vivo.

**Conclusion:** We have established a complementary suite of pre-clinical model systems that accurately recapitulate the histopathological and molecular features of PDAC. These model systems will provide platform tools for characterisation of the behaviour of ductal epithelial cells that will assist us in better understanding PDAC progression. Ultimately, this will guide the discovery of new therapeutic opportunities and provide a model system for future pre-clinical drug trials.

# CANCER BASIC SCIENCE SCHEDULE

# CANCER
# Clinical and Translational

## SCHEDULE

### SESSION 1

| | | |
|---|---|---|
| 08.45 – 09.00 | **SMAD4 as a potential gatekeeper for genomic instability and mTOR-mediated tumourigenesis in oesophageal adenocarcinoma**<br>Julia Milne | 23 |
| 09.00 – 09.15 | **CRISPR screen identifies DNA repair and cell cycle as synthetic lethal pathway in SRSF2P95H mutated cells in vitro**<br>Jane Jialu Xu | 24 |
| 09.15 – 09.30 | **Sulforaphane attenuates cancer-induced muscle wasting in C2C12 myotubes**<br>Chloe (Wenlan) Li | 25 |
| 09.30 – 10.00 | **Blocking short-form Ron kinase eliminates breast cancer metastases by reactivating anti-tumor immune responses**<br>**Keynote Speaker:** Prof. Alana Welm | |

### SESSION 2

| | | |
|---|---|---|
| 10.30 – 10.45 | **MAIT cells regulate NK cell mediated tumour immunity**<br>Emma V. Petley | 26 |
| 10.45 – 11.00 | **Reprogrammed CRISPR-Cas13 suppresses tumour and viral RNAs with single-nucleotide precision**<br>Wenxin Hu | 27 |
| 11.00 – 11.30 | **Cellular plasticity – a non-genetic mechanism driving cancer progression and therapy-resistance**<br>**Keynote Speaker:** A/Prof. Christine Chaffer | |

### SESSION 3

| | | |
|---|---|---|
| 17.30 – 17.45 | **Metabolic crosstalk in the tumour microenvironment**<br>Srimayee Vaidyanathan | 28 |
| 17.45 – 18.00 | **Yap regulates an SGK1/mTOR/SREBP-dependent lipogenic program to fuel liver cancer**<br>Talhah M. Salmi | 29 |
| 18.00 – 18.15 | **Nutrient availability regulates tumour immune escape through disruption of antigen presentation pathways in breast cancer**<br>Keziah E Ting | 30 |
| 18.15 – 18.30 | **Loss of Keap1 in zebrafish leads to post-developmental liver dysfunction and Nrf2-mediated lethality**<br>Athena Ong | 31 |
| 18.30 – 19.00 | **Head and neck cancer organoids and their potential to predict patient therapy response**<br>**Keynote Speaker:** Dr. Rosemary Millen | |

# Cancer

## *Basic Science*

## Keynote Speakers

**Professor Alana L. Welm**
**Huntsman Cancer Institute**
**University of Utah**

**Session 1 09.30 - 10.00 am**

Dr. Welm received her undergraduate degree in Microbiology from the University of Montana. She then completed a PhD in Cell and Molecular Biology at Baylor College of Medicine in Houston, TX under the supervision of Gretchen Darlington, PhD. She then went onto conduct postdoctoral training in Dr. J. Michael Bishop's laboratory at the University of California, San Francisco, where her work focused on developing new models of breast cancer metastasis. Dr. Welm started her laboratory at the University of Utah's Huntsman Cancer Institute in 2007. She now holds the Ralph E. and Willia T. Main Presidential Endowed Chair in Cancer Research and is Senior Director of Basic Science and Co-Director of the Cell Response and Regulation Program at Huntsman Cancer Institute. She has been awarded multiple grants from the National Cancer Institute and has received DOD Era of Hope Scholar and Susan G. Komen Scholar awards. She serves on advisory boards for the PDX- Integrator Group (Cambridge, United Kingdom), the J. Michael Bishop Institute for Cancer Research (Chengdu, China), the Baylor College of Medicine (BCM) Patient- Derived Xenograft and Advanced in vivo Models Core, the BCM SPORE, and the Indiana University Precision Health Initiative- Triple Negative Breast Cancer Center for Excellence.

Tumor grafts derived from women with breast cancer authentically reflect tumor pathology, growth, metastasis and disease outcomes.
DeRose YS, Wang G, Lin Y-C, Bernard PS, Buys SS, Ebbert MTW, Factor R, MatsenC, Milash BA,Nelson E, Neumayer L, Randall RL, Stijleman IJ, Welm BE, and **Welm AL**. (2011) *Nat Med* 17(11):1514-20. PMCID:PMC3553601

**A/Professor Christine Chaffer**
**Garvan Institute of Medical Research**
**University of New South Wales**

**Session 2 11.00 - 11.30 am**

A/Prof Christine Chaffer is a laboratory head at the Garvan Institute. Her research focuses on the study of tumour-initiating cells (TICs) and cellular plasticity in breast cancer. Her original research changed paradigms in cancer research by establishing that the unidirectional tumour-initiating model could in fact operate as a bidirectional model, where non-TICs and TICs readily interconvert. These findings were published in Cell, PNAS and recently in Nature Cell Biology. She has authored multiple perspective pieces and review articles considering the role of cell plasticity in cancer progression published in Science, Cancer Discovery and Nature Medicine.

Christine's lab uses models of mammary gland biology, breast cancer biology and cancer stem cells/tumour-initiating cells to study cellular transitions, including the epithelial-to-mesenchymal (EMT) and the reverse process, the mesenchymal-to-epithelial (MET) transition. Her lab investigates their role in driving cancer development, progression and metastasis. Her work also aims to provide translational therapeutic benefits.

Recently Christine was awarded the Rebecca Wilson Fellowship in Breast Cancer Research from the The Nelune Foundation and Garvan Institute, The Miriam Douglas Blue Sky Endowment (2019) and she was a finalist for the Alan Skyring Memorial Award (ASMR). Christine has >10,000 career citations. Her work is currently funded by NHMRC, NBCF and CINSW.

IL-1β inflammatory response driven by primary breast cancer prevents metastasis-initiating cell colonization
Castaño Z, San Juan BP, Spiegel A, Pant A, DeCristo MJ, Laszewski T, Ubellacker JM, Janssen SR, Dongre A, Reinhardt F, Henderson A, Garcia del Rio A, Gifford AM, Herbert ZT, Hutchinson JN, Weinberg RA, **Chaffer CL****, McAllister SS**. (2018). *Nature Cell Biology*. 20(9):1084-1097

# Cancer

## *Basic Science*

## Keynote Speakers

**Dr. Rosemary Millen**
**Hubrecht Institute**
**Utretch University**

**Session 3 6.30 - 7.00 pm**

Rosie completed her PhD in April 2019 at University of Melbourne through Peter MacCallum Cancer Centre and St. Vincent's Hospital under Prof. Rob Ramsay and Prof. Kumar Visvanathan. Her research focused on understanding the function of tumor infiltrating lymphocytes (TILS) using patient-derived organoid models from colorectal cancer patients.

Rosie moved to Utrecht, The Netherlands in September 2019 to undertake her first postdoc at the Hubrecht Institute in the lab of Prof. Hans Clevers who developed organoid technology. She is now working on a clinical trial establishing organoids from patients with head and neck cancer. Her current project focuses on performing high-throughouput chemoradiotherapy drug screens in vitro to see if organoid models can be used as a predictive platform to guide clinical decision making.

Tumor Infiltrating Lymphocyte Function Predicts Response to Neoadjuvant Chemoradiotherapy in Locally Advanced Rectal Cancer
*Kong J, Guerra G & ***Millen R**, et al. *Journal of Precision Oncology*, 2018

# ABSTRACTS

## CANCER
## Basic Science

### SMAD4 as a potential gatekeeper for genomic instability and mTOR-mediated tumourigenesis in oesophageal adenocarcinoma

Julia Milne[1,2], Jovana Gotovac[1,2], Kenji Fujihara[1,2], Kaylene Simpson[1,2,3], Cuong Duong[1,2], Wayne Phillips[1,2,4] & Nicholas Clemons[1,2]

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[2] Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Victoria, Australia
[3] Victorian Centre for Functional Genomics (VCFG), Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[4] Department of Surgery (St Vincent's Hospital), The University of Melbourne, Parkville, Victoria, Australia

**Introduction:** Oesophageal cancer is the 8th most common cancer worldwide and has the 6th highest mortality rate of all cancers. The 5-year survival rate following oesophageal adenocarcinoma (OAC) diagnosis is dismal at <15%, indicating a dire need for improved therapeutic strategies and early detection. OAC develops stepwise following exposure to chronic gastric reflux: From pre-malignant Barrett's metaplasia, through stages of low- and high-grade dysplasia until developing into invasive cancer. Mutation or loss of common tumour suppressor genes TP53 and SMAD4 act as markers for cancer progression, occurring in high-grade dysplastic tissue and invasive OAC, respectively. This study aimed to investigate co-operate drivers of tumourigeneis in OAC as well as identify potential synthetic lethal interactions in SMAD4-deficient tumours.

**Methods:** Our group have developed a novel in vivo tumourigenesis model that demonstrates progression of Barrett's metaplasia to OAC. We conducted parallel genome-wide CRISPR-Cas9 knockout screens, both in vitro and in vivo, on a background of either wildtype-SMAD4 or SMAD4 knockout cells. Functional validation of hits was performed using cell-based assays identifying markers of genomic instability, such as copy number alteration analysis and detection of yH2AX foci.

**Results:** In our in vivo tumourigenesis model, SMAD4-deficient Barrett's metaplasia cells form tumours in immunodeficient mice after a period of latency and in a dose-dependent manner. The delayed tumour growth onset in this model suggests further drivers, in addition to loss of SMAD4, are required for oncogenesis, and these SMAD4-deficient cells and tumours display a greater degree of genomic instability than wildtype-SMAD4 controls. A genome-wide CRISPR-Cas9 knockout screen unveiled a synthetic lethal relationship between SMAD4-deficiency and cell cycle checkpoint inhibition, suggesting a role for SMAD4 in maintaining genomic stability and a potential novel therapeutic avenue for SMAD4-deficient OAC. Additionally, a concurrent in vivo CRISPR-Cas9 tumourigenesis screen produced tumours 4-fold faster than the previous model and identified regulators of mTOR signalling as co-operative drivers of tumourigenesis in OAC. Wildtype-SMAD4 cells failed to generate tumours despite undergoing the same genetic perturbations, indicating a potential gatekeeping effect of SMAD4 in mTOR-mediated OAC tumourigenesis.

**Conclusion:** In sum, loss of SMAD4 acts as a double-edged sword, increasing genomic instability and thereby rendering OAC cells sensitive to cell cycle checkpoint inhibition, whilst simultaneously co-operating with modulated mTOR signalling to promote tumourigenesis in OAC xenograft models.

## CANCER
## Basic Science

### CRISPR screen identifies DNA repair and cell cycle as synthetic lethal pathway in SRSF2P95H mutated cells in vitro

Jane Jialu Xu[1,2], Monique Smeets[1,2], Alistair Chalk[1,2], Iva Nikolic[3], Kaylene Simpson[3] & Carl Walkley[1,2,4]

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**Introduction:** Current strategy to target RNA splicing mutant cells involves disruption of normal splicing activities, which confers severe toxicity to wild-type cells demonstrated in clinical trial of spliceosome inhibitors. Proposal of targeting splice-specific aberrant protein could bypass the issue. However, such events are yet to be identified. We decided to analyze mis-splicing events of SRSF2P95H mutant samples from both human and murine datasets across multiple myeloid diseases (AML, MDS, CMML). We extracted targets that are mis-spliced across multiple datasets and found that DNA repair and cell cycle are among the top mis-spliced pathways.

**Methods:** To determine which pathway is essential for SRSF2P95H cells, I performed a genome-wide pooled CRISPR negative selection screen using Cas9-Hoxb8 GMCSF Srsf2P95H/+ and Srsf2+/+ cell lines (n=3). Mutant or wild-type cells were transfected with Mouse Brie library, which targets 19,674 genes. After CRISPR-Cas9 mediated gene deletion and activating Srsf2P95H/+ mutation, DNA were collected at three timepoints: day 4 (immediate after Srsf2P95H/+ activation), day 11 (one-week post Srsf2P95H/+ activation) and day 18 (two-week post Srsf2P95H/+ activation) to determine gRNA dropouts.

**Results and Conclusion:** Overall, the screen achieved good coverage in both wild-type and Srsf2P95H/+ cell lines (wild-type: 371x, Srsf2P95H/+: 344x). At FDR of 0.01, there are 762 genes dropped out in Srsf2P95H/+ cells, comparing to 235 in wild-type controls. Pathway analysis suggested that DNA repair, DNA replication and cell cycle are the top synthetic lethal pathways, besides mRNA splicing. Testing of Palbocilib. a CDK6 inhibitor, showed preferential sensitivity in Srsf2P95H/+ cell lines comparing to wild type.

## CANCER
## Basic Science

### Sulforaphane attenuates cancer-induced muscle wasting in C2C12 myotubes

Chloe Li[1], Kristy Swiderski[1], Kate T. Murphy[1] & Gordon S. Lynch[1]

[1] Centre for Muscle Research, Department of Physiology, The University of Melbourne, Victoria, 3010, Australia

**Introduction:** Cancer cachexia describes the progressive muscle wasting and weakness observed in cancer patients, which reduces both the response to treatment and overall quality of life. It accounts for nearly one-third of all cancer-related deaths and there is currently no standard treatment for cancer cachexia. One of the main contributing mechanisms to the development of cancer cachexia is oxidative stress. Compounds that attenuate oxidative stress could potentially protect against cancer-related muscle loss. Sulforaphane (SFN) is a natural antioxidant abundant in cruciferous vegetables such as broccoli, Brussels sprouts, and cabbage, that activates the nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathway to decrease oxidative stress. SFN reduces cancer cell proliferation in vitro and attenuates tumour growth in both rodents and cancer patients by mitigating oxidative stress. SFN can also attenuate muscle wasting associated with different diseases and exercise-induced muscle damage in mice. Whether SFN can attenuate muscle wasting in the presence of cancer cells remains to be determined.

**Methods:** To investigate whether SFN can attenuate cancer cell-induced muscle wasting, differentiated C2C12 myotubes were cultured in the presence or absence of colon-26 (C-26) cancer cells for 48 h. The chemotherapeutic agent, 5-fluorouracil (5-FU, 10 nM) or vehicle control (dimethyl sulfoxide, DMSO) were added to the myotubes to mimic cancer treatment clinically. SFN (10 μM) or vehicle (DMSO) were added for the final 24 h period. At the conclusion of treatment, myotubes were collected for immunostaining and western immunoblotting.

**Results:** In the presence of cancer cells, C2C12 myotube width was reduced by ~40% ($P<0.001$) and 15% ($P<0.01$) without and with 5-FU, respectively. The atrophic effect was partially attenuated with addition 5-FU. Also, SFN significantly attenuated the decrease in myotube width caused by co-culture with C-26 cells in both the presence and absence of 5-FU. Western immunoblotting revealed SFN administration increased Nrf2 protein expression in all conditions, confirming the signalling pathway and antioxidant action of SFN. Activation of Akt was also increased with SFN treatment, suggesting enhanced protein synthesis.

**Conclusion:** These exciting in vitro data support the chemoprotective and antioxidative function of SFN in C2C12 myotubes and highlight the therapeutic potential for SFN to attenuate cancer-related muscle wasting. Further investigation regarding the potential of SFN for treating cancer cachexia in vivo is warranted.

## CANCER
## Basic Science

### MAIT cells regulate NK cell mediated tumour immunity

Emma V. Petley[1,2], Hui-Fern Koay[3,4], Melissa A. Henderson[1,2], Kevin Sek[1,2], Kirsten L. Todd[1,2], Simon P. Keam[1,2], Junyun Lai[1,2], Imran G. House[1,2], Magnus Zethoven[2,5], Amanda X. Y. Chen[1,2], Amanda J. Oliver[1,2], Jessica Michie[1,2], Andrew J Freeman[1,2], Lauren Giuffrida[1,2], Jack D. Chan[1,2], Angela Pizzolla[1,2], Jeffrey Y. W. Mak[6,7], Fernando Souza-Fonseca-Guimaraes[8], Conor Kearney[1,2], Rosemary Millen[1,2], Robert G. Ramsay[1,2], Nicholas D.Huntington[9-11], James McCluskey[3], Jane Oliaro[1,2,12], David P. Fairlie[6,7], Paul J. Neeson[1,2], Dale I. Godfrey[3,4*], Paul A.Beavis[1,2,12,*] & Phillip K. Darcy[1,2,12,13*]

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The success of immunotherapies, such as immune checkpoint blockade, has highlighted the importance of the immune system in controlling tumours. The presence of conventional T cells within the tumour microenvironment have been intensively studied and correlates with patient outcomes, however, the role of mucosal-associated invariant T (MAIT) cells in cancer is relatively unknown. MAIT cells are abundant in humans and enriched in mucosal tissues, such as the colon and lung, and some recent studies have reported the presence of these cells within primary and metastatic tumours. However, it is unclear whether MAIT cells contribute to anti-tumour immune responses. Here we show that MAIT cell-deficient mice are more resistant to subcutaneous and lung metastasis B16F10 tumour growth compared to control mice, an effect that was associated with enhanced natural killer (NK) cell numbers and was NK cell-dependent. Analysis of this interplay in cancer patients also revealed that a high expression of a novel MAIT gene signature negatively impacted the prognostic significance of NK cells. Paradoxically, pre-pulsing tumour cells with MAIT cell antigens, or antigen-mediated MAIT cell activation in vivo, enhanced immunity against B16F10 and E0771 lung tumour metastasis. Furthermore, MAIT cell activation effectively reduced metastatic burden in a more stringent model of established lung metastases in mice. These effects were associated with enhanced NK cell responses and increased expression of both IFNγ-dependent and inflammatory genes in NK cells, which was neutralised by IFNg blockade. Importantly, activated human MAIT cells also enhanced the function of NK cells isolated from patient tumour samples. These findings provide insight into the contrasting roles that MAIT cells can play in controlling anti-tumour immune responses depending on their activation status, in both mice and humans, and suggest potential therapeutic avenues for exploiting their potential anti-tumour properties for cancer treatment.

## CANCER
## Basic Science

### Reprogrammed CRISPR-Cas13 suppresses tumour and viral RNAs with single-nucleotide precision

Wenxin Hu[1], Joseph Trapani [1]& Mohamed Fareh [1]

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**Introduction:** CRISPR-Cas systems confer bacteria adaptive immunity against invading pathogens through sequence-specific recognition and cleavage of foreign nucleic acids. Reprogrammed CRISPR-Cas effectors offer a great opportunity to silence disease-associated genes at the DNA or RNA level. CRISPR-Cas13 system was recently reported as a bacterial nucleoprotein that targets bacteriophages' RNAs with high efficacy and specificity. The molecular bases that govern Cas13 targeting remain largely unknown, which limits future therapeutic use of this promising tool to silence tumour and viral RNA.

**Methods and results:** To study the molecular mechanisms of RNA recognition used by Cas13b, we developed innovative silencing assays in mammalian cells where the spacer sequence of various gRNAs is designed to fully base pair with a reporter transcript at various locations. We demonstrate that Cas13 loaded with rationally designed gRNAs can eliminate up to 99% of the targeted transcript. Notably, several target sequences exhibited a poor silencing efficiency despite a full base-pairing with the spacer sequence, suggesting the existence of hidden parameters that control Cas13b binding and silencing. To uncover these hidden rules, we developed new bioinformatic pipelines and single-nucleotide resolution screening approaches and interrogated how the landscape of a target RNA impacts Cas13b recognition at the nanoscale level. The single-nucleotide resolution dataset revealed that Cas13b is not constrained by any protospacer-flanking sites (PSF or PAM-like), and therefore highlights its extremely high design flexibility. Strikingly, we revealed that poor and ultrapotent gRNAs clustered together in mutually exclusive RNA locations, suggesting that roadblocks such as structured RNA hairpins are the main obstacles that limit Cas13b target accessibility. Furthermore, we explored Cas13b target specificity through the investigation of spacer-target interaction at the single-nucleotide level. Our comprehensive mutagenesis analysis revealed that Cas13b is highly specific since mismatches greater than 3 nucleotides destabilized spacer-target interaction and largely impaired Cas13b silencing in vivo. Thus, we demonstrate that Cas13b outperforms other RNA interference tools in term of specificity and efficacy, revealing its immense therapeutic potential to silence oncogenic and viral RNAs in sequence-specific manner. As a proof-of-concept, we show that reprogrammed Cas13b can silence three different gene fusion transcripts (BCR-ABL1, SFPQ-ABL1, and SNX2-ABL1) that drive acute lymphoblastic leukaemia. Likewise, we reprogrammed Cas13b against SARS-CoV-2 RNA genome and demonstrated >90% suppression of viral replication in infected mammalian cells.

**Conclusion:** We believe these findings will pave the way for the development of Cas13b therapeutics to silence or manipulate any transcript of interest with single-nucleotide precision.

## CANCER
## Basic Science

### Metabolic crosstalk in the tumour microenvironment

Srimayee Vaidyanathan[1,2], Andrew G Cox[1,2,3] & Kristin K Brown[1,2,3]

[1] Peter MacCallum Cancer Centre, Melbourne, Australia
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[3] Department of Biochemistry and Molecular Biology, The University of Melbourne, Melbourne, Australia

**Introduction:** In order to proliferate without control, cancer cells exhibit increased biosynthetic demands relative to normal tissues. These demands are met through reprogramming of cellular metabolism and nutrient utilisation. Cell-intrinsic regulators of cancer cell metabolism, such as oncogenic mutations, have been extensively studied. However, less is known about cell-extrinsic/microenvironmental regulation of cancer cell metabolism. A key component of the tumour microenvironment is the extracellular matrix (ECM), a macromolecular network that, in addition to acting as a scaffold to organise cells within a tissue, has a major impact on cell behaviour. Dysregulation of ECM is a key feature of cancer, with solid tumours frequently exhibiting excessive collagen deposition and altered organisation and modification of various ECM proteins. ECM dysfunction actively promotes tumour progression in invasive breast cancer by facilitating local invasion of cancer cells and promoting pro-oncogenic signalling. Emerging evidence also suggests that the cancer-associated ECM influences cancer cell metabolism. Moreover, recent studies indicate that ECM remodelling may be directly underpinned by metabolic reprogramming. The goal of our study is to characterise the metabolic crosstalk between breast cancer cells, cancer-associated fibroblasts (CAFs) and the cancer-associated ECM.

**Methods:** Using a physiologically-relevant cell culture system, we have depleted single amino acids from cell culture medium and subsequently studied the effect of nutrient availability on ECM production by cancer cells and CAFs. We have also utilised transcriptomic analyses (RNA-seq) to investigate the impact of oncogenic perturbation on transcriptional regulation of the cancer-associated ECM.

**Results:** We have shown that physiological cell culture media enhances the production of ECM components such as fibronectin in both cancer cells and CAFs, when compared to conventional cell culture media. Additionally, we have found that the depletion of specific amino acids, such as methionine, results in increased deposition of collagen by normal fibroblasts, but not by CAFs. Transcriptomic
analyses have revealed that YAP, an oncogenic transcriptional coactivator and master regulator of metabolism, plays a key role in regulating ECM composition and the expression of ECM modifying proteins.

**Conclusion:** Emerging studies suggest that pathological ECM remodelling is underpinned by metabolic reprogramming. Our data demonstrate that both oncogenic perturbations and changes in the availability of specific nutrients modulate ECM production, thus indicating that both intrinsic and extrinsic factors are important in regulating crosstalk between tumour metabolism and the cancer-associated ECM. By better understanding the bidirectional relationship between cancer cell metabolism and cancer-associated ECM, we hope to elucidate metabolic vulnerabilities that can be targeted for breast cancer therapy.

## CANCER
## Basic Science

### Yap regulates an SGK1/mTOR/SREBP-dependent lipogenic program to fuel liver cancer

Talhah M. Salmi[1,2,3,*], Srimayee Vaidyanathan[1,2,*], Malcolm J. McConville[3], Kristin K. Brown[1,2,3, ⌘] & Andrew G. Cox[1,2,3, ⌘]

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[3] Department of Biochemistry and Molecular Biology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Parkville, Victoria, Australia
[*] These authors contributed equally to this work
[⌘] These authors contributed equally to this work

**Introduction:** Hepatocellular carcinoma (HCC) is the most common form of liver cancer. At the molecular level, HCC is driven by transcription factors that reprogram metabolism to support tumorigenesis. Yes-associated protein (Yap) is the nuclear effector of the Hippo pathway, which is responsible for regulating organ size control. In our previous studies, we found that Yap integrates the anabolic demands of tumour growth by reprogramming glucose and glutamine metabolism. The central aim of this study was to determine the role that Yap plays in regulating lipid metabolism in liver cancer.

**Methods:** In this study, we used zebrafish as a model organism to investigate the role of Yap in lipid metabolism. We took advantage of the optical transparency of zebrafish larvae and performed multiphoton microscopy. This enabled us to image the formation of lipid droplets in the liver at cellular resolution in vivo. We also performed paired-end RNA sequencing on micro-dissected liver tissue to examine the transcriptional changes induced by Yap. Finally, we also utilized CRISPR/Cas9 technology to knockouts genes involved lipid metabolism.

**Results:** We utilized a larval zebrafish model where a hyperactivated form of Yap is specifically expressed in hepatocytes (lf:YapS87A;lf:NLS-mcherry). Consistent with previous work, we observed that Yap hyperactivation resulted in liver hyperplasia. Upon closer examination we found that Yap hyperactivation was sufficient to stimulate de novo lipogenesis (DNL) and lipid droplet formation in hepatocytes (steatosis). Our transcriptomic analyses revealed that Yap hyperactivation caused an increase in the expression of Sterol regulatory-element binding proteins (SREBP) target genes responsible for DNL. Given that the maturation of SREBP is dependent on the mTOR pathway, we examined the effect of rapamycin treatment. We found that the inhibition of mTOR by rapamycin suppressed Yap driven DNL and hyperplasia. We demonstrated that the Yap target gene serum/glucocorticoid regulated kinase 1(SGK1) was required for Yap to induce mTOR-dependent hyperplasia. To determine whether the stimulation of DNL was required for Yap-dependent oncogenic growth, we targeted two critical enzymes in DNL, namely FAS and SCD, and examined the impact on growth at the cellular level in vivo using multiphoton microscopy. We observed that both chemical and genetic perturbations of DNL suppressed Yapdependent hyperplasia, whilst having no effect on normal liver.

**Conclusion:** Together, these findings suggest that oncogenic Yap-driven growth is conditionally dependent upon the SGK1/mTOR/SREBP-mediated stimulation of DNL. Consequently, these studies provide a rationale for examining the clinical efficacy of DNL inhibitors to combat liver cancer.

## CANCER
## Basic Science

### Nutrient availability regulates tumour immune escape through disruption of antigen presentation pathways in breast cancer

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**Introduction:** Nutrient availability in the tumour microenvironment (TME) has a profound impact on the metabolism, growth and survival of a variety of cell types that occupy the TME. Emerging research has revealed that changes in nutrient availability, for example glucose restriction, have a dramatic impact on T cell function and anti-tumour activity. It is becoming increasingly apparent that tumour cells employ a variety of mechanisms for immune escape, including the release of immunosuppressive molecules, downregulation of antigen presentation and acquisition of immune checkpoints. The impact of nutrient availability on tumour cell immune escape mechanisms is poorly understood.

**Method:** Using a cell culture model with enhanced physiological relevance, we have monitored the impact of specific changes in nutrient availability on the expression of antigen presentation molecules and immunosuppressive molecules using RT-PCR, immunoblotting and flow cytometry. Additionally, we have applied genetic and pharmacological approaches to interrogate the impact of select metabolic pathways on antigen presentation by tumour cells.

**Results:** We found that breast cancer cells cultured in conventional cell culture media (DMEM) are dependent on glucose for the normal regulation of MHC class I presentation. In this model, glucose depletion reduced basal and interferon-gamma-induced MHC class I expression. In contrast, glucose depletion had little effect on the regulation of MHC class I presentation when cells were cultured in a medium designed to mimic nutrient availability that cells would be exposed to in vivo. In this model, we found that the availability of specific amino acids greatly impacted the expression of basal and interferon-gamma-induced MHC class I and PD-L1 expression.

**Conclusion:** We have shown that changes in the availability of specific nutrients promotes tumour cell immune escape mechanisms including downregulation of the antigen presentation molecule, MHC class I, and upregulation of the immunosuppressive marker, PD-L1. By studying the impact of nutrient availability on immune escape, we hope to reveal fundamental insights regarding how tumour cells exploit cellular metabolism to evade immune control.

## CANCER
## Basic Science

### Loss of Keap1 in zebrafish leads to post-developmental liver dysfunction and Nrf2-mediated lethality

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**Introduction:** Kelch-like ECH-associated protein 1 (Keap1) is a CUL3-ubiquitin ligase complex adapter that negatively regulates the transcription factor known as nuclear factor erythroid 2-related factor 2 (Nrf2). Activation of the Nrf2 pathway, which results from disruption of Keap1-Nrf2 binding, is known to induce genes involved in detoxification and antioxidant defense. Emerging evidence suggests an important role for Nrf2 in the regulation of cellular metabolism. Activating mutations in Nrf2 or inactivating mutations in Keap1 are observed in approximately 19% of hepatocellular carcinoma (HCC) patients, leading to constitutive activation of the Nrf2 pathway.

**Methods:** In this study, we utilized zebrafish as a model organism to investigate the biological consequences of Keap1 deletion. Zebrafish have two orthologs of Keap1, keap1a and keap1b. Keap1a/b loss-of-function (LOF) larvae were generated by microinjecting CRISPR/Cas9 editing complexes targeting both keap1a and keap1b in 1-cell stage zebrafish embryos (crispants). Keap1a/b crispants were characterized by live imaging analysis (multiphoton microscopy), transcriptomic analysis (RNA-seq), metabolomic analysis (LC-MS-based metabolomics), and histologic analysis.

**Results:** Loss of keap1a/b induces a lethal phenotype at around 8 to 10 days post fertilization (dpf), which was reproducible in the F1 generation. Interestingly, keap1a/b crispants exhibited severe liver abnormalities with features including a deformed liver, enlarged hepatocytic nuclei, and liver sinusoidal dilation. Transcriptomic and metabolomic analyses highlighted extensive metabolic reprogramming in the keap1a/b crispants. Remarkably, Nrf2 depletion rescued the lethal phenotype observed in keap1a/b crispants, suggesting that the phenotypic effects of keap1a/b loss are predominantly driven by Nrf2. Finally, since there is a co-occurrence of p53 LOF mutations and Nrf2 pathway hyperactivation in HCC, we knocked out keap1a/b in p53-deficient larvae. In addition to retaining the phenotypes of the keap1a/b crispants, keap1a/b/p53-deficient larvae exhibited features consistent with the early stages of HCC.

**Conclusion:** We have demonstrated that loss of keap1 induces a lethal phenotype that is preceded by severe developmental defects in the liver and widespread changes in the transcriptome and metabolome. The lethal phenotype associated with keap1a/b knockout is rescued by the knockout of Nrf2. Finally, we have demonstrated that keap1a/b knockout in p53-deficient larvae induces features consistent with HCC suggesting that this represents a novel model to study the biological mechanisms underlying HCC development and progression.

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