2015 AGTA Conference

AUSTRALASIAN GENOMIC TECHNOLOGIES ASSOCIATION

11-14 October

CROWNE PLAZA HUNTER VALLEY

agtaconference.org

HANDBOOK

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CONFERENCE MANAGERS

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2015 AGTA Conference

AGTA Executive Team

Ruby C Y Lin (President), Asbestos Diseases Research Institute

Carsten Kulheim (Vice President), Australian National University

Mark van der Hoek (Treasurer), South Australian Health and Medical Research Institute

Vikki Marshall (Secretary), Melbourne Neuroscience Institute, University of Melbourne

Alicia Oshlack, Murdoch Children's Research Institute

Richard Tothill, Peter MacCallum Cancer Centre

Erik (Rik) Thompson (Founding AMATA President)

Jac Charlesworth, Menzies Institute for Medical Research

Daniel Catchpoole, The Children's Hospital at Westmead

Ryan Lister, The University of Western Australia

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Liam Williams, Auckland University

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Kirby Siemering, Australian Genome Research Facility

Mark Crowe, QFAB Bioinformatics

Andreas Schreiber, Centre for Cancer Biology

Nicole Cloonan, QIMR Berghofer Medical Research Institute

Robert Day, CTCR University of Otago

AGTA 2015 Conference Organising Committee

Marcel Dinger, Garvan Institute of Medical Research (co-convenor)

Carsten Kulheim, The Australian National University (co-convenor)

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Torsten Thomas, University of New South Wales

Jean Yang, University Of Sydney

WELCOME FROM THE AGTA PRESIDENT

Dear Delegates and Invited Guests,

On behalf of the Australasian Genomic Technologies Association managing executives, I welcome you to the 15th Annual Scientific Meeting for AGTA in the heart of the wine country, Hunter Valley, New South Wales, Australia.

This meeting marks the first year of the association under the new banner of AGTA and we remain the premium platform to connect with many of Australia's leading scientists in the field of genomics. This is where people from academia, industry, research and the clinic converge to have rigorous discussion. For the newcomers to the Association, this is where you form long-term friendships, networks and collaborations, and find career opportunities.

We have had a busy year consolidating our infrastructure, governance and communication with our members. We have finalised and registered our new constitution as AGTA. Our society continues with the Small Grant Scheme, which resulted in two successful recipients, announced in June 2015. We continue our collaboration with QFAB who host our website, ww.agtagenomics.org.au. We have revamped the news section to include job postings and introduced notifications of workshops in AGTA members' respective states. To increase communication with our members, we are active on Facebook, Twitter and LinkedIn and we have introduced a 3-year membership category upon members' feedback. We hope these interactions and support continue as our membership grows into the future. We are proud to maintain AGTA meetings as gender balanced and family friendly. This year we farewell our executives, Mark Crowe, Daniel Catchpoole and Ian Paulsen. I would like to take this opportunity to thank them for their time, contribution and support on the AGTA managing executive committee and I am happy to say that they remain firm supporters of AGTA.

This year, it is only befitting that we have a theme on genomics of plants and fine wine, being in the Hunter Valley. We also have focussed themes on transcriptomics, developmental genomics, cancer genomics, clinical genomics, quantitative genetics, microbial and single cell genomics. On behalf of the managing executives and the local conference organising committee, I would like to welcome our international keynote speakers to Hunter Valley. We hope you enjoy and take the time to explore our beautiful country. We are also thankful to our invited speakers and national chairs. AGTA 2015 committee is very proud to showcase many early career scientists including students, who are AGTA members. I would like to thank each one of you for contributing to this dynamic line-up and I hope that you enjoy the program ahead.

We are very thankful for the participation of our Gold Sponsor BD Biosciences, Silver Sponsors; Roche Diagnostics and Illumina, and Qiagen and DNAnexus for sponsored speakers. We are also thankful for some twenty exhibitors, without whom this meeting would not be possible. We recognise the importance technology companies play in the evolution of genomics in Australia and we strongly encourage you to take the time and opportunity to interact with these leading companies.

It is my pleasure to welcome you to AGTA 2015 on behalf of the convenors, Marcel Dinger and Carsten Külheim, the AGTA 2015 conference organising committee and the AGTA managing executives. We trust that you will enjoy AGTA 2015.

Dr Ruby CY Lin
President
Australasian Genomic Technologies Association

WELCOME FROM THE CONFERENCE CONVENORS

Dear Delegates and Invited Guests,

On behalf of the AGTA Executive Committee and the 2015 AGTA Conference Organising Committee, we extend to you a very warm welcome to the Hunter Valley and the 15th Annual Conference of the Australasian Genomic Technologies Association.

New technologies and innovations are reshaping scientific research at unprecedented rates - enabling new approaches to solve biological problems that could not be foreseen even a few years ago. What better place to appreciate the biological insights derived from next-generation sequencing and related technologies than the Hunter Valley, especially when they are related to wine.

The organising committee has been overwhelmed by the very high calibre of research presented in submitted abstracts, making it a challenge to select a limited number of oral presentations. However, the committee has managed to compile what we consider to be an exciting and broad scientific program that encompasses transcriptomics, small and non-coding RNAs, disease, data handling and analysis, population genetics and epigenomics.

Along with the excellent scientific program we hope you will enjoy the scenery and hospitality of the Hunter Valley. The AGTA (formerly AMATA) meetings have been the birthplace for many friendships, collaborations and good memories. We trust that this year's meeting will continue this tradition and remind us that some of Australasia's best science has been the product of strong scientific networks.

We gratefully acknowledge the invited international, national and guest speakers for their time, energy, and invaluable contribution to AGTA 2015, and to our sponsors for their support without which this conference could not take place.

Once again welcome, thank you for your contribution, and please savour the insights good science, and maybe the odd wine, brings.

Associate Professor Marcel Dinger
Garvan Institute of Medical Research

Dr Carsten Külheim
Australian National University

GENERAL INFORMATION

REGISTRATION DESK

Please direct any questions you may have regarding registration, accommodation or social functions to Leishman Associate staff at this desk.

Registration Desk Opening Times

Sunday 11 October 2015
2:00pm - 8:00pm

Monday 12 October 2015
7:30am - 5:30pm

Tuesday 13 October 2015
7:30am - 5:30pm

Wednesday 14 October 2015
8:00am - 2:00pm

ACCOMMODATION

If you have any queries relating to your accommodation booking first speak to the staff at your hotel or alternatively Leishman Associates staff at the Registration Desk.

Your credit card details were supplied to the hotel you have selected, as security for your booking. If you have arrived 24 hours later than your indicated arrival day you may find that you have been charged a fee. You will be responsible for all room and incidental charges on check out and may be asked for an impression of your credit card for security against these charges. This is standard policy in many hotels.

CONFERENCE NAME BADGES

All delegates, speakers, sponsors and exhibitors will be provided with a name badge, which must be worn at all times within the conference venue, as it is required for access to all the conference sessions and social functions.

With thanks to our Name Badge Sponsor:

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CONFERENCE PROCEEDINGS

Speaker PowerPoints and abstracts will be available on the AGTA website following the conclusion of the conference. Speakers will be requested to sign a release form. This is not compulsory.

CONFERENCE WIFI

Wireless internet will be available throughout the conference venue for the duration of the conference. A username and password will be given to you when you register at the conference.

DRESS CODES

Dress throughout the day is smart casual or informal business.

EMERGENCY MEDICAL CARE

For any medical emergency please telephone 000. The staff at your hotel will have information if you require contact details for a doctor, dentist or other health professional.

EXHIBITOR PRIZE DRAW

An exhibitor passport will be given to all delegates at registration. The AGTA 2015 organising committee encourages you to visit each trade exhibitor and have your passport stamped, to go into the draw to win some great prizes!

SOCIAL PROGRAM ENTRY

The Welcome Reception is included in the cost of each full conference registration.

With thanks to our Welcome Reception Sponsor:

BD

The Conference Dinner IS NOT included in any registration type. Social events ARE NOT included in the cost of day registrations or for accompanying partners. Places for day registrants and additional guests for these events may still be available at an additional cost. Bookings can be made at the registration desk subject to availability.

All delegates who are registered to attend the dinner will receive a named sticker at registration. You MUST place your sticker on a table located on poster boards next to the registration desk. You must allocate yourself to a table no later than 11.00 am Tuesday 13 October 2015.

STUDENT FUNCTIONS

All conference students and early career researchers are invited to a casual function on Monday 12 October. Please forward enquiries to the registration desk. Further information about this event can be found on page 19.

PHOTOGRAPHS, VIDEOS, RECORDING OF SESSIONS

Delegates are not permitted to use any type of camera or recording device at any of the sessions unless written permission has been obtained from the relevant speaker.

SPEAKERS AND SPEAKER'S PREPARATION ROOM

All speakers should present themselves to the Speaker's Preparation Room, located next to the conference registration desk at least 4 hours before their scheduled presentation time, to upload their presentation.

Speakers are requested to assemble in their session room 5 minutes before the commencement of their session, to meet with their session chair and to familiarise themselves with the room and the audio visual equipment. For information on the chairperson attending your session, please see the Registration Desk.

A technician will be present in the speaker's preparation room during registration hours. There will be facility to test and modify your presentation as required.

ORAL PRESENTATIONS

Please refer to the program for the time allocated for each presentation, as these do vary. The chairperson for your session will give you a 3 minute warning, however you are asked to stick to your time allocation so that the program remains on schedule.

POSTER PRESENTATIONS

Posters will be displayed in the Exhibition Centre of the Crowne Plaza for the duration of the conference. There will be a poster session on Monday 12 October 2015 from 1.30pm to 3.30pm and on Tuesday 13 October at 1.05pm to 3.00pm.

SPECIAL DIETS

All catering venues have been advised of any special diet preferences you have indicated on your registration form. Please identify yourself to venue staff as they come to serve you and they will be pleased to provide you with all pre-ordered food. For day catering, there may be a specific area where special food is brought out, please check with catering staff.

SECURITY

The members of the conference organising committee, Leishman Associates and The Crowe Plaza Hunter Valley accept no liability for personal accident or loss or damage suffered by any participant, accompanying person, invited observer or any other person by whatever means. Nor do we accept liability for any equipment or software brought to the conference by delegates, speakers, sponsors or any other party.

Please protect your personal property. Do not leave laptops, cameras, and other valuable items unsecured. Be conscious of individuals who appear out of place and do not wear a conference name badge. Advise Leishman Associates staff if this does occur.

PARENTS ROOM

A private room will be available at the conference venue for nursing mothers and others with sensitive personal health needs. Please note that this room will not be staffed. Attendees are not permitted to utilise this room for babysitting services. Please see the Leishman Associates staff at the registration desk for further information

DISCLAIMER

The 2015 AGTA Conference reserves the right to amend or alter any advertised details relating to dates, program and speakers if necessary, without notice, as a result of circumstances beyond their control. All attempts have been made to keep any changes to an absolute minimum.

CONFERENCE PROGRAM

SUNDAY
11 October 2015

PRE-CONFERENCE WORKSHOP		**Cellar Room 2**
1130 - 1630	**GENOTYPING-BY-SEQUENCING: A LOW COST TOOL FOR POPULATION GENETICS WORKSHOP** Mr Aaron Chuah, The Australian National University, ACT, Australia Mr Rob Elshire, The Elshire Group Limited, New Zealand Professor Justin Borevitz, The Australian National University, ACT, Australia	
1400 - 2000	Conference Registration Open	Galleria
OPENING ORATION **CHAIR: DR RUBY CY LIN**		**Sauvignon Room**
1700 - 1800	**STUDYING CANCER AT SINGLE NUCLEOTIDE RESOLUTION** Professor Sean Grimmond Wolfson Wohl Cancer Research Centre, Institute for Cancer Sciences, University of Glasgow, Scotland, U.K	
1800 - 2000	Welcome Reception & Trade Exhibition Proudly sponsored by BD	Exhibition Centre
2000	Free evening for delegates	

Guest Speaker | Early Career Researcher | Student | Invited Speaker | Keynote

CONFERENCE PROGRAM

MONDAY
12 October 2015

0730 - 1730	Registration Desk Open & Welcome Refreshments	Galleria
0800 - 1730	Trade Exhibition Open	Exhibition Centre
0830 - 0845	Official Welcome and Conference Opening	Sauvignon Room

SESSION 1: TRANSCRIPTOMICS AND THE REGULATION OF THE GENOME
CHAIRS: DR PHILLIPPA TABERLAY & DR TIMOTHY MERCER — Sauvignon Room

0845 - 0930	**DIFFERENTIAL ANALYSIS OF BIFURCATING SINGLE-CELL GENE EXPRESSION TRAJECTORIES** Assistant Professor Cole Trapnell University of Washington, U.S.A	
0930 - 0955	**INSIGHTS INTO MAMMALIAN CELL TYPES** Professor Alistair Forrest Harry Perkins Institute of Medical Research, WA, Australia	
0955 - 1015	**ALTERATIONS IN THREE-DIMENSIONAL ORGANISATION OCCUR COINCIDENT WITH LONG-RANGE EPIGENETIC DEREGULATION OF THE CANCER GENOME** Dr Phillippa Taberlay Garvan Institute of Medical Research, NSW, Australia	
1015 - 1030	**3'ÚTR DYNAMICS PREDICT mRNA FATE** Dr Traude Beilharz Monash University, VIC, Australia	
1030 - 1045	**DYNAMIC EXPRESSION OF LONG NONCODING RNAs AND REPEAT ELEMENTS IN SYNAPTIC PLASTICITY** Mr Jesper Maag Garvan Institute of Medical Research, NSW, Australia	
1045 - 1115	Morning Refreshments & Trade Exhibition	Exhibition Centre

SESSION 2: GENOME EVOLUTION AND BIOINFORMATICS — Sauvignon Room
CHAIRS: DR NATALIE THORNE & DR JOSEPH POWELL

1115 - 1200	**WHAT WE HAVE LEARNED FROM SEQUENCING ARCHAIC HUMAN GENOMES** Dr Janet Kelso Max Planck Institute for Evolutionary Anthropology, Germany	
1200 - 1225	**USING GENE CO-EXPRESSION NETWORKS TO DISCOVER EPILEPSY GENES** Associate Professor Melanie Bahlo Walter + Eliza Hall Institute of Medical Research, VIC, Australia	

CONFERENCE PROGRAM

MONDAY
12 October 2015

1225 - 1245	**DEEP GENE EXPLORATION OF HUMAN CHROMOSOME 21** Dr Timothy Mercer Garvan Institute of Medical Research, NSW, Australia	
1245 - 1300	**MAPPING STEM CELL BIOLOGY BY HIGH RESOLUTION TEMPORAL TRANSCRIPTOMICS** Dr Brian Gloss Garvan Institute of Medical Research, NSW, Australia	
1300 - 1400	Lunch & Trade Exhibition	Exhibition Centre
1330 - 1530	Poster Session One & Afternoon Refreshments	Exhibition Centre
SESSION 3: DEVELOPMENTAL GENOMICS AND THE ORIGINS OF DISEASE **CHAIR: PROFESSOR ANDREW PERKINS & DR KATE HOWELL**		Sauvignon Room
1530 - 1555	**HIGHLY CONSERVED EPIGENOME REMODELLING DURING THE VERTEBRATE PHYLOTYPIC PERIOD** Professor Ryan Lister The University of Western Australia, WA, Australia	
1555 - 1615	**GENOME-DRIVEN INSIGHTS TO DISEASE MECHANISMS** Associate Professor Robyn Jamieson Children's Medical Research Institute, NSW, Australia	
1615 - 1635	**ADVANCES IN THE UNDERSTANDING OF MUTATIONAL SIGNATURES IN HUMAN SOMATIC CELLS** Dr Mirana Ramialison Australian Regenerative Medicine Institute, Monash University, VIC, Australia	
1635 - 1650	**REPLI-G SINGLE CELL SEQUENCING: DRIVING THE NEXT FRONTIER OF GENOMIC AND TRANSCRIPTOMIC ANALYSIS** Mr Colin Baron Qiagen Life Sciences, U.S.A Proudly supported by QIAGEN	
1650 - 1705	**UNCOVERING HIDDEN GENES IN INTERGENIC GWAS REGIONS** Dr Nenad Bartonicek Garvan Institute of Medical Research, NSW, Australia	

CONFERENCE PROGRAM

MONDAY
12 October 2015

1705 - 1720	**VISUALISATION OF VARIANTS USING AQUARIA: NON-SYNONYMOUS SNPs IN THE CONTEXT OF PROTEIN STRUCTURE** Dr Neil Saunders Digital Productivity Flagship, CSIRO, NSW, Australia
1720	Free evening for delegates
1800 onwards	**Student Function** **The Lovedale Bar** *Students and early career researchers are invited to join fellow delegates for a fun night of genomics trivia. Finger food and limited beverage service will be provided.* *Please confirm your attendance to this function by advising the staff at the conference registration desk.*

DON'T FORGET to visit the Trade Exhibitors and have your Passport stamped! You could win a $200 JB HI-FI Voucher

CONFERENCE PROGRAM

TUESDAY
13 October 2015

0730 - 1730	Registration Desk Open & Welcome Refreshments	Galleria
0800 - 1730	Trade Exhibition Open	Exhibition Centre
0825 - 0830	Welcome to Day Two	Sauvignon Room
SESSION 4: CANCER GENOMICS AND PRECISION MEDICINE **CHAIRS: PROFESSOR DAVID THOMAS & DR NIC WADDELL**		Sauvignon Room
0830 - 0910	**ADVANCES IN THE UNDERSTANDING OF MUTATIONAL SIGNATURES IN HUMAN SOMATIC CELLS** Dr Serena Nik-Zainal Wellcome Trust Sanger Institute, Cambridge, U.K	
0910 - 0945	**DEVELOPMENTAL ANOMALIES AND PEDIATRIC CANCER: A GROWING CONNECTION** Dr Todd Druley Washington University School of Medicine, U.S.A	
0945 - 1015	**HIGHLY PARALLEL MEASUREMENT OF THE IMPACT OF MUTATIONS IN PROTEINS** Assistant Professor Douglas Fowler Department of Genome Sciences, University of Washington, U.S.A	
1015 - 1030	**GENOMIC CATASTROPHES DRIVING TUMORIGENESIS IN ESOPHAGEAL ADENOCARCINOMA** Dr Katia Nones QIMR Berghofer, QLD, Australia	
1030 - 1045	**THE HISTONE H3 LYSINE 4 PRESENTER WDR5 IS A BIOMARKER IN N-MYC-INDUCED TRANSCRIPTIONAL ACTIVATION AND NEUROBLASTOMA PROGRESSION** Dr Yuting Sun Children's Cancer Institute, NSW, Australia	
1045 - 1115	Morning Refreshments & Trade Exhibition	Exhibition Centre
SESSION 5: CLINICAL GENOMICS AND THE FUTURE OF HEALTHCARE **CHAIRS: DR CAS SIMONS & DR DENIS BAUER**		Sauvignon Room
1115 - 1155	**FROM GENES TO GENOMES IN MEDICAL RESEARCH AND PATIENT CARE** Professor Joris Veltman Radboud University Medical Centre and Maastricht University Medical Centre, The Netherlands	

CONFERENCE PROGRAM

TUESDAY
13 October 2015

1155 - 1220	**WHOLE GENOME SEQUENCING BASED CLINICAL GENOMICS** Dr Mark Cowley Garvan Institute of Medical Research, NSW, Australia Proudly supported by DNAnexus	
1220 - 1235	**STRUCTURAL VARIATION CALLING FROM HiSeq X WHOLE GENOME SEQUENCING DATA IN A CLINICAL SETTING** Dr Andre Minoche Garvan Institute of Medical Research, NSW, Australia	
1235 - 1250	**SHARED ANALYSIS FOR GENOME TESTING IN THE HEALTH CARE SETTING** Dr Natalie Thorne Melbourne Genomics Health Alliance, VIC, Australia	
1250 - 1305	**BRAIN-cX – AN INTERACTIVE WEB-TOOL FOR GENE PRIORITISATION AND MORE** Dr Saskia Freytag The Walter + Eliza Hall Institute of Medical Research, VIC, Australia	
1305 - 1500	Lunch, Poster Session Two & Trade Exhibition	Exhibition Centre
1430 - 1500	Afternoon Refreshments	Exhibition Centre
SESSION 6: GENOMICS OF PLANTS AND FINE WINE **CHAIRS: PROFESSOR JUSTIN BOREVITZ & DR ROSE ANDREW**		Sauvignon Room
1500 - 1515	**INTRODUCTION TO WINE TASTING BY GUNDOG ESTATE**	
1515 - 1555	**ORIGIN AND CONSEQUENCES OF GENETIC AND EPIGENETIC VARIATION IN ARABIDOPSIS THALIANA AND ITS RELATIVES** Professor Detlef Weigel Max Planck Institute for Developmental Biology, Germany	
1555 - 1630	**DEMOCRATISING GENETIC ANALYSIS AND BREEDING WITH GENOTYPING BY SEQUENCING** Mr Rob Elshire The Elshire Group Limited, New Zealand	
1630 - 1645	**UNRAVELLING THE MāNUKA GENOME: A METAGENOMIC APPROACH** Ms Amali Thrimawithana The New Zealand Institute for Plant & Food Research Limited, New Zealand	

CONFERENCE PROGRAM

TUESDAY
13 October 2015

1645 - 1700	**THE SMRT WAY TO SEQUENCE A YEAST GENOME** Dr Richard Edwards University of New South Wales, NSW, Australia
1700 - 1730	**WINE 'OMICS: AT THE CUTTING-EDGE OF THE OLDEST BIOTECHNOLOGY** Dr Anthony Borneman Australian Wine Research Institute, SA, Australia
1900 - 2300	**Conference Dinner** **Lindemans Hunter Valley** *Optional function at $130.00 per person. Bookings are essential.* *Please assemble in the Crowne Plaza Foyer for a 1830 coach departure to Lindemans.* *Coaches will operate a return shuttle to Crowne Plaza from 2145.*

CONFERENCE PROGRAM

WEDNESDAY
14 October 2015

0800 - 1400	Registration Desk Open & Welcome Refreshments	Galleria
0800 - 1330	Trade Exhibition Open	Exhibition Centre
0855 - 0900	Welcome to Day Three	Sauvignon Room
SESSION 7: QUANTITATIVE GENETICS AND DECODING THE GENOME CHAIR: DR HELEN SPEIRS & DR ALEXANDRA LIVERNOIS		Sauvignon Room
0900 - 0930	**CAN WE EXPLORE THE GENOMICS OF CANINE WORKING BEHAVIOUR WITH SELECTIVE SWEEP ANALYSIS?** Professor Claire Wade Faculty of Veterinary Science, The University of Sydney, NSW, Australia	
0930 - 0945	**PROGRAMMABLE RNA TARGETING AND CLEAVAGE BY CRISPR/CAS9** Dr Mitchell O'Connell Doudna Lab, Department of Molecular and Cell Biology, University of California, U.S.A	
0945 - 1000	**EXPRESSION QUANTITATIVE TRAIT LOCI (eQTLs) OF ENDOMETRIOSIS RISK LOCUS AT 1p36.12** Dr Jenny Fung QIMR Berghofer Medical Research Institute, QLD, Australia	
1000 - 1045	Morning Refreshments & Trade Exhibition	Exhibition Centre
	AGTA Annual General Meeting	Sauvignon Room
SESSION 8: MICROBIAL AND SINGLE CELL GENOMICS CHAIRS: DR KIRBY SIEMERING & DR CLARE STIRZAKER		Sauvignon Room
1045 - 1130	**ILLUMINATING MICROBIAL DARK MATTER VIA SINGLE-CELL GENOMICS** Dr Christian Rinke University of Queensland, QLD, Australia	
1130 - 1150	**HIGH THROUGHPUT CELL SORTING FOR DOWNSTREAM GENOMIC ANALYSIS** Dr J Clark Mason BD Biosciences, U.S.A Proudly supported by	

CONFERENCE PROGRAM

WEDNESDAY
14 October 2015

1150 - 1205	**SINGLE-CELL ANALYSIS OF BREAST CANCER MOLECULAR SUBTYPE REVEALS CLINICALLY RELEVANT HETEROGENEITY** Ms Laura Baker Garvan Institute of Medical Research, NSW, Australia
1205 - 1220	**THE EXTREME MICROBIOME PROJECT (XMP): THE METAGENOMICS OF LAKE HILLIER, A PINK HYPERSALINE LAKE** Dr Ken McGrath The Australian Genome Research Facility, QLD, Australia
1220 - 1235	Awarding of Prizes, Conference Close and 2016 Conference Launch
1235 - 1315	Lunch & Trade Exhibition Exhibition Centre
1330	Coach Transfer departs Crowne Plaza to Sydney Domestic Airport *Please assemble in the Crowe Plaza Foyer by 1320 for a prompt coach departure at 1330.*

CONFERENCE SOCIAL PROGRAM

Welcome Reception

Date: Sunday 11 October 2015
Venue: Crowne Plaza Hunter Valley, Exhibition Centre
Time: 6.00pm – 8.00pm
Dress: Smart Casual

Join us for the official Welcome Reception for the AGTA 2015 Conference. Enjoy networking with old and new acquaintances, and familiarising yourself with the trade exhibitors, whilst enjoying drinks and canapés.

The Welcome Reception is included in a full registration only. Additional tickets can be purchased at $70.00 per person.

Proudly supported by:

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Student Function

Date: Monday 12 October 2015
Venue: Crowne Plaza Hunter Valley, The Lovedale Bar
Time: 1830 onwards

Students and early career researchers are invited to join fellow delegates for a fun night of genomics trivia. Test your knowledge of genomics technologies, bioinformatics tools, the history of sequencing and much more! As in real life genomics, your team will have a diverse range of backgrounds, so will have to work together to win the prize! Teams will form on the night, and points will be issued for both correct and creative answers.

We will provide finger food and your first few drinks.

Please see Brigitte or Annika at the conference registration desk to register for this function.

Conference Dinner

Date: Tuesday 13 October 2015
Venue: Lindemans Winery
Time: 7.00pm – 11.00pm
Dress: Smart Casual
Attendance: By booking and paying prior to the conference. You are still able to book at the conference, however it will be subject to availability.

The conference dinner is the social highlight of the conference and should not be missed.

Come and join us for another chance to network and meet with colleagues, whilst enjoying a great night of food, wine and dancing.

IMPORTANT INFORMATION

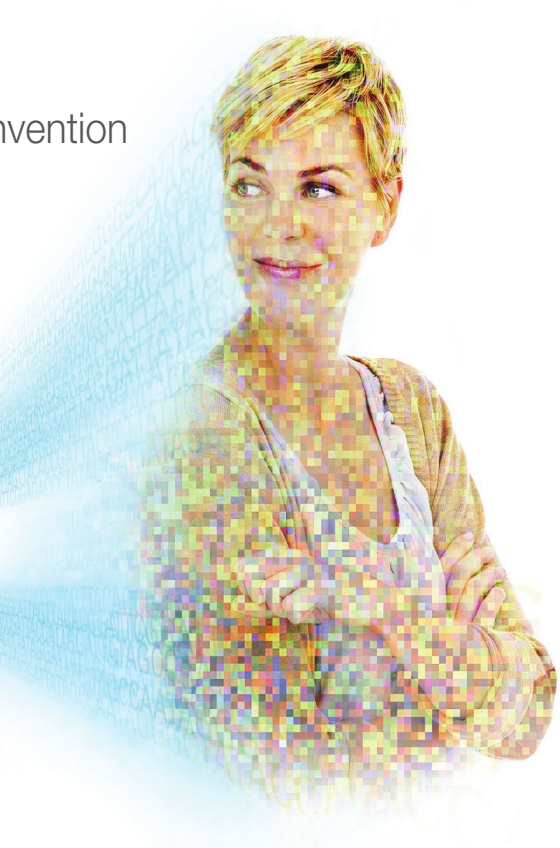
Seating and table allocation for the AGTA Dinner will be by way of sticker allocation. All delegates registered to attend the AGTA Dinner will receive a sticker to be placed on the table sheets near the Registration Desk. These sheets will be available from Monday 12 October and will be taken down at the end of morning refreshments on Tuesday 13 October or as they become full.

If you do not have a sticker please see the Registration Desk staff, DO NOT write your name directly on the board, as you will NOT be allocated a seat.

Historical Breakthroughs

Breathtaking Progress

Radical Reinvention



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2015 AGTA Conference

ABSTRACTS AND BIOGRAPHIES

PRE-CONFERENCE WORKSHOP

GENOTYPING-BY-SEQUENCING: A LOW COST TOOL FOR POPULATION GENETICS WORKSHOP

Mr Aaron Chuah, The Australian National University, ACT, Australia
Mr Rob Elshire, The Elshire Group Limited, New Zealand
Professor Justin Borevitz, The Australian National University, ACT, Australia

Date: Sunday 11 October 2015
Venue: Cellar Room 2, Crowne Plaza Hunter Valley
Time: 11.30am – 4.30pm

This is an optional workshop at $125.00 per person. Bookings are essential.

Genotyping-by-sequencing (GBS) can be performed cheaply and with a large number of samples, with or without a reference sequence, enabling a wide range of environmental, conservation and population genetics projects. Our target audience are wet-lab biologists who wish to perform their analyses in-house. We will be covering the lab preparation and basic bioinformatic analysis of this exciting new technology.
If attendees wish to try their own hand at analysing GBS data during the live data analysis session they should bring:

A suitable laptop with at least an hour's battery life, loaded with:

- R v3.2.1 from http://cran.csiro.au/
- Rstudio from https://www.rstudio.com/products/rstudio/download/
- Installed R libraries: 'compiler', 'ape', 'RColorBrewer', 'NCBI2R'

This is entirely optional and is NOT necessary to take to part in the session.

SUNDAY
11 October 2015

ORATION

Chaired by Dr Ruby Lin

1700-1800

STUDYING CANCER AT SINGLE NUCLEOTIDE RESOLUTION

PROFESSOR SEAN GRIMMOND
Wolfson Wohl Cancer Research Centre,
Institute for Cancer Sciences,
University of Glasgow, Scotland, U.K

BIOGRAPHY

Over the last 20 years Prof Grimmond's research has focused on discovering the underlying genetics controlling key biological processes (pluripotency and organogenesis) and pathological states (cancer) through genomic & transcriptomic approaches. He has a broad range of scientific achievements which include:- i) mapping out the complexity and dynamics of the mammalian transcriptome, ii) studying the role of RNA mediated control in cancer and development, iii) pioneering of transcriptome and cancer genome sequencing technology, iv) resolving root causes and driving events behind Pancreatic, Ovarian and Oesophageal Cancer and v) leading Australia's International Cancer Genome Consortium program. In 2013, Prof Grimmond moved to the UK and recently became a founding co-chair of the Scottish Genomes Partnership; an ambitious patient sequencing program to drive diagnosis of rare genetic disease, cancer genome discovery and genome-directed stratified clinical trials for a variety of recalcitrant cancers.

ABSTRACT

It is now well established that a cancer's mutational burden drives tumour formation, influences disease progression and can dictate sensitivity to chemotherapy. Over the last 6 years, we have pioneered large-scale cancer genome & transcriptome sequencing and methylome profiling of approximately 700 pancreatic, Ovarian and Oesophageal patients, primarily as part of the International Cancer Genome Consortium (ICGC). These data have been used to address three core questions: i) What are the mutational mechanisms responsible for each patient's tumour, ii) What are the core pathway-mutations promoting each individual's tumour initiation, disease progression and chemo-resistance, and iii) how can personalised cancer-genome information be used to improve patient outcome? These efforts have provided the foundations for a new program focused on genome-directed clinical trials in advanced pancreatic cancer patients. The strategies behind the transition from cohort-based to personalised genome sequencing and its clinical application will be discussed.

MONDAY
12 October 2015

SESSION 1

TRANSCRIPTOMICS AND THE REGULATION OF THE GENOME

Chaired by Dr Phillippa Taberlay and Dr Timothy Mercer

0845-0930

DIFFERENTIAL ANALYSIS OF BIFURCATING SINGLE-CELL GENE EXPRESSION TRAJECTORIES

ASSISTANT PROFESSOR COLE TRAPNELL
University of Washington, U.S.A

BIOGRAPHY
Dr. Trapnell studies stem cells and differentiation, primarily using high throughput transcriptome sequencing. He earned his Ph.D. in Computer Science from the University of Maryland, College Park, where he was jointly advised by Steven Salzberg and Lior Pachter. As a postdoc in John Rinn's lab at Harvard's Stem Cell and Regenerative Biology department, he pioneered methods for analyzing differentiation with single cell transcriptome sequencing. He is the principal developer of several widely used open-source software tools for analyzing high-throughput sequencing experiments. At the University of Washington, his lab will focus on finding genes that govern stem cell maintenance and cell differentiation, primarily through single-cell genomics. The lab will operate at the interface between genomics and experimental cell biology to answer how cells make fate decisions.

ABSTRACT
Single-cell trajectory analysis is a powerful approach for studying gene regulatory changes during cell differentiation and other dynamic processes. Recently, we showed that individual cells can be ordered according to progress through differentiation by analyzing their transcriptomes with unsupervised algorithms. Previous studies by our group and others have been limited to linear trajectories tracking unipotent progenitor cells. Such cellular trajectories have only one outcome. However, during development, cells make fate decisions that lead to one of several mutually exclusive states in the adult. How to reconstruct and analyze single-cell trajectories that include and span fate decisions is an open problem.

Here, we describe an approach for reconstructing single-cell trajectories that include bifurcations corresponding to cell fate decisions. We then describe statistical methods for identifying genes that are differentially expressed between trajectory outcomes. We illustrate the power of this technique by analyzing differentiating bronchoalveolar progenitor cells undergoing specification into type I and type II pneumocytes. This analysis reveals hundreds of genes with lineage-dependent expression. Our approach, which encodes a topological description of the trajectory as continuous predictors in a generalized linear model, can distinguish, for example, genes that become lineage-dependent proximal to the fate specification from those that are restricted to a lineage later in differentiation. We conclude with an analysis of bifurcations in settings other than development to argue that single cell trajectory analysis can help

pinpoint the genes that drive a process from those more downstream.

0930-0955

INSIGHTS INTO MAMMALIAN CELL TYPES

PROFESSOR ALISTAIR FORREST
Harry Perkins Institute of Medical Research, WA, Australia

BIOGRAPHY

Alistair Forrest is a research professor at the Harry Perkins Institute of Medical Research, UWA. He is an expert in transcriptomics and is most well-known for his work within the Functional annotation of mammalian genomes projects (FANTOM2-5). He is the scientific coordinator of the FANTOM5 project. This work, which profiled a large collection of primary cell types, cell lines and tissues using cap analysis of gene expression (CAGE), has generated landmark maps of promoters and transcribed enhancers in human and mouse genomes. Prof Forrest is a multidisciplinary researcher with a BSc in Biotechnology from Murdoch University, a Masters in information technology from Queensland University of Technology and a PhD from the Institute for Molecular Bioscience, University of Queensland. In 2007, he joined RIKEN in Yokohama Japan on a CJ Martin Fellowship, where he was later promoted to team leader of a large bioinformatics group. He has recently returned to Western Australia to head the newly formed Systems Biology and Genomics group. His current research concentrates on mammalian systems biology with a focus on transcriptional regulatory networks (TRNs) and cell-cell communication networks (CCCNs).

0955-1015

ALTERATIONS IN THREE-DIMENSIONAL ORGANISATION OCCUR COINCIDENT WITH LONG-RANGE EPIGENETIC DEREGULATION OF THE CANCER GENOME

DR PHILLIPPA TABERLAY
Garvan Institute of Medical Research, NSW, Australia

BIOGRAPHY

Dr Taberlay earned her PhD in Medicine from the University of Tasmania under the supervision of Dr Adele Holloway. She then joined the lab of Professor Peter Jones as a postdoc at the Norris Comprehensive Cancer Center at the University of Southern California, Los Angeles where she discovered that distal regulatory elements were important for epigenetic plasticity by demonstrating that epigenetic signatures of enhancers determined whether a cell could be trans-differentiated by (for example, from skin to muscle). She returned to Australia and joined the Epigenetics Research Laborotory of Professor Susan Clark to continue investigating epigenomic remodelling and enhancer dynamics in prostate and breast cancers. Her group is interested in long-range interactions and understanding the role of the three-dimensional genome in normal and cancer biology in the context of epigenetic remodelling and cell reprogramming.

ABSTRACT

A three-dimensional chromatin state underpins the structural and functional basis of the genome by bringing regulatory elements and genes into close spatial proximity to ensure proper, cell-type specific gene expression profiles. Here, we perform HiC chromosome conformation to investigate how the three-dimensional organization of the prostate cancer genome is disrupted in the context of

epigenetic remodelling and atypical gene expression programs. We find that the general feature of a chromatin interactome, namely segmentation into megabase-sized topologically associated domains remain a conserved feature of cancer cell genomes, however these domains are generally smaller. Domain boundaries are enriched for insulator binding protein CTCF and histone mark H3K4me3 in both normal and cancer cells, indicating that these factors are involved in the establishment and conservation of topologically associated domains. Importantly, we also identify novel prostate cancer-specific interactions that are enriched for various regulatory elements (enhancers, promoters and insulators). These differential interactions are commonly retained within the confines of topological domains, are associated with differentially expressed genes and overlap long-range epigenetically activated or silenced regions in prostate cancer. Finally, we present a novel visualisation tool to explore the HiC interaction in relation to the transcription and epigenetic changes between normal and prostate cancer cells.

1015-1030

3'UTR DYNAMICS PREDICT mRNA FATE

DR TRAUDE BEILHARZ
Monash University, VIC

BIOGRAPHY

Traude Beilharz heads the RNA-systems biology laboratory at Monash University where she and her team study the mechanisms of global RNA-based regulatory control. Her research is focussed on post-transcriptional of gene expression with a special interest in the 3' UTR dynamics of eukaryotic transcriptomes. That is, how regulated changes to polyadenylation-site (alternative polyadenylation) and changes to steady-state poly(A)-tail length distribution can predict mRNA fate. These changes are conveniently measured genome-wide, by a custom RNA-seq approach she has developed called PAT-seq. Traude will discuss unpublished data that shows how changing poly(A)-tail length-distributions can uncover previously hidden mRNA fate decisions.

ABSTRACT

Changes to RNA metabolism are more and more implicated in in human health and disease. An example is the recent discovery of a wholesale switch to shorter 3'UTRs in many cancers. This results in mRNA with reduced scope for post-transcriptional regulation, such as microRNA-mediated repression. In the case of cancer, this means a worse prognosis for patients as oncogenes become deregulated (Xia et al, 2014). In addition to the changes to the site of polyadenylation; a second dynamic feature of 3'UTRs is the length-control of the Poly(A)-tail. Nascent mRNA undergo a poly(A) length-check as part of quality control prior to nuclear export. However, once in the cytoplasm, long poly(A)-tails can be rapidly trimmed to dial down protein translation, or to initiate decay. Our research capitalises on a new RNA-seq approach developed in our lab called Poly(A)-Test-seq (PAT-seq)(Harrison et al, 2015). The PAT-seq approach accurately records i) mRNA abundance, ii) polyadenylation site choice and iii) poly(A)-length distribution in eukaryotic transcriptomes in a single statistically robust assay. We have applied this approach to better understand how encrypted information in the 3'UTR of mRNA directs when, where and how-often mRNA is translated. We will present unpublished PAT-seq data addressing questions fundamental to understanding the control of post-transcriptional gene expression. For example, we will show how changes to poly(A)-tail length-distribution can identify the substrates of specific RNA binding proteins and regulatory enzymes. Specifically, showing for the first time that

the binding of the pumilio domain protein Puf3 to its target mRNA specifically 'marks' these with changes to their adenylation-state in budding yeast. Moreover we show that such changes to poly(A)-tail length-distribution can also identify the substrates of regulatory cytoplasmic polyadenylation; a process commonly utilised in the brain and germ line to activate translation. Importantly, the measure of these changes in 3'UTR dynamics are often more sensitive in their read-out of mRNA fate than traditional antibody-based approaches.

1030-1045

DYNAMIC EXPRESSION OF LONG NONCODING RNAs AND REPEAT ELEMENTS IN SYNAPTIC PLASTICITY

MR JESPER MAAG
Garvan Institute of Medical Research, NSW

BIOGRAPHY
Jesper Maag is a third year PhD-student in the Genome Informatics lab under A/Prof Marcel Dinger at the Garvan Institute of Medical Research. Jesper completed a master degree in pharmaceutical sciences at Uppsala University, Sweden. He wrote his master's thesis in the pharmacology department at the University of Adelaide, where he explored the effect of cannabinoids on Alzheimer's disease.

Jesper continued his academic career with a transition to a PhD in Genomics in Sydney.

ABSTRACT
Long-term potentiation (LTP) of synaptic transmission is recognized as a cellular mechanism for learning and memory storage. Although de novo gene transcription is known to be required in the formation of stable LTP, the molecular mechanisms underlying synaptic plasticity remain elusive. Non-coding RNAs have emerged as major regulatory molecules that are abundantly and specifically expressed in the mammalian brain. By combining RNA-seq analysis with LTP induction in the dentate gyrus of live rats, we provide the first global transcriptomic analysis of synaptic plasticity in the adult brain. Expression profiles of mRNAs and long noncoding RNAs (lncRNAs) were obtained at 30 minutes, 2 hours and 5 hours after high-frequency stimulation of the perforant pathway. The temporal analysis revealed dynamic expression profiles of lncRNAs consistent with involvement in LTP. In light of observations suggesting a role for retrotransposons in brain function, we examined the expression of various classes of repeat elements. Our analysis identifies dynamic regulation of LINE1 and SINE retrotransposons, and tRNA. These experiments reveal a hitherto unknown complexity of gene expression in long-term synaptic plasticity involving the dynamic regulation of lncRNAs and repeat elements. Our analyses provide a foundation for understanding the molecular underpinnings of synaptic plasticity in both the healthy brain and in neurodegenerative and neuropsychiatric disorders. The dynamic expression of retrotranspons points towards a mechanism for genetic somatic mosaicism observed in the brain and supports the idea that dynamic reprogramming of the genome may be an important mechanism underlying memory formation.

SESSION 2

GENOME EVOLUTION AND BIOINFORMATICS

Chaired by Dr Natalie Thorne and Dr Joseph Powell

1115-1200

WHAT WE HAVE LEARNED FROM SEQUENCING ARCHAIC HUMAN GENOMES

DR JANET KELSO
Max Planck Institute for Evolutionary Anthropology, Germany

BIOGRAPHY

Janet Kelso is the Bioinformatics research group leader at Max-Planck Institute for Evolutionary Anthropology in Leipzig.

Her research interests include analysis of ancient genomes, primate comparative genomics and gene expression. Her group uses computational approaches to gain insights into genome evolution and have a special interest in the development of novel software for processing and analysis of high-throughput sequence data.

Janet received her PhD from the South African National Bioinformatics Institute under the supervision of Winston Hide. She is author of more than 50 peer-reviewed scientific publications, and is currently the joint Executive Editor of the journal, Bioinformatics and an Associate Editor of the journal, Database.

ABSTRACT

The genomes of our nearest extinct human relatives, the Neandertals and Denisovans, offer a unique opportunity to identify genetic changes that have come to fixation or reached high frequency in modern humans since their divergence from Neandertals and Denisovans, as well as regions of modern human genomes that have been impacted by admixture with archaic humans. Some of these changes may have important functional effects in modern humans.

We have sequenced to high-coverage the genomes of two archaic hominin groups: Neandertals [1] who lived in Europe and Western Asia until approximately 30 000 years ago, and Denisovans [2], a group related to Neandertals that was recently described based on the genome sequence generated from a bone found in Southern Siberia. Using these genome sequences we have identified gene flow between archaic and modern humans. About 2.0% of the genomes of present-day non-Africans derive from Neandertals, while about 4.8% of the genomes of present-day Oceanians derive from Denisovans.

A map of the Neandertal haplotypes in present-day non-Africans has allowed us to characterize some of the functional impacts of Neandertal ancestry on modern humans [4], while the lengths of these introgressed regions in an early modern human have provided information about the date of admixture. Further we have identified sequence differences that have come to fixation or reached high frequency in modern humans since their divergence from Neandertals and Denisovans, some of which may have important functional effects in modern humans.

1200-1225

USING GENE CO-EXPRESSION NETWORKS TO DISCOVER EPILEPSY GENES

ASSOCIATE PROFESSOR MELANIE BAHLO
Walter + Eliza Hall Institute of Medical Research, VIC

BIOGRAPHY
Associate Professor Melanie Bahlo is the co-Division Head of the Population Health and Immunity Division at the Walter and Eliza Hall Institute of Medical Research. She graduated in 1998 with a PhD in population genetics from Monash University, Melbourne. She currently holds a National Health and Medical Research Council Senior Research Fellowship. In 2009 she was awarded the Moran Medal by the Australian Academy of Science and in 2015 the Genetics Society of Australasia's Ross Crozier medal. Her research areas cover statistical genetics, bioinformatics and population genetics with a focus on neurological disorders and infectious disease. Her statistical analyses have led to the identification of novel genes for disorders such as epilepsy and deafness. She has also developed new methods and software for the analysis of genetic data.

ABSTRACT
Epilepsy is a disease which forty years ago wasn't even thought to have a genetic basis. It can be further subcategorized phenotypically, with some subphenotypes showing strong Mendelian segregation. To date more than one hundred epilepsy genes have been discovered, leading to the recognition that epilepsy is genetically highly heterogeneous. Large NGS studies have been highly successful, in particular with some clinical subphenotypes, such as epileptic encephalopathies. NGS cohort studies yield many hits that do not have sufficient weight of evidence to be able to be declared as new epilepsy genes. We have made use of several large-scale gene expression datasets to show that (i) known epilepsy genes co-express in a limited number of sub networks, and (ii) these networks can be used to prioritise which genes to target for further testing. Our approach has been very successful for epileptic encephalopathies (Oliver et al 2014, PLoS ONE). Performance evaluation of the prioritization approach applied to 179 candidate genes has seen six of these genes now validated as true epileptic encephalopathy since 2014, with all but one prioritized by us. We have now expanded this approach to encompass all available large brain expression microarray datasets, further increasing the power of this method, which also works in other neurogenetics disorders such as brain malformation disorders.

1225-1245

DEEP GENE EXPLORATION OF HUMAN CHROMOSOME 21

DR TIMOTHY MERCER
Garvan Institute of Medical Research, NSW, Australia

BIOGRAPHY
Dr Timothy Mercer undertakes research into RNA biology (noncoding RNAs, gene organization, expression and splicing), genome informatics and bioinformatic and sequencing innovations. He currently leads a research group at the Garvan Institute of Medical Research, Sydney.

ABSTRACT
The human genome encodes an unknown diversity of protein-coding and noncoding RNAs. The vast diversity and wide dynamic range of gene expression limits the capacity of RNA sequencing to resolve the transcriptome and, as a result, current

reference catalogs provide an incomplete profile of human gene content. Here, we target RNA sequencing to human chromosome 21 and syntenic regions of the mouse genome to obtain saturating coverage over a cross-section of the mammalian transcriptome. This reveals the full size, structure and composition of coding and noncoding RNA populations and enables interrogation of their expression, splicing and evolution at unprecedented resolution. We show that noncoding exons, in contrast to coding exons, are universally alternatively spliced to generate a near-inexhaustible diversity of isoforms. This isoform diversity is regulated by local cis-elements that are sufficient to recapitulate human alternative splicing profiles in a mouse cell. This is despite the noncoding RNA populations of human and mouse having largely diverged, with orthologs rare between the two species. Together, these findings demonstrate that the coding and noncoding RNAs are fundamentally distinct in their organization and evolution and forecasts the full breadth and diversity of genes encoded in the human genome.

1245-1300

MAPPING STEM CELL BIOLOGY BY HIGH RESOLUTION TEMPORAL TRANSCRIPTOMICS

DR BRIAN GLOSS
Garvan Institute of Medical Research, NSW, Australia

BIOGRAPHY
Brian Gloss has been a postdoctoral researcher in the Genome Informatics research lab at the Garvan Institute under A/Prof Marcel Dinger since 2013. His research interests revolve around unravelling transcriptional complexity in health and disease.

Brian is involved in a number of collaborative projects world-wide using existing and emerging transcriptomic technologies to answer key questions in normal development and disease processes.

He currently holds a Cancer Institute of NSW early career fellowship and a conjoint lecturer position at UNSW.

Brian has published eight papers in the last five years including three first and two second author publications. He also holds an international patent for a novel method of using epigenetic marks for diagnosing cancer. In 2012, he received his PhD for work on the whole genome identification and characterisation of novel epigenetically silenced genes in ovarian cancer.

ABSTRACT
Despite increasing recognition of the role that long noncoding RNAs (lncRNAs) play in the regulation of gene expression, little is known about their dynamic changes, which in turn limits the understanding of how and where these molecules act within regulatory networks. Investigations of transcriptional responses during biological processes commonly use transcriptome profiling by microarray or RNA-Seq over 24-hourly time-courses. However, to date such experiments are typically designed around principles to examine protein-coding transcripts, limiting their potential to explore the transcriptional dynamics of lncRNAs. In addition to their relatively poor annotation and difficulty of detection due to low expression levels compared to protein-coding transcripts, lncRNAs are turned over more rapidly than mRNAs. Therefore, we hypothesized that existing transcriptome profiling experiments were inadequately powered in terms of both temporal resolution and sequencing depth to gauge the majority of their dynamics and that rapidly turned over regulatory transcripts may have evaded detection entirely. To test this hypothesis, we evaluated coding

and noncoding gene expression dynamics in differentiating mouse embryonic stem cells at unprecedented temporal resolution (6-hourly) and sequencing depth to examine the effects of this increased experimental power on the characterization of the molecular processes underlying stem cell differentiation. We show that many key transcriptional changes, including regulatory network interactions, gene expression changes in coding and noncoding genes, periodically expressed genes, and alternative splicing events, cannot be derived from existing developmental time-courses. Moreover, we identify hundreds of novel transiently expressed lncRNAs that are only detectable by high frequency sampling. As these findings have important implications upon the investigation of regulatory dynamics and networks of any biological process, we present experimental design considerations and methodologies that can be utilized in future studies.

SESSION 3

DEVELOPMENTAL GENOMICS AND THE ORIGINS OF DISEASE

Chaired by Professor Andrew Perkins and Dr Kate Howell

1530-1555

HIGHLY CONSERVED EPIGENOME REMODELLING DURING THE VERTEBRATE PHYLOTYPIC PERIOD

PROFESSOR RYAN LISTER
The University of Western Australia, WA

BIOGRAPHY

Ryan Lister leads a research group exploring the epigenome at the University of Western Australia and the Harry Perkins Institute of Medical Research. After receiving his PhD from UWA, Ryan undertook postdoctoral studies at The Salk Institute for Biological Studies from 2006. There he developed methodologies for utilizing new high-throughput DNA sequencing technologies to map the epigenome, the molecular code superimposed upon the genome that plays crucial roles in regulating the information contained in the underlying DNA sequence. His research has yielded new insights into the composition and function of the epigenome in a variety of systems, including plants, the brain, and stem cells. Having returned to UWA in 2012, Ryan's laboratory is focused upon understanding how these complex epigenomic patterns are established and altered, how they affect the readout of underlying genetic information, their role in brain development and function, and developing molecular tools to precisely edit the epigenome.

ABSTRACT
The vertebrate body plan and organs are shaped during a highly conserved embryonic phase called the phylotypic stage, however the mechanisms that guide the epigenome through this transition and their evolutionary conservation remain elusive. Here we report widespread DNA demethylation of thousands of enhancers during the phylotypic period in zebrafish, Xenopus and mouse. These dynamic enhancers are linked to essential developmental genes that display coordinated transcriptional and epigenomic changes in the diverse vertebrates during embryogenesis. Phylotypic stage-specific binding of Tet proteins to (hydroxy)methylated DNA, and enrichment of hydroxymethylcytosine on these enhancers, implicated active DNA demethylation in this process. Finally, disruption of Tet activity demonstrated that this highly coordinated epigenome reconfiguration event is dependent upon the Tet proteins. Overall, this reveals a novel regulatory module required during the most conserved phase of vertebrate embryogenesis and uncovers an ancient developmental role for the Tet dioxygenases.

1555-1615

GENOME-DRIVEN INSIGHTS TO DISEASE MECHANISMS

ASSOCIATE PROFESSOR ROBYN JAMIESON
Children's Medical Research Institute, NSW

BIORGRAPHY
Associate Professor Robyn Jamieson is the Genomics Research Lead of the Western Sydney Genetics Program at The Children's Hospital at Westmead, Sydney, and heads the Eye Genetics Research Group at the Children's Medical Research Institute, The Children's Hospital at Westmead and Save Sight Institute, University of Sydney. She is also the Lead Clinical Geneticist at Eye Genetic Clinics at The Children's Hospital at Westmead, and the Westmead Adult Hospital, Sydney. Her group's work has been integral in establishment of genomic approaches for genetic diagnosis of eye diseases in Australia, and development of animal and cell-based systems for functional understanding of novel disease genes and variants, and pathways to treatment.

ABSTRACT
Many of the genetic factors and their functions contributing to human disease are not yet known. Genomic strategies provide an unprecedented opportunity for identification of novel factors and mechanisms causing human disease. We use interrogation of genomic structural rearrangements and whole genome sequencing for single pathogenic variant detection, to identify novel regulatory mechanisms and candidate disease genes. We use a functional genomics pipeline, including CRISPR/Cas9 genome engineering in cell-based and animal model studies, to determine pathogenicity of the identified genomic variants and novel disease genes. Our studies reveal new factors critical in cell polarity and adhesion, epithelial to mesenchymal transition, cell division, ciliogenesis and regulation of Wnt signalling. Correlation with patient phenotypes facilitates prioritization of functional studies, aimed at development of treatments for the conditions.

1615-1635

A FUNCTIONAL GENOMICS APPROACH TO PREDICT NOVEL GENETIC DETERMINANTS FOR HEART DEVELOPMENT AND DISEASE

DR MIRANA RAMIALISON
Australian Regenerative Medicine Institute, Monash University, VIC

BIOGRAPHY
Dr. Ramialison is head of the Systems Developmental Biology Laboratory at the Australian Regenerative Medicine Institute in Melbourne. She is an NHMRC/NHF Career Development Fellow and leads a multi-disciplinary team of bioinformaticians and molecular biologists, to study heart development, evolution and disease. She takes a systems biology approach to uncover the gene regulatory networks that control gene expression during cardiac development, and identify abnormal interactions that cause congenital diseases. Prior to joining ARMI in February 2014, Dr Ramialison was an EMBO and HFSP post-doctoral Fellow at the Victor Chang Cardiac Research Institute in Sydney. She received her Engineering degree from the University of Luminy (France) and PhD at the European Molecular Biology Laboratory (Germany).

ABSTRACT
In 2001, the release of the first human genome draft sequence provided a breakthrough in the knowledge of our genetic repertoire, albeit the function of the newly discovered genes remained largely unknown. In 2012, international consortia (ENCODE, FANTOM) released the first functional map of the mouse and human genomes, thereby providing an exhaustive picture of gene expression and gene regulation in a temporal and tissue-specific manner. These multi-million dollar public efforts enable us to systematically investigate the genetic networks regulating any specific biological process.

We have a long-standing interest in unravelling the exact genetic components that build a healthy heart. In a bid to systematically investigate the players involved in cardiogenesis, we took advantage of our unique bioinformatics expertise to mine the publicly available cardiac-specific datasets recently released by the consortia. We discovered regulatory patterns that are specific to genes controlling heart development. We used these patterns to predict novel genes having an essential function in cardiogenesis and are currently validating the function of these genes using the mouse and zebrafish model systems. Given that 80% of Congenital Heart Disease (CHD) cases are of unknown genetic cause, this study will expand our knowledge on genes responsible for CHD.

1635-1650

REPLI-G SINGLE CELL SEQUENCING: DRIVING THE NEXT FRONTIER OF GENOMIC AND TRANSCRIPTOMIC ANALYSIS

MR COLIN BARON
QIAGEN LIFE SCIENCES, USA

BIOGRAPHY
Colin Baron currently serves as the Sr. Director of Product Management at Qiagen Life Sciences and the Head of NGS & Single Cell Technologies. Prior to joining Qiagen, Colin worked for 6 years at Illumina where he led product management teams covering Ilumina's core sequencing chemistries and was responsible for the reagent launches for all major platform releases from the early

days of the Genome Analyzer to the launch of the HiSeq X 10 and NextSeq systems.

Colin holds degrees in Microbiology and Economics and a Master of Business Administration from the University of California, Davis and worked for 8 years at the UC Davis Cancer Center where he led research teams studying Copy Number and gene dosage effects in children with Autism.

ABSTRACT
Single-cell genomic analysis enables researchers to gain novel insights across a wide array of applications, including developmental biology, tumor heterogeneity and disease pathogenesis and progression. Typically, conducting single-cell genomic analysis using next-generation sequencing (NGS) methods is challenging because the amount of genomic DNA present in a single cell is very limited. PCR-based whole genome amplification methods tend to have high error rates, low coverage uniformity, extensive allelic drop-outs and limited amplification yields.

Qiagen has designed a portfolio of Single Cell products for genomics applications, including NGS, using our unique Multiple Displacement Amplification (MDA) approach that eliminates PCR-related bias and provides a high accuracy view into the genome and transcriptome diversity between cells.

We describe a new, streamlined workflow for single-cell NGS library construction that uses Multiple Displacement Amplification (MDA) to amplify the whole genome with high uniformity and fidelity, and library construction with high adaptor ligation efficiency. The entire procedure generates high-quality sequencing libraries without PCR amplification, thereby eliminating PCR-related bias and errors and reducing handling steps. Our data demonstrate that this PCR-free method for single-cell sequencing library preparation can be integrated into typical High Throughput and Benchtop NGS systems, and affords highly uniform sequence coverage and high library complexity with minimal sequence bias.

Highlighting research from our customers, we will demonstrate how high accuracy, single cell sequencing can cut through the biological noise that occurs when analyzing heterogeneous, bulk samples. With lower sequencing depth requirements, researchers can scale the size and statistical power of their studies.

1650-1705

UNCOVERING HIDDEN GENES IN INTERGENIC GWAS REGIONS

DR NENAD BARTONICEK
Garvan Institute of Medical Research, NSW, Australia

BIOGRAPHY
Nenad Bartonicek is a postdoctoral researcher in the group of Marcel Dinger at Garvan Institute of Medical Research since 2013. He received his PhD from University of Cambridge, UK while working at the European Bioinformatics Institute.

ABSTRACT
The majority of SNPs linked with diseases through genome-wide association studies (GWAS) reside in intergenic regions. These “gene deserts” can result from the blind spot of current sequencing methods for lowly abundant and tissue specific transcripts. In order to address the hidden transcription in linkage disequilibrium blocks around GWAS SNPs, we employed the recently developed RNA capture sequencing (CaptureSeq) on 21 human tissues. CaptureSeq was designed to enrich for 560 intergenic GWAS regions, covering 2.3 percent of the genome. After transcript assembly, quantification and filtering, we identified ~1000 novel, high-confidence (multi-exonic, FPKM>10)

genes, with 80% regions containing at least one high-confidence transcript. The genes contained major hallmarks of active transcription, such as enrichment for typical epigenetic marks and CAGE tags, and were similar to other ncRNAs in composition of isoforms, exons and splice junctions. About 50% of transcription loci were previously observed in EST databases, although mostly with only a fraction of sequence overlap (<5%). In total, 5500 high-confidence transcription events were observed across all tissues, with 232 genes showing tissue specificity. Finally, we used information from 13 melanoma samples in combination with TCGA studies to identify a number of previously unreported melanoma associated transcripts.

1705-1720

VISUALIZATION OF VARIANTS USING AQUARIA: NON-SYNONYMOUS SNPs IN THE CONTEXT OF PROTEIN STRUCTURE

DR NEIL SAUNDERS
Digital Productivity Flagship, CSIRO, NSW

BIOGRAPHY
Neil did his Ph.D. in Biochemistry at the University of Oxford and his first postdoc in the Department of Molecular Cell Physiology at the Free University of Amsterdam. He moved to the University of New South Wales in 2000 and commenced a second career in bioinformatics, working on the genomes of Archaea isolated from Antarctica. In 2006 he moved to the University of Queensland to work on the computational prediction of protein-protein interactions. He has been with CSIRO since 2009, where he is currently a statistical bioinformatician in the Transformational Bioinformatics Team, part of the eHealth Research Program, and works on the analysis of large “omics” datasets for human health.

ABSTRACT
Functionally annotating genomic variants is a crucial step in elucidating the biological processes that manifest in certain phenotypes, such as disease. A commonly employed annotation is whether a variant results in a non-synonymous amino acid substitution and whether they are predicted to be deleterious. However, while this is likely conclusive in cases of protein truncations, it may not offer insights into variants causing structural changes. This is particularly the case for instances where seemingly deleterious variants co-mutate resulting in matching changes of the interacting amino acids in the 3D structure. The first step towards elucidating such complex interactions is to visualize the variant locations within a protein structure to provide more insight as to potential consequences.

We therefore introduce Visualization of Variants using Aquaria (VVA), a web-based tool to assist researchers with this task. While previous approaches focus on visualizing preprocessed SNP data [1-4], VVA allows the user to provide a list of patient-specific variants (such as a VCF file) containing their chromosomal coordinates as well as a protein ID of interest. The Ensembl REST API is then employed to label which of the supplied variants result in non-synonymous amino acid mutation for the protein of interest. Genomic (nucleotide) coordinates are converted to amino acid sequence positions and the mutation data are uploaded to Aquaria [5], so as the variant location within the corresponding protein structure can be visualized.

We will outline the development of the variant visualization system and present specific examples highlighting the value of visualizing variants in the context of the 3D protein structure.

TUESDAY
13 October 2015

SESSION 4

CANCER GENOMICS AND PRECISION MEDICINE

Chaired by Professor David Thomas and Dr Nic Waddell

0830-0910

ADVANCES IN THE UNDERSTANDING OF MUTATIONAL SIGNATURES IN HUMAN SOMATIC CELLS

DR SERENA NIK-ZAINAL
Wellcome Trust Sanger Institute, Cambridge

BIOGRAPHY

Serena is a Career Development Fellow (CDF) Group Leader in the Cancer Genome Project and an Honorary Consultant in Clinical Genetics at Addenbrooke's Hospital in Cambridge. She is pursuing biological understanding of the mutational signatures that have been identified in primary human cancers.

Serena qualified in medicine from the University of Cambridge in 2001, trained as a physician and subsequently specialised in Clinical Genetics. Serena undertook a PhD at the Wellcome Trust Sanger Institute (WTSI) in 2009 with Mike Stratton exploring breast cancer using next-generation sequencing (NGS) technology. She demonstrated how detailed downstream analyses of all mutations present in whole-genome sequenced breast cancers could reveal mutation signatures, imprints left by mutagenic processes that have occurred through cancer development. In particular, she identified a novel phenomenon of localised hypermutation termed "kataegis".

In 2013, Serena was awarded a Wellcome Trust Intermediate Clinical Fellowship to pursue biological understanding of the signatures identified during her research training. She joined the Sanger Institute faculty team in 2014 and leads the Signatures of Mutagenesis group. Serena continues to hunt for mutation signatures in large cancer datasets using computational approaches. She explores these signatures biologically through cell-based model systems. Serena runs a clinical project, Insignia (www.mutationsignatures.org), recruiting patients with DNA repair/replication defects, aging syndromes and neurodegeneration, and people who have been exposed to environmental/occupational mutagens to gain biological insights into mutational phenomena in these patients.

ABSTRACT

Somatic mutations in human cancers are generated by multiple mutational processes operating at various times in the cellular lineage between the fertilized egg and the cancer cell, each composed of specific DNA damage and repair components and leaving its own characteristic imprint, or mutational signature, on the genome[1,2]. Exploiting the scale offered by modern sequencing technologies, complete catalogues of somatic mutation can be comprehensively explored and mathematical methods[3] have been employed to identify mutational signatures in human cancer (http://cancer.sanger.ac.uk/cosmic/signatures)[1-3].

We now continue to explore the breadth and depth of mutation signatures in somatic cells. In particular, I will present results from an analysis of 560 breast cancers,

the largest collection of whole genome sequenced cancers of a single cancer type to date. This powerful dataset reveals novel insights into how DNA repair, replication, transcription and chromatin organization influences breast mutagenesis. I will also explain our plans to further the biological understanding of mutational signatures in somatic cells[4].

0910-0945

DEVELOPMENTAL ANOMALIES AND PEDIATRIC CANCER: A GROWING CONNECTION

DR TODD DRULEY
Washington University School of Medicine, U.S.A

BIOGRAPHY

Dr Druley is a faculty member in the Division of Pediatric Hematology and Oncology. His research is based in the hypothesis that much of pediatric disease presentation and treatment is heavily influenced by an individual's unique combination of rare, inherited DNA variations. Dr. Druley's laboratory focuses on adapting the latest genomic technologies toward characterizing these germline variants on a population-based scale as well as examining how these mutations interact within an individual to influence a variety of diseases, particularly pediatric and infant leukemia. The long-term goals are to better understand the pathophysiology of pediatric cancer as well as to identify all of the pertinent germline variants within a pediatric cancer patient prior to starting therapy in order to provide a genetically customized treatment plan designed to maximize anti-cancer activity while minimizing toxicity and morbidity.

ABSTRACT

The Druley lab is focused on the translational integration of computational and molecular biology to study the connection between human development and pediatric cancer. Multiple studies suggest that most pediatric cancers lack the number of somatic mutations necessary for a single cell to transform to malignancy, suggesting other factors are required. In addition, there is growing recognition that children born with congenital anomalies have a higher incidence of childhood cancer and as many as one-third of pediatric cancer patients are predisposed to cancer. These observations have led us to develop genomic assays that allow us to explore profiles of germline variation, which disrupt normal human developmental mechanisms and result in uncontrolled proliferation. Our initial model to test this hypothesis is infant leukemia (IL), which is the deadliest of all pediatric leukemias with <50% survival. IL arises in utero and presents equally as ALL or AML with ~75% of cases harboring a rearrangement in MLL. Yet these translocations alone are unable to generate leukemia in animal models when expressed at physiologic levels. We find that IL patients harbor significant germline variation in genes comprising the COMPASS-like complexes, which regulate gene expression via histone modification during mesoderm and hematopoietic development in model systems. Using patient-specific iPS lines, we can model hematopoietic differentiation and characterize genomic targets of histone modification, chromatin accessibility and subsequent gene expression leading to infant leukemogenesis. Using cell free DNA in maternal circulation, these genetic profiles would improve prenatal risk prediction as well as postnatal surveillance and therapeutic selection.

0945-1015

HIGHLY PARALLEL MEASUREMENT OF THE IMPACT OF MUTATIONS IN PROTEINS

ASSISTANT PROFESSOR DOUGLAS FOWLER
Department of Genome Sciences, University of Washington, U.S.A

BIOGRAPHY
Dr Fowler focuses on developing and implementing new technologies to address difficult problems in protein science and genomics. He is currently an Assistant Professor of Genome Sciences and Affiliate Assistant Professor of Bioengineering at the University of Washington in Seattle.

His lab currently works to understand how variation in protein coding regions of the genome relates to disease, as well as to develop new methods for understanding proteins. Dr Fowler's did his graduate work at The Scripps Research Institute, where he discovered and characterized the first mammalian functional amyloid protein, Pmel17. During his postdoctoral work at the University of Washington, he developed high-throughput methods for analyzing the effect of mutations on protein function.

ABSTRACT
Deep mutational scanning is a method that marries selection for protein function amongst a large library of protein variants with high-throughput DNA sequencing to measure the activity of hundreds of thousands of variants simultaneously. The result is a sequence-function map that describes the impact of all possible single and many double mutants on protein function. We have shown that sequence-function maps have many uses. For example, we are analyzing them to learn about protein properties like structure, aggregation, stability and enzyme mechanism; to guide the interpretation of coding variants in genomes; and to better understand protein evolution.

1015-1030

GENOMIC CATASTROPHES DRIVING TUMORIGENESIS IN ESOPHAGEAL ADENOCARCINOMA

DR KATIA NONES
QIMR Berghofer, QLD

BIOGRAPHY
Katia is a genome biologist at QIMR Berghofer. She works on the interpretation of next generation sequencing and array data in cancer research. She is a member of the Australian International Cancer Genome Consortium (ICGC) and her research has been focused on using genomic, epigenomic and expression data in multi-discipinary fields with focus in cancer research. Her current research focuses on the analysis of whole-genome sequencing and methylome in esophageal adenocarcinomas to better understand this disease in the hope to suggest alternative treatment opportunities.

ABSTRACT
Esophageal adenocarcinoma (EAC) incidence is rapidly increasing in Western countries. EAC has one of the poorest outcomes of all solid tumors, with only 14% of patients surviving 5 years. A better understanding of the EAC genomic landscape underpins efforts to improve early detection and treatment outcomes. Recent studies using exome sequencing have reported recurrent loss of function mutations in EAC but oncogenic driving events have been under-represented. To address this we used a combination of whole genome sequencing (WGS) (n=56) and SNP-arrays (n=71) and found that genomic catastrophes are frequent in EAC, with approximately one third (33%, n=42/127) of tumors showing evidence of chromothripsis. We showed

that catastrophes may lead to oncogene amplification through chromothripsis-derived double minute chromosome formation (MYC and MDM2) or breakage-fusion-bridge (KRAS, MDM2 and RFC3). Our finding of prominent telomere shortening in EAC samples bearing localized genomic catastrophes, as compared to their matched normal samples, suggests that physical stress during cytokinesis could give rise to chromosomal shattering in these samples. Mutational signatures analysis showed a high frequency of T>G mutation at TT sites, providing some evidence of an environmental mutagenic effect. Additionally, 5% of EAC tumors display a higher contribution of BRCA signature that suggests potential defective DNA repair in a small fraction of tumors. These findings suggest that genomic catastrophes play a significant role in the malignant transformation of EAC in at least a third of cases, and reveal less common mutagenic factors through signature analysis.

1030-1045

THE HISTONE H3 LYSINE 4 PRESENTER WDR5 IS A BIOMARKER IN N-MYC-INDUCED TRANSCRIPTIONAL ACTIVATION AND NEUROBLASTOMA PROGRESSION

DR YUTING SUN
Children's Cancer Institute, NSW

BIOGRAPHY

Dr Yuting Sun is a Research Officer and Conjoint Associate Lecturer in Children's Cancer Institute at University of New South Wales. She received her Medicine Degree from Harbin Medical University in China and worked at the Department of Gynaecology in the 2nd Affiliated Hospital of Harbin Medical University. In 2014, she completed her PhD research in Paediatric Oncology from UNSW. Dr Yuting started her post doctorate since August 2014 and won the Researcher of the Month award at Faculty of Medicine in UNSW September 2014. She has published 4 manuscripts in peer-reviewed journals and presented her research at many international conferences. Dr Sun main research focuses on cancer biology, epigenomics and epigenetics, as well as novel drug discovery.

ABSTRACT

Myc oncoproteins induce cancers by binding to Myc-responsive element E-boxes at target gene promoters, leading to transcription activation. Histone H3 lysine 4 (H3K4) trimethylation at target gene promoters is a strict pre-requisite for Myc-induced transcriptional activation. The histone H3K4 presenter WDR5 plays an essential role in H3K4 trimethylation. Here we identified both canonical and non-canonical E-boxes at the WDR5 gene core promoter and showed that N-Myc up-regulated WDR5 gene expression in neuroblastoma cells. Affymetrix microarray studies demonstrated that WDR5 target genes included those with E-Boxes at promoters, such as MDM2. GSEA analysis showed that knockdown WDR5 preferentially down-regulated the expression of genes with E-boxes at promoters, and ChIP-Seq data revealed that repression of WDR5 reduced H3K4 trimethylation at Myc-binding gene promoters. Protein co-IP and ChIP assay demonstrated that WDR5 formed a protein complex with N-Myc, but not p53, at the MDM2 gene promoter, leading to histone H3K4 trimethylation and MDM2 gene transcription. We have also found that knocking-down WDR5 considerably up-regulated the expression of wild type but not mutant p53 protein, leading to neuroblastoma cell growth inhibition and apoptosis. In addition, WDR5 was over-expressed in pre-cancer ganglia and neuroblastoma cells from MYCN transgenic mice, compared with normal ganglia cells. In neuroblastoma patients, high levels of WDR5 expression in tumor tissues independently predicted poor overall survival. Our

findings therefore identify WDR5 as an important biomarker for N-Myc-regulated transcriptional activation and tumorigenesis, and as a novel therapeutic target for N-Myc over-expressing neuroblastoma.

SESSION 5

CLINICAL GENOMICS AND THE FUTURE OF HEALTHCARE

Chaired by Dr Cas Simons and Dr Denis Bauer

1115-1155

FROM GENES TO GENOMES IN MEDICAL RESEARCH AND PATIENT CARE

PROFESSOR JORIS VELTMAN
Radboud University Medical Centre and Maastricht University Medical Centre, The Netherlands

BIOGRAPHY
Professor in Translational Genomics and head of Genome Research division at the Department of Human Genetics, Radboud University Medical Centre in Nijmegen and the Department of Clinical Genetics, Maastricht University Medical Centre in Maastricht, The Netherlands. My research focuses on the identification and interpretation of genomic variation, with a particular interest in the role of rare de novo mutations and copy number variations in severe neurodevelopmental and psychiatric diseases. With my research group I study the genomes of patients using next generation sequencing technology and combine laboratory experiments with novel bioinformatic approaches. I am also actively involved in the implementation of these novel genomics approaches in routine clinical diagnosis.

ABSTRACT
Rapid developments in genomics technologies now allow us to sequence all genes (the exome) or even the entire genome of thousands of patients in research and diagnostics. This is completely changing the way genetics studies are done, and allows us to take full advantage of the power of genomics in medicine. Exome sequencing is now a routine diagnostic test in our laboratory for more than 16 different genetic disorders, and we are in the process of moving to clinical whole genome sequencing using a novel high-throughput sequencing platform. With this, the identification of genetic variations is not a bottleneck anymore, and we can now focus on the major remaining bottleneck; Interpretation of the enormous amount of genomic variation in the context of a clinically heterogeneous phenotype. Solving this will require a concerted clinical, biological and bioinformatics approach, international agreement on phenotype ontologies, sharing of clinical and genomic data, optimization of variant interpretation tools and the validation of these using relevant biological models. I will demonstrate the progress made in the last few years and discuss some of the remaining issues using severe intellectual disability as a model disorder.

1155-1220

WHOLE GENOME SEQUENCING BASED CLINICAL GENOMICS

DR MARK COWLEY
Garvan Institute of Medical Research, NSW

DNAnexus

BIOGRAPHY

Dr Mark Cowley is an early career fellow with the Cancer Institute of NSW, and the Team Leader of Translational Genomics, at the Kinghorn Centre for Clinical Genomics, within the Garvan Institute.

His group develops tools and approaches to comprehensively characterise the human genome, using predominantly Whole Genome Sequencing data. We aim to identify, understand and interpret the functional impact of genetic variation. The group has a strong translational focus, aiming to improve clinical care through applying genomics in a clinical environment. We have focussed on using WGS to help diagnose patients with inherited genetic disease, particularly kidney disease, and more recently, on the application of WGS to characterise patient tumours, with the goal of obtaining therapeutic insights.

Mark received a BSc (Bioinformatics) from University of Sydney in 2003, then a PhD from University of New South Wales in 2009. He has been at the Garvan Institute since late 2008, working initially in the Peter Wills Bioinformatics Centre, and then from 2011 with Andrew Biankin in the Australian Pancreatic Cancer Genome Initiative and the International Cancer Genome Consortium. He has been with the KCCG since 2013.

ABSTRACT

Targeted sequencing, whole exome sequencing (WES), and more recently, whole genome sequencing (WGS) have had a remarkably rapid, and positive impact upon patients. Diagnostic rates for patients with rare monogenic diseases have risen to on average 25% under WES, and 42-60% using WGS in patients with intellectual disability. As genomics is translated into routine medicine, one key challenge will be to meet the rigorous demands of operating in a clinical environment, whilst still being agile enough to keep the process up to date with advances in academia, at significant patient numbers. The incredible opportunity is that if patient genotype-phenotype data can be stored in suitable databases, these datasets can be mined for research, and drive further improvements to patient care, and our understanding of the impact of genetic variation on phenotype.

Since the introduction of the Illumina HiSeq X, the cost of WGS has plummeted, and is expected to continue to fall, making WGS-based diagnostics an attractive single-platform, which can be validated once, and repurposed to different diseases. In order to meet the anticipated scale of WGS-based diagnostics, we have developed a number of key platforms, including Patient Archive, for capturing machine-readable patient phenotype from clinical notes, Sabretooth for local- and cloud-based genomic analysis pipelines, and Seave, a comprehensive variant filtration and interpretation platform. We are currently seeking clinical accreditation, and as such have embarked upon extensive validation of the entire process, from patient to clinical, both through sequencing reference materials (eg NA12878), and clinical samples. In one case study, for patients with Autosomal Dominant Polycystic Kidney Disease, we obtained much higher diagnostic yield from WGS vs WES (86% vs 50%), due to coding variants missed by WES, and multi-exon deletions detected by WGS. Here, we will present the platforms that we have developed, the

findings supporting clinical validation of WGS, and a number of case studies of WGS applied to patients with rare monogenic disorders, or cancers with no available treatment options.

1220-1235

STRUCTURAL VARIATION CALLING FROM HiSeq X WHOLE GENOME SEQUENCING DATA IN A CLINICAL SETTING

DR ANDRE MINOCHE
Garvan Institute of Medical Research, NSW, Australia

BIOGRAPHY

Andre completed his Master of Science in Biotechnology at the École supérieure de biotechnologie Strasbourg in 2008, a trinational biotech engineering school in the heart of Europe.

After that he did a PhD in Bioinformatics in affiliation with the Max Planck Institute for Molecular Genetics, Berlin, Germany and the Centre for Genomic Regulation, Barcelona, Spain. During his PhD, Andre assembled complex genomes de novo, annotated them and investigated the genome sequence variability and genome evolution.

He completed his PhD with magna cum laude in 2013, published his main research work in Nature, and joined the Garvan Institute in 2014.

ABSTRACT

Genomic structural variations (SVs), including copy number variants (CNVs) affect 100 fold more nucleotides and arise de novo 1,000-fold more frequently than single nucleotide variants (SNVs). SVs are recognised to cause many complex developmental, neuro-cognitive and neuro-behavioural phenotypes. Although microarrays have been the mainstay of diagnosing CNVs in patients, the broad and uniform depth of coverage from Illumina HiSeq X whole genome sequencing data presents a unique opportunity to develop improved methods to detect CNVs and SVs across the entire size gamut from hundred's of nucleotides to entire chromosomes, in a clinical setting. A comprehensive assessment of SV is challenging due to their diversity in their manifestation, including deletions, duplications, inversions, translocations, their size differences, their possibility to superpose forming complex rearrangements, and their prevalence in genome repeats. We address this challenge by integrating SV calls made from discordant read pairs, split reads and read depth, and by applying multiple independent algorithms to detect large and small SVs. Additional post-filtering is implemented to address the shortcomings of each method, and to identify deletion-duplication events, which represent the most common form of superposed SV. We have developed a streamlined visualization procedure, allowing inspection of SV with their underlying evidence in genome browsers. We have performed extensive benchmarking against the cell line NA12878 and obtained sensitivity and precision up to 90% for deletions between 1-10kb. Compared to microarrays currently used in clinical genetic testing to detect copy number events >50kb, WGS detects 25% more gold standard deletions. Additionally, we detect 4,000 CNVs below the resolution of microarrays as well as 144 copy neutral deletion duplication events and 17 inversions. We present our findings from applying this workflow to ~100 whole genomes from clinical samples, including a cohort of 60 dilated cardiomyopathy patients.

We conclude that WGS is superior to current best-practice use of microarrays in the clinic in terms of both analytic sensitivity and precision.

1235-1250

SHARED ANALYSIS FOR GENOME TESTING IN THE HEALTH CARE SETTING

DR NATALIE THORNE
Melbourne Genomics Health Alliance, VIC

BIOGRAPHY
Natalie Thorne is the project manager for clinical bioinformatics and genomics in the Melbourne Genomics Health Alliance. After a degree majoring in mathematics and statistics and minoring in genetics, Natalie completed her PhD at the Walter and Eliza Hall Institute's Bioinformatics division in 2004. She worked for Cancer Research UK at the Cambridge Research Institute for nearly 5 years before returning to the Walter and Eliza Hall Institute. In her current role in the Melbourne Genomics Health Alliance, she has the unique experience of managing clinical and diagnostic bioinformatics aspects across 10 organisations who are collaboratively working to implement genomic testing into the health care system in Victoria.

ABSTRACT
Enormous efforts have been put into translating genomic tests into the clinical setting, particularly in major research, medical and diagnostic centres across the world. To achieve this, change in the health care system and collaboration is needed. The ten members of the Melbourne Genomics Health Alliance are working together to implement common systems and standards for genomics for Victoria. These include a common bioinformatics pipeline, variant curation database and genome data repository. The Alliance pipeline, Cpipe (Cpipeline.org *), now being utilised by member organisations, is undergoing accreditation in two laboratories. Development is progressing in a collaborative manner and driving standardisation. In addition, the Alliance has modified and enhanced the popular LOVD3 to create a tool MG-LOVD. MG-LOVD combines the functionality of locus specific and public variant databases with clinical diagnostic analysis workflows for variant curation, interpretation and reporting in a multi-institutional setting. Modifications have also been made to allow variant data sharing among a local network of instances within the Alliance. This is an initial step towards sharing via a single data repository.

An overview of how Cpipe and MG-LOVD are implemented and used in the Alliance will be presented. The key challenges and benefits arising from sharing a common pipeline and database will also be discussed.

* http://www.genomemedicine.com/content/7/1/68

1250-1305

BRAIN-cX – AN INTERACTIVE WEB-TOOL FOR GENE PRIORITISATION AND MORE

SASKIA FREYTAG
The Walter + Eliza Hall Institute of Medical Research, VIC

BIOGRAPHY
Saskia studied Statistical Science at UCL in London. After finishing she moved to Germany to pursue a PhD in Biostatistics focusing on GWAS analysis. In 2014 she moved to Melbourne where her research focus is mircoarray cleaning, co-expression analysis and the development of interactive analysis tools.

ABSTRACT
Whole-exome sequencing is a valuable clinical tool for human disease. However, for many sporadic patients this approach yields hundreds of credible mutations that could be the cause of the patients' disorder. Sifting through these mutations individually is a time-consuming and taxing process and

often fails to establish a feasible list of follow-up candidates. Gene prioritisation methods promise to identify the most interesting mutations located in genes using computational methods, which are ideally applied to tissue-specific genomic data. Unfortunately, results from these methods are not usually readily available to clinicians, as the generation of such methods, and often their interpretation, requires trained bioinformaticians. We have developed an intuitive web-tool for gene prioritisation in neurological disorders: brain-coX.

brain-coX incorporates and combines six large datasets on gene expression in the developing and ageing human brain. These datasets are adaptively cleaned of unwanted variation, maximising information for the disease of interest. In addition to gene prioritisation brain-coX's functionality includes extensive network visualization options as well as interactive analysis tools to explore changes in the gene-gene network along brain development. In the future, we hope to extend brain-coX offering interactive tools that visualize differences between brain regions.

Currently, our clinical collaborators and we are extensively testing brain-coX to prioritize candidate genes for patients with childhood epilepsies. We find that the use of brain-coX not only empowers clinicians and biologists with no programming or significant statistical knowledge, but also leads to better communication between collaborators.

brain-coX is available via shiny.bioinf.wehi.edu.au/freytag.s

SESSION 6

GENOMICS OF PLANTS AND FINE WINE

Chaired by Professor Justin Borevitz and Dr Rose Andrew

1515-1555

ORIGIN AND CONSEQUENCES OF GENETIC AND EPIGENETIC VARIATION IN ARABIDOPSIS THALIANA AND ITS RELATIVES

PROFESSOR DETLEF WEIGEL
Max Planck Institute for Developmental Biology, Germany

BIOGRAPHY
Detlef Weigel is a German-American scientist. He studied biology and chemistry in Bielefeld and Cologne, and received a PhD from the University in Tübingen in 1988. For his postdoctoral work at Caltech, he switched from Drosophila to plants. He joined the faculty of the Salk Institute in La Jolla in 1993, and has been a director at the Max Planck Institute for Developmental Biology since 2002. The work of Detlef and his group has been recognized by several awards, including the Gottfried Wilhelm Leibniz Award of the Deutsche Forschungsgemeinschaft. He is a member of the US National Academy of Sciences, the German National Academy of Sciences Leopoldina and the Royal Society.

The first major finding from the Weigel lab was that a gene from Arabidopsis thaliana could dramatically accelerate the flowering of trees; this established a proof of concept

for Arabidopsis genetics as a platform for biotechnological discoveries. His group later discovered the first plant microRNA mutant, and they identified the factor that is now known to be the long sought-after mobile flower-inducing signal. In collaboration with his Salk colleague Joanne Chory, Detlef was one of the first to exploit Arabidopsis natural genetic variation for understanding how the environment affects plant development. In recent years, his work in the areas of evolutionary genetics and genomics has focused on plant immunity and epigenetics. In addition to hypothesis-driven research, the Weigel group has a long history of providing new technologies and resources to the community. They have pioneered several new forward genetic methods, and produced the first haplotype map outside of mammals, which put Arabidopsis at the forefront of genome-wide association studies. This has culminated in an effort to sequence the genomes of 1001 natural A. thaliana strains (The 1001 Genomes Project).

Detlef has an extensive record of service to the scientific community. He has been a co-organizer of over a dozen international conferences, and he has served on several editorial boards as well as advisory boards of biotech firms and research institutes. He is also a forceful advocate of open access publishing. He was among the initial editorial board of PLoS Biology, and is now Deputy Editor of eLife, the new high-level journal supported by HHMI, Wellcome Trust and Max Planck. He is a co-founder of three startups in the biotechnology arena, most recently Computomics, which provides bioinformatics services, and CeMeT, which provides human metagenome analyses.

Detlef would be particularly keen to discuss publication strategies, organization of scientific meetings, social media outreach and new technologies in genomics.

ABSTRACT

My group is addressing fundamental questions in evolutionary biology that inform also applications in breeding: (i) Where do new genetic variants come from? (ii) Why do some variants increase in frequency? (iii) And why are some combinations of new variants incompatible with each other?

In collaboration with other labs (Bergelson, Ecker, Mott, Nordborg & K. Schmid), and with the help of Monsanto, we have been describing whole-genome variation in natural accessions of A. thaliana (http://1001genomes.org). In addition to resequencing efforts, this increasingly includes de novo assemblies. To better understand the patterns we observe in A. thaliana, we are comparing within-species variation with differences to the closest relative, A. lyrata, and to variation in a related genus, Capsella (with Neuffer, Nordborg & Wright labs).

On the other end of the spectrum, we are analyzing new DNA mutations and epigenetic variants that have arisen spontaneously under laboratory conditions or in a natural mutation accumulation experiment. The latter studies take advantage of an A. thaliana lineage that was apparently introduced to North America in historic times and accounts for about half the population there (with Bergelson and Burbano labs). We have been able to support what we see in the extant North American population by whole-genome sequencing of herbarium samples from the 19th century.

The ultimate goal of our top-down studies is to understand how new genetic and epigenetic variation interact with reassortment of variants after crosses and natural selection to shape geographic patterns of diversity. To this end, we are following natural populations during the season and over consecutive years. This work in turn is complemented by forward genetic analyses, especially of detrimental combinations of sequence variants found in separate lineages (with Dangl lab).

Additional information about our work can be found on our website, http://weigelworld.org.

1555-1630

DEMOCRATISING GENETIC ANALYSIS AND BREEDING WITH GENOTYPING BY SEQUENCING

MR ROB ELSHIRE
The Elshire Group Limited, New Zealand

BIOGRAPHY
Rob is a Principal Scientist with The Elshire Group Limited with a long history working with molecular markers in agriculture. Rob was the inaugural director of the Illinois Genetic Marker Center at the University of Illinois. This facility provided the agricultural research community there access to molecular marker technology in a cost effective manner. At Cornell University, he developed a low cost, high-throughput genotyping method commonly known as genotyping-by-sequencing (GBS). While the impetus for developing GBS was to serve the needs of the plant breeding community, the technology has enjoyed wide adoption in many areas of biological research.

In addition to developing the molecular method, he has collaborated in transnational research projects, organized numerous workshops and contributed code to analyze GBS data in a reproducible way. He continues these efforts with his current work which focuses on collaboratively building New Zealand capability in GBS and related technologies to enable genetic analysis in a wide range of NZ specific biological questions.

Rob is an enthusiastic supporter of Free / Libre and Open Source Software and was presented the New Zealand Open Source People's Choice award in 2014 for his genotyping-by-sequencing contributions to the community.

Rob is keen to discuss applications of marker technologies, managing and analyzing large data sets and potential collaboration opportunities with like-minded scientists.

ABSTRACT
Genotyping-by-Sequencing (GBS) is a high throughput method for generating many thousands of genetic markers using next generation sequencing. The method was developed with simplicity of deployment and an open source philosophy in mind. We published the method in 2011 in an open access journal so that as many researchers as possible could benefit from its use and potentially modify or extend it. The method has been adopted by many researchers. In addition to plant breeders in commodity species, GBS is being used by breeders of orphan crops as well as in the ecological sciences. Simplicity, low cost and openness of the method have allowed many researchers to jump into the genomics era and leveled the research playing field. However, more than a good molecular method is needed to democratise genetic analysis.

The Biospectra by Sequencing project aims to develop a set of community resources. There are two core components. One is an interactive information repository to contain useful information that is not often published in the literature. The other is a Free / Libre Open Source Software (FLOSS) project developing the software tools for best practice in data quality, automation and reproducibility. Working together, we will reduce duplication of efforts, provide a high quality set of information and tools and further reduce the barriers to entry in genomics research. We aim to enable researchers to do better research at a lower price than previously possible.

1630-1645

UNRAVELLING THE MāNUKA GENOME: A METAGENOMIC APPROACH

MS AMALI THRIMAWITHANA
The New Zealand Institute for Plant & Food Research Limited, New Zealand

BIOGRAPHY
Amali is a Bioinformatician at the New Zealand Institute for Plant and Food Research Limited since 2011, after graduating with a Masters of Bioinformatics from University of Auckland. She has been involved in research projects focusing on fungal pathogens, insect pests and plants where she has undertaken bioinformatics analysis including de novo assembly and annotation of genomes and transcriptomes, differential expression as well as comparative genomics. Her current major areas of interest focus on understanding insect pests of important horticultural crops as well as genome exploration of native New Zealand plant species.

ABSTRACT
Mānuka (Leptospermum scoparium), is a shrub indigenous to eastern Australia and New Zealand. The species is well known for its phenotypic plasticity, resulting in a range of chemotypes. This plasticity has resulted in a wide range of products fromthis shrub, including mānuka honey, essential oils and pharmaceutical products with unique antimicrobial activity. Currently, fundamental knowledge on the molecular biology of mānuka is minimal and hampered by a lack of availability of a whole genome sequence for the species. Acquisition of a whole genome sequences is complicated by the presence of endophytic fungi, with mānuka commonly associated with one or more endophytic fungal species in the wild. DNA from field-grown mānuka was sequenced and assembled using ALLPATHS-lg, with further scaffolding carried out by SSPACE2. As expected, assembled scaffolds represented the metagenomic content of the field-grown mānuka. Several approaches were taken to differentiate the various fractions of the metagenome. The final assembly of the plant “partition” resulted in an assembly containing 2505 scaffolds representing 298Mb, with an N50 of 262Kb and an overall CEGMA score of 94%. Gene prediction (aided by RNAseq data and expressed sequence tags (ESTs) from Eucalyptus grandis) on the plant partition scaffolds predicted 43,716 genes. The resulting gene predictions were then used to carry-out comparative genomics to explore the gene space of mānuka further.

1645-1700

THE SMRT WAY TO SEQUENCE A YEAST GENOME

DR RICHARD EDWARDS
University of New South Wales, NSW

BIOGRAPHY
Rich Edwards received his undergraduate and postgraduate training in genetics at the University of Nottingham in the UK. He moved to Dublin in 2001 for a postdoctoral position in bioinformatics before returning to the UK in 2007 to establish his own research group at the University of Southampton. Rich moved to UNSW in 2013 as a senior lecturer in Bioinformatics.

Research interests in the Edwards lab stem from a fascination with molecular basis of evolutionary change and how to harness the genetic sequence patterns left behind to make useful predictions about contemporary biological systems. Core research in the lab is the study of Short Linear Motifs (SLiMs), which are short regions of proteins that mediate interactions with other proteins. Rich is also excited about the new

opportunities for functional genomics that the new generation of long read sequencing technologies are making possible.

ABSTRACT
PacBio Single Molecule Real Time (SMRT) sequencing is rapidly becoming the technology of choice for de novo whole genome sequencing. The long read lengths and random error of PacBio data should make genome assembly considerably easier and more accurate than Illumina short read data. Indeed, the hope is that adoption of this technology will enable highly accurate and complete genome sequences to be generated in the absence of either a reference genome or extensive bioinformatics support.

Here, we report on the de novo genome assembly of three yeast genomes from SMRT data generated using the new PacBio RSII at the UNSW Ramaciotti Centre for Genomics. A haploid reference yeast genome strain, S288C, and two novel diploid strains were sequenced as part of a larger functional genomics project. For each strain, 20kb SMRT Bell library preps were performed and sequenced on two SMRT Cells using the P6-C4 chemistry. Between 1.74 Gb and 2.55 Gb of usable sequence data was generated for each strain, with read lengths of up to 53.3 kb. Whole genome de novo assemblies are then generated through the PacBio SMRT Portal.

We are using the S288C data to explore performance in comparison to the published genome as a reference. An initial assembly of S288C yielded over 99.9% genome coverage at 99.997% accuracy on only 29 unitigs, versus 17 reference chromosomes (16 nuclear chromosomes plus mitochondrion). Of these, 15 chromosomes were essentially returned as a single, complete unitig. We are now using the S288C data to optimise the assembly process and derive assembly settings for two novel strains. To this end, we have developed a new pipeline for the comparative assessment of high quality whole genomes against a reference. Genome assembly using the PacBio SMRT Portal is a two-step process, with HGAP generating a “pre-assembly” of error-corrected “seed” reads that are subsequently assembled using the Celera assembler. We explore the trade-off between accuracy and sequencing depth of this pre-assembly for different seed read length cutoffs and how this affects the final assembly. The effect of DNA loading concentration will also be discussed. Optimised assemblies will also be compared to results from the developmental FALCON diploid assembler.

1700-1730

WINE ‘OMICS: AT THE CUTTING-EDGE OF THE OLDEST BIOTECHNOLOGY

DR ANTHONY BORNEMAN
Australian Wine Research Institute, SA

BIOGRAPHY
Anthony obtained his PhD from the University of Melbourne where he studied the regulation of morphology in the fungal pathogen Penicillium marneffei and spent four years as a postdoctoral associate with Prof. Michael Snyder at Yale University, applying whole-genome techniques to compare transcriptional networks across yeast species. Anthony is currently a Principle Research Scientist at the Australian Wine Research Institute. His research is focused on applying genomics, systems- and synthetic-biology to understand the genetic basis of phenotypic diversity in industrial microorganisms, with particular focus on the wine yeasts Saccharomyces cerevisiae and Brettanomyces bruxellensis.

ABSTRACT
Wine is arguably the oldest biotechnological endeavour, with evidence of winemaking dating back at least 7,000 years. Despite its artisan nature, pioneering scientists such as Lavoiser and Pasteur positioned wine research at the cutting-edge of the biological and chemical sciences, a position it still holds to this day. In a modern day context, the application of technologies such as genomics, metagenomics, systems biology and metabolomics are revolutionizing wine research by yielding insights into the true breadth of genetic diversity that exists across the varied biological inputs that are central to this age-old industry and how this diversity translates into metabolomic, and therefore taste and aroma, impacts on the finished wine.

WEDNESDAY
14 October 2015

SESSION 7

QUANTITATIVE GENETICS AND DECODING THE GENOME

Chaired by Dr Helen Speirs and Dr Alexandra Livernois

0900-0930

CAN WE EXPLORE THE GENOMICS OF CANINE WORKING BEHAVIOUR WITH SELECTIVE SWEEP ANALYSIS?

PROFESSOR CLAIRE WADE
Faculty of Veterinary Science, The University of Sydney, NSW

BIOGRAPHY
Claire Wade began her career in quantitative genetics before making the leap to genomics in 2002 when she began a position with the Whitehead Institute for Biomedical Research at Massachusetts Institute of Technology. The genomics group at the Whitehead later became one of the founding groups of what is now the Broad Institute. While in the USA, Claire worked on several mammalian genome projects including the mouse, dog and horse (for which she was the lead researcher).

Claire's research interests include unravelling the secrets of genome biology using next generation sequencing. In particular, she studies the application of new genomic technologies to improve our understanding of diseases and behavioural

traits in domestic animals and wildlife and our understanding of the links between DNA and phenotype in general.

Projects currently underway are as diverse as studying the genetics of durability in Thoroughbred race horses, finding genes underlying canine separation anxiety and working dog performance, improving captive animal management using new genetic resources, and developing new methods for the computational analysis of high throughput sequencing data. Other projects involve mapping genes causing congenital disorders in dogs including cleft palate and deafness using whole genome association analysis and genotyping by sequencing.

ABSTRACT
Selective sweeps are genomic signatures of human or natural intervention in animal fitness. The predominant feature of a selective sweep is that there is a long region in the DNA that has little remaining variation in the cohort of animals under selection. While most studies have in the past compared widely different dog breeds, that are expected to exhibit divergence over a large portion of the genome, we have been concentrating our analyses within single dog breeds that have been subjected either to a formalised breed split, or to very different selective pressures. Here, we focus on selection for working behaviour in two breed groups. The Kelpie is a breed that was developed in Australia for working stock (predominantly sheep and cattle). Pedigrees for Kelpies are maintained by two registration organisations, one that focuses on working ability, and the other that focuses on companionship and conformation. Dogs are rarely if ever mixed between these registries in Australia. New South Wales Guide dogs are derived from a mixture of Golden Retriever and Labrador breeds, but by genomic clustering the dogs are predominantly Labrador Retriever at the genomic level. We have employed a selective sweep analysis to determine regions that might be of importance in Guide Dog success in the NSW Guide Dog Association. Our analyses reveal strong divergent sweep signals in both of these breed groups.

0930-0945

PROGRAMMABLE RNA TARGETING AND CLEAVAGE BY CRISPR/CAS9

DR MITCHELL O'CONNELL
University of California, Berkeley, USA

BIOGRAPHY
Mitchell received his PhD in Biochemistry from the University of Sydney in 2013, where he worked in Prof. Joel Mackay's group to develop artificial zinc-finger proteins to specifically recognize RNA for sequence-specific RNA-targeting applications. In 2013, Mitchell moved to the University of California, Berkeley to take up a postdoctoral position in the lab of Prof. Jennifer Doudna. In the Doudna lab, Mitchell has focused on exploring the molecular mechanisms of RNA-mediated gene regulation and the development of tools to interrogate these processes. In early 2012, the Doudna laboratory was the first to show the programmable, sequence-specific DNA recognition and cleavage ability of a CRISPR-associated protein known as Cas9. This research led to an explosion in the use of CRISPR/Cas9 as a genome-editing tool in multiple cell types and organisms. However, this protein had been thought to be incapable of targeting RNA. In a recent publication in Nature, Mitchell and colleagues were able to show that this is not the case and Cas9 can be used as a readily programmable sequence-specific RNA-binding and cleavage enzyme. This discovery paves the way for sequence-specific tools to explore the myriad of RNA species implicated in gene regulation and disease. Mitchell is now building on this work by exploring a number of applications of

CRISPR/Cas9 for untagged RNA transcript analysis, detection and manipulation.

ABSTRACT
The CRISPR-associated protein Cas9 is an RNA-guided DNA endonuclease that uses RNA–DNA complementarity to identify target sites for sequence-specific double-stranded DNA (dsDNA) cleavage. CRISPR/Cas9 has proven to be a versatile tool for genome engineering and gene regulation in a large range of prokaryotic and eukaryotic cell types, and in whole organisms, but it has been thought to be incapable of targeting RNA. I will present our research showing that Cas9 is able to bind with high affinity to single-stranded RNA (ssRNA) targets in a guide-RNA programmable manner when an additional short DNA oligonucleotide containing a required motif known as the protospacer adjacent motif (PAM) is provided in trans. Furthermore, we have shown that these PAM-presenting oligonucleotides (PAMmers) stimulate site-specific endonucleolytic cleavage of ssRNA targets, similar to PAM-mediated stimulation of Cas9-catalysed DNA cleavage. Using specially designed PAMmers, we have shown that Cas9 can be specifically directed to bind or cut RNA targets while avoiding corresponding DNA sequences, and we demonstrate that this strategy enables the isolation of a specific endogenous messenger RNA from cells. We envisage that Cas9 will enable new ways of investigating and manipulating many aspects of RNA function, including targeted degradation of RNAs, isolation and identification of RNA-associated proteins, and in vivo imaging of RNAs.

0945-1000

EXPRESSION QUANTITATIVE TRAIT LOCI (eQTLs) OF ENDOMETRIOSIS RISK LOCUS AT 1p36.12

DR JENNY FUNG
QIMR Berghofer Medical Research Institute, QLD

BIOGRAPHY
Dr Jenny Fung obtained her PhD from the University of Queensland in 2013. Under the supervision of Prof. Chen Chen and A/Prof. Lisa Chopin with a project aimed at investigating the underlying mechanisms for endocrine hormones on endometrial cancer cell progression by mRNA and protein expression analyses on cancer cell lines and clinical samples, functional assays and lentiviral gene silencing in cancer cells and mouse xenograft models. In June 2013, Jenny took up a post-doctoral appointment in Prof. Grant Montgomery's Molecular Epidemiology Laboratory to conduct large genetics and gene expression studies. Her research is focused on understanding the complex mechanisms underlying the associated genomic regions and identifying the important biological pathways increasing endometriosis risk by applying extensive functional studies and genetics and genomics statistical methods.

ABSTRACT
Endometriosis is a common gynaecological disease associated with chronic pelvic pain, reduced fertility and dysmenorrhea. It affects 6-10% of women of reproductive age in Australia and is a complex disease influenced by multiple genetic and environmental factors. The causes and molecular mechanisms underlying the condition are largely unknown. We have used genome-wide association studies (GWAS) to understand the genetic architecture and discover genomic regions associated with risk for endometriosis.

Although GWAS has been successful at finding common single nucleotide polymorphisms (SNPs) at risk loci, to enable translation of these results, a major challenge remains to pinpoint the causal SNPs, identify their target genes and pathways contributing to endometriosis risk and to characterize their functional effects.

GWAS and replication studies have identified seven genomic regions with strong evidence for association with endometriosis risk. To examine how genetic variants influence gene expression, expression Quantitative Trait Loci (eQTL) approach has been used, where gene expression data and genetic variation data from the same individuals are integrated for statistical genetic analyses. Results from eQTL studies in peripheral blood samples from 962 individuals in the Brisbane System Genetics Study (BSGS) and a meta-analysis in world largest cis-eQTL study on peripheral blood samples from ~5000 individuals identified two strong cis-associations mapped to endometriosis risk loci at 1p36.12 with target genes, CDC42 (p= 9.8x10-198) and LINC00339 (p = 5.01x10-53). The target tissue for functional effects is not known, but current theories suggest changes in the endometrium. We are conducting studies of gene expression in samples of endometrium in carriers of the risk alleles. Integrating the GWAS findings and functional characterization will provide a more comprehensive picture of the molecular links between disease-associated variants and target genes and will greatly expand our understanding of the mechanisms underlying the endometriosis susceptibility loci.

SESSION 8

MICROBIAL AND SINGLE CELL GENOMICS

Chaired by Dr Kirby Siemering and Dr Clare Stirzaker

1045-1130

ILLUMINATING MICROBIAL DARK MATTER VIA SINGLE-CELL GENOMICS

DR CHRISTIAN RINKE
University of Queensland, QLD, Australia

BIOGRAPHY

Christian Rinke is a Research Officer at the Australian Centre for Ecogenomics (ACE), University of Queensland, Australia. He received his PhD in Zoology from the Marine Biology Department at the University of Vienna, Austria and has since shifted his focus to the microbial world.

His research interests include genomics and the phylogeny and ecology of symbiotic and free living microbes. He focuses in particular on the uncultured majority of microbes (99%) which elude current culturing efforts. This so called “Microbial Dark Matter” can only be explored with culture-independent methods. Chris pioneered methods in high throughput single-cell genomics, the separation and sequencing of single bacterial and archaeal cells, and also employs metagenomics (the direct sequencing of environmental samples) to illuminate microbial dark matter.

ABSTRACT

Our view of microbial genomic diversity is severely skewed with the majority of all sequenced bacterial and archaeal genomes

belonging to only four bacterial phyla. This bias results in part from our inability to cultivate most microbes, a necessary step for traditional whole genome sequencing. Through cultivation-independent approaches such as single-cell genomics, one can now explore the genetic diversity and metabolic potential of uncultivated environmental microorganisms. We successfully amplified several hundred single cells from free-living and symbiotic populations without cultured representatives, known as microbial dark matter. The single-cell genomes allowed us to explore their intra- and inter-phylum-level relationships, to decipher encoded pathways, and to discover novel metabolic features. The single- cell reference genomes also facilitate the interpretation of metagenomic data sets and substantially improve phylogenetic anchoring of up to 20% of metagenomic reads in some habitats. While there is still much ground to cover, single-cell-genomics has proven to be a valuable tool to improve our understanding of microbial evolution on earth.

1130-1150

HIGH THROUGHPUT CELL SORTING FOR DOWNSTREAM GENOMIC ANALYSIS

DR J CLARK MASON
BD Biosciences, USA

BIOGRAPHY
Dr J. Clark Mason is Senior Director, Genomics Innovation with BD Biosciences, where his focus is strategic platform development for the cell analysis market. He came to BD with more than 15 years' experience as a marketing executive, bringing many key instrument and reagent platforms to the marketplace, for leading global life science companies. Clark holds a B.Sc. degree & Ph.D. He was awarded postdoctoral clinical and research fellowships in the UK (Queen's University Belfast) and USA (University of Chicago) and has held travel fellowships in South America, and Switzerland, and an Honorary University Fellowship in the UK (University of Manchester). In addition, he won a Silicon Valley award for innovative web design, published numerous, per reviewed, original research papers and has 4 assigned patents.

ABSTRACT
Fluorescent activated cell sorting (FACS) has the ability to select, characterize and quickly deposit single cell(s). It does this with high precision into PCR plates that can be preloaded with reagents suitable for further downstream genomic analysis. It also has the ability to connect cell phenotype with genomic data. Here we describe two novel FACS innovations – detection through total internal reflection, and automated droplet monitoring, that brings the power of flow cytometry within the reach of individual genomic labs.

1150-1205

SINGLE-CELL ANALYSIS OF BREAST CANCER MOLECULAR SUBTYPE REVEALS CLINICALLY RELEVANT HETEROGENEITY

MS LAURA BAKER
Garvan Institute of Medical Research, NSW

BIOGRAPHY
I'm a PhD student at the Kinghorn Cancer Centre (Garvan Institute of Medical Research). My research focuses on the intra-tumoural heterogeneity observed clinically in the diagnosis and treatment of breast cancer. We are further investigating what drives these fundamental cell differences by using single-cell gene expression techniques combined with breast

cancer subtyping analysis. This will enable understanding of the clinically relevant single-cell heterogeneity that is masked when samples are analysed on a bulk tumour level.

Another focus of my research is investigating a transcriptional regulator involved in mammary stem cell hierarchy and cellular differentiation as well as the regulation of poor prognosis basal-like breast cancer. Unbiased proteomic (Rapid Immunoprecipitation and Mass Spectrometry of Endogenous proteins) and genomic techniques (ChIP-exonuclease sequencing, ChIP-sequencing, RNA-sequencing) are yielding incredible insight into the molecular function of this protein.

ABSTRACT
Breast cancers display significant clinical and cellular intra-tumoral heterogeneity that accounts for differential patient therapeutic responsiveness, local recurrence and metastasis. Molecular studies permit detection of the five main molecular subtypes of breast cancer through the introduction of microarray technologies. The PAM50 subtype predictor uses a panel of 50 genes to predict molecular subtype using bulk patient RNA samples, however, this prevents analysis of intra-tumoral heterogeneity and simply measures average gene expression levels. In contrast, single-cell technologies enable analysis of gene expression variation in individual cells and can molecularly inform on the wide variation in gene expression observed through standard histological methods. Similarly, single-cell analysis of molecular subtype may provide invaluable information on clinically relevant tumour heterogeneity. Through this research, we investigate whether the PAM50 signature of bulk tumour samples is simply an average of diverse cellular states or if single cells can possess an independent PAM50 signature. In this study, we apply the PAM50 subtype predictor to examine single-cell intra-tumoral heterogeneity of breast cancer subtypes across a range of models including breast cancer cell lines, patient derived xenografts (PDX) and fresh patient tumours. Analysis of five breast cancer cell lines shows clear cellular gene expression diversity and single cells within a cell line possess different PAM50 subtypes. Together these results suggest a high degree of heterogeneity within commonly studied breast cancer cell lines. This heterogeneity is an important consideration when using models of breast cancer, as selected cell lines more accurately recapitulate the complex heterogeneity observed using histological methods in clinical samples.

1205-1220

THE EXTREME MICROBIOME PROJECT (XMP): THE METAGENOMICS OF LAKE HILLIER, A PINK HYPERSALINE LAKE

DR KEN MCGRATH
The Australian Genome Research Facility, QLD

BIOGRAPHY
Ken McGrath is the National Sequencing Manager and Node Manager at AGRF Brisbane. He obtained his PhD in 2005 at the Uni. of Qld, and has a research background in microbial community genetics, including human and environmental microbiomes and metagenomics analysis. Ken is currently involved with several sequencing projects, including the US-based extreme microbiome project (XMP), as well as evaluating emerging technologies such as the Oxford Nanopore MinION

ABSTRACT
The Xtreme Microbiome Project (XMP) is a global scientific collaboration to characterize, discover, and develop new pipelines and protocols for extremophiles and novel organisms. The XMP has chosen a range

of extreme environments, including the oil-spilled deep sea brine lakes of the Gulf of Mexico, “The Door to Hell” gas crater in Turkmenistan, the public surfaces of the New York Subway System, and even the walls of the International Space Station.

As part of this project, the AGRF collected samples from Lake Hillier. This lake is a bright pink hypersaline lake located on Middle Island, part of the Recherche Archipelago in Western Australia. The constant colour of the lake is different to other pink lakes in the area, and is thought to be a result of unique microbial composition, including halophilic algae, archaea, and bacteria.

We analysed several sample types (lakeside bank sediment, surface water, submerged water, and lake sediment) using a wide variety of metagenomics techniques, including amplicon-based diversity profiling (16S V1-V3, 16S V3-V4, Archaeal 16S, Algal 18S, Fungal ITS; sequenced on MiSeq), shotgun metagenomics (HiSeq), metatranscriptomics (HiSeq), and long-read metagenomics (MinION). This data was compared to organisms confirmed to be present in the lake using culture-based techniques.

The resulting microbial profiles revealed distinct populations that inhabit the lakes various strata, and even hint at the historical misuse of the area. The analysis highlights the strengths and weaknesses of each method for microbiome analysis, as well as provides a detailed insight into the composition of an iconic feature of the Australian landscape.

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POSTERS

POSTER PRESENTATIONS

Monday 12 October 2015

#	POSTER TITLE	PRESENTING AUTHOR	
1	A Bioinformatics Analysis of the Transcription Factors Associated with the Interferon Response in Human and Mouse Models	Dr Ross Chapman	
2	RNA-Seq: What difference does a strand-specific protocol make?	Dr Susan Corley	
3	Host microRNAs are promising biomarkers of infectious diseases	Dr Christopher Cowled	
4	Whole Genome Sequencing Identifies Structural Variation and Non-Coding Variants in the Region Overlapping the CMTX3 and CMTX4 Loci	Dr Alexander Drew	○
5	De novo trancriptome assembly and identification of cytokine genes in Pogona vitticeps	Dr Ali Livernois	
6	The Novel Long Non-Coding RNA RP1X Promotes Neuroblastoma Cell Proliferation by Stabilizing N-Myc Protein	Mr Bernard Atmadibrata	
7	DNA Methylation in Patients with a Strong Family History of Early Onset Coronary Heart Disease	Professor Vicky Cameron	
8	Using population sequencing data to investigate the evolutionary role and functional impact of inversion polymorphisms	Mr Haojing Shao	○
9	Whole Genome vs Targeted Sequencing: Which Provides Better Diagnostic Yield for Disease-Causing Variants?	Mr Mark Pinese	○
10	Bulked Segregant - genotyping-by-sequencing: Cost-effective and background independent genetic mapping of mutants and QTL	Mr Kokulapalan Wimalanathan	○
11	Maize - GO Annotation Methods Evaluation and Review (Maize-GAMER)	Mr Kokulapalan Wimalanathan	○
12	Genetic Characterisation of the Evolution of a Novel Metabolic Function in Yeast	Dr Åsa Pérez-Bercoff	○

○ Early Career Researcher ○ Student

2015 AGTA Conference

#	POSTER TITLE	PRESENTING AUTHOR	
13	An immune transcriptional regulatory network approach to Multiple Sclerosis	Dr Margaret Jordan	
14	“Profiling the profilers”: Evaluating current bioinformatics methods for characterising the diversity of microbial communities	Mr Naga Kasinadhuni	
15	Human Whole Genome Sequencing with Low and Ultralow DNA Inputs	Dr Kirby Siemering	
16	The Expression of Small Nucleolar RNAs in Human Tissues	Mr Hyun Jae Lee	
17	Evaluating the efficiency and reproducibility of genotyping by sequencing.	Dr Rust Turakulov	
18	Quantification of cellular features using novel image analysis algorithms	Mr Matloob Khushi	
19	Non-coding mutations in cancer alter G-quadruplex stability and affect its regulatory role in the 5’ untranslated region of mRNA	Mr Mahdi Zeraati	
20	Small ribosomal subunit profiling quantifies conformational changes in initiating and terminating ribosomes.	Dr Stuart Archer	
21	Cancer gene-interaction analysis using a data-driven inverse covariance matrix approach	Dr Denis Bauer	
22	Functionally characterizing every single mutation in Your Favorite Gene	Dr Alan Rubin	
23	Promiscuous DNA-binding of a mutant zinc finger protein corrupts the transcriptome and derails erythroid differentiation	Professor Andrew Perkins	
24	Characterisation of novel hypomorphic and null mutations in Klf1 derived from a genetic screen for modifiers of alpha-globin transgene variegation	Professor Andrew Perkins	

POSTER PRESENTATIONS

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26	Two Orthogonal Processes Underlie Survival of Patients with Resected Pancreatic Cancer: A Successful Application of Expression Deconvolution	Mr Mark Pinese	
27	Discovering genomic hotspots for columnar growth In Malus X domestica with GBS	Ms Cecilia Deng	
28	Gene Ontology enrichment analysis for gene subsets of distinctive function	Dr Denis Bauer	
29	The effect of ADAR3 deficiency on RNA editing in mouse hippocampus	Dr Dessislava Mladenova	
30	Harnessing the power of serum microRNAs to predict surgical outcome for women with ovarian cancer	Mr Jaynish Shah	
31	Application of genome wide analysis in developmental eye disease	Dr Ivan Prokudin	
32	Disentangling Genetics and Methylation in the Major Histocompatibility Complex	Dr Jovana Maksimovic	
33	A Novel Variable Short Tandem Repeat in the Upstream Regulatory Region of the Estrogen-Induced Gene EIG121 is Potentially Involved in Cancer Risk	Mrs Katherine Bolton	
34	Deleterious Passenger Mutations as a Marker for Progression towards Liver Cancer	Ms Magdalena Budzinska	
35	Loss-of-function germline FGFR1 mutation identified in a patient with prolactinoma	Dr Mark McCabe	
36	Simultaneous “multi-omic” measurement of gene fusions, mRNA and proteins at 800-plex using single-molecule optical barcodes.	Dr Michael Rhodes	
37	Wild Wine: metagenomic analysis of microbial communities during wine fermentation.	Dr Peter Sternes	

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38	High quality RNA isolation from rat spinal cord motor neurons using Laser Capture Microdissection	Dr Prachi Mehta	
39	Impact of Gadolinium Oxide Nanoparticles on Viability of Human Liver-Derived Cell Line	Dr Saad Alkahtani	
40	Genomic insights into the nitrate assimilation potential of Brettanomyces bruxellensis isolates.	Mr Ryan Zeppel	
41	Epithelial, metabolic and innate immunity transcriptomic signatures differentiating the rumen from other sheep gastrointestinal tract tissues	Dr Ruidong Xiang	
42	ROS Mediated Apoptosis and DNA Damage Induced by Barium Nanoparticles In Mouse Embryonic Fibroblasts	Professor Saud Alarifi	
43	Seave: a Comprehensive Variant Filtration Platform for Clinical Genomics	Dr Velimir Gayevskiy	
44	DEAR-O: Differential Expression Analysis based on RNA-seq data -Online	Ms Zong-Hong Zhang	
45	Analysis of Metastasis Progression in High Grade Mucinous Ovarian Cancer by Whole Genome Sequencing of Multiple Autopsy Sites	Dr Matthew Wakefield	
46	Functional Characterisation of Human Pseudogene Transcription using Targeted RNA Sequencing	Dr Daniel Thomson	
47	The presence of the rs17878362 polymorphism in breast cancer is associated with a low Delta-40p53:p53 ratio and outcome.	Dr Kelly Avery-Kiejda	
48	A High Density SNP-based Genetic Linkage Map of Sweet Potato Established by Scaffolding an Ipomoea Trifida (H. B. K.) G. Don. de novo Assembly	Mr Chenxi Zhou	
49	A novel technology for whole genome amplification from single cells and limited material	Ms Martha Hinton	
50	A single-tube NGS library prep workflow integrating enzymatic fragmentation results in high yields and low sequence bias	Ms Martha Hinton	
51	Cooking up a pathway analysis with roast and fry	Dr Goknur Giner	

MONDAY
12 October 2015

POSTER 1

A BIOINFORMATICS ANALYSIS OF THE TRANSCRIPTION FACTORS ASSOCIATED WITH THE INTERFERON RESPONSE IN HUMAN AND MOUSE MODELS

Ross Chapman, Helen Cumming, Linden Gearing, Paul Hertzog

ABSTRACT
Interferons play a vital role in mammalian genetic responses to bacterial and viral infections and to tumour development. The interferon response following disease challenge is highly modulated; the host response must be sufficient to protect the host, while excessive responses can cause toxicity and even death. Furthermore, the interferon response follows a highly structured temporal response, with stimulation precipitating an organised sequence of transcriptomic events. Transcription factors play an important role in the regulation of genetic transcription, influencing the timing and intensity of expression of individual genes. Here we present a study of the relationship between transcription factors and the genetic responses to interferon stimulation in human and mouse model systems, conducted using two bioinformatics tools: 1) the Interferome on-line database of interferon-regulated genes (http://interferome.its.monash.edu.au/ interferome/home.jspx), and 2) the Enrich custom software, which is powerful and intuitive tool for revealing transcription factors involved in the regulation of co-expressed genes.

The analysis revealed populations of transcriptions factors that were enriched among genes that were regulated by interferon in both human and mouse. Many transcription factors were common to both species, indicating that the regulation of the genetic response is highly conserved between the two species. However, notable differences between the species were detected for some transcription factors, indicating that some divergent evolution in the interferon response might have occurred between the two species. Potential inter-species diversity in the regulation of the interferon response is worthy of experimental validation.

POSTER 2

RNA-SEQ: WHAT DIFFERENCE DOES A STRAND-SPECIFIC PROTOCOL MAKE?

Susan Corley, Zara Ali, Karen MacKenzie, Marc Wilkins

ABSTRACT
RNA-Seq technology is capable of detecting all forms of RNA transcribed from the genome (including mRNA coding for proteins, microRNA, snoRNA, lincRNA, and mtRNA). Until recently RNA-Seq experiments were generally conducted using a single stranded protocol. Using this protocol it was not possible to detect whether transcription had occurred from the forward or reverse strand of DNA. However, recent developments in sequencing chemistry have made it feasible to routinely identify the DNA strand from which any RNA transcript has originated (strand-specific protocol). Here we compare the outcomes of read mapping and feature counting using both a non-stranded and a strand-specific protocol. Our data is derived from 2 studies using human primary hematopoietic cells. Sequencing was performed using the Illumina NextSeq platform and the RNA libraries were prepared using Illumina's TruSeq Stranded Total RNA kit with Ribozero pulldown. Over 40 million 75 bp paired-end

reads were produced per sample. Reads were mapped to the human reference (Ensembl GRCh37) using Tophat2 and reads mapping to features were counted using HTSeq. Here we present a breakdown of the types of RNA, coding and non-coding RNAs detected using the strand-specific and non-strand specific protocols and compare the outcomes of differential expression analysis using these protocols.

POSTER 3

HOST MICRORNAS ARE PROMISING BIOMARKERS OF INFECTIOUS DISEASES

Christopher Cowled, Cameron Stewart, Chwan-Hong Foo, Andrew Bean

ABSTRACT
Molecular diagnostic tests for infectious diseases may be either direct or indirect. Direct tests target pathogen-derived molecules (such as protein antigens or nucleic acids), while indirect tests target host-derived molecules, such as antibodies. Direct tests can face problems with fast-evolving pathogens such as viruses, or highly localized infections, or agents that replicate at very low levels. In contrast, antibodies are generally undetectable for the first week of infection, frequently cross react against related pathogens, and cannot easily distinguish current from past infections. There is therefore a constant need for new and better diagnostic tests. Quantitative 'omics' including transcriptomics, proteomics and metabolomics are well suited for identification of host-derived biomarkers. The chemical uniformity of RNA makes it a particularly attractive target, and RNA-Seq enables detailed measurement of transcripts over a large dynamic range. One promising category of biomarkers are microRNAs, which exhibit several attractive characteristics: Easy extraction from blood or serum, reduced transcriptional complexity (no splicing and moderate diversity), and each sequencing read corresponds to exactly one count (no need to adjust for transcript length). Despite these advantages, difficulties still remain. In particular, microRNA quantification is somewhat platform-dependent. Reasons for this include difficulty with normalization due to skewed sample composition (the single most abundant miRNA can make up > 95% of some samples), and the natural occurrence of isomiRs can influence abundance estimates. Nevertheless, host microRNAs are a promising class of infectious disease biomarkers.

POSTER 4

WHOLE GENOME SEQUENCING IDENTIFIES STRUCTURAL VARIATION AND NON-CODING VARIANTS IN THE REGION OVERLAPPING THE CMTX3 AND CMTX4 LOCI

Alexander P. Drew, Megan H. Brewer, Andrzej Kochański, Aditi Kidambi, Gonzalo Pérez-Siles, Adrienne Grant, Joanna Kosińska, Dagmara Kabzińska, Rafal Płoski, Irena Hausmanowa-Petrusewicz, and Garth A. Nicholson and Marina L. Kennerson

ABSTRACT
Previously we reported a family with a Mendelian inherited, axonal Charcot Marie Tooth disease, which is genetically unsolved (Kochanski, Kennerson et al. Neurology 2005; 64:533-535). We performed genome wide linkage analysis (Linkage V Panel) in which all the autosomes were excluded and several suggestive linkage peaks were identified on chromosome X. Fine mapping refined the chromosome X linkage peak (Zmax = 1.7 at zero recombination; DXS8041) to a 17.2-Mb interval flanked by the markers rs2050030 and DXS1227. A disease haplotype segregates with all affected males and obligate female carriers. Interestingly, this region overlaps both the

CMTX3 and CMTX4 disease loci. Whole exome sequencing did not identify any mutations in the coding region of genes in the CMTX3 or CMTX4 locus (including the known CMT gene AIFM1).

We present analysis of this linkage region using whole genome sequence (WGS) of an affected male to identify the causative mutation. We confirmed the absence of mutations in the coding regions of genes within the linked region. We examined the region for structural variation (SV) and non-coding variants. Four candidate variants were identified that localise within the critical disease interval. They include an inversion that disrupts the CXorf48 gene, a deletion in the 5'UTR of the FGF13 gene, a deletion upstream of the SMARCA1 gene, and a non-coding point mutation in the 3'UTR of the SOX3 gene. No novel candidate mutations or SV were identified that affect the AIFM1 gene in the CMTX4 locus. The variants identified in this family may help to identify the unknown gene affected in CMTX3 or be a new disease locus on chromosome X. Future studies will confirm if these candidate variants are a pathogenic cause of axonal CMT.

POSTER 5

DE NOVO ASSEMBLY AND IDENTIFICATION OF CYTOKINE GENES IN POGONA VITTICEPS

Alexandra Livernois, Alexie Papanikolaou, Kristine Hardy, Renae Domoaschenz, Sudha Rao, Tariq Ezaz, Arthur Georges, Stephen Sarre, Janine Deakin

ABSTRACT

Cytokines are small proteins that play an important role in the immune response in vertebrates. Extensive study of cytokine genes in mammals has demonstrated the importance of their time and place of expression to achieve an appropriate immune response. Similar analyses in divergent taxa, such as the central bearded dragon (Pogona vitticeps) can provide important insight into the essential molecular mechanisms and evolution of cytokine regulation. The genome of P. vitticeps was recently sequenced, but many immune genes were not annotated. Automated annotation techniques are not sensitive enough to detect rapidly evolving genes, such as cytokines, and they must be manually curated. Consequently, key cytokines have not yet been characterized in P. vitticeps. In order to characterize cytokine expression and regulation in the immune response in P. vitticeps, we first need to determine the complete nucleotide sequences of key cytokine genes. We sequenced the transcriptomes of unstimulated and stimulated spleen cells and constructed full-length transcripts from short paired-end read RNA sequencing data using the Trinity platform. De novo transcript reconstruction and conserved synteny analysis allowed us to identify candidate cytokines that are missing from the P. vitticeps genome annotation, including interleukin 2 (IL2), for which transcriptional activation events have been well documented in mouse and human. Identification of key cytokines in P. vitticeps will reveal cytokine genes conserved across vertebrates and thus likely to be essential to the vertebrate immune response. In addition, the nucleotide sequences of key cytokines in P. vitticeps will enable us to characterize the immune response for comparison with mammals.

POSTER 6

THE NOVEL LONG NON-CODING RNA RP1X PROMOTES NEUROBLASTOMA CELL PROLIFERATION BY STABILIZING N-MYC PROTEIN

Bernard Atmadibrata, Pei Yan Liu, E-Young Tan, Jesper Maarg, Andrew Tee, Jo Vandesompele, Pieter Mestdagh, Marcel Dinger and Tao Liu

ABSTRACT

Rationale: MYC oncogenes encode transcription factors commonly overexpressed in many types of cancers. Neuroblastoma is a childhood solid tumour that arises from neural crest cells of the sympathetic nervous system. MYCN gene amplification, which leads to overexpression of N-Myc protein, occurs in approximately 40% of patients with aggressive neuroblastomas.

Results: RNA-sequencing identified 5 transcripts, including RP1X, considerably differentially expressed between MYCN gene amplified and non-amplified human neuroblastoma cell lines. Knocking-down N-Myc expression with siRNAs reduced RP1X gene expression, and chromatin immunoprecipitation assays showed that N-Myc protein bound to the RP1X gene promoter. Affymetrix microarray studies revealed that DEPDC1B was one of few genes considerably down-regulated in neuroblastoma cells after transfection with RP1X siRNAs. Depletion of RP1X or DEPDC1B significantly reduced N-Myc protein phosphorylation at Serine 62, N-Myc protein stabilization and neuroblastoma cell proliferation/survival. In human neuroblastoma tissues from the European Neuroblastoma Research Consortium, high levels of RP1X gene expression correlated with N-Myc target geneset activation, DEPDC1B gene expression and poor patient prognosis.

Conclusion: This study identified the novel long non-coding RNA RP1X as an N-Myc target gene. RP1X up-regulates DEPDC1B gene expression, leading to N-Myc protein phosphorylation at Serine 62, N-Myc protein stabilization and neuroblastoma cell proliferation.

POSTER 7

DNA METHYLATION IN PATIENTS WITH A STRONG FAMILY HISTORY OF EARLY ONSET CORONARY HEART DISEASE

Vicky Cameron, AP Pilbrow, AF Faatoese, RW Troughton, AM Richards and J.F Pearson

ABSTRACT

Coronary heart disease (CHD) is a leading cause of morbidity and mortality in Aoteoroa/New Zealand. Having a first-degree relative with early-onset CHD doubles the risk of CHD [1]. The mechanism by which our environment influences the expression of our genes is through epigenetics, such as methylation of the DNA. DNA methylation has been associated with CHD at specific loci [2, 3], but there have ben no previous studies of DNA methylation in a cohort with a very strong family history of early onset CHD. The Christchurch Family Heart Study (FHS) patients are unrelated individuals who have had a documented premature CHD event (<50 years in men, <60 years in women) and who have at least one first-degree relative with an early CHD event (total 80 to date). Controls from the Canterbury Healthy Volunteers (HVOLs) with no prior diagnosis of any cardiovascular disease were age and gender-matched to the FHS patients.

To assess the association of DNA methylation on risk for those in this tightly defined cohort with a very strong family history of early onset CHD, we have performed a screening study examining

the methylation status of peripheral blood samples from 71 people, 50 from the FHS and 21 HVOLs, using illumina's HumanMethylation450 beadchips (485,000 methylation sites, covering 99% of RefSeq genes). The results of our analysis pipeline confirm associations of methylation status with age and gender previously reported for population studies, and no differences in methylation associated with white cell profiles between FHS and HVOLs. Differential methylation between FHS and HVOLs was observed at 24 sites (adjusting for age and gender, FDR corrected $p<0.05$). Using genotypes derived from the Illumina iSelect Cardio-MetaboChip (220,000 SNPs associated with cardiovascular and metabolic traits), we can show clear evidence of sites where methylation is associated with genetic variations both local and at a distance, known as methylation QTLs.

POSTER 8

USING POPULATION SEQUENCING DATA TO INVESTIGATE THE EVOLUTIONARY ROLE AND FUNCTIONAL IMPACT OF INVERSION POLYMORPHISMS

Haojing Shao, Devika Ganesamoorthy and Lachlan Coin

ABSTRACT
Inversions are a class of functional polymorphisms in human which remains poorly understood. In particular, detection of inversions mediated by Non Allelic Homologous Recombination(NAHR) is complicated by the fact that they are flanked by long (>2000bp) Inverted Repeat sequence and so hard to efficiently detect by next generation sequencing method. We generated a whole genome IR map to cover all possible NAHR inversions. By target capturing and third generation sequencing 407 IR regions, we could apply computational method to genotype inversion by its breakpoint and will finally get a human genome inversion map.

POSTER 9

WHOLE GENOME VS TARGETED SEQUENCING: WHICH PROVIDES BETTER DIAGNOSTIC YIELD FOR DISEASE-CAUSING VARIANTS?

Mark Pinese, Marcel E Dinger and Mark J Cowley

ABSTRACT
Many diagnostic laboratories have adopted targeted next generation sequencing (eg TruSight One, or Whole Exome), and have made significant advances in terms of diagnostic yield and turn around time. Although Whole Genome Sequencing (WGS) is recognised for its broad- and uniform-depth of sequencing coverage across the genome, its diagnostic performance has largely not been demonstrated. Here, we evaluate the diagnostic performance of WGS compared to targeted sequencing in a controlled clinical diagnostic setting.

We selected two modern best-in-class technologies for comparison: Illumina HiSeq X WGS at 30X depth and the Illumina TruSight One target panel at 78X average target depth. Reads of NA12878 reference DNA from each technology were processed by a common GATK best practices pipeline, and calls compared to the Genome in a Bottle consortium gold-standard variants. To simulate the performance on clinically relevant variants, comparisons were restricted to coding exon variants that were within 30 bases of a Human Gene Mutation Database pathogenic locus.

HiSeq X WGS provided superior diagnostic yield to the TruSight One panel across all mutation types, at both homozygous and heterozygous loci. For single nucleotide variants, WGS data provided a sensitivity

of 99.9%, with one false positive in over 1.6 million bases examined; despite its greater depth, the TruSight One panel only achieved a sensitivity of 95.5%, with a higher false positive rate. The difference was even more marked for multi-nucleotide substitutions and small insertions/deletions, in which WGS detected 19/19 events, whereas the panel only identified 13/19 (sensitivity of 68.4%).

For the detection of variants near known disease loci, WGS provides greatly superior diagnostic sensitivity to panel sequencing, despite its lower average depth. This difference is especially marked for multi-nucleotide substitutions and indels, for which the sensitivity of panel sequencing is only approximately 70%.

In summary, our results anticipate that WGS will improve diagnostic yields over targeted panels, even when considering only those genes targeted by the panel.

POSTER 10

BULKED SEGREGANT - GENOTYPING-BY-SEQUENCING: COST-EFFECTIVE AND BACKGROUND INDEPENDENT GENETIC MAPPING OF MUTANTS AND QTL

Kokulapalan Wimalanathan, Rebecca Weeks and Erik Vollbrecht

ABSTRACT

Genetic mapping of new mutants, which allows us to map a mutant phenotype to a causal locus or loci in the genome, is a crucial step in forward genetics. Construction of a mapping population that consists of mutant and normal individuals is essential for genetic mapping. The mapping population can be used by different high-throughput methods for genetic mapping. Single Nucleotide Polymorphism (SNP) arrays and Sequenome-based methods detect presence and absence of pre-discovered SNPs, and therefore are not background independent. In contrast, high-throughput sequencing (HTS) based methods used for genetic mapping are generally background independent. Some HTS methods such as Genotyping-by-sequencing (GBS) and RAD-seq use DNA for mapping, while other methods such as BSR-seq and MMAPPR use RNA. Current DNA-based methods barcode DNA extracted from each individual in the mapping population to construct the sequencing library, and RNA-based methods construct a separate library from each of two pools, namely mutant and normal. Both approaches provide high resolution maps to identify causal loci, but are not cost-effective for screening a large number of mutant families such as may be recovered from an enhancer/suppressor screen. Here we present a low-resolution, but cost-effective, HTS-based method for genetic mapping. For each new mutant we pooled tissue from phenotyped individuals to create a mutant pool and a normal pool. We adapted the original GBS method to construct sequencing libraries, prepared libraries for several pairs of pools and determined rough map positions. Our method is cheaper than the current GBS protocol, easier than using RNA for library construction, and without sampling biases inherent in using RNA expressed in a certain tissue type(s). We are currently fine mapping the intervals identified by BS-GBS, and extending the method to map natural modifiers. Here we present the pipeline and results from these genetic mapping efforts in maize.

POSTER 11

MAIZE - GO ANNOTATION METHODS EVALUATION AND REVIEW (MAIZE-GAMER)

Mr Kokulapalan Wimalanathan, Carson Androf and Carolyn Lawrence-Dill

ABSTRACT

Maize is an important agricultural crop - based on metric tons, maize is the #1 production grain crop in the world (http://faostat.fao.org). Largely as a result of plummeting sequencing costs, the growing availability of whole genome sequences has led to an increased demand for high-throughput omics studies. Interpretation of the results of these studies often requires the analysis of functional annotations of genes. The Gene Ontology (GO) is a widely used database that consists of terms that describe gene product function and property. The majority (~99%) of the GO annotations in maize are inferred from electronic annotations by high-throughput pipelines such as Ensembl. On the contrary, only about half of the GO annotations in Arabidopsis are inferred from electronic annotations. Clearly there is a need to evaluate the confidence of existing GO annotations for maize and improve the overall quality of functional predictions in this well-studied species. Here we present a pipeline that annotates GO terms to maize gene models using multiple functional annotation methods along with an evaluation of confidence for these annotations.

Our pipeline uses three approaches to assign GO terms: BLAST-based methods, functional domain-based methods, and advanced methods (machine learning and statistical approaches). Using a test dataset that contains high-quality manual annotations from MaizeGDB (~750) and reviewed annotations from UniProt (~6500), we are in the process of evaluating the performance of our approaches, comparing the performance to existing annotations, and creating a designated set of high-confidence functional annotations for maize genes. Review of these annotations by experts will substantially improve the confidence of annotations predicted using the pipeline, so we are designing a user-friendly system to leverage crowdsourcing for manual review of the predicted GO annotations. We plan to expand and adapt the pipeline to other species once it has been implemented and tested in maize.

POSTER 12

GENETIC CHARACTERISATION OF THE EVOLUTION OF A NOVEL METABOLIC FUNCTION IN YEAST

Åsa Pérez-Bercoff, Tonia L. Russell, Philip J.L. Bell, Paul V. Attfield and Richard J. Edwards

ABSTRACT

One of the central questions in biology is how novel biochemical pathways evolve. In sexual populations this is particularly complex. Recombination and the random assortment of chromosomes during meiosis means that an enormous diversity of genotypes can be generated from the standing variation present in a population. The relative contribution of this genetic variation versus novel mutations in the evolution of novel traits is yet to be established. We are using laboratory-evolved yeasts to investigate the early stages of evolving a novel metabolic activity, using a novel approach of mapping population metagenomic data onto multiple ancestral genomes.

We are working with a population of Saccharomyces cerevisiae generated from a starting population consisting of 30 S. cerevisiae strains. The population was grown under selection on xylose minimal media (XMM), undergoing sexual mating

every two months for 1463 days, in which time it developed the ability to effectively utilise xylose – a trait not present in any of the ancestral strains. We are using a combination of PacBio long-read single molecule real time (SMRT®) and Illumina short-read sequencing to investigate the evolution of this population. As a pilot study, three of the ancestral strains from the starting population, including two diploids, were sequenced with the new PacBio RSII long read sequencing service at the Ramaciotti Centre for Genomics. High quality complete genomes were assembled de novo using the hierarchical genome-assembly process (HGAP3) using only PacBio non-hybrid long-read SMRT sequencing data, and corrected using Quiver. In addition, we have shotgun metagenomic Illumina data from one of the early populations exhibiting adaptation to growth on XMM. We are developing methods to map these short-read data onto multiple high quality ancestral genomes in order to estimate the relative contribution of each ancestor's genetic variation to the evolved population, and to identify possible sites of recombination. In addition, metagenomic data is being mapped against the official S. cerevisiae reference strain S288c to conduct variant calling to identify single nucleotide polymorphisms (SNPs) that are not present in any of our genomes. These will be compared to the publicly available "100 yeast genomes" and partitioned into natural variation and candidates for novel mutations. By doing these comparisons we hope to elucidate how the population has evolved to acquire its novel characteristics, setting the scene for a more in-depth study.

POSTER 13

AN IMMUNE TRANSCRIPTIONAL REGULATORY NETWORK APPROACH TO MULTIPLE SCLEROSIS

Margaret Jordan, M. Gresle, L. Laverick, D. Stanley, L. Smith, T. Spelman, H. Butzkueven and A.G. Baxter

ABSTRACT

Multiple Sclerosis (MS) is the most common disabling neurological disease affecting young adults in developed countries. Approximately 25,000 Australians and as many as 2.5 million worldwide have MS and of these, 48% have profound or severe disability. It is a complex disease associated with the effects of multiple genes in combination with lifestyle and environmental factors. Among the environmental associations are the "latitudinal incidence gradient", adolescent Epstein Barr Virus infection, smoking and obesity, whilst the strongest genetic association, with an odds ratio (OR) of up to 30:1, is an Anglo-Celtic ethnicity compared to an East Asian background. The strongest individual genetic risk variation is the carriage of the HLA-DR2 haplotype, with an OR of 2.5:1. To date, genome-wide association studies (GWAS) have identified 110 disease-associated single nucleotide polymorphisms (SNPs) but although a few tagging SNPs used in GWAS affect transcript splicing, in general the GWAS approach tests disease associations with individual variants that are unlikely to be causal. In addition, comparisons of family-based estimates of heritability with simple models of aggregated genetic risk, demonstrate that, to date, the cause of only ~28% of the heritability of MS has been identified. In essence, the risk factors' individual associations with MS are so weak that on their own they contribute little meaningful understanding to the disease liability. We thus hypothesised that the complex genetic phenotype is driven by a

co-ordinated expression of transcriptional regulatory networks.

To test this, we generated a gene co-expression network based on pooled Affymetrix Human Gene 1.0 ST array analyses of magnetic bead sorted lymphocytes, including B cells, CD4 and CD8 T cells, NK cells and monocytes, from 67 untreated relapsing/remitting (RR) MS patients and 102 Healthy Controls (HC) – a total of 712 microarrays. The Affymetrix CEL files were normalised using RMA background subtraction in Bioconductor and batch effects were removed using the nonparametric CombatR algorithm. Variability of transcripts across all arrays was ranked by standard deviation and the 19,659 most variable were used for network construction. Application of the WGCNA algorithm in R generated a weighted gene co-expression network of 5,762 nodes and 198,937 edges assigned to 16 significantly co-expressed modules containing between 23 and 1,690 transcripts each. For each leukocyte population, the strength of differential expression between patients and HC was assessed, by ranking genes by Mann Whitney U test and ANOVA, in order to test for each transcript across the network. Of particular interest was a group of transcripts we named the “Black” module, which was strongly down-regulated in monocytes of patients and contained 12 of 22 highly differentially expressed (HDE) transcripts ($p<10-34$, c2 test). The Black module contains 181 transcripts, of which 14 are encoded by genes adjacent to MS-associated single nucleotide polymorpohisms (SNP) and seven encode transcription factors (TF). We now aim to test our hypothesis by manipulating the identified genes in an animal model of MS, experimental autoimmune encephalomyelitis (EAE), as well as by in-vitro techniques, to control the expression of the whole black module as an integrated unit. This may provide a new perspective on the aetiology of complex genetic diseases and offer novel therapies for MS.

POSTER 14

“PROFILING THE PROFILERS”: EVALUATING CURRENT BIOINFORMATICS METHODS FOR CHARACTERISING THE DIVERSITY OF MICROBIAL COMMUNITIES

Naga Kasinadhuni, Lavinia Gordon, Ken McGrath, Rachael McNally

ABSTRACT

Microbial diversity profiling through amplicon sequencing is a popular technique for determining the relative proportions of microbial taxonomic groups in a mixed microbial community. Whilst best-practice methods for library preparations and sequencing techniques are well established, there are a variety of bioinformatics methods available to analyse the data. Most of the current publications on taxa characterization utilize tools like the Quantitative Insights into Microbial Ecology (QIIME), UPARSE, mothur, MEtaGenome ANalyzer (MEGAN) and the MetaGenomic Rapid Annotation using System Technology (MG-RAST). Along with these sophisticated tools there are many databases like Greengenes, Silva, Genbank, User-friendly Nordic ITS Ectomycorrhiza (UNITE) databases compiling various sequences.

To explore the variance generated using these different methods, we analysed amplicon data from an extreme halophilic microbial population from a remote and isolated pink salt lake (Lake Hiller, Western Australia) for several targets (Bacterial 16S:V1-V3, 16S:V3-V4, Fungal ITS1-2, Eukaryotic 18S, Archaeal V1-V3) across each analysis pipeline, and compared the microbial profiles generated.

Our results reveal that each method generates a different outcome, with significantly varied performance at each stage from pair-read assembly, quality tolerance, and to the accuracy of Taxonomic Resolution, along with vastly different demands on computational resources.

These comparisons not only highlight the importance of selecting an appropriate bioinformatics methodology, but demonstrate the dangers of comparing microbial profiles generated in separate studies that have used different analysis tools.

POSTER 15

HUMAN WHOLE GENOME SEQUENCING WITH LOW AND ULTRALOW DNA INPUTS

Kirby Siemering, Jafar S. Jabbari, Lavinia Gordon, Matt Tinning, A/Prof. Marcel Dinger, Dr. Maria Lubka-Pathak, Ms Dahlia Saroufim and David Miller

ABSTRACT
There are several instances in which DNA availability for next generation sequencing library preparation is limited. Examples include: ChIP, FFPE and cell free as well as when scarce tissue DNA will be used for multiple applications. This becomes a particular issue for whole genome sequencing where good coverage of the whole genome is necessary. To address this issue, we investigated the characteristics of libraries prepared from low, ultra-low, and standard fragmented inputs using the Rubicon ThruPLEX® DNA-seq kit and sequenced on both the HiSeq 2500 and HiSeq X systems. We present data on important metrics such as library diversity, SNV calls, GC bias and coverage and demonstrate the feasibility of sequencing previously inaccessible low input samples on the HiSeq X system.

POSTER 16

THE EXPRESSION OF SMALL NUCLEOLAR RNAS IN HUMAN TISSUES

Hyun Jae Lee, Cas Simons, Joanna Crawford, Lachlan Coin, Ryan Taft

ABSTRACT
Small nucleolar RNAs (snoRNAs) are a class of non-coding RNAs traditionally assumed to have restricted housekeeping role in rRNA and snRNA modifications. More recently, however, various studies have uncovered great complexity in snoRNA biology, warranting a deeper insight into various aspects of snoRNAs. To explore the expression of snoRNAs, we sequenced intermediate-sized RNAs obtained from 12 different human tissues, and we showed that the expression of snoRNAs could be determined at much improved resolution, and for the first time, we were able to identify the differences in expression of snoRNAs with high sequence similarity, especially the clusters of snoRNAs playing a key role in Prader-Willi syndrome. Analysis of these data sets also revealed that many snoRNA loci give rise to various different isoforms, including longer RNAs originating from SNORD115 cluster and nontemplate additions of adenosines to snoRNA 3' ends. We further identified novel box C/D and H/ACA snoRNA candidates that have lower expression and less evolutionarily conserved relative to the currently annotated snoRNAs. Contrary to previous studies, sequencing of small RNAs from 12 different human tissues revealed that small RNAs derived from snoRNAs (sdRNAs) are highly variable in length. However, we observed that the highly abundant sdRNAs with specific length also originate from distinct positions relative to parent snoRNAs. Finally, we show that some sdRNAs with miRNA-like characteristics display tissue-specific expression. These findings suggest that snoRNAs are a dynamic group of non-coding RNAs with

diverse characteristics and physiological roles.

POSTER 17

EVALUATING THE EFFICIENCY AND REPRODUCIBILITY OF GENOTYPING BY SEQUENCING

Rust Turakulov, Jafar Jabbari, Gai McMichael, Paul Gooding

ABSTRACT
Genotyping by sequencing (GBS) is a sequencing-based method for the large scale discovery and genotyping of genetic polymorphisms. It is suitable for population studies, germplasm characterization, breeding, and trait mapping in diverse organisms. It is amenable to multiplexing making it high-throughput and cost-effective. GBS is based on fragmenting genomic DNA with restriction enzymes, followed by sequencing a library prepared from the small portion of the genome adjacent to the restriction sites. The AGRF has established a multiplex GBS protocol that uses two enzymes, resulting in longer reads and increased sequencing output. To complement the protocol, the AGRF has built an analysis pipeline based on Stacks (J. Catchen et al. 2013 Stacks: an analysis tool set for population genomics. Molecular Ecology. 22:3124-3140). Here we present the results of one study where libraries were made from identical control DNAs sourced from E. coli. In that experiment, 48 libraries were made from the same DNA source, sequenced and compared. The results looked at genotyping errors, batch effects and reproducibility in terms of the numbers of shared tags.

POSTER 18

QUANTIFICATION OF CELLULAR FEATURES USING NOVEL IMAGE ANALYSIS ALGORITHMS

Matloob Khushi and Jonathan W. Arthur

ABSTRACT
Digital microscopes are routinely used in laboratories to understand biological processes. Current technology makes it easy to automatically generate a very large number of images. Researchers thus require new methods to analyse the images precisely and quickly. Manual quantification of features in an image is subjective and can be prone to human error. Therefore, we have developed three novel algorithms to automatically quantify various commonly studied cellular features using MATLAB (MathWorks USA) language and tools. Algorithm-I identifies protein locations and their co-localisation stained in different colours: a common technique for determining the potential for two proteins to interact with each other. A graphical interface is provided to visualise and fine tune vari-ous parameters such as applying median or Wiener adaptive filtering to improve signal to noise ra-tio. Command-line mode of the script allows batch processing of all images in a directory. Users can also calculate statistical significance of the observed protein co-localisations against overlap by ran-dom chance by computing the P-value using the Student's t-test. Algorithm-II measures area, length, width, angles, and shape of stained DNA and the mitotic spindle in order to identify the features as-sociated with normal or diseased cells. The shape is reported by calculating the eccentricity of the feature, a measure of the degree of circularity or linearity. Algorithm-III measures the length of te-lomeres, as short telomere lengths are known to be associated with a number of diseases. These novel algorithms have enabled us to precisely, efficiently, and

automatically quantify cellular fea-tures for large numbers of images.

POSTER 19

NON-CODING MUTATIONS IN CANCER ALTER G-QUADRUPLEX STABILITY AND AFFECT ITS REGULATORY ROLE IN THE 5' UNTRANSLATED REGION OF MRNA

Mahdi Zeraati, Aaron L. Moye, Mark J. Cowley, Jason W. Wong, Tracy M. Bryan, Daniel U. Christ and Marcel E. Dinger

ABSTRACT
Substantial efforts have been made to characterize the cancer genome. The advent of next generation sequencing has enabled affordable and rapid large-scale sequencing of cancer genomes. The Cancer Genome Atlas (TCGA)1 and the International Cancer Genome Consortium (ICGC)2 are examples of large-scale cancer genomics projects to catalogue cancer-associated mutations. Extensive efforts have focused on characterizing mutations in protein-coding regions, which has improved the understanding of the pathogenicity of coding mutations. However, knowledge regarding the effect of non-coding mutations in cancer development is very limited. One possible effect of non-coding variations is in affecting secondary structures in regulatory regions, such as promoter and 5' untranslated region (5'UTR) of mRNA.

Guanine rich DNA and RNA sequences can fold into a non-canonical four-stranded secondary structures called G-quadruplexes (G-quads)3. RNA G-quads are computationally predicted to be prevalent in the 3' and 5' UTR of mRNAs. This observation strengthens the hypothesis that these motifs have critical regulatory roles in the posttranscriptional control of gene expression4.

Using TCGA and ICGC databases, we have found mutations in cancer patients that overlap G-quad coordinates in 5'UTRs. We have analyzed the effect of these mutations on the stability of G-quads using RNAfold software5 and showed that mutations could either destabilize or stabilize G-quads. We have validated the effect of some of these mutations by luciferase reporter assays and circular dichroism spectroscopy. Among the validated mutations is a recurrent mutation that has been reported in two patients with B-cell lymphoma and malignant lymphoma. This mutation destabilizes the G-quad in the 5'UTR of BCL2; which is an oncogene and overexpressed in lymphomas. Luciferase reporter assays showed that this mutation increases the translation of BCL2. Using a RNA G-quad stabilizing molecule, N-methyl mesoporphyrin IX (NMM), we showed that the destabilizing effect of this mutation is reversible. Our results demonstrate a potential role of a non-coding mutation in cancer and show that mutations that effect G-quad stability can be targeted, which presents opportunities for highly targeted therapies.

POSTER 20

SMALL RIBOSOMAL SUBUNIT PROFILING QUANTIFIES CONFORMATIONAL CHANGES IN INITIATING AND TERMINATING RIBOSOMES.

Stuart K. Archer, Nikolay E. Shirokikh, Thomas Preiss

ABSTRACT
A large fraction of variation in gene expression in eukaryotes is not accounted for by differences in mRNA abundance but rather by regulation of translation initiation, however we have an incomplete understanding of this complex process. Here we employ deep sequencing to profile nuclease footprints of the small ribosomal subunit, which is the first subunit to make

contact with the mRNA during initiation and compare these to footprints from translating complexes made up of both small and large ribosomal subunits in living cells. We observe stark differences in footprint size for small subunits before and after encountering the start codon, reflecting conformational changes of both mRNA exit and mRNA entry channels. This enabled us to quantify the relative abundances of initiation complexes at different stages of translation initiation, in vivo. Small subunit footprints were also identified on the termination codons of ORFs, allowing us to investigate post-termination events leading to ribosome recycling. These results confirm and expand on current structural models of translation initiation, and provide a framework to probe both generalities and transcript-specific variations in the translation initiation process.

POSTER 21

CANCER GENE-INTERACTION ANALYSIS USING A DATA-DRIVEN INVERSE COVARIANCE MATRIX APPROACH

Denis C. Bauer, Robert Dunne, Aidan O'Brien, William Wilson and Peter Molloy

ABSTRACT

Gene expression is tightly coordinated for normal biological processes such as cell division, proliferation and differentiation. Misregulation of these processes may lead to diseases like cancer. Patterns of gene expression can be studied by way of differential gene expression analysis or regulatory gene network comparisons. Recognizing the need for condition-specific regulatory networks, most recent approaches integrate expression data with known protein-protein interaction networks [1], thereby joining data driven analysis and databases of accumulated biological information.

Comparing these approaches, ours is data driven to a later stage, in that it models expression as well as gene-interaction by estimating the inverse covariance matrix. Our approach therefore, integrates data to achieve a richer data structure, and utilises expert data (KEGGpathways) for validation.

The high dimensionality of the problem has hampered its application in the past. We overcome this limitation by assuming that the inverse covariance matrix is sparse, and divide the problem into two parts; a) estimating the pattern of non-zero entries, and; b) estimating the entries given this template [2]. This produces a resulting data structure containing genes that are differentially expressed or differentially connected, as well as housekeeping genes that are observed to be active in the analysed data but are not related to the experimental condition.

We applied this methodology to identify the abnormal gene-interactions in tumor samples containing a point mutation in the K-Ras gene (n=65 compared to the wild type n=75). When applying traditional methods, OLFM4 is identified as differentially expressed in colon cancer studies, however, our method identifies 133 genes in the olfactory transduction pathway to be differentially interacting. Separate to their canonical function, olfactory receptors have been demonstrated to promote cancer cell invasiveness and metastasis emergence [3]. This phenotype is also consistent with the disruption of the Ras protein, which plays an important role in the propagation of early signals from the cell membrane into the nucleus, as well as the 68 other genes found to be differentially interacting in the cytokine-cytokine receptor interaction pathway. Our method also identifies differentially interacting genes in known cancer pathways such as PI3K-Akt and MAPK.

POSTER 22

FUNCTIONALLY CHARACTERIZING EVERY SINGLE MUTATION IN YOUR FAVORITE GENE

Alan F Rubin, Stanley Fields, Terence P Speed, Douglas M Fowler

ABSTRACT

Although high-throughput DNA sequencing has rapidly expanded catalogues of normal and disease-associated variation, the functional consequences of most mutations are unknown. In deep mutational scanning, selection for protein function applied to a library of protein variants is combined with high- throughput DNA sequencing, allowing direct measurement of the activity of hundreds of thousands of variants of the protein easily and cheaply. This approach helps to bridge the gap between variant identification and interpretation, enabling researchers to elucidate sequence-function relationships at high resolution. The resulting data can be used in a variety of contexts, from aiding the assessment of clinical variants to guiding protein engineering. Despite the growing popularity of deep mutational scanning, there are few formal statistical methods available to help analyze these complex datasets. Here we present a novel method for assigning functional scores and statistical significance to all variants in a deep mutational scanning dataset based on weighted regression. These methods are implemented as part of Enrich 2, a user-friendly software package that makes the initial data analysis accessible to experimental biologists while providing an extensible framework for bioinformaticians manipulating these large datasets. For illustration, we show the results of applying this method to deep mutational scans of diverse targets, including BRCA1 and the WW protein-binding domain of YAP65.

POSTER 23

PROMISCUOUS DNA-BINDING OF A MUTANT ZINC FINGER PROTEIN CORRUPTS THE TRANSCRIPTOME AND DERAILS ERYTHROID DIFFERENTIATION

Andrew C. Perkins, Kevin R. Gillinder, Melissa Ilsley, Danitza Nébo, Ravi Sachidanandam, Mathieu Lajoie, Graham W. Magor, Michael R. Tallack, Timothy Bailey, Michael J. Landsberg, Joel Mackay, Joel H. Graber, Luanne L. Peters and James J. Bieker

ABSTRACT

The rules of engagement between zinc finger transcription factors and DNA have been partly defined by in vitro DNA-binding and structural studies, but less is known about how these rules apply in vivo. Here we demonstrate how a missense mutation in the second zinc finger of Krüppel-like factor-1 (KLF1-E339D) leads to degenerate DNA-binding specificity in vivo, resulting in ectopic transcription and anemia in the Nan mouse model. We employed ChIP-seq and 4sU-RNA-seq (Figure) to identify the direct transcriptional consequences of aberrant DNA-binding events genome wide. We expressed wild type and mutant KLF1 zinc fingers in bacteria as GST fusion proteins, purified these and used EMSA and surface plasmon residence to determine the affinities for various DNA-binding motifs in vitro. We have discovered a novel biochemical mechanism for disease which also has implications for zinc finger nuclease design and off target effects.

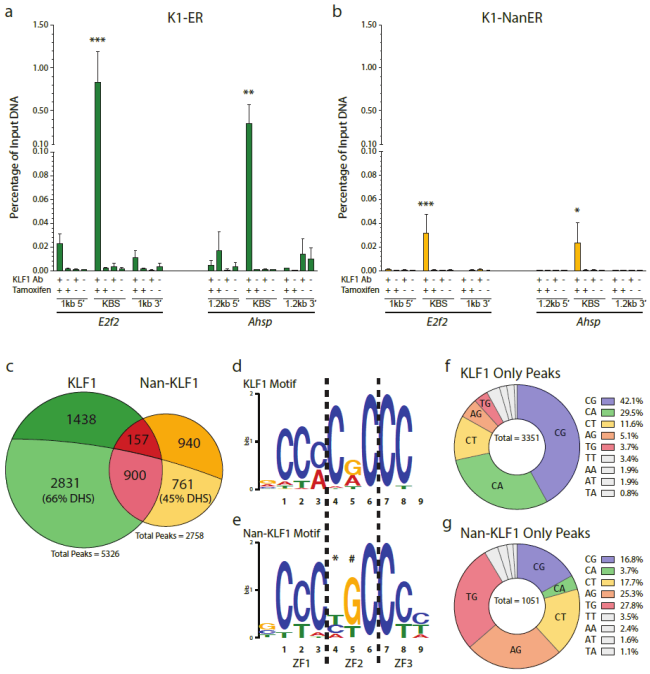
POSTER 24

CHARACTERISATION OF NOVEL HYPOMORPHIC AND NULL MUTATIONS IN KLF1 DERIVED FROM A GENETIC SCREEN FOR MODIFIERS OF A-GLOBIN TRANSGENE VARIEGATION

Andrew C. Perkins, Stephen Huang, Anabel Sorolla, Michael R. Tallack, Harald Oey, Sarah K Harten, Lucia Clemens-Daxinger, Graham W. Magor, Alex N Combes, Melissa Ilsley, Kevin Gillinder and Emma Whitelaw

ABSTRACT

Position-effect variegation of transgene expression is sensitive to the chromatin state. We previously reported a forward genetic screen in mice carrying a variegated a-globin GFP transgene to find novel genes encoding epigenetic regulators. We named the phenovariant strains Mommes for Modifiers of murine metastable epi-alleles. Here we report positional cloning of mutations in two Momme strains which result in suppression of variegation; i.e. an increased percentage of GFP+ circulating red blood cells. Both strains harbour point mutations in the erythroid specific transcription factor, Klf1. One (D11) generates a stop codon in the zinc finger domain. D11 homozygous mice die in utero of anaemia at 14.5DPC. The other (D45) generates an amino acid transversion (H350R) within a conserved linker between zinc fingers two and three. Homozygous MommeD45 mice have mild compensated microcytic anaemia which models the phenotype in a recently described human family. Mice Carrying the H350R mutation were interbred with Klf1+/- mice. Klf1H350R/- mice have severe perinatal haemolytic anaemia and marked splenomegaly. Furthermore blood haemoglobin content, haematocrit and red blood cell size (MCV) were significantly reduced in Klf1H350R/- mice compared to wildtype and D45 homozygous offspring of the same age. Analysis of Klf1H350R/- by flow cytometry showed an increase in circulating immature red blood cells. In the bone marrow, a lack of mature red blood cells was observed. Flow cytometric analysis of the spleen from Klf1H350R/- animals revealed an expansion of erythroid cells and a relative reduction in B and T Cells. Electromobility gel shifts assays (EMSA) of a recombinant Klf1 zinc finger protein with the H350R mutation showed normal binding to the b-globin promoter sequence but weak binding to the Alas2 intronic enhancer site. Furthermore b-globin gene expression was near normal whereas expression of other known Klf1 target genes was decreased. We will discuss how H350R disrupts function from ChIP-seq and RNA-seq in primary fetal liver tissue. Previous studies of the linkers in C2H2 zinc finger transcription factors have revealed their necessity as structural and regulatory components for the C2H2 class of transcription factors. Our results show that the second linker of Klf1 has a role in maintaining the integrity of Klf1 function (at a subset of Klf1-occupied sites,) and does not act just as a spacer for the zinc fingers.



TUESDAY 13 October 2015

POSTER 25

ELUCIDATING THE FUNCTION OF THE EVX1 PROTEIN CODING/LNCRNA SENSE-ANTISENSE LOCUS DURING GASTRULATION

Andrew C. Perkins, Charles Bell, Kevin Gillinder, Graham Magor, Lorena di Lisio, Seth Cheetham, Pierre Tangermann, Paulo Amaral3, Anton Karlsbeek, Michael Tallack, John Mattick and Marcel Dinger

ABSTRACT
A number of recent studies demonstrate the bidirectional transcription is a pervasive phenomenon at mammalian promoters. In particular, long non-coding RNAs are commonly transcribed antisense to highly transcribed protein coding genes. Whether or not these lncRNAs have a function other than regulation of the associated protein coding gene remains a topic of debate. At the Evx1 locus, the homeodomain protein EVX1 and the lncRNA, Evx1as, are spatially and temporally co-expressed from a bidirectional promoter during gastrulation. Homologs of the transcription factor EVX1 have previously been shown to regulate anterior-posterior patterning, however the direct and indirect targets of EVX1 are unknown.

To elucidate the potential function of EVX1 and Evx1as during mouse gastrulation, we performed extensive CRISPR-Cas9 mediated manipulation of the Evx1 locus in mouse embryonic stem cells (mESCs). As hypothesized, loss-of-function gene editing of Evx1 resulted in an anterior-posterior patterning during gastrulation defect as determined by mRNA-seq. EVX1 KO resulted in an increase in expression of anterior streak derivatives, such as Sox17, Cer1 and Foxa2, along with a corresponding decrease in expression of posterior streak derivatives, such as Mixl1, Mesp1 and Hoxa1/2. EVX1 is hypothesized to function primarily as a repressor, but the direct targets are unknown. We have successfully used CRISPR-Cas9 to V5 tag the endogenous EVX1 protein to perform ChIP-seq. We are currently in the process of optimizing the ChIPseq protocol for the V5 antibody and will report on our progress.

To determine whether Evx1as has a function beyond that of Evx1, we used CRISPR-Cas9 to remove the shared promoter region of Evx1 and Evx1as. Although removal of the promoter almost completely ablated Evx1 expression, it resulted in only 50% knockdown of the Evx1as transcript. We subsequently removed the shared promoter and the majority of Evx1as transcript (2.3kb). By qPCR we were unable to observe a phenotype in the Evx1/Evx1as KO beyond the phenotype observed in the Evx1 KO. Therefore Evx1as does not function in trans. This does not however rule out the possibility that Evx1as may function in cis to regulate Evx1. However, we believe that Evx1as most likely represents functionally inconsequential transcription from a bidirectional promoter.

POSTER 26

TWO ORTHOGONAL PROCESSES UNDERLIE SURVIVAL OF PATIENTS WITH RESECTED PANCREATIC CANCER: A SUCCESSFUL APPLICATION OF EXPRESSION DECONVOLUTION

Mark Pinese, Mark J Cowley, and Andrew V Biankin, for the Australian Pancreatic Cancer Genome Initiative

ABSTRACT
Identifying the biological processes that determine cancer patient survival remains a

substantial challenge, particularly in highly heterogeneous tumours like pancreatic ductal adenocarcinoma. Gene expression measurements are an attractive starting point when searching for processes active in a cell, as they integrate diverse information on genetic and epigenetic status, metabolic flux, and signalling activity. However, this mixing of inputs makes it very challenging to deconvolve a transcriptional state into its component biological processes, and provide a simple biological interpretation of a complex transcriptional mix.

Methods for expression deconvolution based on the non-negative matrix factorization (NMF) have recently achieved popularity, but are almost universally used in modes that induce artificial clustering in the data, and so may not reflect the true underlying expression dynamics. There is little guidance on how to best apply NMF techniques for expression deconvolution, particularly when searching for transcriptional programs that are associated with a covariate, such as patient survival.

We describe a successful application of NMF to identify two orthogonal signatures of survival in pancreatic cancer, that correlate closely with the discrete processes of proliferation and the epithelial-to-mesenchymal transition. Both signatures validate in independent cohorts, and are also prognostic in other solid cancers. The novelty of our approach is its use of a sparsity constraint on the NMF, that does not promote artificial sample clusters, and produces decompositions that are more reflective of smooth activation of transcriptional programs. The approach we present can form a general template for expression deconvolution that is particularly valuable when small, biologically-simple expression programs that are associated with a covariate are desired.

POSTER 27

DISCOVERING GENOMIC HOTSPOTS FOR COLUMNAR GROWTH IN MALUS X DOMESTICA WITH GBS

Cecilia H. Deng, Wirsich M, Brauksiepe B, Hilario E, Schröder M-B, Chagné D and Braun P

ABSTRACT

Columnar fruit trees, also known as urban fruit trees, are bred to grow upright in a narrow column. These types of trees bear fruit on the main stem with short spurs, rather than growing long side branches. Their elegant shape and space-saving growth pattern make them suitable for landscaping in small gardens or patios in urban areas with limited space. The first series of columnar apples were released in 1989 (the “Ballerina” series), but further breeding activities have resulted in better quality cultivars. Previous research shows a region on the Malus chromosome 10 (Co region) plays an important role in generating the columnar tree phenotype compared to normal growth apple trees, due to the insertion of the Ty3/Gypsy retrotransposon “Gypsy-44” into the transposon “Gypsy-33”. Our GWAS (genome-wide association study) experiment with GBS (genotyping-by-sequencing) of more than 200 apple trees not only confirmed a high association between the columnar phenotype and the genomic regions on chromosome 10, but also revealed a genomic hotspot on chromosome 12. QTL (quantitative trait locus) mapping and genetic map construction will improve our understanding of the genomic nature of the columnar growth in apple. Comparative genomics of the regions of interest may also help our research of columnar growth in other fruit crops in the Rosaceae family, such as pear and peach.

POSTER 28

GENE ONTOLOGY ENRICHMENT ANALYSIS FOR GENE SUBSETS OF DISTINCTIVE FUNCTION

Denis C. Bauer, Firoz Anwar, William Wilson, Jason Ross, Peter Molloy

ABSTRACT

Gene Ontology (GO) enrichment analysis can provide insight into the underlying biology function common to a list of interesting genes, e.g. differentially expressed (DE) genes. To determine whether a GO term is over/under-representated in this set, one needs to compare the frequency of this term in a set of genes considered baseline (background). The choice and size of the background can influence the identified terms and their significance, potentially resulting in misleading biological interpretation. This problem is specifically pronounced in situations where enrichment is performed in an already very distinctive subset of the genome, e.g. mitochondrial proteins.

We therefore propose a new approach for selecting the background and pruning the GO term tree for the analysis of gene subsets with distinctive function. To compare our method against traditional approaches, we perform GO enrichment analysis using goseq [1] on 93 differentially expressed (DE) mitochondrial genes (mitochondrial protein compendium, MitoCarta [2]) between visceral and subcutaneous adipocyte cells in human (3 matched biological replicates) using different background and pruning approaches.

Performing the GO analysis on the 93 DE genes using the full set of GO terms and all non differentially expressed genes in the genome as background (57,818) we obtain 161 significant terms. However, the most significant terms cover broad mitochondrial function. For example, the top three terms are the cellular compartment terms ‘intracellular’, ‘cytoplasm’, ‘mitochondrion’ and are hence not capturing the regulatory difference of the mitochondrial genome between the different fat types. To focus on mitochondrial function, we limit the background to only cover MitoCarta genes (1041), however this results in no significant terms being identified. We know that mitochondria play a crucial role in adipogenesis and hence the two tissues are likely to have different function. This highlights the need for constructing a purpose-built background.

Starting from the GO terms associated with MitoCarta genes, we include all genes that share these GO terms as the background, which reveals 163 enriched terms. Extending this approach, we also remove the GO terms not associated with MitoCarta genes as they are not able to reach significance and impede the multiple testing correction. This final approach of tailored background and pruned GO tree results in 226 enriched. These new terms where particularly enriched in GO categories containing less than 500 genes. These considerably more specific GO terms relate to relevant biological processes such as beta-oxidation of fatty acids and acetyl-CoA metabolism. This finding suggests that by constructing a purpose-built background set of genes and a pruned GO tree we are able to identify some fundamental difference in the catabolism of fats between visceral and subcutaneous adipocytes.

POSTER 29

THE EFFECT OF ADAR3 DEFICIENCY ON RNA EDITING IN MOUSE HIPPOCAMPUS

Dessislava Mladenova, Lotta Avesson, Guy Barry, Mark Pinese, Bryce Vissel and John S. Mattick

ABSTRACT

RNA editing refers to the deamination of adenosines or cytosines to alter the sequence of RNA, presumably in response to environmental cues, and is most active in the brain. RNA editing may have played an important role in cognitive evolution, as it has expanded greatly in mammalian and especially primate lineages. Adenosine to inosine (A-to-I) editing is catalyzed by three members of adenosine deaminase acting on RNA (ADAR) protein family. Dysregulation of A-to-I editing has been associated with a number of neurological and neurodegenerative disorders and polymorphisms of the vertebrate-specific ADAR3 are strongly associated with extreme old age.

ADAR3 catalytic deaminase activity has not been detected in vitro, and ADAR3 is thought to act by blocking the action of ADAR1 and/or ADAR2. Here we asked how ADAR3 deficiency affects RNA editing in the mouse hippocampus. We generated Adar3 knockout mice and performed RNA sequencing from mouse hippocampal tissue.

On average 49.8 million reads per mouse were obtained. 800 A-to-I(G) sites met the criteria of sufficient coverage (>20 reads) and an average editing level of at least 5% per sample. Additional stringent criteria were applied to obtain 282 high confidence candidate editing sites, the majority of which (61.7%) occurred in untranslated regions of mRNAs (UTRs), while only 13 sites were located in protein-coding sequences. There was no global change in the editing level of ADAR3-deficient compared to control mice; however there were pronounced differences in the editing frequencies of individual sites.

16 (5.7%) of the candidate editing sites showed statistically significant differences in editing level between the Adar3 wild type and knockout mice, most of which were located in the UTRs of protein-coding genes in repetitive retroelement sequences known as Short Interspersed Nuclear Elements (SINEs). The functional consequence of RNA editing in UTRs is not known, although reports have suggested effects on transcript stability and translation. Nine of these sites (56%) were within predicted miRNA seed binding sites. Six of the sites showing significant changes in editing are located in genes implicated in neurological disorders. ADAR3 deficiency resulted in a significant reduction of the editing level of 13 out of the 16 sites, indicating that ADAR3 can enhance the editing frequency of specific sites in vivo.

In conclusion this is the first report indicating that ADAR3 can modulate the RNA editing levels of specific genes in vivo.

POSTER 30

HARNESSING THE POWER OF SERUM MICRORNAS TO PREDICT SURGICAL OUTCOME FOR WOMEN WITH OVARIAN CANCER

Jaynish S Shah, Gregory B Gard, Jean Yee Yang, Patsy Soon4 and Deborah J Marsh1

ABSTRACT

Introduction: Optimal cytoreduction, complete surgical rem¬oval of the tumour, is one of the most important prognostic factors for women with ovarian cancer (OC), yet remains challenging to predict prior to surgery. A molecular tool to assist in this prediction, in combination with other clinical factors, could help plan surgery and decide the best treatment options for individual patients. Circulating short RNAs, called

microRNAs, have been referred to as a 'gold mine' of non-invasive biomarkers due to ease of access, remarkable stability and disease-specific expression.

Aims: (1) To test if circulating microRNAs could separate women with OC from healthy women and, further, predict their surgical outcome. (2) To compare the performance of CA-125, a serum protein used for the diagnosis of OC, with candidate microRNAs for both purposes.

Materials and Methods: The study was conducted in training and test sets containing 15 healthy, 15 optimally and 13 suboptimally cytoreduced (>10 mm) OC patients each. Pre-surgical sera were sourced from the Kolling's Tumour Bank. Expression of 167 microRNAs was measured using the Serum/Plasma focus panel (Exiqon) in the training set. A total of 48 microRNAs including promising candidates, endogenous reference microRNAs and various controls were validated using the Custom Pick-&-Mix panel (Exiqon) in the test set. Levels of the serum biomarker CA-125 were measured by sandwich ELISA (R&D Systems). Data were analysed using GenEx software (v 6.0, Exiqon) and the statistical language R using 'limma', 'ROCR' and 'ClassifyR' packages.

Results and Conclusions: Predictive features and their parameters were estimated from the training set data using machine learning algorithms DLDA and SVM, and their performance was measured on the test set. In addition, robust performance measures were calculated from the pooled data using 100-times 4-fold cross validation. Four microRNAs were differentially expressed in the sera of healthy women compared to OC patients at 5% false discovery rate (FDR), but their performance was lower than CA-125. Two microRNAs were elevated by more than 1.5-fold in suboptimally compared to optimally cytoreduced patients at 5% FDR. Both microRNAs individually outperformed CA-125 (AUC: 0.73 or 0.77 vs 0.69) in predicting surgical outcome. The addition of CA-125 to both microRNAs increased the AUC to 0.81 with classification accuracy of 77%. In conclusion, our data suggest that a combination of microRNAs and CA-125 could predict surgical outcome for women with OC.

POSTER 31

APPLICATION OF GENOME WIDE ANALYSIS IN DEVELOPMENTAL EYE DISEASE

Ivan Prokudin, Anson Cheng, Rebecca Greenlees and Robyn V. Jamieson

ABSTRACT

Developmental eye diseases cause severe visual abnormalities and include microphthalmia, coloboma, anophthalmia, anterior segment dysgenesis and cataracts. A number of disease genes including SOX2, OTX2, CHX10, BMP4 and RAX, are known to contribute to these conditions, whereas the majority of disease genes are yet to be revealed. Identification of causative genetic factors is often hampered by variable penetrance and expression of these conditions which may be linked to the multigenic nature of the diseases and presence of genetic modifiers.

Various signalling pathways including WNT, BMP, Retinoic Acid, Notch, Hedgehog and others are critical for embryonic eye development. Many different genes play important roles in these signalling pathways. We propose delineation of the components of these signalling pathways and other important components in developmental eye disease in a genome-wide approach for interrogation of genetic causes in these conditions.

We applied whole exome sequencing in a cohort of over 25 patients displaying

developmental eye disease. Subsequent analyses were combined with data obtained from 123 similarly affected patients from UK10k project (http://www.uk10k.org).

Bioinformatic analysis revealed a cluster of genes enriched in these conditions. Multi-genic inheritance pattern was observed for at least 2 familial cases.

Subsequent functional analyses to interrogate the ability of identified mutations to alter expression of the corresponding pathways were performed. Mutations were cloned in and subjected to luciferase assay with the corresponding reporter system.

Our findings demonstrate a key approach in hypomorphic of novel critical genetic factors in developmental eye diseases.

POSTER 32

DISENTANGLING GENETICS AND METHYLATION IN THE MAJOR HISTOCOMPATIBILITY COMPLEX

Jovana Maksimovic, Damjan Vukcevic, Justine Ellis, Stephen Leslie, Alicia Oshlack

ABSTRACT

Many GWAS of autoimmune diseases have identified SNP associations in the major histocompatibility complex (MHC) region, particularly within and proximal to the human leukocyte antigen (HLA) genes. Certain HLA alleles have also been shown to be associated with various autoimmune diseases, such as multiple sclerosis (MS). However, many individuals who harbour known risk alleles do not develop autoimmune disease, suggesting that the genetic risk is modulated by other factors.

Epigenetic marks such as methylation might play a role in modifying genetic risk; although, unlike DNA, methylation varies substantially between cell types. This is problematic if the affected tissue is not accessible or samples are from a mixed cell population, such as blood. Thus, even if methylation contributes to the disease process, the signal may be absent in unaffected tissue or is diluted in a cell mixture and thus difficult to detect.

To understand the effect of methylation on disease in a complex region such as the MHC, the relationship between the genetics, cell-type specific methylation and methylation differences between individuals need to be explored. Using cell-sorted, 450k methylation data from the blood of 6 individuals we show that within the MHC there is a subset of CpGs that are highly cell-type specific, whilst another subset varies amongst individuals but is relatively uniform between cell types, presumably due to different genetic backgrounds between individuals. A recently published set of MHC CpGs associated with MS falls almost exclusively in the subset of CpGs that vary between individuals in the cell sorted data. We have obtained a cohort of individuals with both 450k methylation array data and imputed HLA alleles to elucidate whether methylation differences between individuals are completely associated with certain HLA haplotypes or whether there is within-haplotype variability that may moderate disease risk.

POSTER 33

A NOVEL VARIABLE SHORT TANDEM REPEAT IN THE UPSTREAM REGULATORY REGION OF THE ESTROGEN-INDUCED GENE EIG121 IS POTENTIALLY INVOLVED IN CANCER RISK

Katherine A. Bolton, Elizabeth G. Holliday, Mark McEvoy, John Attia, Anthony Proietto, Geoffrey Otton, Nikola A. Bowden, Jason P. Ross, Kelly A. Avery-Kiejda and Rodney J. Scott

ABSTRACT

The estrogen-induced gene 121 (EIG121) encodes a transmembrane protein that has been associated with endometrial, pancreatic and gastric cancers. In genome-wide investigations, using the recently created Short Tandem Repeats in Regulatory Regions Table (STaRRRT)[1], we found that EIG121 contains a short tandem repeat (STR) located in the upstream regulatory region. Polymorphic STRs can alter levels of gene expression affecting transcription and hence protein function. This can have major consequences for disease risk and severity.

The aim of this study was to analyse the variability of the EIG121 STR and to determine any association between its length and the risk of developing endometrial or breast cancer.

In this study, DNA from 204 endometrial cancer patients, 206 breast cancer patients and 220 healthy controls was analysed. STR length was determined by PCR, fragment analysis and sequencing. Statistical analysis included Mann Whitney rank sum tests, Cox proportional hazard regression and Kaplan-Meier analysis.

We found this repeat to be highly variable. Statistical analysis revealed a trend towards an association between lower age at diagnosis for endometrial cancer and length of the EIG121 STR short allele when adjusted for BMI (HR = 1.055, p = 0.019). A longer short allele is correlated with earlier age at diagnosis for endometrial cancer with the median difference in age at diagnosis for endometrial cancer being 6 years when length of the STR is dichotomised around 37 repeats (p = 0.0085). No association was identified between the length of this STR and breast cancer risk (p = 0.982) or age at diagnosis for breast cancer (p = 0.302).

We have uncovered a highly polymorphic STR in the upstream regulatory region of EIG121 which appears to be associated with a lower age at diagnosis for endometrial cancer. This novel variable STR could be responsible for altered EIG121 expression and have implications for disease risk in endometrial and other cancers.

POSTER 34

DELETERIOUS PASSENGER MUTATIONS AS A MARKER FOR PROGRESSION TOWARDS LIVER CANCER

Magdalena A. Budzinska, Thomas Tu, Fabio Luciani and Nicholas A. Shackel

ABSTRACT

Hepatocellular carcinoma (HCC) is associated with hundreds of passenger mutations, which have generally been ignored but can alter cell survival and thus may act as marker for cancer progression. A previous study has shown that deleterious passenger mutations (DPMs) occur frequently and accumulate in tumours. Therefore, we aim to detect DPMs in liver disease progression and hypothesise that DPMs accumulate in hepatocytes in precancerous conditions leading up to HCC.

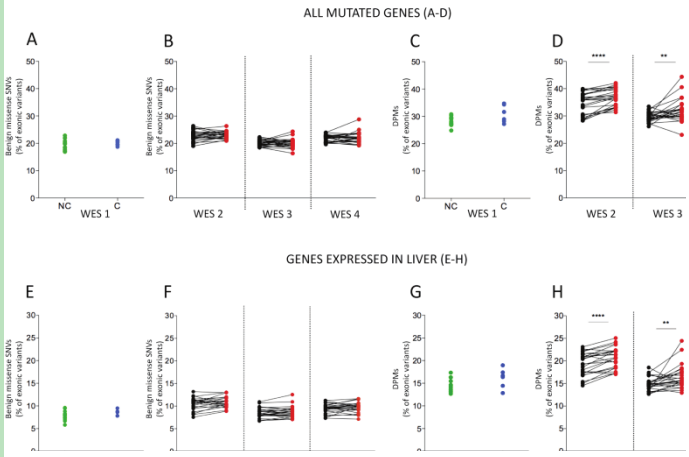
We have performed whole exome sequencing of pre-cancerous liver tissues: 12 patients with limited level of liver injury and 6 HCV-positive patients with liver

cirrhosis. We have also analysed 3 publically available datasets of paired HCC and surrounding non-tumour liver (total of 148 samples). Further, we determined whether these DPMs were likely to alter genes expressed in the hepatocytes by filtering out those genes not detected in liver tissue by microarray analysis.

Increasing numbers of DPMs were observed in patients with progressively worse liver disease leading up to HCC (Figure 1). The pattern of observed DPMs in HCC is consistent over multiple algorithms for scoring deleterious effect, in multiple aetiologies of HCC, and in multiple datasets. This strongly suggests that DPM accumulation is a general mechanism in tumour evolution. Moreover, precancerous alterations were found in non-tumour tissue, despite being used in prior studies as normal paired controls.

In summary, we have shown that DPM accumulation could act as a potential biomarker for risk towards HCC development without having first to identify rare and unknown HCC driver mutations.

Figure 1. Increased proportion of DPMs is associated with HCC compared to surrounding non-tumour tissue.



POSTER 35

LOSS-OF-FUNCTION GERMLINE FGFR1 MUTATION IDENTIFIED IN A PATIENT WITH PROLACTINOMA

Mark J McCabe, Anthony R Lam, Tanya J Thompson, Ann I McCormack and Marcel E Dinger

ABSTRACT

Background: Familial pituitary tumours are thought to be rare, occurring in approximately 5% of pituitary tumour cases (Tichomirowa et al. 2011). Germline mutations in MEN1, AIP, p27 and PRKAR1A are known to be involved (Elston et al. 2009), however recently SDHx and GPR101 have been added to the expanding list of genes implicated in the hereditary predisposition to pituitary tumours (Gill et al. 2014; Trivellin et al. 2014). Utilising next generation sequencing technology, we have developed a 300+ gene panel incorporating genes known to be involved in pituitary tumour pathogenesis, pituitary embryogenesis and broad cancer genes. We have commenced screening familial pituitary and young sporadic pituitary tumour cases with this panel. Using this approach, we identified a rare missense, heterozygous variant in fibroblast growth factor receptor 1 (FGFR1) (c.485A>C; p.D162A), in a male with a childhood-onset prolactinoma whose daughter has congenital hypopituitarism. Germline mutations in FGFR1 have been implicated in congenital hypopituitarism.

Aim: To determine whether the identified FGFR1 variant p.D162A is functionally deleterious using an established culture model, in vitro.

Method: Rat L6-myoblasts which contain very low levels of endogenous FGF receptors and ligands, were transfected with wild-type and mutant FGFR1 pcmv-SPORT6 expression vectors along with a luciferase

reporter driven by 6 tandem repeats of the osteoblast-specific core binding sequences of the FGF responsive osteocalcin promoter (Kim et al. 2003). Cells were treated with recombinant human FGF2 ligand and then lysed for luciferase assay 24 hours later. Treatments were conducted in triplicate and cultures repeated three times.

Results: FGFR1 [p.D162A] variant exhibited a 40% reduced function ($p<0.001$) compared to wildtype.

Conclusion: Using our custom pan-cancer gene screening panel, we have identified a loss-of-function mutation in FGFR1 in a patient with a pituitary tumour. Identification of the same mutation in the daughter and in other families may also implicate FGFR1 in the hereditary predisposition to pituitary tumours.

POSTER 36

SIMULTANEOUS "MULTI-OMIC" MEASUREMENT OF GENE FUSIONS, MRNA AND PROTEINS AT 800-PLEX USING SINGLE-MOLECULE OPTICAL BARCODES

Michael Rhodes

ABSTRACT

Both the ENCODE and TCGA projects showcased the value of quantifying multiple biomarker classes (DNA, RNA, protein) from cancer tumor samples, providing a much broader view of the underlying cancer-biology. Combining multiple data types together into a single correlated analysis, however, is adversely effected by the drastically different methodologies utilized for measurement (i.e., the "detection harmonization" problem). For example, the fluorescence signal intensity obtained from a camera imaging a protein array (e.g., RPPA) is very difficult to correlate directly with an RNA-Seq count of a clonally amplified, cDNA-converted, mRNA molecule. New developments in multiple biomarker-class optical barcode counting significantly reduce this problem. Recent work from the Weissleder-lab [1] has shown how optical barcode technology can be utilized for multiplexed digital counting of proteins, and be combined with simultaneous digital counting of nucleic-acids on a single platform.

In this study we describe single-molecule digital counting of mRNA, proteins, and gene-fusions in a single simultaneous reaction using a few thousand cells as input. Cells were fixed, permeabilized, and then profiled using: (1) PanCancer Pathway Panel (770 mRNAs associated with pathways linked to key driver mutations) (2) PanCancer Immune Profiling Panel (770 mRNAs associated with immune response) (3) up to 30 key cancer protein targets (+/- phosphorylation) and (4) multiple gene-fusions. The current assay is configured to allow "mixing-and-matching" of different biomarker-classes up to a total of 800-plex in a single reaction. All data collected in this manner are completely harmonized: within the same field-of-view of the detection microscope (nCounter system) optical barcodes associated with each biomarker class are simultaneously counted, while the software keeps track of which barcodes originate from DNA, RNA, and Protein. Protein phosphorylation-state changes measured by barcodes were also correlated with spatially resolved fluorescent immunohistochemistry images of the same cells.

POSTER 37

WILD WINE: METAGENOMIC ANALYSIS OF MICROBIAL COMMUNITIES DURING WINE FERMENTATION.

Peter Sternes, Danna Li, Darek R. Kutyna, and Anthony R. Borneman

ABSTRACT

Wine is a complex beverage that is comprised of thousands of metabolites that are produced through the action of yeasts and bacteria in fermenting grape must. To ensure a robust and reliable fermentation, most commercial wines are now produced through the inoculation of freshly crushed grapes with large amounts of the major wine yeast Saccharomyces cerevisiae. However, there is a growing trend towards the use of classical, uninoculated or "wild" fermentations in which only those yeasts and bacteria that are naturally associated with the vineyard or winery perform the fermentation. This generally results in a far more complex progression of non-Saccharomyces fungal species, with S. cerevisiae only becoming dominant much later in the fermentation process. The varied metabolic contributions of these non-Saccharomyces species have been shown to impart desirable taste and aroma attributes to wild ferments when compared to their inoculated counterparts. Accordingly, it is generally believed that differences in these resident microflora between vineyards and wineries play a key role in defining unique regional expression of wine characteristics.

In order the map the microflora of spontaneous fermentation, metagenomic techniques have been used to monitor the progression of fungal species during a collection of wild fermentations from around Australia. Both amplicon-based ITS phylotyping and shotgun metagenomics were used to assess community structures, with the isolation, sequencing and de novo assembly of individual strains of the dominant wine-associated species also being performed in order to aid the analysis.

Initial results support the view that uninoculated ferments begin with a diverse ecosystem of fungal species, but converge on the wine yeast S. cerevisiae as the ferment progresses. Notable differences between regions, vineyards and wineries were also apparent and these can be broadly defined by the resulting microbial composition of the wild ferments.

POSTER 38

HIGH QUALITY RNA ISOLATION FROM RAT SPINAL CORD MOTOR NEURONS USING LASER CAPTURE MICRODISSECTION

Prachi Mehta and Renée Morris

ABSTRACT

Objective: To use a Laser Capture Microdissection (LCM) system for isolating RNA from motor neuron cell bodies in a rat model of spinal cord injury.

Background: Spinal cord motor neurons play a central role in bridging the connection between the brain and the skeletal muscles. Information regarding the fate of motor neurons below a spinal cord injury (SCI) that have lost their supraspinal input is thus essential to understand the pathophysiology of SCI. As motor neurons represent less than 10% of the total cell population in the spinal cord, the transcriptional profile of motor neurons below a transection cannot be characterized from spinal cord homogenates. A laser capture approach is thus ideal for analyzing the mRNA profile in these neurons. Here, we describe the protocol, optimized in our laboratory, for identification and efficient capture of enriched populations of motor neurons by LCM system. This protocol preserves the

RNA integrity (RIN) of the specimens by rapidly freezing spinal cord sections, thus avoiding RNA damage by endogenous and exogenous RNases.

Methods: The rats were anesthetized by intraperitoneal (ip) injection of Euthal (~0.7ml intraperitoneal for 250g rat) and perfused with either only 0.1M PBS or 2% PFA & PBS for about 2 minutes. Segments C2-C3/C4-C5 of the cervical spinal cord were dissected out, rinsed for 10 seconds in RNase free water and placed in a cryomold filled with O.C.T.. The mold was then placed in a shallow tray containing 2-methylbutane pre-cooled with liquid nitrogen to fast freeze the spinal cord segments to avoid RNA degradation. The O.C.T embedded block was stored at -80°C or immediately sectioned to produce 50 µm sections on RNase-free slides. The tissue sections were then stained with Azure B to identify the motor neurons. LCM system (PALM Microbeam, Carl Zeiss) was subsequently used to identify and capture the stained motor neurons directly in the cap of a small microfuge tube containing 30µl guanidine thiocyanate lysis buffer. RNA was isolated using an RNeasy Micro Kit (Qiagen) according to the protocol provided for LCM tissue. RNA integrity (RIN) was determined with 2µl sample on a capillary electrophoresis microfluidics chip (Agilent Bioanlyser 2100). The entire procedure was carried out under RNase-free conditions. In addition, to identify and confirm that the collected cells were motor neurons, we performed antibody staining with anti-Chat antibody (Millipore AB144p). We performed an RT-PCR analysis to confirm the presence of microdissected transcripts as an additional RNA quality control. cDNA was synthesised using SuperScript III First Strand Synthesis System (Invitrogen, Life Technologies). We examined expression of transcripts for GAPDH, a common reference gene. Total RNA from spinal cord homogenate served as a positive control.

Results: The procedure described above produced good quality RNA from fresh as well as PFA treated samples, with a RIN above 7 from 800-1200 spinal cord motor neurons for C2-C3 and C4-C5 segments by LCM technique. Rapidly excising and freezing the spinal cord segments maintained the RNA integrity. Real-time or quantitative PCR (qPCR) using RNA isolated from small populations of cells can be challenging, due to lack of sensitivity and reproducibility. In this report, we demonstrate that motor neurons isolated by LCM produce amplified cDNA from as little as 5 ng of RNA.

Conclusions: We conclude that LCM is an ideal system for the identification and isolation of motor neuron cell bodies to generate intact and high quality RNA while preserving their morphology. This system is therefore well suited for downstream quantitative PCR studies for gene expression analysis. In the spinal cord, such preparation from motor neurons by LCM will provide valuable tools to advance our understanding of the molecular mechanisms in SCI as well as in many neurologic and neurodegenerative diseases.

POSTER 39

IMPACT OF GADOLINIUM OXIDE NANOPARTICLES ON VIABILITY OF HUMAN LIVER-DERIVED CELL LINE

Saad Alkahtani, Daoud Ali and Saud Alarifi

ABSTRACT

Gadolinium oxide (Gd2O3) nanoparticles used in multimodal imaging agents, drug carriers and therapeutic agents. The objective of this study is to investigate Gd2O3 nanoparticles induced cell viability and underlying mechanisms in human liver-derived (HepG2) cell line. MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) and

neutral red uptake (NRU) assays were applied to assess cell toxicity due to Gd2O3 nanoparticles. To clarify the underlying mechanisms, we measured the intracellular production of reactive oxygen species using dichlorofluorescein diacetate as a fluorochrome. The level of reduced glutathione was declined and malondialehyde level was increased due to Gd2O3 nanoparticles. A significant dose and time dependent increase of DNA strand breaks was found after treatment with Gd2O3 nanoparticles for 48 hour. Increases in ROS level and the caspase-3 activity were also observed. The DNA strand breaks induced by Gd2O3 nanoparticles were almost prevented in HepG2 cells pretreated with NAC (10 mM) for 24 hour. Our results thus indicated that Gd2O3 nanoparticles exert cytotoxic effects on HepG2 cells, most likely through oxidative stress.

POSTER 40

GENOMIC INSIGHTS INTO THE NITRATE ASSIMILATION POTENTIAL OF BRETTANOMYCES BRUXELLENSIS ISOLATES

Ryan Zeppel, Chris Curtin and Anthony Borneman

ABSTRACT
Brettanomyces bruxellensis is a yeast species that is well-adapted to fermentative ecosystems, thanks to characteristics such as ethanol accumulation and tolerance, acid tolerance and the assimilation of limited or alternative nutrients. It is known to spoil wine via the production of phenolic metabolites that impart off aromas (e.g. 4-ethylphenol, 4-vinylphenol); however, the species is used to add complexity to the flavour profiles of some specialty beer styles. B. bruxellensis also holds potential as a candidate for use in continuous fermentations for bioethanol production, due to its high stress tolerance and alternative carbon and nitrogen metabolism.

Despite its industrial importance, there are very few molecular genetic techniques that can be applied to B. bruxellensis. As a consequence, the understanding of the biology of B. bruxellensis lags well behind that of other industrial fungal species, particularly the major industrial yeast, Saccharomyces cerevisiae. However, the recent falling costs of next-generation DNA sequencing have facilitated an acceleration in the understanding of B. bruxellensis biology through comparative genomics.

A potentially important factor in the adaptation of B. bruxellensis to fermentative ecosystems is its ability to metabolise alternative nitrogen sources, such as nitrate, that S. cerevisiae is unable to consume. Interestingly, it is the only fungal species that is commonly found in wine that is known to assimilate nitrate. However, nitrate assimilation is not a global characteristic of the species as only around half of B. bruxellensis show this nitrate assimilatory phenotype.

In order to determine the basis for the variable ability in nitrate assimilatory potential, forty five B. bruxellensis isolates were phenotyped and their assimilatory status correlated with whole genome sequence information. Of twenty nitrate-positive isolates, eleven were found to be heterozygous across the nitrate assimilation gene cluster, while nine exhibited four different homozygous nitrate gene alleles. Four nitrate-negative isolates were found to harbour a deletion of all, or part of, the predicted nitrate assimilation gene cluster. Surprisingly, a large number of nitrate-negative isolates were found to possess a common homozygous complement of the gene cluster. However, it appears that at least some isolates of this type switch from nitrate-negative to -positive at a rate of approximately 1 in every 105 cells. Research is now directed towards understanding the

genetic mechanism behind this phenotype switch.

POSTER 41

EPITHELIAL, METABOLIC AND INNATE IMMUNITY TRANSCRIPTOMIC SIGNATURES DIFFERENTIATING THE RUMEN FROM OTHER SHEEP GASTROINTESTINAL TRACT TISSUES

Ruidong Xiang, V. Hutton Oddy, Richard Talbot, Alan Archibald, Phil Vercoe, Brian P. Dalrymple

ABSTRACT
Background: Ruminants are very successful herbivorous mammals, in part due to specialized forestomachs, the rumen complex, which facilitates the conversion of feed to soluble nutrients by micro-organisms.

Results: Sixteen gene expression clusters were identified from 11 tissues covering the sheep gastrointestinal tract (GIT), two stratified epithelial tissues and controls. The clustering of the rumen, skin and tonsil was driven by genes from the epidermal differentiation complex, and genes encoding stratified epithelium keratins and innate immunity proteins. Consistent with its high turnover rate the whole GIT showed a marked enrichment of cell cycle process genes (P=1.4E-46), relative to liver and muscle, with highest expression in the cecum followed by colon and rumen. The expression patterns of several membrane transporters (Chloride, Zinc, nucleosides, amino acids, fatty acids, cholesterol, bile acids and lactate) along the GIT was very similar in sheep, pig and humans. In contrast, short chain fatty acid uptake and metabolism appeared to be different between the species and different between the rumen and colon in sheep. The importance of nitrogen and iodine recycling in sheep was highlighted by the highly preferential expression of SLC14A1-urea (rumen), RHBG-ammonia (intestines) and SLC5A5-iodine (abomasum). The gene encoding a novel, poorly characterized member of the maltase-glucoamylase family (MGAM-like), predicted to play a role in the degradation of starch or glycogen, was highly expressed in the small and large intestines.

Conclusions: The rumen is probably not a modified stomach or colon with a cornified epithelium, but may be a modified oesophagus with some liver-like and other specialized metabolic functions.

POSTER 42

ROS MEDIATED APOPTOSIS AND DNA DAMAGE INDUCED BY BARIUM NANOPARTICLES IN MOUSE EMBRYONIC FIBROBLASTS

Saud Alarifi, Daoud Ali and Saad Alkahtani

ABSTRACT
Barium nanoparticles are an important industrial material and are widely used in polymer and paints. The objective of this investigation was to measure possible apoptosis and genotoxic effects of barium nanoparticles in mouse embryonic fibroblasts (L929) cells. In vitro cytotoxicity assays were performed for barium nanoparticles in L929 cells. Mild cytotoxicity was observed due to barium nanoparticles in L929 cells. Results showed that barium nanoparticles slightly induced thiobarbituric acid reactive substances and superoxide dismutase and reduced the levels of glutathione in L929 cells. A concomitant by the generation of ROS, the loss of mitochondrial membrane potential, activation of caspase-3 were observed in barium nanoparticles treated L929 cells. In addition, in the single cell gel test we exposed barium nanoparticles (50-300 µg/ml) at two treatment times 24 and 48 hour. There was dose and time-dependent increase of DNA

damage observed in the single cell gel test. Therefore, the obtained results indicate that barium nanoparticles may exhibit genotoxic effects in cultured L929 cells, due to induction of oxidative stress.

POSTER 43

SEAVE: A COMPREHENSIVE VARIANT FILTRATION PLATFORM FOR CLINICAL GENOMICS

Velimir Gayevskiy, Ying Zhu, Tony Roscioli, Marcel E Dinger and Mark J Cowley

ABSTRACT
With rapid gains in accessibility and dramatically increased diagnostic yields, whole genome sequencing (WGS) is poised to become a routine test in the diagnosis of inherited disease. However, the interpretation of genomic variants remains complex and time consuming. WGS identifies millions of variants per individual that must be annotated using disparate data sources, interpreted and reported before being made available to clinical geneticists or researchers. The recent release of GEMINI (Paila et al., 2013) saw this process significantly improved allowing joint-called variant files to be readily converted into databases that are then interrogated using SQL statements. GEMINI combines a number of data sources to comprehensively annotate each variant with its impact, quality, prevalence in human populations and clinical significance. However, as GEMINI is a command-line tool, and researchers must construct custom SQL queries, this software is impractical for routine use in a clinical setting. To enable rapid and easy access to the GEMINI platform, we have built Seave, a web-based variant filtration interface, designed for genome researchers and clinical geneticists, to easily interpret whole-exome and whole-genome-scale datasets, easily handling datasets of hundreds of patients. Seave extends the power of GEMINI by adding powerful family-based filters, as well as an interactive gene list curation tool, and extensive integration with disparate annotation databases. This allows the phenotype and inheritance pattern of the condition to be used to power the analysis. Seave's simple web interface means that filtering and searching a database of millions of variants within a family trio based on 10+ criteria is performed in a matter of minutes. Here we demonstrate the capability of Seave through the analysis of genomes derived from >40 families with unsolved genetic diseases.

POSTER 44

DEAR-O: DIFFERENTIAL EXPRESSION ANALYSIS BASED ON RNA-SEQ DATA - ONLINE

Zong-Hong Zhang, Naomi R. Wray and Qiongyi Zhao

ABSTRACT
Differential expression analysis using high-throughput RNA sequencing data is widely applied in transcriptomic studies. Many software packages have been developed for the identification of genes that are differentially expressed between groups. There continues to be active development in updating of current software tools as well as an emergence of many new tools. The optimal choice of software tool for differential gene expression analysis is difficult to evaluate as different software tools, and different versions of the same tool, perform differently. Comparison studies could become out-of-date if one software tool were upgraded to a new version. In order to enable researchers to make timely evaluations of the performance of different software tools with different versions, we propose a user-friendly web server that allows end-users to perform a comparison study using different RNA-Seq tools and versions. This web server is built based on

our previous comparative study on software tools for RNA-Seq differential expression analysis. Software tools currently included in this web server are various major versions of DESeq, DESeq2, edgeR and Cuffdiff2. Data currently used on the server are publicly available mouse and lymphoblastoid cell lines RNA-Seq data. The web server will be maintained and updated to ensure new major versions of current tools or new tools are included. It is open to include new software tools and new benchmarking data sets in the future. Our web server will serve the RNA-Seq community and provide timely guidance for researchers to select optimal software tool for RNA-Seq differential expression analysis.

POSTER 45

ANALYSIS OF METASTASIS PROGRESSION IN HIGH GRADE MUCINOUS OVARIAN CANCER BY WHOLE GENOME SEQUENCING OF MULTIPLE AUTOPSY SITES

Matthew Wakefield, Dane Cheasley, Katherine Alsop, Mark Shackelton, Heather Thorne, David Bowtell, Martin Kobel, Prue Allan, Andrew Stephens, Tom Jobling, Sumi Ananda, Orla McNally, Rufaro Diana Jaravaza, Ian Campbell, Clare Scott and Kylie Gorringe

ABSTRACT

Mucinous ovarian carcinomas (MOC) are a distinct histological subtype of epithelial ovarian cancer, with late stage and high-grade MOC often resistant to standard chemotherapeutic regimens. Controversy exists over whether high-grade MOC arise in the ovary or represent metastases from distant sites with secondary ovarian involvement.

We present here the first whole-genome sequencing analysis of a high-grade mucinous ovarian carcinoma collected from multiple sites at autopsy (CASCADE study). The patient, aged just 41 at diagnosis of a Stage I ovarian mucinous tumor, had a 26-month progression-free interval, including normal CA125 and CA19.9 measurements at 21 months. The primary tumor was mostly borderline in appearance, with only a small focus of carcinoma. At autopsy, the carcinoma was widespread in the body, and whole-genome sequencing data was obtained from deposits in the omentum, iliac lymph node, para-aortic lymph node and upper diaphragm.

Whole genome sequencing (Illumina X Ten, Kinghorn Centre for Clinical Genomics) and single nucleotide variants (SNVs) identified with multiSNV (Josephidou 2015) are being used to reconstruct the relationship between metastatic sites. We are exploring the ability of the observed mutant allele frequency to infer subclonal structure and history of progression using various unsupervised clustering methods. Preliminary analysis suggests a greater diversity of mutations with lower mutated allele frequencies in the omental metastasis, and increased private or strongly selected mutations in the diaphragm, right illiac node and para-aortic lymph node. Subclonal structure between sites appears complex, and inference of the relationship between sites is sensitive to chosen thresholds and analysis methods.

POSTER 46

FUNCTIONAL CHARACTERISATION OF HUMAN PSEUDOGENE TRANSCRIPTION USING TARGETED RNA SEQUENCING

Daniel W Thomson and Marcel Dinger

ABSTRACT

Degenerate copies of genes called pseudogenes are ubiquitous in mammalian genomes, in humans there are 14467 annotated pseudogenes (Gencode v21). The most abundant subtype, 'processed pseudogenes' arise through retrotransposition of cellular RNAs. Colloquially known as 'jumping genes', retrotransposons have shaped the human genome over time forming repetitive DNA estimated to contribute to ~70% of the genome. Transcriptomic studies suggest that at least 9% of pseudogenes are actively transcribed. This provides evidence towards pseudogene function as non-coding RNA where protein coding potential in limited, however these estimates are constrained by the limitation of aligning short read sequences to pseudogenes, which by definition have highly homologous genomic repeats.

To investigate transcription of human pseudogenes in a way capable of distinguishing between homologous transcripts, we have appled RNA CaptureSeq coupled with long-read Pacific Biosciences (PacBio) sequencing. CaptureSeq is a powerful genomics approach capable of detecting very low abundance transcription, we will capture pseudogene regions and apply both Illumina and PacBio sequencing. This novel application of the technology will give unprecedented depth and accuracy of analysis to pseudogene transcription. We will perform these analyses on human testes and brain samples following reports of active retrotransposition in these regions and our own preliminary analysis showing these tissues are the most transcriptionally active for pseudogenes. This will equip us to investigate the function of the huge proportion of the genome thought to be non-functional DNA relics. We will concentrate on two putative mechanisms for pseudogene function; 1) The shuffling of pseudogene exons to produce new chimeric RNA isoforms in the evolution of new genes, 2) Identification of antisense transcription and endogenous pseudogene derived siRNAs (endo-siRNAs) and their role in silencing somatic retrotransposition. Understanding why pseudogenes are so profuse in higher eukaryote genomes and how pseudogene transcription contributes to cell maintenance and cell defense will be crucial to understanding how genomes evolve as well as how cancer cells hijack these mechanisms for their own proliferation.

POSTER 47

THE PRESENCE OF THE RS17878362 POLYMORPHISM IN BREAST CANCER IS ASSOCIATED WITH A LOW Δ40P53:P53 RATIO AND BETTER OUTCOME.

Kelly A Avery-Kiejda, Brianna C Morten, Michelle W Wong-Brown and Rodney J Scott

ABSTRACT

Breast cancer is the most common cancer in women, but surprisingly it has relatively low rates of p53 mutations, suggesting other mechanisms are responsible for p53 inactivation. We have shown that the p53 isoform, Δ40p53, is highly expressed in breast cancer, where it may contribute to p53 inactivation (Avery-Kiejda et al. Carcinogenesis 2014; 35 (3):586–596). Δ40p53 can be produced by either alternative splicing of p53 in intron 2, or alternative initiation of translation. The alternative splicing of p53 to produce Δ40p53 is regulated by the formation of

G-quadruplex (G4) structures in p53 intron 3, from which the nucleotides forming these structures overlap with a common intronic polymorphism (rs17878362). The presence of this polymorphism alters P53 splicing to decrease the expression of the fully spliced p53 form following ionising radiation in vitro. Hence, the presence of this polymorphism may be an important mechanism to regulate the ratio of Δ40p53 to full-length p53 in breast cancer. This study aimed to determine if the rs17878362 polymorphism was associated with altered Δ40p53 and p53 expression and outcome in breast cancer. We sequenced P53 in 139 breast cancers and compared this to the relative mRNA expression of the Δ40p53 and p53 transcripts using real-time qRT-PCR. We found that the ratio of Δ40p53:p53 was significantly lower in tumours that were homozygous for the polymorphic allele compared to those who were wild-type. Furthermore, there was a lower proportion of polymorphic alleles in breast cancers from patients who subsequently developed metastasis compared to those who did not. Finally, we show that patients whose tumours were homozygous for the polymorphic allele had significantly increased disease-free survival. These results show that the rs17878362 polymorphism is associated with low Δ40p53:p53 ratio in clinical breast cancer specimens and that this is associated with better disease outcome.

POSTER 48

A HIGH DENSITY SNP-BASED GENETIC LINKAGE MAP OF SWEET POTATO ESTABLISHED BY SCAFFOLDING AN IPOMOEA TRIFIDA (H. B. K.) G. DON. DE NOVO ASSEMBLY

Chenxi Zhou, Muhammad A. Khan and Lachlan JM Coin

ABSTRACT

Despite being a critical worldwide food resource, sweet potato (Ipomoea batatas (L.) Lam.) remains a less well studied crop due to its genetic complexity (2n = 6x = 90). As a result the availability of sweet potato genomic resources is highly limited [1, 2]. Here we propose a novel method for constructing high density genetic linkage maps and scaffolding de-novo assemblies of polyploid crops using Genotyping-by-Sequencing (GBS) data from a large full-sib family. By inferring transmission of parental haplotypes to each progeny, we are able to calculate the recombination fraction (RF) between every pair of contigs, from which we can iteratively cluster contigs into chromosomes, and finally resolve the contig ordering by use of a genetic algorithm which minimizes the RF sum along each chromosome. Our method also uses the shared haplotype structure in the family together with the allelic depth information to call high quality SNP genotypes.

Application of our approach to simulated datasets indicates that we are able to accurately reconstruct the correct clustering and ordering of contigs. We have used this approach to construct a high density genetic linkage map consists of 6,428 SNPs from 25 chromosomes by scaffolding a de novo assembly of Ipomoea trifida (H. B. K.) G. Don., the most likely ancestor of sweet potato but of much less genetic complexity (2n = 2x = 30) calls. We anticipate this method may help in constructing high quality genetic linkage maps for more plants.

POSTER 49

A NOVEL TECHNOLOGY FOR WHOLE GENOME AMPLIFICATION FROM SINGLE CELLS AND LIMITED MATERIAL

Martha Hinton (presenter only), Ángel J. Picher, Patricia Garrido, Armin Schneider, Oliver Wafzig and Luis Blanco

ABSTRACT
TruePrime™ is a novel technology dedicated to the amplification of whole genomes and DNA from various sources. TruePrime is based on the combination of the highly processive Phi29 DNA polymerase with the recently discovered primase/polymerase TthPrimPol. In this setup, TthPrimPol synthesizes the DNA primers needed for Phi29 DNApol, which allows for the exponential amplification of target DNA. TthPrimPol is a thermostable member of a recently discovered family of enzymes named PrimPol. TthPrimPol is a monomeric enzyme (34 kDa) that displays a potent primase activity, preferring dNTPs as substrates unlike conventional primases. This DNA primase activity can be activated by magnesium or manganese ions, having a wide sequence specificity for template recognition. Key advantages of the TruePrime technology include complete absence of primer artefacts, insensitivity to external DNA contaminations, reduced amplification bias compared to methods using random synthetic primers, and an exquisite reproducibility when amplifying from single cells or minute DNA amounts. Moreover, TruePrime™ shows superior sensitivity, is easy to use and works perfectly well with commonly used NGS platforms such as Illumina or IonTorrent. We believe that TruePrime will advance human genetic analyses from single cells or otherwise limited input material.

POSTER 50

A SINGLE-TUBE NGS LIBRARY PREP WORKFLOW INTEGRATING ENZYMATIC FRAGMENTATION RESULTS IN HIGH YIELDS AND LOW SEQUENCE BIAS

Martha Hinton (presenter only), B. Miller, M. Appel, .V. Van Kets, B van Rooyen, H. Whitehorn, M Ranik, P. Jones, A. Geldart, R. Kasinskas and E. van der Walt

ABSTRACT
Continuous improvements to library preparation for next-generation sequencing (NGS) are necessary to achieve the highest data quality. One of the crucial steps within library preparation is the initial DNA fragmentation, which can be accomplished through either mechanical or enzymatic processes. Mechanical methods for DNA fragmentation are difficult to scale or automate, and require large investments in expensive instrumentation. Current enzymatic solutions for DNA fragmentation typically exhibit sequence bias, provide poor control over fragment length distribution, and are highly sensitive to input amount.

To address these challenges, we have developed the KAPA HyperPlus Library Preparation Kit by integrating an enzymatic DNA fragmentation technology with fast and efficient library construction to provide a streamlined, easy-to-automate, single-tube solution for preparing NGS libraries from 1 ng – 1 µg of dsDNA.

POSTER 51

COOKING UP A PATHWAY ANALYSIS WITH ROAST AND FRY

Goknur Giner and Gordon K. Smyth

ABSTRACT
Gene set tests are often used in differential expression analyses to explore the behaviour of a group of related genes. This is useful for

identifying large-scale co-regulation of genes belonging to the same biological process or molecular pathway. One of the most flexible and powerful gene set tests is the ROAST method in the limma package. ROAST uses residual space rotation as a sort of continuous version of sample permutation. Like permutation tests, it protects against false positives caused by correlations between genes in the set. Unlike permutation tests, it can be used with complex experimental design and with small numbers of replicates. It is the only gene set test method that is able to analyse complex “gene expression signatures” that incorporate information about both up and down regulated genes simultaneously.

ROAST works well for individual expression signatures, but has limitations when applied to large collections of gene sets, such as the Broad Institute’s Molecular Signature Database with over 8000 gene sets. In particular, the p-value resolution is limited by the number of rotations that are done for each set. This makes it impossible to obtain very small p-values and hence to distinguish the top ranking pathways from a large collection. As with permutation tests, the p-values for each set may vary from run to run.

This talk presents Fry, a very fast approximation to the complete ROAST method. Fry approximates the limiting p-value that would be obtained from performing a very large number of rotations with ROAST. Fry preserves most of the advantages of ROAST, but also provides high resolution exact p-values very quickly. In particular, it is able to distinguish the most significant sets in large collections and to yield statistically significant results after adjustment for multiple testing. This makes it an ideal tool for large-scale pathway analysis.

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Trade Booth 25-26

BD

BD is a leading medical technology company that partners with customers and stakeholders to address many of the world's most pressing and evolving health needs. Our innovative solutions are focused on improving medication management and patient safety; supporting infection prevention practices; equipping surgical and interventional procedures; improving drug delivery; aiding anesthesiology and respiratory care; advancing cellular research and applications; enhancing the diagnosis of infectious diseases and cancers; and supporting the management of diabetes. We are more than 45,000 associates in 50 countries who strive to fulfill our purpose of "Helping all people live healthy lives" by advancing the quality, accessibility, safety and affordability of healthcare around the world. In 2015, BD welcomed CareFusion and its products into the BD family of solutions.

www.bd.com

AGTA 2015 DELEGATE LIST

First Name	Last Name	Organisation	State/ Country
Saud	Alarifi	King Saud University	SAU
Saad	Alkahtani	King Saud University	SAU
Rose	Andrews	University of New England	NSW
Stuart	Archer	Monash Bioinformatics Platform	VIC
Nicola	Armstrong	Murdoch University	WA
Jonathan	Arthur	Children's Medical Research Institute	NSW
Bernard	Atmadibrata	Children's Cancer Institute Australia	NSW
Kelly	Avery-Kiejda	Hunter Medical Research Institute and the University of Newcastle	NSW
Warren	Bach	Millennium Science	VIC
Melanie	Bahlo	Walter + Eliza Hall Institute of Medical Research	VIC
Laura	Baker	Garvan Institute of Medical Research	NSW
Colin	Baron	Qiagen	USA
Nenad	Bartonicek	Garvan Institute of Medical Research	NSW
Brant	Bassam	Bio-Strategy	VIC
Denis	Bauer	CSIRO	NSW
Traude	Beilharz	Monash University	VIC
Natalie	Beveridge	University of Newcastle	NSW
Katherine	Bolton	University of Newcastle	NSW
Justin	Borevitz	Australian National University	ACT
Anthony	Borneman	The Australian Wine Research Institute	SA
Nikola	Bowden	University of Newcastle	NSW
Rachel	Boyle	Auckland University of Technology	NZL
Timothy	Budden	University of Newcastle	NSW
Magdalena	Budzinska	Centenary Institute	NSW
Murray	Cairns	University of Newcastle	NSW
Vicky	Cameron	University of Otago	NZL
Dan	Catchpoole	Children''s Hospital at Westmead	NSW
Ross	Chapman	Hudson Institute of Medical Research	VIC
Fadi	Charchar	Federation University	VIC
Hsiufen	Chua	Partek	SGP
Aaron	Chuah	Australian National University	ACT
Megan	Clarey	Illumina	VIC
Nicole	Cloonan	QIMR Berghofer Medical Research Institute	QLD
Joe	Copty	Kinghorn Centre for Clinical Genomics	NSW
Susan	Corley	Systems Biology Initiative UNSW	NSW
Christopher	Cowled	CSIRO	VIC
Mark	Cowley	Garvan Institute of Medical Research	NSW

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Marina	Donskoi	Mater Health	QLD
Evan	Doods	Illumina	VIC
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Janette	Edson	Queensland Brain Institute	QLD
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Goknur	Giner	Walter + Eliza Hall Institute of Medical Research	VIC
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John	Graham	ANZAN	NSW
Sean	Grimmond	University of Glasgow	GBR
Paul	Harrison	Monash Bioinformatics Platform	VIC
Karl	Herron	Agena Bioscience	QLD
Martha	Hinton	GeneWorks	SA
Kate	Howell	University of Western Australia	WA
Gyorgy	Hutvagner	University of Technology Sydney	NSW
Robyn	Jamieson	Children's Medical Research Institute	NSW
Margaret	Jordan	Comparative Genomics Centre	QLD
Ben	Kaehler	Australian National University	ACT
Naga	Kasinadhuni	Australian Genome Research Facility	QLD
Janet	Kelso	Max Planck Institute For Evolutionary Anthropology	GER
Matloob	Khushi	Children's Medical Research Institute	NSW
Steve	Kujawa	Pacific Biosciences	USA
Carsten	Kulheim	Australian National University	ACT

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Jesper	Maag	Garvan Institute Of Medical Research	NSW
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Vikki	Marshall	Melbourne Neuroscience Institute	VIC
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Åsa	Pérez-Bercoff	University of New South Wales	NSW
Andrew	Perkins	Mater Research Institute	QLD
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Mark	Pinese	Kinghorn Cancer Centre	NSW
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Torsten	Seemann	University of Melbourne	VIC
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Peter	Sternes	Australian Wine Research Institute	SA
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Alex	Stuckey	University of Auckland	NZL
Yuting	Sun	Children's Cancer Institute	NSW
Alex	Swarbrick	Garvan Institute of Medical Research	NSW
Andrew	Szentirmay	Gene Target Solutions	NSW
Phillippa	Taberlay	Garvan Institute of Medical Research	NSW
David	Thomas	Garvan Institute of Medical Research	NSW
Daniel	Thomson	Garvan Institute of Medical Research	NSW
Natalie	Thorne	Melbourne Genomics Health Alliance	VIC
Amali	Thrimawithana	The New Zealand Institute For Plant & Food Research Limited	NZL
Sonia	Timmis	Bio-Strategy	VIC
Yash	Tiwari	Thermo Fisher Scientific	VIC
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Nikki	Tsoudis	Scientifix	VIC
Rust	Turakulov	AGRF	VIC
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Mark	Van der Hoek	South Australian Health & Medical Research Institute	SA
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Matthew	Wakefield	Life Sciences Computational Centre	VIC

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Liam	Williams	University of Auckland	NZL
Kokulapalan	Wimalanathan	Iowa State University	USA
Tanja	Woyke	Joint Genome Institute	DEU
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Jean	Yang	University of Sydney	NSW
Amanda	Yip	Becton Dickinson Holdings	SGP
Monika	Zavodna	University of Otago	NZL
Ryan	Zeppel	University of Adelaide	SA
Mahdi	Zeraati	Garvan Institute of Medical Research	NSW
Zong-Hong	Zhang	Queensland Brain Institute	QLD
Chenxi	Zhou	University of Queensland	QLD

Exhibition Floor Plan

BOOTH	EXHIBITOR
5	Agena Bioscience
7	Partek
8	Agilent Technologies
9	Thermo Fisher Scientific
10	GeneWorks
11	Macrogen Oceania
12	DNA Genotek
13	OnQ Software
14	Gene Target Solutions
15	Illumina Australia
16	Australian Genome Research Facility
17	Roche Diagnostics
18	Roche Barista Cart
19	Scientifix
20	Genesearch
21	Millennium Science
22	Ramaciotti Centre for Genomics
23	Kinghorn Centre for Clinical Genomics
24	Bio-Strategy
25 & 26	BD Biosciences


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Australasian Genomic Technologies Association
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