AMATA 2010 Conference

APPLYING BREAKTHROUGH TECHNOLOGIES TO GENOMICS RESEARCH • 14-17 September 2010

Hotel Grand Chancellor Hobart, Tasmania www.amatameeting.org

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Conference Handbook

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CONFERENCE MANAGERS

Leishman associates
conference and event management

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WELCOME

Dear Delegates and Invited Guests,

On behalf of the AMATA Executive Committee and the AMATA-2010 Organising Committee, welcome to Hobart, Tasmania and to the 10th Annual Conference of the Australasian Microarray and Associated Technologies Association.

The world is in the midst of an exciting genomics technology revolution and you have the opportunity to absorb some of this at AMATA-10, in a most beautiful, rugged and historical part of Australia. We thank you for taking time out of your busy professional and personal lives to be here; to be informed and to interact with global specialists in the genomic technology arena. We gratefully acknowledge the invited international, national and guest speaker(s) for their time, energy, and invaluable contribution to AMATA-10, and to our sponsors for an unprecedented level of support, without which this conference could not take place.

As in previous years, the organising committee has been struck by the very high calibre of research presented in submitted abstracts, making it a challenge to select the required number of presenters for the oral program given the very high standard of worthy submissions. However, the committee has managed to compile what we consider to be an exciting and informative scientific program comprising oral presentations on a diverse range of topics, poster presentations and interactive workshops. We also have a terrific social program and a record level of trade sponsorship and support at AMATA-10, that promises fruitful and consultative interaction.

Tasmania has a past history that is highly relevant to genetic studies. It was used as a penal colony from 1804 to 1853 with some 76,000 people being transported from the 'mother country' during this time. Therefore, accurately detailed genealogical records are available, making Tasmania an ideal population in which to base genetic linkage studies on complex genetic diseases, such as glaucoma and multiple sclerosis.

Tasmania is home of the Tasmanian ("Tassie") Devil, a carnivorous marsupial that has become an icon of Tasmania, and is featured on the AMATA-10 conference logo. The Tassie Devil was classified as an endangered species in May 2008 due to the ravage of a transmissible cancer of the face called Devil Facial Tumor Disease (DFTD).

At AMATA-10, we will benefit from oral and poster presentations describing advanced studies that utilise Second Generation DNA Sequencing (2GS) to study DFTD, and which have the potential to save this animal from extinction.

Of course, AMATA-10 will also be an opportunity to hear the latest research on advanced genomics technologies themselves and their application to advancing our knowledge of human disease including cancer, behavioural disorders and heart disease to name just a few.

Along with an excellent social program that includes a formal invitation from His Excellency, the Governor General to attend the opening of the conference at Tasmania's Government House, the conference Gala Dinner at one of Tasmania's top wineries, Moorilla Estate Winery, and diverse pre- and post-conference touring options, we are confident you will have a wonderful scientific and social experience at AMATA-10. We hope that AMATA-10 will be a magnificent way to mark 10 years of AMATA's contribution and involvement in the Australasian genomic technology arena.

Once again welcome, thank you for your contribution, please absorb the science, and enjoy.

Vikki Marshall

Vikki Marshall
Conference Convenor
AMATA-2010

AMATA

CONFERENCE GENERAL INFORMATION

Accommodation

If you have any queries relating to your accommodation booking, please see the staff from Leishman Associates at the Registration Desk, or alternately the staff at your hotel.

Your credit card details have been transferred to the hotel you have selected – please confirm this on check in with your hotel. If you have arrived 24 hours later than your indicated arrival day you may find that you have forfeited your deposit.

Banking

Banking hours in Hobart are Monday to Friday 9.30am – 4.00pm. There is an ATM in the foyer of the Hotel Grand Chancellor. Alternatively there are ATMs located in Salamanca Place and Brooke Street, about a five minute walk from the venue.

Conference Name Badges

All delegates and exhibitors will be provided with a name badge, which will give you access to all events that are included in your registration or that you have purchased. Please ensure that you wear your name badge at all times.

Disclaimer

The 2010 AMATA 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.

Emergency Medical Care

The Australia wide '000' emergency telephone number connects with the 24 hour communications centre for emergency response from ambulance, fire brigade and police services anywhere in Australia.

Entry to Conference Sessions

It is suggested that delegates arrive at preferred sessions promptly to ensure a seat.

Entry to Social Events

Entry to most social events will be via a checklist situation, with the attendees and additional guests appearing on a checklist.

Mobile Phones

As a courtesy to other delegates, please ensure that all mobile phones are turned off or in a silent mode during sessions and social functions.

Public Telephones

These are available in the hotel lobby, standard phone charges apply.

Registration Desk

The Registration Desk is located on the Mezzanine level of the Hotel Grand Chancellor. Please direct any questions you may have regarding registration, attendance, account or social functions here to the staff from Leishman Associates.

The Registration Desk will be open at the following times:

Tuesday 14 September	1200 – 1700
Wednesday 15 September	0800 – 1700
Thursday 16 September	0800 – 1700
Friday 17 September	0800 – 1700

Speakers

All speakers are asked to make themselves known to the staff at the Registration Desk and to pre-load their presentation onto the conference computer AT LEAST four hours before they are scheduled to present – this may mean the day before your presentation. An audio visual technician will be available throughout the conference. The staff at the Registration Desk will introduce you to the AV technician.

A speakers preparation room is located alongside the Registration Desk. You will be welcomed by the team from Alive Technologies.

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 or conference staff.

Smoking

Smoking is not permitted in any of the venues associated with the conference. Designated smoking areas are available at each venue. Delegates should check with the venue staff.

Tours

If you've booked a tour or activity through the conference organisers, you will have received information prior to the commencement of the Conference. If you have any questions please see the staff from Leishman Associates at the Registration Desk.



CONFERENCE PROGRAM

▲ Keynote ▲ Plenary ▲ Guest ▲ Trade ▲ Student

* Denotes eligible for Early Career Prize

TUESDAY 14 SEPTEMBER 2010

1200 – 1800 Registration Desk Open — *Mezzanine Foyer*

1200 – 1800 Trade Exhibition Open — *Federation Ballroom*

Opening Oration & Welcome Reception

1800 – 1835 ▲ **Guest Speaker: Prof Joe Sambrook** — *Grand Ballroom 2/3*
Director of kConFab, Peter MacCallum Cancer Centre, Melbourne, Australia

Revolutions in Molecular Biology – Past and Future
Chair: Vikki Marshall

1835 – 2000 Welcome Reception — *Harbour 1*
Entertainment by Strings on Fire

WEDNESDAY 15 SEPTEMBER 2010

0730 – 1800 Registration Desk Open and WELCOME REFRESHMENTS — *Mezzanine Foyer*

0800 – 1730 Trade Exhibition Open — *Federation Ballroom*

0825 – 0830 Official Welcome and Conference Opening

Session 1: Translational Cancer Genomics — *Grand Ballroom 2/3*

Chair: Richard Tothill

0830 – 0915 ▲ **Dr Paul Spellman**
Lawrence Berkeley National Laboratory, USA

Molecular Subtype Specific Responses to Anti-cancer Compounds in Breast Cancer

0915 – 0950 ▲ **Prof Andrew Biankin**
Garvan Institute of Medical Research, Sydney, Australia

The Australian Pancreatic Cancer Genome Initiative

0950 – 1010 **Assoc Prof Ian Campbell**
Peter MacCallum Cancer Centre, Melbourne, Australia

Identification of breast cancer susceptibility genes using whole exome sequencing

1010 – 1030 **Dr Logan Walker***
Queensland Institute of Medical Research, Brisbane, Australia

The role of germ-line DNA copy number variation in familial breast cancer risk

1030 – 1100 MORNING REFRESHMENTS — *Federation Ballroom*

Session 2: Profiling Technologies 1 — *Grand Ballroom 2/3*

Chair: Adele Holloway

1100 – 1145 ▲ **Prof Richard (Dick) McCombie**
Cold Spring Harbour Laboratories, New York, USA

Finding a needle in the Haystack

1145 – 1220 ▲ **Prof Susan Clark**
Garvan Institute of Medical Research, Sydney, Australia

Mapping the Cancer Epigenome

1220 – 1240 **Dr Clare Stirzaker**
Garvan Institute of Medical Research, Sydney, Australia

High resolution DNA methylation epigenome sequencing of formalin-fixed paraffin embedded tissue (FFPET) DNA identifies novel epigenetic markers in breast cancer

1240 – 1300 **Dr Mark Corbett***
SA Pathology, Adelaide, Australia

Discovery of mutations that cause epilepsy and intellectual disability using sequence enrichment and next-generation sequencing

1300 – 1400 LUNCH — *Federation Ballroom*

Session 3: Profiling Technologies 2 — *Grand Ballroom 2/3*

Chair: Vikki Marshall

1400 – 1445 ▲ **Dr Philip Stephens**
Wellcome Trust Sanger Centre, Hinxton, UK

Next generation cancer genome sequencing

1445 – 1505 ▲ **Dr Jeff Jeddeloh**
Roche NimbleGen, USA

Genomics technology development for large plant genomes: combining aCGH and array based complexity reduction technology affords base-pair resolution of genomic variation

1505 – 1525 **Dr Michal Janitz**
The University of New South Wales, Sydney, Australia

RNA-Seq global analysis of transcriptome activity and alternative splicing patterns in human hippocampus

1525 – 1545 Dr Marcel Dinger*
IMB, The University of Queensland, Brisbane, Australia

Characterization of long noncoding RNAs by ultra deep sequencing of the human transcriptome

1545 – 1600 ▲ **Mr Lam Son Nguyen**
The University of Adelaide, Adelaide, Australia

Genome-wide identification of nonsense-mediated mRNA surveillance targets by RNA-SEQ and exon array

1600 – 1730 Poster session and AFTERNOON REFRESHMENTS — *Federation Ballroom*

1800 Depart for Government House (please bring your invitation) — *Assemble in Foyer of HGC*

1815 – 1915 GOVERNMENT HOUSE RECEPTION — *Government House*

CONFERENCE PROGRAM

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* Denotes eligible for Early Career Prize

THURSDAY 16 SEPTEMBER 2010

0730 – 1800 Registration Desk Open and WELCOME REFRESHMENTS *Mezzanine Foyer*

0800 – 1700 Trade Exhibition Open *Federation Ballroom*

Session 4: Population Genetics *Grand Ballroom 2/3*

Chair: Ian Campbell

0830 – 0915 ▲ **Prof Vanessa Hayes**
J Craig Venter Institute, USA
Defining the extent of Human Genome diversity in our oldest living descendents

0915 – 0950 ▲ **Dr Tony Papenfuss**
Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia
Sequencing the transcriptome of the Tasmanian devil facial tumour disease

0950 – 1010 **Dr Elizabeth Murchison***
Wellcome Trust Sanger Institute Hinxton, UK
Genome sequences of the Tasmanian devil and its transmissible cancer

1010 – 1030 **Dr Desiree Petersen***
Children's Cancer Institute Australia, NSW, Australia
Unique admixed population with out-of-Africa roots holds potential to advance complex disease loci identification

1030 – 1100 MORNING REFRSHMENTS *Federation Ballroom*

Session 5: Bioinformatics *Grand Ballroom 2/3*

Chair: Gordon Smyth

1100 – 1145 ▲ **Dr Leming Shi**
National Centre for Toxicological Research, US FDA, Arkansas, USA
Genomics, Bioinformatics, and Personalized Medicine: The MicroArray Quality Control (MAQC) Project

1145 – 1205 **Dr Mark Robinson***
Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia
Joint analysis of copy number and enrichment-based epigenomics sequencing data

1205 – 1225 **Dr Kim-Anh Le Cao***
QFAB, The University of Queensland, Brisbane, Australia
MixOmics for integration and variable selection of 'omics' data sets

1225 – 1245 ▲ **Ms Katherine Smith**
Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia
Refining genetic associations with Hepatitis C treatment response using targetted MPS of pooled DNA samples following GWAS

1245 – 1300 ▲ **Mrs Anna Campain**
The University of Sydney, Australia
Integrating gene expression and clinical data in melanoma prognosis predictions

1300 – 1400 LUNCH *Federation Ballroom*

1300 – 1400 Optional Lunchtime Workshop *Harbour 2*

Sponsored by Millennium Science

Zuwei Qian, PhD,
Associate Director of Scientific Affairs and Collaborations at Affymetrix

From whole genome screens to single copy detection: new solutions from Affymetrix

Session 6: Model Systems and Functional Genomics *Grand Ballroom 2/3*

Chair: Michal Janitz

1400 – 1445 ▲ **Prof Simon Foote**
Menzies Research Institute, University of Tasmania, Australia

1445 – 1520 ▲ **Dr Ross Dickins**
Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Modeling cancer therapy using transgenic and retroviral RNA interference in mice

1520 – 1540 **Dr David Fung***
University of New South Wales, Sydney, Australia

Systems modelling of myocardial infarction in Mus musculus using microarray expression data

1540 – 1600 ▲ **Ms Charity Law**
Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia

A novel method of measuring erythropoiesis in anemia using gene expression data from bone marrow

1600 – 1630 AMATA AGM *Grand Ballroom 2/3*

1600 – 1630 AFTERNOON REFRESHMENTS *Federation Ballroom*

1830 Depart for Conference Dinner *Assemble in Foyer of HGC*

1900 – 2300 10th Anniversary AMATA Conference Dinner *Moorilla Estate Winery*

AMATA

CONFERENCE PROGRAM

▲ Keynote ▲ Plenary ▲ Guest ▲ Trade ▲ Student

* Denotes eligible for Early Career Prize

FRIDAY 17 SEPTEMBER 2010

0730 – 1800 Registration Desk Open and WELCOME REFRESHMENTS *Mezzanine Foyer*

0800 – 1700 Trade Exhibition Open *Federation Ballroom*

Session 7: Gene Regulation 1 *Grand Ballroom 2/3*

Chair: Alicia Oshlack

0900 – 0945 ▲ **Assoc Prof Xiaole Shirley Liu**
Dana-Farber Cancer Institute, Boston, USA
Inferring transcription regulatory mechanism from nucleosome dynamics

0945 – 1020 ▲ **Prof Frances Shannon**
John Curtin School of Medical Research ANU, Canberra, Australia
Determining the basal chromatin signature of inducible genes in immune cells

1020 – 1040 **Dr Sudha Rao***
John Curtin School of Medical Research ANU, Canberra, Australia
Chromatin-associated protein kinase C-θ regulates an inducible gene expression program and microRNAs in human T lymphocytes

1040 – 1100 ▲ **Mr Matthew Young**
Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia
Using ChIP-seq to identify distinct and functionally correlated classes of PRC2 binding across genes in mouse

1100 – 1130 MORNING REFRESHMENTS *Federation Ballroom*

Session 8: Gene Regulation 2 *Grand Ballroom 2/3*

Chair: Susan Clark

1130 – 1205 ▲ **Prof Liz Musgrove**
Garvan Institute of Medical Research, Sydney, Australia
Using large-scale gene expression and functional genetic analyses to identify mechanisms of estrogen action and endocrine resistance in breast cancer

1205 – 1240 ▲ **Dr Rohan Williams**
John Curtin School of Medical Research ANU, Canberra, Australia
Detecting trans-acting regulatory variation in mammalian transcriptomes

1240 – 1300 **Assoc Prof Thomas Lufkin**
Genome Institute of Singapore, Singapore
Sox9-directed Gene Regulatory Network Controlling Murine Embryonic Skeletal Development

1300 – 1315 Awarding of Prizes and Conference Close *Grand Ballroom 2/3*

1300 – 1400 LUNCH for those attending workshops *Mezzanine Foyer*

Optional Workshops

1400 – 1700 **Workshop 1: AGRF Bioinformatics... A key tool in enhancing your NGS Output** *Sponsored by* agrf Australian Genome Research Facility Ltd — *Harbour 1*

1400 – 1700 **Workshop 2: Partek(R) Genomics Suite Next-Generation Sequencing (NGS) data analysis** *Sponsored by* Partek turning data into discovery® — *Harbour 2*

1400 – 1700 **Workshop 3: Next Generation GWAS – Illumina's Omni Roadmap for Rare Variant Discovery and Imputation** *Sponsored by* illumina® — *Grand Ballroom 1*

SATURDAY 18 SEPTEMBER 2010

0900 – 1600 **Optional GenePattern Workshop**

Broad Institute Tools for Integrative Genomics Analysis
Menzies Research Institute, Medical Sciences Building 1, 17 Liverpool Street

GenePattern
A platform for integrative genomics

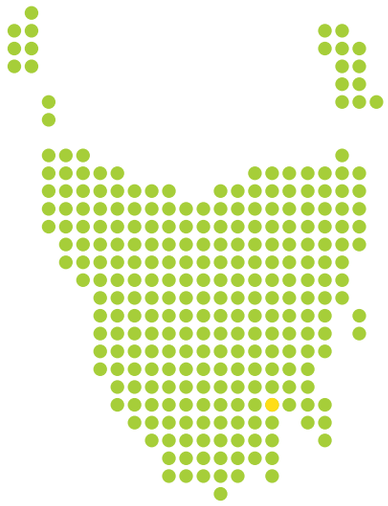
Dr Michael Reich
Director of Cancer Informatics Development, Broad Institute of MIT and Harvard

Dr Helga Thorvaldsdottir
Senior Project Manager, Broad Institute of MIT and Harvard

Menzies Research Institute Tasmania

LOCATION GUIDE

1. Hotel Grand Chancellor - 1 Davey Street (Conference Location)
2. Zero Davey Boutique Apartments - 15 Hunter Street
3. The Old Woolstore Hotel - 1 Macquarie Street
4. Salamanca Inn - 10 Gladstone Street
5. Brooke St Pier
6. Cascade Brewery
7. Tasmanian Travel Centre - Cnr Elizabeth and Davey St
8. Mures Restaurant
9. The Drunken Admiral Seafood Restaurant
10. The North Hobart Restaurant Strip
11. Salamanca Place – Various Restaurants
12. Menzies Research Institute (Gene Pattern Workshop Location)



Welcome Reception "Taste of Tasmania"

Date:	Tuesday 14 September 2010
Time:	1835 – 2030
Dress:	Business or Smart Casual
Location:	Hotel Grand Chancellor, Harbour 1, overlooking Sullivans Cove
Entertainment:	Strings on Fire

IMPORTANT INFORMATION: The Welcome Reception will be a great opportunity for you to renew acquaintances and meet people; we encourage you to mingle and introduce yourself to colleagues.

Beverages will be served from 1835 to 2030 and will comprise, red and white wines, beers, softdrink, water and orange juice. Spirits are not available.

Food will be served from 1845 to 2015 and will be a combination of tray service and food stations.

Delegates are encouraged to wander the food stations, the menu selection includes:

Cold Selections

- Spring bay scallops with Tasmanian wasabi mayonnaise
- Smoked Tasmanian pancake tart
- Selection of sushi & Californian rolls ponzu sauce & pickled ginger
- Antipasto olives, capsicum, roasted pumpkin and green stuffed olives
- Dips – elderberry balsamic, Ashbolt extra virgin olive oil and turkish bread, lemon hummus and flat bread, tomato salsa, guacamole, sour cream and crostini

Hot Selections

- Calamari sticks with aioli
- Cajun prawns with chilli jam
- Tandoori chicken and raita
- Minced lamb pide with yogurt and coriander
- Homemade Italian sausage rolls with tomato chutney
- Highland goat cheese, tomato, pepper berry turn-over
- Fried blue eye trevalla with sour cream mayonnaise & wedges
- Stir fried beef with Singapore noodles

Government House Reception

Date:	Wednesday 15 September 2010
Time:	1815 – 1915
Dress:	Business Attire (no denim, thongs or singlets)
Departure Time:	1800
Location:	Government House, Hobart
Assembly Point:	Campbell Street Hobart (just outside the Hotel Grand Chancellor)
Transport:	Coaches will depart from the Campbell Street entrance of the Hotel Grand Chancellor at 1745

Delegates are requested to be on time for the departure.

IMPORTANT INFORMATION: Please note it was a requirement to advise if you would like to attend the Government House Reception, which is hosted by His Excellency, The Hon Peter Underwood, Governor of Tasmania.

We are not able to offer invitations to those delegates who have not requested an invitation prior to the conference. Please note: if you have requested an invitation, it is expected that you will attend the function and an invitation from Government House will be issued to you at registration. There are strict protocols around Government House, including dress codes, and it is very much appreciated if these can be adhered to.

Conference Gala Dinner

Date:	Thursday 16 September 2010
Time:	1900 – 2300
Dress:	Business or 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.
Departure Time:	1830
Location:	Moorilla Estate Winery
Assembly Point:	Campbell Street Hobart (just outside the Hotel Grand Chancellor)
Transport:	Coaches will depart from the Campbell Street entrance of the Hotel Grand Chancellor at 6.30pm.
	Coaches will return you to your hotel after the Conference Dinner.

Delegates are requested to be on time for the departure.

IMPORTANT INFORMATION: Seating will be based on allocating your name to a specific table number. Each delegate who is registered to attend a dinner will have a label with their name on it available at the registration desk. Each delegate will be asked to place their label on the table plan which will be displayed from 2400 on Tuesday. There is only one label per person, so if you don't have a label you aren't registered to attend the dinner. Please only allocate your own label. Under no circumstances can you remove someone from a table plan without their permission.

Additional Tickets: Conference Social Program

The Welcome Reception and Government House Reception are included in the cost of a full conference registration. Additional tickets for the Welcome Reception may still be available at a cost of $75. The Conference Dinner is an optional event, tickets may be available at a cost of $95. Check with staff at the Registration Desk.

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Come and discover New Solutions with Zuwei Qian from Affymetrix on Wednesday, 15th September 2010 at 1:00pm

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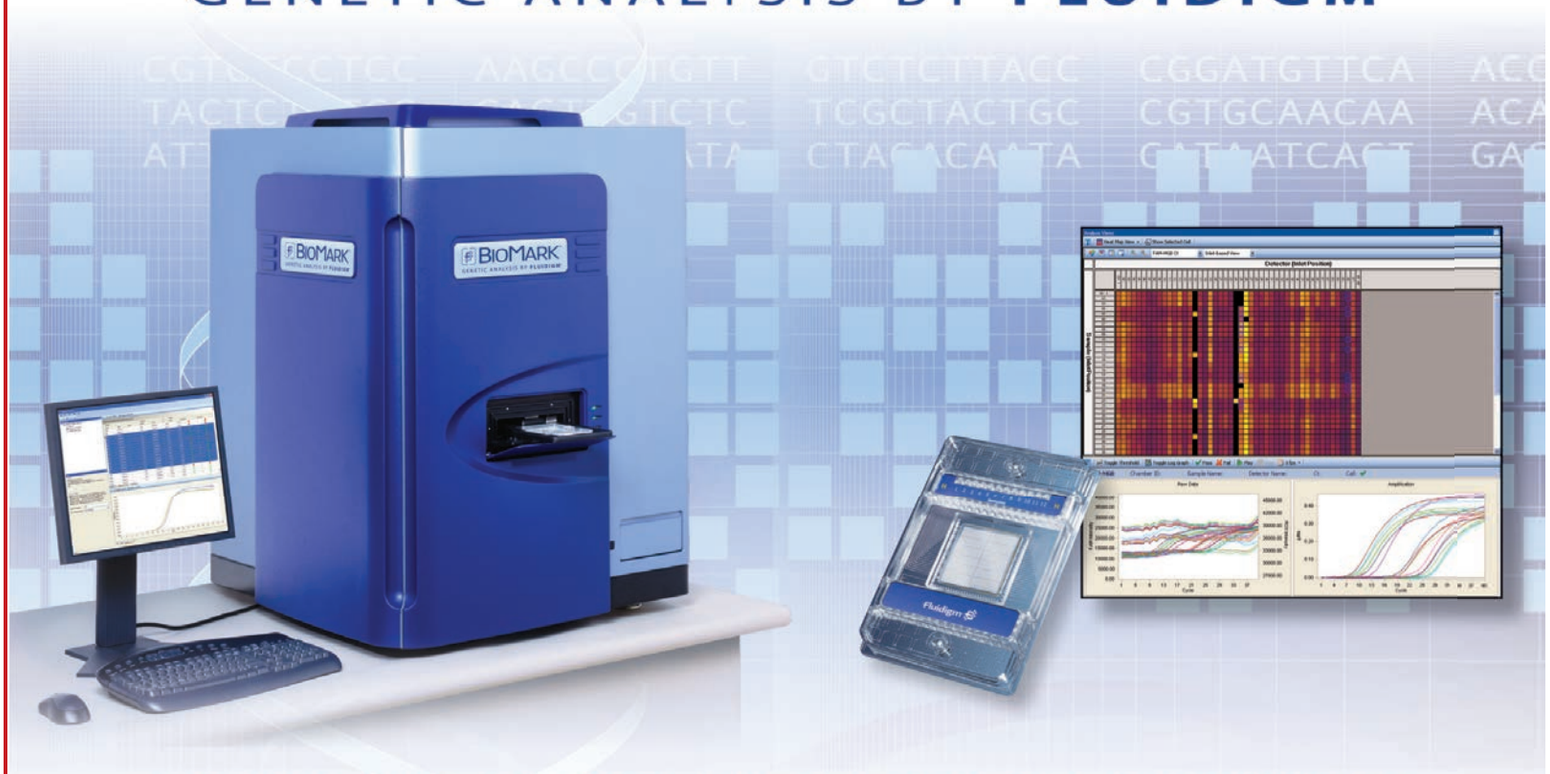

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DAY 1: TUESDAY 14 SEPTEMBER 2010

GUEST SPEAKER

Chair: Vikki Marshall
Grand Ballroom 2/3

1800 – 1835

Prof Joe Sambrook

Director of kConFab, Peter MacCallum Cancer Centre, Melbourne, Australia

Revolutions in Molecular Biology – Past and Future

BIOGRAPHY

Professor Joe Sambrook is internationally renowned for his studies of DNA tumour viruses and the molecular biology of normal and cancerous cells, which have effectively changed our understanding of the cellular development of many forms of cancer.

During the course of his distinguished career he has worked at a number of leading scientific institutions, including the Laboratory of Molecular Biology at Cambridge in England, the Salk Institute in California, the Cold Spring Harbor Laboratory in New York and the University of Texas South Western Medical Centre in Dallas.

Professor Sambrook was Foundation Director of Research of the Peter MacCallum Cancer Centre in Melbourne until 2000, and under his stewardship, scientific staff had increased in number from 75 to nearly 200, across a range of new programs. Joe is an inspirational speaker and his published works include three editions of the best-selling, highly influential laboratory manual "Molecular Cloning", currently the most-cited book in Google Scholar.

ABSTRACT

Science seems to advance at an uneven rate, with periods of slow consolidation punctuated by revolutionary bursts. In his talk, Joe Sambrook will discusss the revolutionary ideas and technical advances that have mark the spectacular progress of molecular biology from Darwin to DNA and beyond. Unsurprisingly, many of these revolutionary bursts have been fuelled by larger-than-life scientists with quite odd personalities.

DAY 2: WEDNESDAY 15 SEPTEMBER 2010

SESSION 1: Translation Cancer Genomics

Chair: Richard Tothill
Grand Ballroom 2/3

0830 – 0915

Dr Paul Spellman

Lawrence Berkeley National Laboratory, USA

Molecular Subtype Specific Responses to Anti-cancer Compounds in Breast Cancer

BIOGRAPHY

Dr Spellman is interested in using genetic, genomic, and proteomic data to understand and model the biology of cancer and to develop methods to effectively deploy therapeutic agents in the age of personalized medicine. He is interested in the effects of genomic dysregulation in cancer, particularly ovarian cancer. The group collaborates extensively with researchers from Berkeley Lab, UC Berkeley, and UCSF in this work

ABSTRACT

Breast cancer is clinically heterogeneous and is composed of numerous pathologically and molecularly distinct subtypes. Patient responses to conventional and targeted therapeutics differ among these subtypes, which implies that the therapeutic agents currently under development should be tested and eventually deployed in only the most responsive patient populations. Collections of breast cancer cell lines mirror many of the molecular subtypes found in tumors, suggesting that treatment of cell lines with candidate therapeutic compounds can lead to discovery of associations between molecular subtypes and drug response. In a test of 77 therapeutic compounds, nearly all drugs show differential responses across these cell lines and a significant fraction of drugs show subtype – and/or genomic aberration-specific responses. These observations indicate that the use of molecular subtype information will lead to clinical deployment of compounds that can be performed more quickly, for lower cost, and with more benefit to patients than is currently achievable.

0915 – 0950

Prof Andrew Biankin

Garvan Institute of Medical Research, Sydney, Australia

The Australian Pancreatic Cancer Genome Initiative

BIOGRAPHY

Andrew is a Surgeon Scientist who specializes in Pancreatic Diseases, particularly focusing on Pancreatic Cancer and its precursor lesions. His clinical practice is part of a specialist unit treating pancreatic disease. His research is focused on translating scientific discoveries into patient care through improved application of current therapies, early detection and novel therapeutics.

He is the clinical lead of the Australian Pancreatic Cancer Genome Initiative with Prof. Sean Grimmond of the QCMG (scientific lead), which aims to sequence the genome, transcriptome and epigenome of ~400 pancreatic cancers as part of the International Cancer Genome Consortium.

ABSTRACT

Pancreatic cancer (PC) is the fourth leading cause of cancer death in Western societies with an overall 5-year survival rate of less than 5%. Advances in neoadjuvant and adjuvant chemotherapeutic regimens have resulted in some improvement in outcome, but pancreatectomy remains the single most effective treatment modality for PC, and offers the only potential for cure. Only 20% of patients present with localised, non-metastatic disease, which is suitable for resection. Those who undergo resection and receive adjuvant therapy have a median survival of 12-22 months and a 5-year survival of 20-25%. Consequently there is a great need to develop novel therapeutic and early detection strategies for PC.

The International Cancer Genome Consortium (ICGC; http://www.icgc.org/) has been organized to launch and coordinate a large number of research projects that have the common aim of elucidating the genomic changes present in the majority of cancers that contribute to the burden of disease world-wide 1. Australia is a member of the ICGC, and is contributing by sequencing the genome, epigenome and transcriptome of pancreatic and ovarian cancer. The primary aims of the Australian Pancreatic Cancer Genome Initiative (APGI) are too deeply sequence tumour and normal gDNA, survey global gene expression (RNAseq) and determine genome wide patterns of methylation of ~400 prospectively accrued pancreatic cancers.

The overall goals of extensively characterizing cancer genomes are to refine current treatment through defining markers of therapeutic responsiveness or resistance, and identifying targets for the development of novel therapeutic strategies 2,3. A current global challenge is the ability to interpret large data sets of the type that are generated by the ICGC to distinguish "driver" mutations from the more common "passenger" mutations and exploit opportunities for direct translation into the clinic.

The approaches used by the APGI to define, interpret and apply cancer genomic data, together with early findings will be presented. Sequence data is summarised to identify aberrations with likely functional consequences (structural variants, gene fusions, copy number variations, deletions, non-synonymous mutations etc.). These analyses use software prediction models and may be based on known characteristics of cancer drivers, signalling pathways and functional nodes that are either known, or suspected to be important in carcinogenesis. Direct potential clinical applications include the delineation of phenotypes based on patterns of genomic aberrations co-segregating with clinico-pathological endpoints. In addition, other approaches such as the detection of tumour specific genomic abnormalities in blood would have applications in early detection of recurrence and surrogate markers of therapeutic responsiveness. Integrated multidimensional datasets bring together global data concerning the transcriptome, methylome and other "-omic" technologies to facilitate the interpretation of genomic data to better define potential mechanisms which are important biologically and may be druggable, or already have compounds developed that are used in other scenarios.

0950 – 1010

Assoc Prof Ian Campbell

Peter MacCallum Cancer Centre, Melbourne, Australia

Identification of breast cancer susceptibility genes using whole exome sequencing

BIOGRAPHY

Ian has over 21 years of experience in cancer genetics and is head of the VBCRC Breast Cancer Genetics Laboratory at the Peter MacCallum Cancer Centre. He has an international reputation in ovarian and breast cancer genetics and genome-wide analyses.

ABSTRACT

The ability to identify disease-causing mutations in high risk breast cancer families has broad implications for those affected, in terms of risk assessment and management as well as treatment. With as much as 75% of the excess familial risk of breast cancer yet to be attributed to genetic variants (in genes such as *BRCA1* and *BRCA2*), it is likely that additional moderate to high risk breast cancer genes remain to be discovered, each accounting for a small percentage of high risk families. Recent advances in technology have opened up the possibility of using massively parallel short-read (or 'next generation') sequencing to uncover predisposing mutations in individuals with inherited cancer in an unbiased manner. To this end, wwe are performing whole exome sequence analysis of germline DNA from multiple affected relatives from over 75 high risk non-BRCA1/non-BRCA2 breast cancer families with the aim of identifying segregating, rare, non-synonymous variants that are likely to include novel predisposing mutations.

Initial experiments using the NimbleGen Human Exome Array (to capture 180,000 coding exons and 551 miRNAs) and the Illumina GAIIx platform (combining 75 bp single end data from three flow cell lanes) generated approximately 3 Gb of mappable sequence data with 54% target specificity. The average fold-coverage within the target regions was 60x and importantly, 95% of targeted nucleotides were covered by at least eight sequence reads. Single nucleotide polymorphisms (SNPs) are identified using MAQ-SNP and short insertions and deletions (indels) are identified using novoalign. After excluding all variants reported in dbSNP, an average of 5 novel nonsense SNPs and 20 frame-shift indels are identified per index case. The number nonsense and frameshift indels variants shared by affected relatives is further reduces the candidate gene list to less than 5 per family. To date, two potential breast cancer predisposing genes have been identified and these genes are being screened in a larger panel of BRCAx families. In summary, whole exome sequencing of multiple individuals from within each cancer family is proving to be an efficient strategy for rapidly identifying novel familial predisposing mutations.

1010 – 1030

Dr Logan Walker

Queensland Institute of Medical Research,
Brisbane, Australia

The role of germ-line DNA copy number variation in familial breast cancer risk

BIOGRAPHY

Logan Walker completed his PhD in 2007 from the University of Otago (New Zealand) entitled "Genetic aberrations in breast cancer". In 2007, he joined the Molecular Cancer Epidemiology Laboratory (Lab head – Dr Mandy Spurdle) at the Queensland Institute of Medical Research and has been involved in various projects studying the genetic mechanisms for increased susceptibility of disease in multi-case breast cancer families. He currently holds the John Gavin Post-Doctoral Fellowship (Genesis Oncology Trust, NZ).

ABSTRACT

A significant proportion of breast cancers arise in a subset of women from breast cancer-affected families, presumably due to inherited genetic changes that increase cancer risk. However, for most of these women the changes underlying their disease remain undetermined. Inherited genomic copy number variants (CNVs) are thought to cover >10% of the human genome and are therefore an important factor in genetic variation. Recent genome-wide studies using single nucleotide polymorphism (SNP) arrays reported associations between CNVs and susceptibility to human diseases, such as cancer and neurodevelopmental disorders. However, the contribution of rare CNVs towards the development of breast cancer has not been investigated to any great depth. We have conducted a study to determine whether rare inherited CNVs contribute to increased risk in breast cancer affected families. We used high-density SNP arrays to identify CNVs in germ-line DNA from 26 familial breast cancer cases that do not carry a deleterious mutation in a known breast cancer susceptibility gene, and from 14 healthy controls. We identified 260 putative CNVs in breast cancer affected women of sizes ranging from 1.4 kb to 4.7 Mb, and 85 CNVs in healthy controls of sizes ranging from 6.4 kb to 2.3 Mb. Novel putative CNVs (defined as those not previously described on the Database of Genomic Variants) overlapping coding exons were predicted in 14/26 (54%) of cases versus 2/14 (14%) of controls. Furthermore, pathway analysis of genes affected by novel CNVs showed an enrichment of genes associated with tissue development, cellular development and cancer pathways. These results suggest that rare CNVs altering cancer related pathways contribute to breast cancer development. CNVs identified as likely candidate risk variants will be validated and assessed in family members of each proband carrier identified with the target CNV. Results from analyses to date will be presented.

SESSION 2: Profiling Technologies 1

Chair: Adele Holloway
Grand Ballroom 2/3

1100 – 1145

Dr Richard (Dick) McCombie

Cold Spring Harbour Laboratories, New York, USA

Finding a needle in the Haystack

BIOGRAPHY

One of the most exciting areas of research to arise from genomics is the role of sequence variation among individuals of the same species in determining their phenotype in areas as disparate as behaviour and the susceptibility to diseases. Next generation DNA sequencing allows us to generate billions of bases of sequence in a short amount of time at unprecedented low cost. As a research focus, we utilise these technologies to elucidate the role of genomic variation in causing two major disease classes, cognitive disorders (such as schizophrenia) and cancer.

ABSTRACT

Revolutionary changes in DNA sequencing capabilities promise rapid advances in improving our understanding of genetic contributors to a wide range of human phenotypes, including cognitive disorders. However, each of the approaches that one can deploy involves the interaction of technical compromises with a potentially variable genetic architecture underlying the phenotype.

I will use examples of how we apply next generation sequencing in different studies of the genetics of cognitive disorders but will focus on the application of next generation sequencing to "completely sequence" exomes and genomes.

The results presented will show the strengths and weaknesses of whole exome versus whole genome approaches. They will also show the utility of multiple technical approaches to whole genome sequencing. Lastly the results will show the value of linking study design in terms of sample type with sequencing strategy and computational analyses.

1145 – 1220

Susan Clark

Garvan Institute of Medical Research, Sydney, Australia

Mapping the Cancer Epigenome

BIOGRAPHY

Professor Susan Clark has a highly acclaimed international reputation for her pioneering work in mammalian epigenetics. Susan heads the epigenetics research program at the Garvan Institute of Medical Research in Sydney, Australia. She graduated in 1982 with a PhD in Biochemistry at the University of Adelaide and then spent ten years in the Biotechnology Industry before returning to basic research in gene regulation in 1992. Her studies over the last sixteen years have initiated profound questions about the importance of epigenetics in early development and in disease, especially in cancer. She has made extensive ground-breaking discoveries relating to DNA methylation patterns in normal and cancer genomes, that have led to new tests for early cancer detection. The techniques she pioneered in the early 1990s, including bisulphite sequencing, have revolutionised and now underpin a new era in epigenetics research. She has a number of awards including the RPAH Research Medal in 2002, Julian Wells Medal in 2003, Ruby Payne-Scott Award for contribution of women in science in Australia; "Biochemisch Analytik Preis" for outstanding contribution for Methylation analysis in 2004 and in 2006 was elected a Fellow of the World Technology Network for Biotechnology.

ABSTRACT

Despite the completion of the Human Genome Project we are still far from understanding the molecular events underlying epigenetic change in cancer. Even though it is now accepted that tumour suppressor genes, with CpG island-associated promoters, are commonly hypermethylated and silenced in cancer, and repeat regions are commonly demethylated and genes activated, we do not understood what triggers this process or when it occurs during carcinogenesis. Epigenetic gene deregulation has always been envisaged as a local event silencing discrete genes, but recent data indicates that large regions of chromosomes also can be co-ordinately deregulated. To determine the propensity of genes deregulated in domains in cancer cells, we have integrated *in vivo* gene expression profiles from clinical samples and epigenome tiling arrays, copy number arrays and next generation sequencing to map DNA methylation and histone modifications. We now find that in addition to regional repressive changes in cancer, adjacent genes are also commonly changed to the same epigenetic active state, by progressive DNA demethylation and gain of active histone marks. Our results imply a resetting of the cancer epigenome commonly occurs in domains promoting either repression or activation of adjacent genes.

1220 – 1240

Dr Clare Stirzaker

Garvan Institute of Medical Research, Sydney, Australia

High resolution DNA methylation epigenome sequencing of formalin-fixed paraffin embedded tissue (FFPET) DNA identifies novel epigenetic markers in breast cancer

BIOGRAPHY

Clare Stirzaker is Senior Research Officer in Sue Clark's Epigenetics Laboratory, in the Cancer program at the Garvan Institute of Medical Research, Darlinghurst, Sydney. She has performed extensive Chip-on-chip in prostate cancer cell lines (Coolen and Stirzaker et al, Nat Cell Biology, Vol 12 No3, March 2010) as well as developing genome-wide DNA methylation analysis using MBDCapture technique on microarrays and more recently MBDCap followed by Illumina sequencing. She has extended this to analysing the methylation profile of clinical samples in breast cancer samples.

ABSTRACT

Despite the completion of the Human Genome Project we are still far from understanding the molecular events underlying epigenetic change in cancer. Even though it is now accepted that tumour suppressor genes, with CpG island-associated promoters, are commonly hypermethylated and silenced in cancer, we do not understood what triggers this process or where it occurs during carcinogenesis. Since most archival cancer samples are from formalin-fixed paraffin embedded tissue (FFPET), the DNA extracted is often limiting and degraded presenting challenges for genome-wide DNA methlyation studies. We have optimized MBDCap-Seq, a method whereby methylated DNA isolated by the MBD2 capture technique (MethylMiner™) is sequenced using next generation Illumina sequencing. We have used MBDCap-Seq to identify novel DNA methylation changes in breast cancer and matched lymph node metastasis. We have built a comprehensive breast cancer methylation map that we will us to validate these changes in a larger cohort of breast cancer samples.

1240 – 1300

Dr Mark Corbett

SA Pathology, Adelaide, Australia

Discovery of mutations that cause epilepsy and intellectual disability using sequence enrichment and next-generation sequencing

BIOGRAPHY

My primary research aim is to identify common points in biological pathways associated with neurological disorders, with a view to understanding the biology of cognition and to provide an in-road for therapies for these devastating conditions. I was awarded my PhD in 2004 from the Children's Medical Research Institute in Westmead characterising the first mouse model for the congenital muscle disease nemaline myopathy. From there, I shifted focus on the study of neurological disorders from muscle to the brain by joining the Neurogenetics Research Program headed by Prof Jozef at the Women's and Children's Hospital in Adelaide. I have progressed towards my research aim by contributing to the discovery and characterisation of mutations, in a host of genes with diverse molecular functions, associated with intellectual disability (for a review see, Shoubridge & Corbett (2009) Trends genet. 25: 308 – 16). This task is achieved using a combination of bioinformatic, cell and molecular biology approaches. Recently, I have successfully endeavoured to accelerate our gene discovery process using the latest technology of targeted sequence enrichment and next-generation sequencing.

ABSTRACT

The epilepsies and intellectual disabilities (ID) are commonly observed, genetically and clinically heterogeneous neurological disorders. In 21% of cases of epilepsy there is clinical overlap with ID suggesting a common underlying genetic basis. The genes identified thus far that are associated with these neurological disorders have diverse functional roles and this confounds novel mutation discovery using candidate gene screening approaches. To circumvent this, we mapped the chromosomal locus harbouring the disease causing mutation in a family with autosomal recessive epilepsy and ID using linkage and then used all expressed sequences, based on EST data, as well as putative promoters 2 kb upstream of known genes in the interval as the template to design arrays for sequence enrichment and next-generation sequencing. Up to 8 million, 65bp reads from the Illumina GA II platform were assembled against the reference sequence using open-source software to get an average of 60 fold coverage of target regions. We filtered out known, single nucleotide polymorphisms using available public data and prioritised analysis of rare variants occurring within open reading frames of known genes. We discovered a mutation in a previously uncharacterised, putative Rho GTPase activator *TBC1D24*. We show this gene to be a powerful modulator of neuronal cell morphology and that the mutation we identified ablates this function. Targeted sequence enrichment and next generation sequencing is revolutionising novel disease gene discovery. We will discuss how, this technology has allowed us to take a direct, unbiased and highly effective approach from phenotype to the mutation.

SESSION 3: Profiling Technologies 2

Chair: Vikki Marshall
Grand Ballroom 2/3

1400 – 1445

Dr Phillip Stephens

Wellcome Trust Sanger Centre, Hinxton, UK

Next generation cancer genome sequencing

BIOGRAPHY

Dr Phil Stephens gained his PhD at Oxford University in clinical genetics. He joined the Cancer Genome project at the Wellcome Trust Sanger Centre, UK at its inception in 2000 and is now a senior scientist. Dr. Phil Stephens has used high throughput mutation detection techniques, capillary DNA sequencing and more recently, Next Generation DNA Sequencing to investigate the genetics/ genomics of multiple cancer types, predominantly breast cancer.

ABSTRACT

Using next-generation sequencing technology, we can now sequence the entire genome of cancer samples, allowing the generation of comprehensive catalogues of somatic mutations of all classes. In addition, it is also possible to focus on more selected regions of the genome, such as protein coding genes or regions that are rearranged. The findings from our first handful of genomes illustrate the potential for next-generation sequencing to provide unprecedented insights into mutational processes, cellular repair pathways and gene networks associated with cancer development. I this talk, I will also review possible applications of these technologies in a diagnostic and clinical setting, and the potential routes for translation.

1445 – 1505

Dr Jeff Jeddeloh

Roche NimbleGen, USA

Genomics technology development for large plant genomes: combining aCGH and array based complexity reduction technology affords base-pair resolution of genomic variation

BIOGRAPHY

Dr Jeddeloh has been with Roche NimbleGen in Madison WI for over two years. He has been a Group Leader in Research and Development focused upon Sequence Capture technology application development and has recently moved into a Directorship within the Business Development group. Before this position he spent six years as a technology developer for Orion Genomics, a DNA methylation technology company in St. Louis, MO, focused upon discovering human cancer associated DNA methylation biomarkers. His undergraduate degree in Biology was received from Washington University in St. Louis in 1992. He completed his Doctoral training in molecular genetics in 1998, having stayed at Washington University. The focus of this work was Arabidopsis DNA methylation mutants. He held an investigators position working on pathogenic Burkholderia sps. for the United States Army in Frederick, MD. Dr Jeddeloh has more than 20 peer-reviewed publications centered upon genome analysis in bacteria, plants, and animals with a focus upon the role of DNA methylation in each genome as a system.

ABSTRACT

High density (>2 million probes) long-oligo arrays underlie variation detection platforms from the coarse level of resolution (1000bp +), with comparative genomic hybridization (aCGH), down to the single nucleotide level, with enrichment and re-sequencing. These two technologies when combined with total design flexibility provide an inexpensive approach to discover, map and characterize genomic variation from large plant genomes like that of soy, canola, cotton, maize and wheat. Variation may take the form of a change in ultra-structure, copy number, or sequence composition. The ploidy and abundance of repetitive elements in large plant genomes has provided technical challenges to base pair resolution of such variation in the past. The utility of coupling different levels of array resolution with next generation sequencing technology in plant genomics will be highlighted by presentation of the aCGH and Sequence Capture results obtained from characterization of 5 crop species and their relatives. Enrichment and re-sequencing results obtained from more than 130,000 exons in maize and soy offer the prospect of making crop genomes into *Arabidopsis* sized analytical units. Strategies for taming poorly characterized genomes will be a highlight of the presentation.

1505 – 1525

Dr Michal Janitz

The University of New South Wales

RNA-Seq global analysis of transcriptome activity and alternative splicing patterns in human hippocampus

BIOGRAPHY

Dr Michal Janitz is a senior lecturer in the School of Biotechnology and Biomolecular Sciences (BABS), the University of New South Wales. Before joining UNSW Michal had been a group leader in the Department of Vertebrate Genomics headed by Prof. Hand Lehrach at the Max Planck Institute for Molecular Genetics (MPIMG) in Berlin, Germany. At the MPIMG Michal focused on the application of genomic technologies, such as DNA microarrays and transfected-cell arrays, in studying mechanisms of transcription in the mammalian cell both in health and disease. In 2008, Michal turned his interest to the emerging next-generation sequencing technologies with the goal of applying them to comprehensive transcriptome studies. Commencing a Senior Lecturer position he implemented the RNA-Seq technology pipeline at BABS in collaboration with the Ramaciotti Centre for Gene Function Analysis (UNSW) and the group of Prof. Marc Wilkins, thus contributing to building the national and international recognition of BABS and the University of New South Wales as a leader in ground-breaking human genome research.

ABSTRACT

The brain is the most complex of human organs with multiple distinct regions each contributing to the cellular heterogeneity of the tissue. Taken with the knowledge that the average mammalian cell expresses at least 350,000 mRNAs we expect to see a complex picture forming. Among the different regions of the brain, the hippocampus has been the subject of intense study due to its essential role in the formation of new episodic and long-term memories. The hippocampus has also been implicated in a number of neurological and psychiatric disorders including epilepsy and Alzheimer's disease. Therefore, a precise determination of the hippocampal transcriptional landscape might provide new insights into the cellular vulnerability underlying the pathogenesis of human neurological disorders. Direct cDNA sequencing (RNA-Seq) is a new tool for whole-transcriptome analysis. The RNA Seq can unequivocally identify splicing and RNA editing products with a single molecule per cell resolution. The depth of RNA-Seq analysis is variable, providing a dynamic range typically an order of magnitude greater than seen with a hybridization array. In this study, we used Illumina Genome Analyzer-driven RNA-Seq analysis to investigate the global transcriptomic landscape of human hippocampus. Unique gene expression levels and specific alternative splicing patterns, as compared to cerebellum and liver transcriptome profiles, were identified. The presentation will also cover the results of the functional analysis of individual gene candidates and discussion of their putative role in the physiology of the hippocampus.

1525 – 1545

Dr Marcel Dinger

IMB, The University of Queensland

Characterization of long noncoding RNAs by ultra deep sequencing of the human transcriptome

BIOGRAPHY

Marcel Dinger completed his undergraduate studies and PhD at the University of Waikato in New Zealand. For his PhD, he studied the DNA-binding proteins of thermophilic microorganisms, with particular focus on archaeal chromatin and its role in transcriptional regulation. To pursue his interest in the control of gene expression, in 2005, he applied and was awarded a postdoctoral fellowship from the New Zealand government to work in the Mattick lab on noncoding RNAs. Marcel was recently awarded a Smart Futures fellowship from the Queensland Government to continue his work with the Mattick group and is also a recipient of a NHMRC Career Development Award.

ABSTRACT

Recent studies show the human genome is pervasively transcribed mostly as long noncoding RNAs (lncRNAs), which have been shown to have diverse functions in cell and developmental biology, including transcriptional co-activation, epigenetic modification, and post-transcriptional regulation. We have shown the expression of specific lncRNAs to be associated with various diseases and developmental processes, including melanoma, breast cancer, HIV infection, ES cell differentiation, T-cell activation and neurogenesis. The recognition that lncRNAs contribute towards disease aetiology and development motivated us to undertake a comprehensive annotation of lncRNAs in the human genome. Using data originating from the Illumina HiSeq 2000 sequencing platform, which comprises more than five billion directional 100 bp and 50 bp paired-end RNA-seq reads from 16 different human tissues, we have assembled the human transcriptome with unprecedented depth. Analysis of the data identifies thousands of novel long noncoding RNAs, the majority of which are transcribed in a differentially regulated manner and many that are In addition to intergenic lncRNAs, lncRNAs are also often found close to protein-coding genes, and can be organized in diverse contexts, including bidirectional, intronic, antisense or overlapping the 3′ or 5′ UTRs. To further understand the implications of these contexts on gene regulation, we performed a comparative analysis of the expression of protein-coding genes and their associated ncRNAs. Our preliminary analyses identify hundreds of lncRNAs that may be directly involved in regulating mRNA expression. Finally, the pervasive transcription of the genome prompts a reconsideration of disease-linked SNPs in noncoding regions of the genome. Our annotation comprises an initial step in considering the majority of disease risk-variants that lie beyond the exome and adds considerable value to genome-wide association studies and personal genomics.

1545 – 1600

Mr Lam Don Nguyen

The University of Adelaide

Genome-wide identification of nonsense-mediated mRNA surveillance targets by RNA-SEQ and exon array

BIOGRAPHY

Lam Son Nguyen is a PhD student from the University of Adelaide. His interests include studying the development of neuronal networks using the latest technology in sequencing and microarray. His PhD project, overseen by Prof. Jozef Gecz and Dr. Mark Corbett, explores the involvement of non-sense mediated mRNA decay surveillance complex in pathology of intellectual disability

ABSTRACT

Nonsense-mediated mRNA decay (NMD) functions to degrade transcripts bearing premature stop codon (PTC) and is also a crucial regulator of gene expression. The complete network of genes that are normally regulated by NMD is unknown. We recently discovered loss of function mutations in UPF3B, a member of the NMD surveillance complex, as the cause of various forms of intellectual disability (ID). We aimed to assess the impact of these UPF3B null mutations on the transcriptome and thus identify genes regulated by NMD that are important for neuronal development. Whole genome expression profiling by RNA-SEQ (Illumina) of polyA RNA extracted from lymphoblastoid cell lines of patients (n=4) identified 597 genes that were de-regulated by at least 2 fold compared to control samples (n=2). These results were validated by Affymetrix Human Exon 1.0 ST array (90% of genes had the same trend of de-regulation) and qPCR (14/15 genes tested). Using RNA-SEQ, we are currently assessing the changes in alternative splicing events, transcription at intronic as well as intergenic regions, where NMD is involved and where exon array cannot confidently detect. Among the de-regulated genes we observed that ARHGAP24, a negative regulator of Rho-GTPase, was highly up-regulated in patients with UPF3B mutations. Primary hippocampal neurons overexpressing ARHGAP24 showed significant reduction in axon length, suggesting that overexpression of this gene contributes to the phenotypes seen in patients with UPF3B mutations. We have identified the bona-fide targets of NMD and further highlight the role of NMD during development, especially that of the brain.

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DAY 3: THURSDAY 16 SEPTEMBER 2010

SESSION 4: Population Genetics

Chair: Ian Campbell
Grand Ballroom 2/3

0830 – 0915

Prof Vanessa Hayes

J Craig Venter Institute, USA

Defining the extent of Human Genome diversity in our oldest living descendents

BIOGRAPHY

Vanessa Hayes has headed a Cancer Genetics Group first at the Garvan Institute for Medical research and then the Children's Cancer Institute Australia in Sydney since 2003. In 2010 she will join the J Craig Venter Institute as Professor of Human Genomics.

Her team has made major contributions to advancing knowledge of genetic susceptibility to prostate cancer in Australian men. Through her initial research work in HIV/AIDS susceptibility in Southern Africa and her interest in understanding the genetic contribution to the observed ethnic differences in prostate cancer incidence and mortality rates, has highlighted the importance of defining human genetic diversity globally. With Sub-Saharan Africa being the roots of anatomically modern humans the team is focused on generating not only a database of human genome diversity that challenges the extremes of modern human genome variation, but adds important content (both rare and common variation) to current databases. This research will contribute to our understanding of human evolution (forager to farmer, as well as out migration out-of-Africa) and disease evolution. Ultimately how genetic variation impacts disease at the level of population-wide susceptibility, initiation and development, disease cause and outcome, as well as individual response to therapy.

ABSTRACT

Southern Africa is not only believed to be the birthplace of all modern humans, but is also home to a wealth of populations as defined linguistically as the Khoisan 'click' speakers and the over 500 Niger-Congo Bantu speakers. The Kalahari Bushmen (Khoisan peoples) represent one of the last remaining hunter-gatherer societies, living for centuries along side agricultural Bantu. With a focus on recently diverged populations, indigenous peoples have largely been excluded from the era of genomics in projects such as the Human Genome Project, the HapMap Project, the 1000 Genomes Project and the emergence of personalized genomes. In this study we present the first complete indigenous personal genomes of a Southern African Bushmen and Bantu individuals, namely !Gubi and the Archbishop Desmond Tutu. Additional exome sequencing of three named Bushmen, as well as genome-wide genotyping of extended populations, provides a glimpse into modern mans evolutionary past. We define the most divergent genomes sequenced to date, with over 1.3 million newly described variants. These sequence variants may not only reflect ancient adaptation to a foraging lifestyle, shed light into human transition and expansion as farmers, but importantly will contribute to a better understanding of current disease allele classifications and pharmacogenetics. The novel variant content is being used to better define genetic diversity across the diverse Southern African Bushman and Bantu populations. Our preliminary studies show the Bushmen represent an anciently divergent population, with as much genetic diversity between two Bushmen as between a European and an Asian. Defining the extent of genetic diversity within modern man will advance a global understanding of the human species and importantly human disease.

0915 – 0950

Dr Tony Papenfuss

Walter & Eliza Institute of Medical Research,
Melbourne, Australia

Sequencing the transcriptome of the Tasmanian devil facial tumour disease

BIOGRAPHY

Tony was originally trained as a mathematician and obtained his PhD from Monash University. For the last 6 years he has been in the Bioinformatics Division at the Walter and Eliza Hall Institute of Medical Research, where he is now head of the Genomic Sequence Analysis lab.

His research is focused on sequence analysis, particularly the development of computational methods and tools for analysing next generation sequence data and for comparative genomics. He applies methods developed in these areas to study diseases like malaria, cancer and the Tasmanian devil facial tumour disease. He has also contributed to 4 eukaryotic genome projects—most recently the wallaby and Great Barrier Reef coral.

ABSTRACT

The Tasmanian devil is threatened with extinction by an unusual contagious tumour known as devil facial tumour disease (DFTD). The disease has caused the wild population to drop from ~150,000 to ~30,000 animals. We know that the tumours are clonal and spread from animal to animal by biting, but we do not fully understand why they are not recognized as a foreign by the host's immune system. One reason for this may be a lack of diversity in MHC class I genes. However, skin grafts between devils are quickly rejected, suggesting that the tumours may have developed additional mechanisms to avoid immune detection. Also we now also see multiple tumour karyotypes in the wild, which could mean they are evolving, though we do not know if they are under selection. Until recently we did not even know what tissue the cancer had emerged from.

To develop further insight into DFTD, and in particular to address questions about its origins, evolution and immunology, we adopted a genomics-approach. We have sequenced the DFTD transcriptome using both the Roche 454 and Illumina GA2x platforms. We have also sequenced the transcriptomes of several normal tissues using the Roche 454 platform. To complicate analyses there is currently no publicly available genome sequence, so we are using a de novo assembly of the transcriptomic data as a reference sequence against which to analyse the Illumina data.

In this talk, I will discuss how we have analysed transcriptomic data from this non-model species and what we have learnt so far.

0950 – 1010

Dr Elizabeth Murchison

Wellcome Trust Sanger Institute Hinxton, UK

Genome sequences of the Tasmanian devil and its transmissible cancer

BIOGRAPHY

Elizabeth Murchison is an NHMRC Overseas Post-doctoral Fellow at the Cancer Genome Project at the Wellcome Trust Sanger Institute. She graduated with a Bachelor of Biomedical Science in 2002 from the University of Melbourne and obtained a PhD in 2007 from Cold Spring Harbor Laboratory in New York. Elizabeth's interest is in the genetics and evolution of clonally transmissible cancers. There are only two known cancers that can be naturally transmitted by the physical transfer of living cancer cells. These are Tasmanian devil facial tumour disease (DFTD) and canine transmissible venereal tumour (CTVT). DFTD is an aggressive facial tumour that affects the Tasmanian devil, the world's largest marsupial carnivore. Spread by biting, DFTD is threatening the Tasmanian devil with extinction. CTVT is a venereal tumour that is spread during coitus and affects dogs worldwide. Genetic studies suggest that CTVT may have first arisen thousands of years ago, making it the oldest known somatic cell line. At the Cancer Genome Project, Elizabeth is using next generation sequencing technologies to sequence the genomes of clonally transmissible cancers. By sequencing the genomes of geographically distinct DFTD and CTVT tumours, she is identifying and analysing genetic variation in the two cancer clones. Her recent previous work has been to use next generation transcriptome sequencing to identify the Schwann cell origin of DFTD.

ABSTRACT

Tasmanian devil facial tumour disease (DFTD) is a clonally transmissible cancer spread by the physical transmission of viable cancer cells between individuals by biting. First observed in 1996, the disease has rapidly spread through the Tasmanian devil population and is threatening to cause extinction of the species in the wild. DFTD results in the appearance of tumours most frequently on the face or inside the mouth of affected Tasmanian devils. The tumours develop into large ulcerating masses which frequently metastasise, and usually cause death of their hosts within months.

The clonal nature of DFTD is supported by both genetic and cytogenetic data. In an effort to characterize the mutational events that have occurred during the evolution of the DFTD clone, we have sequenced the genomes of the Tasmanian devil and its cancer using the Illumina HiSeq2000 platform to approximately 85-fold sequence coverage. In addition, we sequenced mate pair libraries with insert sizes ranging from 3 to 10kb using the Illumina Genome Analyzer II platform.

Using the Phusion2 assembly pipeline, we have produced a draft reference genome assembly for the Tasmanian devil. The genomes of two DFTD cancers isolated from geographically distant devils have been sequenced and aligned against the reference genome to identify genetic variants. We present initial results of our analysis of somatic mutations in the DFTD cancer, and provide evidence for the emergence of distinct phylogenies within the transmissible cancer clone.

1010 – 1030

Dr Desiree Petersen

Children's Cancer Institute Australia, NSW, Australia

Unique admixed population with out-of-Africa roots holds potential to advance complex disease loci identification

BIOGRAPHY

Desiree Petersen is a Research Officer in the Cancer Genetics group at Children's Cancer Institute Australia (CCIA). She obtained her PhD degree (Human Genetics) in 2006 from the University of Stellenbosch, South Africa. During her postgraduate studies she performed research at the University of Maastricht, The Netherlands; National Cancer Institute, U.S.A; and the Garvan Institute of Medical Research, Australia. In December 2006, she was recruited as a postdoctoral fellow to join the Cancer Genetics Group at the Garvan Institute of Medical Research where her research focused on genetic analysis of inflammatory cytokines and their involvement in predisposition to complex diseases, including prostate cancer. In February 2008, she relocated with the Cancer Genetics research team to CCIA where she is currently involved in research projects investigating genetic diversity and complex diseases.

ABSTRACT

Africa has played a key role in expanding our understanding of human evolution and subsequently global genetic diversity amongst populations. We recently demonstrate that the Khoisan (Bushmen) and Bantu people of Southern Africa represent the most diverse populations sequenced to date. Khoisan population numbers are however small within these isolated groups of hunter-gatherers, while many of the click-speaking languages have been lost. The genetic make-up of these survivors from a time period past may however still remain in the present-day admixed populations of Southern Africa. Using over 1 million genome-wide genetic markers, we recently described the genetic structure of a unique admixed group, known as the Coloured population that arose approximately 350 years ago on the southern shores of South Africa. Our analysis predicts genetic contributions from at least four distinct sub-population groups, including Europeans, South Asians, Indonesians and Southern Africans (Bantu), yet only speculates on the possible contribution of the Khoisan people. One of the limitations of our current analysis is the population-bias in the content of genome-wide genotyping arrays towards European and Asian population groups. The use of genome-wide arrays containing novel content of Bantu and Khoisan genetic markers, as well as allele fixation and gender-biased analysis, could potentially attempt to define the contribution of these indigenous populations (Bantu and Khoisan) to the Coloured. We further address the importance of defining population admixture and the significance that recently admixed populations such as the Coloured hold to identify novel highly informative disease loci.

SESSION 5: Bioinformatics

Chair: Gordon Smyth
Grand Ballroom 2/3

1100 – 1145

Dr Leming Shi

National Centre for Toxicological Research, US FDA, Arkanas, USA

Genomics, Bioinformatics, and Personalized Medicine: The MicroArray Quality Control (MAQC) Project

BIOGRAPHY

Leming Shi received a B.Sc. in analytical chemistry from Hunan University, M.Sc. and Ph.D. in computational chemistry from the University of Science and Technology of China and the Chinese Academy of Sciences, respectively, where he also worked as an assistant and associate professor for three years. Between 1994 and 2001, Dr. Shi worked in the US on various positions at Case Western Reserve University, the National Cancer Institute, R.O.W. Sciences at the FDA, Wyeth, and BASF. Dr. Shi was a co-founder and director of informatics at Chipscreen Biosciences Ltd. in Shenzhen, China (2001-2003), where he and his team designed several novel drug candidates that have shown promising profiles in Phases I, II and III clinical trials for treating cancer and type 2 diabetes. Dr. Shi joined the FDA's National Center for Toxicological Research, Jefferson, Arkansas in April 2003, where he conceived and has been leading the MicroArray Quality Control (MAQC) project to properly utilize genomics and bioinformatics for personalized medicine. Dr. Shi has co-authored over 100 peer-reviewed papers and is a coinventor of nine issued patents. Dr. Shi is also an adjunct professor of medicine at the University of Arkansas for Medical Sciences' Myeloma Institute for Research and Therapy.

ABSTRACT

The MicroArray Quality Control (MAQC) project was originally launched by the US Food and Drug Administration (FDA) in 2005 to address concerns about the reliability microarray technologies as well as data analysis issues (http://edkb.fda.gov/MAQC/). The first phase of MAQC (MAQC-I) evaluated technical performance of various microarray gene expression platforms and assessed advantages and limitations of competing data analysis methods for identifying differentially expressed genes (http://www.nature.com/nbt/focus/maqc/). MAQC-II tried to reach consensus on "best practices" of developing and validating microarray-based predictive models for clinical and preclinical applications. MAQC-III (SEQC) is evaluating technical performance and addressing bioinformatics challenges of next-generation sequencing technologies in transcriptome analysis. With broad participation from the academia, industry, and government sectors, the MAQC project is enhancing our capabilities of understanding, predicting, and preventing serious adverse drug reactions with patient-specific genomic information in MAQC-IV (PADRE) toward personalized medicine.

1145 – 1205

Dr Mark Robinson

Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia

Joint analysis of copy number and enrichment-based epigenomics sequencing data

BIOGRAPHY

Mark is a postdoctoral fellow jointly between the Bioinformatics Division at WEHI (Melbourne) and the Epigenetics Laboratory at the Garvan Institute (Sydney). With a background in Statistics (B.Sc. 1999, M.Sc 2001), Mark joined a Functional Genomics laboratory in Toronto (Tim Hughes), followed by a stint at a proteomics biotechnology company (MDS Proteomics) and a year in the Probabilistic and Statistical Inference group (Brendan Frey) in 2004. In 2005, Mark undertook Ph.D. studies with Terry Speed and Gordon Smyth at WEHI Bioinformatics, studying the statistical analysis of microarray and other genomic datasets. In 2008, Mark joined Sue Clark's Epigenetics lab as the lead statistical bioinformatician.

ABSTRACT

Epigenetics, the study of heritable somatic phenotypic changes unrelated to DNA sequence, has emerged as a critical component of gene regulation. Among others, two important epigenetic mechanisms are the modification of histone proteins and methylation of DNA, primarily in the CpG dinucleotide context. One of the popular techniques for studying DNA methylation genome-wide is the capture of methylated DNA using immunoprecipipation, either to 5-methylcytosine (MeDIP) or methyl-CpG binding domain proteins (MBDIP). Similarly, the only technique for studying histone modifications is chromatin immunoprecipitation (ChIP). As might be expected, all immunoprecipitation-based techniques are susceptible to copy number aberrations of the underlying genome and failing to account for these can impact both absolute and differential analysis of epigenomes. Such copy number aberrations are especially prevalent in the analysis of cancer genomes. We demonstrate the impacts of copy number of enrichment-based epigenomics data and propose a statistical approach that integrates copy number estimates into the analysis of sequencing-based epigenomic data. The method can use copy number information from any platform, such as SNP arrays, competitive genome hybridization or genomic sequencing.

1205 – 1225

Dr Kim-Anh Le Cao

QFAB, The University of Queensland, Brisbane, Australia

MixOmics for integration and variable selection of 'omics' data sets

BIOGRAPHY

Dr Kim-Anh Le Cao obtained her Ph.D in Statistics from University of Toulouse and the Institut National de la Recherche Agronomique in 2008 and was awarded the Marie-Jeanne Laurent Duhamel prize from the French Statistical Society for the best thesis in applied statistics. She currently works as a Biostatistician in the Queensland Facility for Advanced Bioinformatics (QFAB) at the University of Queensland. Kim-Anh's research is focused on the development of statistical approaches to co-jointly analyse high dimensional biological data sets, in particular microarray and other `omics' data sets.

ABSTRACT

With the availability of many `omics' data, such as transcriptomics, proteomics or metabolomics, the integrative or joint analysis of multiple datasets from different technology platforms is becoming crucial to unravel the relationships between different biological functional levels. However, the development of such an analysis is a major computational and technical challenge as most approaches suffer from high data dimensionality, as the number of measured variables p is much greater than the number of samples n.

Partial Least Squares methods offer a great flexibility and can be applied to various high dimensional problems. In particular, it has been specifically designed to integrate two data sets. Recently, we further improved PLS by introducing Lasso penalizations to simultaneously perform variable selection on two data sets (e.g. transcriptomics and metabolomics) where the variables are measured on the same samples (Le Cao et al. 2008, 2009a,b). This internal variable selection step enables the identification of relevant variables that covary.

We illustrate the versatility of sparse PLS on several biological studies and demonstrate the biological relevance of the obtained results in terms of selected genes and metabolites. With the use of valuable graphical outputs, we show that the results of sPLS are easy to interpret for the biologists. Relevance networks and Clustered Image Maps were also proposed to better understand the correlation structure between the different types of variables.

Sparse PLS and other exploratory approaches such as regularized Canonical Correlation analysis are now implemented in the mixOmics R package.

1225 – 1300

Ms Katherine Smith

Walter & Eliza Institute of Medical Research, Melbourne, Australia

Refining genetic associations with Hepatitis C treatment response using targetted MPS of pooled DNA samples following GWAS

BIOGRAPHY

Katherine Smith is currently employed in Dr Melanie Bahlo's Statistical Genetics group, which is part of the Bioinformatics Division at the Walter and Eliza Hall Institute of Medical Research, Melbourne. She holds an undergraduate Honours degree in Genetics and a Masters in Biostatistics.

She uses SNP genotyping arrays to map mutations that cause familial epilepsies, as well as working on massively parallel DNA sequence data.

ABSTRACT

Background: Four independent genome-wide association studies (GWAS) have identified associations between response to treatment of chronic Hepatitis C infection and the IL28A/IL28B region on chromosome 19. We aimed to further refine association signals in this region using massively parallel sequencing (MPS) of individuals from the GWAS performed by Suppiah et al (Nat Genet 41(10),1100; 2009).

Methods: DNA samples from 100/131 responders and 99/162 non-responders were pooled separately. PCR was used to amplify a continuous 100 Kb region around IL2A/IL2B for each pool, with 75 bp paired-end reads generated using Illumina's Genome Analyzer II technology. BWA was used to align reads to the human genome, VarScan to identify single nucleotide variants (SNVs) and indels, and the allele-based chi-squared test to compare allele frequencies at SNVs following rescaling of allele counts to the number of chromosomes in each pool.

Results: Optimisation was required to avoid misalignment of reads due to the 97% sequence similarity between IL28A and IL28B. 8x or better coverage was achieved for >98.5% of the target region for both cohorts. VarScan identified around 5,000 putative SNVs and 100 putative indels across the two cohorts. Of these, around 40 showed stronger association with treatment response than the best SNP identified by the original GWAS (i.e. p>4 x 10^-5). Laboratory validation of these results is in progress.

Conclusions: Aligning short reads to regions containing gene duplications is challenging. MPS of pooled DNA samples following GWAS has identified a number of variants that warrant further study.

1245 – 1300

Mrs Anna Campain

The University of Sydney, Australia

Integrating gene expression and clinical data in melanoma prognosis predictions

BIOGRAPHY

Anna Campain is a PhD student in the School of Mathematics and Statistics at the University of Sydney. She is completing her PhD under the advisement of Dr Jean Yang and Dr Samuel Mueller. Her research interests include the application of statistics to problems in genomic and medical research.

ABSTRACT

Melanomas are common in a large demographic of the population. Considered a relatively minor cancer when treated successfully, a significant percent of melanoma patients metastasise from their primary sight. Of those that metastasise, about 40% go on to live cancer free, but another 40% succumb to the disease in less than 1 year. Here, we examine statistical issues and methods that aim to produce a prediction method by incorporating different types of data.

We examine predictive models that integrate both a clinical signature, obtained through the interaction of clinical, pathological and mutation predictors as well as a molecular signature developed through the expression data. Developing a clinical signature is potentially cumbersome. Clinical data offers a diverse range of challenges that need to be overcome. For example, missing data within clinical, pathological and mutation variables are common and problematic. We examine how the proportion of missing data can affect regression coefficients and how this translates into issues with clinical data. Missing datum can be overcome through careful multiple imputation when missingness is not too great. When subgroups of particular variables, especially pathological and mutation variables, are small, care is needed to ensure the development of a stable model. In addition, we discuss issues and challenges associated with agreement between the molecular signature obtained through our expression data and other signatures within literature. The process of combining clinical and molecular signatures is non-trivial and we explore issues associated with this including scaling and validation.

Prof Simon Foote

Menzies Research Institute, University of Tasmania, Australia

The genetics of the host-malarial parasite interaction

BIOGRAPHY

Professor Simon Foote is director of the Menzies Research Institute Tasmania. His research interests revolve around the genetic analysis of disease. He uses mice to study the host response to infectious disease and his laboratory is working towards a new range of antimalarial compounds mimicking the natural genetic mutations mediating clinical resistance in endemic populations. He is also involved with teams mapping susceptibility genes in humans, notably Multiple Sclerosis, Haematological Malignancies and Renal Failure. He was involved in the early days of the human genome mapping project at the Whitehead Institute, MIT and was one of the founders of the Australian Genome Research Facility

ABSTRACT

The complicated interaction between the host and the malarial parasite has been studied by our group using several model systems. We have been interested in genes that mediate outcome to infection. Originally we have mapped quantitative trait loci using differential susceptibility outcomes between inbred strains of mice. This has resulted in one locus that may give up a gene, however all other loci mapped have been complex with phenotypes diluting to unmappable levels as small effect loci are separated on congenic backgrounds.

We have therefore turned to a Mendelian approach to map genes responsible for host response to malarial infections. We use ENU to mutate the genome of susceptible male mice and then breed them to isogenic females, challenging the offspring (G1) with malaria, screening on survival. Further crossing to an isogenic mouse and challenge of the offspring (G2) confirms (or not) the genetic origin of an increase in resistance to the parasite. These loci are then mapped and the mutation identified by either sequencing candidate genes or by selection of exons by array capture and then nextGen sequencing the captured products. To date we have over progeny-tested 25 mutant lines and we have mapped 6 of these lines and have identified one mutation.

1445 – 1520

Dr Ross Dickins

Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia

Modeling cancer therapy using transgenic and retroviral RNA interference in mice

BIOGRAPHY

Ross Dickins did his PhD with Professor David Bowtell at the Peter MacCallum Cancer Centre/University of Melbourne. As a postdoc in Professor Scott Lowe's laboratory (Cold Spring Harbor Laboratory, New York) he developed RNA interference technology allowing the stable or reversible inhibition of endogenous gene expression in cultured cells, and reversible, tissue-specific gene knockdown in transgenic mice. Ross returned to Melbourne in 2008 and is currently a VESKI Fellow, Nossal Fellow, and group leader at the Walter and Eliza Hall Institute. His laboratory uses in vitro and in vivo RNAi to investigate haematopoiesis in the mouse, with particular focus on developing new models and treatment strategies for leukaemia.

ABSTRACT

Leukaemia results from multiple genetic mutations that disrupt the normal regulation of self-renewal, proliferation, differentiation, and apoptosis of blood cell progenitors. Recent SNP-based copy number analyses of lymphocytic (B and T cell) leukaemias from large patient cohorts have identified frequent mono-allelic deletions in Pax5 and Ikaros, two transcription factors that normally orchestrate lymphocyte differentiation. To model the leukaemogenic effects of these hypomorphic mutations, we have used RNAi to inhibit Pax5 or Ikaros expression in mice. Infection of cultured hematopoietic progenitor cells with retroviral vectors that co-express a short hairpin RNA (shRNA) and GFP allows us to track the effects of gene knockdown on lineage commitment, either in culture or in reconstituted chimeric mice. In keeping with the known role of Pax5 in B cell commitment, its knockdown blocks B cell differentiation in vivo but is not leukaemogenic. In contrast, Ikaros knockdown causes aggressive, GFP+ T cell leukaemias in mice. To model 'differentiation therapy' we have recently engineered leukaemia's that are driven by reversible Ikaros knockdown, and find that shutting off Ikaros shRNA and restoring endogenous Ikaros expression leads to rapid leukaemia regression in vivo. By examining the mechanisms of tumour cell clearance and the early, global gene expression changes that occur upon Ikaros restoration, we hope to shed light on the mechanisms by which this transcription factor normally suppresses leukaemogenesis. These studies provide proof of principle for the use of retroviral and transgenic RNAi technology to mimic genetic lesions that disrupt lineage differentiation in human leukaemias. By modeling genetic changes recently associated with human leukaemia, we have produced new animal models for testing therapeutic responses. We are currently using retroviral shRNA pools in combination with next generation sequencing technology to perform shRNA 'loss of representation' screens that may identify potential new drug targets in these leukaemias.

1520 – 1540

Dr David Fung

University of New South Wales, Australia

Systems modelling of myocardial infarction in *Mus musculus* using microarray expression data

BIOGRAPHY

David moved from molecular genetics to bioinformatics in 2000 and after finishing his PhD in 2010, he moved to systems biology. David's defines systems biology as a discipline of complex systems research. Since all complex systems can be modeled as a network, he decided to specialize in modelling expression data as a network. His first network model constructed was on the molecular system of hepatocellular carcinoma (HCC) which integrated gene-gene co-expression, protein-protein interaction, microRNA-gene interaction, gene-disease relationships, and gene-Gene Ontology (GO) relationships. Currently, he is trying to understand the systems biology of myocardial infarction in collaboration with Dr Ruby Lin of the University of New South Wales and Dr Julie McMullen of the Baker IDI Heart and Diabetes Institute, Melbourne.

ABSTRACT

Myocardial infarction (MI) is a common life-threatening cardiac condition associated with atherosclerosis. Previous studies using transgenic mouse models suggested that the targeting of the IGF1R-PI3K (p110alpha) pathway could be a potential therapeutic strategy against MI [1]. The current consensus is that this pathway, when activated, regulates physiological hypertrophy and cardiac protection whereas activation of other signalling cascades including those downstream of G protein-coupled receptors (GPCRs) regulates pathological hypertrophy. Recently, we demonstrated the protective role of PI3K(p110alpha) against MI in transgenic mice with a constitutively active (ca) mutant of PI3K(p110alpha). In contrast, transgenic mice with a dominant negative (dn) mutant of PI3K developed heart failure sooner when suffering from MI than control mice. However, the underlying mechanism remains poorly understood. In order to investigate the systems effect of PI3K(p110alpha) inactivation on the network of known pathways, we first computed the differential co-efficients from microarray data obtained from ventricles of non-infarcted (Sham) and MI operated caPI3K and dnPI3K transgenic mice (relative to non-transgenic controls). We then overlaid the differential co-efficients for each condition (Sham or MI) onto the REACTOME pathway map using SkyPainter. Such an approach allowed us to visually compare the two conditions for their global differences in differential gene expression in the context of cellular pathways

In the Sham condition (dnPI3K vs caPI3K), the dnPI3K mutant is relative inactive in signalling, transport and metabolism compared to its caPI3K counterpart with the global down-regulation of all pathways. In particular, over half of the molecular interactions in diabetes-related, haemostasis, energy integration and apoptosis pathways were down-regulated. Approximately half of the protein interactions in GPCR signalling pathways were also down-regulated. In contrast, the global up-regulation of pathways has been observed in the MI condition. Over half of the molecular interactions in apoptosis, carbohydrate metabolism, and lipid metabolism were up-regulated in the dnPI3K mutant. One interesting finding is that the global variance of differential coefficients in the Sham condition is comparable to its counterpart in the MI condition (F-test score = 0). That means the global down-regulation seen in the Sham case varies as much as the global up-regulation seen in the MI case. Together, these observations suggest that PI3K(p110alpha) is a pivotal point in the molecular network for maintaining cardiomyocyte homeostasis. The abrogation of PI3K(p110alpha) activation may have led to the network phenomenon called cascading failure in which a successive series of transcriptional down-regulation had occurred. When challenged by the extreme physiological stress exert by MI, cardiomyocyte in the dn mutant has to up-regulate numerous pathways to compensate for the loss of PI3K activation.

Another interesting finding is the differential co-efficient of several genes that are junction points to multiple pathways are comparable between both conditions. This suggested to us that several pathways consisting of up-regulated genes in the MI condition may be de-coupled but its significance to heart failure is yet to be further investigated.

In conclusion, the comparison between the Sham and MI conditions for their difference in gene expression using REACTOME mapping revealed to us the pivotal role of PI3K(p110alpha) in cardiomyocyte homeostasis.

1540 – 1600

Ms Charity Law

Walter & Eliza Hall Institute, Melbourne, Australia

A novel method of measuring erythropoiesis in anemia using gene expression data from bone marrow

BIOGRAPHY

Charity is a first-year PhD student at The Walter and Eliza Hall Institute of Medical Research. Under the supervision of Gordon Smyth, my area of research is in statistical bioinformatics. Charity has mainly worked on Illumina microarrays with a focus on malaria

ABSTRACT

Malarial anemia is a serious health concern, accounting for more than half of all childhood deaths from malaria in Africa. In severe malarial anemia, replacement of the large number of destroyed erythrocytes is thought to be inadequate due to suppression of erythropoiesis, the process of erythrocyte differentiation via erythroid progenitor, erythroblast and reticulocyte stages. Very little is known about erythropoietic suppression in human malarial anemia because of the lack of accurate methods for quantifying erythropoiesis.

In this microarray study, we had the unique opportunity of studying gene expression in bone marrow of a large cohort of anemic children from Mozambique. We have developed two new tools of quantifying erythropoiesis: a flow-cytometric tracking of erythroid differentiation and an expression score based on genes expressed in erythroblasts (EB score). Both of these measures are highly correlated with the numbers of orthochromatic erythroblasts in the bone marrow.

The two methods were used to evaluate the usefulness of measurements of peripheral blood and we found that the RDW (red cell distribution width) is better measure of erythropoiesis than the commonly used percentage of peripheral reticulocytes. We discovered that erythropoiesis was mainly regulated at the transcriptional level. The erythropoietically suppressed anemics had significantly lower EB scores than the active group, but surprisingly, their EB scores were higher than those of a mildy anemic control group, indicating that their erythropoiesis is only partially suppressed.

Some interesting aspects of microarray data analysis will be discussed, including the identification and correction of batch effects by subtracting an estimate from the normalized and background corrected expression scores. The analysis using the EB score demonstrates the usefulness of transcriptional signatures constructed from microarray data.

DAY 4: FRIDAY 17 SEPTEMBER 2010

SESSION 7: Gene Regulation 1

Chair: Alicia Oshlack
Grand Ballroom 2/3

0900 – 0945

Assoc Prof Xiaole Shirley Liu

Dana-Farber Cancer Institute, Boston, USA

Inferring transcription regulatory mechanism from nucleosome dynamics

BIOGRAPHY

Our laboratory focuses on the design of statistical and computational algorithms to discover and explore the genomic sequence elements related to gene regulations. We are especially interested in Chromatin ImmunoPrecipitation coupled with DNA microarray analysis (ChIP-chip) to study the effect of transcription factor binding on transcription regulation. ChIP-chip studies the in vivo transcription factor binding locations in the genome. In the past few years, our laboratory has excelled in computational sequence motif finding and has developed a number of widely-used motif-finding algorithms for different biological applications

ABSTRACT

Transcription factor (TF) ChIP-seq has been widely adopted to study transcriptional control over important biological processes and diseases. However, three major challenges exist for TF ChIP-seq: knowledge of the TFs of interest beforehand, availability of ChIP-quality antibodies for the TFs, cost of doing individual TF ChIP-seq separately. We describe a method to detect in vivo cell type and condition specific transcription factor binding locations through an integrative analysis of differentiation – or stimulus-induced shifts in nucleosome occupancy and DNA sequence data. We use a Bayesian statistical framework to integrate histone mark ChIP-seq data on nucleosome occupancy shifts with DNA sequence and transcription factor binding motifs to estimate probabilities of transcription factor binding at sites flanked by two positioned nucleosomes. Using this method we screen a library of known transcription factor DNA binding motifs to infer transcription factor binding sites and the identity of transcription factors that are the key regulators of cell differentiation or a response to a stimulus.

0945 – 1020

Prof Frances Shannon

John Curtin School of Medical Research ANU, Canberra, Australia

Determining the basal chromatin signature of inducible genes in immune cells

BIOGRAPHY

Professor Frances Shannon is Deputy Vice Chancellor Research at the University of Canberra with responsibility for developing and implementing the research strategy of the university, research education and training, university research centres and research and research student management. Professor Shannon was educated in Ireland at University College Dublin completing a BSc (Hons) and a PhD in biochemistry there before moving to Australia.

Professor Shannon was previously interim Director (2008-2009) and Deputy Director (2007-2008) of the John Curtin School of Medical Research (JCSMR) at the Australian National University. She has also served as head of the Division of Molecular Bioscience at JCSMR and her underlying academic role was as Professor and Group Leader, Gene Expression and Epigenomics Laboratory. Prior to moving to the ANU she was a postdoctoral fellow at the University of Adelaide and then Founding Member of the Hanson Centre for Cancer Research at the Institute of Medical and Veterinary Science in Adelaide, South Australia.

Professor Shannon has had a successful career in biomedical research, research supervision and administration. She has a significant record in attracting major competitive grants and infrastructure support, in publishing her research in high impact international journals and in training PhD students and postdoctoral fellows. She has developed a number of productive national and international research collaborations that have provided important contributions to understanding immune cell function and development. She remains a Professor (honorary) of the Australian National University where she continues to run her research laboratory.

Professor Shannon has served on numerous national bodies and assessment panels especially for the National Health and Medical Research Council and has recently contributed to the national agenda for investment in bioplatform technologies and "omics" technologies through Bioplatforms Australia and NCRIS. During 2009, she was instrumental in developing the ANU strategy for bioscience research as the University restructured and developing a university – wide strategy for genomics technology investment.

Professor Shannon is leading the development of research at the university by devising and implementing a strategy to improve the quality and quantity of research activity. The major areas of development include; identifying clear areas of research focus based on current capability and future opportunity, developing innovative research training strategies and creating productive national and international research linkages.

ABSTRACT

Covalent histone modifications such as acetylation, methylation and phosphorylation provide landmarks in the chromatin, are associated with specific gene expression states and play a role in controlling gene transcription. Using cells of the immune system as a model with both genome-wide (ChIP-chip and ChIP-seq) and gene-focused (ChIP-qPCR) approaches we asked whether inducible genes displayed a specific chromatin signature in the basal state. We found that inducible genes with low basal expression, especially rapidly induced primary response genes, are more likely to display the chromatin characteristics of active genes than their non-responsive counterparts with the same low basal expression profile. In addition, inducible genes are also more likely to have RNA polymerase II at their promoters in the basal state with the vast majority of genes with an active chromatin signature also having promoter PolII. These data suggest a possible poised state for many inducible genes that has been shown in studies of yeast and Drosophila. However, we find that many genes with promoter PolII also display evidence of elongation as measured by chromatin marks and DRB inhibition studies with a relatively small number having promoter PolII but lacking elongation marks (ie. truly poised). Despite evidence of ongoing transcription in the basal state, the majority of genes examined show an increase in PolII recruitment and elongation marks but little or no change in the other active chromatin marks. These data suggest that the mRNA expression level for many inducible genes is controlled at the level of PolII recruitment and elongation rate.

1020 – 1040

Dr Sudha Rao

John Curtin School of Medical Research ANU, Canberra, Australia

Chromatin-associated protein kinase C-θ regulates an inducible gene expression program and microRNAs in human T lymphocytes

BIOGRAPHY

Dr Sudha Rao's research focuses on deciphering the epigenetic signatures in the context of the immune system. She has extensive experience in transcriptional biology and genomic technologies that spans both pharmaceutical and academic settings

ABSTRACT

Studies in yeast have demonstrated that signalling kinases with well-known cytoplasmic functions have a surprisingly active role in the nucleus, where they are tethered to chromatin and modulate gene expression programs. Despite these seminal studies, the nuclear mechanism of how signalling kinases control transcription of mammalian genes is in its infancy. Here we provide evidence for a hitherto unknown function of the signal transduction kinase, protein kinase C-theta (PKC-θ), which physically associates with the proximal regulatory regions of key inducible immune response genes in human T cells. Chromatin-anchored PKC-θ forms a previously undescribed active nuclear complex by interacting with RNA polymerase II, the histone kinase MSK-1 and the adaptor molecule 14-3-3ζ. Genome-wide analysis reveals that PKC-θ binds directly to both the promoter and transcribed regions of a distinct cohort of protein-expressing genes, as well as to the promoters of specific microRNAs crucial for cytokine regulation. Additionally, these microRNA genes are implicated in cell migration and invasion, which may contribute to PKC-θ's importance in breast cancer, as shown here in an epithelial to mesenchymal transition system. Our results for the first time provide a molecular explanation for the role of PKC-θ not only in normal T cell function, but also in circumstances of its ectopic expression in cancer. These findings exemplify a more general role for signalling kinases as regulators of gene transcription in mammalian cells that act by two distinct mechanisms; (1) cytoplasmic signalling to the nucleus, and (2) direct association with chromatin-bound transcription complexes at activated target genes.

1040 – 1100

Dr Matthew Young

Walter & Eliza Institute of Medical Research, Melbourne, Australia

Using ChIP-seq to identify distinct and functionally correlated classes of PRC2 binding across genes in mouse

BIOGRAPHY

Matthew Young completed his undergraduate studies at the University of Melbourne, receiving a Bachelor of Arts/Bachelor of Science in 2007. In 2008 he completed an honours year studying astrophysics in the physics department, also at the University of Melbourne. Since then he has been working for the Bioinformatics Division at the Walter & Eliza Hall Institute, specializing in the analysis of sequencing data. His particular focus has been on the analysis of technical biases in RNA-seq and the analysis of ChIP-seq data for histone modifications.

ABSTRACT

The Polycomb Repressor Complex PRC2 is a methyltransferase that catalyses trimethylation of Histone 3 at Lysine 27 (H3K27). To investigate the role of PRC2 during differentiation we used chromatin immunoprecipitation followed by high throughput second-generation sequencing (ChIP-seq) to study the complex in mouse ES cells and the more differentiated G1ME blood cell line. Antibodies specific for H3K27 trimethylation and RNA-pol II were used to measure PRC2 binding and the presence of transcriptional machinery. We developed a ChIP-seq visualization tool that enabled us to identify genes with distinct binding patterns. Specifically, we identified three distinct classes of PRC2 binding in and around genes. By combining our ChIP-seq data with publicly available expression and histone modification data, we found that these distinct classes are strongly correlated with functional properties such as gene expression level. We further showed that genes enriched for H3K27me3 can undergo major changes in their pattern of H3K27me3 during differentiation. As further validation of our findings, we showed that the same classes of binding can be found in other, publicly available, ChIP-seq H3K27me3 data for mouse embryonic fibroblasts (MEFs). Surprisingly, we found that genes with strong trimethylation of H3K27 upstream of their transcriptional start site were more highly expressed than average. This result was consistent in ES cells, G1ME cells and MEFs, indicating that PRC2 has a key role in tuning the expression level of a small subset of actively transcribed genes.

SESSION 8: Gene Regulation 2

Chair: Susan Clark
Grand Ballroom 2/3

1130 – 1205

Prof Liz Musgrove

Garvan Institute of Medical Research, Sydney, Australia

Using large-scale gene expression and functional genetic analyses to identify mechanisms of estrogen action and endocrine resistance in breast cancer

BIOGRPAHY

Prof Liz Musgrove's research aims to elucidate mechanisms of cell cycle control in breast cancer and to understand the impact of their deregulation on cancer development, progression and therapeutic responsiveness. She uses a systems biology approach to understanding steroid hormone action on the cell cycle by identifying regulators of breast cancer cell proliferation, elucidating their inter-relationships, and dissecting their functions using techniques including functional genetic screens. This knowledge will be used to identify clinically useful markers of disease progression or therapeutic response and to develop a mechanistic understanding of endocrine resistance, a major limitation to the successful treatment of breast cancer.

ABSTRACT

Estrogen regulates cell proliferation and survival in the normal breast and breast cancer and consequently the antiestrogen tamoxifen has been the most widely used adjuvant endocrine therapy for estrogen receptor-positive breast cancer patients for over 20 years. Unfortunately, intrinsic and acquired resistance to tamoxifen limits its clinical utility. Cyclin D1 and Myc are estrogen target genes that can mimic estrogen's ability to promote cell cycle progression and cause antiestrogen resistance when overexpressed in vitro. To dissect the relative contributions of pathways downstream of cyclin D1 and Myc to estrogen action, and potentially to antiestrogen resistance, we have undertaken a comparative analysis of transcript profiles of MCF-7 breast cancer cells following estrogen treatment in the presence or absence of siRNAs targetting Myc or cyclin D1, and following Myc induction. Pathway analysis based on functional annotation of the estrogen-regulated genes identified gene signatures with known or predicted roles in cell cycle control, cell growth (i.e. ribosome biogenesis and protein synthesis), cell death/survival signaling and transcriptional regulation. Genes regulated by cyclin D1 and Myc made different contributions to these distinct cellular processes. For example, genes regulated following c-Myc induction accounted for half of all estrogen-regulated genes, and half of the genes in the cell cycle signature. However, 85% of genes in the cell growth signature were c-Myc-regulated, and c-Myc induction was necessary for estrogen regulation of ribosome biogenesis and protein synthesis. Thus, although estrogen regulates the cell cycle by effects on both c-Myc and cyclin D1, it regulates cell growth principally via c-Myc. To aid the identification of genes that have a critical role in mediating antiestrogen effects on cell proliferation we are also undertaking functional genetic screens to identify genes whose increased or decreased expression modifies sensitivity to antiestrogen-mediated growth arrest in cultured MCF-7 cells. The libraries used include genes that are estrogen-regulated or expressed at low levels in women who had a poor response to tamoxifen treatment. Integration of the results of these screens with our transcript profiling data is expected to reveal cellular responses and pathways that are potential mediators of therapeutic response. This in turn should aid in identification of the specific genetic events that cause resistance, and means by which they can be targetted therapeutically

1205 – 1240

Dr Rohan Williams

John Curtin School of Medical Research ANU, Canberra, Australia

Detecting trans-acting regulatory variation in mammalian transcriptomes

BIOGRAPHY

Rohan Williams has worked in genetics, genomics and bioinformatics since 2003 following completion of his PhD in gastrointestinal clinical physiology (UNSW). Between 2004 and 2007 he was an NHMRC Peter Doherty Fellow at the University of New South Wales with Peter Little. He was appointed Group Leader at the John Curtin in 2007. He and his group are interested in modern approaches to genotype-phenotype correlations and the mechanisms underlying inter-individual variation, particularly at the level of global gene expression, variation in epigenomic phenomena and the applications of these ideas in developing personalised biomarkers for preventative health applications.

ABSTRACT

Determining how genetic variation influences global gene expression is a key problem in our understanding of genotype-phenotype relationships. Current approaches to measuring expression variation, based on genome-wide genetic linkage or association analysis, are quite successful at measuring cis-regulatory variants, while detection of trans-regulatory variation remains challenging. I will describe our recent work on this problem, employing regulatory motif data from the human genome, in combination with transcriptomic and genotype data from large study cohorts, to develop new approaches to the identification of regulons influenced by trans-acting regulatory variants.

1240 – 1300

Assoc Prof Thomas Lufkin

Genome Institute of Singapore, Singapore

Sox9-directed Gene Regulatory Network Controlling Murine Embryonic Skeletal Development

BIOGRAPHY

Thomas Lufkin is a Senior Group Leader in Stem Cell & Develelopmental Biology, Genome Institute of Singapore Associate Professor, Dept. Biological Science, National University of Singapore Associate Professor, School of Biol. Science, Nanyang Technological University

He completed postdoctoral training at the LGME, Strasbourg, France, in Molec Embryology (with Pierre Chambon) He received his PhD from Cornell University in Molecular Biology and Virology He received his AB from the University of California, Berkeley in Cell Biology He received the March of Dimes Basil O'Conner Jr. Faculty Award, was a Lucille B Markey Scholar in Molecular Biology, received an Alfred P Sloan Research Fellowship in Neuroscience, an American Cancer Society Postdoctoral Fellowship and a Morton J Levy Predoctoral Fellowship. He is serving as an editorial board member of 3 reputed journals. He has 74 publications

ABSTRACT

Sox9 is critical for embryonic chondrogenesis and skeleton formation, yet few direct target genes are known, limiting our understanding of this biological process. We reveal here for the first time a highly detailed gene regulatory network (GRN) anchored by Sox9. Expression profiling of wildtype, heterozygous and null Sox9 cells isolated from staged living embryos, identified 6124 differentially expressed genes as Sox9 "downstream" targets. In situ hybridization validated key targets, including Col2a1, Matn4 and Hapln1. In parallel Sox9 chromatin immunoprecipitation-sequencing (ChIP-Seq) mapped the Sox9 binding genomic loci. Along with the canonical Sox9 binding motif, we also identified 2 novel Sox9 motifs and further confirmed their direct binding and regulation by Sox9. The integration of gene expression profiling and Sox9 DNA binding data has enabled us to identify a set of Sox9 direct and in-direct target genes and successfully led to the elucidation of the Sox9-directed GRN controlling mammalian skeletogenesis.

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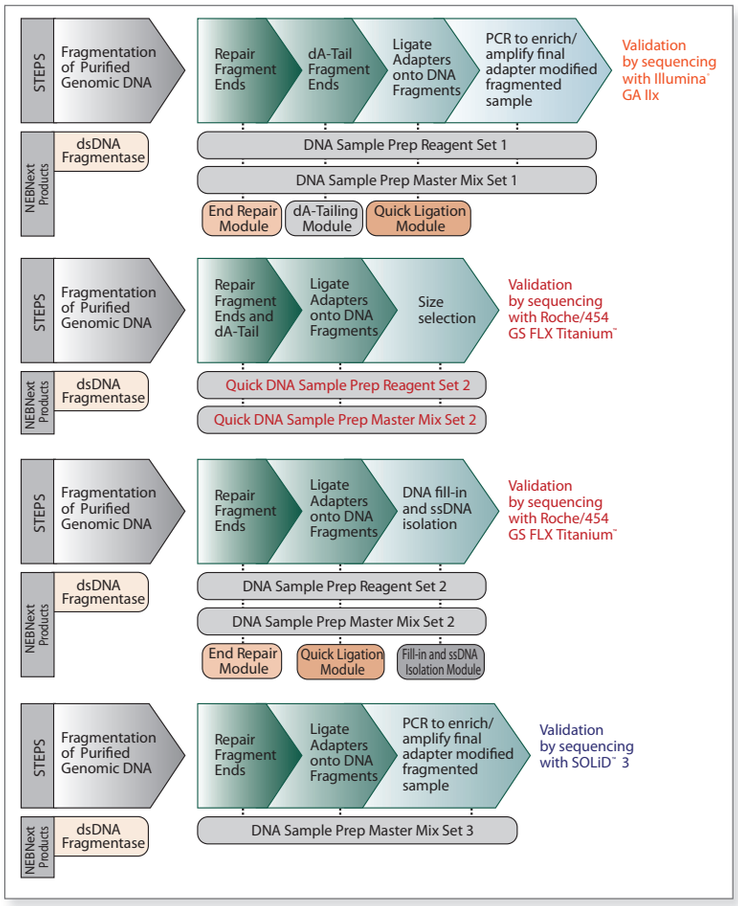
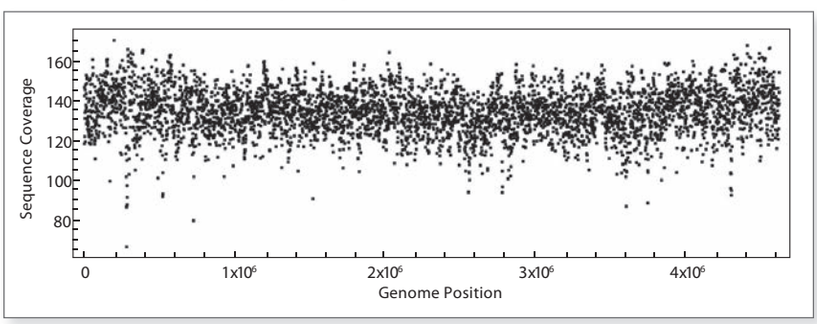


Genome sequence coverage of a library prepared with NEBNext DNA Sample Prep Reagent Set 1



Depth of coverage across the E. coli MG1655 genome (average 1,000 bp window). Library was prepared with NEBNext DNA Sample Prep Reagent Set 1 and sequenced on an Illumina Genome Analyzer II.

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DAY 4: FRIDAY 17 SEPTEMBER 2010

1400 – 1700

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Workshop 2

Harbour 2

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Partek(R) Genomics Suite Next-Generation Sequencing (NGS) data analysis Workshop

ABSTRACT

In this workshop, we will present a brief overview of Partek(R) Genomics Suite capabilities for analyzing high-throughput sequencing data. Specific example applications will include RNA-seq analysis for whole transcriptome and ChIP-seq analysis for transcription factor binding. By following the step-by-step RNA-seq workflow, all known and novel RNAs can be visualized together with transcript information from public databases such as RefSeq or AceView. Estimation of differential expression, alternative splicing, and isoform abundances are calculated on known mRNAs. Coding SNPs can be discovered for allele specific expression identification. For ChIP-seq studies, we will detect enriched regions to discover de novo motif as well as search for known motifs. Partek can also overlap detected regions with genes to identify genes that are possible candidates for transcription factor regulation. Finally, sequence comparison across multiple samples will also be shown.

IMPORTANT NOTE: Lunch and afternoon tea will be provided for those delegates who have registered to attend the optional workshops.

DAY 4: FRIDAY 17 SEPTEMBER 2010

1400 – 1700

Workshop 3

Grand Ballroom 1

Generously supported by illumina

Next Generation GWAS – Illumina's Omni Roadmap for Rare Variant Discovery and Imputation

Presenters:
Arjuna Kumarasuriyar, Illumina Product Marketing Manager South Asia Pacific
Derek Campbell , Illumina Senior Field Application Scientist, Australia and New Zealand

ABSTRACT

Building upon the HapMap Project, massive re-sequencing efforts, such as the 1000 Genomes Project, are delivering a catalogue of human variation at an unprecedented scale. These data are already offering a much richer understanding of the true spectrum of genetic variation across human populations. The 2010 Omni Roadmap leverages proven intelligent tagSNP selection and the ability to type up to 5 million markers per sample, delivering the power needed to fuel new genetic discoveries and enable an expanded understanding of how genetic variation contributes to human health and disease. In this workshop we will provide an overview of our next generation microarrays which contain rare variant content down to 1% MAF. In addition we will outline the process and applications available for imputation enabling you to leverage existing studies.

DAY 5: SATURDAY 18 SEPTEMBER 2010

0900 – 1600

Optional GenePattern Workshop

GenePattern
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Medical Sciences Building 1
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Broad Institute Tools for Integrative Genomics Analysis

Presenters:
Dr Michael Reich, Director of Cancer Informatics Development, Broad Institute of MIT and Harvard
Dr Helga Thorvaldsdottir, Senior Project Manager, Broad Institute of MIT and Harvard

Integrative genomics provides unprecedented power to increase our understanding of basic biological processes and determine the mechanisms of disease. This approach – the combining of evidence from multiple data modalities such as gene expression, copy number, epigenetic, and mutation data to find the genomic causes of a disease state has resulted in the identification of novel mutations, the discovery of causal relationships between genomic aberrations and clinical pathologies, and other important insights in the short time it has been in practice. To take advantage of this wealth of data, new tools are needed that can span data modalities and support the very large datasets characteristic of integrative efforts. The Broad Institute has produced a number of software tools to facilitate integrative genomics investigations, including GenePattern, a suite of over 120 tools for the analysis of gene expression, copy number, proteomics, flow cytometry, and other data, along with extensive capabilities for combining these tools to create complex, reproducible methodologies; and the Integrative Genomics Viewer (IGV), a flexible, scalable, high-performance tool for the concurrent visualization of multiple large scale datasets. These freely available tools are used by tens of thousands of researchers worldwide to improve our understanding of cancer, immunology, microbial genomics, stem cell biology, and other fields.

Participants will learn the major features and benefits of GenePattern and IGV and will understand how these tools may be applied in their own research.

IMPORTANT INFORMATION: Delegates will be required to sign in at the Menzies reception. Your Conference name badge must be worn at all times so that you can be easily identified by security staff.

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Profiling Technologies 1 – Cancer Research

Federation Ballroom

POSTER 1

Aaron Jeffs, Anshul Awasthi , Sigurd Wilbanks, Joel Tyndall

GLIPR1 mediates invasive potential in melanoma cells

ABSTRACT

Melanoma skin cancer can rapidly progress from a slow-growing surgically curable lesion to aggressive metastatic disease, with high mortality and poor response to current therapies. There are few treatment options once metastasized, and new biomarkers that aid diagnosis, predict clinical outcome, and suggest new therapies are required. We are investigating the molecular basis of melanoma by defining genomic signatures that correlate with invasiveness and tumour phenotype in a panel of melanoma cell lines. Microarray analysis of 27 melanoma cell lines revealed differential expression of the microphthalmia-associated transcription factor (MITF) and related developmental transcriptional networks. Migration assays confirmed that down-regulation of lineage specification genes in the expression signature correlated with increased invasiveness of the cell lines. Expression of GLI pathogenesis related 1 (GLIPR1) was inversely correlated with MITF and other developmental genes, and positively correlated with increased cell motility and invasive potential. siRNA-mediated GLIPR1 knockdown in strongly invasive melanoma and glioma cell lines caused a decrease in cell motility and invasion, whereas knockdown of MITF resulted in increased GLIPR1 transcription that corresponded with increased invasion in weakly invasive melanoma cells. This study links differential expression of developmental genes with invasive potential in melanoma, and shows for the first time that up-regulation of GLIPR1 is associated with increased invasion in melanoma cells.

POSTER 2

Aaron Statham, Clare Stirzaker, Jenny Song,
Dario Strbenac, Mark Robinson, Susan Clark

Discovery of epigenetically dysregulated genes in cancer by Illumina sequencing

ABSTRACT

Despite the completion of the Human Genome Project we are still far from understanding the molecular events underlying epigenetic change in cancer. The advent of next-generation sequencing has allowed the genome-wide assessment of epigenetic marks on an unprecedented scale, resulting in a deluge of data.

One of our laboratory's primary interests is the discovery of novel epigenetically dysregulated genes in cancer. To assess DNA methylation genome-wide, we used MethylMiner (Invitrogen) to enrich for methylated DNA from normal prostate epithelial cells (PrEC) and the LNCaP prostate cancer cell line and sequenced the enriched fragments on an Illumina GA IIx. To enable the integration of expression, tiling array and next-generation sequencing data, we have developed a bioinformatics package for the R project named Repitools, freely available from http://Repitools.R-Forge.R-Project.org.

DNA methylation is largely absent from gene promoters in PrEC irrespective of expression but is strikingly enriched at the promoters of lowly expressed genes in LNCaP cells, exposing a change in the mechanism of gene suppression in cancer cells. We have extended this study to perform MethylMiner-seq on formalin fixed paraffin-embedded clinical samples, with good results when sufficient DNA quantity is available. We are currently in the process of optimising this procedure to improve performance with lower amounts of starting material.

POSTER 3

Bente Talseth-Palmer, Elizabeth Holliday, Tiffany-Jane Evans, Mary McPhillips, Claire Groombridge, Allan Spigelman, Rodney Scott

Modifier genes influencing breast cancer incidence in HNPCC/Lynch syndrome

ABSTRACT

Hereditary non-polyposis colorectal cancer (HNPCC)/Lynch syndrome (LS) is an autosomal dominantly inherited cancer syndrome characterised by early-onset epithelial cancers. Modifier genes may contribute to variation in disease expression, and reports have suggested that breast cancer belongs within the context of HNPCC/Lynch syndrome.

The aim of the current study was to identify genomic aberrations including copy number (CN) gains and losses and allelic loss (AL) which differentiate: a) HNPCC-positive individuals from healthy controls, and; b) breast cancer positive families within the HNPCC group. A total of 100 individuals diagnosed with HNPCC and 384 healthy controls were included in the study; controls were drawn from the Hunter Community Study cohort. All individuals were genotyped using the Illumina Human610-Quad array

We detected a CN gain on chromosome 8p11.23-p11.2 which was observed in 30% of the 10 HNPCC Ca+/BrCa+ cases but in none of the controls (p-value of 1.19E-05; Q-value of 0.017). We also identified a region of AL on chromosome 2p11.2-p11.1 in 100% of the HNPCC Ca+/BrCa+ probands but none of the 384 healthy controls (p-value=4.25E-20; Q-value=2.03E-15). The AL can also be seen at high frequency in other HNPCC cases, with increased statistical significance. Comparison of total and average CNV length between groups revealed a higher average CNV length in all HNPCC cases compared with controls (p-value = 0.039).

In conclusion, preliminary CNV analysis identified a locus associated with breast cancer in HNPCC/LS patients and 3 loci differentiating HNPCC/LS patients from healthy controls. We are currently validating the results utilising other algorithms.

POSTER 4

Brian Gloss, C Barton, W Kaplan, N Hacker, R Sutherland, P O'Brien, S Clark

Whole Genome Pharmacoligcal Induced Epigenetic Re-expression and DNA Methylation PRrofiling Reveal a Panel of Potential Biomarkers for Ovarian Cancer

ABSTRACT

Objective: This study aims to use whole genome array technologies to uncover new genes which are repressed in epithelial ovarian cancer (EOC) with aberrant DNA methylation. These genes will facilitate the development of a methylated biomarker panel for early diagnosis as well as shed light on the development of the disease.

Methods and Results: Affymetrix HGU133Plus2.0 gene expression profiles of 5-Aza-2'-deoxycytidine induced methylated gene re-activation for two EOC cell lines A2780 & CaOV3, revealed ~2300 potentially methylated genes. DNA methylation profiles using gene promoter tiling GeneChip arrays (meDIP-ChIP) were generated. These indicated that methylation at gene promoters was enriched when selecting gene candidates with CpG islands and evidence of repression in EOC compared to normal ovarian surface epithelium (OSE) from publicly available expression profiles. DNA methylation of candidate genes was quantified by Sequenom massARRAY revealing that 16/21 selected genes exhibited hypermethylated in a panel of ten EOC cell lines relative to three OSE. ROC curves showed that average methylation of a panel of seven genes was able to distinguish a high proportion of EOC from OSE (n=27 and 17 respectively). In addition, a single gene was also shown to be hypermethylated in 44% EOC and 0% OSE.

Conclusions: Whole genome expression and methylation profiles of cell lines, integrated with publicly available gene expression and annotation data revealed a seven gene panel which may form the basis for a diagnostic screen for EOC and a new gene whose suppression by methylation may be important in EOC development.

POSTER 5

Bryce van Denderen, Eliza Soo, Dexing Huang, Gregory Goodall, Angels Fabra-Fres, Izhak Haviv, Tony Blick, Erik Thompson

Micro-RNA Profiling of Epithelial-to-Mesenchymal Transition in PMC42 Breast Cancer Cell Lines

ABSTRACT

Micro-RNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression. The majority of more than 700 miRNA's identified to date negatively regulate gene expression by binding to the 3'UTR of target mRNA's leading to transcript degradation or inhibiting translation. Important roles for miRNAs in the initiation and progression of various cancers have been recently demonstrated, including the regulation of epithelial-to-mesenchymal (EMT) changes in breast cancer metastasis. The PMC42-ET and PMC42-LA breast cancer cell lines provide an ideal tool to study miRNA expression profiles in EMT in response to either EGF and TGFβ driven EMT changes, as well as the reverse mesenchymal-to-epithelial transition (MET). We undertook miRNA profiling of control and EMT-induced PMC42-ET and LA cells using the mirVana probe set V1 (Ambion). Several miRNAs were reproducibly up or downregulated in response to EMT-inducing treatments as well as between untreated LA and ET sub-lines. Whilst a number of these have already been implicated in cancer (miR-21, 29a and 200c), we identified other novel miRNAs that were consistently regulated in association with EMT. We will present results of our attempts to confirm and extend these findings using Next Generation sequencing of small RNAs. Once validated, we shall overexpress these miRNAs using a lentiviral expression system to investigate whether they can attenuate the effects of EMT-inducing cytokines, and whether they may be utilized to drive MET processes.

POSTER 6

Cletus Anthony Pinto, Tony Blick, Mark Waltham, Erik Thompson

Translation of Breast Cancer Epithelial-Mesenchymal Plasticity into Therapeutics

ABSTRACT

Despite significant progress in the detection and treatment of breast cancer, and a corresponding increase in breast cancer survival over the last decad, better diagnostic and therapeutic options are required for certain breast cancer subtypes (e.g. basal breast cancers), pre-existing metastases and for recurrence. Epithelial-Mesenchymal Transition (EMT) refers to a process that results is acquisition of migratory and morphological changes of mesenchymal cells by a relatively non motile epithelial parental cell. EMT-like changes in carcinoma cells often lead to a 'hybrid/metastable' phenotype comprising both mesenchymal and epithelial traits. Epithelial mesenchymal plasticity (EMP) encompasses the phenotypic interconversions between epithelial and mesenchymal states, and vice versa.

We have used pharmacogenomics to identify small molecule compounds predicted to affect EMP as well as those that could affect the mesenchymal state. We have used the dataset against the EMP phenotype to develop a list of the top 100 compounds that is predicted to affect the EMT process using the Cmap algorithm (Broad Institute). Our analysis extends into the NCI-60 with the aim to develop correlations between gene signatures characteristic of EMP to compounds that would target EMT. Further analysis incorporates the use of siRNA libraries and shRNA pools with the aim to develop gene targets that perturb the EMT phenotype. In addition, as these data sets continue to evolve along with additional new datasets, we will continue to identify concordances within candidate drug targets, gene signatures and diseased state.

POSTER 7

Eva Tomaskovic-Crook, Izhak Haviv, Erik Thompson

Analysis of Alternatively Spliced Genes Following EGF-Induced Epithelial to Mesenchymal Transition in PMC42 Cells

ABSTRACT

The human PMC42 cell line system is a useful tool for the study of epithelial to mesenchymal transition (EMT) in breast cancer. Although the parental 'PMC42-ET' cells exhibit a more mesenchymal phenotype compared to the PMC42-LA subline, they exhibit epidermal growth factor (EGF)-inducible EMT-like changes, including further increased high vimentin expression and a reduction of already low E-cadherin levels. Furthermore, PMC42 cells grown as a 2-dimensional (2D) monolayer or in a 3D collagen matrix allows for the study of altered transcriptional changes following EMT related to cellular organisation. Alternative splicing is a common mechanism used by eukaryotic cells to regulate gene expression and has been suggested to contribute to cellular identity. Recently it has been shown that alternative splicing occurs in mammary epithelial cells following induction of EMT, resulting in the downregulation of epithelial splicing factor proteins and a switch from an epithelial to mesenchymal splicing pattern. We aimed to identify differential expression of alternatively spliced genes in PMC42-ET cells undergoing EGF-inducible EMT in 2D and 3D collagen culture using Affymetrix GeneChip Human Exon 1.0 ST whole genome exon arrays. Preliminary analyses confirm that genes previously shown to be alternatively spliced in EMT also occur in PMC42-ET cells following EMT. We will present alternatively spliced genes that are differentially expressed due to culture conditions. Importantly, differential alternative splice analysis may identify genes that are important in cell specification and EMT and further define a diagnostic signature for EMT in breast cancer.

POSTER 8

Georgina Ryland, Maria Doyle, Jason Ellul, Jason Li, Kylie Gorringe, Ian Campbell

Next generation sequencing of candidate ovarian tumour suppressor genes

ABSTRACT

Mapping regions of loss of hetrozygosity (LOH) is a common approach used to identify cancer genes inactivated by mutation (tumour suppressor genes, TSGs). The application of high throughput sequencing technologies has rapidly transformed our ability to characterise cancer genome mutation profiles at high resolution. We aim to identify candidate TSGs in invasive epithelial ovarian cancer within common regions of LOH, which were recently identified in a genome wide LOH and copy number survey of 106 primary ovarian tumours (1). We are using the Agilent SureSelect Target Enrichment System to selectively enrich for coding exons of candidate genes followed by massively parallel short read sequence analysis of ~80 microdissected primary ovarian tumour DNA samples. By also sequencing germline DNA samples from the same patients, we aim to identify recurrent somatic mutations which would suggest a tumour suppressive role for the underlying gene. Initial experiments of samples indexed and pooled prior to in-solution capture (3.25Mb) and single-end 75bp sequencing on the Illumina GAIIx platform consistently yields ~1.5Gb of mappable sequence data per lane. 60% of this data is target specific with a mean fold coverage of >20x and 97% of targeted nucleotides covered by at least one sequence read. We are currently using MAQ-SNP and Novoalign for the detection of single base variants and short insertions and deletions respectively. Targeted enrichment of specific loci of cancer genomes is a promising approach to enable sequencing based studies in large tumour cohorts where clinical samples are limited.

(1) Gorringe K et al. (2009) Genes Chromosomes Cancer 48: 931-942

POSTER 9

Julie Johnson, N Waddell, KK Khanna, M Brown, kConFab, G Chenevix-Trench

Gene expression microarray analysis after nonsense-mediated mRNA decay inhibition to identify breast cancer susceptibility genes

ABSTRACT

Transcipts containing premature termination codons (PTCs) are rapidly degraded by the nonsense-mediated mRNA decay (NMD) pathway. Pharmacological inhibition of the NMD pathway stabilises mutant transcripts, which can be detected using gene expression microarray analysis. This technique known as GINI (Gene Identification by Nonsense-mediated mRNA decay Inhibition) has proved successful in identifying mutations in colorectal, prostate, melanoma and breast cancer cell lines. However, the approach has not yet been applied to identify germline mutations.

Only about 30% of all familial breast cancer cases can be explained by the known moderate – and high-risk breast cancer susceptibility genes. It is likely that rare mutations exist in novel breast cancer genes that explain some of the multiple-case families. Hence we have optimised and applied the GINI technique on lymphoblastoid cell lines (LCLs) derived from affected and unaffected family members of three non-BRCA1/2 hereditary breast cancer families in order to identify candidate susceptibility genes harbouring nonsense codons.

NMD was inhibited using caffeine (7.5mM) and GINI treatments were performed in triplicate resulting in a total of 144 samples that were hybridised to Illumina HT12 v3 expression arrays. BeadStudio, the R-Bioconductor package Limma and GeneSpring 10.0 were used to transform the data and determine significant differences after GINI.

To identify candidate genes, each sample was compared to itself before and after NMD inhibition with caffeine treatment. Candidate 'BRCAx' genes were identified by comparing affected and unaffected individuals within families, and by subtracting "global caffeine response" genes that were upregulated following GINI in all samples from the candidate gene list. Although sequencing of exons and splice sites has not revealed any nonsense mutations, haplotyping is underway to investigate if regions surrounding the candidate genes segregate with disease in their respective families.

POSTER 10

Justin Wong, William Ritchie, Ryan Taft, Cas Simons, Jeff Holst, John Mattick, John JEJ Rasko

Next-generation sequencing of nuclear-enriched non-coding RNAs from bone marrow derived myeloid cells

ABSTRACT

Next-generation sequencing has enhanced the profiling of non-coding RNA and mRNA molecules from numerous tissue types. Little is known about the repertoire of non-coding RNAs, let alone their functions in myelopoiesis. Here we sought to identify and curate differentially regulated nuclear-enriched non-coding RNAs in myeloid cell populations at progressive stages of differentiation. We applied a well-defined fluorescence-activated cell-sorting protocol to isolate promyelocytes, myelocytes and mature neutrophils from the bone marrow of mice. Nuclear non-coding RNA libraries created for these samples were sequenced using Illumina's Genome Analyzer II. Our next-generation sequencing data revealed 2200 nuclear-enriched non-coding RNAs that are differentially regulated during myeloid differentiation. These RNA species include 335 miRNAs, 59 snoRNAs and 1802 RNA molecules that are hitherto uncharacterised. Our data also showed for the first time the presence of a novel class of 17-18 nt RNA termed spliRNA in primary myeloid cells1. Our present study revealed thousands of differentially regulated nuclear enriched non-coding RNAs that may play crucial roles in myelopoiesis. Functional studies on these molecules should advance our understanding of myelopoiesis and shed light into potential mechanisms of leukemogenesis as well as directing pathways for therapeutic interventions.

POSTER 11

Manasa Ramakrishna, Louise Williams, Jennifer Bearfoot, Samantha Boyle, Anita Sridhar, Sally Davis, Michael Anglesio, Karen Sheppard, Richard Pearson, Kylie Gorringe, Ian Campbell

Identifying novel oncogenes in ovarian cancer with microarrays and siRNAs

ABSTRACT

The ovarian cancer genome is often characterised by a complex alterations and over several decades high resolution methods and technologies have emerged to disentangle these changes and deduce their impact on the disease. Well known oncogenes such as MYC, PIK3CA, CCNE and well known tumour suppressors such has TP53, PTEN, RB1 have been associated with genomic alterations in this type of solid tumour but do not completely explain the lethality of this disease.

Categorisation and prioritising of all existing alterations in ovarian cancers, their target genes and pathways provides useful insights into the disease and an opportunity to develop successful therapies against the same. With this goal in mind, we briefly present copy number and expression data in 68 ovarian cancer patients surveyed on the highest resolution microarray platforms to date and the identification of potential oncogenic drivers of the disease. Early bioinformatic analyses yielded 2 potentially novel oncogenes – RAB2A and PUF60 (SIAHBP1) that showed a similar relationship between copy number and expression as did a well known ovarian cancer oncogene PRKCI. Preliminary tests for proliferation gave us reason to refine our methods of prioritising candidates. With the new analyses implemented, we have identified 4 higher confidence oncogenic candidates on chromosomes 3, 8 and 20 – MYNN, PTK2, PLEC1 and TPX2. They are currently being tested extensively in in-vitro systems and the results of these experiments will be presented at the conference.

POSTER 12

Michael Gartside, Mitchell Stark, Kelly Holohan, David Youngkin, Jane Palmer, Lauren Aoude, Ken Dutton-Regester, Christopher Schmidt, Elizabeth Gillanders, Kevin Brown, Nicholas Hayward

A multi-faceted approach to discover new familial melanoma genes

ABSTRACT

The incidence of cutaneous melanoma is increasing worldwide; approximately 90% of all cases are sporadic, with the remainder being familial. To date, 3 high penetrance melanoma susceptibility genes have been identified (CDKN2A, CDK4 and ARF) but collectively account for less than half of all familial melanoma. Uveal melanoma is a cancer of the uveal tract in the eye and accounts for approximately 1% of all melanoma cases. These tumours arise from the pigment cells (melanocytes) that reside within the uvea and interestingly are often found to occur in association with familial cutaneous melanoma.

With this study we sought to identify genes responsible for susceptibility to either uveal or cutaneous melanoma in large, multi-case families, via use of intersecting approaches. Families were chosen on the basis that they did not have a mutation in CDKN2A, CDK4 or ARF; had at least 1 uveal melanoma case and a minimum of 3 cutaneous melanoma cases; and had previously been included in a genome-wide linkage study. We will present preliminary results from a combination of Illumina GAII sequencing of whole-exome libraries (Roche-NimbleGen), commercial whole-genome sequencing (Complete Genomics) and linkage analysis in these melanoma families. Overlaying these different sources of data from the same families has begun to provide us the necessary means by which to narrow down regions of interest in the search for new loci that play a role in the aetiology of familial melanoma and to identify some strong candidate genes that require confirmation in a larger sample of melanoma patients.

POSTER 13

Mitchell Stark, Michael Gartside, Sonika Tyagi, Volker Lennerz, Thomas Wölfel, Chris Schmidt, Nicholas Hayward

Melanoma exome sequencing for novel epitope discovery

ABSTRACT

Immune responses against tumour-specific T-cell epitopes encompassing mutations cannot be limited by central tolerance and should not damage normal tissues. As a proof-of-principle experiment we used exome sequencing to 'rediscover' known, dominant, mutated T-cell epitopes in two melanoma patients who had complete clinical responses to autologous dendritic cell vaccines. To originally identify the key epitopes targeted by the observed anti-tumour immune responses, short-term autologous mixed lymphocyte–tumor cell cultures (MLTCs) were used in combination with an IFN-γ enzyme-linked immunospot (ELISPOT) assay to screen a cDNA library derived from each tumour. The cDNAs which elicited tumour-specific responses were sequenced and the corresponding mutations discovered. Blinded to the identity of the mutated epitopes previously identified, we used Roche-NimbleGen whole-exome libraries to sequence DNA, derived from melanoma and lymphoblastoid cell lines from each patient, on an Illumina GAII sequencer. Following alignment of sequence reads to the human genome reference sequence (hg19), we used custom perl scripts to filter the ~100,000 variations down to ~300-400 novel non-synonymous somatic mutations. We rediscovered many previously known mutations in key melanoma associated genes in these samples (BRAF and TP53), along with the epitope mutations discovered via the ELISPOT assays. It is likely that other mutations identified in these samples present sub-dominant epitopes capable of initiating a T-cell response. Thus, the use of whole-exome sequencing has the potential to be utilised as a rapid method to identify neoantigens that may be used to develop patient-specific polyvalent vaccines designed to prime the patient's own immune system to attack their cancer.

POSTER 14

Nicholas Wong, Zac Chatterton, Katrina Bell, Adam Kowalcyk, Justin Bedo, Joe Wang, Izhak Haviv, Elizabeth Algar, David Ashley, Jeff Craig, Richard Saffery

DNA methylation profiling of TEL/AML1 (RUNX1/ETV6) positive childhood acute lymphoblastic leukaemia

ABSTRACT

Acute Lymphoblastic Leukaemia (ALL) is the most common form of cancer in children. Although up to 80% of cases can be characterised by either abnormal chromosome number (hyper – or hypo – diploidy) or a specific chromosome translocation, a significant proportion of cases do no exhibit any major chromosome abnormality. Indeed no common gene mutation has been found to be associated with childhood leukaemia. This suggests that epigenetic modifications, in particular, DNA methylation may also play a significant role in ALL pathogenesis and that understanding the specific epigenetic changes associated with this disease is important for predicting onset and disease outcome.

From our cohort of over 450 childhood leukaemia cases we analysed 12 cases of childhood ALL that carried the TEL/AML1 (RUNX1/ETV6) chromosome translocation using Illumina Infinium Human Methylation27 bead arrays. Infinium bead arrays interrogate 27,578 CpG methylation sites across the human genome covering each of the known 14,495 RefSeq gene promoters. We analysed matching leukaemia and remission bone marrow from each of the 12 cases to look for DNA methylation signatures that are associated with leukaemia.

We used a number of methods to determine the DNA methylation signatures associated with childhood ALL including LIMMA, Centroid Analaysis and Support Vector Machine modelling. We found that the methylation status of 16 probes are sufficient to define a leukaemia sample from a remission sample.

We are currently validating our results using high throughput SEQUENOM on the remaining cases in our cohort. These methylation changes may help diagnose ALL and describe the pathogenesis of leukaemia.

POSTER 15

Nicholas Wong, Gavin Meredith, Bryan Beresford-Smith, Adam Kowalcyk, Sebastian Lunke, Izhak Haviv, Elizabeth Algar, David Ashley, Richard Saffery, Jeff Craig

DNA methylation profiling of childhood acute lymphoblastic leukaemia using DNA methylation enrichment and next generation sequencing technology

ABSTRACT

Acute Lymphoblastic Leukaemia (ALL) is the most common form of cancer in children. Although up to 80% of cases can be characterised by either abnormal chromosome number (hyper – or hypo – diploidy) or a specific chromosome translocation, a significant proportion of cases do no exhibit any major chromosome abnormality. Indeed no common gene mutation has been found to be associated with childhood leukaemia. This suggests that epigenetic modifications, in particular, DNA methylation may also play a significant role in ALL pathogenesis and that understanding the specific epigenetic changes associated with this disease is important for predicting onset and disease outcome.

Aware of the significant limitations of DNA methylation profiling using DNA microarrays, we decided to embark on profiling using DNA methylation enrichment using the MBD2 methylated DNA binding protein and sequencing the enriched fractions using next generation sequencing technology.

We selected a relapsed childhood ALL case with a normal karyotype in the tumor for DNA methylation enrichment and NGS. In addition we performed enrichment on model leukaemia cell line samples, CCRF-CEM and JURKAT; and JWL a non-leukaemic lymphoblast cell line.

In addition, we performed Illumina Infinium Human Methylation27 bead array analysis of these samples to compare with NGS data accumulated.

This is still a work in progress but we hope to find novel DNA methylation changes using NGS that would not have been picked up using current DNA microarray technologies highlighting the potential utility of NGS for DNA methylation profiling.

POSTER 16

Paul Hertzog, BN Bidwell, N Withana, N Mangan, D Andrews, S Samarajiwa, R Anderson, BS Parker

Innate Immune signatures in breast cancer matastases

ABSTRACT

The mechanisms whereby disseminated beast cancer cells stimulate a growth environment in bone and the influence of immune surveillance on this process are largely unknown. Using a unique immunocompetant murine model of spontaneous bone metastasis and genome-wide expression analysis using the INTERFEROME database and associated tools, we demonstrate that breast tumour cells isolated from bone have suppressed a specific innate immune pathway, namely the interferon regulatory factor, Irf7, and about 300 of its target genes. Restoration of this pathway by overexpression of Irf7 significantly reduced bone metastases and extended metastases-free survival. This Irf7-driven rescue was not observed in immunocompromised mice suggesting that the mechanism of metastases suppression in immunocompetent mice is due to an anti-tumour immune response triggered by products of this innate immune defence pathway. Furthermore, we demonstrate that treatment of mice bearing tumours with IFNα1, which induces Ifr7, also significantly prolonged metastasis-free survival and reduced metastatic burden in bone. Thus our findings demonstrate that breast cancer cells have an intrinsic innate immune pathways that dictate the control of metastatic spread. In this case, tumour cell production of type I IFNstimulates an immune response directed against metastasis; and that intrinsic suppression of this pathway allows immune evasion and outgrowth of metastatic deposits in distant tissues such as bone.

POSTER 17

Sarah Song, Peter Simpson

Understanding the molecular heterogeneity of the luminal breast cancer subtype

ABSTRACT

Breast cancer is a heterogeneous disease with considerable variation in outcomes and responses to standard therapies. Tumours can be classified by gene expression profiling into molecular subgroups termed luminal A, luminal B, HER2 and basal-like. It is clear that even within these subgroups there is considerable heterogeneity, both biologically and clinically. Luminal tumours are oestrogen and progesterone receptor positive and so patients are treated with endocrine-based therapy, for which a significant number of patients develop resistance.

The aim of this study is to i) investigate the molecular heterogeneity of the luminal subtype using publically available gene expression and genomic data sets; and ii) to determine activated pathways in different subgroups and the mechanisms underlying activation of these pathways.

Using the NKI295 dataset, we identified 1958 genes significantly differentially expressed between luminal A and luminal B subgroups (as defined by Hu et al SSP). The expression of these genes stratified a minimum of 4 luminal subgroups (A, B and 2 distinct mixed A/B groups). Genes located within 17q23-25 were overexpressed in the luminal B subgroup and correlated with the worst outcome. HER2 tumours also overexpress these genes and this genomic region is gained in luminal versus non-luminal tumours.

The heterogeneity of the luminal tumour phenotype can be stratified according to integration of genomic and gene expression data. Gain of 17q23-25 is contributing to the aggressive behaviour of a subset of luminal tumours. Further data sets and genomic regions commonly altered in luminal tumours are being investigated.

Bioinformatics

POSTER 18

Alicia Oshlack, Matthew Young, Mark Robinson

Analysis and normalization of RNA-seq data for detecting differential expression

ABSTRACT

High-throughput sequencing of steady state RNA in a sample is commonly referred to as RNA-seq. RNA-seq promises to unravel transcriptional complexities across the genome that were not accessible using previous technologies, such as microarrays. Not only can expression levels of genes be interrogated without specific prior knowledge, novel splice variants, alternative promoters and SNPs can be detected. An important aspect of dealing with the vast amounts of short read sequencing data generated from RNA-seq is the processing methods used to extract and interpret the information. In order to discover biologically important changes in RNA-seq data, we show that normalization continues to be an essential step in the analysis. In this talk, we will outline the basic steps in the RNA-seq analysis pipeline, starting from raw reads and ending in a list of differentially expressed genes that can be used for systems biology analysis. In doing so, we outline a simple and effective method for performing normalization and show dramatically improved results for inferring differential expression (DE) in simulated and publicly available data sets.

POSTER 19

Belinda Phipson, Gordon Smyth

Finding the most important differentially expressed genes

ABSTRACT

With the advent of microarray technology, it has become routine to look at gene expression changes across the whole genome under different biological conditions. The main focus of analysing microarray experiments has been to identify genes that are differentially expressed. However, within a list of differentially expressed genes, a ranking indicating the most important changes would be most beneficial. Observed log fold change as a predictor of the true fold change naturally comes to mind as a ranking statistic, as genes with large fold changes are likely to be more important than genes with small observed fold changes. Unfortunately, the observed fold change is not a reliable ranking statistic as it is highly influenced by technical effects such as binding affinities of probes. The ideal ranking statistic would consistently identify the same important genes should the experiment be repeated.

We propose using the predicted fold change; a measure that takes into account both the observed fold change and the uncertainty of the estimate. The log fold change for each gene is "shrunk" towards zero by an amount depending on the precision with which it is estimated and the observed log fold change. Using an empirical Bayes hierarchical model framework, we have derived a closed form estimator for the predicted fold change. The predicted log fold change should be a more consistent measure to reliably rank genes, as it focuses on reproducible fold changes. We compare the performance of the predicted log fold change for reliably ranking genes with observed log fold change, moderated t-statistic and the TREAT statistic.

POSTER 20

Caroline Kerr, JM Shaw, CA Kerr, C McSweeney, S Kang, MJ Buckley, T Lockett, P Pavli

Defining the host mucosal and gut microflora interactions in Crohn's disease using redundancy analysis on microarray datasets

Introduction: Crohn's disease (CD) is an inflammatory bowel disease that is characterised by chronic relapsing inflammation of the digestive tract. There is a significant body of evidence that suggests the intestinal mucosal microbiome interacts with the immune response to produce pathological inflammation and together these factors play a major role in the pathogenesis of CD. The aim of this study is to investigate interactions between the human intestinal mucosal transcriptome and mucosal microbiome using multivariate redundancy analysis on microarray datasets.

Methods: DNA and RNA were extracted from the same mucosal biopsies collected from CD patients (terminal ileum: n=5 from sites with active disease, n=4 from inactive sites (tissue with normal histology); colon: n=8 from active and n=6 from inactive sites). RNA was used to study the human intestinal mucosal transcriptome (Affymetrix GeneChip® Exon 1.0 ST arrays) and DNA was used to study the resident microbiota using a custom phylogenetic microarray. The latter was designed using published gastrointestinal microbiota 16S rRNA sequences with ~ 40-mer oligonucleotides targeting 765 bacterial species. Through examining the expression arrays, 30 differentially expressed inflammatory response genes of interest were selected. Correlations between expression patterns for these genes were assessed. Representatives (TNFRSF1B, IL2RA, IL8) of three groups of inflammatory genes with highly correlated expression and three uncorrelated genes of interest (CXCL11, IL-13RA1 and TIRAP) were used. Multivariate relationships between the expression of the six representative inflammatory response genes and the abundance of microbial species in colon or terminal ileum, in patients with active or inactive disease was examined using redundancy analysis using the vegan package in R1. Correlations between the expression of individual inflammatory response genes and the abundance of individual microbes were also investigated.

Results: There appears to be a significant relationship between changes in the abundance of some microbial species in intestinal mucosa with active disease and the expression of the six representative inflammatory response genes. However, this was not the case in the normal (inactive) mucosa of these patients. Where there was active disease the expression of the six genes were predicted by members of the sulfite-reducing bacteria Clostridia class (p-value 0.02-0.005) in the colon, and the Betaproteobacteria (p-value 0.02) and Clostridia (p-value 0.03) class members in the ileum. In the normal (inactive) mucosa of CD patients, there were no bacterial species that significantly predicted the expression of inflammatory immune response genes. There was also some evidence that the expression of the pro-inflammatory cytokine, IL8, predicted changes in the abundance of microbes in inactive colon (p-value 0.04) and that TIRAP (toll-Il1 receptor domain containing adaptor protein), involved in the innate immune system's recognition of microbial pathogens, was predictive of the pattern of microbial abundance in active ileum (p-value 0.05).

Conclusions: Our findings begin to define the unique host-microbial responses associated with CD.

POSTER 21

Cas Simons, Ryan Taft, Satu Nahkuri, Harald Oey, Darren Korbie, Timothy Mercer, Jeff Holst, William Ritchie, Justin Wong, John Rasko, Daniel Rokhsar, Bernard Degnan, John Mattic

Identification of a novel species of nuclear-localized small RNAs associated with splice sites in metazoans

ABSTRACT

We have recently shown that transcription initiation RNAs (tiRNAs) are derived from sequences immediately downstream of transcription start sites. Using small RNA high-throughput sequencing datasets we have identified a second class of nuclear-specific ~17 – to 18-nucleotide small RNAs whose 3′ ends map precisely to the splice donor site of internal exons. These splice-site RNAs (spliRNAs) are in the sense strand when compared to their host gene and are detectable using mapping strategies that consider either exon-exon or exon-intron boundaries.

SpliRNAs are expressed at very low levels, but are greater than 35 fold overrepresented in the nucleus and are associated with highly expressed genes. By analysis of small RNA datasets from human, mouse, Drosophila and C. elegans and the marine sponge we have shown that spliRNAs are conserved across all major metazoan lineages. However, no evidence of spliRNAs could be found in small RNA datasets derived from Arabidopsis thaliana or budding yeast, strongly suggesting that spliRNAs are an animal-specific phenomenon.

The expression of spliRNAs is not affected by the loss of Dicer or DGCR8 in mouse embryonic stem cells, nor altered in C. elegans germline mutants, indicating that spliRNA biogenesis is not intimately connected with the pathways that produce miRNAs or siRNAs.

We are currently working to identify both biogenesis pathway of spliRNAs and to identify their role in the cell. Indeed, given the recent findings showing that nucleosomes and specific histone marks are preferentially enriched at internal exons we are currently investigating the possibility that spliRNAs are involved in the epigenetic regulation of gene expression.

POSTER 22

Dan Catchpoole, N Ho1 , G Morton , D Skillicorn , P Kennedy

Data-mining gene expression and genomic microarray datasets of Acute Lymphoblastic Leukaemia

ABSTRACT

Acute lymphoblastic leukaemia (ALL) is the most common childhood malignancy. Current risk stratification and treatment of ALL is based on clinical and pathological presentation. There are opportunities for incorporating biological knowledge extracted from gene expression and genomic variation data into the risk stratification criteria. Common approaches identify gene(s) of interest by selecting only those with the strongest association to outcome. However, this process discards subtle yet potentially important biological signals. We applied a more inclusive data-mining approach. Gene expression data from Affymetrix U133 chips and non-synonymous single nucleotide polymorphisms (SNP) genotype data from Illumina NS12 chips were generated using diagnostic bone marrow and remission blood samples, respectively, from 138 ALL patients treated at the Children's Hospital at Westmead. We applied principal components analysis (PCA) to explore the global similarities between patients based on gene expression data in an unsupervised manner. We used NIPALS PCA for SNP genotype data as it can handle missing data. We show a relationship between hyperdiploidy and gene expression levels, whilst genomic data highlighted the ethnic diversity of ALL patients, which may have to be accounted for prior to deeper analysis. Multiple random forests on an integrated gene expression and genomic dataset removed attributes with weak power for predicting response to outcome. Singular value decomposition used combinations of the remaining informative genes, which are a large majority of the dataset, to build a predictive model. The results show the potential for data mining models to predicting treatment outcome based on integrated data.

POSTER 23

David Lovell, Paul Greenfield, Stuart Stephen, Jen Taylor

"k" is the loneliest number

ABSTRACT

…how fixed-length sequences can help us characterise, compare and correct nucleotide sequence data

This talk is about k-mers — oligonucleotide sequences of length k. The title refers to the fact that as k increases, the space of possible k-mers grows exponentially while the actual set of k-mers in a given genome or transcriptome stays fixed, becoming lonelier and lonelier in the increasingly empty space of higher dimension.

The loneliness of the long-sequence k-mer has implications for sequence error correction and alignment. In this talk we present a high-level view of

- Empirical and theoretical observations about kmer differences within and between genomes
- Within-sample k-mer strategies for error correction and their impact on genome assembly
- The impact of relaxing mismatch stringency on short-read alignment problems.

We contend that k-mers afford a useful (but perhaps underused) means to characterise, compare and correct nucleotide sequence data. In this talk, we seek to raise your awareness of the value of the value of k-mers, to stimulate discussion about how k-mer representations are currently being used, and to see whether there is scope for k¬-mers to be used to even greater effect by the sequencing community.

POSTER 24

Davis McCarthy

Accounting for Counts – Differential Expression Analysis for RNA-seq

ABSTRACT

RNA-seq represents a powerful approach for investigating the transcriptome, but the analysis of RNA-seq data requires new tools. RNA-seq generates count data, a discrete measure of gene expression, so the many successful methods for analysing gene expression from microarray data are not directly applicable. Nevertheless, lessons learned from the analysis of microarrays guide our approach. In particular, the idea of sharing information between genes to improve inference is applied to RNA-seq data.

We will discuss statistical models and testing procedures for RNA-seq data, as well as some of the challenges posed by this experimental context. Accurate and reliable assessment of evidence for differential expression requires consideration of the small sample-sizes typical of designed biological experiments, appropriate modelling of variability in the data and accounting for biological variation.

The Bioconductor package 'edgeR' provides software tools for differential analysis of count data. The package implements the statistical methods we have developed and has been shown to work well on real RNA-seq data. Three particularly notable features distinguish the package. First, the edgeR methods can separate biological from technical variability in the data. Second, these methods can estimate the biological variation even in experiments with the smallest possible sample size. Third, the package has the ability to conduct exact tests, which are the most appropriate testing method for small counts and few samples. As well as discussing the theory underpinning the package, we will demonstrate the use of the edgeR package on publicly available data. Finally, we will broach limitations of current analytical methods and present further extensions to the package and statistical methods designed to address these shortcomings

POSTER 25

Di Wu, Gordon Smyth

Relating patterns across independent datasets

ABSTRACT

Nowadays, multiple independent datasets may be available for studying one relevant research question. The datasets can be gene expression from different tissues, different platforms, or different types of genomic data, for example mRNA, copy number and epigenetics. In an example of gene expression, one dataset is from the breast cancer subtypes, another is from the human mammary gland subpopulations. Relating these datasets answers the question of cell origin in cancer subtypes. In another case, one dataset is from the tumorigenesis mouse models with Gata3 knock-in or over-expression, another is from samples of mouse mammary subpopulations. Relating these datasets helps understanding how Gata3 affects mouse tumorigenesis. These datasets can not be directly merged together due to the large effects caused by different array experiments.

Various methods have different sensitivities in identifying the associations between samples across datasets. The methods of low sensitivities pick up obvious patterns and generate easily interpretable results. The methods of high sensitivities discover similarities when only a small amount of genes contribute the pattern in small scale. We will talk about unsupervised clustering including multi-dimensional scaling plots, supervised clustering including regularized linear discriminating function, transcriptome signatures and gene set tests. Corresponding plots present results visually. We find the gene set tests are capable to relate datasets even with weak signals, in the context of breast cancer research. Choosing the right methods depends on both the biological hypothesis and the data structure.

POSTER 26

Joseph Powell, AK Henders, AF McRae, GW Montgomery, PM Visscher

Estimating across tissue correlation in the genetic control of gene expression in humans

ABSTRACT

Recently there has been considerable interest in understanding the genetic basis of gene expression and how this varies amongst tissue types. Numerous studies indicate that variation in gene expression levels is heritable, with expression quantitative trait loci (eQTL) being mapped in both humans and model organisms. eQTL represent genomic regions that control either local (cis) or distant (trans) gene expression and without replication across tissues should be considered specific to the tissue or cell-type they are detected in. Whilst there are a large number of studies that show differences in tissue or cell type specific expression profiles, to our knowledge no studies have reported correlations of the genetic control of expression between tissue or cell types.

Here we report the analysis of gene expression levels performed using linear mixed models in lymphoblastoid cell lines (LCLs) and whole blood (PAX) from a sample of 50 monozygotic (MZ) twin pairs. Using Illumina arrays, transcripts from the ~8500 LCLs and ~9000 PAX genes shown to be significantly expressed in all samples were analysed for the proportion of expression variation that is explained by genetic factors. In LCLs, on average, the effect of twin pairs accounted for 51% of the variance in normalised gene expression levels, whilst in PAX samples this was 55%. This can be considered an estimate of broad sense heritability in the absence of common environmental factors. Comparison of the intra-class correlations of the ~7000 gene overlap between the two tissues found a slight negative correlation (-0.11) between LCLs and PAX samples. This indicates little concordance in the genetic control of expression levels between these two tissues.

POSTER 27

Natalie Thorne, Catherine Bromhead, Elizabeth Fitzpatrick, David Amor, Martin Delatycki, Paul Lockhart, Melanie Bahlo

RNA-Seq in a family context: Borrone's Syndrome

ABSTRACT

Family studies are a powerful framework for identifying genes (and mutations thereof) for human diseases. The pedigree and SNP genotyping information is utilised in a linkage analysis to find regions associated with disease. Massively Parallel Sequencing (MPS) is being adapted for family based studies, and the results in the literature have been promising. In particular, RNA-seq offers both SNP genotypes and expression information in one experiment and is a viable alternative to exome and array capture MPS.

We explore RNA-seq data in a family with suspected Borrone's syndrome. We have data from a single affected and from a pool of 3 unrelated control individuals. Borrone's syndrome is a rare recessive condition affecting the dermito, cardiac and skeletal systems. Features of the syndrome include thick skin, acne conglobata, 'coarse' face, brachydactyly , and mitral valve prolapse. Linkage analysis based on SNP-chip data returned over 7 regions of association (3.3% of the autosome).

We present the results on our analysis of differential expression between the affected and control pool and on the filtering of SNP calls to help identify the causative mutation. In addition we compare the SNPs from the RNA-seq and SNP-chip data respectively. Due to the likely impact of alignment and variant calling methods, we perform our analyses with different alignment and variant calling algorithms – the results of which will also be discussed.

The analysis of this data is helping to inform us of the design and analysis issues involved in future applications of RNA-seq in the linkage setting.

POSTER 28

Stuart Stephen, Jen Taylor, David Lovell

Informing next-gen aligners with intragenomic sequence edit distance properties

ABSTRACT

Most current next generation sequencer short read alignment algorithms utilise sequencer generated quality scores to guide a limited number of induced substitutions when aligning short reads to a targeted genome assembly. An exhaustive empirical analysis of substitution edit distances (Hamming distances) between all intragenomic subsequences of the same length over a number of representative model genome assemblies shows that the number of allowed aligner induced substitutions can be significantly increased by utilising Hamming distances instead of the quality scores, with resultant improved alignments in terms of improved aligner sensitivity and reduced false discovery rates.

In this talk, results from an analysis of Hamming distances in human, fly, worm, Arabidopsis, and yeast will be presented with a focus on Arabidopsis indicating that Hammings should be used as an informative guide in the interpretation of aligned read distributions, including desserts, within functionally characterised genomic regions and individual annotation feature associations.

POSTER 29

Elizabeth Tindall, Aakrosh Ratan, Stephan Schuster, Webb Miller, Vanessa Hayes

Assessing the accuracy of minimal coverage Titanium 454-sequencing data for single base variant identification without a reference genome: lessons from the Tasmanian devil Genome Project

ABSTRACT

Global estimations are that 25% of all land mammals are at risk of extinction. Population diversity is critical for species survival and it is thus predicted that a lack of genetic diversity may be attributable for the current threat against several of these species including the Tasmanian devil (Sarcophilus harrisii). Using the Tasmanian devil as a model, we endeavoured to predict the current level of diversity within a threatened species by applying next generation sequencing technology to generate de novo sequencing data, combined with high throughput genotyping. Generating a genome sequence de novo is, however, still relatively laborious and not a viable option for all global species under threat. We therefore propose a computational pipeline called DiAL (De novo identification of Alleles) that allows for identification of single-base substitutions from minimal coverage, long-read, whole genome shotgun sequencing data of two geographically diverse reference animals. We test our approach at two time points of minimal Titanium Roche/454-sequencing coverage of 0.3x and 2x. To follow, we validate over 1,500 variant calls using high throughput genotyping and assess seemingly non-polymorphic sites using direct Sanger sequencing. Our approach allows for a comprehensive evaluation of 454-sequencing accuracy at low coverage and evaluation of our proposed computational method. The success of our approach allows for rapid genome-wide marker identification for implementation in defining the genetic diversity of an endangered species. This information can be directly utilised as a tool to drive captive breeding programs and help improve the chance of species survival.

POSTER 30

Ellis Patrick, Michael Buckley, Jean Yang

Optimising a Genomic Annotation for the Analysis of RNA-Seq Data

ABSTRACT

RNA sequencing (RNA-Seq) makes it possible to measure transcription at a remarkable precision and throughput. While ideally we would like to work at the transcriptome level there may still be a need or want to work on a genomic level. In order to focus on the overall expression of a gene, rather than isoform-specific expression, Bullard et al (2010) define a Union-Intersection (UI) annotation for a gene. This UI definition is quite restrictive and lead to the exclusion of large amounts of data. We propose a method, inspired by the work of Xing et (2006) on exon arrays, which leads to a more suitable and optimal genomic annotation. We illustrate this method on publicly available data and show that when evaluated against a set of criteria it performs well.

POSTER 31

Gavin Huttley, Julien Epps, Hua Ying

Statistical support for the period-10 dinucleotide encoding of nucleosome positioning in yeast and mouse

ABSTRACT

Nucleosomes are the fundamental packaging unit of eukaryote DNA and serve a critical function in the epigenetic control of gene regulation. Consisting of ~146 bp of DNA wrapped around a histone octamer, nucleosomes affect the accessibility of DNA to the gene regulatory apparatus. A role for DNA sequence in encoding nucleosome locations has been conjectured for some time with a ~10 bp periodicity of certain dinucleotides being identified as a nucleosome positioning sequence. We refer to these period-10 nucleosome positioning dinucleotides as the NPS. The functional significance of NPS have been convincingly demonstrated experimentally in a number of independent studies.

Direct evaluations of the association between NPS and individual nucleosome locations have not been done due in part to the lack of suitable methods for identifying NPS. This is due in part to the lack of suitable methods for identifying NPS. We examined the statistical properties of different period detection techniques and, for the most robust of these, develop significance testing suitable for biological sequences. We specifically developed a confirmatory period estimation technique that addresses the objectives of detecting the strength of a given (e.g. putatively dominant) periodic component and determines its significance relative to the remaining sequence components. We applied the resulting technique to the entire genomes of yeast and mouse. We found the expected striking NPS distribution in yeast. We also found strong support for the period-10 occurrence of NPS in the mouse genome. These results remove a critical barrier for evaluating the role of periodic elements in encoding nucleosome positioning.

POSTER 32

Izhak Haviv, Geoff Macintyre, James Bailey, Adam Kowalczyk

is-rSNP: A novel technique for in silico regulatory SNP detection

ABSTRACT

Determining the functional impact of non-coding disease associated SNPs identified by genome-wide association studies (GWAS) is challenging. Many of these SNPs are likely to be regulatory SNPs (rSNPs): variations which affect the ability of a transcription factor (TF) to bind to DNA. However, experimental procedures for identifying rSNPs are expensive and labour intensive. Therefore, in silico methods are required for rSNP prediction. We have designed an algorithm for in silico regulatory SNP detection called is-rSNP. We employ novel convolution methods to determine the complete distributions of PWM scores and ratios between allele scores, facilitating assignment of statistical significance to rSNP effects. We have tested our method on 41 experimentally verified rSNPs, correctly predicting the disrupted TF in 28 cases. We also analysed 146 disease associated SNPs with no known functional impact in an attempt to identify candidate rSNPs. Of the 11 significantly predicted disrupted TFs, 8 had previous evidence of being associated with the disease. These results demonstrate that is-rSNP is suitable for high-throughput screening of SNPs for candidate rSNPs. This is a useful and important tool in the interpretation of GWAS.

POSTER 33

Izhak Haviv, Justin Bedo, Albin Steininger,
Adam Kowalczyk

DNA Annotation Induction: from RefGene on Human Chr.~22 to Genome-wide CAGE for Human and Mouse

ABSTRACT

Recent proliferation of genome-wide data fuelled by the availability of NGS technologies put pressure on the development of robust statistical and machine learning techniques for data analysis and functional annotation of DNA sequences from a variety of organisms. Transcriptions start site (TSS) prediction on the human genome (using RefGene annotations) has recently been extensively studied as a benchmark problem for such applications, and supervised learning techniques were demonstrated as a very robust approach that outperformed other competing approaches. We show that these techniques are capable of even more: they can extract novel knowledge from a small samples of annotated DNA and build predictive models capable of accurate annotation of the same or even another species, generalising beyond the apparent scope of the initial annotation.

We have shown that the knowledge of DNA sequences and functional annotation such as RefGene locations of transcription start sites on the smallest autosomal human chromosome (22) – – 1/60th the size of the whole genome – – is sufficient to build models capable of robust prediction of genome-wide CAGE tags not only for human tags but also for mouse.

For instance, for human we detect the top 10^4 and 10^6 tags with precision ~95% and ~40% out of the total ~11*10^7 choices, respectively. Similar performance was observed for four additional predictive models, two developed using human chromosome 22 with broad ChIP-Seq raw peaks for Pol-II binding and CAGE tags, and two models trained on mouse chromosome 18 using mouse RefGene TSS locations and mouse CAGE tags.

Based on this genome wide analysis we conclude that a significant fraction of transcription start and CAGE tags locations are associated with very similar local DNA properties.

POSTER 34

Jianmin Wu1, Tea Vallenius, Kristian Ovaska,
Jukka Westermarck, Tomi Mäkelä, Sampsa Hautaniemi

PINA: an integrated network analysis platform for protein-protein interactions

ABSTRACT

High-throughput protein-protein interaction (PPI) detection technologies have resulted in identification of large sets of PPIs. There is an increasing demand for network analysis of the growing amount of PPI data, especially for medium-size PPI network studies, in which protein interactors for tens or hundreds of proteins are analyzed simultaneously. This scale is interesting because an increasing number of protein lists of this size are being generated or inferred from functional genomics, proteomics and metabolomics studies. To facilitate studies of PPI networks of this scale, we developed a web-based Protein Interaction Network Analysis platform (PINA)1, which integrates protein-protein interaction data from six manually curated databases and provides network construction, filtering, functional and topological analysis, and visualization tools. Users can also modify, save and publish their interaction networks. With PINA, we generated and analyzed the protein interaction network for LKB1 and its 14 substrate kinases and suggested a possible link between LKB1 and TGF-ß signaling. In another case study, we identified 36 proteins that interact with both p53 and c-Jun, providing candidates for which these transcription factors could compete to execute their antagonist biological functions. PINA allows the advanced use of PPI data through network analysis and facilitates the translation of fragmented knowledge in PPI databases to testable predictions. PINA is freely available at http://csbi.ltdk.helsinki.fi/pina/.

POSTER 35

Matthew Anderson, Amanda Miotto, Nick Matigian, Othmar Korn, Jarny Choi, Carolyn de Graaf, Nick Seidenman, Tobias Sargeant, Doug Hilton, Alan Mackay-Sim, Alistair Chalk, Sean Grimmond, Christine Wells

The Australian Stem Cell Data Portal: A database of stem cell gene expression

ABSTRACT

The stem cell community needs biologist-friendly databases containing curated stem cell gene expression data. We want to address questions about gene expression in the context of the stem cell differentiation hierarchy, for example: "How does the expression of gene X in my dataset relate to other datasets?"

In our system, users are first able to select from a set of available gene expression datasets including their own data, data shared via collaboration and public datasets. Next, a gene expression overview for their selected gene is displayed, with the option to drill down to explore transcriptional complexity within the gene, including transcript and exon level expression.

To manage, store and visualise the data, we developed a transcriptional framework database schema for our expression datasets and constructed a secure web application framework to query the data.

The web portal provides a platform for collaboration between stem-cell and computational biologists, and allows in-depth analysis of expression for functionally related sets of genes.

As part of future development we plan to implement ontology-aware querying to enhance the biological utility of the system.

POSTER 36

Mhairi Marshall, Donald Gardiner, John Manners, Kemal Kazan, Annette McGrath

Implementing a pipeline to identify novel genes in fungal genomes from a draft next generation sequencing genome assembly

ABSTRACT

Fungi are very important plant pathogens and infect economically important cash crops including wheat and barley. Fusarium pseudograminearum is one such pathogen that infects wheat and is the major cause of crown rot disease in Australia. It is responsible for AU$79M in losses annually and is chronic across much of the Australian wheat belt. Next generation sequencing is having a big impact on the study of disease-causing organisms as ready access to large amounts of sequence data at a low cost and in a short timeframe is allowing researchers to quickly and cheaply gain an overview of their genome of interest. Analysis of that data will help to determine models for the methods of pathogenicity. Several fungal genomes have already been published and their complete genomes and annotations are freely available for download.

A draft genome for the closely related F. pseudograminearum was generated by de novo assembly of short read sequence data from the illumina GAII platform. The aim of this work was to implement a pipeline to allow the identification of novel genes in the draft genome of F. pseudograminearum that were not present in previously published fungi including the closely related Fusarium graminearum. It is expected that many of these genes identified will be involved in the infection process unique to F. pseudograminearum.

Three commonly used gene prediction programs were used: Augustus, GeneMark-ES and FGENESH. Using the reference genome and the manually refined gene annotation for Fusarium graminearum available from the Broad Institute we first benchmarked the tools, comparing the analysis of these three gene prediction tools with the annotated genes in the published gene dataset to determine how accurate their predictions were.

POSTER 37

Peter Hickey, Richard Huggins, Melanie Bahlo

X Chromosome Association Testing in Genome Wide Association Studies

ABSTRACT

The problem of testing for genotype-phenotype association with loci on the X chromosome in genome wide association studies (GWAS) has received surprisingly little attention. There exist several methods in the literature, however, to date there has been no study comparing these methods to one another and it is unclear which is the optimal method. To address this issue we have performed a simulation study under a wide variety of experimental designs, allele frequencies and disease models to evaluate the performance of eight popular statistical tests from the literature.

Our results show that two tests proposed by David Clayton have high power across a range of experimental designs and genetic models, however, the optimal test depends on the experimental design and disease model. We show that two tests implemented in the popular GWAS analysis software PLINK are vastly underpowered when compared to other existing methods for X chromosome analysis. Our results also highlight that experimental design features, such as the proportion of females in the study, greatly affect the power to detect associations on the X chromosome.

Using the knowledge gained from our simulation study we are re-analysing the X chromosome data from the ANZgene GWAS of multiple sclerosis. The two main subtypes of multiple sclerosis (relapsing remitting and primary progressive) have quite different prevalence rates in men and women, indicating a potential role for the X chromosome in determining multiple sclerosis disease severity

POSTER 38

Philip Church, Adam Wong, Andrzej Goscinski, Christophe Lefevre

EXP-PAC: facilitating comparative analysis of microarray gene expression data through e-research

ABSTRACT

With the growing size of microarray experiments and next generation sequencing, management of data is a key issue. In response we have developed EXP-PAC, a web based software package for upload, management and analysis of gene expression and sequence data. This package makes use of SQL based querying of gene expression datasets to isolate key probes. Data querying is provided through a simple web interface allowing users to find probes based on annotation, intensity or through fold changes. Uploaded statistical data can also be linked to a microarray experiment allowing for more complex analysis to be performed.

In addition to SQL based data filtering, EXP-PAC also provides distributed normalization of CEL files and analysis of gene expression data across experiments and species through UniGene IDs. Distributed normalization allows for multiple normalization algorithms to be applied to microarray data in the same time as running one normalization method. Combining distributed normalization and multi data comparison allows for discovery of crucial regulated genes that can be hidden due to errors in a single normalization.

EXP-PAC has been integrated with data from the international milk genomic consortium web portal (http://milkgenomics.org/content-root/mamexp-imgc) and used in a recent prostate cancer study by the ARC Centre of Excellence in Bio-informatics. The EXP-PAC source code is also available which can be hosted on a Windows, Linux or Mac APACHE server connected to a private or public network.

POSTER 39

Stephen Pederson, Gary Glonek, Simon Barry

Development of a Bayesian Mixture Model for Analysis of Exon Array Data

ABSTRACT

Early generations of Affymetrix® microarrays have been shown to provide consistent & accurate estimates of comparative gene expression levels. Whilst these arrays use probes targeting the 3' end of an mRNA transcript, the newer generations of expression arrays, i.e. Exon Arrays, use probes which target the entire length of a transcript. The probe-level modelling approaches used for analysis of 3' Arrays have been commonly used for analysis of Exon Arrays, but are subject to bias in the presence of splice variation between samples. The Bayesian Mixture model proposed here is a simple modification of existing probe-level approaches which accounts for this bias, thus enabling more accurate assessment of gene expression levels, and providing a more powerful method of alternative isoform detection than existing methods

POSTER 40

Yunshun Chen

The Cox-Reid Adjusted Profile Log-likelihood Estimation of Negative Binomial Dispersion

ABSTRACT

The quantile-adjusted conditional maximum likelihood (qCML) estimation is used in estimating the dispersion parameter of the negative binomial distribution in two-group comparison. When it comes to more than two factors, we have to use generalized linear models to handle the analysis. We derive the Cox-Reid adjusted profile log-likelihood approach using the conditional likelihood and the concept of residual maximum likelihood estimation (REML). Its performance is compared, in terms of bias, to qCML method. We also test this method in a case study where GLMs are fitted.

POSTER 41

Yuri Nikolsky, Weiwei Shi, Marina Bessarabova, Richard Brennan

Revealing the biology of predictive gene signatures: functional analysis of MAQC II classifiers

ABSTRACT

Gene expression signatures of toxicity and clinical response benefit both safety assessment and clinical practice. However, difficulties in understanding the association of the signatures to the predicted endpoints have limited their application. The MAQCII project generated 262 signatures for ten clinical and three toxicological endpoints from six gene expression datasets. A comprehensive functional analysis of these signatures and their non-redundant unions was conducted using ontology enrichment, biological network building and interactome connectivity analyses. Different signatures for a given endpoint were more similar at the level of biological entities and transcriptional control than at the gene level. Signatures tended to be enriched in function and pathway in an endpoint and model-specific manner, and showed a topological bias for incoming interactions. Importantly, the level of biological similarity between different signatures correlated positively with the average accuracy of the signature predictions. These findings have implications for the design, analysis, understanding and application of predictive genomics.

Profiling Technologies 2 – Disease and Discovery

POSTER42

Alen Faiz, Judith Black, Brian Oliver, Janette Burgess

Gender effects on gene expression in airway smooth muscle cells in asthma

ABSTRACT

Asthma contributes substantially to the cost/burden of patient care, affecting at least 1 in 10 people in Australia. Persistent severe asthma is associated with structural changes in the airway wall, termed remodelling. The airway smooth muscle (ASM) cell may have a central role in the pathophysiology of asthma as it not only contributes to the structural remodelling in the airway, but also has a role in modulating the inflammatory milieu and extracellular matrix (ECM) protein deposition. Here, we compare the gene expression profiles in ASM cells isolated from asthmatic and nonasthmatic volunteers with the aim of identifying relevant growth factors/cytokines which may then be therapeutically modified.

To profile the gene expression of asthmatic ASM cells Affymetrix GeneChip HuGene 1.0 ST Arrays were used. Asthmatic and non-asthmatic ASM cells were treated in vitro with three different stimuli chosen to mimic the processes known to occur in the asthmatic airway: foetal bovine serum (FBS) (pro-proliferative), transforming growth factor-β (TGF-β) (pro-fibrotic) and the cytokine interleukin 1β (IL-1β) (pro-inflammatory).

For this study we focussed on a subset of genes that had previously reported associations with asthma to validate our dataset. Most of the genes reflected the reported differential expression in asthmatics, however the regulation and alternative splicing of a subset of these genes were found to be gender specific.

These results provide genetic evidence that certain effects of asthma may be gender specific, having ramifications for the interpretation of genetic profiling related to asthma research and may have implications for future novel gender based asthma treatments.

POSTER 43

Coleen Elso, S Ivory, T Brodnicki

Sleeping Beauty transposon mutagenesis in NOD mice

ABSTRACT

The Sleeping Beauty (SB) transposon mutagenesis system provides a powerful tool for the random disruption and rapid identification of genes in the mouse. We have chosen to use transposon mutagenesis in the nonobese diabetic (NOD) mouse, which is predisposed to different autoimmune diseases with complex genetic aetiology, including type 1 diabetes, Sjogren's syndrome, and thyroiditis. Mobilisation of the SB transposon is mediated by the SB transposase through a 'cut-and-paste' mechanism resulting in excision of the transposon and insertion elsewhere in the genome. We have produced transgenic mice on the NOD genetic background carrying either the SB transposase or SB transposon and intercrossed them to produce G0 mice carrying both constructs. The transposon contains a polyA trap with a green fluorescent protein (GFP) reporter gene, allowing for efficient detection of potentially mutagenic transposition events in offspring. Ten GFP+ G1 offspring have been identified, confirming that the SB tagged-mutagenesis system is functional in the NOD mouse. Traditionally, identification of the mutated gene is determined by ligation-mediated PCR followed by cloning and sequencing. We wish to utilise next-generation sequencing of pooled ligation-mediated PCR products, thus increasing the efficiency of mapping the transposon insertion sites. This will expedite the identification of any disrupted genes, allowing us to quickly prioritise them for further characterisation. This mutagenesis strategy may lead to new insights on autoimmune pathogenesis, and demonstrate the utility of the SB transposon-mutagenesis system for disease gene discovery, which can be applied to other mouse models of complex genetic disease.

POSTER 44

Dan Belluoccio Carlos Pabón-Peña, Douglas Roberts, Scott Happe, Angelica Giuffre, Barbara Novak, Marc Visitacion, Swati Joshi, Joseph Ong, Susan Hunt, Eric Lin, Emily Leproust

The Agilent Technologies' SureSelect Target Enrichment System for Next-Generation Sequencing Demonstrates High Performance and Enables Diverse Applications

ABSTRACT

The discovery of rare polymorphisms, structural variants, and novel transcripts has been accelerated dramatically by next-generation sequencing technologies. However, it remains cost-prohibitive to sequence entire genomes in large cohort studies. To enable larger sample size, Agilent Technologies has developed the SureSelect platform, allowing focused analyses on specific genomic loci at considerable cost savings. Agilent is continuing to expand its portfolio to increase the number of applications available to users. First, we demonstrate high performance across Illumina, SOLiD, and 454 platforms, as measured by capture efficiency, uniformity, reproducibility, and SNP detection. Custom design across all platforms and multiple model organisms is simplified using a desktop version of the eArray software. Next, we create multiple unique SureSelect panels such as sequences encoding the human kinome or whole exome to highlight flexibility across a wide range of target size and complexity. These catalog designs enable standardized studies across multiple research sites. Third, for smaller targeted regions, we demonstrate the ability to index samples in a single lane, thereby further decreasing the cost of large studies. For more comprehensive genome analysis, we reveal expanded utility and scope of the All-Exon catalog product by increasing read depth uniformity and target coverage to include regulatory regions, small RNAs, and content from multiple databases including CCDS and RefSeq. SureSelect applications will continue to expand as users harness the power of next-generation sequencing.

POSTER 45

Emily Wong, Anthony Papenfuss, Andreas Heger, Arthur Hsu, Chris Ponting, Robert Miller, Jane Fenelon, Marilyn Renfree, Richard Gibbs, Katherine Belov

Transcriptomic analysis supports similar functional roles for the two thymuses of the tammar wallaby

ABSTRACT

The thymus plays a critical role in the development and maturation of T-cells. Diprotodont marsupials are unusual because they have two thymuses: a pair of thoracic thymuses (found in all mammals) and a larger pair of cervical thymuses. Researchers have known about the presence of the two wallaby thymuses since the 1800s, but no genome-wide research has been carried out into possible functional differences between the two thymic tissues. To understand the functional differences between these organs we used pyrosequencing to explore the transcriptomes a cervical and thoracic thymus from a single 178 day old tammar wallaby.

We show that both the tammar thoracic and the cervical thymuses displayed gene expression profiles consistent with roles in T-cell development. Both thymuses expressed genes that mediate distinct phases of T-cells differentiation, including the initial commitment of blood stem cells to the T-lineage, the generation of T-cell receptor diversity and development of thymic epithelial cells. Crucial immune genes, such as chemokines were also present. Comparable patterns of expression of non-coding RNAs were seen. 67 genes differentially expressed between the two thymuses were detected, and the possible significance of these results are discussed.

This is the first study comparing the transcriptomes of two thymuses from a single individual. Our finding supports that both thymuses are functionally equivalent and drive T-cell development. These results are an important first step in the understanding of the genetic processes that govern marsupial immunity.

POSTER 46

David Humphreys, Jennifer Clancy, Carly Hynes, Hardip Patel, Grace Wei, Thomas Preiss

Small RNA profiling of the cardiac HL-1 cell line using next generation deep sequencing

ABSTRACT

The murine atrial cardiomyocyte-derived HL-1 cell line is unique in that it maintains a differentiated cardiac phenotype and spontaneously contracts in culture. Because of these features is frequently used as a model system to understand cardiac biology. We performed SOLiD™ sequencing on small RNA obtained over a 4-day growth time-course as HL-1 cells transition from a progenitor – to a beating heart-like state. Using a quality-score weighting approach to deal with sequencing errors we mapped 43-million reads to miRBase v15 (average length 22nt). We found a 45% global increase in miR levels across the time-course, with few miRs exhibiting differential expression. Many miRs with known roles in cardiac biology are highly expressed in HL-1 cells (eg miR-1, miR-133). Interestingly, we detect expression of many miR variants. 6.8% of miR reads represented 5' iso-miRs (starting position offset to miRBase entry); in some cases the isomiR was the most abundant species (e.g. 'cardiac' miR-133a). 6% miR reads mapped to the '*' strand of the miR duplex; for some miRs this represented the major species (e.g. the 'cardiac' miR-208a). A further 5-million reads mapped uniquely to other sites in the genome. Sites of notable expression (>100 reads) included those overlapping with annotated features such as snords, tRNAs, repeat sequences, and intronic/UTR regions. Our data reveal surprising complexities in the expression of known miRs, document the existence of novel miRs and other small RNAs, and provide a compendium of cardiomyocyte small RNAs that can inform future research into cardiac biology and disease.

POSTER 47

Elizabeth Fitzpatrick, D Amor, H Mountford, M Bahlo, P Mill, E Hall, C Bromhead, K Pope, S Aftimos, I Jackson, R Savarirayan, M Delatycki, PJ Lockhart

Using SNP genotyping arrays and copy number variation analysis to identify a novel gene mutated in short rib polydactyly syndrome

ABSTRACT

Genome-wide single nucleotide polymorphism (SNP) genotyping platforms have made an important contribution to the identification of genes causing human diseases. Data from SNP platforms have the dual potential for linkage and association studies and copy number detection. The ability to maximise information obtained from high throughput experiments can greatly facilitate gene identification in small families previously considered underpowered for traditional mapping studies.

Here we report on the power of such an approach, whereby SNP data was analysed for linkage and CNV, resulting in the identification of a gene for a rare skeletal disorder. The short rib-polydactyly (SRP) disorders are a heterogenous group of autosomal recessive lethal skeletal dysplasias characterised by short ribs and limbs, polydactyly and abnormal viscera. We previously identified a family with an unclassifiable SRP that displayed laterality defects, suggestive of ciliary dysfunction. We performed SNP analysis on five family members and identified three regions with a LOD>1. Analysis of inferred haplotypes suggested that a single region at chromosome 2p24.1 was homozygous by descent in affected members. CNV analysis identified a homozygous deletion within the linkage peak that disrupted the WDR35 gene. Immunocytochemical analysis localised WDR35 to the cilial axoneme of control fibroblasts. No cilia were observed in patient-derived fibroblasts. The disruption of wdr35 in the mouse resulted in abnormal cilia, randomised laterality, polydactyly and neural tube defects, features consistent with the human phenotype. In conclusion, our studies have identified a novel ciliopathy gene and extended our understanding of the pathogenesis of SRP.

POSTER 48

Grant Montgomery, Jodie Painter

SNP discovery through sequencing in DNA pools

ABSTRACT

Endometriosis is a gynaecological disease associated with severe pelvic pain and sub-fertility affecting 6-10% of women of reproductive age. We have conducted linkage and association studies to map genes and variants associated with the disease. Fine mapping of disease associated regions is an important step to identify genes and pathways implicated in mechanisms leading to implantation of lesions outside the uterus and subsequent progression of the disease. One approach is to sequence the regions in cases and controls to identify all rare and common variants for further genotyping and subsequent functional studies. Despite improvements in multiplexing, current high-throughput sequencing methods remain expensive. Sequencing in carefully constructed DNA pools might be one way to reduce sequencing costs, since we have shown previously that DNA pooling strategies can be successfully applied for genotyping in genome-wide association studies. Long range PCR was used to amplify a region of 252.3 kb in two pools of 384 endometriosis cases and 384 controls and products were sequenced at high coverage at deCODE Genetics. Coverage for the region was 96.8% in cases (9.5kb are missing) and 94.0% in controls (18kb are missing). Results identified 351 known SNPs and a further 2766 SNPs that passed deCODE quality control for the SNP calling, an eight fold increase. Of these additional SNPs, 1110 had high quality scores within the range of the known SNPs. Individual genotyping of DNA samples making the pools will be conducted to validate the SNP discovery.

POSTER 49

Grant Parnell, B Tang, D Booth, S Huang, M Nalos, A McLean

Expression of Inflammation and Immune Response Genes in Severe and Mild Influenza Infection

ABSTRACT

Background: Dysregulation of inflammatory response is thought to drive the progression from mild to severe influenza infection. Here we use gene expression microarray to compare the host response to mild and severe influenza infection, focusing our attention on expression of inflammation and immune response genes in circulating leukocytes.

Method: PAXgene blood samples were collected for days 1 – 5 of ICU stay for severe influenza group (n=4) and at peak symptoms (mean 3.5 days) for mild influenza group (n=8). Severe influenza samples were assayed using Illumina HT-12 beadchips and processed using Illumina Beadstudio. The mild influenza cohort was accessed from published data using the Affymetrix U133A platform. Data analysis was carried out using BRB-Arraytools and GeneGo Metacore. Fold change compared to healthy controls was determined for inflammatory and immune response genes.

Results and Conclusions: Other than TNF and IL-beta, inflammation-related genes well established in influenza infection do not discriminate between severe and mild groups. Also, expression of interferon response genes does not differ significantly between mild and severe. In severe influenza patients, immune response genes, in particular interferon response and viral detection genes, decrease over time to quiescent levels, correlating with infection resolution and clinical improvement.

POSTER 50

Greg Peters, Artur Darmanian

Human genome copy number variants of uncertain significance: Review of CNVs encountered during three years of diagnostic screening, via a recent classification technique.

ABSTRACT

DNA microarray testing for constitutional change in copy number has become common in clinical genetics laboratories. This technology has improved detection of clinically relevant copy number changes, from around 3-4% [as found via microscopy], to 12%-15% of relevant test referrals. Furthermore, this technology has made possible the discovery of new genomic disorders [examples are the 17q21.31 1 and 2q23.1 2 microdeletion syndromes].

A major problem, though, has been the simultaneous detection of many copy number variants of unknown [and probably no] clinical significance. These latter require exclusion as potential causes of disease, usually by expensive follow-up testing of other family members.

Around the world, many such CNVs have been collected into various databases. These can now be used to devise methods affording [we hope] some a priori prediction of phenotype, or lack of it. Some ability to discriminate benign from pathogenic CNVs would be most valuable, especially when family testing is inconclusive, or unavailable.

Depending on the power they can achieve, these multi-factor discriminators may also teach us much about what, and what proportion, of genes are dosage-sensitive. Such information may also allow identification of those classes of genes [eg within certain pathways] that are most likely to be dosage sensitive. One such tool, recently published[3], is a naïve Bayesian tree classifier named "GeCCO" [for "Genomic Classification of CNVs Objectively"].

We here apply the GeCCO classifier, and simpler discriminators, to our own set of approx. 2000 array test cases, to evaluate the utility of these approaches.

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POSTER 51

Harald Oey, Neil Youngson, Emma Whitelaw

Small RNA population and strain-specific variations in mouse sperm

ABSTRACT

Small RNAs are now known to be both ubiquitous and indispensable in most cells and are intimately involved in most pathways and regulatory mechanisms. Several different functional classes have been described, including microRNAs, siRNAs and piRNAs, and others are likely still to be discovered. In testis important functions of small RNAs, particularly represented by the piRNAs, are well documented. Mature sperm cells on the other hand are believed to be transcriptionally silent and the RNA they contain believed to represent remnants of RNAs expressed during spermiogenesis. We have characterized the small RNA composition of mature mouse sperm cells extracted from mice from the C57BL/6 and FVB backgrounds. We find that mature sperm cells contain RNA from most of the small RNA classes that one would normally expect, particularly including microRNAs, primary piRNAs, secondary piRNAs and an abundance of small RNAs derived from structural non-coding RNAs. Furthermore, despite indications of wide-spread RNA degradation and RNA loss in mature sperm we find that the abundance of most RNA species is very similar between the two mouse strains investigated and in the case of microRNAs most species are found to vary less than 2-fold between the two strains, with some notable differences. Curiously, we find that the ratio of the total number of microRNAs to the total number of piRNAs is not the same between the two strains and we suggest possible explanations and implications of this variation

POSTER 52

Hugh French, Kristine Hardy, M Frances Shannon, Rohan Williams

Inducible genes are affected by genetic variation

ABSTRACT

Because activation of the immune response is dependent on extensive changes in gene expression, it is likely that a major component of inter-individual variation in the immune response is ultimately mediated at the level of gene regulation. Here, we examine the influence of genetic variation on inducible gene expression in the murine immune response. We extracted primary CD4+ splenocytes from inbred strains A/J, C57BL/6J, BALB/c, DBA/2J, and 129x1/SvJ (>3 animals/strain) and measured mRNA transcript levels using microarrays in both basal state and four hours after stimulation with PMA/Ionomycin. We defined an expression change occurring during activation as the difference in measured expression intensity between stimulated and basal conditions. We identified genetically influenced genes using a gene-wise single-factor (strain) ANOVA (B-H corrected $P<0.05$). We identified 2607, 1145 and 506 transcripts whose expression levels are under potential genetic influence in basal state, stimulated state and during activation, respectively. Preliminary analysis using the FIRMA algorithm suggests a number of instances of genetically-variant differential splicing. These differentially activated genes are ideal candidates for further study into the influence of genetic variation on the mechanisms of gene induction, and provide mechanistic insight into inter-individual variation in the host response to infection.

POSTER 53

Jason Ross, Peter Molloy

Development of a new method, strepavidin bisulfite ligand methylation enrichment (SuBLIME) to enrich for methylated DNA prior to deep bisulfite genomic sequencing.

ABSTRACT

Bisulphite genomic sequencing (BGS) has been adapted to deep sequencing technologies allowing unprecedented resolution of genome-wide cytosine methylation status across whole DNA methylomes. In organisms with large genomes this is still prohibitively expensive for application to multiple samples. We sought to develop a BGS method that offers nucleotide level resolution but significantly reduces the amount of deep sequencing required for adequate methylome coverage. SuBLIME enriches for the genomic library fraction containing methylated cytosines by capturing biotin-labelled bisulphite-treated methylated DNA on streptavidin-coupled magnetic beads. Quantitative PCR of spike-in controls show significant enrichment of biotin-labelled material on the magnetic beads. An obvious application of this technology is in the identification of putative epigenomic biomarkers in larger patient cohorts.

In a complexity-reduced methylome pilot study, covering 9.5% of genomic CpG sites, we apply SuBLIME to the detection of differential methylation in three colorectal cancer cell lines relative to normal blood. Two technical replicates of each were sequenced; amounting to 83.8M high quality aligned SOLiD-3 reads, including 57.1M uniquely aligned. We found approximately 9400 CpG sites differentially methylated between normal blood and all three colorectal cancer cell lines. These include many published biomarkers. Interestingly, and perhaps analogously to the CpG island shore hypothesis, most differential methylation was outside of defined promoters and in the gene body next to transcription start sites.

SuBLIME has broad utility and is suitable for the study of mammalian, plant and insect genomes using Applied Biosystems SOLiD or Illumina GAIIx technology.

POSTER 54

Jocelyn van den Bergen, Amanda Notini, Dan Belluoccio, Denise Miles, Stefan White, Andrew Sinclair, Patrick Western

Male Fetal Germ Cell Differentiation

ABSTRACT

The germ cell lineage is unique in that it must become highly specialized to support gametogenesis but must also ensure that the genome retains the complete developmental potential (totipotency). Germ cells must differentiate along the male or female pathways, a process that requires commitment of the bi-potential primordial germ cells to the spermatogenic (male) pathway and their entry into mitotic arrest, or to the oogenic pathway (females) and entry into meiosis. Sex specific differentiation of the germ line involves robust control of pluripotency and cell cycle regulatory networks. However in some circumstances male germ cell differentiation fails, pluripotency is reactivated and testis tumours form. Our work aims to understand the mechanisms controlling differentiation, pluripotency and cell cycle in early male and female germ cell differentiation. We have conducted gene expression profiling on purified mouse embryonic germ cell populations from male and female gonads during the developmental window of germ cell differentiation embryonic day (E)12.5, E13.5, E14.5 and E15.5. A male versus female germ cell analysis of this data set identified a novel set of genes that are potentially involved in differentiation of the male germ line. Using biological contextualization tools we have focused on a subset of genes that are conserved in human and mouse and have been associated with cancer, chromatin / epigenetic regulation and control of cell cycle. Together with a number of previously known male germ cell genes we refer to these combined gene sets as the Male Germ Identity Collection (MaGIC). To examine potential epigenetic regulation of male germ cell development we have designed high-density custom microarrays and conducted ChIP-on-chip experiments for a subset of associated 'activating' (H3K4me3) and 'repressive' (H3K9me3 and H3K27me3) histone modifications on the MaGIC promoters. Further understanding of these processes promises to lead to a greater understanding of the fundamental molecular mechanisms underlying control of pluripotency, cell cycle and differentiation in the germ line and the initiation of germ cell-derived testis tumours.

POSTER 55

Maree O'Sullivan, Guy Abell, Jeff Ross, Stanley Robert, Levente Bodrossy, Steve Wakelin, Adrienne Gregg

Sediment microbial metagenomics: linking microbial communities with environmental parameters

ABSTRACT

Microbial communities (Bacteria and Archaea) are responsible for the majority of biogeochemical processes in the environment. The diversity of these organisms, their functioning and the relationship between this diversity and ecosystem processes are not well understood. The management of our environment will be greatly improved by the ability to monitor and predict impacts of environmental variables on microbial communities and their functioning. We are interested in investigating the relationship between microbial community composition, the functioning of these organisms and environmental variables. Through the identification of associations between these parameters we hope to gain new insight into how microbial diversity is linked to environmental variables.

In order to achieve this we are combining analysis of microbial community composition with measurement of abiotic drivers such as nutrient flux and other environmental measures. Species abundance was examined using the Phylochip array platform, which enables rapid assessment of microbial biodiversity in an environmental sample. Limma (Smyth, G. K. (2005)) was used to analyse the array data and identify changes in species abundance which were, subsequently, related to changes in nutrient flux and other environmental measures. Given the cost of measuring key environmental variables such as nutrient flux, we are investigating the possibility of using estimates of species abundance, derived from phylochip analysis, as a surrogate for environmental variables.

POSTER 56

Margaret Jordan, JM Fletcher, R Jose, S Chowdhury, D Pellicci, AG Baxter

Identifying Genes Controlling Nkt Cell Numbers By Expression Microarray Analysis

ABSTRACT

Nonobese diabetic (NOD) mice have a deficiency of type 1 NKT cells, compared to C57BL/6 and BALB/c mice. As this cell population regulates a broad range of immune functions, our aim is to identify genes controlling them. Previously, we mapped genetic control of NKT cell numbers in a backcross from C57BL/6 to the NOD.Nkrp1b mouse strain, which revealed significant linkage on chromosomes 1 and 2. Strongest linkage on chromosome 1 was at D1mit15, in the same region as the mouse lupus susceptibility gene Babs2/Bana3 and linkage on chromosome 2 co-localised with Idd13, a murine diabetes-susceptibility gene. Congenic lines were established for the chromosome 1 and 2 linkage regions (NOD. Nkrp1b.Nkt1 b and NOD. Nkrp1b.Nkt2 b) and verified for increased NKT cell numbers. Microarray data comparing NOD.Nkrp1b.Nkt1 b to the control group (NOD.Nkrp1 b) revealed a total of 28 highly differentially expressed genes (P<0.02), with 21 of the locatable genes mapping within our congenic region (~1.6% of genome; 2=1.381;df=1;p<10-300). Fifteen of these 21 genes lie within the 95% confidence limits of the original linkage analysis. Slamf1 and Slamf6 were thought to be the most prominent candidates for control of NKT cell numbers, as signalling through SAP (SLAM associated protein) is essential for thymic positive selection of NKT cells. Candidates were validated by RT-PCR and flow cytometric analyses of an independent sample set. To formally establish Slamf1 as the NKT control gene, Nkt1, a NOD.Nkrp1b-Tg(hCD2-Slamf1) was created, and its effect on NKT cell numbers was compared to the NOD.Nkrp1b parental strain.

POSTER 57

Matthew Ritchie, M V Granovskaia, L Juhl Jensen, J Toedling, Y Ning, P Bork, W Huber, LM Steinmet

Tiling the cell cycle: A high-resolution transcriptional atlas of mitosis in budding yeast

ABSTRACT

Extensive transcription of non-coding RNAs has been observed in eukaryotic genomes and is thought to constitute an additional layer in the regulation of gene expression. Despite this role, their transcription through the cell cycle has not been investigated, with existing genome-wide profiling studies focusing on protein-coding genes. To explore the complex transcriptome architecture underlying the budding yeast cell cycle, we used tiling arrays to generate a 5 minute-resolution, strand-specific expression atlas of the whole genome. We observed both cycling and stably expressed antisense transcripts and unannotated intergenic non-coding RNAs. Periodic expression coupling of sense and antisense transcript pairs, including antisense transcripts opposite key cell-cycle regulators was also detected. Our dataset reveals periodic expression of both protein-coding and non-coding RNA and profiles the expression of non-annotated RNAs throughout the cell cycle for the first time. This data enables hypothesis driven mechanistic studies concerning the functions of non-coding RNAs.

POSTER 58

Rae-Anne Hardie, Menna Jones, Stephan C Schuster, Vanessa Hayes

Mitochondrial genome diversity in Tasmanian devils, now and 100 years ago

ABSTRACT

The largest living marsupial carnivore, the Tasmanian devil (Sarcophilus harrisii), is threatened with extinction due to a transmissible cancer known as Devil Facial Tumor Disease. Previous indications suggest that low genetic diversity within the species is a major factor in the animal's inability to reject these tumors. Determining genetic diversity is therefore critical, as it not only defines a species' ability to respond to environmental changes, but also provides a window into previous species declines. In this study we performed Roche/454-sequencing on thirteen specimens sampled prior to and post the disease outbreak, reporting complete mitochondrial sequence analysis that dates back up to 100 years. Genotyping almost 200 animals across the island of Tasmania allows us to determine the extent of whole mitochondrial genome genetic diversity that currently exists within the wild population. We expand our analysis to make predictions based on global extinction rates and discuss the implication of our findings for selection of insurance populations for captive breeding programs and species survival.

POSTER 59

Vikki Marshall & QBI Molecular Genetics Committee

Advanced Genomics Technologies at the Queensland Brain Institute (QBI), University Queensland, Australia

ABSTRACT

The Queensland Brain Institute (QBI) located in the University of Queensland is the first medical research institute in Australia to procure the new Illumina HiSeq2000 second-generation DNA sequencing instrument, taking delivery in August of 2010.

The QBI is renowned for its high-quality research to advance our understanding not only of memory and learning, but also the cause and treatment of neurological disease and mental ill health, including: Attention Deficit Hyperactivity Disorder (ADHD), autism, brain tumor, dementia, depression and anxiety, multiple sclerosis (MS), neurotrauma (e.g.) spinal cored injury, schizophrenia and stroke.

QBI is similarly renown for its 'vision' and rapid uptake of advanced technologies, including the need for a world-class genomics platform that includes that latest technology available in Second Generation DNA Sequencing.

QBI's new HiSeq2000 Second Generation DNA Sequencing instrument will be housed within our newly established Molecular Genomics Research Facility (MGRF), complementing the existing suite of Advanced Technologies platforms at QBI that include: the ACRF Brain Tumour Research Centre, 16.4T Magnetic Resonance Imaging (MRI) Spectrometer, Advanced Microscopy Facility, All Weather Bee Flight Facility, Flow Cytometry, Peter Goodenough and Wantoks Research Laboratory (Motor Neuron Disease, MND) and the Ultra High-Field Micro-Magnetic Resonance Imaging Facility

The Molecular Genetics Research Facility will accommodate the needs of QBI researchers and their collaborators firstly, as well as researchers across the University of Queensland (UQ) and Brisbane medical research precinct affiliated with UQ. It is expected that spare capacity on the instrument will be made available to external researchers in approximately February 2011, and this will be on a cost-recovery basis for QBI. Initially the access for external researchers will be 'runs only'. The facility aims to maximize the output of high quality DNA sequence from every sequencing run, thereby maximizing access and minimizing per-sample cost. Most sequencing applications will be offered to internal researchers, including targeted re-sequencing and whole-exon capture.

We also plan to play an educational role by promoting the use of advanced molecular technologies in medical research amongst students of both biology and of bioinformatics.

QBI's choice of advanced technologies is purely research-driven. Our operational model promises to enhance collaborative interactions, to assist in the generation of high quality, reliable molecular data to advance knowledge in pure and applied molecular science alike. Some of the many applications that the facility will offer shall be discussed.

POSTER 60

Matt Harrison, WMH d'Avigdor, M Stapelberg, GW McCaughan, M Lee, FJ Warner, NA Sharkel

Correlation of miRNA and mRNA expression profiles differentiating Hepatitis C (HCV) genotypes 1 and 3 liver injury

ABSTRACT

HCV genotypes 1 and 3 (G1, G3) are characterized by poor interferon responsiveness and increased steatosis/insulin resistance. Previous work showed distinct mRNA and miRNA expression in G1 and G3 liver injury. We aimed to correlate mRNA and miRNA expression and identify pathways involved.

HCV G1, G3 and control liver groups were compared using Illumina Human Sentrix 6v2 microarrays (mRNA expression); and Applied Biosystems' TLDA miRNA arrays (miRNA expression). MetacoreTM (GeneGo) was used for pathways analysis.

mRNA transcript expression of HCV G1 (n=16) and G3 (n=23) biopsies with varying fibrosis scores (F0-F4) were compared to donor liver controls (n=6). Irrespective of genotype, miRNA expression was compared to donor liver (n=4); fibrosis score F0-F2 (n=8); fibrosis score F3-F4 or having HCC (n=22); and alcoholic liver disease (n=4). miR-148a was significantly down-regulated in G1 and G3. 137 and 90 of TargetScan's predicted targets overlapped with those mRNA transcripts significantly up-regulated in G1 and G3, respectively. In G3, DNA damage BRCA1; and Estrogen Receptor 1 signalling were identified. In G1, lipid and fatty acid metabolism, PDGF signalling, TGF-β receptor signalling and cytoskeleton remodelling were observed. miR-200b and miR-429 were both up-regulated in G1 and G3. 174 and 154 of TargetScan's predicted targets overlapped with mRNA transcripts significantly down-regulated in G1 and G3, respectively. Of the top 50 pathways, 18 were common to both G1 and G3.

Distinct mRNA and miRNA expressions are associated with HCV infection and distinguish G1 from G3 liver injuries. The identified pathways may regulate important aspects of intrahepatic HCV pathogenesis not be directly merged together due to the large effects.

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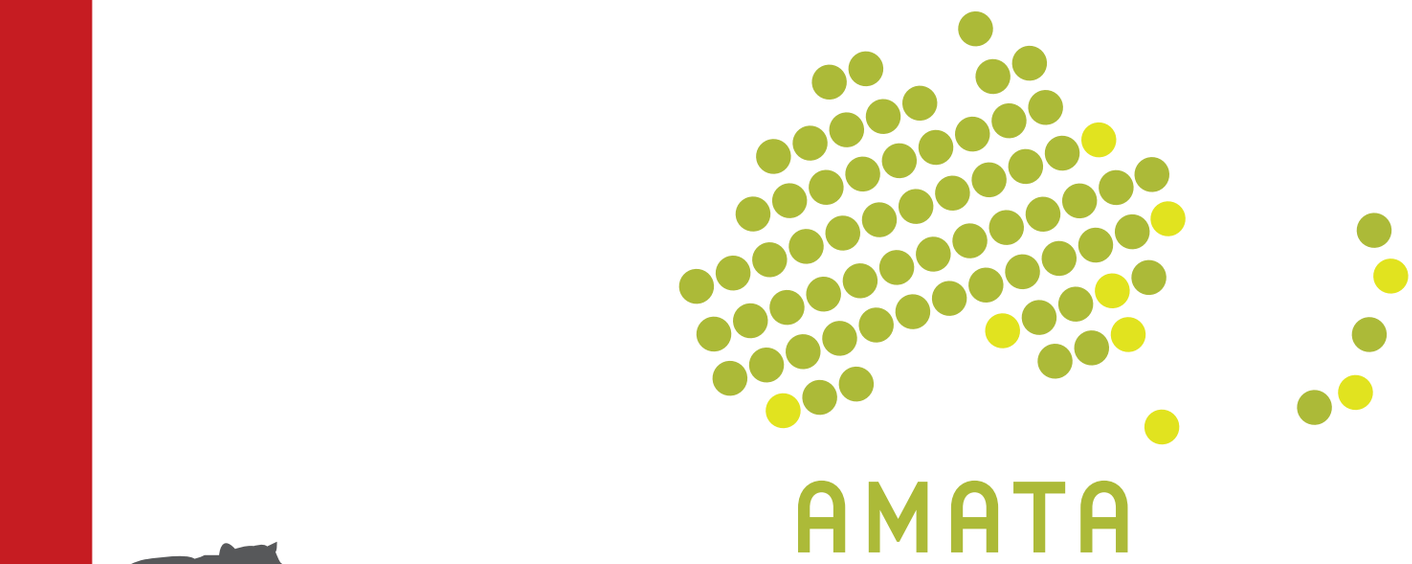

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NOTES

NOTES

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AMATA

conference canberra 2011

The Shine Dome, Canberra, Australia

9-12 October 2011

AMATA invites you to attend the 11th Australasian Microarray and Associated Technologies Association Annual Conference, to be held in Canberra, Australian Capital Territory, on 9th–12th October 2011.

The conference venue is the historic Shine Dome, situated in the heart of Canberra, near Lake Burley Griffin, the Floriade flower festival, national museums and galleries.

AMATA 2011 will showcase the latest advances in Next Generation sequencing and other high-throughput platforms, bioinformatics and their applications to diverse areas in biology and biomedical research. The Canberra meeting will bring together leaders in the fields of transcriptomics, epigenetics, phenomics, translational medicine and bioinformatics.

We are certain you will enjoy this opportunity to interact and learn from world leaders in the application of high throughput technologies, and the Biotechnology companies that are inventing the future of biological research.

We look forward to seeing you in Canberra for AMATA 2011.

CONFIRMED INVITED SPEAKERS

Steve Jacobsen, USA (Epigenomics)
Ana Pombo, UK (Epigenomics)
Jurg Bahler, UK (Transcriptomics)

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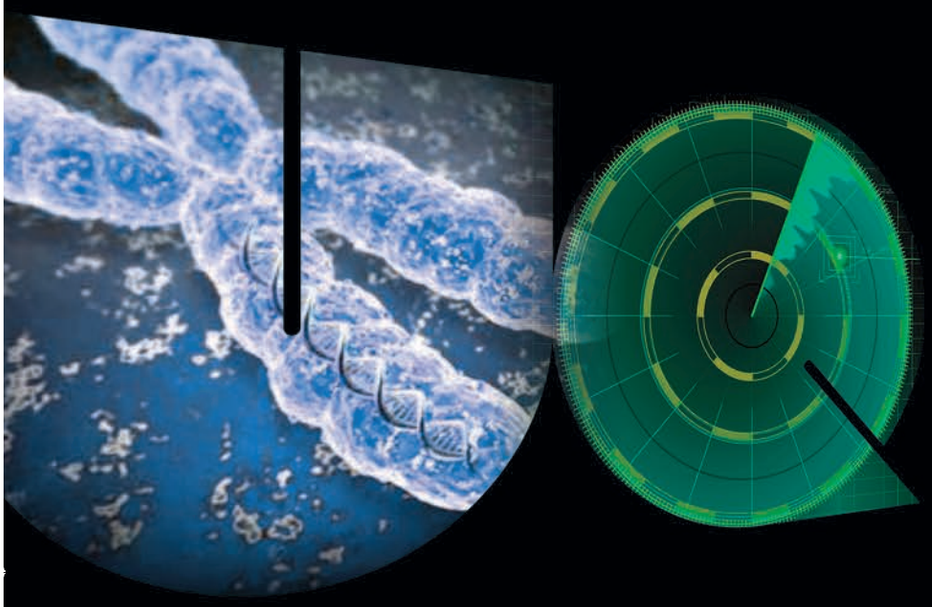

The New
Molecular Genetics Research Facility

The **Queensland Brain Institute** (QBI) at The University of Queensland is a neuroscience research-intensive facility where an accelerated pathway to discovery is made possible by utilising the world's most advanced technologies.

QBI's newly established Molecular Genetics Research Facility (MGRF) houses the latest Second Generation DNA Sequencing (2GS) platform, the Illumina HiSeq 2000 sequencing system, capable of 25Gb/day of sequence output or 500 million 'short reads' per flow cell. **QBI is the first research institute in Australia to utilise this latest 2GS technology platform.**

Applications utilised by QBI researchers include:

- Whole Genome Sequencing
- mRNA-seq: DGE, transcriptome
- Targeted re-sequencing (exome)
- small RNA-seq
- chIP-seq
- others as required

Expressions of interest for collaborative or joint projects utilising this technology in 2011 are welcome now.

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