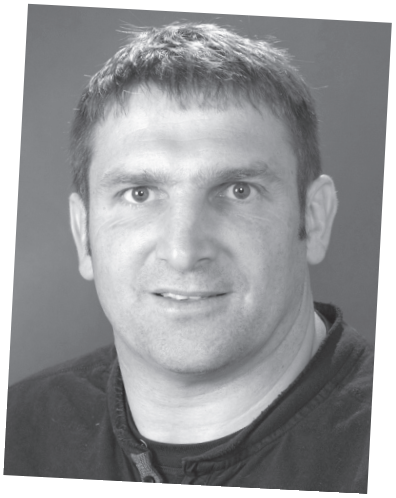
welcome from AMATA 2008 Co-ordinator



We extend a very warm welcome to AMATA 2008: to our international and national presenters, delegates from research groups in New Zealand, Australia and other parts of the world, and our generous sponsors.

The program we present includes innovative approaches and fresh ideas which we hope will inspire you to apply these methodologies and ideas to your own research areas.

This single session meeting covering a diverse range of fields, topics and technologies should be both stimulating and rewarding. It has become almost essential to apply a wide range of technologies and skills in a multidisciplinary manner to our current research programs. This integrated approach is reflected in the topics and range of speakers selected for the meeting. Researchers attending the meeting should take the opportunity to mix with researchers from different disciplines and forge collaborations which will enhance both their knowledge and research outputs.

On your behalf, I would like to thank the committee for their hard work and dedication in putting the 2008 program together: Tony Reeve, Mik Black, Tony Merriman, Rob Day, Andrew Holloway. And to Mik Black, Gordon Smyth and Mark Robinson, thank you for the expertise and organisation of the Saturday Bioconductor/Limma Workshop. As those of you who organise meetings will know, there is much work behind the scenes in bringing it all together for a successful meeting. Thanks also to the venue staff and caterers for their professionalism and assistance.

AMATA 2008 has been supported by a number of sponsors to whom we are very grateful. Generous support was received from Platinum Sponsors: Illumina, Millennium Science and Pacific Laboratory Products; Gold Sponsors: Applied Biosytems, Inc., and Roche Diagnostics; Silver Sponsors: BioLab Analytical Technologies, MDS Analytical Technologies, Miltenyi Biotec; Exhibition: AGRF - Australian Genome Research Facility. AMATA and The University of Otago are major supporters. Please take the time to visit the exhibition stands and read the information in your program and satchels.

We welcome you and thank you for coming to our university city. Dunedin has a proud academic history and is a fitting setting for AMATA 2008. I trust that the talks and discussion will challenge and inspire and result in new ideas.

Les McNoe,
Co-ordinator, AMATA 2008
Dunedin, November, 2008

Program-at-a-Glance

Tuesday 11th November

11 am - 2:00 PM	**Exhibition and Posterboard bump-in**	*Otago Daily Times Gallery*
2:00 PM - 4:00 PM	**Applied Biosystems Workshop**	*The Auditorium, Dunedin Public Art Gallery*
4:00 PM - 4:30 PM	ABI Afternoon Tea	*ABI Stand, Otago Daily Times Gallery*
4:30 PM - 5:00 PM	**Illumina Product Launch**	*The Auditorium, Dunedin Public Art Gallery*
5:00 PM - 5:30 PM	llumina Drinks	*Illumina Stand, Otago Daily Times Gallery*
2:00 PM - 6:00 PM	Registration opens	*Otago Daily Times Gallery*
5:55 PM - 6:00 PM	**Welcome and opening remarks**	*The Auditorium, Dunedin Public Art Gallery*
6:00 PM - 7:00 PM	**Session 1: Opening Oration: John Mattick**	*The Auditorium, Dunedin Public Art Gallery*
7:00 PM - 9:00 PM	**Welcome Reception and Exhibition**	*The Auditorium, Dunedin Public Art Gallery*

Wednesday 12th November

9:00 AM - 10:30 AM	**Session 2: Plenary I: Rob Martienssen; Plenary II: Heather Cunliffe**	*The Auditorium, Dunedin Public Art Galley*
10:30 AM - 11:00 AM	Coffee and Exhibition	*Otago Daily Times Gallery*
11:00 AM - 1:00 PM	**Session 3: High throughput sequencing**	*The Auditorium, Dunedin Public Art Galley*
1:00 PM - 2:00 pm	Lunch and **PLP Workshop**	*Otago Daily Times Gallery/The Auditorium*
2:00 PM - 3:30 PM	**Session 4: Cancer Genetics I**	*The Auditorium, Dunedin Public Art Gallery*
3:30 PM - 4:00 PM	Afternoon Tea and Exhibition	*Otago Daily Times Gallery*
4:00 PM - 5:30 PM	**Session 5: Developmental Biology**	*The Auditorium, Dunedin Public Art Gallery*
5:30 PM - 7:00 PM	Dinners around The Octagon (own cost)	*The Octagon, Central Dunedin*
7:00 PM - 9:00 PM	**Poster Session, Wine and Exhibition**	*Otago Daily Times Gallery/Conference Room*

Program-at-a-Glance

Thursday 13th November

9:00 AM - 10:30 AM	**Session 6: Plenary III: Peter Campbell; Plenary IV: Cris Print**	*The Auditorium, Dunedin Public Art Gallery*
10:30 AM - 11:00 AM	Coffee and Exhibition	*Otago Daily Times Gallery/Exhibition area*
11:00 AM - 12:30 PM	**Session 7: Plant and Animal Genetics**	*The Auditorium, Dunedin Public Art Gallery*
12:30 PM - 1:30 PM	Lunch and AGM	*Otago Daily Times Gallery/The Auditorium*
1:30 PM - 3:30 PM	**Session 8: Bioinformatics**	*The Auditorium, Dunedin Public Art Gallery*
3:30 PM - 4:30 PM	Posters, Afternoon Tea and Exhibition	*Otago Daily Times Gallery/Exhibition area*
4:30 PM - 6:10 PM	**Session 9: Human Disease**	*The Auditorium, Dunedin Public Art Gallery*
6:30 PM	Coaches to Conference Dinner	*Meet at the front of the Gallery, on the Octagon*
7:00 PM - 11:00 PM	Conference Dinner	*Historic University Staff Club, Otago University*

Friday 14th November

8:30 AM - 10:00 AM	**Session 10: Plenary V: Rebecca Doerge; Plenary VI: Lance Miller**	*The Auditorium, Dunedin Public Art Gallery*
10:00 AM - 10:30 AM	Coffee	*Otago Daily Times Gallery/Exhibition area*
10:30 AM - 11:10 AM	**Session 11: Special Plenary Lecture: David Bentley**	*The Auditorium, Dunedin Public Art Gallery*
11:10 AM - 12:30 PM	**Session 12: Cancer Genetics II**	*The Auditorium, Dunedin Public Art Gallery*
12:30 PM - 12:40 PM	Conference Close and Awards	*The Auditorium, Dunedin Public Art Gallery*

AMATA

The role of AMATA is to support and promote high throughput technologies including microarrays within the Australasian scientific community. AMATA has enabled strong co-operation and the sharing of knowledge between a diverse range of disciplines including statistics, bioinformatics, genetics, and biochemistry. This co-operation is essential in an increasingly complex area of research. Through its annual meetings, AMATA has also facilitated the introduction of new technologies and fostered close collaborations both within Australasia and the wider scientific community. A strong Association is imperative to the advancement of the field, and we invite those not already members to join us - subscription and payment are available on-line at http://www.amata.org.au

Scholarships and bursaries are offered to early career researchers and students for attendance at the annual meeting and other high-profile, aligned meetings. AMATA awarded travel bursaries for attendance at AMATA 2008 as follows: Early Career Researchers: Nicole Cloonan (Institute of Molecular Bioscience, Qld), Mark Cowley (Garvan Institute of Medical Research, NSW), Dale Garsed (Peter MacCallum Cancer Centre, Vic), Ruby Lin (University of New South Wales), Alicia Oshlack (Walter and Eliza Hall Institute of Medical Research, Vic), Logan Walker (Queensland Institute of Medical Research). Students: Anna Campain (University of Sydney, NSW), Chung Hoow Kok (IMVS and Hanson Institute, South Australia), Debbie Leader (University of Auckland), Manasa Ramakrishna (Peter MacCallum Cancer Centre, Vic), Ashley Waardenberg (CSIRO, Qld). The Gene Expression and Proteomics Theme, the University of Otago also awarded the following prizes to ECR's and students of the University. Early Career Researcher: Tina Summerfield. Students: Thomas Allen, Fathin Faiz, Sarah Morgan, Margriet van Kogelenberg. Congratulations to all awardees.

Sponsors

The entire meeting has received very welcome support from our corporate sponsors in 2008 and we especially wish to acknowledge and thank them: Platinum Sponsors: Illumina, Millennium Science, PLP (Pacific Laboratory Products); Gold Sponsors: Applied Biosystems, Inc. and Roche; Silver Sponsors: MDS Analytical Technologies, Miltenyi Biotec and BioLab Analytical Technologies; Exhibition: AGRF - Australian Genome Research Facility Ltd. We look forward to continued association between corporate and scientific communities, an imperative in this fast moving area of research.

2008 Executive

The Association meets together annually, rotating through the States of Australia and for the first time at AMATA 2008, in Dunedin, New Zealand. Members serving on the Executive of the Association are listed below.

Hon. President: Dr. Sean Grimmond, IMB Node, Brisbane
Hon. Vice-President and Public Officer: Dr. Gordon Smyth, WEHI Node, Melbourne (President elect)
Hon. Treasurer: A/Prof Nigel R Swanson, LSMAF WA Node, Perth
Hon. Secretary: Dr Andrew Holloway, PMCC Node, Melbourne

VICTORIA

SVI Node, Melbourne: A/Prof. Erik Thompson;
Dr. Mark Waltham
PMCC Node, Melbourne: Prof. David Bowtell;
Dr. Andrew Holloway;
AGRF Node, Melbourne: Prof. Sue Forrest; Dr. Stephen Wilcox; *WEHI Node, Melbourne:* Dr. Gordon Smyth

NEW SOUTH WALES

UNSW Node, Sydney: Prof. Ian Dawes;
Dr Ruby Lin: *Garvan Node, Sydney:* A/Prof Chris Ormandy;
Westmead Node, Sydney: Dr Daniel Catchpoole

WESTERN AUSTRALIA

LSMAF WA Node, Perth: A/Prof Nigel R Swanson (Hon Treas); *UWA Node, Perth:* A/Prof. Richard Lake

QUEENSLAND

IMB Node, Brisbane: Dr. Sean Grimmond;
Griffith Node, Brisbane: Dr. Christine Wells;
Herston Node, QIMR, Brisbane: A/Prof. Nick Hayward

AUSTRALIAN CAPITAL TERRITORY

ACT Node, Canberra: Dr Stephanie Palmer/
Dr. Aude Fahrer

SOUTH AUSTRALIA

Adelaide Node, Adelaide: Mr Mark van der Hoek

TASMANIA

Tasmanian Node, Hobart: Dr. James Vickers;
Dr. Adrian West

NEW ZEALAND

Otago Node, NZ: Les McNoe

General information

ACCOMMODATION: The conference hotel is the **Scenic Circle SOUTHERN CROSS** (there are two Scenic Circle hotels in Dunedin...) Ours is the 4-star heritage-listed building near the Casino,
Address: The Scenic Circle-Southern Cross hotel
118 High Street (CNR Princess Street), Dunedin
The Scenic Circle-Southern Cross hotel is located in the heart of the city, just a short walk to the Octagon and the Dunedin Public Art Gallery, our conference venue. Check in is after 2pm and checkout by 10am. Please note that accommodation is room-only. There is a gym on the 7th floor of the hotel; a Guest laundry is located on Levels 2 & 5; convenient dry cleaning service is available; parking is complimentary for guests. If sharing a room, please check out together to assist hotel staff with bill payment. The concierge will be happy to assist you in booking your shuttle back to the airport. Allow plenty of time for the booking.

AGM: The AMATA AGM will be held at lunchtime on Thursday 13th November, 2008 from 12:30-1:30pm in The auditorium at the Dunedin Public Art Gallery. All financial members are encouraged to attend this business meeting. Lunch will be served at the auditorium as well as in the exhibition area. Please note that food and beverage may not be carried through the galleries.

AWARDS and PRIZES
AMATA will award two prizes each for Poster and Podium presentations at the Dunedin Meeting. One prize will be awarded for the best oral presentation delivered by a Young Investigator and similarly by a student. The Poster prize will be awarded one to a Young Investigator and one to a student for the best poster presentations. The Prizes are each valued at $500. For the purposes of adjudicating the prizes, a young Investigator is classified as a research scientist under 35 years of age.

BANKING and TIPPING: All major credit cards are accepted in New Zealand. The New Zealand currency is the dollar. ATMs are located at the hotel - through the Caf´d'Oro, in the Casino Foyer. Please enquire of the Concierge. ATMs also located in the streets close to the Octagon. Tipping is not required although a small tip may be given for exceptional service.

BROADBAND:
Broadband is available in rooms and at stations in the foyer. Connection is not wireless and please check the usage - if 24hrs charge taken, must remain connected for 24 hours.

CLIMATE: November is springtime in Dunedin, but it is always essential to have a jacket with you – Dunedin is quite far South (lovely, long evenings...) and the winds and weather can turn quite cold. A jacket and umbrella are advised for the short walk from your hotel to The Octagon. The days are relatively long, with sunrise at 6am and sunset around 8:45pm. The average temperatures range from about 14°C during the day to 8°C at night. For those of us from warmer climes, this will feel cold!

CONFERENCE DINNER: Tickets are pre-purchased – if still available, they may be purchased through the Registration desk. The dinner will be held in the beautiful and historic Staff Club at the University of Otago. Coach transport leaves from The Octagon outside the Art Gallery to take guests to the venue, returning by 11pm to the conference hotel, Scenic Circle-Southern Cross. Dress is smart casual.

DATA/VIDEO PROJECTION:
A-V Technicians will assist you load your talk. You may bring your own computer; you can also give your talk on a labelled USB stick to the technicians at any time for uploading, but preferably well before the session in which you are speaking! If you are using your own computer, be sure to bring any necessary cables and connections. Both Mac and IBM-compatible platforms will be used. If you use a presentation format other than PowerPoint, or Video clips are incorporated into your talk, please advise the technicians/registration desk immediately on arrival.

ELECTRICITY: The electrical supply is 240 volts, 50 Hz, and typically 10 AMPS. Hotels provide 110 volt outlets for shavers. An adaptor to charge your computer, mobile/cell phone and/or razor may be purchased locally. Enquire of the Concierge, if needed.

General information, *continued*

EXHIBITORS and SPONSORS
We are grateful to our generous sponsors for their support for AMATA 2008: Platinum Sponsors: Illumina, Millennium Science, PLP – Pacific Laboratory Products, and the University of Otago. Gold Sponsors: Applied Biosystems, Inc., and Roche Diagnostics. Silver Sponsors: BioLab Analytical Technologies, MDS Analytical Technologies, Miltenyi Biotec. Exhibitors: AGRF - Australian Genome Research Facility.

Please visit our exhibitors' stands over the course of the Conference. Sponsors are located in the Otago Daily Times Gallery on the second level. There are stairs (beautiful local wood) up to the Exhibition level, and also a lift. New Zealanders are so fit – they walk everywhere, and climb hills and stairs with alacrity – perhaps it has something to do with the climate…

HOST CITY
Dunedin is noted for food, fashion and coffee – to that we might also add Pubs, breweries and chocolate factories! Dunedin's location, close to the sea and a rich agricultural hinterland, means fresh, high-quality produce - beef, venison, lamb from Central Otago and seafood fresh from the Pacific Ocean. Central Otago wines, New Zealand wines in general and of course, international wines complement the restaurant fare. It is also noted for wildlife (the feathered kind) and sea mammals, and as an original seat of learning in the country.

NAME BADGES AND REGISTRATION: Entrance to all scientific sessions and social functions is by name badge only. Please assist the gallery staff by wearing your name badge at all times. As you can appreciate there are important art works in the buiding, and security though unobtrusive is important. Your registration gives entry to all conference sessions, teas and lunches over the days of the conference. Your AMATA 2008 satchel contains the conference program and abstract book, sponsors materials etc. and is available from the Registration desk, which is open Tuesday afternoon from 2pm, generally an hour before sessions commence and during the day.

POSTERS: Poster boards are located in the Conference Room, on the upper level the Otago Daily times Gallery level of the Art Gallery. Posters should be placed on the numbered boards early on Tuesday. Boards are numbered according to ordered abstracts in this Conference Program and Abstract book. Velcro dots will be provided on the boards. Posters should be removed at the end of afternoon tea on Thursday. No responsibility is taken for posters not removed at the appointed time.

SMOKING is prohibited in all gallery buildings.

SOCIAL PROGRAM: the Welcome Reception, included in registration, will be held in the Otago Daily Times Gallery, following the opening Oration. The Conference Dinner will be held at 7.00 pm on the 13th November, in the magnificent, heritage Staff Club at the University of Otago. The Conference dinner is not included in the registration fee. Tickets are strictly limited, and if still available may be purchased from the Registration Desk, at a cost of NZD85.00 per head. Please enquire.

TELEPHONES AND MOBILES: Mobile coverage is excellent. There are Pay Phones located at the Visitors Centre across The Octagon. Please ensure that all mobile phones are switched off or are in silent mode during conference sessions.

VENUE AND PARKING:
The conference venue is the Dunedin Public Art Gallery, right in the centre of the City.
Address: The Dunedin Public Art Gallery
30 The Octagon, Dunedin.
Parking is limited, but is available around the Octagon at variable cost.

The Gallery are happy to store luggage on the last morning of the conference, after check out from your hotel.

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Exhibition

agrf

Tuesday 11th November

11 am - 2:00 PM **Exhibition and Posterboard bump-in**

Otago Daily Times Gallery

2:00 PM - 4:00 PM **Applied Biosystems Workshop** *The Auditorium, Dunedin Public Art Gallery*

4:00 PM - 4:30 PM **ABI Afternoon Tea** *ABI Stand, Otago Daily Times Gallery*

4:30 PM - 5:00 PM **Illumina Product Launch** *The Auditorium, Dunedin Public Art Gallery*

5:00 PM - 5:30 PM **Illumina Drinks** *Illumina Stand, Otago Daily Times Gallery*

2:00 PM - 6:00 PM **Registration opens** *Otago Daily Times Gallery*

5:55 PM - 6:00 PM **Welcome and opening remarks: Les McNoe**

The Auditorium, Dunedin Public Art Gallery

6:00 PM - 7:00 PM **Session 1: Opening Oration: John Mattick**

The Auditorium, Dunedin Public Art Gallery

Chair: Sean Grimmond

6:00 PM **1** **The genome is the transcriptome**

Mattick, J

Institute for Molecular Bioscience, University of Queensland, 306 Carmody Road, St Lucia, Brisbane, QLD 4072, Australia

7:00 PM - 9:00 PM **Welcome Reception and Exhibition**

Otago Daily Times Gallery/Conference Room

09:00 PM - 11:00 pm **Scotia Whisky Tasting (limited numbers see Registration Desk)**

Scotia Whisky Bar

Wednesday 12th November

9:00 AM - 10:30 AM Session 2: Plenary I: Rob Martienssen; Plenary II: Heather Cunliffe

Chair: Tony Merriman

The Auditorium, Dunedin Public Art Gallery

9:00 AM **15** **Gene regulation and DNA methylation.**
Slotkin, K*, Tanurdzic, M*, Vaughn, M*, Kloc, A*, Zaratiegui, M*, Irvine, D*, Colot, V#, Doerge, RW^ and Martienssen, R#

** Cold Spring Harbor Laboratory, Cold Spring Harbor NY11724; # Unité de Recherche en Génomique Végétale (URGV), INRA/ CNRS/UEVE, 2 Rue Gaston Crémieux, 91057 Evry Cedex, France; ^ Department of Statistics, Purdue University, West Lafayette IN 47907*

9:45 AM **16** **New molecular targets in breast cancer**
Cunliffe, H

Head, Breast & Ovarian Cancer Research Lab, Translational Genomics Research Institute , 445 N. Fifth Street, Phoenix, Arizona 85004, USA

10:30 AM - 11:00 AM Coffee and Exhibition *Otago Daily Times Gallery/Exhibition area*

11:00 AM - 1:00 PM Session 3: High throughput sequencing *The Auditorium, Dunedin Public Art Gallery*

Chair: Dan Catchpoole

11:00 AM **17** **Sequencing the mammalian transcriptome in toto**
Grimmond, S
Expression Genomics Laboratory, Institute for Molecular Bioscience, University of Queensland, Brisbane, 4072, QLD Australia. S.grimmond@imb.uq.edu.au

11:45 AM **18** **Transcriptome analysis using RNA-seq**
Oshlack, A and Wakefield, MJ
Bioinformatics, Walter and Eliza Hall Institute of Medical Research, 1G Royal Pde, Parkville, VIC 3050, Australia

12:10 PM **19** **Cell cycle transcriptome profiling via massive-scale next-generation sequencing.**
Cloonan, N, Brown, MK, Wani, S, Steptoe, AL, Gongora, M, Gardiner, BBA, Nourbakhsh, E and Grimmond, SM
Expression Genomics Laboratory, Institute of Molecular Bioscience, 306 Carmody Road, St Lucia, 4072, Australia

12:35 PM **20** **Sequencing transcriptomes using the GS FLX**

Stanton, JL

Anatomy and Structural Biology, University of Otago, 270 Great King Street, Dunedin, Otago 9054, New Zealand

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1:00 PM - 2:00 pm **Lunch and PLP Workshop** *Otago Daily Times Gallery and The Auditorium*

Dan Belluoccio – Agilent eArray 5.3:

A live-demonstration on how to design your own microarray

*(for those attending the PLP Workshop, please go directly to the Auditorium - lunch will be served there and also in the Exhibition area. **Food may not be carried through the Galleries**)*

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2:00 PM - 3:30 PM **Session 4: Cancer Genetics I** *The Auditorium, Dunedin Public Art Gallery*

Chair: Aaron Jeffs

2:00 PM **21** **Identification of novel ovarian cancer genes using an integrative genomics approach**

Ramakrishna, M*#, Williams, LH§, Bearfoot, JL*#, Sridhar, A*, Gorringe, KL*# and Campbell, IG*#

** VBCRC Cancer Genetics Laboratory, Peter MacCallum Cancer Centre, St Andrew's Pl, East Melbourne, Melbourne, Victoria 3002, Australia; # Department of Pathology, University of Melbourne, Parkville, Victoria, Australia; § Genetic Hearing Research, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Victoria, Australia*

2:20 PM **22** **Use of DNA damaging agents and RNA pooling to assess expression profiles associated with BRCA1, BRCA2, and BRCAX mutation status in breast cancer patients**

Walker, LC*, Thompson, B*, kConFab Investigators^, Waddell, N* and Spurdle, AB*

**Queensland Institute of Medical Research, Australia; ^Peter MacCallum Cancer Centre, Melbourne, Australia*

2:40 PM **23** **Identification of a proliferation signature and an associated PI3K-Akt-mTOR pathway driving cell proliferation, but not survival, in a leukaemia-inducing activated receptor mutant, and its role in Acute Myeloid Leukaemia.**

Kok, CH*^, Brown, AL*^#, Wilkinson, CW¶, Perugini, M*, Salerno, DG* and D'Andrea, RJ*^#

**Joint Haematology and Oncology Program, The Queen Elizabeth Hospital and Division of Haematology, Institute of Medical and Veterinary Sciences and Hanson Institute, Adelaide, South Australia; ^School of Paediatrics and Reproductive Health, Department of Paediatrics, University of Adelaide; #Women's and Children's Health Research Institute; ¶School of Mathematical Sciences, University of Adelaide*

3:00 PM **24** **Interrogation of breast cancer cell line databases confirm EMT status and reveals a link between EMT and breast cancer stem cells.**

Blick, T*, Widodo, E#^, Hugo, H*#, Lenburg, ME¶, Neve, RM§, Waltham, M*# and Thompson, EW*#

**St. Vincent's Institute and #University of Melbourne Dept. of Surgery, St. Vincent's Hospital, Fitzroy, Australia; ^ Faculty of Medicine, Brawijaya University, East Java, Indonesia; ¶Department of Genetics and Genomics, Boston University School of Medicine, Boston, MA, USA; §Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA.*

3:30 PM - 4:00 PM Afternoon Tea and Exhibition *Otago Daily Times Gallery/Exhibition area*

4:00 PM - 5:30 PM Session 5: Developmental Biology *The Auditorium, Dunedin Public Art Gallery*

Chair: Rob Day

4:00 PM **25** **Epigenetics in the placenta: A genome-wide methylation analysis of first trimester trophoblasts**
Daly, EC and Morison, IM
Cancer Genetics Laboratory, Department of Biochemistry, University of Otago, P.O. Box 56, Dunedin, New Zealand

4:25 PM **26** **Whole genome expression analysis from micro-dissected mouse cartilage tissues**
Belluoccio, D
Pacific Laboratory products, 15-33 Alfred street, level 1, Blackburn, VIC 3130, Australia

4:50 PM **27** **Probing the architecture of developmental plasticity**
Dearden, PK
Laboratory for Evolution and Development, National Research Centre for Growth and Development, Biochemistry Department, University of Otago

5:30 PM - 7:00 PM Dinners around The Octagon (own cost) *The Octagon, Central Dunedin*

7:00 PM - 9:00 PM Posters and Wine, and Exhibition

Exhibition area, Otago Daily Times Gallery and Conference Room

2 **Search for the black bile: Biomarkers of antidepressant exposure.**
Harley, JA, Doudney, K, Joyce, PR and Kennedy, MA
Departments of Psychological Medicine and Pathology, University of Otago Christchurch, New Zealand.

3 **The Smad2 gene, the Idd21.1 locus and autoimmune diabetes in the non-obese diabetic mouse**
Faiz F, McNoe L, Phipps-Green M, Hollis-Moffatt J, Hook S and Merriman T
Department of Biochemistry, University of Otago, 710, Cumberland Street, Dunedin, Otago 9001, New Zealand

4 **Molecular correlates of life history tradeoffs.**
Morgan, SM, Dearden, PK and Raubeheimer, D
Biochemistry, University of Otago, 710 Cumberland Street, Dunedin, Otago 9054, New Zealand

5 **The honeybee polyphenism**
McCartney, RC and Dearden, PK
Biochemistry, Otago University, 710 Cumberland Street, Dunedin, Otago 9016, New Zealand

6 **Gene expression signatures of invasion and survival in melanoma**
Jeffs, A, Glover, M, He, S, Baguley, B* and Eccles, M
*Department of Pathology, Dunedin School of Medicine, University of Otago, New Zealand; *Auckland Cancer Society Research Centre, University of Auckland, New Zealand.*

7 The use of genetic tools to investigate the variability in meat tenderness

Hyndman, D*, Fisher, P^, Cullen, NG#, Morris, CA#, Hickey, SM#, Mclaren, R* and Wilson, T*

** AgResearch Molecular Biology Unit, Department of Biochemistry, University of Otago, Dunedin, New Zealand; # AgResearch Ruakura, Hamilton, New Zealand; and ^ AgResearch Invermay, New Zealand*

8 An integrated transcriptome analysis approach to characterise adult neural stem cells and study complex disease

Matigian, NA, Chalk, AM, Beckhouse, A, Cecil, R, Vitale, A, Mellick, G, Mackay-Sim, A and Wells, C

National Center for Adult Stem Cell Research, Eskitis Institute for Cell and Molecular Therapies, Griffith University, Brisbane, QLD 4111, Australia.

9 Is DNA methylation altered by in vitro fertilisation?

Oliver, V*, Cutfield, W, Miles, H**, Hofman, P** and Morison, I***

Department of Biochemistry, University of Otago, 710 Cumberland Street, Dunedin North, Dunedin, Otago 9054, New Zealand;Liggins Institute and the National Research Centre for Growth and Development, University of Auckland, Private Bag 92019, Auckland, New Zealand*

10 Investigating the mode of action of the Karenia brevisulcata toxin by chemical genomic profiling in yeast.

Heathcott, RW*#, Maass, DR*#, Truman, P* and Atkinson, PH#

**Environmental Science and Research, Porirua, New Zealand; *Chemical Genetics Laboratory, School of Biological Sciences, Victoria University of Wellington.*

11 Analysis of differential splicing from exon array data

Robinson, MD, Purdom, E and Speed, TP

Walter and Eliza Hall Institute of Medical Research, 1G Royal Pde, Parkville, VIC 3050, Australia

12 Antler stem cells and developmental pathways.

Harper, AN and Li, C and Wang, W and Haines, SR

Ag Research Invermay, Puddle Alley, Mosgiel, Otago 9053, New Zealand

13 Association analysis between the b-3-Adrenergic Receptor (ADRB3) and the Starvation/Exposure Death risk trait in Ovis aries

Clarke, SM, Everett-Hincks, JM and Auvary, B

Animal Genomics, AgResearch Limited, Invermay, Puddle Alley, Private Bag 50034 Mosgiel, New Zealand

14 Performance and application of the GoldenGate assay for the analysis of SNPs in formalin-fixed paraffin-embedded tissue samples

Wayte, N*^ and Chenevix-Trench, G*

** The Queensland Institute of Medical Research, Brisbane, Australia; ^ School of Molecular and Microbial Bioscience, The University of Queensland, Brisbane, Australia*

53 Using reconstructed gene networks to assist with prognosis prediction in breast cancer

Allen, T and Black, M

Department of Biochemistry, University of Otago, 710 Cumberland Street, Dunedin

Thursday 13th November

9:00 AM - 10:30 AM Session 6: Plenary III: Peter Campbell; Plenary IV: Cris Print

The Auditorium, Dunedin Public Art Gallery

Chair: Erik (Rik) Thompson

9:00 AM 28 **Identification of somatically acquired rearrangements in cancer using genome-wide massively parallel paired-end sequencing.**

Campbell, P

Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton,Cambridgeshire CB10 1SA, United Kingdom

9:45 AM 29 **Mixing and matching data from different sources to understand disease**

Print, C

Molecular Medicine & Pathology, School of Medical Sciences, The University of Auckland, Private Bag 92019, Auckland, Auckland 1142, New Zealand

10:30 AM - 11:00 AM Coffee and Exhibition *Otago Daily Times Gallery/Exhibition area*

11:00 AM - 12:30 PM Session 7: Plant and Animal Genetics *The Auditorium, Dunedin Public Art Gallery*

Chair: Peter Dearden

11:00 AM 30 **Strategies for high throughput identification of imprinted genes in plants**

Day, RC

Biochemistry Department, University Of Otago, Cumberland Street, Dunedin, Otago 9054, New Zealand

11:20 AM 31 **Using a model cyanobacterium to investigate the transcriptional response to changing environments**

Summerfield, T*# and Sherman, L#

**Biochemistry, University of Otago, 710 Cumberland Street, Dunedin, Otago 9054, New Zealand; #Department of Biological Sciences, Purdue University, West Lafayette, IN, 47907, USA*

11:40 AM **32** **Using a virtual muscle model to interpret muscle development and growth by linking gene expression with protein spatial location**
Waardenberg, AJ*#, Reverter, A*^, Hudson, N*, Wells, CA# and Dalrymple, BP*^
**Food Futures Flagship, CSIRO, St. Lucia, QLD, Australia; #Eskitis Institute for Cell and Molecular Therapies, Griffith University, Nathan, QLD, Australia; ^Livestock Industries, CSIRO, St. Lucia, QLD, Australia*

12:00 PM **33** **Creation of an ovine genome skim assembly and a 50K+ Illumina SNP iSelect™ BeadChip**
McEwan, JC*, Payne, GM*; on behalf of International Sheep Genomics Consortium#
** AgResearch, Invermay Agricultural Centre PB 50034, Mosgiel, New Zealand; # http://www.sheephapmap.org*

12:30 PM - 1:30 PM **Lunch and AGM** *Otago Daily Times Gallery/Auditorium*

1:30 PM - 3:30 PM **Session 8: Bioinformatics** *The Auditorium, Dunedin Public Art Gallery*

Chair: Gordon Smyth

1:30 PM **34** **Identification of microRNAs with regulatory potential using matched microRNA-mRNA timecourse data**
Jayaswal, V*, Yang, YH*, Lutherborrow, M# and Ma, D#
** School of Mathematics and Statistics, The University of Sydney, NSW, Australia; # Blood Stem Cell and Cancer Research Unit, St Vincent's Hospital Applied Biomedical Research, Darlinghurst, NSW, Australia*

1:50 PM **35** **Transcriptome profiling of human islets to determine predictors of clinical islet transplant outcomes**
Cowley, MJ *#, Weinberg, A ^#, O'Connell, PJ #¶, Kaplan, W *# and Grey, ST ^#
**Peter Wills Bioinformatics Centre, and ^Gene Therapy and Autoimmunity Group Garvan Institute of Medical Research, 384 Victoria St Darlinghurst, Australia. #The Australian Islet Transplant Consortium. ¶The Centre for Transplant and Renal Research, Westmead Hospital, Westmead, Australia.*

2:10 PM **36** **A framework for assessing microarray normalization methods with respect to precision, bias and signal to noise ratio**
Shi, W and Smyth, GK
Bioinformatics Division, The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, Melbourne, Victoria 3050, Australia

2:30 PM **37** **ROAST, a gene set testing method for laboratory generated microarray data**
Wu, Di and Smyth, Gordon
Bioinformatics, WEHI, 1G Royal Parade, Parkville , Melbourne, VIC 3050 , Australia

2:50 PM **38** **Integrating gene expression studies via statistical synthesis**
Campain, A and Yang, J
Mathematics and Statistics, University of Sydney

3:10 PM **39** **Issues in normalisation of one colour CHiP-chip data for chromatin modification**
French, HJ, Hardy, K, Burden, C, Peng, K, Shannon, MF and Williams, RBH
The John Curtin School of Medical Research, 131 Garran Road, Acton, Canberra, ACT 0200, Australia

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3:30 PM - 4:30 PM **Posters, Afternoon Tea and Exhibition** *Otago Daily Times Gallery/Exhibition area*

4:30 PM - 6:10 PM **Session 9: Human Disease** *The Auditorium, Dunedin Public Art Gallery*

Chair: Andrew Holloway

4:30 PM **40** **Biology-driven clinical management of paediatric acute lymphoblastic leukaemia through integrative data mining and visualization of genome-wide gene expression and SNP profiles.**

Catchpoole, D*#, Guo, D*, AlOqaily, A#, Kennedy, P# and Simoff, S#^

** The Tumour Bank, Oncology Research Unit, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, Sydney, NSW 2145, Australia; # Faculty of Engineering and Information Technology, The University of Technology Sydney, NSW, Australia; ^ The School of Computing and Mathematics, University of Western Sydney, NSW, Australia*

4:50 PM **41** **MicroRNA and mRNA expression profiling in a mouse model of myocardial infarction with enhanced or depressed PI3K activity**

Lin, RCY, Williams, RBH, Du, XJ, Gao, XM, Kiriazis, H, Cowley, MJ, Speirs, HJ and Dawes, IW; McMullen JR

Ramaciotti Centre for Gene Function Analysis, University of New South Wales (RCYL, HJS, IWD); Molecular Systems Biology Group, John Curtin School of Medical Research, Australian National University (RBHW); Baker IDI Heart & Diabetes Institute, Melbourne, Victoria 8008 (XJD, XMG, HK, JRM) and Peter Wills Bioinformatics Centre, Garvan Institute of Medical Research, Australia (MJC)

5:10 PM **42** **Gene expression changes during eosinophil differentiation**

de Graaf, CA, Robinson, A, Baldwin, T, Smyth, G and Hilton, D

Molecular Medicine, 1G Royal Parade, Parkville, Victoria 3050, Australia

5:30 PM **44** **Identification of genomic rearrangements in the neuronal migration disorder periventricular heterotopia**

van Kogelenberg, M*, van Bokhoven, H and Robertson, SP***

** Department of Paediatrics and Child Health, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; ** Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*

5:50 PM **45** **GenePattern@Otago: local tools for the analysis of microarray data**

Black, M

Department of Biochemistry, University of OTAGO, Dunedin, 710 Cumberland Street, Dunedin, Otago New Zealand

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6:30 PM **Coaches to Conference Dinner** *Meet at the front of the Gallery, on the Octagon*

7:00 PM - 11:00 PM **Conference Dinner** *Historic University Staff Club, Otago University*

Friday 14th November

8:30 AM - 10:00 AM Session 10: Plenary V: Rebecca Doerge; Plenary VI: Lance Miller

The Auditorium, Dunedin Public Art Gallery

Chair: Mik Black

8:30 AM 46 Whole Genome Expression Quantitative Trait Loci (eQTL) Analysis of Arabidopsis

Doerge, R

Department of Statistics, Department of Agronomy, Purdue University, West Lafayette, IN 47907 USA

9:15 AM 47 Tell-Tale Genes: Harnessing Genomics for Breast Cancer Prognosis and Oncogene Discovery

Miller, L

Department of Cancer Biology, Wake Forest University School of Medicine, Medical Center Blvd., 4th Floor, Hanes Building, Winston-Salem, NC 27157, USA

10:00 AM - 10:30 AM Coffee *Otago Daily Times Gallery/Exhibition area*

10:30 AM - 11:10 AM Session 11: Special Plenary Lecture: David Bentley

The Auditorium, Dunedin Public Art Gallery

***Chair:** Tony Reeve*

11:00 AM 48 Enabling human genomics with new sequencing technology

Bentley, D and collaborators

Illumina Inc., Chesterford Research Park, Cambridge, UK, Industrial Blvd. Hayward, CA & 9885 Towne Centre Drive, San Diego, CA and collaborators at the Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK

11:10 AM - 12:30 PM Session 12: Cancer Genetics II

The Auditorium, Dunedin Public Art Gallery

Chair: Tony Reeve

11:10 AM 49 Architectural mapping of a cancer associated neochromosome

Garsed, DW*, Holloway, AJ*, Grimmond, SM~ and Thomas, DM*

** Sarcoma Genomics and Genetics, Peter MacCallum Cancer Centre, 12 St Andrew's Place, East Melbourne, Victoria 3002, Australia; ~ Institute for Molecular Bioscience, The University of Queensland, St Lucia, Brisbane, Australia*

11:30 AM 50 Changes in microRNA expression and cancer

Tsykin, A*#, Goodall, GJ*, Gregory, PA*, Knew-Goodall, Y*, Michael, MZ^, Van der Hoek, M*, Hussey, DJ^ and Wijnhoven, BPL^

** Hanson Institute, Frome Road, Adelaide, South Australia; # School of Mathematics, University of Adelaide, South Australia; ^ Flinders Medical Centre, Bedford Park, South Australia*

11:50 AM 51 Eliminating normal CNVs from array CGH cancer genome profiles

Jewell, UR, Moon, SY and Morris, CM

Pathology, University of Otago at Christchurch, 3, Riccarton Avenue, Christchurch, Canterbury 8001, New Zealand

12:10 PM 52 Incorporating Biological Information into the Tumor Classification Process

Debbie Leader

University of Auckland, 23 Omana Ave, RD1, Helensville, Auckland 0874, New Zealand

12:30 PM - 12:40 PM Conference Close and Awards

The Auditorium, Dunedin Public Art Gallery

END OF AMATA 2008 CONFERENCE PROGRAM

Saturday 15th November:

Differential expression analysis of microarray data:
Workshop on Bioconductorand limma software

PRESENTERS:	**Gordon Smyth, WEHI Bioinformatics**
	Mik Black, University of Otago
	Mark Robinson, WEHI Bioinformatics
VENUE:	**The University of Otago**
PROGRAM:	**9:00 AM - 3:00 PM**
9:00 AM - 10:30 AM	**Workshop Session 1: Introduction to R, two-colour arrays, moderated t-tests**
10:30 AM - 11:00 AM	**Morning Tea**
11:00 AM - 12:30 PM	**Workshop Session 2: Affymetrix arrays, linear models and gene set tests**
12:30 PM - 1:30 PM	**Light Lunch**
1:30 PM - 3:00 PM	**Workshop Session 3: Time course experiments, array weights and pointers to other Bioconductor tools**

Debrief in one of Dunedin's famous University Pubs

1 THE GENOME IS THE TRANSCRIPTOME

Mattick, J

Institute for Molecular Bioscience, University of Queensland, 306 Carmody Road, St Lucia, Brisbane, QLD 4072, Australia

It appears that the genetic programming of mammals and other complex organisms has been misunderstood for the past 50 years, because of the assumption - largely true in prokaryotes, but not in complex eukaryotes - that most genetic information is transacted by proteins. The numbers of protein-coding genes do not change appreciably across the metazoa, whereas the relative proportion of non-protein-coding sequences increases markedly with increased developmental complexity. Moreover, it is now evident that the majority of the mammalian genome is transcribed in a developmentally regulated manner, and that most complex genetic phenomena in eukaryotes are RNA-directed. Evidence will be presented that (i) regulatory information scales quadratically with functional complexity; (ii) current estimates of the amount of the human genome under evolutionary selection are simplistic and probably based on a false premise; (iii) there are thousands of non-protein-coding transcripts in mammals that are dynamically expressed during differentiation and development, many of which show precise expression patterns and subcellular localization in the brain; (iv) many 3'UTRs are expressed separately from their associated protein-coding sequences to transmit genetic information in trans; and (v) there are large numbers of small RNAs, including new classes, expressed from the human and mouse genomes, that may be discerned in deep sequencing datasets. There is also genome-wide evidence of editing of noncoding RNA sequences, especially in the brain and especially in humans (in Alu elements), which may form an important part of the molecular basis of learning and memory. Thus the majority of the human genome appears not to be junk but rather is devoted to a highly sophisticated RNA regulatory system that directs developmental trajectories and mediates gene-environment interactions via the control of chromatin architecture and epigenetic memory, transcription, splicing, RNA modification and editing, mRNA translation and RNA stability.

2 SEARCH FOR THE BLACK BILE: BIOMARKERS OF ANTIDEPRESSANT EXPOSURE.

Harley, JA, Doudney, K, Joyce, PR and Kennedy, MA

Departments of Psychological Medicine and Pathology, University of Otago Christchurch, New Zealand.

Melancholia, the excess production of black bile, was described by Hippocrates and others to explain the condition now known as major depression. Therapies for depression are primarily pharmacological and are efficacious. However challenges remain: the lag to therapeutic response is long and many patients do not respond to the first antidepressant they are prescribed. An ability to inform patients of their prognosis following initiation of therapy would be empowering for patients, their families and physicians alike.

The actions of antidepressants are closely linked to the promotion of neurogenesis and the modulation of synaptic plasticity, events that require modification of gene expression in the brain. Changes induced in the brain by these drugs may be reflected by expression differences in a more readily sampled tissue, the blood.

With the development of advanced molecular biology techniques including whole genome expression arrays we have the capability of screening for new markers such as changes in transcription of RNA in Peripheral Blood Mononuclear Cells (PBMCs). PBMCs are mixed population of lymphocytes and monocytes which are exposed to antidepressants in plasma. They have previously been shown to express the serotonin transporter and expression changes have been observed in studies of post-traumatic stress disorder.

We aim to identify new biomarkers of antidepressant response by performing whole genome expression arrays on PBMCs collected from rats treated with citalopram or fluoxetine. Candidates from the arrays will be confirmed by quantitative PCR. The ultimate aim is to transfer assays of PBMC mRNA to cohorts of human patients at the initiation of antidepressant therapy to determine if these putative biomarkers have clinical utility.

3 THE SMAD2 GENE, THE IDD21.1 LOCUS AND AUTOIMMUNE DIABETES IN THE NON-OBESE DIABETIC MOUSE

Faiz F, McNoe L, Phipps-Green M, Hollis-Moffatt J, Hook S and Merriman T

Department of Biochemistry, University of Otago, 710, Cumberland Street, Dunedin, Otago 9001, New Zealand

Type 1 diabetes is an autoimmune disease caused by impact of the environment on an individual who has inherited a complement of genetic susceptibility variants. Previously we have mapped an autoimmune diabetes locus, Idd21.1, using the non-obese diabetic (NOD) mouse model of human type 1 diabetes, to an ~15 Mb region of distal chromosome 18. This was done by congenic mapping, whereby the 15 Mb segment of DNA from a disease-resistant strain (ABH) was introgressed onto the NOD genome. The resultant congenic strain (NOD.ABH.Idd21.1) had reduced diabetes incidence. The Idd21.1 locus is of interest because it is orthologous to IDDM6, a region of human chromosome 18q12-q21 linked to type 1 diabetes. We had previously demonstrated that Idd21.1 influences autoimmune diabetes through the adaptive immune system and we had identified a phenotypic difference in activated dendritic cells between NOD and NOD.ABH.Idd21.1. The aim of the work presented here was two-fold: one, to use congenic mapping to fine-map Idd21.1 to a smaller genomic region; and two, to use microarray gene expression analysis to identify any differences in gene expression between NOD and NOD.ABH.Idd21.1 due to Idd21.1. By constructing a series of novel Idd21.1 sub-congenic strains and measuring diabetes incidence in the novel strains we mapped Idd21.1 to a <6 Mb region (76.3-82.1 Mb). Microarray experiments conducted on the NOD and NOD.ABHIdd21.1 strains showed that 103 genes were differentially expressed in activated dendritic cells. Smad2 located in the Idd21.1 region had 2-fold increased expression in NOD. These results implicate the Smad2 (Madh2) gene as containing the genetic variant underlying Idd21.1 in murine autoimmune diabetes. Smad2 competes with Smad3 for binding to Smad4, thus inhibiting expression of Smad3-dependent genes involved in apoptosis.

4 MOLECULAR CORRELATES OF LIFE HISTORY TRADEOFFS.

Morgan, SM, Dearden, PK and Raubeheimer, D

Biochemistry, University of Otago, 710 Cumberland Street, Dunedin, Otago 9054, New Zealand

The life history trade off between longevity and reproduction is seen in a variety of animals. Organisms able to produce a large amount of offspring in a short amount of time invariably have a shorter lifespan than their reproductively frugal counterparts. This has been taken a step further with the model organism Drosophila melanogaster in that regulation of lifespan and reproduction rates have been linked with various ratios of protein to carbohydrate diet ingested by the flies throughout their lifetime.

Dietary Restriction and its effects on lifespan have been studied for many years, with consistent results seen between vastly different organisms. Restriction of caloric intake is known to extend lifespan in these different organisms. Initially called Caloric Restriction, it has been shown in Drosophila that isocaloric diets of yeast (as a protein source) and sugar, in varying ratios, results in organisms portraying the typical trade-off between lifespan and reproduction implying that it is macronutrient status rather than caloric restriction that is extending lifespan. Isocaloric is the term used to describe diets of differing component ratios, while maintaining the same calorie value. When given the option, Drosophila are able to self regulate diet intake and maximise lifetime reproduction.

The aim of the current study is to determine the patterns of gene expression associated with longevity and reproduction in fruit fly. The Drosophila are fed varying ratios of a protein/carbohydrate diet, whole fly RNA will be extracted and gene expression will be assayed via Affymetrix microarrays, and differentially expressed genes will be verified with qRT-PCR. Once candidate genes have been identified, mutation studies will be used to further validate the results and identify pathways that control the trade-offs between reproduction and longevity.

5 THE HONEYBEE POLYPHENISM

McCartney, RC and Dearden, PK

Biochemistry, Otago University, 710 Cumberland Street, Dunedin, Otago 9016, New Zealand

The honeybee (Apis mellifera) is a commercially valuable [1] and biologically interesting organism. The sequencing of the honeybee genome in 2006 [2] provides an opportunity to study the phenomenon of polyphenisms. Polyphenisms occur when one genome gives rise to two or more phenotypes in response to an environmental stimulus [3]. In Apis mellifera a change in diet during early development creates two very different female castes. The queen bee is larger, differs in colour and behaviour, has a greatly increased lifespan and is reproductively capable compared to sterile workers. These two castes have identical genomes indicating these differences arise through gene regulation.

There have been several different approaches aimed at investigating how the diet fed to larvae during development leads to the production of two diverse adult forms. Early studies of polyphenisms using in vitro translation established that queen and workers have different mRNA profiles [4]. Since then RNA differential display [5], subtractive hybridisation[6], differential-display reverse transcription [6] have been used to try and isolate the genes and pathways involved in the developmental processes that give rise to queen or worker bees. These studies have been useful but are limited by the number of genes that can be investigated.

This study aims to identify differentially regulated genes in queen and worker bees using a honeybee microarray which will allow the simultaneous analysis of expression levels of all known honeybee genes. The array is made up of 60-69mer oligos and includes all predicted genes identified by the sequencing consortium, expressed sequence tags, bee pathogen genes and miRNA genes. Queen and worker expression profiles will be compared at various points during larval development. The arrays will provide candidate genes which will then be validated using RT-PCR. RNAi will then be used to test the role of these genes in queen development.

1. Gallai, N., et al.,, Economic valuation of the vulnerability of world agriculture confronted with pollinator decline. Ecological Economics, 2008. Article in Press.

2. Insights into social insects from the genome of the honeybee Apis mellifera. Nature, 2006. 443(7114): p. 931-49.

3. Evans, J.D. and D.E. Wheeler, Gene expression and the evolution of insect polyphenisms. Bioessays, 2001. 23(1): p. 62-8.

4. Severson, D.W., et al., Caste-specific transcription in the female honeybee. Insect Biochemistry, 1989. 19(2): p. 215-220.

5. Corona, M., E. Estrada, and M. Zurita, Differential expression of mitochondrial genes between queens and workers during caste determination in the honeybee Apis mellifera. J Exp Biol, 1999. 202(Pt 8): p. 929-38.

6. Hepperle, C. and K. Hartfelder, Differentially expressed regulatory genes in honey bee caste development. Naturwissenschaften, 2001. 88(3): p. 113-6.

6 GENE EXPRESSION SIGNATURES OF INVASION AND SURVIVAL IN MELANOMA

Jeffs, A, Glover, M, He, S, Baguley, B* and Eccles, M

*Department of Pathology, Dunedin School of Medicine, University of Otago, New Zealand; *Auckland Cancer Society Research Centre, University of Auckland, New Zealand.*

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. The mechanisms underlying melanoma progression and resistance to therapeutic agents are not well understood. 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 metastatic melanoma cell lines. Microarray analysis of 27 cell lines revealed a putative invasive/proliferative gene signature featuring differential expression of the microphthalmia-associated transcription factor (MITF) and related transcriptional networks. We suspected that decreased expression of MITF-mediated melanocyte lineage specification genes might reflect a de-differentiated cell type with increased invasive and metastatic potential. Migration assays confirmed that the gene signature correlated with the invasiveness of the cell lines, and external validation using publicly available data indicated that tumours with the invasive gene signature may be more aggressive. Decreased MITF expression defined a melanoma subtype within a group of patients with significantly shorter survival time, suggesting this signature may be of prognostic benefit to patients with metastatic disease.

7 THE USE OF GENETIC TOOLS TO INVESTIGATE THE VARIABILITY IN MEAT TENDERNESS

Hyndman, D*, Fisher, P^, Cullen, NG#, Morris, CA#, Hickey, SM#, Mclaren, R* and Wilson, T*

** AgResearch Molecular Biology Unit, Department of Biochemistry, University of Otago, Dunedin, New Zealand; # AgResearch Ruakura, Hamilton, New Zealand; and ^ AgResearch Invermay, New Zealand*

Research on meat tenderness has covered every aspect of the production pathway from paddock to plate. These have included nutrition, pre-slaughter treatment and carcass handling, but even when consistent and quality protocols are followed, variability in tenderness continues to be a negative factor for the beef industry.

It has been shown that genetic variation plays an important roll in a tough or tender outcome. The discovery of QTL in the location of candidate genes involved in proteolysis gave weight to the theory that variability in the protease gene Calpain1 was associated with tenderness. To investigate the presence of other genetic factors that are associated with Calpain1, we used a microarray experiment where we compared muscle samples from beef cattle carrying the CC allele (tender) with samples containing the GG (tough) allele. After pathway analysis using Ingenuity and literature assessment, a selection of candidate genes were then screened for the presence of SNPs for testing against a panel of mixed cattle breeds phenotyped for tenderness. The data was analysed for association both with tenderness and with the Calpain1 SNP itself. Our objective was to find a set of markers which could account for a greater percentage of variability in meat tenderness. This approach may complement Genome Wide Association studies for marker discovery, and lead to increased understanding of the biochemical processes in meat aging.

8 AN INTEGRATED TRANSCRIPTOME ANALYSIS APPROACH TO CHARACTERISE ADULT NEURAL STEM CELLS AND STUDY COMPLEX DISEASE

Matigian, NA, Chalk, AM, Beckhouse, A, Cecil, R, Vitale, A, Mellick, G, Mackay-Sim, A and Wells, C

National Center for Adult Stem Cell Research, Eskitis Institute for Cell and Molecular Therapies, Griffith University, Brisbane, QLD 4111, Australia.

Research into the molecular mechanisms of the disease processes for neurological disorders is hindered by lack of access to the affected brain tissues or the lack of contextual relevance of commonly used cells of non-neural origin such as fibroblasts and blood lymphocytes. Human Olfactory Stem Cells (hOSCs) are an easily accessible source, with neural origin, which can be obtained from a wide variety of donors, including those with neurological disorders. We present transcriptome data (Illumina Beadarray, Agilent miRNA, Affymetrix Exon arrays, Capped Analysis of Gene Expression (CAGE) and whole genome genotyping) from patient-derived hOSCs. We show that this integrated data can characterise these donor-derived cell lines compared to other published datasets of neuronal cells, stem cell and neural tissues and that we can retain the unique patient characteristics through the culturing process. Additionally, we can elucidate differences between disease and non-diseased states, for two distinct neurological conditions, Parkinson Disease and Schizophrenia, indicating that these cells provide a more relevant alternative to tissues of non-neuronal origin, without the disadvantages of the post-mortem brain

9 IS DNA METHYLATION ALTERED BY *IN VITRO* FERTILISATION?

Oliver, V*, Cutfield, W, Miles, H**, Hofman, P** and Morison, I***

Department of Biochemistry, University of Otago, 710 Cumberland Street, Dunedin North, Dunedin, Otago 9054, New Zealand;Liggins Institute and the National Research Centre for Growth and Development, University of Auckland, Private Bag 92019, Auckland, New Zealand*

In vitro fertilisation (IVF) potentially provides a profoundly abnormal environment for an embryo. Studies with mice, sheep and cattle have indicated that the culture environment of the embryo can affect the imprinting of genes and the phenotype of the animal. Approximately 2% of human births worldwide are conceived using IVF. Recent studies have suggested that IVF causes a small but increased risk of epigenetic imprinting aberrations such as Angelman syndrome and Beckwith-Wiedemann syndrome. Given that mosaicism for the imprinting defect has been observed in Angelman syndrome and Beckwith-Wiedemann syndrome, we hypothesised that low-level, mosaic imprinting defects may be present in phenotypically normal individuals conceived using IVF.

DNA samples from peripheral blood were obtained from 69 IVF-conceived pre-pubertal children and 71 matched controls. DNA methylation of CpG sites within the H19, IGF2, SNRPN and KvDMR1 loci was accurately quantified using methylation-sensitive restriction digest followed by real-time quantitative PCR (MSQ-PCR). Global DNA methylation was also examined by using MSQ-PCR on the Satellite 2 repeat region. No differences in the percentage of methylation between the IVF-conceived and control children were observed at the examined CpG sites.

Physiological measurements of these IVF children revealed that they were taller, have higher levels of the growth hormone IGF-II and also have higher levels of high-density lipoprotein than their non-IVF counterparts. To discover differentially methylated genes between the IVF and control cohorts immunoprecipitation with an anti-methylcytosine antibody (meDIP) was used to pull down methylated DNA. This was compared to total DNA using the Aviva Systems Biology directed selection and ligation (DSL) technology on 20K promoter arrays.

Currently several differentially methylated genes have been identified using this approach and are undergoing validation using Sequenom.

10 INVESTIGATING THE MODE OF ACTION OF THE KARENIA BREVISULCATA TOXIN BY CHEMICAL GENOMIC PROFILING IN YEAST.

Heathcott, RW*#, Maass, DR*#, Truman, P* and Atkinson, PH#

**Environmental Science and Research, Porirua, New Zealand; *Chemical Genetics Laboratory, School of Biological Sciences, Victoria University of Wellington.*

Toxic blooms of the algal species Karenia brevisulcata kill marine life and can cause respiratory symptoms and skin irritation in humans. Chemical genomics is the study of the interaction of small molecules and gene products on a genome-wide scale. Here we describe a chemical genetic approach in yeast to study the biological activity and mode of action of the marine algal toxin KBT.

The Yeast Genome Deletion Set (YGDS) was constructed by an international consortium as a collection of 5000 mutants, each with one open reading frame of the Saccharomyces cerevisiae genome deleted and replaced with an antibiotic resistance marker. Each deletion is flanked by unique 20mer barcode tags allowing identification of the mutant. The YGDS is available as haploids, homozygous and heterozygous diploids. Growth of the deletion pool in the presence of the toxin and in parallel with an untreated control, followed by PCR of the pool's genomic DNA using universal primers and microarray hybridisation, allows identification of the barcodes present and thus strains sensitive or resistant to the toxin. The pooled heterozygous deletion set can provide direct information on drug targets.

Preliminary results of this research show genes involved in sterol modification, endosomal sorting and protein catabolism via the multivesicular body pathway are important in the cellular response to KBT.

11 ANALYSIS OF DIFFERENTIAL SPLICING FROM EXON ARRAY DATA

Robinson, MD, Purdom, E and Speed, TP

Walter and Eliza Hall Institute of Medical Research, 1G Royal Pde, Parkville, VIC 3050, Australia

Expressed sequence tag data and bioinformatic analyses suggest that alternative splicing is a widespread phenomenon. Many DNA microarray providers now offer exon and tiling microarrays, giving researchers the opportunity to study alternative splicing on genome wide scale. This talk presents a method, finding isoforms using robust multichip analysis (FIRMA), for detecting differential alternative splicing in exon array data. We have evaluated the method using simulated data, and have applied it to a public tissue panel dataset from Affymetrix. Several examples illustrate the procedure.

12 ANTLER STEM CELLS AND DEVELOPMENTAL PATHWAYS.

Harper, AN, Li, C, Wang, W and Haines, SR

Ag Research Invermay, Puddle Alley, Mosgiel, Otago 9053, New Zealand

The antlers of red deer (Cervus elaphus) are remarkable in biology as the only known example of organ regeneration in mammals. This process occurs on an annual basis. Antlers are a complex organ composed of developing cartilage and bone infiltrated with blood vessel and nerve cell networks. There is now significant evidence to demonstrate that this is a stem cell driven process [1] [2] [3]. Antler growth originates from two pools of adult stem cells contained in tissues termed the antlerogenic periosteum (AP) and the pedicle periosteum (PP). The AP covers a crest in the skull located just above the eye socket and appears to be a piece of postnatally retained embryonic tissue [4]. Removal of this tissue before puberty prevents pedicle and thus antler growth [5]. Transplantation of the AP induces ectopic pedicle and antler formation [7]. During puberty the pedicle develops from the AP and contains the PP. The antlers subsequently cast and regenerate from the PP of the pedicle each year [6]. Cells of the AP and the PP express embryonic stem cell markers [1] and are highly plastic. They can be stimulated to differentiate into muscle, nerve, bone or cartilage type cells in vitro (unpublished data).

Our studies of the proteome of these adult stem cells and the interactions of strongly over-expressed proteins indicate that several key pathways associated with development are enhanced namely; PI3K/Akt, Myc, TP53, 14-3-3, jun/fos, Wnt and SMAD. Understanding how antler stem cells utilise these developmental pathways would not only increase knowledge of antler growth processes but also of stem cell biology leading to novel insights into human development with potential applications in regenerative medicine.

1. Li C, S.J. Recent Progress in antler regeneration and stem cell research. in The 6th International Deer Biology Congress. 2006. Prague, Czech Republic: Research Institue of Animal Production, Prague, Czech Republic.
2. Kierdorf, U., H. Kierdorf, and T. Szuwart, Deer antler regeneration: cells, concepts, and controversies. J Morphol, 2007. 268(8): p. 726-38.
3. Rolf, H.J., et al., Localization and characterization of STRO-1 cells in the deer pedicle and regenerating antler. PLoS ONE, 2008. 3(4): p. e2064.
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13 ASSOCIATION ANALYSIS BETWEEN THE B-3-ADRENERGIC RECEPTOR (ADRB3) AND THE STARVATION/EXPOSURE DEATH RISK TRAIT IN OVIS ARIES

Clarke, SM, Everett-Hincks, JM and Auvary, B

Animal Genomics, AgResearch Limited, Invermay, Puddle Alley, Private Bag 50034 Mosgiel, New Zealand

Lamb losses of up to 40% have been recorded between pregnancy scanning and tailing in New Zealand flocks (average lamb loss 20%). Current lamb death rates cost New Zealand farmers over $620 million annually. Starvation and exposure related deaths claim about one quarter of lambs that die soon after birth. The b-3-adrenergic receptor (ADRB3) is a major mediator of thermogenic effects of high catecholamine concentrations in brown adipose tissue. Recently, variation in the ovine ADRB3 has been associated with lamb survival. The DNA sequences of eight ADRB3 haplotypes (A-H) have been deposited in GenBank. Single nucleotide polymorphisms (SNPs) found within these sequences were utilised to distinguish the haplotypes to produce a SNP multiplex assay. This iPLEX assay was used to genotype sires from the AgResearch Lamb Survival Resource to look for association between the different haplotypes and the starvation / exposure death risk trait.

14 PERFORMANCE AND APPLICATION OF THE GOLDENGATE ASSAY FOR THE ANALYSIS OF SNPS IN FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUE SAMPLES

Wayte, N*^ and Chenevix-Trench, G*

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The development of SNP genotyping technology has greatly increased possibilities for genetic analysis. However, for certain applications this technology remains largely inaccessible. In particular, few published reports demonstrate the successful application of genome-wide SNP microarrays for the analysis of formalin-fixed paraffin-embedded (FFPE) tissue. Development in this area holds significant interest in medical research because global archives of FFPE tissue collected and stored over decades represent a rich resource of information. Unlocking this information has proven difficult due to the degraded nature of the tissue and the presence of DNA cross-links resulting from the fixation process. To this end we have assessed the performance of FFPE DNA on the GoldenGate assay (Illumina), a SNP genotyping platform specifically designed for short DNA fragments such as those obtained from FFPE material.

We compared the performance of DNA extracted using several commercial and non-commercial methods in order to determine whether a particular method is more suited for the GoldenGate Assay. Because DNA from FFPE material is often limited we compared varying starting amounts of DNA ranging from 50ng of DNA to the recommended 250ng starting amount. Importantly, we assessed the performance of a panel of FFPE tumours that range in tumour site, age and processing pathology lab on the GoldenGate assay. Included in this panel are tumours of the breast, ovary, colon, testis, pancreas, brain, stomach, thyroid and melanoma. The blocks range in age between 2-20 years and are sourced from different pathology labs around Australia. We will demonstrate the application of the GoldenGate assay to detect concurrent analysis of DNA copy number changes and loss of heterozygosity (LOH) aberrations in a panel of FFPE tumours and compared to matching fresh frozen tumours. We have applied this approach to tumours from several 'cancer dense' families which have a significant excess of multiple cancer types. Our aim is to identify common regions of allelic loss/retention shared by tumours within a family in order to identify novel cancer susceptibility genes.

15 GENE REGULATION AND DNA METHYLATION

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Heterochromatin is composed of transposable elements (TE) and related repeats which silence genes located nearby, and play a major role in epigenetic regulation of the genome. In plant and mammalian genomes, silencing depends in part on DNA cytosine methylation. We have been using microarrays and next generation sequencing technologies to investigate the roles of DNA and histone modification, as well as small RNA, in heterochromatic silencing and transposon control.

Far from being inert, heterochromatin is transcribed and small interfering RNA corresponding to heterochromatic sequences can be detected in plants, animals and fission yeast. In plants, small interfering RNA (siRNA) corresponding to some classes of TE depends on DNA methyltransferase MET1, the SWI/SNF ATPase, DDM1, or both, but not on the histone deacetylase SIL1/HDA6. All three genes are required for silencing transposons in the absence of siRNA, and we are exploring the roles of these complementary mechanisms in the inheritance of epigenetic silencing from generation to generation, and in dividing cells during development.

In fission yeast and in Arabidopsis, centromeric repeats are transcribed, but the transcripts are rapidly turned over by RNA interference, through the combined action of DNA dependent RNA polymerase, Argonaute and RNA dependent RNA polymerase, each of which is associated with heterochromatin. Histone H3 lysine-9 dimethylation (H3K9me2) depends on RNAi, mediated by the Rik1-Clr4 complex. We have found that heterochromatin is lost transiently during chromosomal replication, allowing heterochromatic transcripts to accumulate. Rapid processing of these transcripts into small RNA during S phase promotes restoration of heterochromatic modifications and the retention of cohesin in G2. These results explain how "silent" heterochromatin can be transcribed, and lead to a model for epigenetic inheritance during replication.

16 NEW MOLECULAR TARGETS IN BREAST CANCER

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In the United States, Breast Cancer is the leading cause of cancer related death in non-smoking women. The extensive heterogeneity of breast tumors underscores the significant challenge associated with predicting response to therapy, metastatic potential and development of treatment refractory disease. Fortunately, data generated through microarray-based research has shed significant light on breast tumor cell complexity, revealing the presence of more homogeneous molecular subtypes. The shared characteristics of identifiable tumor subtypes indicate a degree of similarity of activated oncogenic signaling pathways within subtypes, and perhaps not unexpectedly, more predictable responses to selected therapies. These observations are paving the way toward development of personalized treatment strategies targeted to measurable disease biology.

Research conducted in the Cunliffe laboratory leverages knowledge gained through whole genome surveys to define and understand molecular pathology operating within tumors of related biological context, and how these mechanisms govern malignant progression, including evolution of drug-resistance. The objective of this research is to gain a functional understanding of context-specific drivers of oncogenic signaling and tumor cell survival mechanisms and translate these discoveries for enhanced disease management. Data will be presented on two studies where key malignant signaling axes have been identified to play pivotal roles in breast cancer progression. Importantly, these studies will highlight the power of array-based research to discover and validate novel and tractable molecular targets in breast cancer.

17 SEQUENCING THE MAMMALIAN TRANSCRIPTOME IN TOTO

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Since the sequencing of the mouse and human genomes, there has been a concerted effort to define their complete transcriptional output and study its role in controlling biological states and gene function. Massive scale EST & full length cDNA sequencing plus the transcriptome annotation efforts by FANTOM, ENCODE and others have revealed that mammalian loci can generate as many 6-10 transcripts on average, with alternate promoters, splicing and 3'UTRs being commonplace. While these data have provided an excellent atlas of what RNA can be generated from mammalian genomes, putting this transcriptional complexity into a biological context has proven very difficult. Array based profiling may be an excellent tool for assessing overall gene activity but it lacks the required sensitivity and discrimination to study complete transcriptome content and dynamics.

Recently, we have developed methods for performing exhaustive shotgun sequencing of transcriptomes and developed approaches to assess locus activity, the relative abundance of variants and perform genome-wide transcriptome discovery. We have also established approaches to identify expressed variation in sequences. We have recently used these tools to perform systematic analysing multiple fractions of the mammalian transcriptome (mRNA, polysome, and/or miRNAs) at single nucleotide resolution in a series of mammalian cell models and solid tumours. These studies have provided accurate estimates of mRNA and miRNA complexity, defined the coding variants actively being translated in specific biological states and novel insights into locus control, and define the transcriptional networks driving specific biological states at unprecedented resolution.

18 TRANSCRIPTOME ANALYSIS USING RNA-SEQ

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Several recent studies have demonstrated the effectiveness of deep sequencing for transcriptome analysis (RNA-seq) in mammals. This has lead to suggestions that widely available and cost effective sequencing will make microarrays redundant in the near future. Several limitations of microarray technology may be overcome with a sequencing approach such as the restriction to genes for which probes are included on the array and contamination by cross-hybridization. However, RNA-seq has its own limitations and biases which will need to be considered and explored thoroughly if the heralded benefits of the new technology are to be fully realized. In this presentation I will discuss the structure of the data emerging from RNA-seq. I will discuss and compare some of the advantages and disadvantages of sequencing and microarrays using previously published data. I will present a new data set from the Illumina Genome Analyser platform which allows us to develop a rigorous statistical analysis pipeline for RNA-seq data.

19 CELL CYCLE TRANSCRIPTOME PROFILING VIA MASSIVE-SCALE NEXT-GENERATION SEQUENCING.

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We have recently developed a massive-scale RNA sequencing protocol, which generates Short Quantitative RNA Libraries (SQRL), optimized for next-generation short-tag sequencing. These libraries capture the genomic landscape of RNA expression, state-specific RNA expression, single-nucleotide polymorphisms (SNPs), RNA editing events, the transcriptional activity of repeat elements, and both known and novel alternative splicing events, all within a single experiment. We have used this approach to explore the polyA+ transcriptomes of synchronized HeLa cell populations (G1-phase, S-phase, and G2/M-phase), and identify novel components of the cell-cycle progression machinery. These include both novel cell cycle-regulated loci, and previously unstudied splice-variants of known cell cycle-regulators. We have confirmed their involvement in cell cycle progression by qRT-PCR of other synchronized cell lines, and we have explored the function of these new components by siRNA knockdown and over-expression studies. For the first time, we have assessed the impact of transcriptional complexity on the cell cycle, showing that our understanding of this highly-studied biological model is far from complete.

20 SEQUENCING TRANSCRIPTOMES USING THE GS FLX

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Massively parallel sequencing technologies (or Next Generation Sequencing) have revolutionised the way we view and use sequence data, particular when applied to non-model organisms. Though originally targeted at genomes, Next Generation sequencing is now being applied to the study of transcriptomes. Transcriptomes bring with them challenges not applicable to genome sequencing. In this seminar, these challenges will be identified and possible solutions discussed.

21 IDENTIFICATION OF NOVEL OVARIAN CANCER GENES USING AN INTEGRATIVE GENOMICS APPROACH

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Epithelial Ovarian Cancer (EOC) is one of the most fatal cancers in women, claiming an estimated 230,555 lives worldwide in 2007. The lethality of this disease can be attributed mainly to the lack of reliable early detection strategies. The identification of marker genes of the disease has proven difficult due to the complex nature of genetic alterations and also lack of high resolution technology in the past. To identify drivers of ovarian cancer we have surveyed over 100 ovarian tumours for copy number aberrations using Affymetrix 500K or SNP 6.0 Mapping arrays. Subsets of these samples have also been analysed on Affymetrix Human GeneST1.0 arrays and Agilent Human microRNA arrays.

The current study aims to discover novel drivers of ovarian cancer by integrating data across these platforms. The copy number data will help isolate (i) focal regions of copy number gain or loss (0.5Mb-10Mb) (ii) regions with high level amplifications (copy number >5) (iii) regions of copy number change that are observed in multiple samples and (iv) regions of copy number change that may be specific to certain subtypes of ovarian cancer (such as serous, endometrioid, mucinous, and clear cell). The genes identified in these candidate regions will then be tested for correlation with mRNA and microRNA expression data in an effort to narrow down the list of candidate genes. Early results of this integration will be presented for the frequent amplifications on chromosomes 3, 8 and 19.

22 USE OF DNA DAMAGING AGENTS AND RNA POOLING TO ASSESS EXPRESSION PROFILES ASSOCIATED WITH BRCA1, BRCA2, AND BRCAX MUTATION STATUS IN BREAST CANCER PATIENTS

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Approximately 5-10% of breast cancer cases occur in multiple-case families, and are attributable to inherited mutations of highly penetrant breast cancer susceptibility genes, including BRCA1 and BRCA2. However, 10-20% of the reported sequence changes in BRCA1 and BRCA2 are currently of unknown clinical significance. Classification of these sequence changes is important for facilitating clinical management of patients. A recent study from our lab suggested that post-irradiation gene expression data from lymphoblastoid cell lines (LCLs) derived from blood of patients with sequence alterations in BRCA1, BRCA2 and from blood of familial breast cancer patients without such alterations (BRCAX) has potential to predict BRCA1, BRCA2 and BRCAX mutation status with up to 62% accuracy. In view of improving prediction accuracy, we have subsequently performed a pilot mRNA expression study to assess the effect of two DNA damaging agents (irradiation and mitomycin C) on cellular response in relation to mutation status. In this study, we treated nine LCLs from each of the BRCA1, BRCA2 and BRCAX patient groups, and from nine healthy controls, with each DNA damaging agent at a range of doses and isolated mRNA after various incubation times. To reduce costs, we generated three mRNA pools of three samples per patient group per treatment prior to microarray analysis. Expression profile differences identified by mRNA pooling replicated differences shown by virtual sample pooling of microarray data, thereby supporting the use of pooling mRNA samples for this microarray experiment. Results from microarray data analysis suggest that treating individual LCLs with 0.4 microM mitomycin C and measuring the gene expression profiles 120 minutes post-treatment had the greatest potential to discriminate BRCA1, BRCA2 and BRCAX mutation status. Furthermore, evidence suggests that the perturbation of LCLs by mitomycin C may affect the B-cell survival pathway. We have identified 36 genes that are differentially expressed between BRCA1, BRCA2 and BRCAX pools, and that are mitomycin C responsive in affected carrier pools but not in healthy controls. Validation of these results is currently underway. Identifying genes whose expression is associated with BRCA1, BRCA2 and BRCAX mutation status may prove to be a valuable method of screening individuals from multiple case breast cancer families for the presence of pathogenic mutations.

23 IDENTIFICATION OF A PROLIFERATION SIGNATURE AND AN ASSOCIATED PI3K-AKT-MTOR PATHWAY DRIVING CELL PROLIFERATION, BUT NOT SURVIVAL, IN A LEUKAEMIA-INDUCING ACTIVATED RECEPTOR MUTANT, AND ITS ROLE IN ACUTE MYELOID LEUKAEMIA.

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Acute Myeloid leukaemia (AML) is a malignant blood disease characterised by uncontrolled growth of leukaemic blasts. Multiple mechanisms can lead to the constitutive activation of signalling pathways in leukaemic cells contributing to aberrant proliferation, survival and a block in differentiation. Granulocyte-Macrophage Colony Stimulating Factor Receptor (GMR) is known to be involved in myeloid proliferation, differentiation and survival. We have previously demonstrated that a trans-membrane activating mutation (V449E) in the GMR results in development of AML in a mouse model, and confers factor independent growth upon myeloid cell lines [1,2]. Introduction of an additional tyrosine mutation at position 577 (Y577F) in GMR-V449E selectively abolishes the factor-independent growth of myeloid cell lines expressing the V449E receptor but retains factor-independent cell survival [3]. To further examine the differences between the V449E activated mutant and the Y577F derivative, cells expressing these two mutants were compared using microarray gene expression analysis. Using linear modelling (LIMMA) of GMR-V449E vs. GMR-V449E/Y577F over 72 hours we identified gene-sets associated selectively with V449E-activated proliferation or survival. Subsequently, we utilised the Connectivity Map database (CMAP) [4] to identify pathway associated with activated receptor proliferation or survival. We found that PI3K-Akt-mTOR pathway gene signatures, identified in CMAP via a number of chemical inhibitors, are significantly associated with the GMR-V449E proliferation signature. This was confirmed experimentally by the observation that GMR-V449E-induced proliferation is abolished by inhibition of the PI3K/Akt pathway with LY294002 and Wortmannin. Additionally, GMR-V449E displays activated Akt but is lost in GMR-V449E/Y577F. We are currently using CMAP LY294002, Wortmannin and Sirolimus signatures to identify genes in common with the V449E proliferation signature. Such genes may be important downstream effectors involved in driving proliferation in leukaemic cells. To establish the relevance of the V449E gene expression signatures to AML we are using gene set enrichment analysis (Wilcoxon Rank Sum Test) to identify association of the GMR V449E proliferation signature with the gene expression signatures that define different classes of AML (based on expression profiling of 285 AML patients) [5].

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24 INTERROGATION OF BREAST CANCER CELL LINE DATABASES CONFIRM EMT STATUS AND REVEALS A LINK BETWEEN EMT AND BREAST CANCER STEM CELLS.

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Epithelial mesenchymal transition (EMT) has long been associated with breast cancer cell invasiveness but evidence of EMT processes in clinical samples has been lacking. In contrast, human breast cancer cell lines show clear evidence of EMT, with a growing number of cell lines exhibiting mesenchymal features or undergoing EMT in response to an ever-growing collection of stimuli (reviewed in (1). Building on gene expression profiling of breast cancer cell lines (2), we devised a literature-based classifier (EMT-SIG) and independently confirmed an EMT association within the invasive subgroup (Basal B/ Mesenchymal). EMT-SIG was notably under-expressed in luminal breast cancer cell lines. This coordinate expression of EMT-SIG genes in basaloid cells supports both a role for EMT in defining the phenotype and regulating the biology of aggressive breast tumour subtypes.

We also observed that the Basal B cell lines are characterised by the CD44hiCD24lo/- phenotype which has been used to isolate and characterise breast cancer stem cells (BCSC; (3, 4)). We found strong concordance between gene products associated with the EMT phenotype in HBC cell lines and cells sorted from clinical specimens (5), consistent with EMT attributes being advantageous for stem cells. Loss of CD24 correlated tightly with degree of mesenchymal gene expression, and 27 of 60 gene products correlating tightly with CD24 status in Basal B cell lines were also differentially expressed in the Shipitsin data set ($P < 0.0001$). Gene expression data from a series of aggressively treated early stage breast cancers (6) was clustered into established, prognostically relevant subgroups by EMT-SIG, which further substratified individual tumours within the Basal and Luminal subgroups. In the Basal subgroup, tumours enriched for EMT-SIG showed a trend towards poorer overall and disease-free survival. These new data confirm and extend the importance of EMT and the value of analysing established HBC cell lines for new leads in this area, and support data which recently showed similar findings but also showed increased stem-like capability of EMT-derived human mammary cells (7).

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25 EPIGENETICS IN THE PLACENTA: A GENOME-WIDE METHYLATION ANALYSIS OF FIRST TRIMESTER TROPHOBLASTS

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The human placenta is a highly specialized organ that undergoes extensive structural changes during pregnancy. Trophoblast cells are responsible for the growth and function of the placenta and its attachment to the uterine wall. These cells undergo critically regulated phases of proliferation, migration and invasion during the first trimester of pregnancy to establish a blood supply to the growing fetus. Previous studies have suggested remarkable similarities between the invasive phenotypes of trophoblast and cancer cells. Since epigenetic mechanisms have been linked with the silencing of tumour-suppressor genes and other key regulatory genes involved in cancer, we hypothesize that the epigenetic regulation of first-trimester placental trophoblasts may provide a mechanistic relationship between placental and cancer growth and invasion.

DNA was extracted from trophoblast cells of first-trimester human pregnancy tissues and a genome-wide methylation analysis was performed using Methyl-DNA Immunoprecipitation followed by hybridisation to 20K promoter microarrays. Ten candidate genes were chosen for subsequent validation by Sequenom MASSArray, which will provide quantification of individual CpG-site methylation. We hope to identify methylation changes that occur during different stages of placental development, and thus provide a model system for the epigenetic modification that occurs in cancer. In addition, any epigenetic changes found may provide insight into placental pathology and the origins of adult disease.

26 WHOLE GENOME EXPRESSION ANALYSIS FROM MICRO-DISSECTED MOUSE CARTILAGE TISSUES

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Purpose: To explore the molecular mechanisms of osteoarthritis (OA) initiation and progression, global gene expression profiling was performed on cartilage from mice with surgically-induced OA. We used WT mice, and mice lacking ADAMTS-5 activity (ADAMTS-5Δcat). By comparing the gene expression during OA in these mice we have distinguished the early events leading to aggrecan degradation (pre-fibrillated changes) from the downstream progressive phases that follow loss of aggrecan.
Methods: Mechanical instability was introduced into 10 week old male mouse knee joints by surgical destabilization of the medial meniscus (DMM). In this model focal degeneration, exemplified by loss of aggrecan in the non-calcified articular cartilage, occurs in the medial tibial plateau 2 weeks after surgery in WT mice. After 6 weeks, aggrecan loss had progressed and cartilage fibrillation was evident. In ADAMTS-5Δcat mice aggrecan loss and cartilage erosion is significantly reduced. Non-calcified cartilage from the developing lesion in DMM or sham-operated joints at 1, 2 and 6 weeks post-surgery was harvested by laser microdissection. Chondrocyte total RNA was extracted and cRNA generated by linear amplification (MessageAmp, Ambion), labeled with Cy3/Cy5 and hybridized to 44k whole genome microarrays (Agilent). Data was validated by quantitative PCR of selected genes. **Results**: There was an early upregulation (1 week) in WT mice of cartilage hypertrophy markers, such as collagen X. However in the ADAMTS-5Δcat mice, these were not upregulated until 6 weeks, suggesting that the hypertrophic response of chondrocytes is not an initiating event, but an event downstream of the onset of ADAMTS-5 activity and/or cartilage degeneration. Of particular interest was the upregulation of the inflammatory mediator Ptgs2 (Cox-2) early (1 and 2 weeks) in WT OA mice. Upregulation of Cox-2 was not seen in ADAMTS-5Δcat mice. Dysregulation of several Bmps (eg Bmp7), inflammatory cytokines, Fgfs, members of the Wnt/β-catenin pathway were apparent in WT mice. Expression profiling also showed numerous changes in gene expression that followed the same pattern in both WT and ADAMTS-5Δcat mice, and thus are likely to be independent of ADAMTS-5-mediated aggrecan degradation. These changes include upregulation of several cathepsins (eg cathepsin S), Bmps (eg Bmp7) lumican and fibronectin. **Conclusions**: This well controlled OA model combined with precise microdissection of cartilage from developing cartilage lesions and microarray technology provides new insights into gene expressed during the initiation and progression of OA. Furthermore the comparison of OA gene expression in WT, ADAMTS-5Δcat and other mouse models will allow us to prioritize candidate genes for functional analysis.

27 PROBING THE ARCHITECTURE OF DEVELOPMENTAL PLASTICITY

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Developmental plasticity is poorly understood in animals at the molecular level. Plasticity provides an animal with the ability to produce different morphologies or physiologies in response to their environment. In extreme cases plasticity can produce two or more extremely different animals from a single genome.

The honeybee is an excellent example of extreme plasticity. Larval nutrition can send a female honeybee down a pathway leading to worker development or queen development. In comparison to worker bees, queen bees are larger, reproductively active, behave differently, have different physiology and live five times longer. We are deciphering the molecular architecture of this process by examining changes in gene expression during queen and worker development and then employing RNA interference to test the functions of key genes and pathways.

By understanding how developmental plasticity works in this extreme example we hope to begin to understand more generally how plasticity works, how it might evolve and how it may facilitate the evolution of novel morphologies.

28 IDENTIFICATION OF SOMATICALLY ACQUIRED REARRANGEMENTS IN CANCER USING GENOME-WIDE MASSIVELY PARALLEL PAIRED-END SEQUENCING.

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We are now entering an era in which it will be feasible to catalogue every genetic event in a cancer. Next generation sequencing platforms already offer the capacity to generate gigabases (Gb) of sequence each week at a cost of less than 1 cent per kilobase (kb). Techniques have been developed which allow the detection of genomic rearrangements, copy number changes, point mutations and small insertions and deletions as well as epigenetic alterations on a single instrument. This will be a significant advance on existing approaches to cancer genomics. The analysis will be genuinely genome-wide, cataloguing genetic changes not only in coding sequence but also the other 98% of the human genome including, for example, promoters, enhancers and non-coding RNAs. At the Cancer Genome Project, we have developed protocols for mapping acquired rearrangements to the base-pair level, providing insights into the diversity of aberrant processes sculpting the genome which underlie the evolution and development of cancer.

29 MIXING AND MATCHING DATA FROM DIFFERENT SOURCES TO UNDERSTAND DISEASE

Print, C

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To understand how thousands of individual molecules work together to determine the function of tissues, it may be helpful to combine information from multiple sources. Constructively bringing together different types of information is one of the goals of systems biology. This process is likely to play an important role in developing a better understanding of human disease at a molecular level. For example, it may be useful to combine information from in vitro and in vivo microarray experiments, or from exon arrays with 3' arrays, or to compare transcript abundance and pathway activation between epithelial cells and stromal cells in the same tumour.

Alternatively, it may be useful to combine information about transcription factor specificity with microarray data, or to combine data about mRNA and miRNA abundance in the same tissue. This talk will discuss some experiments where my research group have tried to bring data of these different types together, and some of the challenges that these first attempts at systems biology have revealed.

30 STRATEGIES FOR HIGH THROUGHPUT IDENTIFICATION OF IMPRINTED GENES IN PLANTS

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Imprinting is an epigenetic phenomenon by which genes are expressed predominantly from either their paternal or their maternal allele. In mammals, imprinting occurs in the developing placenta and embryo. Over 100 imprinted genes have been identified in mammals and disruption of imprinting is often associated with disease syndromes and cancers. In contrast, very few imprinted genes have been identified in plants, with only four characterised in the model plant Arabidopsis. The imprinting of these genes appears to be limited to the endosperm, an extra-embryonic tissue similar to the placenta that nourishes the developing embryo. Plant imprinting provides important regulatory controls for seed development via direct effects on endosperm development.

Given the importance of imprinting in controlling seed development and the paucity of information regarding imprinting in plants, we designed a novel strategy to discover new imprinted genes. We used Laser-assisted microdissection (LAM) and microarray analyses to identify the endosperm transcriptome and validated our microarray data using relative quantification of realtime PCR products. Approximately 90 genes were screened for mono-allelic expression using known single nucleotide polymorphisms (SNPs) between Arabidopsis accessions. We have already identified four new imprinted loci. Furthermore, new SNP data and local access to platforms that enable high throughput sequencing and high resolution melting curve analysis make the first high-throughput screen for plant imprinted genes a possibility. By identifying additional imprinted genes, their regulatory controls and function during seed development, we will enable more informed hypotheses to be developed with regard to the role and evolution of plant imprinting.

31 USING A MODEL CYANOBACTERIUM TO INVESTIGATE THE TRANSCRIPTIONAL RESPONSE TO CHANGING ENVIRONMENTS

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As the progenitor of oxygenic photosynthesis, cyanobacteria represent an excellent model system for the study of photosynthesis, nitrogen assimilation, and circadian rhythms. These resilient microbes have a broad habitat range including extreme environments where temperature, pH or salt may be elevated. Their metabolic diversity means that cyanobacteria have potential applications in bioremediation, bioenergy production, biofertilisation and in the identification of novel bioactive compounds. Using DNA microarrays we have determined transcriptional responses to a wide range of environmental conditions that cyanobacteria frequently experience, including: heat shock, light/dark transitions, alkaline pH and anaerobiosis. Microarray data enabled the identification of key regulatory genes for sensing and responding to these varied conditions including both general and specific stress responses. The work was extended by constructing gene knock-out strains targeting the putative regulators and then biochemically and physiologically characterising these new mutants. Based on these experiments, a model of transcriptional interactions among regulatory proteins in Synechocystis sp. PCC 6803 was developed. In addition, these data identified conditions under which a photosynthetic gene cluster was up-regulated, this included a gene previously shown to be transcribed in trace amounts. Similar regulation was found in other cyanobacterial strains.

32 USING A VIRTUAL MUSCLE MODEL TO INTERPRET MUSCLE DEVELOPMENT AND GROWTH BY LINKING GENE EXPRESSION WITH PROTEIN SPATIAL LOCATION

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New approaches for analysing gene expression data are required to avoid focussing on just the dynamically changing gene expression sets. This is especially important for understanding the relationships between broadly expressed and tissue specific genes, which needs to be underpinned by an understanding of the structure-function relationships of their encoded protein products. To assist in understanding the changes in function of structural proteins during development, we have implemented an interactive 3D virtual muscle model (VMus3D) representative of the core structural protein arrangements of striated muscle as an internet-orientated browser that integrates sets of databases with visualisation methods in a simultaneous real-time fashion. This approach has recently been used to describe the connectivity model of muscle development. By integrating a number of publicly available gene expression datasets and using the VMus3D, we observed that the magnitude of gene expression change and the specificity to skeletal muscle increased co-ordinately during development. A transition from genes encoding membrane components (the costamere) to genes encoding central components of a muscle fibre became apparent (Waardenberg et al., BMC Systems Biology, in press). This indicated that many components of the costamere were expressed prior to early muscle development, presumably performing other roles before being constrained into their muscle specific protein arrangements that can be seen in developed muscle. We are now using the VMus3D to interpret the developmental impact of a mutation in a muscle regulatory gene, myostatin (GDF8), between bovine cross-breeds. Myostatin usually acts as a negative regulator of muscle growth; however mutation results in truncation of its protein product which relieves negative regulation, resulting in substantial muscle growth. Through the use of VMus3D it is clear that mutation of this regulatory gene has differential impacts on the development of muscle structural complexes of these cross-breeds during growth. It is anticipated that the continued development of the VMus3D with a more comprehensive integration of various types of data, including gene expression, regulatory site and protein interaction data within the spatial context of VMus3D, will enable us to further understand the programs defining muscle development and the impact of changes in the regulatory machinery.

33 CREATION OF AN OVINE GENOME SKIM ASSEMBLY AND A 50K+ ILLUMINA SNP ISELECT™ BEADCHIP

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 # http://www.sheephapmap.org

The sheep genome was "skim" sequenced to 3X coverage using 6 animals (Romney, Texel, Scottish Blackface, Merino, Dorset and Awassi). Our genome assembly is estimated to cover in excess of 42% of the ovine genome and represent 82% of the non repetitive fraction. This assembly also identified 277,000 high quality SNPs and additional reduced representational sequencing using Illumina's Genome Analyzer (Solexa® Sequencing Technology) on animals from 15 different breeds identified a further 76,000 high quality SNPs. 59,494 SNPs were selected for inclusion on a 50K+ Illumina Infinium iSelect™ SNP BeadChip, giving an average spacing of 46kb across the whole genome. A wide variety of breeds and a linkage mapping resource will be genotyped using this resource. Progress and interim results will be presented.

34 IDENTIFICATION OF MICRORNAS WITH REGULATORY POTENTIAL USING MATCHED MICRORNA-MRNA TIMECOURSE DATA

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MicroRNAs (miRNAs) are small (approximately 22 nucleotides long) RNA molecules that play an important role in gene regulation by (i) repressing the translation of mRNA or (ii) cleaving the mRNA transcript. Over the past few years, some miRNAs have been shown to regulate the expression of cancer genes in humans.

We propose a new model for the identification of miRNAs that potentially regulate gene expression. This model is suitable for timecourse microarray data and allows for – (i) identification of time lag between a change in miRNA expression and that of its target mRNAs, and (ii) ranking of miRNAs after combining results obtained from multiple miRNA target-prediction algorithms like PicTar and miRanda. These features are useful as currently there is no golden rule for the time lag between changes in miRNA and mRNA expression. Also, the miRNA target prediction accuracy varies from one algorithm to another with no one algorithm being distinctly better.

We apply our method to a multiple myeloma dataset comprising matched timecourse expression profiles for miRNA and mRNA. We obtain a few miRNAs with regulatory potential but the experimental validation of our results is currently pending.

35 TRANSCRIPTOME PROFILING OF HUMAN ISLETS TO DETERMINE PREDICTORS OF CLINICAL ISLET TRANSPLANT OUTCOMES

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Type I diabetes is a disease characterized by the destruction of pancreatic beta cells by an innate immune response, leading to inadequate production of insulin. Transplantation of islet cells has the potential to reverse the harmful effects of type I Diabetes, however there is a steady decline in graft function from a ~70% 1 year success rate to ~10% success rate after 5 years, with often up-to 3 transplants required to reach normal glucose tolerance levels. One of the major goals of the Australian Islet Transplant Consortium is to identify molecular markers in the form of mRNA profiles that are predictive of healthy cells with good islet cell function, which will in turn improve transplant outcomes. In this presentation, we shall consider islet cell preparations from 18 donors, from which the mRNA was extracted and purified, then run on Affymetrix HG-U133Plus 2 arrays. Strikingly, this data demonstrates extremely high inter-patient variability, almost on par with data obtained under various cancer conditions. We compared the variability of each ProbeSet on the array to other commonly transplanted tissues, and found that the islet data was on average twice as variable as gene expression data from kidney and heart tissues, with ~13% of all genes exhibiting a >5-fold change. Of the ~1000 most variable genes (standard deviation Z-score > 3), gene ontology analysis revealed that many were involved in glycolysis (P=2.46E-05), response to wounding (P=1.46E-18) and inflammation (P=3.52E-10). Thus, the variably expressed genes were those most essential for beta cell metabolic function, cellular stress responses and beta cell survival. There is also considerable co-regulation of gene expression profiles in this data for genes including insulin, somatostatin and glucagon, which are vital for beta-cell function. We propose that the considerable transcriptome variability that we have observed could contribute to the high failure rate of islet cells. Within this variability, signatures of co-regulated genes that up-regulate genes associated with normal islet function, and down-regulate inflammatory or apoptotic genes may be represent strong candidates for a molecular signature that will be predictive of good islet cell function.

36 A FRAMEWORK FOR ASSESSING MICROARRAY NORMALIZATION METHODS WITH RESPECT TO PRECISION, BIAS AND SIGNAL TO NOISE RATIO

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Microarray data needs to be normalized before downstream analyses can be conducted. Normalization of single channel microarray data typically consists of three steps of processing: background correction, data transformation and between-array normalization, which strive to remove background noise, stabilize the variance and make arrays have the same expression baseline respectively. Assessing the performance of different normalization methods is a challenging issue. Normalization methods can achieve high precision by introducing undesirable bias such as compressed intensity range etc. Good normalization methods should not only have high precision, but also have small bias. And more important than either precision or bias separately, is the combination of the two, producing a desirable signal to noise ratio. In this study we propose a framework for assessing normalization methods which includes three key components: (i) precision, (ii) bias, (iii) signal to noise ratio. Accurate measure of these components is crucial for the successful assessment. Data from spike-in or titration experiments will be useful for these measurements since they have known truth. RT-PCR and independent microarray data might be useful as well since they will provide an independent observation of fold changes and ranking of genes. Positive control probes and negative control probes could also be used since positive control probes are expected to give higher expression intensities than negative control probes. In this talk, we use data from an in-house titration experiment using the Illumina Sentrix Human-6 v1 platform. No "gold standard" normalization method is known for the Illumina microarray platform yet. The normalization methods investigated can differ from each other in any of the three processing steps. In this study, background correction methods investigated include "normexp", "subtraction" and "no background correction", data transformation methods include "log2", "vst" and a new method "evst (empirical variance stabilizing transformation)" and between-array normalization methods include "quantile" and "rsn (robust spline normalization)".

37 ROAST, A GENE SET TESTING METHOD FOR LABORATORY GENERATED MICROARRAY DATA

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Gene set tests have advantages over single gene tests in interpreting microarray data. Gene sets can be defined by biological functions, chromosome locations or other microarray analysis results. A number of gene set tests have been proposed. But all suffer from one or two serious limitations. Sample permutation based methods are only suitable to be used in large sample size and simple designed microarray experiments. On the other hand, gene re-sampling methods do not correctly allow for gene-wise dependence.

The proposed "roast" (rotation set test) uses rotation of residual space instead of permutation of genes or samples. So, gene-wise correlations are retained and the limitation of sample size is relaxed.

This method is suitable for complex designed experiments with multiple groups or multiple factors and small sample sizes. The groups of interest can be part of the larger experiment. This method makes use of all groups of replicates and handles multiple factors in linear models. The test can focus on any relevant comparison or contrast. Block of design, array weights and gene weights are available to give the method more flexibility. Interestingly, four hypothesized directions of gene regulation can be tested.

The proposed method also avoids the granularity problem of permuted p values, while preserves many of the robustness properties. Full power can be achieved in normal case. The method is computed efficiently. The function is build in R and will be available through Limma package. The theory, simulations and an application in cancer research will be discussed.

38 INTEGRATING GENE EXPRESSION STUDIES VIA STATISTICAL SYNTHESIS

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Microarrays are one of the driving forces in biological research. With their explosion in popularity, an increase is also seen in the availability and size of public repositories. These data sets are by no means superannuate, but offer researchers a depth of information if used wisely. We proposed a method that would synthesis data sets taking into account platform effects, such as platform development and hybridisation protocol, probe discrepancies and laboratory. Heuristically if a gene is truly differentially expressed (DE), it should be DE throughout a range of DE measures and experiments. mDEDS is an extension of the Differential Expression via Distance Synthesis method (DEDS), (Yang et al., 2004). This method makes use of permutation tests on the multiple data sets and a plethora of expression measures synthesised through a distance equation to unveil a DE list.

We evaluated the performance of mDEDS using simulations and comparative analyses with predication accuracy as a criterion. Currently available meta-methods; GeneMeta (Choi et al, 2003), metaArray (Ghosh et al., 2008), Fisher, naïve (where a classifier was built purely off one platform) and simple (combined with no adjustment) as well as our proposed mDEDS were utilized within these two studies. In the simulation study with different percentage of DE genes, mDEDS was able to outperform other methods as illustrated with the ROC curve.

In addition, a comparison study based on experimental data was performed. This study utilized three publicly available prostate cancer data sets (Varambally et al., 2005, Yu et al., 2004, Singhet al., 2002) and aimed to classify cancer and benign prostates. In our comparison study we used various meta-method as feature selection algorithms and evaluated their performance based on cross validation at a data set level. mDEDS performed better than other meta-analysis methods, a higher degree of classification accuracy was obtained by a training set that was combined with mDEDS as the meta-method, than when the meta was performed by other methods.

39 ISSUES IN NORMALISATION OF ONE COLOUR CHIP-CHIP DATA FOR CHROMATIN MODIFICATION

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Chromatin immunoprecipitation techniques are increasingly being used in combination with DNA tiling microarrays to locate transcription factor binding sites and to determine chromatin composition a genomewide scale. However, issues remain in the normalisation, visualisation and analysis of the resultant data, required to elucidate where specific DNA binding occurs with high confidence. As with expression microarrays, normalisation is required within- and between-arrays, so that comparative inferences about biological phenomena may be made. There is, therefore, a need for existing microarray normalisation strategies to be adapted for single channel CHiP-chip arrays. Here, we report work-in-progress that seeks to implement existing methods for dualchannel arrays, to reduce noise in single channel CHip-chip data utilising total genomic input replicates as control data on a promoter by promoter basis. We illustrate some of the systematic biases in CHiP-chip data from mouse T-Cells showing H3 histone levels and acetylation on Affymetrix promoter arrays, and demonstrate the development of methods to correct for them. We are implementing these methods in the R statistical computing environment as open-access, open-source software. These approaches should be applicable to all single channel CHiP-chip data, increasing comparability and correlation amongst replicates of single channel CHiP-chip array data.

40 BIOLOGY-DRIVEN CLINICAL MANAGEMENT OF PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA THROUGH INTEGRATIVE DATA MINING AND VISUALIZATION OF GENOME-WIDE GENE EXPRESSION AND SNP PROFILES.

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Childhood acute lymphoblastic leukaemia (ALL), the most common childhood malignancy, is beset with the clinical problem that, despite patients displaying similar clinical presentation, they do not always respond to the same treatment regimes with a proportion relapsing during clinical intervention. There is a vital need for a more defined risk assessment strategy, which will lead to individualized therapeutic management for paediatric ALL patients. It is our hypothesis that patients with similar biology should have equivalent clinical outcome when treated on equivalent therapeutic regimens. We have tested this hypothesis by integrating biological (eg. gene expression, single nucleotide polymorphism (SNP)) and clinical data (eg. medical examinations, pathology) to build a model whereby each patient within a cohort can be compared to each other on the basis of biological similarity, rather than clinical presentation. RNA and DNA were isolated from bone marrow and peripheral blood respectively from a cohort of 140 ALL patients. Gene expression was determined using the Affymetrix HU133 platform whilst the DNA was applied to Illumina whole-genome SNP Beadarrays incorporating 12,000 human non-synonymous SNPs (Illumina NS-12). We have developed and tested an approach to visualise the patient to patient relationships in the integrated datasets based around nonlinear extensions to principal component analysis specifically kernel principal component analysis and multidimensional scaling based methods, such as Neighbor Retrieval Visualizer (NeRV) and Local Multidimensional Scaling (LocalMDS). With this approach, the complex integrated data for each patient is represented in a simple graphical representation. Incorporated prior knowledge about patients, such as treatment protocols, clinical outcome and even the cost of therapy will then be available for data mining. In addition, biplot approaches within the kernel-based analysis allow us to determine which gene and SNP features characterise particular clusters, or indeed, individual patients. Hence, the genes, SNPs or clinical details which have most influenced individual patients can be identified and will facilitate more targeted biological research and 'biomarker' studies in the future.

41 MICRORNA AND MRNA EXPRESSION PROFILING IN A MOUSE MODEL OF MYOCARDIAL INFARCTION WITH ENHANCED OR DEPRESSED PI3K ACTIVITY

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Cardiac hypertrophy is an increasing epidemic in Western society. The aberrant growth of the heart can lead to heart failure, and can be induced either by physiological stimuli eg postnatal development or chronic exercise training; or by pathological stimuli eg pressure/volume overload or in response to myocardial infarction (non-infarcted region). The pathological condition is associated with fibrosis, cardiac dysfunction and increased morbidity and mortality. Previous work (McMullen et al) indicated distinct signalling cascades induce pathological and physiological cardiac hypertrophy (1).

One of the mechanistic processes allowing the heart to enlarge in response to physiological stimuli while maintaining normal or enhanced function is the p110 alpha isoform of phosphoinositide 3-kinase (PI3K). PI3Ks are a family of lipid kinases that induce signals by phosphorylating the hydroxyl group at position 3 of membrane lipid phosphoinositides. PI3K (p110a), which couples to tyrosine kinases, plays a critical role in the regulation of developmental heart growth (2). The underlying regulation is not well understood, however. Activation of genes involved can potentially be a tool for augmenting physiological growth as well as improving cardiac function of the failing diseased heart. We therefore investigated the transcriptome signatures of both mRNA and microRNA, associated with progression of the disease in the non-infarcted “hypertrophied” left ventricle in 6 different mouse models.

Transgenic (Tg) mice expressing a constitutively active (ca) PI3K (p110a) mutant specifically in the heart have a 6.5-fold increase in PI3K activity and a 20% increase in heart weight/body weight (HW/BW) ratio. In comparison, in mice expressing a dominant negative (dn) PI3K (p110a) mutant, PI3K activity was decreased by 77% and the HW/BW ratio was reduced by ~20%. To examine the role of different settings of heart failure, dnPI3K and caPI3K Tg mice were subjected to myocardial infarction (MI). Global gene expression was established for the following 6 models: Ntg-sham, dnPI3K-sham, caPI3K-sham, Ntg-MI, dnPI3K-MI and caPI3K-MI (n = 4 each) using Affymetrix GeneChip® Mouse Genome 430 2.0 arrays for mRNA and Agilent miRNA microarrays for microRNA.

To identify distinctive differential expression patterns according to increasing cardiac stress, we performed statistical analysis from both the mRNA and miRNA data. Interestingly there was an over-represented GO category, namely cellular compartment belonging to mitochondrial genes. The main biological themes according to GO and KEGG are genes involved in mitochondrion metabolism, ribosomal protein biosynthesis and genes involved in cyto-structure. Furthermore, construction of a regulatory network model of mRNA and miRNA interactions is underway. We have, however, identified genes that directly correlate with cardiac function and may represent novel targets for the treatment of heart failure.

1: McMullen JR et al. 2003 PNAS 14:12355-60

2: Shioi et al. 2000. Embo J 19:2537-48.

42 GENE EXPRESSION CHANGES DURING EOSINOPHIL DIFFERENTIATION

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Eosinophils are a type of blood cell that are activated during inflammation and combat infection and parasites. They are also involved in the pathology of allergy and asthma.

However, little is known about the steps involved in the commitment of haematopoietic stem cells to eosinophil progenitors and the subsequent maturation process.

We have sorted cells with various levels of eosinophil commitment and used expression information to confirm the likely developmental order of these cells. This identifies a suite of genes that are gradually changing expression during development. We have used this to identify transcription factors which may be involved in driving eosinophil commitment and development.

44 IDENTIFICATION OF GENOMIC REARRANGEMENTS IN THE NEURONAL MIGRATION DISORDER PERIVENTRICULAR HETEROTOPIA

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Introduction: Periventricular heterotopia (PH) is a neural migration disorder caused by the failure of neurons to migrate correctly within the brain during embryonic development. Other features of PH include epileptic seizures and cardiovascular malformations. Although most individuals with PH do not have a defined aetiology, two genetic forms of the condition have been identified. The most common, X-linked dominant PH, is due to mutations in the gene encoding filamin A (FLNA) whereas mutations in the ARFGEF gene cause a rare autosomal recessive disorder of PH with microcephaly. However, an increasing number of patients with PH have been identified with atypical features and no mutations in the two genetic forms, suggesting the existence of specific syndromic forms of PH with potentially alternative genetic aetiologies.

Objective: To study the genetic aetiology and pathogenesis of the neural migration disorder PH, specifically by identifying genomic rearrangements in PH patients

Methods: The DNA of 16 patients with PH and additional clinical features were analyzed by 250K single nucleotide polymorphism (SNP) array using the Affymetrix platform. The data obtained from the array is visualized using CNAG2.0, followed by analysis in Excel spreadsheets. Possible alterations are checked in a number of data bases (UCSC, Database of Common Variants) to exclude common variants in the normal population. To confirm possible alterations and to narrow down breakpoints, multiplex ligation-dependent probe amplification (MLPA) and genomic qPCR was performed.

Results: A 5 Mb de novo deletion of chromosome 1p was identified in patient 1, a male with PH, epilepsy and developmental delay. The deletion ranges from 1p36.33>1pter and occurs within a region known to be recurrently deleted in individuals with the 1p36 deletion syndrome. Secondly, a 3 Mb de novo deletion of chromosome 22q11 was identified in patient 2, a female with PH, mild global developmental delay and joint hypermobility. This deletion occurs within a region known to be deleted in individuals with the 22q11 deletion syndrome. Finally, a 0.3 Mb deletion on the X chromosome was identified in patient 3 on Xp22 affecting 3 genes. The patient, a male, presented with PH, craniosynostosis, a thinned corpus callosum, facial dysmorphologies, and developmental delay.

Conclusion: This study identified 3 genomic rearrangements in a cohort of 16 patients with PH. Thereby we confirmed our approach to identify novel genetic aetiologies causing PH looking at genomic rearrangements. However, future research needs to point out if the PH in these patients is the results of a monogenic event or that these genomic imbalances can directly lead to the occurrence of PH. Overall this study will provide more insight into how neurons migrate during embryonic development and the genetic components responsible.

45 GENEPATTERN@OTAGO: LOCAL TOOLS FOR THE ANALYSIS OF MICROARRAY DATA

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As part of the REANNZ funded project "Integrated Genomics Resources for Health and Disease", a local installation of GenePattern has been established in the Department of Biochemistry at the University of Otago, and is accessible via the Kiwi Advanced Research and Education Network (KAREN). GenePattern was developed at the Broad Institute (MIT), and provides a web-based interface for the analysis of data from microarray experiments (both expression and SNP arrays). A major strength of the GenePattern software is its ease of use for non-bioinformaticians, as well as its flexibility in terms of being able to add new functionality via the creation of plug-in modules. In addition, the ability to create analysis "pipelines" allows users to exactly replicate previous analyses and results. In this talk GenePattern will be introduced, and some basic functionality will be demonstrated. In particular we will highlight analysis modules that have been developed locally, and are being made available via the GenePattern server located at Otago.

46 WHOLE GENOME EXPRESSION QUANTITATIVE TRAIT LOCI (EQTL) ANALYSIS OF ARABIDOPSIS

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There is increasing interest in understanding the molecular basis of complex traits. Initially, the genetic dissection of quantitative traits involved measurements of gross phenotypes. Most recently, the underlying mechanisms of inheritance have been studied through various approaches that are supported by modern technological and methodological advances, namely quantitative trait locus/loci (QTL) analysis and mutant analysis in genetics; genome sequencing and gene expression analysis in genomics; and protein structure analysis and protein assay in proteomics. Since each technology and approach focuses on specific pieces of the larger, poorly understood systems biology, the challenge is to integrate these different types of information to elucidate the genetic architecture of complex traits. To address one of these challenges we have combined QTL analysis with microarray analysis to characterize the genomic architecture that controls quantitative traits. Using Affymetrix technology and 211 individuals from a segregating Arabidopsis population, the transcript variation (i.e., expression level polymorphisms, ELPs) of 22,810 genes, in both control and treatment conditions, provide data for mapping expression QTL (eQTL). Results from our statistical analysis of the entire genome will be discussed in detail.

***This work is funded by NSF Arabidopsis 2010 in collaboration with Drs. Marilyn West, Hans van Leeuwen, Richard Michelmore, and Dina St.Clair University of California, Plant Sciences Dept, Davis CA, and Dr. Kyunga Kim, Purdue University, West Lafayette, IN, and Seoul National University, Seoul, Korea.

47 TELL-TALE GENES: HARNESSING GENOMICS FOR BREAST CANCER PROGNOSIS AND ONCOGENE DISCOVERY

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The biological and clinical heterogeneity of breast cancer can be explained, to some extent, by information embedded within a complex but ordered transcriptional architecture. Comprising this architecture are transcriptional networks reflecting biochemical and behavorial properties of tumors that might be harnessed to improve disease subtyping, patient prognosis and elucidation of key cancer mechanisms. The ability to parse out these gene networks and assess their mechanistic and clinical implications is a major interest in my laboratory. This presentation will discuss recent work in elucidating a gene expression signature in breast cancer that substantially refines the prognostic value of histologic grade. Additionally, an informatics-driven strategy that seeks to pinpoint cancer-promoting genes through integration of multiple forms of clinico-genomic information will be described.

48 ENABLING HUMAN GENOMICS WITH NEW SEQUENCING TECHNOLOGY

Bentley, D and collaborators

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Accurate and rapid sequencing of individual human genomes paves the way for widespread adoption of genomic information in biomedical and other applications. As a feasibility study for whole human genome sequencing, we generated >30x coverage of the genome of an African male sample (NA18507; Yoruba from Ibadan, Nigeria) and obtained sequence that aligned to >99% of the euchromatic reference, including unique alignments to 93%. We identified 4 million single nucleotide polymorphisms (SNPs), including more than one million novel SNPs. We estimated 99% sensitivity and specificity of SNP calling following comparison of our sequence data to 0.5 million genotype calls from the same DNA sample using the HapMap 550 Beadchip and by genotyping a subset of the novel SNPs. We characterised short indels and larger structural variants by analysis of read pairs supplemented by read depth information. We used de novo sequence assembly algorithms for local assembly to characterise novel breakpoints. All data were viewed in an implementation of the Ensembl browser, called Resembl. Further recent improvements in technology enable generation of >20 Gb high quality data per flowcell, making it practical for large-scale studies of human variation to be achieved accurately, rapidly and economically, as demonstrated by sequencing additional human genomes to comprehensive coverage. Genomics is poised to enter a new era of discovery and biomedical applications, using whole genome sequences in studies of population genetic variation in order to understand, diagnose and treat cancer and other diseases.

49 ARCHITECTURAL MAPPING OF A CANCER ASSOCIATED NEOCHROMOSOME

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Sarcomas are cancers of connective tissues. World-wide, each year there are ~130,000 new cases of sarcoma, comprising 10-20% of cancer in the young, with an overall mortality approaching ~50%. Well-differentiated liposarcoma (WDLPS) comprises 40-50% of liposarcoma, the second most common form of soft-tissue sarcoma. WDLPS is almost unique in being 'driven' by focal, high-level amplification events, typically located in supernumerary 'ring' or giant rod neochromosomes, and found in otherwise diploid karyotypes. Low resolution cytogenetic studies have shown that WDLPS is characterized by high-level amplification of 12q13-q22, thought to result in over-expression of genes with oncogenic properties, the best understood of which are HDM2 and CDK4.

Extremely high-resolution methods of characterising genomes is resulting in paradigm shifts in our understanding of somatic cancer genetics. The WDLPS neochromosome presents a rare opportunity to apply new genomic techniques to characterise a distinct collection of genetic alterations. We have acquired pure preparations of several neochromosomes from cell lines using flow cytometric techniques. Using SNP arrays, we have identified the constituent components of each accessory chromosome, which form two distinct populations of marker chromosomes: one bearing high level amplifications of many small regions, and another bearing low level amplification of several very large regions. We have begun deep-sequencing to more thoroughly define the spatial architecture of the giant rod chromosomes, and identify novel causal genetic events. Our presentation will summarise our findings to date and our further proposed studies.

50 CHANGES IN MICRORNA EXPRESSION AND CANCER

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MicroRNAs (miRNA) are single-stranded, non-coding RNAs of 21 – 23 nucleotides, that typically downregulate their target genes. Hundreds of miRNAs have recently been identified in vertebrates and several have been shown to play crucial roles in determining cellular differentiation and identity. We have used microarrays manufactured at Adelaide Microarray Facility to identify miRNAs involved in various aspects of cancer development and progression.

One study conducted at Hanson Institute, identified miRNAs and their targets which regulate epithelial to mesenchimal transition. The work demonstrated gene expression changes controlled by miRNAs to be an essential early step in tumour metastasis. Another study conducted at Flinders Medical Centre has identified a group of miRNAs deregulation of which may contribute to cancer development in the oesophagus. In addition to improving our understanding of the process, these mRNAs could serve as novel biomarkers to define disease states in oesophageal epithelium. Several more studies are under way.

Factorial designs optimised to address questions of interest specific to more complex projects greatly contribute to their success. Direct co-hybridisation of relevant samples without a common reference permits effective utilisation of available arrays. Use of linear models allows us to generate ranked lists of genes regulated by each experimental factor or by interaction of factors. Questions like "Which genes in the two cell lines have different time profiles in response to the treatment?" can be addressed directly. For most data analysis, we rely on limma package freely available through Bioconductor project.

51 ELIMINATING NORMAL CNVS FROM ARRAY CGH CANCER GENOME PROFILES

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Background: Since the application of high-resolution array comparative genomic hybridisation (array-CGH) in the late 1990's, an increasing number of copy number variations (CNVs) have been detected in the genomic DNA (gDNA) of healthy individuals. Currently more than 17,000 such "normal" CNVs are registered in the database of genomic variants, a number that has tripled over the last year. For cancer studies, distinction between these constitutional CNVs, many of which do not have adverse health effects, from acquired and potentially pathogenic CNVs is essential. **Aim:** To show that reference gDNA sourced from non-pathogenic tissue of the same individual eliminates constitutional CNVs from high-resolution array profiles (SMRT v2.0 array, BCCRC, CA and 1.4MB HumArray UCSF, USA) without compromising resolution, time, or assay quality. **Proof of principle:** Comparison of array-CGH profiles where the sample gDNA is sourced from blood and the reference gDNA is sourced from saliva of the same individual (dual-tissue array, n=4 in duplicate) to array-CGH profiles where both sample and reference gDNA are sourced from the same tissue (same-tissue array, n=4) has shown that there is no significant difference between the noise level in the dual-tissue arrays and that of same-tissue arrays. Statistical comparison of dual-tissue and same-tissue arrays using a paired t-test supports the null hypothesis at a significance level of 99.9% (alpha=0.001) for more than 99% of 10,396 clones included in the test statistics. The threshold for rejection of the null hypothesis for the median t-value of 10,396 clones falls between alpha levels 0.1 and 0.05 (median $t_{10,396(3)}=2.81$, $0.05<p<0.1$).**Application to cancer:** Chronic lymphocytic leukaemia typically manifests as a malignant proliferation of B-lymphocytes. In a pilot study, we compared array-CGH profiles of CLL samples using either a self-reference obtained from non-leukaemic neutrophils of the patient or a generic reference obtained from an unrelated, healthy individual. The majority of clones show consistent copy number status in each of the two hybridisations, with only 147 +/-96 of 2,464 clones exhibiting discrepant ratio values. The number of clones with CNVs is reduced on average by 60% (+/- 27%) in array-CGH profiles of CLL patients if the reference gDNA is sourced from non-leukaemic neutrophils of the same individual (n=4) as opposed to using the generic reference (n=4). Most of the CNVs that were eliminated in array profiles using the self-reference were unique to one CLL sample, whereas four occurred in ≥2 CLL samples.**Conclusion:** We have demonstrated that gDNA sourced from different tissues of the same individual shows reliable consistency in array-CGH profiles. Saliva has the added advantage that gDNA samples can be obtained by non-invasive self-collection techniques. For certain types of cancers, such as CLL, the use of non-leukaemic neutrophils that can be purified from the same blood sample as the CLL cells also provides a convenient source of self-reference. Using self-reference in array-CGH reduces the number of CNVs significantly by eliminating constitutional CNVs from the array-CGH genome profile.

52 INCORPORATING BIOLOGICAL INFORMATION INTO THE TUMOR CLASSIFICATION PROCESS

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The incorporation of biological information into the microarray analysis process has become increasingly important. One reason for doing this is to provide a biologically meaningful interpretation of the analysis results. While the incorporation of such information is well documented in terms of detecting differentially expressed genes, less work has been done on extending these ideas into the classification of biologically distinct samples. We describe a method for incorporating gene set information, such as KEGG pathway or Gene Ontology details, into the classification process. This approach utilises principal co-ordinates analysis (PCO) to create a summary of gene set activity, and then uses these summaries as explanatory variables in the classification and prediction process. This procedure is illustrated via application to three publicly available breast cancer data sets.

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