Urate and gout: genetic control, environmental and drug interactions

A/Prof Tony Merriman (Projects A and B)
A/Prof Nicola Dalbeth (Project C)
Prof Lisa Stamp (Project D)

Vision: Improved health outcomes in gout
Hyperuricemia

Diet:
- Purines
- Fructose
- Alcohol

Overproduction

Diuretics

Underexcretion

Hyperuricemia

Overproduction → Underexcretion → Hyperuricemia
Gout is important: The burden of gout

- The voices of South Auckland men:

“It destroyed me, I thought I was going to die I survived but it was so traumatic I asked my wife to put a pillow over my head”

“It feels like the flesh is trying to rip, like it is going to burst, your skin is stretching and it is going to rip because it is stretching too much that is sort of just how it sort of feels.” Lindsay, Dalbeth et al. J Clin Rheumatol 2011

- Work disability and lower quality of life
- Attacks 1-2 days to chronic and ongoing

34%
The burden of gout cont

• Co-morbid with diabetes, chronic kidney and heart disease
  – Hyperuricaemia/gout independently associated with poor metabolic outcomes
  – The basis for this is poorly understood
  – Gout complicates management of other chronic metabolic conditions

• Affects 12% Māori, 14% Pacific, 4% European men. >1/3 older Māori and Pacific men
  – Disproportionate burden on Māori/Pacific communities
  – A biological basis for this disparity (hyperuricaemia from reduced uric acid excretion)

• Prevalence increasing worldwide
  – Historically under-researched
  – Existing urate-lowering therapies often ineffective

• Both an international and NZ problem
Overarching vision
Improved health outcomes in gout

- Generation of knowledge able to be applied to
  - Basis for new therapeutic targets
  - Personalised approaches
  - Reduction of disparities
- The best possible science with the best people internationally
- Forefront of health research?
  - Nationally (gout and genetics) ✓
  - Internationally (in gout) where NZ has an advantage ✓
  - Research is innovative, cutting edge, standard, with clinical excellence
- Dissemination and advocacy important
- Māori and Pacific participation
Vision
Beyond the five years


08/075, 11/075
Application of genetics to the pathogenesis of common, chronic conditions

New genetic-based discovery
Research with clinical focus
Research with environmental focus
Developing clinical application(s)
Dissemination and advocacy

Functional
Clinical and public health application
Reducing disparity

International collaborations
Clinical data base
Infrastructure
Up-skilling
“The genetic approach to gout needs to be adopted if we are to move forward on this highly prevalent disease” (Reviewer 19)

Genetic variants are important in inter-individual variability and in response to environmental exposures

McCarthy et al. NRG 2008
The projects

Projects B/C
Etiology of urate control

Project D
Allopurinol

Project A
Gout GWAS

Hyperuricemia

Overproduction

Diet: Purines, Fructose, Alcohol

Underexcretion

Diuretics


Project A: GWAS in clinically confirmed gout

[Merriman, Dalbeth, Stamp, Brown, Choi]
Project B: Genetic and environmental control of urate
[Merriman, Stahl, Dalbeth, Stamp, Wilcox, Brown, Choi]

- **Objective:** To better understand the etiology of urate control
- **Approach:** Cutting edge analysis of existing data sets (NZ & publicly available)

**Objective 1**

**Objective 2**

**Objective 3**

- **Outcomes:** Therapeutic targets, personalised intervention, public health evidence base, destigmatisation.
Project C: Gene-environment interactions in urate control: intervention studies
[ Dalbeth, Doughty, Stamp, Merriman ]

- **Objective**: Test genetic variants for interaction with environmental risk factors in serum urate regulation in clinical studies

- **Approach**: Innovative research
  - C.1 (Years 1-3): the effects of genetic variants on renal handling of uric acid following oral frusemide
  - C.2 (Years 3-5): Other variants and fructose or diuretic-induced hyperuricaemia

- **Outcomes**:
  - Understanding of renal uric acid handling in Māori and Pacific people
  - Personalised selection of anti-hypertensive medications and lifestyle advice
Project D: Genetics of allopurinol response
[Stamp, Dalbeth, Wright, Roberts, Merriman]
The Programme: more than sum of projects

Personnel
- Analytical staff
- Recruiters

Infrastructure
- BC|SNPmax
- Galaxy
- Recruitment

Cross-project skills
- Re-sequencing (B informing A/D)
- Data analysis
- Bioinformatics

Clinical resources
- NZ dataset
- Public data
- Ardea Biosciences

Information sharing
- All allopurinol genes (D) resequenced in project B
- New urate genes (B) identified in project A
- Project B informs Years 3-5 project C

Basic discovery
- Gout GWAS

Molecular basis
- Fine-mapping gout
- Fine-mapping urate

Environment
- Genetic interactions
  Selection

Therapy
- Clinical intervention; genotype response
- Allopurinol response variants
  Dosing tool incl. Genotype

Improved health outcome
Collaborations are not new; Multi-disciplinary and expert team; Provide expertise and data sets
We can deliver - track record

• Good international standing
  and

• Excellent publication records
  • Merriman, genetics and biochemistry of urate and gout ($H_{\text{Index}}$ 33)
  • Dalbeth, clinical expert ($H_{\text{Index}}$ 29)
  • Stamp, clinical and allopurinol expert ($H_{\text{Index}}$ 25)
  • Choi, leading gout epidemiologist ($H_{\text{Index}}$ 64)
  • Brown, complex disease and GWAS specialist ($H_{\text{Index}}$ 43)
  • Stahl, cutting edge geneticist ($H_{\text{Index}}$ 25)
  and

• Strong funding history
Management and direction

Informed by current Programme

• Continuation of current approach
  – Regular Skype meetings of PIs
  – Regular Skype meetings of project-specific groups
  – Meet face to face at least four times a year (Merriman/Dalbeth/Stamp)

• International group has face to face meetings 2-3 times per year

• Strategic advice from
  – Interaction with international colleagues
  – Maaori Gout Action Group
  – Ngati Porou Hauora Advisory Group
  – Institutional support group to Director

• Continuation of host institutional support (UoO) (eg BC|SNPmax)
Co and closely-related funding
Relevant other collaborations

• This Programme is leveraging international funding
  – NI Choi: US$200K for Project B (support doc #8). NIH R01 AR056291
  – NIH R21 AR065968: Project B, 2 years; 0.05 FTE TM, 0.15 FTE MPG.
  – Commercial: Project D, NZ$55K and (new) Project A >NZ$300K

• National NZ-EU HRC grant (Eurogout)
  – For administrator to facilitate further recruitment and collaboration in Europe (NZ$200K)
  – Relevant for Horizon 2020 urate-focused bid to which Programme will align
    • Led by Leo Joosten (Nijmegen) including Choi/So/Merriman and several others

• Relevant other collaborations
  – Genetics of diabetes and renal disease in Aotearoa NZ (Rinki Murphy/Merriman/Dalbeth/de Zoysa)
  – Pacific Trust Otago Health and Wellbeing in Teenagers (Taumoepeau/Merriman)
  – Mendelian randomisation in urate cause-effect (Merriman/Choi/Dalbeth)
  – Function; with Horsfield (UoO) in zebrafish, Mount (Boston) in transporters, McKinney (UoO) in innate immune
  – Virtual Institute of Statistical Genetics (Wilcox/Merriman/Black)
  – Genetics of Maori and Pacific Health UoO Research Theme led by Merriman/Wilcox
  – Arthritis UoO Research Theme led by Stamp
Addressing of inequalities

• A focus on dissemination

• Māori and Pacific participation integral
  – Participants
  – Investigators
    • Dr Phillip Wilcox.
      – Background in engagement on biotechnologies.
      – Mandated iwi rep for Rakaipaaka Health and ancestry study.
    • Susan Reid
      – Māori students and recruiters
      – Ngati Porou Hauora

• Kaupapa (protocol)
  – Karakia (prayer) for disposal of DNA preparation by-products
  – Kaitiaki (guardianship) agreement on care of genomic data signed with Ngati Porou Hauora
  – Interaction with Maui Hudson HRC-funded Te Mata Ira project on storage and analysis (Wilcox NI)

• Advisory roopu (group)
Knowledge transfer and translation

- Immediate approach to improve outcomes in gout
- Dissemination to primary health care professionals
  - Outing Gout hui
  - Website
- Annual participant newsletter
- Media
- Scientific dissemination

- Advocacy
  - Team members leaders in advocacy groups (MGAG, NZRA, Fizz)
  - Successes include funding of benzbromarone
- Involvement of leading clinicians
  - Aids timely translation to clinical practice
  - Clinical recommendation committees
- Ardea Biosciences (AstraZeneca)
Training

• Young investigators
  - Roberts
  - Wright
  - Wilcox (new to biomedical research)
    - UoO appointment

• Summer studentships

• Postgraduate students
  - Last 5 years 13 completed (1 Māori) (Merriman/Dalbeth/Stamp)
  - Current 11 supervised (2 Pacific) (Merriman/Dalbeth/Stamp)
  - Funded by University scholarships

• Philip Robinson
  - Rheumatologist and PhD (with NI Brown)
  - Supervised by Dalbeth/Merriman/Choi
  - Mendelian randomisation and gout GWAS
Summary

“The questions proposed will have important local benefit, but will also have consequences for the understanding of gout, and its treatment, throughout the world” (Reviewer 19)