Friend or foe?
Parasites, our immune system and the allergic diseases pandemic

Dr Kara Filbey
In 1984 the former Wellington Institute of Cancer and Medical Research was re-named the Malaghan Institute of Medical Research in recognition of Len and Ann Malaghan, who were avid supporters and generous benefactors for the Institute. **2016 is our 50th anniversary!**

We are a registered **charity**, and our pioneering research programmes are reliant on support from the community, corporate partners, contestable scientific grants and trusts. We are around 90 people.

Although situated in Victoria University’s Kelburn campus, we are an **independent institute**. Several of our students are registered with Victoria, and we have collaborators and use facilities within the School of Biological Sciences and the Ferrier Institute (Chemistry).
What we do

gut microbiome
dietary allergy
gut health and food supplements
skin allergy

basic immunology of parasitic and allergic diseases
immunomodulation by helminths
human hookworm vaccine testing

asthma vaccine/immunotherapy

Dr Elizabeth Forbes-Blom
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Immune Cell Biology Programme Leader

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Deputy Director of Research, Vaccine Therapy Programme Leader

Professor Mike Berridge
Cancer Cell Biology Group Leader

cancer vaccine/immunotherapy
- clinical trials
- optimisation

cell biology
About me

BSc Biological Sciences, Immunology (Hons) at Edinburgh University

2009-2013 PhD in Immunoparasitology at Edinburgh University

2014-now Postdoctoral Research Fellow in Le Gros’ lab at Malagahan Institute

Grew up in Oxfordshire, England
Lived in Scotland for 12 years before moving to NZ
Parasites, our immune system and the allergic diseases pandemic

1. History of the Hygiene Hypothesis
2. Parasitic worms
3. The allergic/autoimmune disease pandemic
4. Immune responses
5. Microbiota
6. New therapies & interventions
7. Our research
Hay fever, hygiene, and household size

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Figure 1 Prevalence of hay fever at the age of 16 in two national British birth cohorts born in 1958 and 1970, by birth order and father's social class.
The Hygiene Hypothesis

“These observations could be explained if allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally.

Over the past century declining family size, improved household amenities and higher standards of personal cleanliness have reduced opportunities for cross-infection in young families. This may have resulted in more widespread clinical expression of atopic (allergic) disease.”
The Hygiene Hypothesis

- **'Developing' countries**
  - Large family size
  - Rural homes, livestock
  - Intestinal microflora-variable, transient
  - Low antibiotic use
  - High helminth burden
  - Poor sanitation, high oroaeal burden

- **'Westernized' countries**
  - Small family size
  - Affluent, urban homes
  - Intestinal microflora-stable
  - High antibiotic use
  - Low or absent helminth burden
  - Good sanitation, low oroaeal burden

- **Non-allergic**
- **Allergic disorders** (asthma, eczema and rhinitis)

**Environment**

**Genes**
Rising incidence of allergic disease

Time trend of allergy related disorders (child 0-5 years) referred to one private practice in Australia
Role of urbanisation
Global distribution of allergy and autoimmunity

**ASTHMA AROUND THE WORLD**

Global studies confirm an association with westernized lifestyles

- **UK**: Prevalence is the highest in the world, reaching 18.4% in Scotland and 15.3% in England.
- **CHINA**: Asthma prevalence is 2.1%, slightly below Russia (2.2%) but higher than Indonesia (1.1%).
- **AMERICAS**: Canada (14.1%) and the US (10.9%) have typically high asthma rates; Brazil and Peru also have high rates, whereas Mexico’s rate is only 3.3%.
- **AUSTRALASIA**: New Zealand and Australia, at 15.1% and 14.7%, respectively, have higher prevalence of asthma than outside the UK.
Global distribution of allergy and autoimmunity
Global distribution of allergy and autoimmunity
Global distribution of helminths

WHO, 2011
Helminth = parasitic worm

- Roundworms
- Whipworms
- Hookworms
- Tapeworms
- Filarial worms
- Flatworms (Bilharzia)
Epidemiological studies

- Some studies have shown an inverse correlation with helminth infection and incidence of allergy

- **Deworming** has been shown to correlate with increased response to allergens

- **Maternal helminth infection** has been shown to protect the infant from allergic disease

- However, some worms infections can CAUSE diseases like asthma and eczema, and the confounding effects of other infections, environmental factors and genetics are hard to separate out
The immune system
The immune system

Nonspecific defenses
- 1st line: Skin, mucous membranes, chemicals
- 2nd line: Phagocytosis, complement, interferon, inflammation, fever

Specific defenses
- 3rd line: Lymphocytes, antibodies

Organs of the immune system:
- Tonsils and Adenoids
- Thymus
- Lymph nodes
- Spleen
- Appendix
- Bone marrow
- Lymphatic vessels
Immune responses need to deal with an array of pathogens.
Immune responses need to deal with an array of pathogens.
Helminths are protective in experimental disease models
Helminths are protective in experimental disease models:

- Inflammatory bowel diseases
- Multiple sclerosis
- Type 1 diabetes
- Asthma
- Food allergy
- Arthritis
- Skin graft/organ rejection
How are worms protective?

**Theory 1**

Our immune systems evolved with parasites! One whole arm of the immune system is designed to deal with them (Th2 response).

Without worms, this arm reacts to other things in the environment (often harmless things like dust, pollen, cat hair etc.) which may share similar molecular structures with worm molecules.
How are worms protective?

Theory 2

Some worms can live in their host for decades! How?

Helminths induce regulatory mechanisms to prevent the immune system from killing them.

These mechanisms will also dampen any other immune response going on at the same time eg. allergic or inflammatory reactions.
Importance of early treatment/prevention of allergy
Helminth therapy

Currently 2 species of worm are being trialled in humans with:

- MS
- Crohn’s disease
- Ulcerative colitis
- Coeliac disease
- Psoriasis
- Food allergy (nut)
- Rheumatoid arthritis
- Asthma

Also self-medication is pretty common, and you can buy worms on the internet – not recommended!!!
Helminth therapy - limitations

- **Bacterial/viral/protozoal infections**
  - Reduced immune responses
  - Increased susceptibility
  - Reduced immunopathology

- **Tumors**
  - Reduced anti-tumor immunity?
  - Tumorigenic factors

- **Vaccine immunity**
  - Reduced immune responses
  - Reduced efficacy

- **Allergy/asthma**
  - Reduced incidence
  - Increased atopy on drug cure
  - No change in clinical trials

- **Autoimmunity**
  - Reduced incidence
  - Suppression of pathology with infection

- **Inflammatory Bowel Disease**
  - Reduced incidence
  - Suppression of pathology in clinical trials
Search for the ‘magic molecules’

Currently Under Investigation

**Live “worm therapy”**
e.g. *Trichuris suis* OVA (TSO)
- **Positives**
  i) Already in clinical trials
  ii) Efficacious in humans
  iii) May provide much needed therapy to patients in near future
- **Negatives**
  i) Possibly infectious
  ii) Immunogenic – broad range of worm proteins
  iii) Lacks specificity
  iv) Production requires animal host
  v) Lack of specificity and unwanted effects on normal immunity?

**Helminth E/S**
e.g. *H. polygyrus* E/S
- **Positives**
  i) No parasite infection required
  ii) Delineate modulatory mechanisms
  iii) Identify immunomodulators
- **Negatives**
  i) Possibly immunogenic
  ii) Lacks specificity / unwanted effects
  iii) Low amounts of native proteins
  iv) Production requires animal host

**Defined products**
e.g. *A. viteae* Cystatin & ES-62
- **Positives**
  i) Selection of non-immunogens?
  ii) Recombinant production
  iii) Confounding effects of other E/S products removed
  iv) Characterisation of defined modulatory pathways possible.
- **Negatives**
  i) Possibly immunogenic
  ii) Limited range of target cells

**Modified products or pharmacological mimics**
- **Positives**
  i) Modification possible to reduce immunogenicity and enhance longevity
  ii) Isolation of active peptides or discovery of pharmacological mimics
  iii) Large scale production and reduced costs
- **Negatives**
  i) Limited range of target cells
  - combination of products needed?

*Fig. 1.* Strategy for the development of helminth-derived therapies for clinical application.
Helminths – friend or foe?

Lack of helminths correlates with increased allergic and autoimmune disease

THERAPY
(live worms, worm ‘magic molecules’)
Helminths – friend or foe?

Lack of helminths correlates with increased allergic and autoimmune disease

Helminths can cause debilitating disease for poorest people in the world

THERAPY
(live worms, worm ‘magic molecules’)

ERADICATION
(Vaccines, anti-helminthic drugs)
Helminths can affect immunity to other pathogens
Human hookworm vaccines

Hookworms feed on their host’s blood. The vaccines are designed to block this feeding, and therefore kill the worms.

The most common symptom of hookworm infection is anaemia.
Our helminth research

THERAPY
Suppression of skin inflammation (models of dermatitis)

ERADICATION
Testing human hookworm vaccines against our worms

Co-infection with 2 different worms – how do they affect immunity against each other?
Our helminth research

Suppression of skin inflammation (models of dermatitis)

Co-infection with 2 different worms – how do they affect immunity against each other?

Testing human hookworm vaccines against our worms

How does the immune system recognise and kill invading pathogens?

What happens during allergy, and how can we control it?
The human microbiome project says the human body has 100 trillion microscopic life forms living in it.

You call this living?
Research into the microbiome has sky-rocketed in recent years

Figure 1: Journal articles and INPADOC (International Patent Documentation Center) families, including patent and patent applications referencing the terms microbiome, microbiota, gut flora, or gut microflora.
Although it’s not a new idea

"The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes"

Metchnikoff E
Lactic acid as inhibiting intestinal putrefaction.
The prolongation of life: Optimistic studies
W Heinemann, London
1907:161-183.

Élie Metchnikoff
Changes in the microbiome are associated with illness

<table>
<thead>
<tr>
<th>Aberration</th>
<th>Most relevant observations and potential correlation</th>
</tr>
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<tbody>
<tr>
<td>Crohn’s disease</td>
<td>Diversity decrease – reduced <em>F. prausnitzii</em></td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Diversity decrease – reduced <em>A. muciniphila</em></td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Global signatures – increased <em>Dorea</em> and <em>Ruminococcus</em></td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>Strong diversity decrease – presence of <em>C. difficile</em></td>
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<tr>
<td>Infection</td>
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<tr>
<td>Colorectal cancer</td>
<td>Variation in <em>Bacteroides</em> spp. – increased fusobacteria</td>
</tr>
<tr>
<td>Allergy/atopy</td>
<td>Altered diversity – specific signatures</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Altered composition, notably in small intestine</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>Signature differences</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Signature differences</td>
</tr>
<tr>
<td>Obesity</td>
<td>Specific bacterial ratios (<em>Bacteroidetes/Firmicutes</em>)</td>
</tr>
</tbody>
</table>
Our microbiome is established early in life

Possible interference to the development of a ‘healthy microbiota’
‘Western lifestyle’ and microbiota
Obesity is transferable with microbiota.
Maternal microbiota transfer

Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer

Nature Medicine, 2016
Faecal transplantation

Currently used successfully in patients with *Clostridium difficile*, which can cause severe diarrhoea, and is the cause of thousands of deaths per year (in US).

Although there have been reports of self-treatment, best to do through a hospital so donor faeces can be screened.

Wellington, Christchurch and Auckland hospitals have used this technique.
Manipulation of the microbiota

Characteristic patterns of dysbiosis have been mapped for various diseases – cause or effect?

- Use these profiles as diagnostic tools for certain diseases?
- Supplementation with specific species of beneficial bacteria
- Synthesis of bacterial products that do a specific job
- New antibiotics that avoid our ‘good’ bacteria and just target the harmful ones
- Supplemented foods (pro- and pre-biotics)
In conclusion......

Less of this
In conclusion......

More
of this
In conclusion......

What we need more of...

...is Science.
I'd like to thank my director, my friends and family, and—of course—the writhing mass of gut bacteria inside me. I mean, there's like one or two pints of them in here; their cells outnumber mine! Anyway, this was a real team effort.