

## SUMMARY REPORT

WUN Satellite workshop: 19-20th May 2012, Southampton

### International Inflammation (*in-FLAME*) Network:

Risk factors, pathways and early preventive strategies  
targeting Inflammation as a common antecedent of NCDs

#### Context:

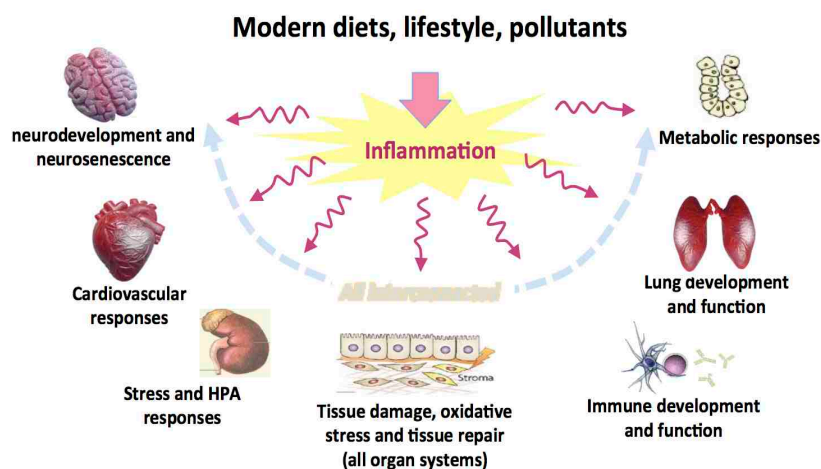
Modern environmental and lifestyle changes are associated with an unprecedented rise in chronic inflammatory noncommunicable diseases (NCDs)<sup>1</sup>. **Inflammation and immune dysregulation are common features of these diverse conditions highlighting a central multisystem role of the immune system<sup>2</sup>. The specific vulnerability of the immune system to recent environmental changes is also reflected in the dramatic increase in virtually all inflammatory disorders and immune diseases.** Furthermore, clinical expression of immune disease within the first year of life together with detection of immune dysregulation at birth, provide clear evidence of very early effects. Environmental risk factors for early immune dysregulation (dietary patterns, environmental pollutants, microbial patterns, and stress) are common risks for many NCDs, highlighting the need for interdisciplinary collaboration focusing on inflammation as a common element and target for NCD prevention (**Figure 1**).

#### Goals:

As part of the WUN Global Public Health Challenge, this WUN Interdisciplinary Research Group (IRG) addresses the risk factors, pathways and strategies to overcome the rising propensity for chronic inflammatory disorders and associated immune dysregulation, with a focus on early effects on the developing immune system. Collaborating institutions will develop **an integrated program of population studies, biological studies and intervention studies** ultimately aimed at preventing inflammation and the burden of subsequent disease.

#### Focus:

This WUN IRG focuses on early life events, early immune modification and interventions in early life. For logistic reasons it will target the most common and earliest manifestations of disease (i.e. allergic disease), while also collecting data on other outcomes and building capacity to assess multi-system effects (i.e. neurodevelopment, metabolic and cardiovascular function).



**Figure 1: Inflammation: a common element in most NCDs, suggests a central role of the immune system**

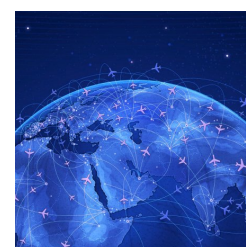
<sup>1</sup> The most common NCD's include allergic conditions, asthma and chronic lung disease, autoimmune disorders (type 1 diabetes, chronic inflammatory bowel disease, thyroiditis, rheumatoid disease) obesity, cardiovascular and metabolic diseases, cancer and neurodegenerative conditions.

<sup>2</sup> Renz H, et al.. Gene-environment interactions in chronic inflammatory disease. Nature Immunology 2011; 12:273-7

**Specific aims of the initial meeting:**

The aims of the inaugural meeting were:

1. To develop multicenter collaborative projects, for mutual and collective benefit.
2. To initiate this process by documenting and developing the capacity of the Network.
  - a. Each centre will map assets (current or proposed cohorts, trials, bio-repositories, expertise, infrastructure, industry links), so that
  - b. synergies, capabilities and common and overlapping goals can be identified.
3. To develop new opportunities based on complementary strengths and common interests.
4. To build in multisystem, interdisciplinary components that value-add to planned and/or existing studies.
5. To establish opportunities for early career researchers (ECR) and research students across the Network.
6. To develop funding avenues, industry partnerships and interactions with other networks and organisations to facilitate research activities.



**Participating Universities (WUN *in-FLAME* Network Centres:**

<b>WUN Partners</b>	
Chinese University Hong Kong	Prof Gary Wong
University of Cape Town	Dr Michael Levin, (Prof Heather Zar) Dr Claudia Gray
University of Southampton	Prof Stephen Holgate, Prof Mark Hanson, Prof Philip Calder, Dr Paul Noakes, Dr Tony Williams, Prof John Holloway, Dr Judith Holloway, Prof. Graham Roberts, Dr Quiza Zolkipli, Prof Geraldine Clough, Dr Louise Michaelis
University of Sydney	Prof Dianne Campbell Prof John Sinn
University of Western Australia	Prof Susan Prescott, Nina D’Vaz, Dr Suzanne Meldrum, Dr Rae Chi Huang, (Prof Karen Simmer)
<b>Plus-WUN Partners</b>	
World Allergy Organisation (President)	Prof Ruby Pawankar
University of Melbourne	Prof Katie Allen, Dr Richard Saffery, Dr David Martino
Université de Nice Sophia-Antipolis, France	Prof Valerie Verhasselt, A/Prof Meri Tulic
University of Marburg, Germany	Prof Harald Renz, Dr Dorthe Kesper
University of Umea, Sweden	Dr Christina (Tina) West
Linköping University, Sweden	Dr Maria Jenmalm
Swansea University, UK	Dr Cathy Thornton
University of Adelaide	Prof Julie Owens, A/Prof Vicki Clifton, (Prof A. Ferrante, Maria Makrides)
Aga Khan University Hospital, Kenya	Dr Rose Kamenwa
PNG Institute of Medical Research / Telethon Institute for Child Health Research	Dr Anita Van Den Biggelaar

# SUMMARY OF PROGRAM, DISCUSSIONS AND OUTCOMES

## DAY 1: Assets, synergies and opportunities (Saturday 19th May):

### SESSION ONE - SETTING THE SCENE: THE GOALS AND SCOPE OF THE WORKSHOP

#### **1.1 WELCOME:**

*Prof Susan Prescott*

The workshop chair and convener welcomed delegates and briefly explained the context, goals and format of the meeting. This included the structure and purpose of WUN (for new members) and the relationship of this initiative to the Global Health Challenge (which has a more public health focus). The role of this IRG is to study the central role of the immune system in the rise in 'modern' disease as evidenced by:

- Vulnerability to environmental changes
- Very early life effects
- Long term multi-system influences

An ultimate goal of the network is to assist in the prevention of NCDs by targeting the underlying antecedent inflammation and immune dysregulation that is common to many conditions. It was stated that, while allergy is one of the most common and earliest NCDs (albeit often overlooked) that the network should aim to keep a broad focus on multi-system outcomes, and a broad range of NCDs.

This network (*in-FLAME*) has a different but complementary focus to the Public Health arm of the WUN Global Health Challenges on NCD prevention;

#### **The key differences and novel perspectives include:**

- The specific focus on the immune system
- NCDs that 1st manifest in childhood (such as allergy and asthma): *This gives an expanded range of health outcomes than those often considered in the NCD agenda.*
- An advantage is that disease outcomes are evident very early in life and that both observational and intervention studies targeting these earlier outcomes can be addressed in a much shorter time frame than many other NCDs, some of which are not evident until adult life.
- Another important element of this IRG is the inter-disciplinary approach, involving researchers from metabolic, cardiovascular, respiratory and neurodevelopmental, neonatal and maternal health disciplines, in addition to those specifically studying immune diseases such as allergy and autoimmunity.

**The key synergies with the public health agenda.** It is intended that this network will interact and complement the public health domains of the Global Health Challenge, contributing to

- Understanding underlying biological mechanisms,
- Identification of common biological pathways (multi-system effects of modern environmental exposures), which may in turn lead to
- More effective interventions, and a better knowledge base for
- Informing translation and policy

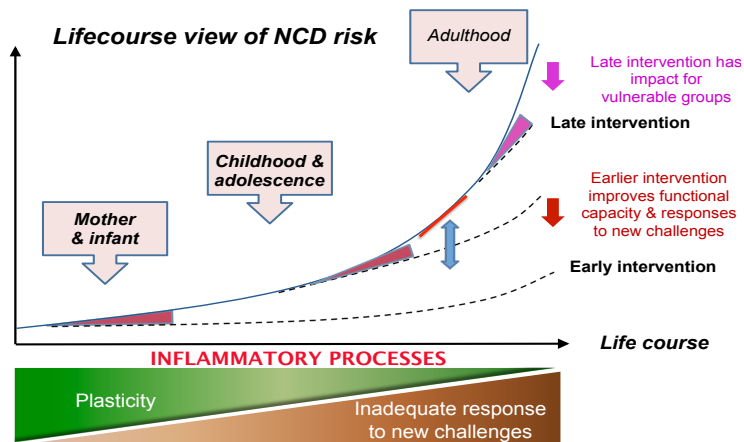
#### **1.2 THE WUN GLOBAL PUBLIC HEALTH CHALLENGE:**

*Prof Mark Hanson*

As leader of the WUN Global Health Challenge, and Chair of the international DOHaD Society, Prof Mark Hanson gave an illuminating overview of the initiative, and the importance of promoting NCD prevention through a life course approach. He highlighted the specific strengths and focus of research at Southampton University, as one of the key proponents of the early life origins of health and disease. He also highlighted the specific vision of Human Development and Health through DOHaD activities, including

- Translation of discoveries in basic sciences into improved health,
- Development of successful interventions for mothers and babies around the world,

- Working relationships between DOHaD researchers and the World Health Organisation, the United Nations and other international organisations
- Maintaining a leading role in WUN Global Health initiatives



**Figure 2:**  
A life-course approach to NCD: risk factors and prevention Strategies

Although late interventions may be effective in vulnerable groups, earlier interventions (when plasticity is greater) have much greater potential to enhance the longer-term capacity to respond to environmental challenges on a much larger scale, and improve long-term population health (Figure 2). Prof Hanson also identified ‘inflammatory processes’ as a key element, as potentially a cause and a consequence of inadequate (or inappropriate) responses to new challenges.

Prof Hansen highlighted that the research landscape is changing and that we are entering an age of complexity. None of these complex modern diseases will have simple pharmaceutical solutions. More than ever, we need to bring together diverse disciplines to address the challenges of modern environmental effects on human health.

### 1.3: INFLAMMATION AS A COMMON RISK FACTOR FOR NCD. Prof Susan Prescott,

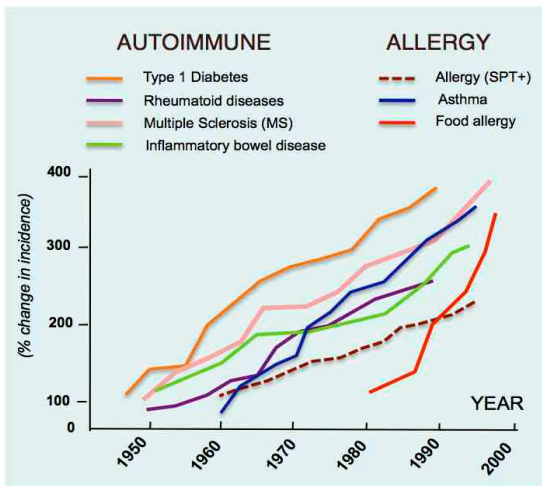
The context for our discussions is the dramatic rise in a wide range of NCDs over the last 50 years:

- |                               |             |
|-------------------------------|-------------|
| - Cardiovascular disease      | - Obesity   |
| - Metabolic disease (NIDDM)   | - COPD      |
| - Psychiatric disorders       | - Cancer    |
| - Chronic liver/renal disease | - Asthma    |
| - (Autoimmunity)              | - (Allergy) |

Now rising in developing countries, the United Nations has identified this as a major global threat. All of these conditions are linked with modern lifestyle changes, and many are also linked with inflammation. There is a persistent focus on adult interventions, and a key aim of the WUN Global Health Challenge is to promote a ‘life course approach’ with a specific focus on early life origins of health and disease.

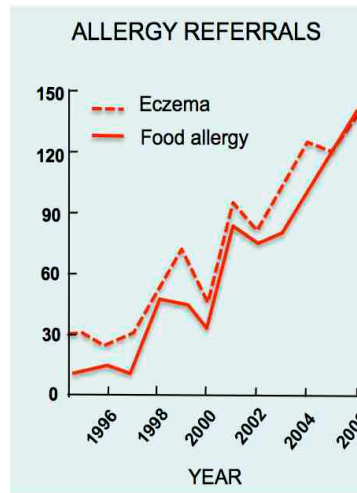
However, the dominant focus of NCD discussion remains cardiovascular disease, obesity, metabolic dysregulation, cancer and COPD. The dramatic rise in virtually all immune diseases (allergic and autoimmune conditions) over the same period indicates the immune system is specifically vulnerable to the effects of modern environmental changes (Figure 3). While these are diverse conditions, the common element to all of these is impaired immune regulation. Although immune diseases (such as allergy) are arguably among the most common NCDs (affecting 30-40% of the world’s population) and potentially life threatening, they are rarely included in the NCD general agenda context. Allergic disease is also the earliest NCD to appear, frequently presenting in the first months of life. The dramatic rise in inflammatory diseases (such as eczema and food allergy) in the last decade (Figures 4 and 5) indicates the environmental effects on the immune system occur very early in development.

Figure 3:



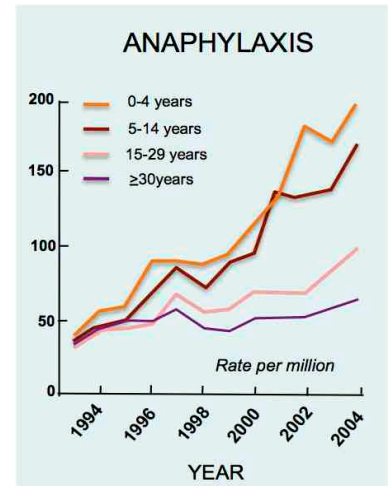
Adapted from Bach NEJM 2002

Figure 4:



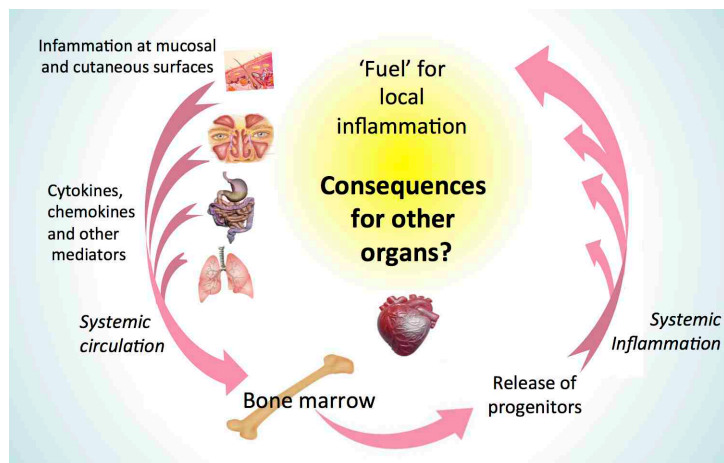
Adapted from Mullins MJA 2007

Figure 5:



This has even greater implications for developing regions undergoing rapid economic transition, such as China. There is evidence that Asian races may be more susceptible to “western” environmental changes than non-Asians. This is seen for cardio metabolic risk, but also for allergic disease, with evidence of higher allergy rates in Asians living in ‘western’ environments, such as Australia, compared with Caucasians. We may therefore anticipate an even greater ‘epidemic’ to come! This also raised questions regarding the longer-term implications for the generation currently experiencing this ‘epidemic of early inflammation’ (Figure 6). It is not clear how this will influence their risk of other later onset NCDs.

Figure 6:  
Allergic inflammation has ‘systemic’ effects: long term implications for other organs disease



The idea of this IRG (the in-FLAME Network) is to promote this in the NCD agenda, and to explore factors underlying inflammation as a common risk factor for many NCDs. As the most common and earliest presentation of immune dysregulation, allergy is a logical early target. But we also need to promote examination of other health outcomes where possible (e.g. metabolic, cardiovascular and neurodevelopmental outcomes through collaborative links) when designing new studies or following up existing cohorts. It was agreed that is happening anyway in an ad hoc way, but it will be good to formalise and promote awareness of the significance of the immune system outside our specific fields.

In summary, modern lifestyle changes are having early effects on the developing immune system which may have implications for many NCDs, in which inflammation appears to be a common risk factor. It is important to take a coordinated inter-disciplinary approach to understanding the common risk factors as these are likely to lead to common solutions.



## **1.4 PRACTICAL STRATEGIES TO DEVELOPING AND FACILITATING OUR NEW NETWORK:**

**Prof Stephen Holgate**

Prof Holgate was very supportive of this new initiative and also highlighted the importance of interdisciplinary, international collaborations to address the global health crisis.

As a highly respected and very experienced international leader in his field, Prof Holgate gave a number of examples of networks he had been involved with over the decades.

From his experience leading and participating in networks he was able to share his “20 points for success”, which resonated with all those present:



### **What makes a successful network?**

1. Having aims that all agree upon
2. Having leadership that embraces the qualities of equality, diversity and openness
3. Ensuring that objectives are realistic within a set time-frame
4. Capturing the richness of expertise of each member
5. Recognising that each member has something to offer and ensuring “buy-in”. A selfless approach is the most successful one in this type of activity
6. Ensure that the technologies are available within the participants appropriate to the Network’s ambition
7. Setting tasks to be achieved by defined time-periods (milestones)
8. Try not to be too ambitious: start with limited aims and build from this.
9. Consider involving industry early in the evolution of the consortium
10. Ensure that the technology and innovation office of each university is aware of your consortium. If necessary work towards a common “agreement”
11. Strong management and governance is crucial to success. This should engage all partners and seek a model that best suits the objectives
12. Regular contact is crucial. This needs both electronic and face-to-face interactions
13. Consider involving patient organisations e.g. charities. The topic will be of great interest to them. Also, involve national and international professional societies. Engage them early on!
14. Develop a website for ease of communication and for creation of a message board
15. Be prepared to scale back the level of ambition if problems arise
16. Ensure that SOPs are in place for clinical and physiological/laboratory measures for phenotyping, data curation and processing of biological samples e.g. Wellcome Trust MRC Biobank facility.
17. If appropriate, use well established technology platforms to deliver novel outputs e.g. the European Molecular Biology Laboratories (EMBL). Decide upon a single site to take responsibility for a specific item
18. Once established consider new partners to add value
19. Make regular presentations at professional societies and related fora
20. No one said this is easy so don’t give up even if things get difficult!!

This was welcomed by all and these was unanimous agreement that we should adopt these philosophies in our planning and in our relationships into the future



The success of the network depends on developing strong links with partner organisations that have mutual or overlapping interests. Our first proposed partnership is with the **World Allergy Organisation** (WAO) and we were very pleased to welcome the President to the WAO, Prof Ruby Pawankar (based in Tokyo, Japan), who explained the role, functions and agenda of WAO to the interdisciplinary members.

**About WAO:** Founded in 1951, WAO is an international umbrella organisation whose members consist of 89 regional and national allergology and clinical immunology societies from around the world. By collaborating with member societies, WAO provides direct educational outreach programs, symposia and lectureships to members in nearly 100 countries around the globe. WAO is a member of the Council for International Organisations of Medical Science (CIOMS) and has a working relationship with the World Health Organisation (WHO).

With around 30-40% of the world population now being affected by one or more allergic conditions, and with over 250 000 avoidable deaths from allergic diseases each year, WAO has recently published The White Book on Allergy to promote awareness of allergic diseases as a global public health concern.

[http://www.worldallergy.org/definingthespecialty/white\\_book.php](http://www.worldallergy.org/definingthespecialty/white_book.php)

WAO has successfully organised 21 major congresses. WAO also sponsors scientific symposia in developing areas throughout the world and jointly sponsors postgraduate programs on allergy and clinical immunology during professional, non-allergy association congresses. WAO is expanding its purview in a direct effort to bring together the member allergists and clinical immunologists who are engaged in research and/or practice throughout the world. The organisation provides advice and active support to member societies with the mission of building a global alliance of allergy societies, which will advance excellence in clinical care, research, education and training in allergy. WAO also welcomes WAO Junior Members. To assure the future of the specialty of Allergy and Clinical Immunology, the World Allergy Organisation (WAO) wants to support and encourage young clinicians and scientists in their professional careers.

#### **Developing partner projects:**

The WUN *in-FLAME* has strong interests in the role of early nutritional practices in the future risk of a number of chronic inflammatory processes that lead to NCDs. A partnership project utilizing the WAO international network, provides a logical avenue to gather basic data from the 89 member societies around the globe, on nutritional practices such as

- Uptake and duration of breastfeeding,
- Age and pattern of starting complementary feeding,
- Patterns of specific nutritional deficiencies,
- Use of specific nutritional supplements
- Estimated prevalence (and changes in prevalence) of early inflammatory disease (with a specific focus on food allergy and eczema)
- Patterns of presentation
- Health care services and areas of need

#### **Draft 'Food and Nutrition' Survey developed:**

A working group developed potential questionnaires

- 1) for the member societies to complete, and
- 2) for the individual members of those societies to complete.

These questionnaires were tabled for feedback from the wider group. Some amendments were suggested. A revised version will be tabled at the WAO Special Committee for Food allergy, for additional comment before setting this into the implementation stage (will be administered on-line). The aim is to launch this for data collection in the next few months.

\* \* \*

At the end of this session it was agreed that we will develop further relationships of this nature with other International Organisations such as WAO into the future (including nutritional societies and other discipline specific societies).

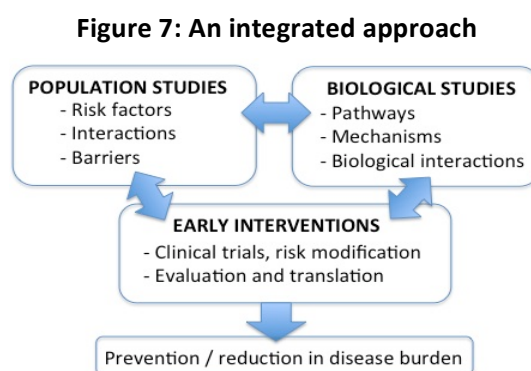
## SESSION TWO – MAPPING ASSETS, CAPABILITIES AND POTENTIAL

The purpose of this session was to facilitate new collaborations by developing a register of assets and skills across the network. This was to better identify synergies, capabilities and common goals, by mapping current (or proposed) cohorts, trials, bio-repositories, expertise, infrastructure, industry links that may facilitate the process for mutual and collective benefit.

We structured this session into 3 domains:

- 1) population studies and cohorts
- 2) intervention studies and
- 3) laboratory and mechanistic studies.

as noted in **Figure 7**



It was acknowledged that most centres engage in more than one of these overlapping activities, the presenters in each session were selected based on key strength in that domain, but others were invited to contribute to discussions in each domain. Prior to the meeting, each participating centre completed a survey (spread sheet), which summarised their activities and expertise across each of these domains. This was tabled at the meeting for ongoing reference. Where possible ECR (early career researchers) were encouraged to present their centres and become involved in planning and discussions.

### 2.1 MAPPING POPULATION STUDIES in the network

**Chair: Prof Dianne Campbell**

**Rapporteur: Dr Tony Williams**

Details of the cohorts of each centre are provided in a separate document. Representatives of each centre gave a summary of their key activities with regards to cohort studies and population studies as follows:

University of Melbourne	Prof Katie Allen, Dr David Martino (Dr Richard Saffery)
University of Cape Town	Dr Michael Levin, Dr Claudia Gray
Chinese University Hong Kong	Prof Gary Wong
University of Southampton	Prof John Holloway, Prof Mark Hanson, Prof Graham Roberts
University of Adelaide	Prof Julie Owens, A/Prof Vicki Clifton
Papua New Guinea Inst. Med Research/ TICHR	Dr Anita Van Den Biggelaar
University of Western Australia	Dr Rae Chi Huang

#### ***Overview of discussions:***

The **University of Melbourne** (represented by **Katie Allen** and **David Martino**) are leading a proposed Clinical Centre of Excellence (Food Allergy and Food induced Immune disorder; Allen CIA) with integration



in Science Park (Parkville Precinct and CSIRO). This will allow broad, deep analysis of the cohorts (>7000 participants), with data links to State and Federal clinical and demographic repositories. They highlighted their very strong access to biostatistics, bioinformatics and links to epigenetics and basic sciences. There was a strong focus on the need for accurate clinical phenotyping and definitions (as developed by this group) and the need for standardisation across the network. They discussed their world-class study of food allergy prevalence (*'Healthnuts'*).

The **Chinese University Hong Kong (CUHK)** (represented by **Gary Wong**) also has multiple cohort sampling from SE china and Hong Kong with associated 'biobanks'. There was considerable interest in difference in allergy and sensitisation prevalence between rural versus urban settings. Those working in other regions were particularly interested in migrational effects of food allergy prevalence. CUHK has strong Industry links. **Both Melbourne and Hong Kong** have strong links with European cohort studies (**Europevall**) and outlined the newly proposed cohort collections from 1-3yr olds recruited from crèche environments.

Michael Levin, from **University of Cape Town** (Heather Zar and Claudia Gray, apologies) outlined the long-standing activities of UCT as a centre of research excellence since 1970's, with early life urban rural comparisons and participation in the ISAAC studies. He highlighted the changing prevalence of asthma in the last 35 years, with greater increase in rural regions (previously 20x less likely to have asthma, and now only 2x less likely to have asthma). There has been an anecdotal increase in food allergy but a lack of good data. He outlined a new study of immediate food allergy in South Africa using a methodology similar to the Healthnuts study. This study will determine the prevalence of challenge proven food allergy, assess differences correlated with socioeconomic class and/or ethnicity, determine local cut-off levels of skin tests and ImmunoCAP tests and their differences according to socioeconomic class and/or ethnicity, and finally assess correlations with environmental and biochemical factors. **The study group is actively seeking collaborators for laboratory investigations and/or human resource injection.** This is an opportunity to collaborate with the *Healthnuts* team (Melbourne) to standardise outcome measures. The groups also identified potential international links through opportunities to compare microbiome across centres.

The **University of Southampton** (represented by **John Holloway**) has a considerable strength in their many cohort studies. This includes mature cohorts (n=1450 from birth to 23 years of age representative of South of England population) and maternal cohorts (n=12,500) with follow on studies of offspring. Third generation birth cohorts provide further opportunity for analysis of epigenetic modifiers/drivers. They are also engaged as a centre in the European 'Europevall' cohort engagement (through EAACI) and in MAVIDOS (intervention study of vitamin D supplementation in pregnancy).

**University of Adelaide (Julie Owens and Vicki Clifton)** outlined a wide range of population studies and interventional cohort studies examining a range of different outcomes including, adiposity and weight gain, asthma and atopy, preterm labour, and neurodevelopment. They have a strong interest in the effects of nutritional patterns in pregnancy, including patterns of maternal weight gain, gestational diabetes, dietary allergen exposure, folate, and polyunsaturated fatty acids (PUFA) on a range of these outcomes. This centre is engaged in a number of dietary intervention studies. Other factors of interest include the effects of ART (assisted reproductive technologies) and stress. Sex-specific differences in fetal responses to these various endogenous and environmental exposures are a particular interest. Adelaide offer stable populations with opportunity for long term follow-up assessments.

The **University of Western Australia** (represented by **Rae Chi Huang, Suzanne Meldrum and Susan Prescott**) has a number of major cohort studies. There is also strong data linkage to State and Federal clinical and demographic repositories. WA history. It is one of the world's first multi-disciplinary DOHaD research cohorts. On this and other smaller cohorts there is good assimilation of biological, biometric and social and demographic data into evolving data analysis and collection. This informs a number of nutritional intervention studies that are active or in preparation (see separate document for full details). Another new cohort, GADS (Longitudinal Childhood Growth and Development) was also discussed. Other groups (**Tina West, University of Umea**) noted new cohort studies were being planned in Sweden.

### **Synergies and key points arising:**

In his summary as rapporteur, Prof Tony Williams highlighted the “**Complementarity and useful replication**” of the collective activities but also the “**need for harmonisation and standardisation**”. We have a wealth of experience and significant cohort assets with biobanks. This will provide the basis for developing basic questions with achievable outcomes in the shorter term, and to use this for more long-term goals.

Some of the clear synergies and strengths were noted through these discussions, including that:

- Multicentre collaborations across diverse settings will facilitate investigation of environmental ‘extremes’ and migration studies,
- Developing regions in transition provide opportunities for studying environmental change (e.g. Africa and Asia where rapid changes are occurring *now*).
- Integration of our data makes the potential of this network much greater than the sum of its parts,
- The network will enable sharing of samples collected (ie stool, cord blood, placenta, breast milk), and a consolidated technical approach and shared return of data,
- There was a common interest in the role of early nutrition (mother and infant) across all network sites,
- Several sites are running/planning studies of food allergy prevalence (as an early presentation of inflammation) providing opportunities to share protocols and standardise methodologies, and outcomes.

### **Action Points**

- ⇒ **Population Study theme leaders** were appointed – **Gary Wong and Katie Allen** (with assistance from **Rae Chi Huang, Mike Levin** and all other interested parties): will oversee and coordinate the activities relating to population and cohort studies
- ⇒ **Plan to review cohort inventory:** further reflection on opportunities on the existing cohorts
- ⇒ **Continue to promote the philosophy of building in multisystem outcomes in all new studies** (e.g. for allergy /neurodevelopment/metabolic/other systems)
- ⇒ **Work towards standardising and optimizing protocols** across the network
  - for measuring environmental exposures
  - For measuring outcomes (definition, criteria, optimal time points etc.)
- ⇒ **Inventory of biostorage** across the network
- ⇒ **Specific Projects suggested** (in association with the “Mechanistic theme”
  - Comparison of early microbiome signatures from different continents (populations from diverse environments represented through the network)
  - Microbiome in migrant populations versus non-migrant population (and according to phenotype (i.e. food allergy)
  - Other possible avenues include comparisons of breast milk (and possibly placenta samples)
  - Opportunity for epigenetic studies in buccal swabs of African cohorts?
- ⇒ **Other goals**
  - Add new centres to network (China, India, Singapore, Canada, USA suggested initially through other collaborations). Noted that we currently do not have collaborators in South America.

## **2.2 INTERVENTION STUDIES**

**Chair:** Dr Rae Chi Huang  
**Rapporteur:** Prof Katie Allen

The following groups summarised the intervention studies occurring in their respective centres. There was a strong focus on nutritional and other dietary interventions.

University of Western Australia	Prof Susan. Prescott, Dr Nina D’Vaz
University of Southampton	Prof J. Holloway, Prof P.Calder, Prof G Roberts, Prof G Clough
University of Umea, Sweden	Dr Christina West
University of Sydney	Prof Dianne Campbell Prof John Sinn

Full details of the intervention studies are noted on the detailed asset register (separate document) completed by each centre.

### **Synergies and key points arising:**

In her summary as rapporteur Prof Katie Allen noted that:

***“nutritional modulation is a common theme; with many smaller studies, much overlap, but that these are not standardised and few are multicentre”***

The areas of shared interest across multiple sites included interventions with

- LC-PUFA (as fish oil capsules or fish)– Southampton, Perth, Adelaide
- Probiotics (Sweden, Perth, Swansea, Melbourne)
- Vitamin D (Perth and Southampton)
- Infant feeding studies (timing of allergenic foods versus allergy: UK, Perth, Adelaide, Sydney, Perth)

**LC PUFA studies** provided the best example of where multi-system outcomes are examined (such as allergy, immune development, growth and adiposity, neurodevelopment, cardio-metabolic outcomes).

**Vitamin D studies** also examine multi-system outcomes (allergy, immune function, cardio-metabolic, bone). While **allergen-feeding studies** are less well suited to this, it was noted that the risk of obesity is often cited as a concern with earlier introduction of complementary feeding, and is an important outcome to consider in this light.

**Synergies between allergen feeding studies** (different but complementary trials across several network sites) noted (and part of an EU 7<sup>th</sup> Framework multicenter collaboration, known as iFAAM (lead by Professor **Clare Mills**), who was also invited to join this (in-FLAME) network.

Future ‘ideal’ studies were discussed (see below) that will be informed by cohort and current intervention studies. We need to move away from ‘single nutrient’ approach, and address the greater complexity of food and lifestyle.

### **Action Points**

- ⇒ **Intervention Study theme leaders** were appointed – **Philip Calder** and **Dianne Campbell** with participation from the rest of the group.
- ⇒ Review trial inventory: reflect further on opportunities on the existing cohorts
- ⇒ Long term goal: to plan the ‘perfect’ multicentre study: this would consist of a ‘multifaceted interventions’ with ‘multiple outcomes’ (i.e. an ‘ideal’ lifestyle study that would include ‘back to basics’ aiming to restore more traditional nutritional patterns and lifestyle behaviours, and examining effects on ‘all’ aspects of health). This intervention would be aimed at pregnancy, lactation and infancy (ideally maternal health at conception although this might not be feasible).
- ⇒ Our multicentre capacity would allow for genetic & environmental diversity.
- ⇒ This will also rely on the work of the ‘Population theme’ and ‘Mechanistic theme’ who will be developing standardised measure and SOP for measuring exposures and outcomes.)
- ⇒ Other studies to consider: hydrolysed foods?
- ⇒ Need to engage industry in our discussions. It is promising that several industry leaders in the maternal and infant nutrition are now focusing on nutrition and lifestyle in ‘the first 1000 days’ (i.e. with a new focus on pregnancy and maternal health from conception).

## 2.3 MECHANISTIC STUDIES

Chair: **Dr David Martino**

Rapporteur: **Dr Tina West**

Biological studies provide a crucial platform for both population cohort studies and intervention studies. All groups with biological studies contributed to this discussion, with specific presentations from the following:

Swansea University	Dr Cathy Thornton
University of Marburg, Germany	Prof Harald Renz, Dr D. Kesper
Université de Nice Sophia-Antipolis, France and University of Western Australia	Prof Meri Tulic Prof Valerie Verhasselt
University of Southampton	Dr Paul Noakes, Prof Geraldine Clough, Dr Louisa Michaelis, Dr Quiza Zolkipli

### Summary of discussions:

At the conclusion of discussion, rapporteur **Dr Tina West** summarised the broad and diverse skill set and technologies available collectively through the network. Here also, cross-disciplinary links are invaluable. **Details of specific technology platforms and expertise are outlined in the separate asset register** (but include genetics, epigenetics, genomics, cell biology, metabolic studies, endothelial studies, and immune function studies as well as links to microbiome pyrosequencing technologies). Many groups have strong track records in mechanistic studies with these already integrated into cohort studies and intervention studies in many cases. Some groups have useful links to new technologies (nano-technology as an example).

### Challenges:

It was recognised that we face a number of challenges, such as the growing complexity of datasets, the increasing need for niche expertise, and the significant (growing) costs of biological studies. It was recognised that there will be an increasing need for high throughput technologies. To be competitive our network needs to develop new collaborators with greater expertise in bioinformatics and systems biology, proteomics, and metabolomics.

### Action Points

- ⇒ Biological Study theme leaders were appointed – **David Martino, Valerie Verhasselt, and Cathy Thornton** with participation from the rest of the group. **Ruby Pawankar** also expressed a specific interest in contributing to this group.
- ⇒ Refine the inventory of technologies based on current list
- ⇒ To work with the 'Intervention' and 'Cohort' groups to review the 'Biological' inventory, and further consider the opportunities that this offers.
- ⇒ To define and standardise methods across the network, including quality control programs for cooperative studies (particularly for new studies). This will include
  - Better measures of exposure (i.e. nutrition)
  - Better measures of biological outcomes
- ⇒ **Scope current opportunities:** review cohort /intervention study bio-repositories for opportunities
  - Specific initial study: to collaborate with the 'Population theme' in multicenter microbiome studies
  - To define and develop other potential cooperative strategies (present proposal at the next meeting, Dec 2012).
- ⇒ Identify key new collaborators to participate in the network.

### Longer term goals:

- ⇒ To develop better predictive biomarkers (for intervention studies)
- ⇒ The results from mechanistic studies ultimately to be used for improving clinical diagnostics/to be further evaluated in intervention studies

## REVIEW AND REFLECTION (DAY 1)

Chairs: Prof John Holloway / Prof Susan Prescott

It was extremely positive to see a resounding theme of openness and collaboration between all the participants, and a strong vision of mutual and collective benefit. There is a high level of enthusiasm for the network, the concepts and the common goals. The wide international membership, including several developing regions undergoing rapid environmental transition (e.g. China and Africa), gives this network some unique opportunities.

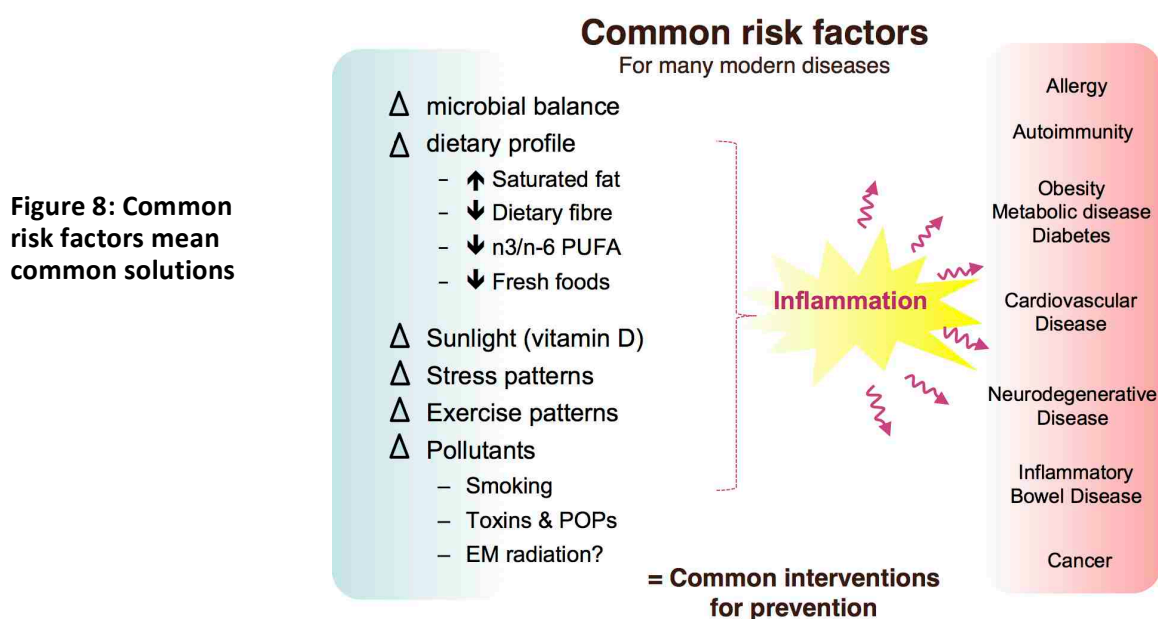
### Action Points

- ⇒ With a clear and unanimous conviction that this network should move forward, we will now formally develop our **governance structure** and **terms of reference** (Susan Prescott)
- ⇒ While there is already rich and diverse expertise, we need to actively **seek out new partnerships** (with academia, community, expert societies, and industry). This will be an ongoing process
- ⇒ All agreed the need for **ongoing regular contact**, capitalizing on other meetings and conferences where possible (see later)
- ⇒ We need to **develop our identity**. Suggested opportunities included
  - A name and logo (still in development but '*inFLAME*' is the currently agreed name.
  - Conference presentations: 'badged sessions'
  - 'Positions statements' or 'expert opinion/conference proceedings papers' from our network
  - Expand and widen membership and partnerships.

## DAY 2: pathways to prevention (Sunday 20th May)

### SESSION 3: SPECIFIC RISK FACTORS

Having set the scene on Day 1 by identifying our capacities, common interests and collective assets, the purpose of Day 2 was to shift the focus to specific risk factors for NCDs. At the outset Susan Prescott restated the need to focus on the multi-system consequences of modern environmental changes (i.e. similar risk factors for many NCDs implies common solutions), and the essential need for greater interdisciplinary collaboration to address the rising global burden of NCDs (**Figure 8**).

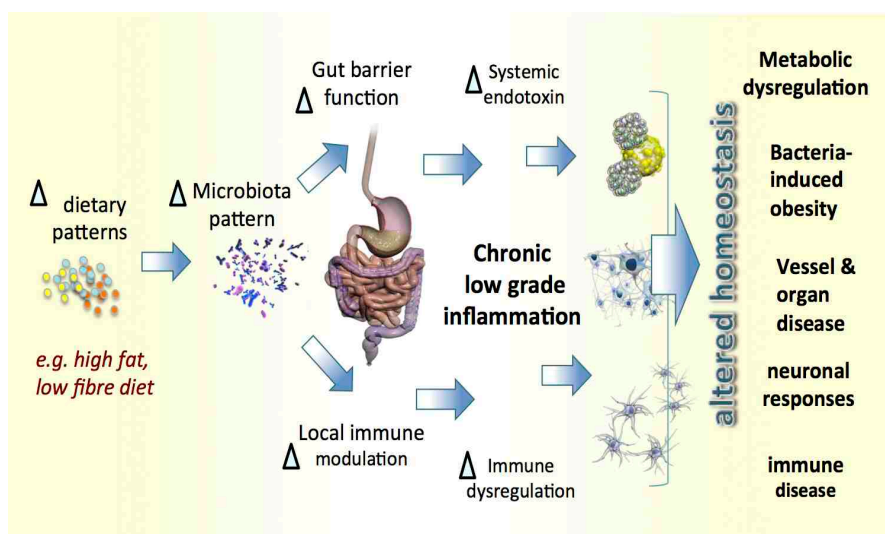


**Tina West** gave an overview of the state of play in the field of ‘microbiome’ studies with a particular emphasis on the gut flora in relation to immune health. This was followed by a general discussion, which focused on a number of key issues:

- The gut microbiome as a key measure of nutritional patterns
- The effects of the microbiome on many aspects of health including
  - Obesity and metabolic regulation,
  - Allergy, autoimmunity and other immune disease
  - Cardiovascular disease risk
  - Neuropsychiatric outcomes
  - Potentially other aspects of health

Again highlighting the need for multi-system outcomes measures in microbial studies and intervention studies using microbial products.

**Figure 9: The need to study multi-system effects of the microbiome in a more integrated way**



**Karen Simmer** (UWA) who could not be present at the meeting has since indicated that they are well positioned to contribute to microbiome studies, as they are currently comparing probiotics vs placebo in a RCT of very preterm infants (with a significant stool repository).

In her summation, as rapporteur **Cathy Thornton** noted that a key strength of the network was the archived material (e.g. stool samples) we have collected across a number of diverse international settings. This could form the basis of a ‘quick start’ project that might examine both temporal changes (in the last 10-15yr) and between centre differences (also in relationship to clinical phenotype). It was also noted that there is still a lack of understanding of ‘normal ranges’ in terms of both diversity and profile patterns (i.e. those most conducive to health).

**Specific comment and suggestions made included:**

- Temporal patterns / serial sampling
- Opportunities to investigate the parallel development of microbiome and immune system
- Opportunities to make comparison by phenotype “multi-system health”; stratify around disease
- Nested studies: extremes of birth weight
- Dietary ‘patterns’: principle component analysis
- Role of genotyping? (increasing complexity)
- Logistic issues: optimal techniques versus cost, funding challenges and access to technology and bioinformatics.



### Action Points

- ⇒ A '**Microbiome Working Group**' was appointed – this overlaps with population, intervention and biological theme groups and currently includes Tina West, Meri Tulic, Paul Noakes, Dorthe Kesper, Cathy Thornton, Katie Allen and Gary Wong. Everyone else was welcomed.
- ⇒ This group held a separate meeting over lunch to discuss plans (populations), including to
  - Scope what we have 'in the bank' across centres
  - Focus on samples collected in first 2 months in breastfed infants
- ⇒ The group also planned to have a follow-up meeting in Geneva (EAACI) in June
- ⇒ Their short term goal is to define enterotypes, and define 'diversity index'
- ⇒ Then in the longer term: work towards prospective (future) studies
- ⇒ Considering industry links and fellowships (EMBL fellowships?)

### 3.2 NUTRITIONAL PATTERNS

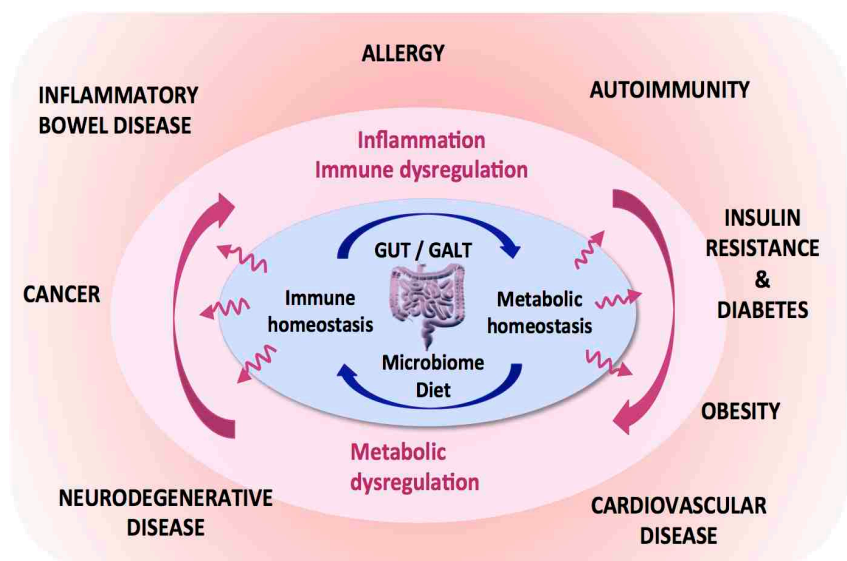
Chairs: **Dr Suzanne Meldrum**  
Rapporteur: **Prof Philip Calder**

**Suzanne Meldrum** set the scene by highlighting the role of nutrition in all aspects of development, and as a key factor in 'all' NCDs. Again the critical bi-directional relationship between nutrition and the gut microbiome was noted with implications for both immune and metabolic homeostasis (**Figure 10**).

The discussion that followed highlighted the following issues:

- We need better tools for accurate 'nutritional profiling'
- Common interest in specific nutrients (such as LCPUFA, prebiotics and vitamin D) with multiple health benefits including neurodevelopment, cardiovascular health, immune health, allergy, bone health (as already noted in discussions of population and intervention studies)
- **HOWEVER:** There is a recognised need to consider the '**complexity of food**' that isolated studies of specific nutrients (e.g. specific supplementation studies) may not capture.
- The complexity of 'poor' nutrition
  - high risk dietary patterns
  - over-nutrition versus under-nutrition versus specific deficiencies
- Role of maternal obesity and weight gain in pregnancy: current studies focus on infant growth patterns and cardiovascular metabolic outcomes, but immune outcomes may also be of interest.
- Some nutrients may have complex effects: e.g. "U-shaped" risk associations with disease (potentially with folate and vitamin D) and differential effects in risk of one disease versus another.

**Figure 10: The central role of the gut and nutrition in maintenance of immune and metabolic homeostasis**



**Philip Calder** restated the need to move towards multifaceted interventions to improve health, ideally starting in or even before pregnancy.

#### **Action Points**

- ⇒ The WAO/WUN Collaborative Survey (above) will provide another ‘quick start’ to develop a collaborative activity on nutrition. It was acknowledged that this would only provide very ‘basic’ nutritional data and serve as a platform for more robust studies.
- ⇒ In the longer term there was agreement that we would like to move towards developing a multifaceted intervention study, that would be informed by the accumulated knowledge currently being derived from both population studies and ‘single nutrient’ studies
- ⇒ The intervention study theme group (Phillip Calder and Dianne Campbell) will consider the **evidence base, and** begin to formulate ideas around an ‘ideal study plan’.
- ⇒ This long term goal would depend on work from other working groups developing standardised protocols/metrics/measures for assessing exposures and outcomes.

### **3.3 LIFESTYLE PATTERNS**

**Chairs: Dr Rae Chi Huang**

**Rapporteur: Prof Susan Prescott**

The focus of this session was on other lifestyle factors (not yet covered) that have been associated with higher risk of inflammatory NCDs, and how optimal lifestyle patterns may help maintain homeostasis and the capacity to ‘cope with challenges’ over the life course. Complex interactions and variations in genetic susceptibility make this area difficult to dissect. The ultimate challenge (even once an ‘optimal lifestyle’ is characterised) will be overcoming the many barriers to translation and implementation. The main factors discussed in this context included:

- Stress (chronic HPA axis activation)
- Sunlight
- Exercise
- Behaviour

Other factors were covered elsewhere in other discussions (nutrition, gestational diabetes and maternal hypertension in pregnancy, smoking and other pollutants).

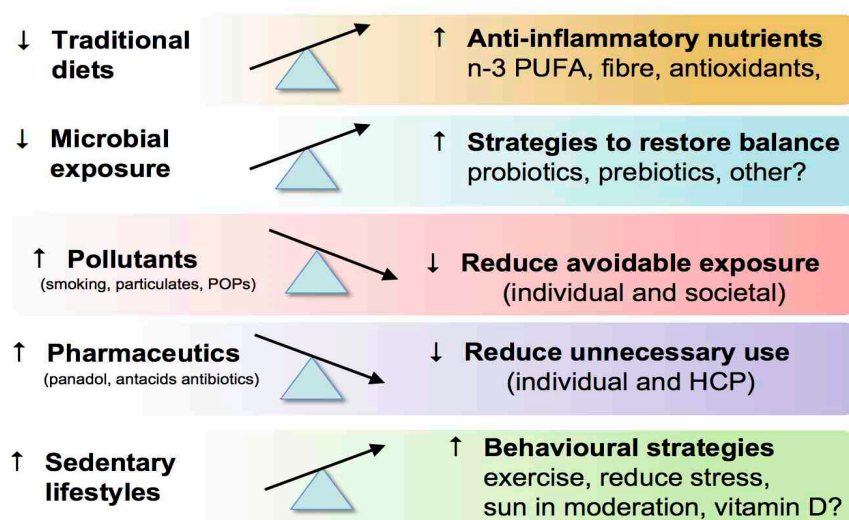
Of these factors, vitamin D was the most logical unifying interest to pursue in initial research, with several vitamin D studies already occurring in several centres in the network (Sydney, Southampton, Melbourne and Perth).

#### **Action Points**

- ⇒ A ‘**Vitamin D working group**’ was formed (initially comprising **John Sinn, Carina Venter, Quiza Zolkipli, Louise Michaelis**. Others welcome!)
- ⇒ This groups suggested additional questions to add to the WAO/WUN Collaborative Survey (above) which will gather information about the rates of vitamin D deficiencies, use (and policy) of vitamin D supplements (in pregnancy, lactation and infancy) in different regions.
- ⇒ John Sinn considered this could be the topic of a systematic review
- ⇒ The ultimate goal was discussed again: to test the concept of an ‘integrated lifestyle intervention’ with multisystem outcomes (**Figure 11**).

## Logical preventive approaches Restoring environmental balance

Figure 11: The 'ideal approach' to reducing modern diseases.



### 3.4 TOXINS AND POLLUTANTS

Chairs: **Dr P. Noakes**

Rapporteur: **Prof Meri Tulic**

Paul Noakes reviewed the current evidence for the adverse effects of environmental pollutants on many health outcomes (including effects on immune, cardiovascular, metabolic and respiratory health, as well as other long term health effect). Pollutants of particular interest included:

Inhaled pollutants

- smoking,
- diesel exhaust particles and
- indoor heating and chemical pollutants

Ingested pollutant (water and food contamination)

- persistent organic pollutants (phthalates/organochlorines/dioxins)
- Heavy metals

As with other exposures, these may have more significant effects in early development. This is best documented for the effects of cigarette smoking. A number of these factors have documented effects on immune function specifically, and several have known epigenetic effects. POPs have been linked to immune diseases (autoimmune conditions) and correlated with IgE production but their role in allergic disease is less clear. The major difficulty of any research in this field is that it is limited to observational studies. It is already clear that exposure to these adverse exposures should be minimised and that the main focus in this domain needs to be on public health policy and education. At this stage the group agreed that it would not pursue specific research in this area, except as it relates to more general interventions related to a 'healthy lifestyle'

## SESSION 4: THE WAY FORWARD

### 4.1 STRATEGIES FOR FACILITATION

**Chairs: Prof Susan Prescott**

**Prof G. Wong**

**Dr Mike Levin**

It was agreed that the key factors needed to facilitate the network in the immediate future should include 1) development of our identity, 2) regular contact and meetings to follow-up the current proposals, and 3) funding strategies (short term and longer term).

#### **A number of strategies were proposed to develop our identify and promote awareness of the network:**

- To publish our 'view point', as either 'perspectives', 'proceedings' or 'position statements' in a range of journals. It is likely that these might initially be in specialty journals, but that we should aim for more general journals.
- To develop ideas for 'sessions' at various national and international meetings. There may be opportunities to 'badge' some existing sessions in the short term.
- To promote awareness through new relationships and new partnerships
  - Develop the network further (new centres)
  - Formal links to Societies (such as our current new relationship with WAO)

#### **General discussion of strategies to facilitate future meetings**

- It is logical and cost effective to capitalise on other meetings that a significant proportion of members may be likely to attend (e.g. next meetings of WAO, DOHaD, WUN, EACCI etc.)

#### **Funding strategies also discussed:**

##### *Short term funding strategies*

- RCA grants to support travel in next rounds (WUN members eligible)
- Progress to RDF (need multiple WUN members as partners)
- Explore funding opportunities and strategic partnerships (industry and NGO) to facilitate Network research activities

##### *Specific projects*

- Initial local/national funding sources (and partnership grants where possible) for each collaborating centre
- Industry support

*The Long term goal* is for large scale funding (but need to be addressed once the network identity, agenda and activities become more established)

### 4.1 FINAL REFLECTIONS AND THE NEXT STEPS

**Chairs: Prof Susan Prescott**

**Prof Katie Allen**

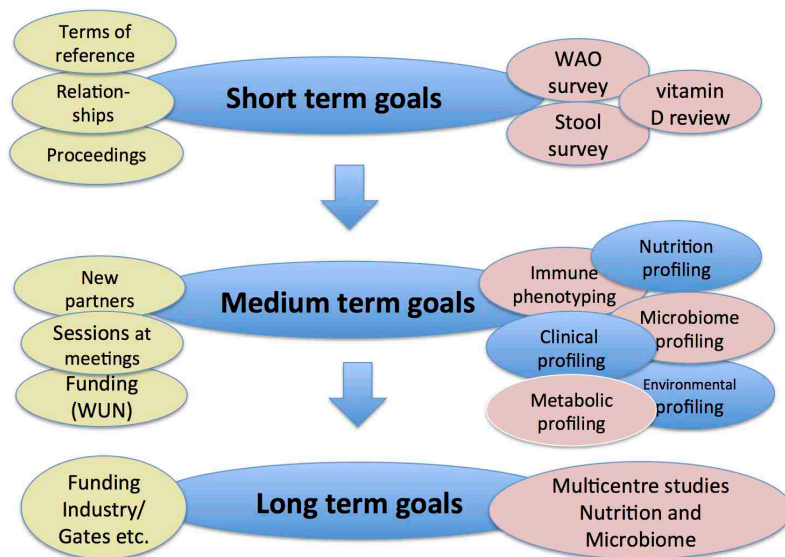
The original objectives of the meeting were revisited together with the discussions and outcomes of each session.

The ultimate vision of the network is to:

- better understand how modern environmental changes are contributing to the dramatic rise in many modern NCD's.
- identify interventions that promote early 'immune health' with long term, multi-system health benefits aimed at reducing the burden of many NCDs,
- promote the important collaborative philosophies that need to underpin an interdisciplinary, life course approach to tackling these global issues

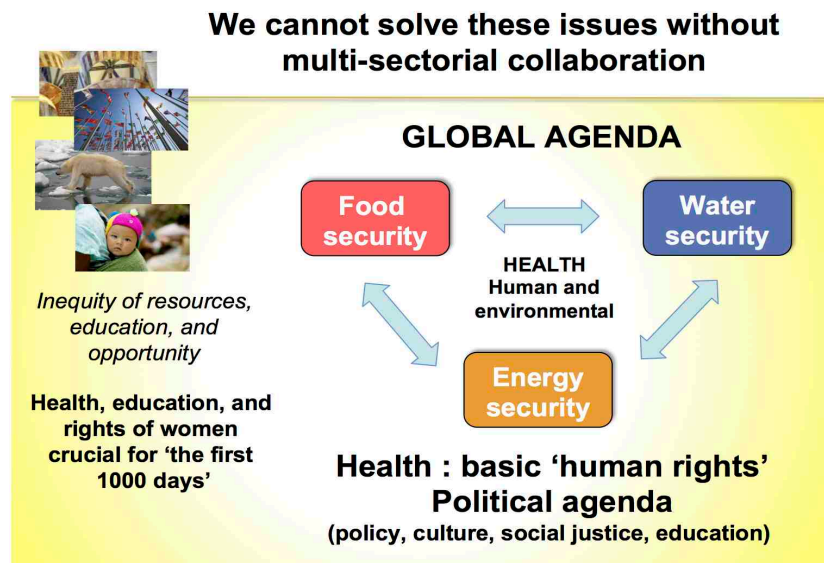
A series of short term, medium term and longer terms goals were outlined (Figure 12).

Figure 12: Overview of Network goals



It was acknowledged that even once ‘biological benefits’ are demonstrated the **main obstacles to effective translational** will remain in the **social, political, economic and cultural determinants of health and behavior**. This highlights the need for multi-sectorial engagement (Figure 13), the importance of maintaining strong links with public health partners, and promoting the DOHaD NCD agenda beyond ‘health’.

Figure 12: The importance of multi-sectorial engagement and collaboration



There was a high level of optimism that the first important steps has been taken in the formation of our network. This will be a work in progress and there was great confidence that this should progress. It was agreed that WUN provides an ideal forum and vehicle to keep driving this process, and that we need to involve all other relevant organisations in an open and collaborative way.

The next meeting of this Network: will be held in Hyderabad, India on 8<sup>th</sup> or 9<sup>th</sup> December 2012 (details to be confirmed) at the WAO International Scientific Congress (WISC), with many thanks to the host (WAO) for assisting with the venue. Individual working groups are asked to reflect on their agendas and allocated tasks ahead of this meeting.