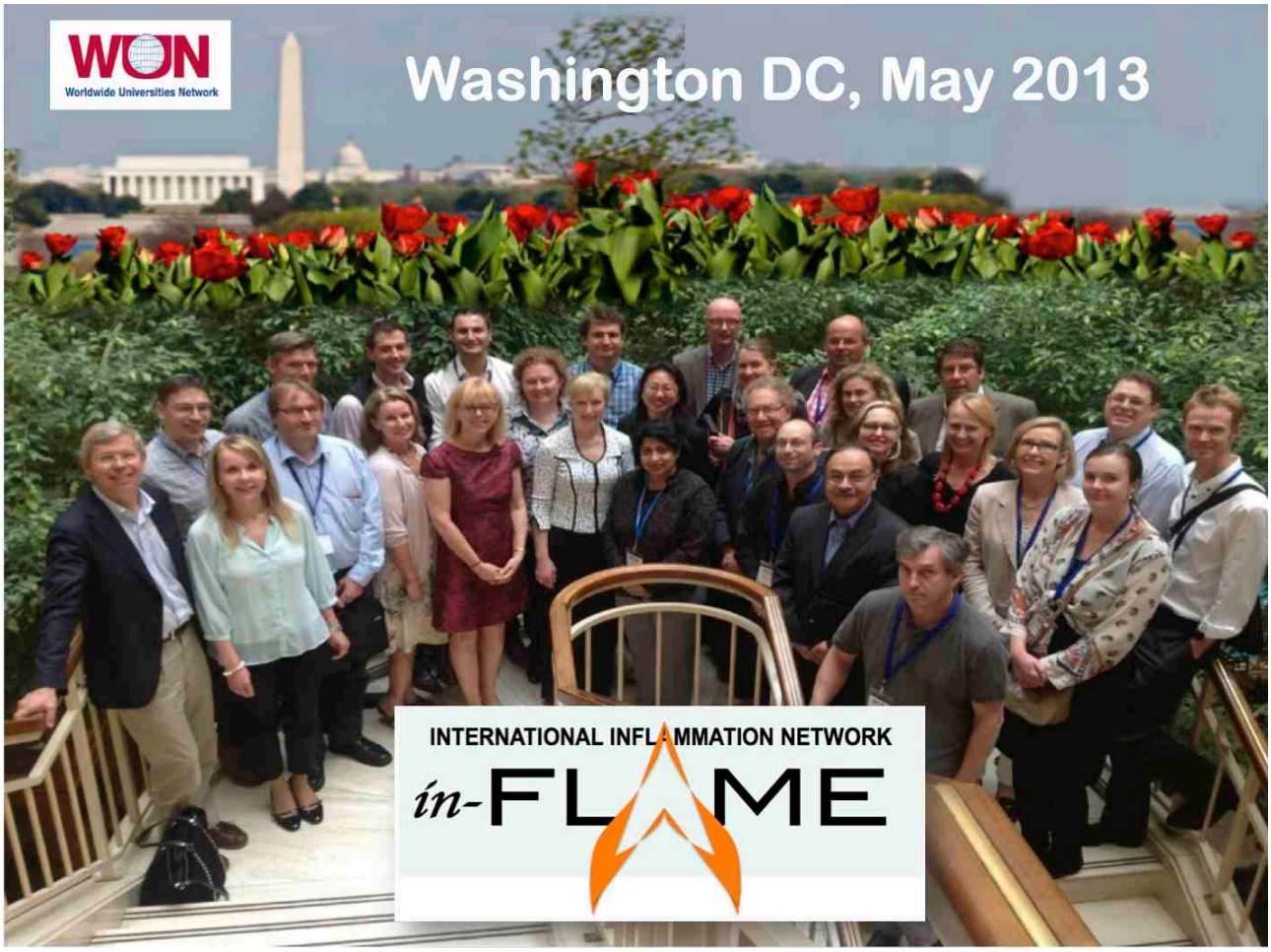
Worldwide Universities Network
Global Public Health Challenge
Non Communicable Diseases (NCDs)

INTERNATIONAL INFLAMMATION NETWORK
in-FLAME

The University of Western Australia
Achieving International Excellence

SUMMARY REPORT

2nd Annual WUN *in-FLAME* workshop, 20-21st May 2013, The Grand Hyatt, Washington D.C.



International Inflammation (*in-FLAME)* Network: Risk factors, pathways and early preventive strategies targeting Inflammation as a common antecedent of NCDs

Context:

The unparalleled rising burden of a diverse range of chronic non-communicable diseases (NCDs)[1] is one of the major global challenges of the 21st century. Chronic low-grade inflammation is a common feature of virtually all NCDs, indicating **a central multisystem role of the immune system**[2] and particular vulnerability of the immune system to modern environmental change.

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.

[1] *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.*

[2] *Renz H, et al.. Gene-environment interactions in chronic inflammatory disease. Nature Immunology 2011; 12:273-7*

Participating Universities (WUN *in-FLAME* Network Centres) as at June 2013: *Present in Washington

WUN Partner Universities	Members
University of Cape Town, South Africa	Dr Michael Levin*, Prof Heather Zar, Dr Claudia Gray
Chinese University Hong Kong, China	Prof Gary Wong
University of Southampton, UK	Prof Philip Calder*, Prof John Holloway* Prof Stephen Holgate, Prof Mark Hanson, Dr Tony Williams, Dr Judith Holloway, Prof. Graham Roberts, Dr Quiza Zolkipli, Prof Geraldine Clough
University of Sydney, Australia	Prof Dianne Campbell*, Prof John Sinn
University of Western Australia	Prof Susan Prescott*, Dr Paul Noakes*, Dr Rae-Chi Huang*, Prof Karen Simmer, Dr Suzanne Meldrum*, Dr Nina D'Vaz, Prof John Newnham, Dr Aveni Haynes, Dr Liz Davis
University of Auckland, New Zealand	Prof Ed Mitchell, Prof Rinki Murphy
University of Bergen, Norway	Prof Cecilie Svanes*, Dr Karl Brokstad*, Prof Roland Jonsson
University of Wisconsin, USA	Prof James Gern (joined since the meeting)
University of Alberta, Canada	Prof Anita Kozyrskyj*, Prof P Mandhane (also from AllerGen)
Plus-WUN Partners	
World Allergy Organisation (President)	Prof Ruby Pawankar* (Tokyo)
University of Melbourne, Australia (and affiliated institutions)	Prof Katie Allen*, Dr Peter Vuillermin*, Dr David Martino*, Prof Mimi Tang, Dr Richard Saffery, Dr Kathryn Holt, Prof Shyamali Dharmage
Monash University, Australia	Prof Charles Mackay*
Otago University, New Zealand	Prof Julian Crane, Dr Kristin Wickens, Dr Thorsten Stanley
University of Adelaide	Prof Julie Owens*, Prof Jodie Dodd, Prof Vicki Clifton*, Prof Sarah Robertson*, Dr Michael Davies, Prof Maria Makrides, Prof Tony Ferrante
Imperial College, London	Prof John Warner, Dr Paul Turner*, Dr Robert Boyle, Dr Daniel Munblit
University of Marburg, Germany	Prof Harald Renz*, Dr Dorthe Kesper
University of Ulm, Germany	Prof Jon Genuneit
University of Munich, Germany	Prof Bert Koletzko*
University of Umea, Sweden	Dr Christina (Tina) West*
Linköping University, Sweden	Dr Maria Jenmalm
Swansea University, UK	Dr Cathy Thornton
AllerGen Network (multiple institutions), Canada	Prof Denburg, Judah*, Chair, AllerGen (McMaster University) Dr Fiona Brinkman*, Diana Royce*, Dr Stuart Turvey (University of British Colombia), Dr Padmaja Subbarao (University of Toronto), Prof Malcolm Sears, Sonia Anand (McMaster University) Prof Allan Becker (University Manitoba)
Chiba University, Japan	Prof Naoki Shimojo
Université de Nice Sophia-Antipolis, France	Prof Valerie Verhasselt, Prof Meri Tulic
Northwestern University, USA	Prof Thomas McDade
Aga Khan University Hospital, Kenya	Dr Rose Kamenwa
University of Helsinki, Finland	Prof Tari Haahtela
University of Turku, Finland	Prof Seppo Salminen
University of Copenhagen, Denmark	Prof Hans Bisgaard, Dr Jakob Stokholm* and COPSAC team
University of Utrecht, Netherlands	Prof Johan Garsson
University of Singapore	Prof Lynette Shek
University of Newcastle, UK	Prof Louise Michaelis
University of Manchester, UK	Prof Adnan Custovic
Nestle Nutrition Institute, USA/Switzerland	Dr Pepe Jose Saavedra
Immune Tolerance Network, USA	Dr Michael Howell

General goals of the *in-FLAME* network:

- This network addresses the risk factors, pathways and strategies to overcome the rising propensity for chronic inflammatory disorders with a focus on early effects on the developing immune system and the consequences of **inflammation in early life for the health and function of many organ systems**.
- We address the **risk factors, pathways and strategies** to overcome the **broad range of inter-related conditions** that are associated with inflammation in early life and throughout the life course including obesity, allergy, asthma, autoimmune disorders, cardiovascular and metabolic diseases, cancer, and neurodegenerative conditions.
- Our global network brings together a diverse interdisciplinary group (across many systems) tasked with developing **an integrated program** of **population studies**, **biological studies** and **intervention studies** ultimately aimed at preventing inflammation and the burden of subsequent disease.

Overall goals of this meeting:

1. **To develop collaborative projects based on the *existing* combined assets of the networks** including cohorts, biorepositories, expertise, and technologies (short term goal),
    a. potentially developing shared grant applications (including an NIH proposal)
    b. generating position statements and review papers on specific topics that will represent the vision and activities of the *in-FLAME* network
2. **To develop new *prospectively harmonized* multi-centre studies ('meta-studies')** that take standardized approaches to facilitate collective and comparative analysis of merged large data sets across many continents (long term goal)

Session 1: Setting the Scene

Meeting and program Chair: Prof Susan Prescott

Introduction:

Susan Prescott set the scene and the context for the meeting. For new members she restated the history and goals of the *in-FLAME* Network, highlighting the importance of collaborative multicentre studies in understanding and solving complex problems.

The concept of 'META-STUDIES':

Susan also introduced the proposed new approach of openly sharing ideas, protocols and proposals for clinical trials and cohorts - essentially 'meta-analysis in reverse' by *prospective* sharing. The intention is that this will generate a collective of *harmonised* 'stand alone' studies that can be readily combined with other datasets to address more complex problems. This aims to dismantle residual traditions of secrecy and competitive, adversarial research. It is directly aligned with the open and collaborative philosophies that *in-FLAME* is founded on (refer to *in-FLAME Terms of Reference*).

The purpose (and advantages) are:

- To '**harmonise'** methods and approaches **prospectively**.
- **Standardisation** will build **large scale future** capacity
- **Sharing grant applications** between centres (for local/national funding)
- Applications will be **more competitive if leveraged** as part of global network.
- 'Stand alone' studies performed in each centre, can still be published separately (as necessary for local reporting requirements)
- Studies can be readily combined (allow pooling/sharing/comparison) for a) meta-analysis b) to address more complex interactions/genetics etc.
- Replication (+/-) in different genetic and environmental settings will allow comparisons that will provide more information about gene-environmental interactions

A legacy for the future:

This is a long-range plan, which can *begin* now. The generation of large data sets and standardised biorepositories will provide a strong asset, long into the future.

To get there we NEED:

- Collaborative intent (which we have demonstrated)
- Specific proposals shared (best way to initiate the process)
- Develop data-sharing capacity
- Standardised approaches (development of SOPs)
- Coordination (ownership of specific aspects)
- ECR engagement: opportunity (understanding this is capacity for *their* future)

It will not take that long to *start* the process

SPECIFIC 'NEW' PROJECTS THAT ARE BEING DEVELOPED AS 'METASTUDIES'

Session Chair: Prof Dianne Campbell (Sydney, Australia)
Rapporteur: Prof Phil Calder (Southampton, UK)

1.1 THE ORIGINS project:

Susan Prescott and **Julie Owens** presented the proposal for a large-scale double-blind randomized controlled trial (DB-RCT) of a multimodal intervention (n-3 PUFA, prebiotics, probiotics, arginine) from early in pregnancy until end of lactation (n=652 in divided groups). The goal is to reduce inflammation (through favorable effects on microbiome, metabolic and immune programming) for multisystem benefits. The primary outcomes relate to allergic disease; secondary outcomes to growth, adiposity, cardiometabolic parameters, immune function and microbiota etc. It will also be an opportunity to examine effects on metabotypes (mother and fetus) and the relationship with the microbiome and immune function.

****NB: This proposal was developed as a direct result of discussions at the 2012 *in-FLAME* meeting in Southampton, and is a clear example of translating discussion into action.**

Progress:

- The proposal has been fully developed with 20 interdisciplinary stakeholders.
- A grant application has been submitted (Adelaide and Perth as 2 centres initially) for $2.8million
- An industry partnership has been established for provision of the product
- SOP and CRFs to be developed.

Discussion: was centred on the rationale for the nutrient mix.

Actions needed:

→ Results of grant application are pending (**November 2013**).
→ Other centres may apply using the same protocol to their own funding bodies.
→ Please contact Susan Prescott or Julie Owens for the grant application, which may be discussed and modified for other centres as appropriate.

1.2 The VITALITY project (RCT of vitamin D supplementation in infants):

Katie Allen presented the rationale for conducting a vitamin D intervention (DB-RCT) in infants at risk of food allergy and then presented the design for such an RCT in infants from age 4 months (n=4000). The rationale is based on data from the Healthnuts study, proposed 'window of tolerance between 4-6 months', and RCT of vitamin D in pregnancy and earlier infancy are already underway (addressing a knowledge gap). Recruitment proposed from 2 months (vaccination clinics). Vitamin D levels at baseline can be determined from Guthrie cards at birth. Outcomes include IgE testing and oral food challenges at 12 months.

Other capacities:

- Serial blood – for epigenetics, immunology and genetics
- Serial faeces – for microbial sampling
- Lifestyle factors – diet, exercise, sun, parental practices
- Citizen science biosampling – sleep patterns, sun exposure

Progress: Draft protocol and grant proposal has been prepared already. Some collaborations are already established (Susan Prescott and Debbie Palmer).

Discussions: centred around vitamin D exposures in different countries and the need to conduct such a trial in a low vitamin D environment (like Australia).

Actions needed:
→ Now need further development of grant application (for submission **February 2014**).
→ Other collaborators invited to participate.
→ Please contact Katie Allen.

1.3 FOOD ALLERGY PREVALENCE STUDIES (SAFFA and beyond)

Mike Levin presented the need for food allergy prevalence studies in *developing* regions. He highlighted the need for standardising methods and definitions for assessing food allergy (from questionnaires, to challenge protocols, to definitions of reactivity). Mike then presented the SAFFA (South African Food sensitisation and Food Allergy) Study, an important study of prevalence of food allergy in the South African context. This is a cross-sectional, observational study of IgE-mediated food allergy in an unselected population of South African children aged 12-36 months – including 1200 children from urban Cape Town and a rural cohort of 400 Xhosa children in the Eastern Cape.

Progress:

- The proposal has been fully developed in collaboration with Katie Allen and the Healthnut teams (for protocols and definitions). Some aspects had to be adapted for the different setting (such as recruitment methods)
- Restrictions include: staffing, partial funding, laboratory work, single country

Actions needed:
→ Opportunities for other partners.
- Staff and student exchanges
- Laboratory work: Partners for mechanistic studies
- Other sites for data collection

→ Please contact Mike
→ To explore grants (such as Africa/Australia alliance – overlap with WUN (CEO Prof Hearn)

1.4 MICROBIOME STUDIES

Tina West reported on *in-FLAME* microbiome studies including:

a) Planning prospective studies and
b) Using what we already have to advantage

She highlighted that the gut microbiota is established over the first 2 years of life, and that there are many factors that influence this (maternal factors, perinatal factors, and infant factors)

Progress (also see Session 6 for initial findings):

- The in-Flame microbiota interest group **has been very active** and produced an inventory of stool samples available from cohort and intervention studies.
- There has been good progress with the study comparing Australian and Swedish babies. Although datasets are small, this has revealed:
  - **Reduced diversity** in the **Australian** vs Swedish infants
  - **Reduced diversity** in the **Allergic** vs the nonallergic infants
- For other cohorts there is large variability and heterogeneity in the methodologies used across these existing studies. At the moment this is creating obstacles for other multi-centre comparative studies.
- The best strategy will be to develop harmonise methods (SOP) for prospective collection (methods and ages etc) as future studies / follow-up visits are planned.

Discussions: where around the meaning of stool microbiota in the context of events occurring further up the GI tract. Interest in the oral cavity microbiota was expressed.

Actions needed:

→ **Tina West** to prepare manuscript for Swedish/Australian data (in collaboration with Susan)

→ **Microbiome Working Group** to work with the **SOP Group** to ensure future studies standardise stool collection, stool storage, other information collected, and proposed sequencing platforms

→ **Microbiome Working Group** are developing a review manuscript to summarize the state of this field from an interdisciplinary perspective

1.5 ADDRESSING THE NIH RO1 CALL FOR "MECHANISTIC INSIGHTS FROM BIRTH COHORTS"

Harald Renz presented the current NIH call for "Mechanistic insights from birth cohorts". The scope of the RO1 call was summarized as follows:

- Proposed studies must take advantage of **existing (or accruing) birth cohorts**, with well-characterized pregnancies, such that targeted mechanistic questions regarding the developmental origins of disease. Will *not fund* new studies or new follow-up.
- This announcement seeks existing mother/child cohorts that have a **rich depth of phenotypic information**, including clinical data and **bio-specimens** (such as cord blood, placenta, tissue, blood, serum, saliva, or urine) **starting in early pregnancy**.
- Applications should **focus on potential mechanisms** that mediate the developmental origins of human disease, including mechanistic links between maternal metabolism and fetal exposures during pregnancy and subsequent disease in the offspring.
- Applications submitted to this FOA should target diabetes or **obesity, renal, pulmonary, or cardiovascular or hematologic disease, neurodevelopmental disorders, or reproductive health**
- Research areas may include, but are not limited to, the following topics.
    - Prenatal exposures that alter the epigenetic profile and predispose to disease susceptibility.
    - Factors that alter the maternal or offspring microbiome.
    - Specific gene-environment interactions influenced by prenatal exposure.
    - Prenatal exposure to maternal disease, condition, or medication.
    - Presence of significant inflammation in utero and how it might be quantitatively related to altered function of specific cell types in the offspring.

Progress:

- A working group has been formed and there have been several teleconference meetings to discuss the proposal.
- Ideas that have been tabled so far (at May 2013) include:
    - Relationship between maternal microbiome and metabolic and immune programming *in-utero* (neonatal outcome)
    - The effect of maternal infections (viral, bacterial) on chronic inflammatory outcomes in the neonate (and later in life)
    - Impact of (maternal) metabolic stress on neonatal inflammatory profile (innate and adaptive)
    - Contribution of maternal obesity to chronic inflammatory disease in the offspring (allergies, obesity, T2D, NAFLD etc.)
    - Effect of specific maternal nutritional exposures (e.g. folate, PUFA, Vit-D) on metabolic and immune programming of the fetus and later in life
    - The immunomodulatory role of placenta (decidua) in transmitting and translating inflammation based on
        - maternal/paternal/own (epi-)genotype
        - maternal immune response during programming
        - maternal disease status

Discussion: A number of issues were raised including:

- The need to identify appropriate cohorts that can address the aims.
- The need for USA partners.
- The need to include several cohorts, but to avoid appearing too piecemeal.
- The need for much further development, and to develop a relationship with the NIH liaison.

Actions needed:

→ **Harald/Susan** to prepare a *DRAFT* of AIMS for circulation and comment *(this has now been completed, see separate document).*

→ **Susan** to contact NIH to confirm timelines *(this has been done and it is confirmed that there are 3 rounds per year until 2016).*

→ **Susan** to invite Prof Jim Gern (from Wisconsin – a WUN partner University) to join the network. Harald to arrange to meet and brief Jim if he agrees. (*This has now occurred and Jim has joined the network).*

→ **Ruby/Susan** to arrange follow-up meeting in Milan (EAACI/WAO) to review progress. (*This has now occurred – see separate minutes of the follow-up meeting).*

→ **The list of CI's and cohorts** to be used is still to be confirmed.

Session 2: Brave new world

Chair: Prof Johan Garssen (Wageningen Netherlands)
Rapporteur: Prof Harald Renz (Marburg, Germany)

The purpose of this session was to **stimulate new thought with 'state of the art' presentations of new technology platforms**. We invited a series of experts to join our network and facilitate access to new technologies and capacity building that will enhance both existing and proposed studies, for mutual benefit. The rationale for this was that complex multisystem interactions that we are examining necessitate access to more sophisticated technologies to measure environmental exposures and their biological effects and to be able to process increasingly complex data including interactions between biological systems and complex gene-environmental interactions.

2.1 BIOSENSING: WHAT IS IT AND WHAT CAN IT DO FOR YOU

Stefan Harrer (IBM)

Stefan gave a very exciting talk about sensing biological materials. There has been an increase in the use of microfabrication technologies in the development of new biosensors. This trend is expected to lead to the emergence of new markets. Among existing markets, the promising, high-volume emerging markets include clinical analysis, healthcare, and environmental monitoring.

He explained the Power of Bio-Nanosensors; bringing biosensing down to nanometer scale enables single particle detection leading to:

- unmatched sensitivity
- maximum reliability
- optimum accuracy

He also discussed the development of IBM mobile health tool kit models around Smartphone applications. In 2011, there were 32 feature phones for every 1 smart phone. Examples of applications with health applications include oximetery, blood pressure, mobile stethoscopes, heart monitors – ECG, microprocessors for drug dosage schedule and fetal development, audio to read phonocardiogram, spirometers for asthma, camera, video, GPS and accelerometer (for physical activity), UV-meter, microscope equivalent – light interacting with bacteria.

Stefan also discussed potential contribution to data collection, data storage, and data analysis - through the IBM "Mobile Health Toolkit":

- wireless data transfer from sensor to hub
- local processing of data on hub device
- open hierarchical event model allows for standardizing sensor data before hub transfer
- a variety of different sensors can be connected to the same hub

He presented the Watson supercomputer as a new way of 'intelligent' analysis - "Watson For Healthcare" There was intensive discussion about opportunities for collaboration, including around the NIH proposal.

2.2 METABOLOMICS – STATE OF THE ART

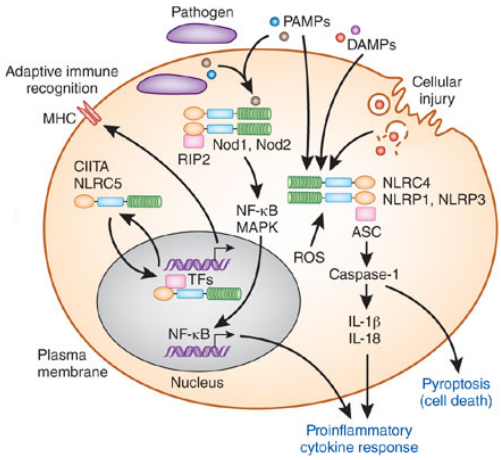
Prof Berthold Koletzko, Munich

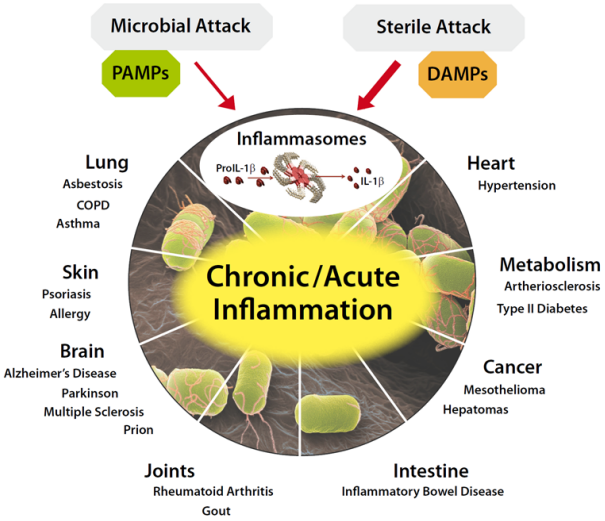
Bert gave a wonderful talk on metabolomics - the closest 'omics' to the phenotype; describing the various approaches to the detection of small molecules in biological samples. He explained the use to identify biomarkers of exposure, biomarkers of outcome, and to gain mechanistic insights. This may be done by a targeted approach versus non-targeted analysis approach, using HPLC and MS key-technologies. Collected mass spectra can potentially detect > 2000 plasma metabolites, including amino acids, phospholipids, Vitamins and metabolites. Depending on the approach there can be issues with sensitivity, specificity and accuracy. The nature of the data highlights the need for powerful and skilled bioinformatics capacities.

2.3 THE INFLAMMASOME – STATE OF THE ART

Prof Harald Renz, Marburg

Harald gave a stimulating analysis of the pathways that lead to immune activation and inflammation. He highlighted the expanding world of effector T-cell subsets and the expanding world of Pattern Recognition Receptors including PAMPs with allergy-protective activities. He emphasised that analysis of immune functions still at the level of targeted approach, and that the challenge is to capture (measure) the dynamics and plasticity of immune responses over time and magnitude of responses. Standardization still a major challenge. He pointed out that definitions are still urgently needed to determine 'what is a 'normal immune response'!





The inflammasome is a multiprotein oligomer expressed in myeloid cells and is a component of the innate immune system. The exact composition of an inflammasome depends on the activator which may be microbial (PAMPs) or non-microbial inflammatory activators (DAMPs) which initiate inflammasome assembly i.e. dsRNA will trigger one inflammasome composition whereas asbestos will assemble a different variant. The inflammasome promotes the maturation of inflammatory cytokines (e.g.IL-1β and IL-18) to induce inflammation and cell 'pyroptosis', a process of programmed cell death distinct from apoptosis – implicated in many NCDs.

2.4 THE MICROBIOME – STATE OF THE ART

Prof Charles Mackay, Melbourne

Charles Mackay gave a fascinating talk illustrating the close interrelationship between diet, microbiome and immunity. He showed how the microbiome is involved in immune regulation by metabolite sensing receptors, using examples such as acetate, butyrate and other short chain fatty acids (SCFA). He highlighted how SCFA are needed in epithelial integrity and T-reg development and that germ free mice produce very little SCFA (mostly undetectable). He showed how changes in dietary fibre could significantly change acetate levels in the blood, and that the anti-inflammatory effects of SCFA are GPR43 dependent. Both low fibre diets and GPR34-/- result in major metagenomic changes (microbiota genes). He showed how a high

fibre diet also inhibits the asthma phenotype in animals and this appears to be mediated by acetate. Tregs were also significantly increased by this diet. He showed how, with other members of the *in-FLAME* group his team is applying this model to study human cohorts (including children with food allergy).

2.5 BIOINFORMATICS – DATA INTEGRATION AND SYSTEMS BIOLOGY Prof Fiona Brinkman (Vancouver)

Fiona Brinkman gave an insightful and encouraging talk on her experience and the need for federated databases as a new way to organize data base, in a way that allowing sharing of data without loss of data control. She highlighted the critical need for data integration in order to look at a complex system, and ontologies as a way to record and store information. As ever the challenge is standardization of data
She discussed the concept of and 'innate' database for interaction and integration.

* * *

There were very enthusiastic group discussions after all of these talks and in his summary at the end of this session, Harald Renz (rapporteur) summarized the major themes of this session as 'Coordination - Sharing - Standardization'

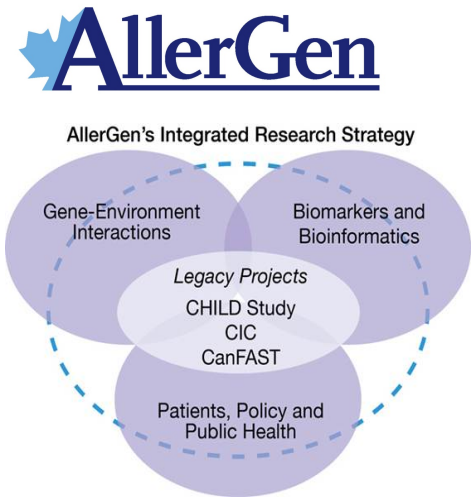
Session 3: New friends

Chair: Prof Julie Owens (Adelaide, Australia)
Rapporteur: Prof John Holloway (Southampton, UK)

The purpose of this session was to learn more about the studies and expertise of these new members who have joined the *in-FLAME* network since our first meeting in Southampton, UK in May 2012. The **Network Asset Register** (hard copies and materials provided), was updated prior to the meeting by **Paul Noakes,** so that full study details were also available.

3.1 THE ALLERGEN NETWORK NCE, AND ASSOCIATED COHORTS Prof Judah Denburg (McMaster)

As the *Scientific Director & CEO* of AllerGen NCE, Judah Denburg described this Canadian 'National Centre of Excellence' which focuses on gene-enviroment interaction in development of Allergy, spanning from basic science to translation. He highlighted the structure, stakeholders and expertise ranging from clinical ascertainment, environmental exposure measurements, genomics, microbiome measurement and informatics. Judah showcased the CHILD study as an example of their experiences with a integrated multidisciplinary birth cohort. The AllerGen network already has an international program with formal agreements. He indicated that the AllerGen has much to offer *In-FLAME*:



- Genomics: GWAS, GxE, GxG studies
- Birth Cohorts, Biobanks and Biological Materials
- Clinical trials (allergic & severe asthma, allergic rhinitis)
- Environmental Exposure Models/Platforms (Stress, Pollutants, Microbiota)
- Animal Models for Validation of Targets, Mechanisms & Novel Diagnostics/Therapies
- Biomarkers: Genome, Transcriptome & Metabolome, 'Exposome'
- Clinical Practice Guidelines, Implementation and Public Policy (food allergy, asthma, allergic rhinitis)
- International Trainee Visit Programme to 2019

Judah made a number of very good points and supported the idea that *In-FLAME* should find focal points to allow the transformation of the group from a collection of interested parties into a real network that can achieve its goals. He ended with a quote in memorial of the late Clyde Hertzman (1953-2013), world famous epidemiologist with focus on early origins of health:

"Early in life, the environment talks to genes, and the genes listen"

Clyde Hertzman (1953-2013)

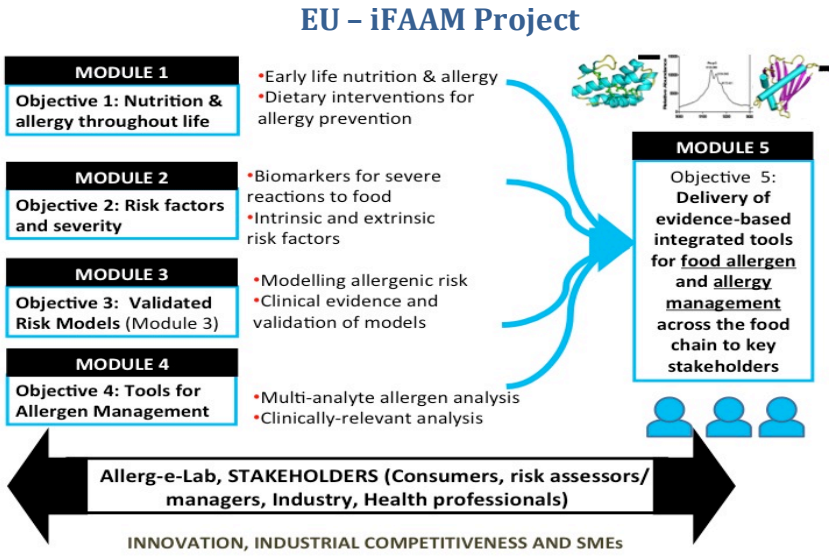
3.2 AN AUTOIMMUNE STORY FROM BERGEN — Karl Brokstad (Clinical Science, University of Bergen)

Karl gave a fascinating presentation on the pathogenesis of SJörgen's syndrome, a chronic systemic autoimmune rheumatic disease. This highlighted the importance for In-FLAME to look beyond allergy and early childhood to try and encompass the development of all inflammatory diseases. Cohorts such as RHINESSA (Cecilie Svanes, Bergen) that are multigenerational and have adult phenotypes may allow exploration of developmental origins of adult inflammatory diseases.

Discussions: Following Karl's talk there was strong support to ensure that autoimmune dimensions were fully considered in the *in-FLAME* agenda.

3.3 IMPERIAL COLLEGE LONDON and COLLABORATORS — Dr Paul Turner, Imperial College, London

Paul gave an elegant summary of the expertise and interests in the school of pediatrics at Imperial College, and bought greetings from **Profs John Warner and Robert Boyle**, who could not be present. His person interest is in exploring the biological mechanisms underlying the symptoms of anaphylaxis and the reasons for variability in symptoms between individuals and with age. Other activities include a Food +/- exercise challenge trial, interest in eosinophilic oesophagitis and a Vitamin D prenatal supplementation randomized controlled trial (n=180).



Paul discussed their role in the EU-funded 'iFAAM' project on Food Allergy (see figure) lead by Prof Clare Mills. It was noted that several other *in-FLAME* members were part of this project (Sydney, Adelaide, Perth as well as the EU centres).

Paul also described a current multicenter study investigating the composition of breast milk in relation to childhood outcomes.

Paul also invited everyone involved in human milk research and child health outcomes to preliminary meeting during ***EAACI/WAO*** in Milan on **Tuesday 25th June, 15:00-17:00 in Suite 09** (to be chaired by Dr Daniel Munblit) *"The purpose is to discuss possible collaborative approaches to understanding influences on breast milk composition and effects of variations in composition on infant outcomes".*

Discussion: As *in-FLAME* already has a **Breast Milk Interest group** (lead by Prof Valerie Verhasselt, Université de Nice Sophia-Antipolis, France) with one collaborative project already underway (below), it was noted that this may be a valuable opportunity to develop a positive, mutually beneficial and fruitful collaboration. This will be discussed further in Milan.

3.4 MUNICH – OVERVIEW OF STUDIES ON EARLY NUTRITION — Prof Bert Koletzko Munich

Bert described the elegant analytical capabilities in metabolomics in his institution and how these are being applied to investigate the relationship between early nutrition and obesity as part of the EU FP7 Early NUTRITION program. He reminded us that many asthma and allergy cohorts will have growth measurements and basic anthropomometry and could contribute to studies investigation growth and obesity. The details of For more information on the details of the 'European Childhood Obesity Trial (n=1757) and the 'Munich mother and Child Cohort' (n=500), please refer to the *in-FLAME* Asset Register.

3.5 A HEALTH ECONOMIST PERSPECTIVE: — Prof Anu Rammohan, Western Australia

Anu Rammohan gave a much needed perspective as a health economist: ultimately the success of any interventions aimed at reducing disease may be determined by the inter-household distribution of

resources and other economic factors. These issues impact on both the biology and the risk of diseases. Her elegant talk illustrated how health economic analysis can identify reasons for disparity in health outcomes in populations and directly inform public policy, identify reasons fro policy failure and identifying points for intervention. She gave examples such as

- Girls have a significantly lower probability of being vaccinated for measles compared to boys across all our models, and in the vaccinated sample, girls have a higher probability of being vaccinated late.
- Household wealth and mother's education improves vaccination outcomes for children, while father's education has no statistically significant influence.

A health economic approach could be useful to In-FLAME in defining the importance of the problem to be studied and convincing national and international funders.

3.6 Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) Dr Jakob Stockholm, Copenhagen

Jakob Stockholm brought greetings from Prof Hans Bisgaard and the COPSAC team in Copenhagen. He described the two COPSAC cohorts COPSAC 2000 (N=411) (high risk cohort, maternal asthma), COPSAC 2010 (N=743) (unselected). COPSAC has taken an approach of extremely detailed phenotyping of early life including fetal growth, biosamples (e.g. Nasal cytokines in infants), microbiome at multiple sites and respiratory infection molecular diagnostics. COPSAC can bring to In-FLAME expertise in comprehensive in depth assessment and novel technical approaches to phenotype measurements. They strongly share the multisystem and interdisciplinary approach to understanding the early life origins of health and this is reflected in their impressive and comprehensive research program.

Session 4: New Ground

Faciliators: Diana Royce (AllerGen, Canada), Prof Katie Allen (Melbourne) A/Prof Michael Levin (Cape Town),

The purpose of this Project Development Breakout Session was to allow smaller working groups session to develop projects depending on interest and expertise. At the end of the session the groups developed a summary in preparation for presentation in the feedback session the following day (see Session 7).

Session 5: Cementing our base

Chair: Prof Vicki Clifton (Adelaide, Australia)
Rapporteur: Prof Sarah Robertson (Adelaide)

The focus of this session was on developing strategies to better standardise and harmonise methods for sample collection, measurements, and definitions**:**

5.1 IMMUNOPHENOTYPING METHODS (Dr David Martino and Dr Paul Noakes)

David and Paul highlighted that there is no good 'single marker' to measure immune responses. This mostly depends on small-scale assays measuring cytokines and/or function in vitro. Systems immunology offers opportunity but still huge challenge, especially for flow cytometry. Platform technologies are emerging to interrogate different parts of the immune responses. Areas that need to be harmonized include cellular immune response, serum factors, humoral responses, cell-cell signaling, TCR repertoire, gene expression and epigenetics.

Stanford University Immune Response Monitoring Centre is leading strategies for standardisation of a range of assays including:

- Flow cytometry for surface markers – preformatted antibody lyophilized cocktails in 96 well plates
- Flow cytometry for internal markers including cytokines
- Mass cytometry (using mass spectrometry) - circumvents many of problems and can do many more markers, but not yet high throughput or readily available.
- Phospho-flow
- Multiplex assays for serum proteins
- Next-Gen (deep) sequencing

BUT none of these is broadly accessible or ready for 'roll-out'.
****Need similar SOP for *collecting* and *analyzing* other samples (including breast milk and stools)**

Discussion: It was agreed that it is unlikely there will ever be a 'one-hit' measure - there will need to be tailored assays depending on research question and individual study. All agreed we need to established some *initial* guides, protocols and SOPs to initiate the process – even though it is recognised these may not be perfect and will evolve with time.

Actions needed:
→ **David Martino (and Paul Noakes)** to draft a list of parameters and tentative SOPs (as part of the working group) that can be circulated for feedback. This will be particularly useful for new studies.
→ **Consideration of strategies to** standardize comparisons between studies. For example there could be utility for "reference samples" (eg. a pooled serum / cell sample held in one centre and disseminated to partner centres).
→ **David Martino and Paul Noakes** to look into the use ITN standardized tools so we don't have to 'reinvest the wheel'.
→ **Draft document expected in the next few months – to the circulated before next meeting**
→ **Prof Dianne Campbell** agreed to **Chair the SOP committee** and oversee this process **

5.2 CLINICAL MEASURES AND DEFINITIONS (Dr Peter Vuillerman, Melbourne)

Peter Vuillerman outlined a range of key parameters for following conditions should be incorporated in protocols:

- Eczema / atopic dermatitis (straightforward but not always easy to standardise)
- IgE-mediated food allergy (straightforward)
- Wheezing/intermitant breathing disturbance (questionnaire as well as physiological assay)
- Neurodevelopment (clinical assessment plus questionnaire)
- Overweight and obesity (densitometry not always available, so need standardized assays for skin-fold thickness)(need to measure mother and father as well)
- Cardiovascular disease (no good clinical markers relevant to early life – even blood pressure is questionable – trans-abdominal ultrasound for aortic IMT)

Discussion: It was agreed that a document with 'ideal' measurements, target ages and 'outcome' definitions could be drafted relatively easily. Individual cohorts could harmonise where possible or choose the 'best fit' with the circumstances and funding.

Actions needed:

→ **The SOP committee** (input from **Peter Vuillerman** and others) to draft a 'map' of clinical outcome measure that would 'ideally' be adopted.

→ SOP that are currently in place for recent cohorts such as **BARWON** and **COPSAC** will provide useful templates that can be used in this process

→ **Draft document expected in the next few months – to the circulated before next meeting**

5.3 PROGRESS TOWARDS NEURODEVELOPMENTAL MEASURES Dr Suzanne Meldrum, Western Australia

Suzanne Meldrum reviewed how 'neurodevelopment' spans 4th week of gestation through to the end of second decade. There are a wide range of tests are available and these vary widely. This is not currently harmonized but we should aim for this in future. Suzanne proposed that there are several issues to consider in achieving this:

- **The timing** – vast growth with age, so not clear when to assess - capabilities evolve and problems can manifest at different times. Some, such as adaptability, are relevant over life course.
- **Test specificity and sensitivity** vary according to test, want to use tests with best predictive validity. Need to think about normalization and generalizability to different populations.
- **Biological plausibility** – need to tap into domains that have relevance to immune and inflammatory status – develop a battery that includes both broad measures and more narrow, specific measures.
- **Site** – often completed in les than ideal environmental conditions.
- **Child and population factors** – time available for assessment is limited according to age. Therefore worthwhile to collect information about child responsiveness, parent attitudes. Ethnicity, education, language can impact results.
- **Data quality assurance and control** – need to consider between investigator variability.

She summarized the wide range of published tests for 4 months- 4 years under following headings:

- Broad/motor-system
- Sensory
- Motor
- Specific disorder
- Social emotional / mental health
- Communication
- Cognition/intelligence

Similar range of tests for beyond four years, with some shift in focus away from broad and towards cognitive and emotional tests. The limitations include the range and complexity of covariables, and amount of time available to dedicate in any assessment – preferably no more than one hour per home visit. There are also school-based tests (such as the in Australia) that can provide a data source. It is also possible to use on-line computer-based tools such as 'monkey survey', Denise Kaplan test, but this has significant limitations and confounding factors are more difficult to assess.

Actions needed:

→ **Suzanne will work with the rest of the SOP committee** to refine a list of neurodevelopment tools and the circumstances in which each is best considered. It was acknowledged that further discussion will be then needed to determine the most appropriate measures given the focus of the network.

→ **Draft document (as part of other clinical outcome measures) expected in the next few months.**

5.4 PROGRESS TOWARDS METABOLIC MEASURES — A/Prof Rae-Chi Huang (Western Australia)

Rae-Chi Huang described how adverse metabolic status is determined by a combination of 'suboptimal fetal programming' and 'suboptimal postnatal environmental'. It is also the result of a complex interplay between both maternal and fetal 'environment, genetics and epigenetics'. She highlighted how measures of metabolic risk (Blood pressure, lipids, the metabolic syndrome and obesity) 'track' from childhood into adult life. For example, the highest quintile of blood pressure measured between 4-14 years predicts metabolic status at age 20 years.

Rae-Chi also reviewed the ***in-FLAME* Asset Register** and noted for 'KEY PARAMETERS':

- Most studies have some measure of **Infant anthropometry** (ranging from weight, BMI; waist/height ratio/waist/hip ratio; skin folds; head circumference; DEXA; bioimpedence).
- **Longitudinal measures** are very valuable and should be considered a high priority. Rising trajectories are associated with hypertension and cardiovascular risk.
- Several studies have **blood pressure, insulin, fasting lipids, trigycerides**, glucose etc., which are known to correlate with anthropometry.
- Some studies have **adipokines** (leptin, adiponectin), and other parameters (inflammatory markers, NAFLD; markers of atherosclerosis; retinal vasculature).

She then emphasized the need to also measure data on 'METABOLIC COVARIATES':

- Infant and child diet,
- Social and psychological functioning,
- Breastfeeding, maternal smoking, maternal hypertension,
- Some studies have several additional metabolic covariates.

Discussion: We need a more specific and comprehensive asset register. **It was noted that different definition as needed for children (**adult ranges aren't appropriate for children). Consensus on childhood definitions is still needed, this may be based on data-driven analyses (e.g. mean and 99% CI based on high and low risk cluster analysis). Regarding SES factors if was noted that latent class analysis might be helpful to generate patterns.

Actions needed:

→ **Rae Chi will work with the rest of the SOP committee** to refine a list of 'ideal' cardio-metabolic tools and best ages to measure these.

→ **Draft document (as part of other clinical outcome measures) expected in the next few months**

5.5 PROGRESS TOWARDS NUTRITIONAL MEASURES — Prof Julie Owens (Adelaide, Australia)

Julie Owens summarized how 'Diet and Nutrient' can be broadly assessed in two ways

- Intake (such as measures of self reported intake)
- Biological measures of nutritional status (biochemical measure in blood)

For intake assessments the GOAL is to obtain a report of all the food and drink consumed by an individual, using standardized food tables to estimate nutrient intake. There are **three broad approaches to assess intake with diminishing precision**

- weighing everything (burdensome),
- 24 h recall by interviewer,
- food frequency questionnaire – only semiquantitative.

The latter two used most often but have own limitations, can be tailored or targeted to pick out certain food groups/nutrients. There are special challenges in infants with breastfeeding and complimentary top-up feeds.

There are **also several approaches to analyzing the data** once it is collected:

- Principal Component Analysis (PCA),
- Comparison to national recommendation,
- Indices, scores e.g. healthy eating index, Mediterranean diet adherence, glycaemic index, western style diet, child feeding indices, complementary feeding utility index.

The *in-FLAME* cohorts and RCTs include a range of different inputs and outputs have been utilized, ranging from early pregnancy through infancy and childhood (up to 3 years). In pregnancy, most assessments are in mid-late gestation (need more earlier). In children, several are in early infancy, fewer into childhood. In future we will be informed by metabolomics and chemical analysis of diets.

Actions needed:

→ **In the short-term the SOP committee (with input from Julie Owens) need** to refine a list of potential nutritional measures and ideal times that these could be administered (graded scale from 'ideal' to 'minimal useful data').

→ **In the medium-longer term we may need a specific** steering group to (1) develop consensus around methods, protocols, analyses, patterns, then (2) Summative database of nutritional measures and outcomes, and (3) move forward into ontology tables etc.

5.6 WEBSITE AND SECURE DATA BASE REPOSITORY — Dr Paul Noakes (Perth, Australia)

Paul Noakes gave a very brief summary of the two (2) websites:

1. Open – external website, as part of the WUN public site for the descriptions of the Global Challenge Programs, list of member groups, etc.
2. Secure site (Meltwater) – password protected site for depositing secure documents eg. SOPs, grant applications. This currently only has minimal information, such as the **in-FLAME Terms of Reference.** Our experience is that it is not very intuitive or versatile and quite difficult to use.

Actions needed:

→ **Short term: A new secure site is needed. David Martino suggested a system that MCRI is currently using and will send the information** to refine a list of potential nutritional measures and ideal times that these could be administered (graded scale from 'ideal' to 'minimal useful data').

→ **In the longer term:** We are ultimately aiming for a federated database but this will require a substantial amount of work.

** This could provide a training opportunity for students / early career researchers to develop and evaluate ways of achieving goals.

At the end of the session Sarah Robertson summarized these discussions and restated the need for formation of a SOP steering group to

1. Develop SOPs for each of above domains, taking into account different issues relevant to each;
2. Consider developing reference standards to be distributed to relevant laboratories, and identify students / early career researchers to develop aspects of this

It was agreed that the SOP committee will comprise: **** See Structure of Network (Session 9)**

Chair: Prof Dianne Campbell
Members: Dr David Martino
Dr Paul Noakes
Dr Suzanne Meldrum
Dr Peter Vuillermin
Dr Rae Chi Huang
(with input from Julie Owens as needed)

Session 6: How far we have come

Chair: Dr Peter Vuillermin (Melbourne, Australia)
Rapporteur: Dr Paul Turner (London, UK)

The purpose of this session was to report on complete projects and provide update on other specific projects and activities that were initiated at the 2012 Southampton Meeting

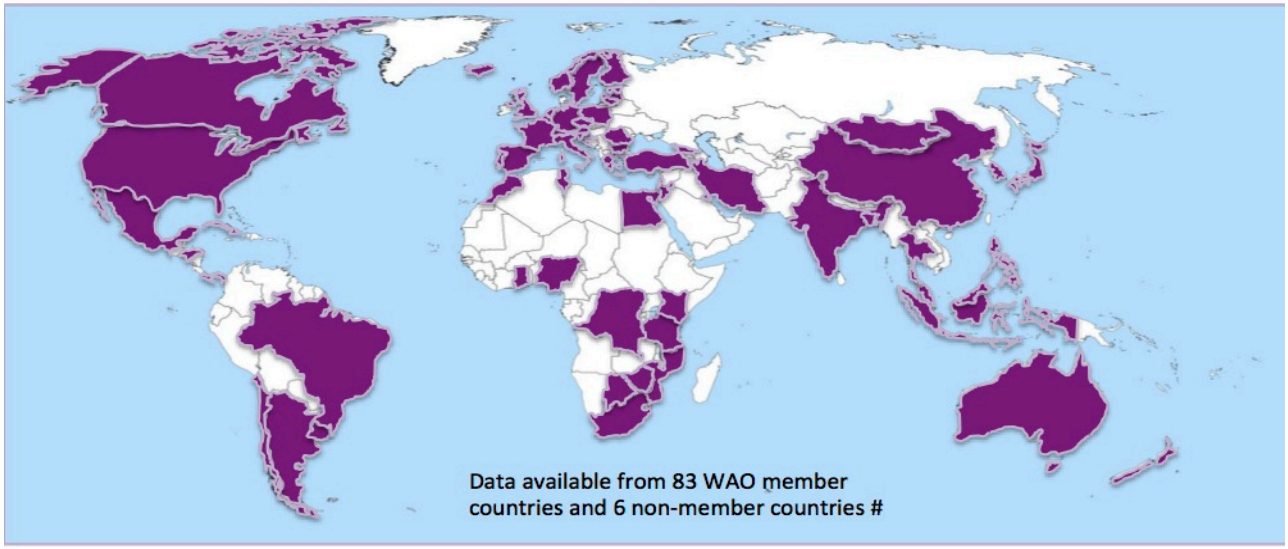
6.1 GLOBAL NUTRITION AND FOOD ALLERGY SURVEY

Prof Ruby Pawankar (Tokyo, Japan)

Ruby Pawankar summarized the Global Survey of food allergy prevalence. This was a partnership project between *in-FLAME and WAO (the World Allergy Prganisation),* initiated at the 2012 in-FLAME meeting in Southampton.

- **The project has now been completed**
- **The manuscript has been drafted and circulated to authors for comment.**
- **We anticipate it will be submitted to the journal (WAOJ) in the next month.**

Europe / Nordic (n=34)			Asia / Oceania (n=18)		Americas (n=15)		Africa (n=12)	Middle East (n=10)
UK	Czech R	Lithuania	Australia	Philippines	Canada	Chile	Ghana #	Israel
Germany	Russia	Slovenia	New Zealand	Indonesia	USA	Cuba	Mosambique #	United Arab Emirates #
Switzerland	Bulgaria	Estonia	China	Malaysia	Colombia	Peru	Tanzania #	Lebanon
Greece	Albania	Croatia	Thailand	Burma	Mexico	Venezuela	South Africa	Iran
Poland	Ukraine	Romania	Taiwan	Bangladesh	Panama	Ecuador	Morocco	Egypt
Netherlands	Moldova	Hungary	Korea	Sri Lanka	Honduras	Paraguay	Kenya	Jordan
Belgium	Denmark	Serbia	Japan	Vietnam	Argentina		Congo #	Kuwait
France	Norway	Georgia	Hong Kong	India	Uruguay		Nigeria	Azerbaijan
Austria	Iceland	Latvia	Singapore	Mongolia	Brazil		Zimbabwe	Afghanistan
Spain	Sweden	Belarus					Tunisia	Pakistan
Portugal	Finland						Botswana #	
Italy	Turkey						Algeria	



The key points: This 2012 survey was performed to collect information on existing data on the global patterns and prevalence of food allergy by surveying all the national member societies of the World Allergy Organisation, and some of their neighbouring countries.

- **Data were collected from 89 countries**, including published data, and changes in the health care burden of food allergy.
- More than half of the countries surveyed (52/89) did not have any data on food allergy prevalence.
- Only 10% (9/89) of countries had accurate prevalence data, based on oral food challenges (OFC).
- The remaining countries (23/89) had data largely based on parent-reporting of a food allergy diagnosis or symptoms, which is recognised to overestimate the prevalence of food allergy.

- Based on more accurate measures, the prevalence of clinical (OFC proven) food allergy in preschool children in developed countries is now as high as 10%.
- In large and rapidly emerging societies of Asia, such as China, where there are documented increases in food allergy, the prevalence of OFC-proven food allergy is now around 7% in pre-schoolers, comparable to the reported prevalence in European regions.
- While food allergy appears to be increasing in both developed and developing countries in the last 10-15 years, there is a lack of quality comparative data.
- This survey also highlights inequities in paediatric allergy services, availability of adrenaline auto-injectors and standardised National Anaphylaxis Action plans.

In conclusion, there remains a need to gather more accurate data on the prevalence of food allergy in many developed and developing countries to better anticipate and address the rising community and health service burden of food allergy. While food allergies and eczema are among the most common chronic non-communicable diseases in children in many countries worldwide, quality data on the burden of these diseases is lacking, particularly in developing countries.

Actions still needed:
→ **Submission to the WAOJ – this is imminent!**

6.2 BREAST MILK PROJECTS (Prof Valérie Verhasselt and Prof Meri Tulic – unable to attend)

As part of an initial international collaboration breast milk samples from Australia (and Brazil) have been sent to Valérie Verhasselt's laboratory in Nice, France, for a number of comparative analyses.

- **A manuscript has been submitted on initial findings (measurements of inhalant allergen levels in breast milk from 3 regions (Europe, South America and Australia) – below.**
- **Other comparative studies are ongoing**

The Verhasselt laboratory is internationally recognised for their work showing OVA in breast-milk associated with TGF-beta and/or specific IgG induced prevention of allergic airways disease in offspring. In these new collaborative studies they have investigated whether airborne HDM allergen (Der p) is found in human colostrum and milk samples and set up a mouse model to assess its impact on allergic outcome in the offspring.

- So far, Der p1 has been detected in a significant proportion of colostrum and mature milk samples with similar concentrations in colostrums in samples from each global region.
- Levels of Der p1 were in the same range as for food antigen and Der p1-containing milks were able to induce degranulation of anti-Der p IgE coated basophils.
- Der p-specific IgG and TGF-beta were found in all samples.
- Mice breastfed by Der p-exposed mothers showed differences in immune markers compared to mice breastfed by naïve mothers (*please contact authors for more details*).

It was also noted that this in-FLAME group will be valuable contributors to the EAACI breast milk group that will meet at EAACI/WAO Milan, June 25th. Susan Prescott has previously put Valérie and Meri in contact with Daniel Munblit (who will organize the Milan Meeting) in the hope that they will be able to come.

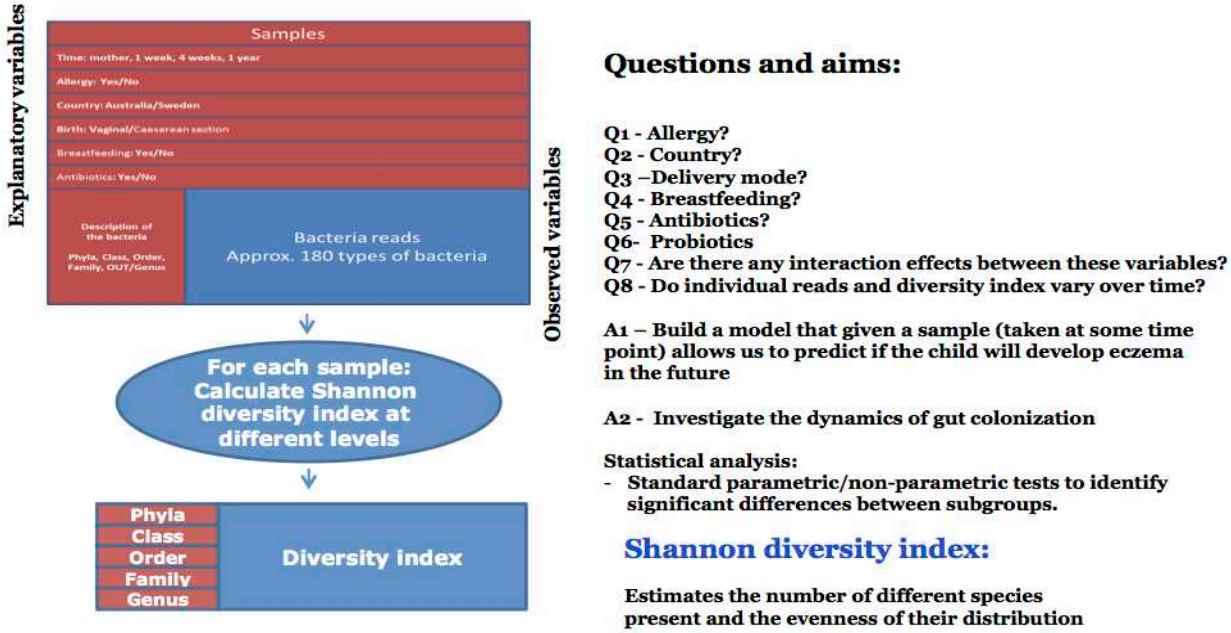
Actions still needed:
→ **Awaiting assessment of initial paper by journal**
→ **Other work is ongoing** and it is hoped that Valérie Verhasselt Prof Meri Tulic will be able to attend the **2014 meeting** to give a further update on the progress with the breast milk studies.
→ **Members of the team to attend the breast milk meeting in Milan** (and have already been in contact with Daniel Munblit)

6.3 MICROBIOME WORKING GROUP REPORT (Ass.Prof Tina West, Sweden)

Tina West presented the results of the first *in-FLAME* microbiome project. As noted above (Session one), this was an initial collaboration between Sweden and Australia to compare infant colonisation and diversity between regions, according to infant allergic outcomes, and according to probiotic supplementation

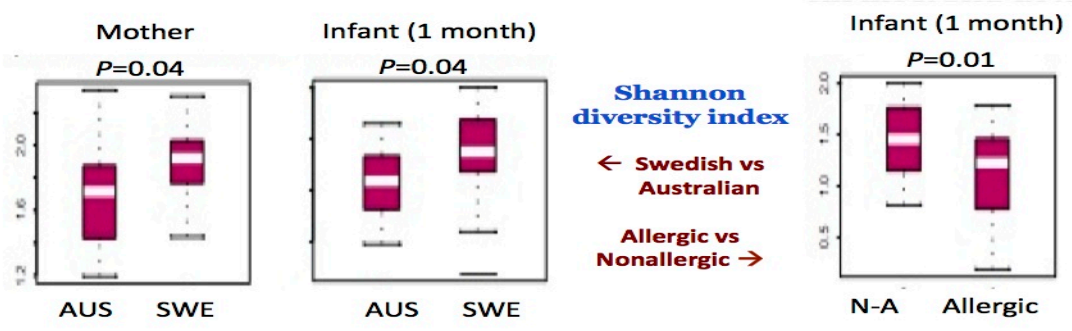
- **This study has been completed**, final statistical multivariate modeling ongoing.
- **The manuscript is in preparation:** West, Engstrand, Tulic, Prescott et al. Gut microbiome development in relation to subsequent development of allergic disease (tentative).

Summary of aims:



Summary of relevant results:

- No difference in diversity according to probiotic supplementation
- Increased diversity in Swedish mothers and babies (1 month)
- Decreased diversity in allergic infants (1 month)



This is consistent with previous findings of others in the WUN in-FLAME (Maria Jenmalm) although previous study did not look at regional differences: Abrahamsson, Björksten, Engstrand, Jenmalm et al Low diversity of the gut microbiota in infants with atopic eczema. JACI 2012;129-434-40.

Actions still needed:

→ **Tina West** will circulate the manuscript to authors soon!

→ **Tina West** is also coordinating A review paper on 'development of the gut microbiome' and possible authors and contributors will have separate focused discussion on this in a satellite meeting here.

→ New members wanted! Please contact Tina

6.4 WUN *in-FLAME* POSITION STATEMENTS AND OTHER PUBLICATIONS (Prof Susan Prescott, Australia)

At the 2012 *in-FLAME* meeting (UK) it was agreed that we should write **'perspectives' and/or position statements or consensus statements t**o raise awareness of the agenda that this network is founded on, namely the interdisciplinary approach to understanding the consequences of inflammation in early life for many organ systems. This was to include raising awareness of the relevance of other NCDs in the allergy field as well as developing publications in other disciplines.

We have had a productive year with successful publications of this nature, one in a high impact journal (JACI) and the other in a more primary care journal.

**** NB: that the paper on breast milk is already the most 'downloaded' articles for that journal this year!**

- **Prescott, S. L. (2013). "Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases." J Allergy Clin Immunol 131(1): 23-30.**
- **Geddes, D. T. and S. L. Prescott (2013). "Developmental origins of health and disease: the role of human milk in preventing disease in the 21(st) century." J Hum Lact 29(2): 123-7.**

Discussions (summarized by Paul Turner):
There were further discussions on progress with plans for *in-FLAME* network development, including new publications, profile at meetings.

- Susan Prescott has mentioned the network in her plenary sessions in both North America and Europe, and encouraged others to do the same.
- The need for more active engagement with US-based partners was highlighted again (particularly in view of the possible NIH funding application)
- Other strategic partners have been engaged including the Immune Tolerance Network (ITN), but could not attend this meeting (have been added to our network email list).
- All agreed that we need to establish our 'niche' as a unique entity that is
    - presenting 'the bigger interdisciplinary DOHaD picture' of inflammation and programming,
    - providing a focus on immune development and inflammatory pathways: atherosclerosis, obesity, neurogenesis and how these might impact on/in parallel with development of atopy/allergic disease

Actions needed:

→ ****NB: ALL Please consider adding the in-FLAME by-line to your list of affiliations when you publish!!** *"International Inflammation (in-FLAME) Network, of the Worldwide Universities Network (WUN)"*

→ ****NB: ALL Please consider using the in-FLAME logo in your talks.**

→ Additional reviews papers are planned: with a specific focus on the long term multisystem implications of inflammatory events and early immune dysregulation; with a focus on may disease processes. Several could be developed with slightly different emphasis for submission to different discipline-based journals to raise awareness of this perspective.

→ **Susan will approach the EAACI journal 'PAI' to see if they will consider a review paper** (Susan and Katie's 2011 review on 'Riding the second wave of food allergy' was the most highly cited paper for the journal in 2012, and they may be receptive for another as this contributed to the increase in their impact factor)

→ **Others to consider the same in their disciplines.**

Session 7: Feedback session

Faciliators: Diana Royce (AllerGen, Canada), Prof Katie Allen (Melbourne) A/Prof Michael Levin (Cape Town),

The purpose of this session was to give feedback on the smaller group discussions that took place the day before. Two main groups were formed – one focusing on new ventures (Group 1) and the other based around the specifics of the NIH proposal (Group 2).

7.1 FEEDBACK FROM GROUP 1: A/Prof Michael Levin (Cape Town)

As summarized by Mike Levin this subgroup set the task of discussing 2 main ideas,

- an 'in silico' mechanistic project
- and a proposal from Johan Garsson regarding interventions with food epitopes and critical molecules.

a) The In silico mechanistic project: involves developing a collaborative platform using health informatics
The group identified themes of particular importance being as follows

- Comparison of cohorts with same outcomes
- Cohort merging, collaborations between cohorts and synergies between cohorts
- Combining exposures and outcomes
- With a view to establishing processes to allow full exploitation of data using a joint platform

The platform at Manchester was identified as a potential partner, and the skills at AllerGen, particularly of data analysis with Fiona was identified as a critical facilitator.

Possibilities for taking this further included

- Applying for funding for existing Manchester platform to take on an additional project. Concern was raised about capacity issues with this idea.
- Applying for the NIH grant (on own, or as a component of another grant).
- There may be opportunities to seek seed funding from AllergGen, FP7 or Manchester

The key people to drive the process were identified as

- John Holloway
- Judah Denburg
- Fiona Brinkman
- Susan Prescott
- Paul Noakes
- Katie Allen
- A US partner (John Gern and/or Fernando Martinez)
- Adnan Custovic (to be approached as not present)

Actions still needed:

→ **John Holloway** agreed to start the process with email linking these people together and introducing the idea, as well as by contacting Adnan directly, and to co-ordinate the process further.
→ **Susan Prescott** agreed to contact **Fernando Martinez** and **John Gern** regarding collaborations.
→ An informal report back should be included at the EAACI / WAO meeting in Milan

b) Food epitopes / critical molecules intervention

Johan Garsson presented the idea of an intervention project using 'modified antigens' (less 'allergenic), either as immunotherapy in established disease or for prevention. It was proposed that it be identified as a potential 'new project', and that possible partners within *in-FLAME* who are interested have further discussions with Johan to develop a proposal further by direct connections. This would be an example of where harmonization and standardization need to be applied from the planning process (as for 'meta-study proposal (Session 1).

Actions still needed:

→ Interested parties to **contact Johan Garsson** for further discussions. The Australian groups expressed interests in performing intervention studies using this concept.

7.2 FEEDBACK FROM GROUP 2: Dianna Royce (AllerGen, Canada)

The focus of this group was to further develop discussions started by Harald Renz in Session 1. The general principles are to develop a better mechanistic understanding of how prenatal exposure contributes to the aetiology of chronic disease, this may include:

1. A better understanding of *in utero* factors that mediate these effects,
2. Define critical periods in prenatal exposure and development,
3. Identify and characterize measurements in biomarkers that predict disease.

It was agreed that within this network we have considerable resources and scientific collaboration that can be channeled into this. The greatest challenge will be coordinating diverse cohorts, trials and assets that have not been harmonized prospectively. This process will be heavily dependent on parallel development of SOP and cohort registries and merged data sets (which will inter-relate to the activities proposed by Group 1 above).

There was extensive discussion on the pathways and outcomes, that need to have a strong focus on both metabolic and immune programming. It was generally agreed that, regardless of the outcome, this opportunity is already providing the impetus to initiate and coordinate collaborative efforts.

Some of the novel aspects discussed:

- We should attempt to include new technologies (such as the platforms that might be available through IBM for both data collection and data management).
- With our recognized strengths in epigenetics, this should be a strong component of the grant.
- We could consider 'virtual RCTs' using mandelian randmomization- as a very novel and cheap and easy approach.

A number of logistic issues were also discussed including the need for leadership, time commitments, agreements and structures that need to be in place and restrictions that may be in place around data sharing in some institutions. Administrative support is also essential. We need to explore options around that, ideally in institutions which already have experience with NIH submissions. It is also essential to involve biostatisticians and bioinformaticians from the outset.

The following people have already expressed an interest as initial stakeholders in this process (to be refined once the final aims are agreed): Harald Renz (lead), Susan Prescott, Julie Owens, Judah Denburg, Cathy Thornton, Peter Vuillermin, Katie Allen, Vicky Clifton, Sarah Robertson, Anita Kozyrskyj, Vicky Clifton, Dianne Campbell (as SOP chair), Ruby Pawankar, Jakob Stokholm, Maria Jenmalm, Paul Noakes, David Martino (as ECR and contributors to mechanisms). Stefan could also have a role in facilitating industry partnership.

A number of other people were named (not present) who may be interested in being involved in some capacity at some stage: Jim Gern, Allan Becker, Adnan Custovic, Hans Bisgaard, Katherine Field, Maria Makrides, Sonia Anand (McMaster), Matt Gillman, Heather Zar.

Actions needed – ** as for Session 1, part 5

→ **Harald/Susan** to prepare a *DRAFT* of AIMS for circulation and comment *(this has now been completed, see separate document)*

→ **Further discussions will take place in Milan on the 25th June to confirm the plans and take the next steps once the draft has been reviewed. (***see separate minutes)*

Session 8: Partnerships for opportunity

Chair: Prof Ruby Rawankar (Tokyo, Japan)
Rapporteur: Prof Philip Calder (Southampton, UK)

The purpose of this session was to explore new partnerships including:

- Academic partnerships (new collaborators)
- Other nonacademic partnerships (private or public sector) such as patient advocate or policy groups
- Commercial partnerships (we have representatives from 3 companies present at this meeting – as academic members at this stage – but may explore other aspects of these relationships).
- Relationships with various societies: our relationship with WAO has been very productive and it is logical to seek similar relationships with other societies with mutual interests. Possible groups include **nutrition societies** such as **ISFAAL.** Groups interested in '**immuno-nutrition'** are also obvious partners (**Phil Calder** is invilced in several of these and may facilitate).
- Other research networks: We have overlapping interests (and common members) with the EU consortium on food allergy **'iFAAM'** (headed by **Clare Mills**) and with the **Centre of Research Excellence (CRE) on Food Allergy** in Australia (headed by **Katie Allen**).
- **John Holloway** introduced the **COST network** which is a multicenter initative focused on early origins of chronic lung disease specifically – but relevant to this network as well. There are funding opportunities for partners outside the EU including Australia. It was said that **Rebecca Cox** is leading a related project
- There are good examples of organisations e.g. Asthma Australia that have strong links with government and policy makers – these may be useful relationships to explore.

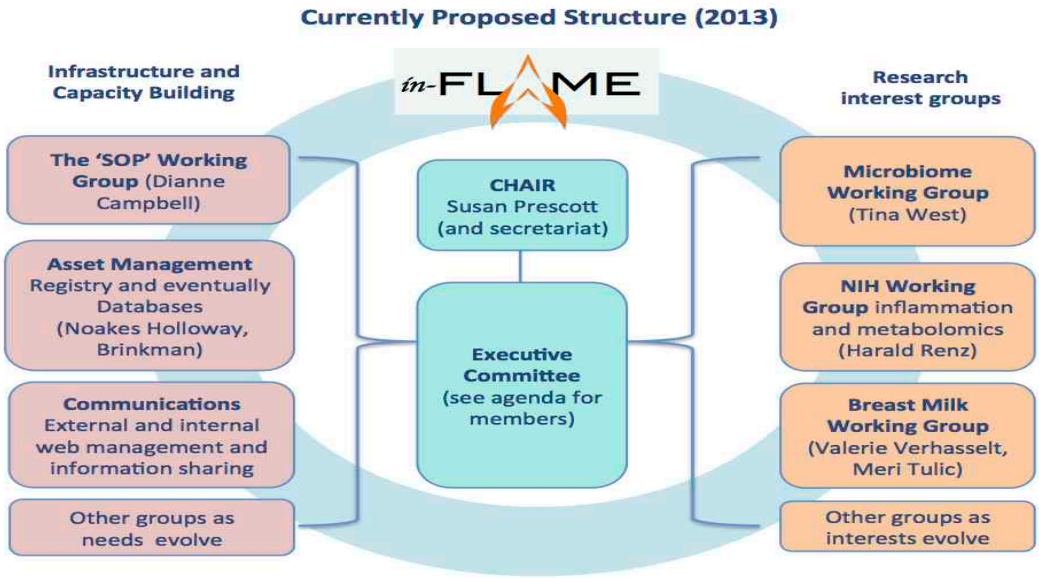
Actions needed:

→ **Susan Prescott and others as appropriate** will initiate discussions with some of these suggested partners in the next 6-12 months.
→ Please contact **John Holloway if you are interested in the COST initiative,** for more information on funding opportunities
→ **Suggestions welcomed from the group.**

Session 9: Steering the ship

Chair: Prof Susan Prescott (Perth, Australia)
Rapporteur: Prof Johan Garssen (Netherlands)

The network has grown dramatically since it began less than 2 years ago. It has also become more active and we already need to review the structure that was established in 2012. The purpose of this session was to **review the network structure** and the need for an **Executive Committee**.



The following points were discussed:

1. **Position of Chair:** Susan Prescott has been leading the *in-FLAME network* as Chair. Others were invited to consider taking over this role. The members presents voted for Susan to continue this process for another 2 years.
2. **Deputy Chair:** Mike Levin was elected to this position. Based in Cape Town he will be ideally placed to assist in the planning of the 2014 meeting
3. **Executive Committee:** This group is intended as a support for the Chair and Deputy Chair, and will assist them in overseeing the activities of the Working Groups. The following members were nominated and agreed to participate (it was agree that this should include several early/mid career researchers)
   - Harald Renz
   - Julie Owens
   - John Holloway
   - Anita Kozyrskyj
   - Jakob Stokholm (ECR)
   - Paul Noakes (ECR)
4. **Society Liaison:** It was agreed that Ruby Pawankar would be a liaison with the WAO (to assist in meeting logistics at WAO/EAACI in June and other future meetings at WAO conferences)
5. **Administration Support:** It was agreed that we need to explore avenues for administrative support for the Chair/ExCom and eventually have an in-FLAME secretariat. In the interim we can use the WUN infrastructure for the annual meetings – but need other options for ongoing activities.

Actions needed:

→ **Susan Prescott** to circulate
- 'Terms of Reference' to members
- 'by-line' for members to acknowledge their affiliation to in-FLAME (i.e. in publications)
- 'Logo' to members
- 'Photo' of the meeting for use in presentations

→ **Ruby Pawankar** to arrange meeting in Milan in June

→ **Suggestions for other working groups welcomed from the group.**

Session 10: Taking it forward

Chair: Prof John Holloway
Rapporteur: Prof Julie Owens

The goal of this final session was initiate plans for the 2014 workshop. Possible options discussed were:

1. conducting another workshop in association with the WUN Conference and AGM (as for 2012 and 2013) which will be in Cape Town in April 2014, or
2. holding a satellite meeting at another society meeting.

There was universal support for another meeting in conjunction with WUN. This was to maintain the multidisciplinary focus and avoid distractions if conducted as part of other meetings. Based on repeating the same format as this year, the proposed timing is as follows:

Working dates are 31st March-1st April 2014 (determined by other parallel WUN Public Health meetings, steering groups and venue availability). Assuming similar format of Public Health, the dates would be:

Saturday 29th – Welcome reception
Sunday 30th – Join Day 1 of WUN Public Health Global Challenge Meeting
Monday 31st – **Day 1 of WUN *in-FLAME meeting***
Tuesday 1st – **Day 2 of WUN *in-FLAME meeting***

Actions needed:

→ **Susan Prescott** and **Ruby Pawankar** arrange a follow-up meeting in Milan (in 4 weeks) for those attending EAACI/WAO to start the program planning.

→ **Susan** will inform WUN Public Health and the WUN secretariat of the proposed *in-FLAME* in

→ ****NB** Members of WUN Universities should contact the WUN Office at their institution to explore local funding for travel to Cape Town.**

→ ****NB** We should try to apply for Research Collaborative Awards (RCA) and Research Development Funds (RDF), as we did this year, again for 2014.**

Susan Prescott closed the meeting with great thanks to all of those who came to participate in the meeting, many considerable distances. Katie Allen also added words of thanks to Susan and to all other participants. All agreed that this meeting was another successful step in the evolution of our network and the strong support and enthusiasm continues.

We look forward to seeing everyone again in Cape Town next year.