

## **SUMMARY REPORT**

### ***'From Parasites To Poisons'***

**3<sup>rd</sup> Annual WUN *in-FLAME* workshop, 30-31st March 2014,  
Cape Town, South Africa.**



**Meeting & program Chair:** Prof Susan Prescott (University of Western Australia, Telethon KIDS Institute)

#### **Context:**

The rising burden of non-communicable diseases (NCDs) now poses the greatest threat to global health. Inflammation is a common element in almost all these diseases, including obesity, allergies, asthma, autoimmune disorders, cardiovascular and metabolic diseases, cancer, and neurodegenerative conditions. A substantial component of the risk of all NCDs is programmed in early life, and early environmental effects on the developing immune system play an especially important role in promoting inflammation with lifelong consequences for many organ systems.

#### **The network:**

To tackle the problem, we formed in-FLAME, the International Inflammation Network in 2012. This is an interdisciplinary collaboration (currently comprising 125 experts across 19 countries) dedicated to understanding the risk factors for inflammation and devising strategies to prevent them, particularly in early life.

#### **The focus of this meeting in Africa:**

This was an important opportunity to examine the early life determinants of immune development and inflammation in a developing world setting, and develop new collaborations in the region.

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**PLEASE REMEMBER ADD THE IN-FLAME BY-LINE AS ONE  
OF YOUR AFFILIATIONS ON ALL OF YOUR RELEVANT PUBLICATIONS:**

**Member of ‘*In-FLAME*’ the International Inflammation Network,  
World Universities Network (WUN).**



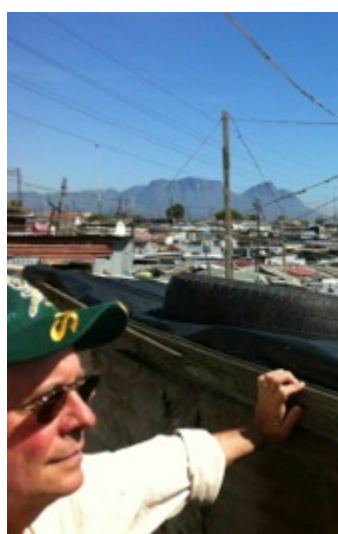
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University of Auckland, New Zealand	Ed Mitchell, Rinki Murphy
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Linköping University, Sweden	Maria Jenmalm
Monash University, Australia	Charles Mackay
Nestle Nutrition Institute, USA/Switzerland	Pepe Jose Saavedra
Northwestern University, USA	Thomas McDade, Rajesh Kumar (Northwestern Memorial Hosp.)
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Rush University, Chicago, USA	Alan Landay
Swansea University, UK	Cathy Thornton*
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University of Singapore	Lynette Shek
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University of Utrecht, Netherlands	Johan Garsson*
University of Verona, Italy	Diego Peroni
University of Wisconsin, USA	James Gern
UVRI Uganda Research Unit on AIDS, Entebbe	Harriet Mpairwe
World Allergy Organisation	Ruby Pawankar (Tokyo)



WUN Visit to 'Graveyard Pond' informal settlement Cape Town, 28<sup>th</sup> March 2014



Tim Takaro (Canada) looks across "Graveyard Pond" Township



Children playing at "Sweet Home" Township



Susan Prescott with Charlotte Adams (left) and home for lunch, with Joyce Cwayi (right). Charlotte built her house herself with her own savings.

## Thinking Outside the Box

**Session Leader:** Prof Johan Garsson

The purpose of this session was to encourage consideration of the wider issues and frame our current activities and interests in the broader context. This was intended to stimulate new ideas and collaborations outside our current sphere.



### **SETTING THE GLOBAL STAGE: Prof Alan Landay: Global Health in the 21st century – breaking down the silos**

This was a wonderful opportunity to welcome Prof Alan Landay, (Rush University, Chicago) to our network. He is internationally recognized for his work in immunology and HIV/AIDS and gave us a perfect perspective on the complex inter-relationships between infectious disease (HIV/AIDS), inflammation aging and NCDs.

He began by summarizing the **major contributors to inflammation and immune activation in the developing countries setting**, including

- Higher GI microbial burden
- Chronic immune activation induced by infections: TB, intestinal parasites
- Low thymic output/B and T dysfunction in the context of malnutrition

**There are similarities between HIV infection and normal ageing**, including immunologic changes, chronic immune activation, inflammation and NCDs. With greatly increased survival of people with HIV, he went on to discuss the ‘lessons learned’ from HIV and Aging. As in the general population, inflammation predicts disease in treated HIV infection, including mortality, cardiovascular disease, lymphoma, venous thromboembolism, type ii diabetes, cognitive dysfunction and frailty.



**Improved survival means that we need to prepare for the new challenges ahead with HIV and aging.** This will be a major challenge in Africa:

- 1 in 8 HIV-infected in Africa are over age of 50
- Rates of co-morbidities higher in Botswana than US
- Community-based chronic care delivery models will be needed to address changing needs

**A number of factors are driving the inflammation that leads to NCDs with HIV**, including:

- Microbial Translocation
- Infections (TB, Malaria, Parasites)
- Loss of regulatory cell populations
- Host factors (smoking, alcohol, diet, genetics)

**The role of Microbial Translocation in Driving Inflammation** was of particular interest. The gut (with rich lymphoid systems) is a major target for the reservoir for HIV. This may contribute to ‘microbial translocation’ and chronic endotoxemia. This is seen in the elderly and a mechanism by which HIV may contribute to NCDs. Comparing plasma LPS levels in young HIV+, both viremic and virologically suppressed on cART, the levels are significantly higher than those in age matched young HIV uninfected. **HIV also reduces GI microbial diversity**, with reduced Phylogenetic Diversity in multiple sites throughout the small and large intestine. The change of GI tract microbiome is characteristic of pathogenic bacteria with limited diversity. There are correlation with systemic inflammatory (IL6) and MT (SolCD14) markers. **This provides basis for interventional studies to modify microbiome in ART-suppressed subjects.**

### ***So, can inflammation and multi-morbidity be reversed or prevented?***

A number of diverse strategies are being considered to address this including:

- Factors that reduce microbial translocation (sevelamer, colostrum, rifaximin, prebiotics, probiotics, isotrentinoin)
- Factors that enhance T cell renewal (growth hormone and IL7)
- Anti-aging strategies : caloric restriction, sirtuin activators, vitamin D, PUFA, sirolimus, diet, exercise
- Anti-coagulants: low dose warfarin, dabigatran, aspirin, clopidogrel
- Anti-inflammatory drugs (chloroquine, hydroxychloroquine, minocycline, NSAIDs (COX-2 inhibitors), aspirin, statins, methotrexate (low-dose; CIRT), thalidomide, lenalidomide, pentoxifylin and biologics (e.g., TNF inhibitors, IL-6 inhibitors, anti-IFN-alpha)

Specific **prebiotics** have been shown to modulate gut microbiota and immune activation in HAART-naïve HIV-infected adults. Results of the “COPA” pilot randomized trial (Gori et al, Mucosal Immunology 2011) show increase in bifidobacteria with prebiotic intake, and effective Reduction on plasma soluble CD14 (sCD14) with prebiotic intake

**Discussion:** This gave an invaluable new dimension to our discussion. This is opening many doors for future NCD research. Alan is involved in unique cohorts dealing with HIV infected individuals (pregnant/lactating women, children and adults). This now brings new opportunities and new relationships to link with experts in Africa. There was also more general enthusiasm for Alan’s experience and insights in immunology and inflammation in general.



**WUN Visit to ‘Sweet Home’ informal settlement Cape Town, 28<sup>th</sup> March 2014**

### **KEYNOTE: Prof Melvyn Freeman**

**Policy issues related to providing NCDs in LMICs and/or how and what research could be beneficial to us in planning NCDs in South Africa.**

*It was our very great privilege to welcome Melvyn Freeman, Chief Director for NCDs at the National Department of Health, South Africa. He was previously a consultant to the WHO, and National Director of Mental Health and Substance Abuse. A clinical psychologist by training, he has played a major role in research, public health policy, advocacy, and legislation for over 30 years.*



### ***NCDs currently cause over 60% of all Global deaths***

- 80% of these deaths occur in developing countries
- Around a quarter of these deaths occur in people under 60 years of age.
- By 2030 it is estimated that NCDs will contribute 75% of global deaths.
- In Africa NCDs are anticipated to overtake mortality from all other (combined) by 2030.
- Globally deaths due to NCDs are projected to increase by 17% over the next ten years, but the greatest increase (24%) is expected in the African region.



**When “out of the box” becomes mainstream, significant progress is usually being made!** Much of what is in the South African strategic plan for NCDs and what we have started to do in the area of NCDs is on the edge of the shift from out of the box to mainstream. “Out of the box” thinking though does NOT mean changes based merely on an innovative thought or idea. Especially “out of the box” thinking requires thorough research and an excellent evidence base!

Things like a “whole of government approach to health” an Integrated Chronic Disease Model; regulations to reduce salt content in food; banning of alcohol advertising and the introduction of the HPV vaccine all fall into this category. As a bureaucracy that is meant to be very slow in introducing change and new and different thinking, the SA government is doing rather well. **The Burden of disease in South Africa is still somewhat different** from the above global picture given the HIV and AIDs and TB epidemics, but as HIV becomes more controlled and people will **live longer as well as high co-morbidities with NCDs**, there is little doubt that burden from NCDs will increase substantially.

### ***South Africa taking the initiative***

Leading up to the 2011 UN High level meeting a national SA summit was hosted by the Minister and Deputy-Minister of Health and was attended by government, non-governmental organizations (including user groups), professional organizations and academics. It was recognized that prevention of NCDs requires a “whole of government” and “whole of society” approach. Plans have started to establish a “National Health Commission” to be chaired from the Presidency and involving all relevant government departments and others. The Deputy Chair will be an expert from outside of government.

### ***A whole of government approach***

- Taking overweight as an example, it is not possible for individuals to simply change their behaviours through education by health promoters or practitioners unless healthy foods are accessible and available to them and facilities for exercising are within reach.
- In 2009 a study of supermarkets in rural South Africa found that healthier foods typically cost between 10% and 60% more than unhealthy ones when compared on a weight basis (R per 100g) and between 30% and 110% more when compared based on the cost of food energy (R per 100 kJ).

### ***Examples of the main risk factors for NCDs through regulation and legislation in South Africa***

- Tobacco legislation
- Regulations were gazetted in March 2013 to reduce the salt content in specified foods.
- Alcohol advertising and warning labels.

### ***Prevention and promotion – community based interventions.***

- Community based interventions include forums such as information sessions with church groups, school level education, support groups, interventions by health promoters etc.
- This level also includes education via the media, internet, cell phones etc.

### ***What about Research?***

- NCD policies and programs need to be based on sound scientific evidence generated through research.
- Research that has a public health impact is critical.
- Interventions that could reduce the burden of NCDs are available – but health systems research is needed to identify the barriers to their effective implementation and effective strategies to scale up such interventions.
- Research is needed to support the effective implementation of population wide interventions
- It is a fallacy that the DOH does not encourage “cutting edge basic sciences” research. However we are particular keen if this research focuses on issues and conditions peculiar to South Africa/Africa.
- More cost-effectiveness/cost benefit research is needed. This requires co-operation between sectors that often don’t talk to each other.
- Researchers are often poor at packaging their results in ways that are meaningful to policy makers. This requires special focus and skill.
- **Health Economics is a critical part of the case for change!**

### Take home example: Health effects of salt research – rapidly translated into policy

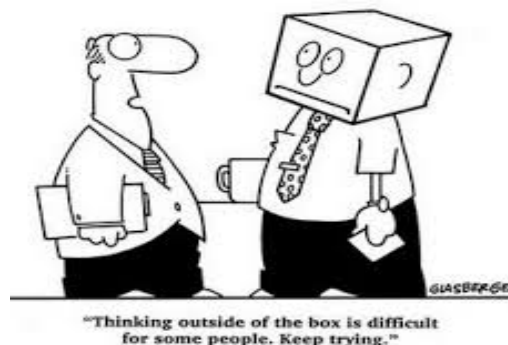
- UCT/MRC requested the DoH to make a presentation to our management meeting (held monthly) on a study done in Cape Town that showed that the reduction in salt in certain food actually brought down rates of hypertension in both hyper and normotensive individuals – without much noticeable change in taste and at very limited additional cost.
- This started a flurry of activities involving international experts coming to SA, meetings with NGOs and industry, liaising with academic involved in nutrition, health economics, medicine etc.
- One of the most important studies that followed showed that salt reduction in 4 products would result in 7,400 fewer deaths due to cardiovascular diseases and 4,300 fewer non-fatal strokes compared with number of events in 2008. Cost saving of R300 million would also occur.
- Within a short time period we had regulation published for public comment, changed and then introduced – with targets for 2016 and 2019.

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### Prevention of diseases is now non-negotiable. Reduction of environmental factors impacting on health is critical.

.....and he ended with some advice for in-FLAME:

.....*“Your core goals appear to be the right way to go but don’t expect policy makers to come running to you. It will need to be you packaging what all this means and what policy makers need to take out it, and ‘selling’ this!”*



## FOCUS 1: Friends and foe – our complex relationship with the microbial world

**Leader:** A/Prof Anita Kozyrskyj (Alberta, Canada)

The Workshop took place in a region in transition where ‘developing’ and ‘developed’ world settings exist in parallel. This provided an opportunity to closely consider research questions relating to the interaction between ‘infectious’ and ‘noninfectious’ microbial exposures in immune health and developmental programming of many organ systems. The platform talks gave context for workshop discussions and new project development.

### Research questions considered during this session:

1. What are current and historic associations between helminthic infection and health in Africa?
2. What are candidate biological pathways for an early programming role for helminthic infection?
3. How would early programming of helminthic infection affect risk for NCDs?

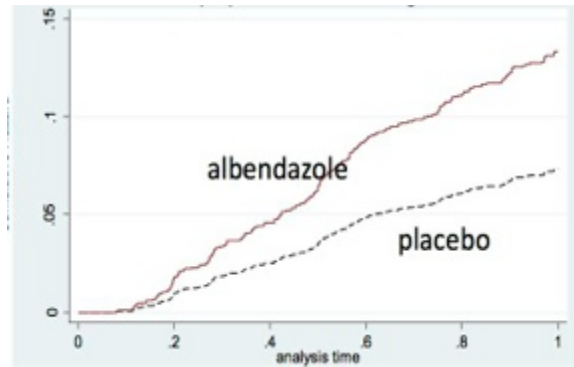


### Platform talk 1: Helminth infection and inflammation in transitioning societies – implications for NCD risk

Dr Harriet Mpairwe, Entebbe, Uganda

Humans have lived with helminths for thousands of years – developed symbiotic relationship. Helminths have developed mechanisms to evade host’s immune system, inducing host immune ‘hypo-responsiveness’ and regulatory processes, which **reduce inflammation in the human host.**





### **Results from the Entebbe Mother and Baby Study (Uganda)**

2,507 pregnant women enrolled, Uganda, RCT single doze albendazole & praziquantel and 2,345 live-born children followed up to 5 years to record eczema, asthma and blood pressure.

- Maternal hookworm in pregnancy inversely associated with eczema in childhood
- Treatment (Praziquantel or Albendazole) in pregnancy increased incidence of eczema in first five years
- Childhood helminths were inversely associated with eczema (0-5years)
- However, more observational and intervention studies are needed
- More studies on underlying immune mechanisms needed

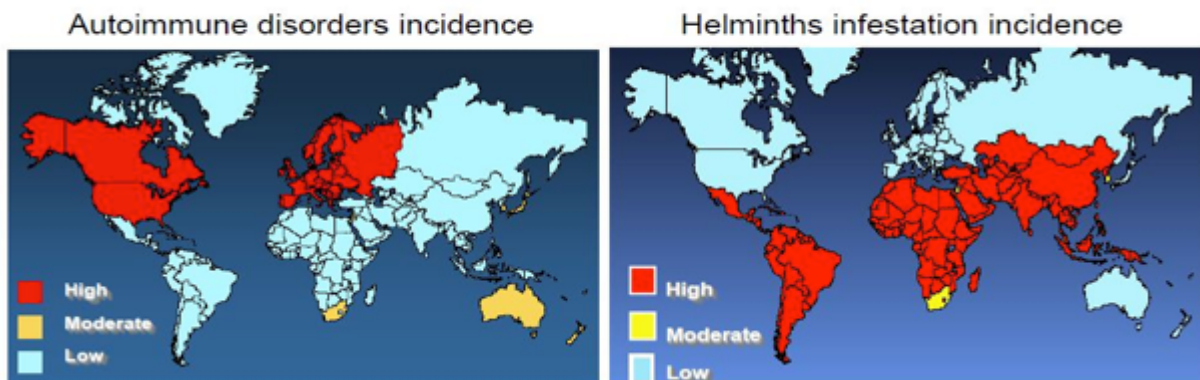
Discussion - highlighted hookworm as an example of a parasite that affects skin, lung and gut- this could be of significant importance for various (early onset) NCDs.

### **Platform talk 2: Helminth infection – the multisystem implications for early programming**

Prof William Horsnell, Cape Town, SA

The initiated immune responses that control helminth infection can alter other aspects of immune function, including altered vaccine responsiveness, changes susceptibility to unrelated infections, protection against autoimmunity. Parasite infection can favorably alter the clinical course of multiple sclerosis, with associated induction of Treg. The immune effects of helminth are complex and include induction of Th2 and Tregs. Other T cell responses are likely to be important. In the lung, helminths also induce immunoregulatory proteins (e.g. surfactant proteins) which enhance AAM, and could protect against a number of pulmonary NCDs.

## **Distribution of Autoimmune Disorders and Helminths**



### **General Discussion** (prior to 2 hour breakout session for project development)

- The network should take advantage of the different settings to be able to address specific questions that cannot be answered in any single setting/cohort alone.

- The current cohort studies in South Africa, Uganda and Kenya were further outlined. Those with relevant biological samples and information on health outcomes (e.g. allergic disease) may be of interest for comparative studies (between various developing and developed settings).
- The SA group (Horsnell) is generating preliminary data to examine the effects of parasite infection on short chain fatty acid (SCFA) production in experimental models.
- There was interest in exploring the link between human stool parasites, SCFA production, microbiome and metabolome profiling in existing cohorts
- The group also identified that pinworm infection was very common in children in developed countries, and that this had not been explored in relation to early onset NCDs such as allergy. This might be of interest in future comparative studies between developed and developing countries
- It was noted that there is a need to distinguish immunomodulatory effects of helminths on *existing* disease versus changing the predisposition to disease.

*(The group divided for a 2 hour break-out discussion)*

## REPORT: Break-out session (friends and foe)

The group identified pregnancy cohorts with at least 1 infant fecal sample collected:

- **Canada** (CHILD n=3300),
- **Denmark** (COPSAC 2000, high risk, n=400) & COPSAC 2010 (, n=700),
- **Australia** (BIS, n=1200),
- **Sweden** (Alladin, n=500) and
- **DCHLS** (South Africa, n=800).

There were 4 cohorts in **Uganda** (EMABS II), **France** (ELFE), **Kenya** and **Sydney** from which infant fecal samples could be collected. Cohort description will be circulated again by Susan.

### Strengths: case for a comparative study between these cohorts

- 1) Geographic variation in infant gut microbiota profiles, pre/postnatal risk factors and child health outcomes
- 2) 16s-based sequencing: MiSeq, 454 Pyro (Alladin)
- 3) Early fecal samples: meconium, 1 week, 1 month
- 4) Multiple, longitudinal fecal samples
- 5) Breast milk samples
- 6) Maternal fecal samples (BIS, Alladin, DCHLS, Sydney); maternal vaginal samples (COPSAC, DCHLS, Sydney); infant nasopharyngeal samples in most
- 7) Common across all cohorts was a 1-year fecal sample. A comparison of infant gut microbiota at this age would enable the inclusion of 1-year fecal samples from **Michael Levin's** multi-ethnic cohort in Cape Town.



### Identified novel and feasible objectives

- 1) Geographic and perinatal differences in infant gut microbiota composition and diversity, **SCFA** metabolites (marker helminth infection), **IgA** (gut immunity) and **calprotectin** (gut inflammation)
- 2) Geographic and perinatal differences in breast-milk microbiota composition and diversity, SCFA metabolites, cytokines, fatty acids (eg LC), and oligosaccharides.

### Actionable versus future objectives, and first steps

- 1) Geographic/perinatal differences in infant gut SCFA metabolites; standard assay & quick to do
  - i. **Anita Kozyrskyj** (CHILD) & **Anne-Louise Ponsonby** (BIS) waiting for SCFA assay funding; cost is at most is \$100/sample for a complete SCFA screen and can be reduced if limit SCFA
  - ii. **Anita Kozyrskyj & Tina West** to distribute GC (gas chromatography) protocol for SCFA
  - iii. **Bill Horsnell** to complete study on SCFA & helminths to solidify link
  - iv. As support for a potential research question, **Harriet Mpairwe** to investigate whether pinworms are as immunostimulatory as hook worms

- 3) Pending discussion with the breast-milk group, the group proposed to write a state-of-the art review paper on environmental influences of breast-milk composition. Such a review would also aid the development of future research questions.
- 4) To date, infant gut microbiota profiles exist only in 3 cohorts (CHILD, COPSAC, Alladin), excluding the cohorts of interest in Africa. Although the MiSeq platform is being used in almost all cohorts, and comparisons between MiSeq and 454 Pyrosequencing are available, challenges remain for direct comparisons among infant gut microbiota profiles. Hence, enthusiasm for this objective as an immediate project was dampened.

**Proposed randomised controlled trial (RCT):**

**Susan Prescott, Debbie Palmer and Charles Mackay** and have submitted an application for a RCT of **prebiotics/probiotics in pregnancy** to assess the effects on maternal gut flora and SCFA production, fetal immune development, metabolic parameters and eczema risk (**Harald Renz, Tina West, Maria Jenmalm and Johan Garson** are associate investigators). They are happy to share the protocol with interested partners.

## FOCUS 2: Pollutants Pesticides and Plastics – ‘new’ invisible noninfectious threats

**Leader:** Prof Ruby Pawankar (in absentia)

This Session explored the role of modern pollutants in the development of many NCDs, with a focus on differences in pollution patterns in developing world settings. We explored opportunities to measure and compare pollutants levels in biological or environmental samples from around the world.



Our visit to “Sweet Home” informal settlement in Cape Town (WUN, April 28<sup>th</sup> 2014)

**Platform talk 1: Phthalate plasticizers – slow, silent multisystem effects in very early life**

Prof Tim Takaro (Simon Fraser University, Canada)

Humans at all ages have exposure to multiple phthalates.

- The molecular mechanisms of phthalate toxicity does not follow a single pathway but appears to vary by health endpoint, organ, and species.
- Some evidence for role of phthalates in the inflammatory response
  - Occupational exposures -> contact dermatitis (Jaakkola 2008)
  - Epidemiologic associations with phthalates in building materials, personal care products and asthma and allergies (Bornehag 2004, Hsu 2012)
  - Maternal exposure (BBzp) & eczema in child (Just EHP 2012)
  - Modulation of lung inflammatory response to co-allergens (1)
  - Increases in FeNO w/ DEP & BBzP (Just AJRCCM)
  - Activation of Peroxisome Proliferation Activated Receptors (PPARs)
  - Association between MBzP in urine and current allergic symptoms in adults (Hoppin 2013) and children in a recent cohort study from Taiwan involving 483 mother/infant pairs with longitudinal urinary phthalate measures (Wang 2014).
  - Wang *et al.* also demonstrated associations between MEHP and serum IgE and MBzP and atopic dermatitis.



- A review of mechanisms by Bolling, et al, showed that for the gene-protein interactions for metabolites of BBP, DBP and DEHP, MEHP had many interactions with PPARs, whereas MBP interacted more frequently with estrogen and androgen receptors.
- Though the research to date is not definitive consumer choice and behavior do influence exposure.

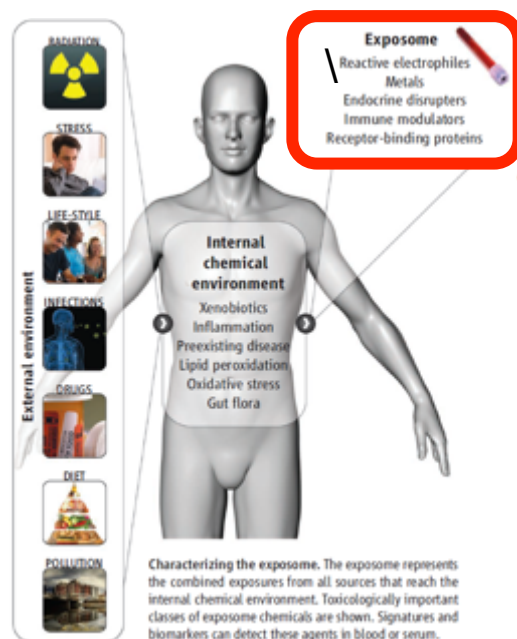
**There is already enough evidence to justify intervention studies that investigate effective approaches to reduce exposures!**

## Platform talk 2: Assessment of chemicals contributing to inflammation - Lessons from birth cohorts

Prof Jeff Brook (University of Toronto, Canada)

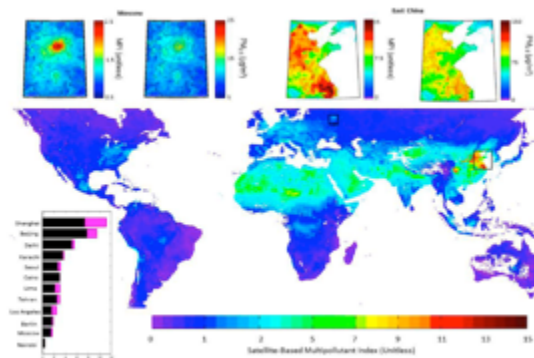
### *There are significant challenges inherent to exposure assessment in cohort studies of NCDs:*

- A wide range of sources or activities contributing to a potentially hazardous exposure
- Relatively limited information on which exposures are important.
- Cost of measuring exposure
- Burden detailed exposure measurement can place on a subject
- Ethical considerations of measuring exposures in homes
- Immense variability in exposure between individuals, and within individuals over time
- Uncertainty about the relevant timing of exposure and windows of susceptibility during development: relative importance of acute vs chronic exposures
- High variability in biologically available dose between individuals
- Lack of specific, quantitative exposure biomarkers
- Lack of precision and accuracy in environmental exposure measurement, especially as compared with genotype determination.



### **Measurement strategies**

- Satellite-based and on ground air pollution measurements
- Air pollution exposure models
- Time activity questionnaires
- Indoor source and activity questionnaires
- Samples of house dust for chemical and biological analysis
- Inexpensive, small personal samplers
- Passive indoor air samplers
- Chemical-specific biomarkers (e.g., Pb, phthalate metabolites, cotinine)



Global Air Pollution Index from Satellites

### **Lessons Learned – Big Picture**

- Harmonizing established cohorts is difficult due to methodological differences. ‘Exposomic approach’ may provide a big advance.
- No single chemical exposure is likely responsible for development of common NCDs. Multiple exposures are acting on multiple pathways, with considerable Individual heterogeneity. Exposures are insufficiently quantified and/or too correlated for isolating their separate effects.
- Interventions at the population level will benefit society. The ongoing challenge in weighing cost of intervention vs. benefits (health economics approach). It is difficult to get compliance when behaviour change is required, since there is no guarantee it benefits the individual.
- Interventions at the individual level do not have a high likelihood of assuring NCD development will be avoided. Understanding gene-environmental interactions will make this possible.
- **It is likely that there are more sensitive periods in very early in life, and this must be understood.**

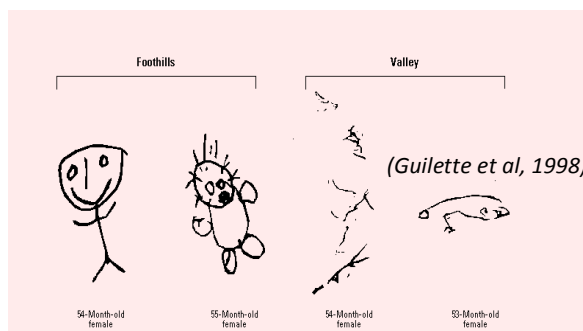
### **The ultimate goals:**

- Better quantification of the relationship between exposure and health effects to guide policy. This means more accurate and more precise risk quantification by population sub-group, large cohorts with more precise exposure, and more complete attribution of risk by including more endpoints and broad consideration of environments.
- We must determine how to measure if an individual is exceeding their safe dose **before** disease development. This means setting guidelines, and understanding, personalized environmental medicine
- Ultimately we need to develop better protective measures for uncontrollable exposures, or treatments or cures (therapeutics)

### **Platform talk 3: Early life exposures to pesticides and other neurotoxicants: Challenges in the developing country context** Leslie London (Cape Town, S. Africa)

#### **Complexity of exposures**

- Shack dwellers: paraffin, pesticides, particulates, indoor CO, infectious agents, TB
- Child Labour
- Hazardous child work – e.g. Waste picking
- Many different agents, used for bedbugs, malaria, agricultural crops (DDT and pyrethroids, both endocrine disruptors)
- Reuse of containers, unauthorised removal for home use (resulting in acute pesticide poisoning and long-term exposures)
- Informal Sector production in the home (e.g. Battery recycling causes acute lead poisoning in children)
- Textiles – home sewing – exposure to dyes, etc
- Proximity of homes to workplace toxins
- Dietary consumption of toxins



#### **Direct Transfer: Water pollution**

About **40% of samples** in the Western Cape from 3 rural sites 1998/99 contained detectable levels of ENDOSULFAN and CHLORPYRIFOS

#### **Aerial application (spraying)**

Rural Sri Lanka: Aerial application endosulfan for cashew nuts - Village below plantation used run-off water, with hormonal effects, increased congenital defects and impaired sexual maturation (Saiyed et al, 2004)

No data in Africa: – hidden from view??

#### **Children's walking routes to school**

- Rodrigues et al, 2012; Harari et al, 2006: neuro-behavioural deficits in children living near spray sources
- Dalvie et al, 2013: Detections in grass, air, dust of pesticides used on neighbour farms, including chlorpyrifos, endosulfan

#### **Effects of trade and economic policies**

**Retailing:** 80-fold proliferation of private retailers in Tanzania under Structural Adjustment. South African children involved in pesticide sales SA Children 'help' sales in informal sector

**Emergent farmers** in South Africa – under pressure to adopt high input agricultural methods

**Environmental Injustice:** The location of hazardous sources of emissions near those with least power to resist



Children we met in "Sweet Home" informal settlement in Cape Town (April 28<sup>th</sup> 2014)



Informal markets: Sale of Class I and II pesticides in informal sector

- Income generation for small traders
- Poorly packaged, often decanted, sold next to food, no instructions or warning  
→ Increase admissions of children for APP in Cape Town (Balme et al, 2010)

Is it possible that the DEHP (and other phthalates) and mercury play a role as **co-factors** in the extremely high rates of **Fetal Alcohol Syndrome (FAS)** in South Africa?

“... if the alcohol doesn't get you, then the toxins will ...”

Contaminants of bulk wine from liquor outlets, Western Cape province, South Africa, 2004

Contaminant		Plastic container (n=35)	Foil bag (n=16)	All samples (n=51)
1. Pesticides	% samples with a detection <sup>a</sup>	40%	25%	35%
2. Metals	% detects of Hg above standard <sup>b</sup>	24%	12%	20%
	Mean Hg (range)		98 µg/L (range 0 to 454 µg/L)	
3. DEHP	% detects above DL <sup>c</sup>	100%	57%	86%
	Mean Diethylhexyl Phthalate (DEHP)		144 (0-2382 µg/l)	
4. Ochratoxin A	% detects above standard <sup>d</sup>	37%	26%	28%
	Mean Ochratoxin A levels (range)		2.89 µg/L (range 0 to 22.6 µg/L)	



Contaminated 'papsak' wine: the choice for poor, rural people contaminated with mercury, ochratoxin and phthalates.

The challenges of studying Neuro-developmental impacts of prenatal and early childhood exposures to pesticides and other neuro-toxicants are large, but not insurmountable!

## REPORT: Break-out session (Pollutants Pesticides and Plastics)

The burden of phthalates, pesticides, other organic pollutants, and air pollution is a major problem worldwide, but presents many unique issues in developing countries where there is more unregulated exposure. This was alarming and very confronting for the group. Pollution exposure is a major public health issue and contributes to major health inequalities and social injustice, yet there is very little community awareness of the risks, sources of exposure or exposure levels. There are little or no warning measures and no strategies or recommendations in place to reduce exposure, particularly in developing regions.

There was a strong agreement that this should remain an important issue on the in-FLAME agenda for a number of reasons:

- Because of the evident effects on the developing immune system, many of which still need to be understood – and by extension the likely impact on the risk and burden of both infectious disease and NCDs.





- Because of the likely interactions between pollutants and other exposures that are of interest to this group, including both the microbiome and nutrition.
- Because of the well documented effects on the developing brain, hormonal and metabolic effects.

The many challenges to research in this area (cost, techniques and measurement variability and interpretation ) that have been identified in develop countries (as outlined in Canada, by **Tim Takaro**) are amplified in developing regions like South Africa (as discussed by **Leslie London**). It was recognized that this will make research studies difficult it would still be of value to try and collect some basic data that may serve to help put a spotlight on this overlooked and neglected issue.

#### What we can do:

- 1) In view of child/adult exposures to hazardous chemicals in Africa and developing regions, it was felt that a position statement, summarizing the issues, the implications, and the unknowns, particularly with the developing world dimension, would be of value. This would highlight the need for education and intervention.
- 2) The biological sampling that is available on African cohorts including South Africa (**Drackenstein** and SAFFA studies) and Uganda (**Entebbe** Mother and Baby Study) could offer opportunities to measure pollutant levels in children / mothers of these cohorts. This could provide basic preliminary data, where there is currently no virtually knowledge. Levels could be compared with measure in other international cohorts. This will be of some value even recognising the limitation. It may help put a spotlight on the problem and encourage



Children we met in “Graveyard Pond” informal settlement in Cape Town (April 28<sup>th</sup> 2014)

#### Actionable first steps:

- 1) **Tim Takaro** will meet **Leslie London** (of Cape Town) for a more detailed discussion
- 2) It is proposed that a writing group is formed to review this literature with the; developing world perspective’ : **Tim Takaro, Jeff Brook, Leslie London, Susan Prescott** and others as interested to discuss next steps.
- 3) We have encouraged the leaders of African cohorts (**Heather Zar, Michael Levin, Harriet Mpairwe**) to develop collaborative links with the those above (particularly **Leslie London** and **Tim Takaro**) to identify what can be done/measured **locally**.
- 4) **Funding:** There are many grants from developed countries (such as the Australia–Africa Community Grants Scheme, and other equalent schemes from other regions) that could be considered once a proposal is developed.
- 5) **Pilot data approach:** To reduce costs, one strategy would be to pool serum samples (or possible spot bloods) from large numbers of individuals as is done for health surveillance. This could be done for different regions (urban vs rural, developed vs developing) to get a ‘general signal’ of comparative levels. This would reduce costs compared with measuring individual samples, and could provide preliminary data that would justify further investigation, or be used for grant applications. This will be further discussed between **Tim Takaro** and **Leslie London**, and the cohort leaders.



## FOCUS 3: Immuno-nutrition and metabolism

Leaders: Prof Rae Chi Huang / Prof Catherine Thornton

We 'are what we eat', but what we eat in early life also determines how *well* we live and how *long* we live. In This Session we continued to explore the core interactions between immune and metabolic programming and the importance of early nutrition. There was very clear overlap between early nutrition and the establishment of the microbiome.

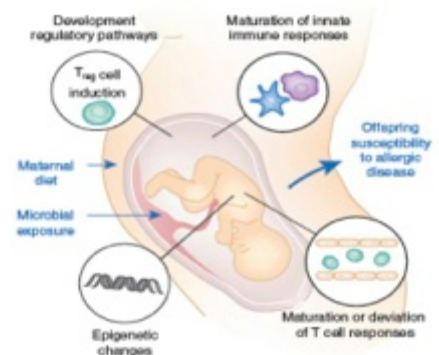


Cash Store at "Sweet Home" informal settlement in Cape Town (April 28<sup>th</sup> 2014) – Coke cheap, easier to get and cleaner than water

### Platform talk 1: Epigenetic control of cytokine gene expression: (potential implications for NCDs)

Prof Harald Renz, Marburg, Germany

Harald began the session by summarizing the epigenetic effects on cytokine production in mother and her offspring, using the German Farming studies (with candidate microbes) in which maternal exposure in pregnancy is associated with asthma and allergy protection in humans. In animal models this was explored with *Acinetobacter lowffii*. Prenatal *A. lowffii* exposure prevents allergic phenotype in the offspring. This proved to be dependent on maternal TLR signaling. **This emphasizes that 'some INFLAMMATION is not necessarily bad!'**



TH1/TH2 balance is epigenetically regulated; IFN gamma promoter methylation (associated with allergy) is associated with changing in methylation in humans (White et al). His studies also show how microbial in utero exposure increase Histone modification in CD4+ T cells of IFN gamma is dependent on increased histone acetylation. This shows how development of T cell function depends on epigenetic reprogramming of T cells following microbial exposure and programs adaptive immune system, cellular response for appropriate responses later in life.

**Extending this to nutrition in pregnancy** he showed data developed in a WUN collaboration with Susan Prescott, Richard Saffery and David Martino, showing how High folate vs. low folate exposure in human pregnancy was associated with differences (high) high TH2/TH1 ratio, and that this was related to increased acetylation GATA3 (master regulator TH2). **He Concluded:** Epigenetics allow interaction between environment and genes. It is important to consider exposure, timing exposure, cells of interest.

## Platform talk 2: How we can use nutrition to enhance immune-metabolic programming

Prof Cathy Thornton, Swansea, UK

Cathy showed novel links between Immune and metabolism based on energy metabolism. Glucose and fatty acids are energy substrates. Energy substrate availability might modulate inflammatory response. Availability of energy substrates impact on multiple facets of immunity

- E.g. Th1 and Th17 cells highly glycolytic
- Treg cells preferentially use oxidative metabolism Inhibit glycolysis - switch Th17 to Treg – implicates metabolic cues in T cell development

### Metabolic changes are a normal feature of healthy pregnancy.

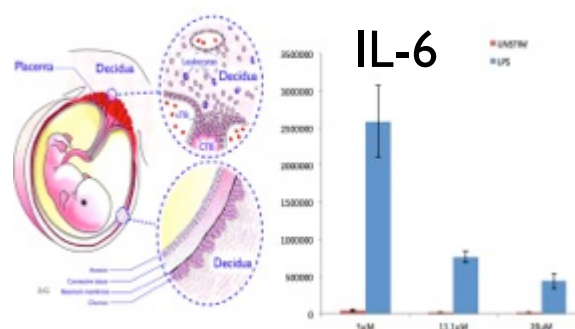
- Insulin resistance increasing from 2<sup>nd</sup> trimester to term – normal physiological response
- Transition to a catabolic state favours the use of lipids by maternal tissues, ensuring the ongoing supply of glucose and amino acids to the placenta and fetus (although maternal lipids are available to and needed by the fetus).
- Disorders of metabolism occur in pregnancy: maternal obesity and/or diabetes alter insulin signaling and glucose transport in skeletal muscle, adipose tissue, and the placenta.
- Energy sensing molecules in the placenta act as in other cells/tissues e.g. AMPK switched on/mTOR down-regulated in response to lower energy status and mTOR is activated in placentas of obese women giving birth to large babies.
- Effects of Calorie restriction – choriodecidua (see figure)

### Summary

- New Methodology (bioenergetics) – “Seahorse” being established
- Availability of energy substrates impact on multiple facets of immunity, notably inflammation
- There is a need to understand the interaction between immunity and metabolism especially in pregnancy and early childhood
- Bioenergetics analysis might offer a platform for this in the first instance
- Metabolic deregulation might be a common phenomenon in a host of disorders with inflammatory etiology

## Innate immunity and metabolism

- Pattern recognition receptors such as TLRs and NLRs (especially inflammasome) have a role in regulating metabolism
- Activation of inflammation in a range of metabolic diseases such as type 2 diabetes, atherosclerosis



## REPORT: Break-out session (Immuno-nutrition and metabolism)

Initial discussion is this group included the need to consider differential effects in underweight and overweight. This could include use existing data or add data to ongoing cohorts. However, few cohorts have detailed nutritional data.

Initial discussion is this group included the need to consider differential effects in underweight and overweight. This could include use of existing data and ensuring that ongoing cohorts take height and weight measurements (as a minimum) on all study participants whenever possible. However, few cohorts have detailed nutritional data; some do have maternal weight gain data.



## Identified novel and feasible objectives

The projects considered included:

- This group made plans to write a review paper on circulating immune biomarkers in childhood NCDs especially those that may be related to maternal BMI and future NCD risk. It was suggested that child age be restricted to pre-puberty to avoid confounding influences of physiologic insulin resistance etc, of puberty.
- They also proposed a collaborative projects comparisons of SCFA levels in infant fecal samples from in-FLAME pregnancy/birth cohorts (which will now work in synergy with the project also proposed by the microbiome 'Friends and Foe' group (above). A more extensive metabolome profiling approach also was discussed.
- The group initiated development of a project to examine how pregnancy overweight influences cord blood mononuclear cells, assessed as epigenetic modification, deep phenotyping and bioenergetics of CD4+ T cells and monocytes. Cord blood has been chosen preferentially on the expectation that a few research groups in the network will be able to spare some of this more abundant sample type. Ongoing discussion will identify a feasible work program and research question which then will be communicated to WUN in-FLAME membership and expressions of interest in contributing material invited.
- The effect of helminthic parasite antigens on human placental cytokine production will be investigated.

## Actionable first steps

- 1) **Review Paper:** Cathy Thornton will prepare an abstract in the next few weeks and circulate this to the rest of the writing group and invite co-authors. The abstract will be sent to Harald Renz for consideration in a JACI perspectives series. A preliminary list of candidate biomarkers was generated at the meeting, this included hsCRP, sCD14, sgp130, sIL-6R, TNFa, IL-1b, procalcitonin, IL-6 and IL-8, adipokines such as leptin and adiponectin, and ghrelin but it is recognized that others will be identified as writing gets underway. Much earlier in life than first anticipated is likely to be the focus as the intention is to review predictive biomarkers and those that might offer some mechanistic insight.
- 2) **The SCFA study:** will work with the microbiome 'Friends and Foe' group (above). Levels in infant fecal and blood (plasma/serum) samples from in-FLAME pregnancy/birth cohorts will be the target. In the meantime other metabolomics approaches are being considered; for example Cathy Thornton is going to undertake oxysterol analysis of meconium to ascertain if this approach could be used more widely. This will be in collaboration with local mass spectrometry experts and Peter Vuillermin for sample preparation protocols.
- 3) **The effects of maternal obesity on fetal immune programming:** The practicalities of multiple analyses of the same sample in different laboratories are being addressed to minimize the amount of sample needed for the study. Once the protocol is refined and the research question formalized all WUN in-Flame members will be invited to participate. Funding opportunities are being explored.
- 4) Extracts prepared from different helminthic worms will be transported from Bill Horsnell's laboratory in Cape Town to Cathy Thornton's at Swansea University, Wales, UK for exposure of human placentas in vitro – cytokine outputs will be monitored; further work will be based on these preliminary findings.
- 5) There will be a review of 'cheap and cheerful' clinical measures which extend beyond allergy and asthma, e.g. skin-folds, blood pressure, to generate a list of these that could be added to projects with little impact on project resources. Some of the parameters from the Barwon Infant Study may be useful.

## **FOCUS 4: BREAST MILK COLLABORATIONS**

**Leaders:** Daniel Munblit and Valerie Verhasselt

Discussion started with Valérie highlighting in her presentation the interest of looking at breast milk to understand NCD development stressing the physiological maternal-child complementarity in mammals for

organ and immune system development. She also presented the possible use of mouse models to assess causality and mechanisms of suspected factors for risk or prevention of NCD in early life.

Discussion of the group then focused on the of human breast milk collection and analysis standardisation and SOP's harmonisation. Participants agreed that despite the difficulty of SOP's standardisation due to different end points of breast milk analysis (e.g. immune assays, proteomics, microbiome) we should provide standard SOP's for a variety of breast milk analysis. Standard SOP's will be circulated within the breast milk research working group members for harmonisation.

Both, Valerie Verhasselt and Daniel Munblit reported significant influence of time of breast milk collection on the levels of immune active molecules in breast milk with levels of immune modulators decline over time. This effect is seen in two independent studies. This data suggests that any future breast milk studies done should take this fact into account and data should be adjusted to colostrum collection time alongside with any other relevant factors. Johan Garssen and Annika Scheynius highlighted a need for more extensive research of microvesicle constituents of breast milk eg exosomes. For collection of more representative breast milk sample, Annika also proposed to collect breast milk over a period of 24 hours.

Robert Boyle assessed if participants were in agreement with the results of a Breast Milk Research consortium (BreMiR) meeting in Milan, 2013 in regards to primary outcome measures for human breast milk research: allergy, autoimmune disease, metabolic syndrome/obesity, HIV, disorders of prematurity, neurodevelopmental outcomes, frequency of infection assessment, respiratory/lung function, vaccine responses, breast cancer, human studies and veterinary work on outcomes in animals, effects of pasteurisation and other processes on bovine milk composition. No other outcomes to focus have been offered during the session.

Daniel reported that BreMiR consortium affiliated with WUN in-FLAME submitted a preliminary COST (European Cooperation in Science and Technology) Action proposal. COST anticipates and complements the activities of the EU Framework Programmes, constituting a "bridge" towards the scientific communities of emerging countries and increases the mobility of researchers across Europe and fosters the establishment of scientific excellence. Winning application chosen for a full proposal submission to be announced 2 June 2014.

#### **Group considered following:**

- Breast milk research group made plans to write a **review paper** on breast milk constituents influence on immunological outcomes, with Valerie Verhasselt responsible for the structure and focus of the paper. Valerie Verhasselt will prepare an abstract in the next few weeks and circulate it to the rest of the writing group and invite co-authors.
- Group decided that there is a good momentum for **Horizon 2020 application** submission. This initiative will be discussed via email with the other collaborators and upon mutual agreement work on application will start.

## FOCUS 5: NIH PROPOSAL DEVELOPMENT

**Leader:** Anne-Louise Ponsonby

Alan Landay has had extensive experience with the NIH grant review process and was able to give valuable insights into the process. Anita Kozyrskyj has recently submitted an application in partnership with the group in Detroit and was also able to give some feedback on her experience with this specific R01 call. She will be resubmitting their application in the second half of 2014. The current plan is for Anne-Louise to prepare an application based on the BIS cohort. She will be in discussion with Charles Mackay regarding the most appropriate US partners, based on his links. She will call on members of the network to contribute expertise or preliminary data as required.

## OTHER NEW PROJECTS – Initiated or developed during the meeting

Several additional projects and writing groups emerged during the meeting:

- 1) **'HPP' Modified allergens project:** John Sinn proposed a project around exploring the use of High Pressure Processing 'HPP' to modify allergens. This is used to inactivate infectious materials in foods, but may also reduce the allergenicity of foods..

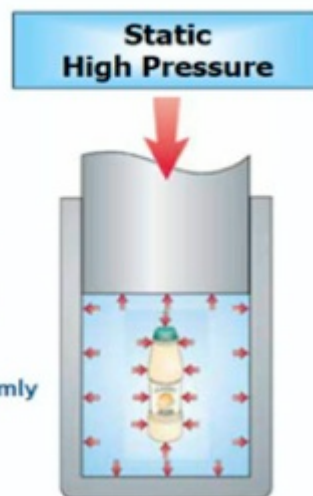
### Aims:

- Review Literature of HPP and Enzyme degradation of common allergen
- Use of manufacture food products for desensitization
- Differences between countries of different Cultivars of common allergen
- Pool data on this novel way to treat food substances to decrease allergenicity
- Often Food technology not linked with clinicians

### Why High Pressure Processing?

#### Features:

- Application of high pressures can cause:
  - Inactivation of Parasites, Plant cells
  - Vegetative micro-organisms
  - Some fungal spores
  - Many food borne viruses
  - Enzymes are selectively inactivated
  - Macro molecules can change conformation
  - Small molecules (eg flavours) are generally unaffected
  - Food Systems - as above plus equilibria may change
- High pressure is instantaneously and uniformly applied to the sample
- Compression is fully reversible



**Action:** John Sinn will lead the literature review and liaise with Dianne Campbell, Johan Garsson, and Susan Prescott, who have expressed interest in joining the group



- 2) **Placenta and parasites:** Cathy Thornton and Bill Horsnell have started a new collaboration that will involve Bill providing some helminth antigen for testing in Cathy's study placentas to assess helminth affects during pregnancy.
- 3) **Review of immune development:** Susan Prescott, Dianne Campbell, Bob Boyle and Cathy Thornton will Co-author an invited review for Clinical Experimental Allergy
- 4) **Invited review from JACI on the human microbiome:** Tina West, Susan Prescott and Harald Renz will lead this review – which will be an extension of the earlier version that was developed.
- 5) **HIV/AIDS collaboration** – Alan Landay's visit has cemented new relationships between South Africa and the USA – form which it is hoped that new opportunities will develop.

## SUMMARY OF IN-FLAME PUBLICATIONS AND GRANTS TO DATE

**\*\*\*REMINDER - TO PLEASE ADD THE IN-FLAME BY-LINE AS ONE OF YOUR AFFILIATIONS ALL OF YOUR RELEVANT PUBLICATIONS: “**

**Member of ‘In-FLAME’ the International Inflammation Network,  
World Universities Network (WUN).**

### Original publications

- 1) SL Prescott, R Pawankar, KJ Allen, DE Campbell, JK Sinn, A Fiocchi, HA Sampson, K Beyer, BW Lee. A global survey of changing patterns of food allergy burden in children. *World Allergy Organ J.* 2013 Dec 4;6(1):21
- 2) H Harb, M Amarasekera, S Ashley<sup>3</sup> MK. Tulic, PI Pfefferle, DP. Potaczek, H Renz, D Martino, DA. Kesper and SL. Prescott. Folate status as a modifier of epigenetic profile in human neonatal CD4<sup>+</sup> T cells. Submitted Dec 2013.
- 3) Macchiaverni P, Rekima A, Turfkruyer M, Mascarell L, Airouche S, Moingeon P, Adel-Patient K, Condino-Neto A, Annesi-Maesano I, Prescott SL, Tulic MK, Verhasselt V. Respiratory allergen from house dust mite is present in human milk and primes for allergic sensitization in a mouse model of asthma. *Allergy.* 2013 Dec 14. doi: 10.1111/all.12332.
- 4) M Amarasekera, D Martino, S Ashley, H Harb, D Kesper, D Strickland, R Saffery and SL Prescott. Genome-wide DNA methylation profiling identifies a folate-sensitive region of differential methylation upstream of *ZFP57* imprinting regulator in humans. *Submitted*
- 5) CE West, P Rydén, D Lundin, L Engstrand, M Tulic, SL Prescott. Gut microbiome and innate immune response patterns in IgE-associated eczema. In preparation

### Review papers / position papers

- 6) SL Prescott. Early life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases (NCDs). *J Allergy Clin Immunol* 2013 Jan;131(1):23-30
- 7) D Geddes. SL Prescott, *Journal of Human Lactation. Developmental Origins of Health and Disease: the role of breast milk in preventing disease in the 21st century* *J Hum Lact.* 2013 May;29(2):123-7.
- 8) CE West, MC Jenmalm, SL Prescott. The gut microbiota and its role in the development of allergic disease. *Clinical Exp Allergy, Accepted March 2014.*
- 9) CE West, SL Prescott, MC Jenmalm, AL Kozyrskij, KJ Allen, P Vuillermin, Hd Renz MD. Gut microbiota modulation in treatment and prevention of inflammatory diseases. In Prep (JACI).

- 10) D Martino, SL Prescott. Progress in understanding the epigenetic basis for immune development, immune function and the rising incidence of allergic disease. *Current Asthma and Allergy Reports* (2013) Feb;13(1):85-92.
- 11) D Martino, D Kesper, H. Harb, M A Marasekera, H Renz, SL Prescott. Epigenetics in immune development and function. *J Reprod Immunol*. Accepted Feb 2014
- 12) SL Prescott, D Palmer. Early events in the development of allergic disease. *Curr Opin Allergy Clin Immunol*. Accepted Jan 2013
- 13) SL Prescott, Disease Prevention in the age of convergence – the need for a wider, long-ranging and collaborative vision. *Allergology International*, Accepted November 2013.
- 14) A Ferrante, SL Prescott. Immunological immaturity of the neonate, protein kinase c zeta and allergy. *Journal Neonatal Biology*, submitted Sec 2013

#### Research grants:

- 1) 2013: Research Collaborative Award, University of Western Australia. \$18,000
- 2) 2012: WUN Research Development Fund. The International inflammation (in-FLAME) network. (15,000 UK pounds)
- 3) 2012: Research Collaborative Award, University of Western Australia. The International inflammation (in-FLAME) network. \$20,000
- 4) 2011: Research Collaborative Award, University of Western Australia: Early origins of immune disease: developing capacity for investigating risk factors, pathways and interventions for preventing inflammatory immune responses in early life \$20,000
- 5) In kind support from MANY of institutions!!

## PROGRESS TOWARDS HARMONISATION AND STANDARDISATION

**Leader:** Dianne Campbell

In the introductory session, Susan Prescott reminded the group that one goal of the network was **prospective harmonization** of new cohorts or intervention studies, particularly around **clinical measures** and the **timing of assessments and biological sampling**.

For **clinical trials or intervention studies**, it is also desirable if we can **share protocols** for parallel studies and parallel grant applications. This will facilitate larger data sets, as well as assessing differential effects in different environmental settings or genetic groups.

Dianne indicated that although it was not realistic to achieve harmonization of all laboratory methods we agreed that sharing of protocols would lead to natural harmonization across the network for future studies. In some key areas it was agreed that standardization should be attempted, particularly in the timing of collection of bio-samples from birth cohorts (stool, breast milk) and methods for storage. Each Chair of the relevant working party has agreed to compile an agreed upon list which will be sent to Dianne to be housed in central web based repository with access for all inflame members (see below). It was agreed that these documents and protocols should be dynamic and iterative and subject to yearly review by the chair of the relevant working party.

## PROGRESS TOWARDS DATA REPOSITORY and mechanisms for Group Interaction

**Leader:** Dianne Campbell

The group discussed what the basic requirements for an inflame website would be, and we agreed that a detailed discussion board was not required at this stage.

We agreed that a password protected site which was well organized with folders and subfolders with protocols and relevant curated documents would be sufficient for the group's current needs and that Dianne would investigate possible user friendly platforms. It was also agreed that massive numbers of protocols/documents would not be useful and that the Chairs of the relevant working parties would act as a curators in association with their working party to send on to Dianne the most relevant documents for uploading. Dianne agreed to be the contact person and inflame member responsible for uploading documents and protocols. It was suggested that the website be referred to as the "inFlame House".

We agreed to trial a bimonthly e-newsletter which would serve as a simple way of keeping communication going in-between face-to-face meetings. Dianne agreed to organize and compile and distribute this e-newsletter, and items for the newsletter will be solicited by email request for any items.

## PROGRESS TOWARDS GOVERNANCE

**Leader:** Katie Allen (in absentia) – Anne-Louise Ponsonby

Several models were presented. The one that seemed most suitable was that of an international cancer network. In that scenario the governance and IP were developed on a case-by-case basis according to the project and the partners involved. The process was overseen by the general umbrella of the network which comprises a relatively small secretariat. This has in-built flexibility and simplicity and seems to suit the evolving and changing needs of our network. At present this is how things are naturally evolving with In-FLAME.

## PLANS FOR 2014-2015

**Leader:** Susan Prescott

There were a number of suggestions raised:

- **A monthly e-newsletter** – which will include reminders as well as updates! Dianne Campbell has offered to organize this.
- **A mid-year teleconference** – to plan the 2015 program (Mike Levin has offered the teleconference facilities of UCT and Nick Haskins at WUN has also offered to support this)
- **A possible informal gathering at EACCI in June 2014**
- **The next 2 day workshop in 2015:** The next WUN meeting is in Hong Kong, April 27-30, 2015, which provides one option. The other option is that Harald Renz has offered the possibility of a small castle in Germany (near Frankfurt, which would be very convenient for most travellers). This could be at any time convenient, but might work if it preceded the EAACI Barcelona





meeting in June (i.e in late May 2015). Harald will explore availability. This avenue would also mean the opportunity of applying for a German grant to support the meeting (around EUR 20,000).

- **Susan will approach members in the coming months to form a workshop organizing committee**

**Regardless of destination there was strong sentiment to remain affiliated with WUN.**

\* \* \*

**Another very successful meeting concluded with many thanks to Susan,  
all session leaders and all participants!**

