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# The Broad Street Pump



## The Tuberculosis Centre of Research Excellence

**Dr Gabriella Scandurra (Executive Officer)**  
*NHMRC Centre of Research Excellence in Tuberculosis Control, TB-CRE*

The Tuberculosis Centre of Research Excellence (TB-CRE) received \$2.5 million of funding from the National Health and Medical Research Council (NHMRC) over a 5 year period (2013—2017). The TB-CRE is a multi-disciplinary centre that supports world-class research to improve coordination between and strengthen existing research initiatives in Australia on public health interventions, epidemiological understanding, basic science approaches and ethical/legal challenges related to TB control. There is an urgent need for better, more accessible, and more affordable diagnostics and therapeutics as well as improved case finding strategies to reduce TB-related morbidity and mortality, and to limit ongoing disease transmission.

The ultimate goal is to minimize TB transmission and the TB-associated disease burden within Australia, and to make substantial contributions to global TB control, especially within the Asia-Pacific region. Priorities on the TB-CRE's research and translation agenda include: improving the management and prevention of childhood TB, reducing the case detection gap, exploring the immunology of TB, discovering new biomarkers and vaccine candidates, and using novel genomic approaches to understand the emergence and spread of drug-resistant *M. tuberculosis* strains. This can only be achieved if the existing and emergent ethical and legal dilemmas related to TB control can be addressed and overcome.  
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Westmead Hospital, Sydney

*Friday, 15 November 2013*

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University of Sydney

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Each of these areas of expertise are covered within the TB-CRE. In addition, we recently employed a post-doctoral fellow with extensive experience in anthropology. Understanding the cultural and social influences within a community are important to the international projects that the TB-CRE are involved in. Currently the TB-CRE has projects funded in Vietnam, Indonesia and China, with existing collaborations in India and the Pacific, further expansion of these are envisaged.

The TB-CRE hopes to help foster the next generation of TB researchers through the national and international collaborations facilitated by the centre. For a more detailed overview of the TB-CRE structure and activities please go to [www.tbcre.org.au](http://www.tbcre.org.au). Regular website updates provide information on TB-CRE activities and recent advances in the field.



## The Fight Against Tuberculosis in Vietnam

**Dr Greg J. Fox, MBBS PhD**  
**Centenary Institute**

A well-known Vietnamese proverb, “*Có chí thì nên*”, can be translated as “where there’s a will, there’s a way”. The saying captures the resolve of the research partnership between the University of Sydney and the Vietnam National Tuberculosis Program (NTP) to combat the deadly disease tuberculosis. Tuberculosis (TB) is an airborne infectious disease that has a major health impact in many developing countries including Vietnam, where its prevalence is among the highest in Asia. Only a half of the 180,000 new cases each year in Vietnam are diagnosed with the disease [1], indicating a major gap in the health care system. To address this issue, we have established several major research projects to improve TB control in Vietnam.

As a respiratory physician and epidemiologist, my main research interests are strategies that enhance the diagnosis and control of TB in high-prevalence settings, as well as factors affecting TB transmission and human genetic susceptibility to the disease. Living in Vietnam from 2009 to 2013, I have worked closely with the Vietnam NTP and Professors Guy Marks and Warwick Britton in Sydney to establish a research office in Vietnam, and implement a number of research projects relating to TB. Over the last four years, our Hanoi office has expanded to include more than 10 full-time staff and two expatriate researchers. In addition, over 300 Vietnamese health care workers have an active role in our projects. We now have a strong platform upon which we can undertake research in Vietnam, ranging from basic science to public health and policy-focused projects.

### **Tuberculosis household contact investigation studies**

The first major research project undertaken by the Woolcock Institute at Sydney University is the ‘ACT2’ contact investigation study. This study, which began in 2009, focuses upon a population at a high risk for developing TB, namely household contacts of patients with infectious TB. While systematic screening of exposed contacts is routinely performed in most developed countries, there has been little evidence to demonstrate its feasibility or effectiveness in resource-limited settings such as Vietnam.

Hence, the ACT2 study aims to compare the diagnostic yield of ‘active’ screening of household contacts to the yield of ‘passive’ diagnosis obtained by routine practice.

This randomized controlled trial enrolled adult TB patients and their household contacts in 70 district TB clinics throughout the country. Contacts are screened four times over two years, using chest X-ray and symptom screening – with microbiological testing performed for contacts with suspected disease. Control subjects were enrolled and followed, without any screening intervention. The study was fully integrated within the NTP, with participant recruitment and follow-up undertaken by government health care workers. A comprehensive monitoring and evaluation process was also implemented to ensure the quality of the research was sustained.

Following a pilot study in 4 districts in Hanoi, the main study has been undertaken in 70 district TB clinics in 8 Provinces throughout the country. Both rural and urban regions were represented. By June 2013, 10,818 patients and 25,329 household contacts had been recruited and 157 contacts had been diagnosed with TB. The follow-up for this NHMRC funded study will be completed in 2015.

### **Community screening for TB study**

Another major study of TB case detection will commence in the second half of 2013. The ‘ACT3’ study is a randomized controlled trial of community-based screening. The study will enroll entire villages of adults in a remote rural province in the far south of Vietnam. Health care workers will perform house-to-house screening, with symptom screening and sputum testing using a mobile nucleic acid amplification test, Xpert MTB/RIF. This ambitious study will recruit 120,000 adults and follow participants for four years. 60,000 people will be screened each year. This study will also use molecular epidemiology and spatial network analysis to explore transmission of TB within the community, and identify sub-populations at high risk of the disease. This project, funded by the NHMRC, will be completed in 2018.

## The Fight Against Tuberculosis in Vietnam

### Host genetic susceptibility to TB study

The Centenary Institute at the University of Sydney has also partnered with the Vietnam NTP to undertake a major study of human genetic susceptibility to TB. Three hospitals in northern Vietnam have enrolled over 1,500 TB patients and 1,500 healthy control subjects, with a goal of comparing their genetic profiles to determine whether there are any specific factors associated with susceptibility to TB. DNA is extracted from blood samples and transported to Sydney, where it is tested for a range of genetic variants that may explain increased susceptibility to human TB. Testing of a number of genetic variants has identified some promising variants, with further recruitment and testing to be conducted in the near future.

### Research capacity building in TB

Over the past three years, we have established a research training program for Vietnamese health care professionals – the Methods in Epidemiological, Clinical and Operations Research (MECOR) training program. Under the leadership of Professor Guy Marks from Sydney University, Professor Sonia Buist from Oregon and Professor Nguyen Viet Nhung from the Vietnam NTP, we have held annual week-long residential courses for pulmonologists, nurses, laboratory staff and allied health workers from throughout Vietnam. The majority of faculty are Vietnamese, teaching alongside researchers from Australia and the United States. The annual live-in course involves the design and implementation of locally relevant research within the Vietnamese setting – with a goal of publication in international peer reviewed

literature. Over 75 students have been through the program, with some students progressing to higher research degrees following the courses. Over time, the goal will be for Vietnamese to take complete ownership of this course, to increase sustainability.

### Lessons learned

The establishment of our Vietnamese collaboration has taught many useful lessons that prepare us well for ongoing activities. Most importantly we have seen that it is essential to have reliable partners, and have a relationship built upon mutual respect and trust. It is essential to try and understand the local context, and before undertaking a project it is important to spend time assessing the capacity and needs of the health care system in which the research is implemented. Careful quality control and monitoring of each aspect of the research is important, particularly at the early stages of implementation. Finally, as in any setting, perseverance is the key to research success in Vietnam. As the above Vietnamese proverb suggests, a strong will and determination are essential to find a way forward, in many areas of life. And this is particularly true when confronting the challenges of TB, in the challenging research environment of Vietnam.

*Acknowledgement: Lead investigators in these research projects include: Professor Guy Marks and Professor Warwick Britton, from Sydney; and Associate Professor Dinh Ngoc Sy and Associate Professor Nguyen Viet Nhung, lead investigators from Vietnam.*

### Time-line of the Woolcock Institute research in Vietnam

Date	Activity
1990s	Establishment of relationship between the Woolcock Institute and Vietnam National Tuberculosis Program
2001-3	PhD student from Vietnam studies in Australia
2009	Commencement of pilot study of contact investigation study (ACT1) in Hanoi, Vietnam Commencement of Host Genetic Susceptibility to TB study (GenTB)
2010	Recruitment commences to ACT2 household contact investigation study in 8 Provinces in Vietnam Establishment of Woolcock and Centenary Institute research offices in Vietnam; Recruitment of first full-time staff Commencement of MECOR Vietnam course
2011	First epidemiology research course (MECOR) held in Hanoi, Vietnam
2013	Community TB screening study (ACT3) commences, southern Vietnam

### Reference

1. World Health Organization (2012) *Global tuberculosis control 2012*. Geneva

## Tuberculosis Research in China

Dr Magda Ellis

Centenary Institute

It is estimated that more than 5 million people in China have active tuberculosis (TB), 80% of whom reside in rural areas [1]. Despite considerable TB control efforts over several decades, the recent 2010 national TB survey indicated that TB has remained constant in China over the past decade. The current prevalence of active cases is estimated to be 459/100,000 with far greater numbers in the western provinces [2]. Ningxia Hui Autonomous Region is the smallest province in North-west China, situated just south of inner Mongolia. Ningxia is one of the poorest provinces with the third lowest GDP and has one of the highest prevalence rates of active TB in the country. From national prevalence surveys, it is clear that Ningxia has been hyper-endemic for TB for several decades [3, 4] and had an estimated prevalence of more than 600/100,000 in 2010.

As a genetic epidemiologist with a strong interest in infectious diseases I have been undertaking research in China for ten years. My research in tuberculosis in Ningxia province began in 2010 to investigate human genetic susceptibility to pulmonary TB in collaboration with Ningxia Medical University with whom I had already worked on other projects. Susceptibility to tuberculosis, like many infectious diseases, is characterised by a disproportionately low number of active disease cases compared to those who have been exposed and remain latently infected during their lifetime. This variability in susceptibility in the population has been attributable, at least in part, to host genetic factors. Evidence to support a genetic effect in TB susceptibility has come from twin studies [5], ethnic clustering of disease [6] and more recently through association studies of both common and rare mutations [7]. Although genetic studies have identified some susceptibility loci, many of the relevant genes that determine susceptibility to TB remain largely unknown. The high prevalence of active TB in Ningxia, in combination with the infrastructure in place for diagnosis and management of active TB cases throughout the province, facilitated rapid recruitment of large numbers of cases and controls with more than 3000 cases and 3000 healthy matched controls recruited to this project in less than two years. High throughput genotyping is currently underway representing the largest genome-wide association study (GWAS) for tuberculosis to date.

During the progress of the study, more collaborative links were established in Ningxia, principally with NIDH, the largest hospital for TB in the province. NIDH diagnoses approxi-

mately 1300 cases/year. Together, we undertook a retrospective case study of all notified cases registered in Ningxia province between 2005 and 2009 to evaluate the current epidemiology of TB in NHAR since the introduction of the Directly Observed Treatment Short-Course (DOTS) across the province in 2004 [8]. One of the most important findings of the study was a reported annual notification rate of only 61/100 000 population highlighting under-diagnosis as a serious problem in this region. This is an important TB control issue, since undiagnosed cases are sources of on-going transmission. This was further exacerbated by long delays with patients often waiting longer than six months after becoming symptomatic to seek medical attention. This was reflected by a high proportion of cases that presented with extensive radiological disease at time of diagnosis. Our study also demonstrated extensive and prolonged use of TB drugs by a large proportion of patients with 10% of patients being on treatment for longer than three years reflecting poor case management and inadequate DOTS implementation [8]. It was hypothesised that such prolonged and inconsistent exposure to TB drugs would have resulted in high levels of drug resistance prompting NIDH to undertake a pilot study to determine the prevalence of DR in the region. Drug sensitivity testing (DST) was undertaken in 180 randomly selected patients on standardised treatment. Drug resistant was evident with 16.6% and 1.7% of cases shown to have multi-drug resistant (MDR) and extreme drug resistant (XDR)-TB, respectively (data unpublished).

These studies combined strongly suggest that new control strategies and interventions are required in this region to reduce transmission of TB and DR-TB. Indeed, the high prevalence of drug resistance in the region has already gained financial support from the national TB control program to undertake drug sensitivity testing for all new cases diagnosed at NIDH as well as all 'treatment non-responders' across the province emphasizing the role of NIDH as the provincial reference laboratory. DST is essential for diagnosis of drug resistant TB, but the slow growing nature of TB results in significant delays to obtain results using standard culture methods as used in Ningxia province. For MDR cases, standard culture also remains the most effective method of monitoring treatment response. Improved methods to identify those at greatest risk of MDR-TB and to predict treatment success or failure in these cases is essential to improve control. New projects have now been developed to tackle some of these issues, shown in table 1 (next page).

## Tuberculosis Research in China

A longitudinal cohort analysis of all patients diagnosed at NIDH was initiated in 2013 to provide a comprehensive overview of drug resistance profiles and treatment outcomes in order to enhance patient care by assisting individual patient management, refining standardized treatment approaches and guiding resource allocation for improved TB control. Combined with detailed risk data (to begin in 2014), this will assist in identifying patients at greater risk of drug-resistance and poor treatment outcomes and who may benefit from alternative treatments and/or management strategies. This will be complemented by a study to identify a panel of biomarkers that predict treatment outcomes in both TB and MDR-TB cases using both transcriptional and protein level markers.

A further study to understand the evolution of drug resistance has also been initiated in 2013. This project will use whole genome sequencing in serial isolates that have acquired drug-resistance during treatment. The aims of this study are to deter-

mine the sequence in which resistance mutations accumulate during treatment, the rate at which MDR-TB is acquired and the impact of these mutations on treatment outcomes as well as identify if specific strains have greater capacity to mutate and develop multi-drug resistance.

Ningxia province has historically been one of the poorest provinces in China. Despite recent funding by the national TB program and Global Fund to improve infrastructure for diagnosis, treatment and case management, TB remains a significant problem in the region. With our strong existing collaborative links within Ningxia Province and support of the local TB control program, our ongoing research projects aim to enhance our understanding of drug resistance in a high burden setting and improve patient care. We hope that findings from this understudied part of China would not only have relevance for other remote parts of China, but also for surrounding countries and for global TB control efforts.

**Table 1. Past, present and prospective studies in NHAR.**

Project description	Project start
A genome-wide association study (GWAS) to identify genetic factors that contribute to risk of disease	Since 2010
An epidemiological evaluation of all notified TB cases from 2005-2009	2010-2012
Spatial and space-time clusters of tuberculosis in Ningxia	Since 2011
Risk factors for MDR-TB and poor treatment outcomes	Since 2013
Evolution of resistance and compensatory mutations during TB treatment	Since 2013
Biomarkers of poor treatment outcomes in TB and MDR patients	To begin 2014

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Nathan undertook post-graduate studies in the School of Molecular Bioscience at the University of Sydney. Pursuing an interest in infectious diseases he applied proteomics to study transmissible *Pseudomonas aeruginosa* strains circulating widely amongst cystic fibrosis (CF) patients in Eastern Australia. Combining a novel *in vitro* culturing model for CF lung infection along with a variety of cutting-edge proteomic approaches Nathan deciphered potential virulence mechanisms utilised by CF epidemic *P. aeruginosa* for successful lung infection, and thereby provide potential vaccine candidates or therapeutic targets.

A key finding included the enhanced production of secreted iron-scavenging molecules specific to the CF lung microenvironment and hence may provide a potential target for therapy. His recent post-doctoral studies have focussed on the molecular adaptations of CF epidemic *P. aeruginosa* as disease progresses from acute to chronic persistent infection, with a view to identifying biomarkers correlated to disease progression.

Nathan also has an interest in post-translational modification of proteins including glycosylation, which has been demonstrated to play a key role in host-pathogen interactions. Nathan has authored a number of papers in prominent journals with clinical relevance to CF lung infection.

As an appointed Post-doctoral research fellow of the Tuberculosis Centre for Research Excellence, Nathan hopes to utilise his experience to contribute to the centres ultimate aim of global elimination of TB by 2050. Under the guidance of Dr Bernadette Saunders at the Centenary Institute, Nathan will be examining the host-response to TB infection to identify biomarkers of disease that may lead to improved diagnostics and novel targets of therapy.

## CONTACT US

For more information on any articles or CIDM-PH & SEIB events, or to join the e-lists and receive regular updates, please contact us at:

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Elena graduated as a clinical biochemist from the University of Uruguay where she developed particular research interest in mechanisms of antibiotic resistance in gram negative bacteria. This interest led to her post-graduate studies at University of Technology, Sydney where she investigated antibiotic resistance modules in the opportunistic pathogen *Pseudomonas aeruginosa*. After earning her PhD at UTS in 2013 Elena joined the CRE in Tuberculosis team in June 2013 as a postdoctoral researcher. Elena is based at the NSW Mycobacterium Tuberculosis Reference Laboratory at the Centre of Infection Diseases and Microbiology (CIDM), ICPMR-Pathology West at Westmead Hospital.

### RESEARCH INTEREST

Elena is passionate about the discovery of novel mechanisms of antibiotic resistance in pathogens of public health significance, from acquisition of resistance clusters to regulation of intrinsic mechanisms. In particular, she is interested in genetic contexts and their influence in the evolution of MDR at regional or global levels. Antibiotic resistance is a global problem with some predicting a return to the pre antibiotic era where a bacterial infection was commonly fatal. Multi drug-resistant (MDR) isolates had emerged by intrinsic and acquired mechanism which often act cooperatively to generate complex MDR phenotypes. Elena studies the different mechanism involved in antibiotic resistance, from acquisition of resistance clusters to regulation of intrinsic mechanisms. In particular, she is interested in genetic contexts and their influence in the evolution of MDR at regional or global levels.

Much of Elena's work has been in explaining resistance profiles where the common resistance determining pathways fail to do. In CIDM she will be continuing to explore antibiotic resistance in the causative agent of human tuberculosis, *Mycobacterium tuberculosis*. Tuberculosis remains a global emergency, where MDR and XDR profiles can't be completely explained by modifications in the already studied chromosomal genes. Further research is necessary assessing more and/or simultaneous mechanisms of drug resistance and their potential fitness costs.



## UPCOMING EVENTS...

### **Healthcare Associated Infections - More Tricks for Old Dogs Symposium**

*Friday, 22 November 2013*

*Westmead Hospital, Sydney*

**Program & Registration:**

*Visit the CIDM-Public Health or SEIB website  
for a full copy of the HAI program and registration form.*

### **CIDM-PH Colloquium**

*Westmead Hospital, Sydney*

*Friday, 15 November 2013*

*Program TBA*

### **SEIB/ SIBRN Colloquium**

*New Law School, University of Sydney*

*Thursday, 5 December 2013*

*More information: [www.sydney.edu.au/seib/](http://www.sydney.edu.au/seib/)*



## Dr Paul Mason

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With fieldwork experience spanning Indonesia, Brazil and India, Paul has commenced research with the TB-CRE to undertake an ethnographic study of Tuberculosis in Vietnam. He studied Biomedical Science at Melbourne University and gained laboratory experience at the Howard Florey Institute, University of Western Sydney, Australian National University and the Université Louis Pasteur. After later completing Honours in physiology at Melbourne University, Paul moved into anthropology where he developed his fieldwork research skills and cultivated his passion for languages, culture, and the study of human experience. He was conferred his PhD in anthropology at Macquarie University in 2012. Since 2006, Paul has taught a range of university courses at Macquarie University, Sydney University, Melbourne University, Latrobe University and the University of Western Sydney. Paul was awarded the Global Leadership Excellence award by Macquarie International in 2011 and was recently ranked twelfth nationally in the Unijobs Lecturer of the Year Awards 2012.

### RESEARCH INTERESTS

Living systems are increasingly being modelled in terms of degeneracy—a term which in biology refers to the structural variation underlying functional plasticity. Degeneracy allows researchers to conceptually model heterogeneous configurations that arise from the interaction of variable factors. Paul has written about the history and philosophy of biological degeneracy and applied this concept to processes at multiple levels of complexity—from biological to cultural systems. His work on degeneracy has been applied in biology, economics, sports science, medicine, and anthropology. Paul brings his ethnographic fieldwork skills and this dynamic systems modelling approach to TB research in Cà Mau, the southernmost province of Vietnam.

### ***HEALTHCARE ASSOCIATED INFECTIONS – MORE NEW TRICKS FOR OLD DOGS SYMPOSIUM***

This symposium will bring you up to date with the latest trends in HAI Prevention and Control research and practice by exploring issues such as the interface between hospital and community; innovative approaches to understanding and influencing healthcare worker behavior using video reflexive methods and advances in surveillance and control of MRSA. Our two keynote speakers, Professors Nicholas Graves and Jon Iredell will present current data on important areas of HAI prevention and control research.

Friday, 22<sup>nd</sup> November 2013

9.00am – 4.00pm

Lecture Theatre 3

Westmead Education & Conference Centre,  
Westmead Hospital, Sydney

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