THE WINSTON CHURCHILL MEMORIAL TRUST OF AUSTRALIA

Report by JUNE LIU

2014 Churchill Fellow

To study the relationship between myxoma virus and rabbits to understand the evolution of infectious agents for predicting emerging diseases in the future

Signed: June Liu Dated: 6, Feb, 2015

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INTRODUCTION

I am an early career scientist with wide experience in working with human pathogens (such as influenza virus and West Nile virus) and rabbit pathogens (rabbit calicivirus and myxoma virus). My career aspiration is to understand infectious pathogens and diseases, and contribute to building a strong biosecurity shield to protect people, livestock and wildlife.

In line with the goal of benefitting Australian society for the long term, Churchill Memorial Trust honoured me with a Fellowship to support my project on understanding the evolution of myxoma virus. This great honour and the exciting experiences I had at the Centre for Infectious Disease Dynamics (CIDD) of Pennsylvania State University (PSU) in the USA were the best things that happened to me in 2014.

My main activities for the project between 16 September and 14 November 2014 were:

- Carrying out animal experiments to determine the virulence of myxoma virus strains: learning to work with animals by participating in intensive animal experiments that examined the phenotype of myxoma virus strains in rabbits and explored the evolution of novel immunosuppressive capacities in recent viruses.
- Learning the pathology of myxoma virus in rabbits and how to undertake autopsies, collect samples and analyse samples to understand the evolution of virulence.
- Actively developing contacts with scientists in the field and attending meetings and seminars to broaden my knowledge in the field of infectious diseases.

The aims of this report are:

1) To communicate the knowledge and skills I learnt from my project;
2) To discuss the importance of establishing a Research Centre for Infectious Disease in Australia;
3) To share the lessons I think we should learn from the 2014 Ebola epidemic;
4) To share the experience of my trip and my passion for contributing to Australian society.

The highlights of this report are the skills I learnt, which are essential for me to work in the field of infectious diseases, more importantly the inspiration gained from working with new people that has developed my thinking and ambition as seen in the recommendation of establishing a Research Centre for Infectious Diseases and the two lessons I think we should learn from 2014 Ebola epidemic.

The potential readers of this report include: leaders in Government and industry, Churchill Fellows, academics, people working in public health and the biosecurity domain, the general public who care about our nation and the world.

Please bear in mind that this is not an academic report but the ideas presented here are based on my experience on performing my research project and working with great scientists.

Acknowledgements

I would like to thank Mr. Paul Tys (CEO of Churchill Trust), Mr. David Trebeck (chairman of ACT selection committee) and the Churchill Fellows of ACT and the National committee for giving me this great honour and opportunity to carry out my project. Ms. Meg Gilmartin, Ms. Louise Hurst and Ms. Sylvia Deutsch made my trip easy to organize and enjoyable – thank you very much!
I am grateful to Dr. Peter Kerr, Dr. Brian Cooke and Dr. Xin Hou for their support for my career development.
I appreciate Dr. Andrew Read, Dr. Isabella Cattadori and their team at CIDD for hosting my project. The intensive academic environment at CIDD inspired me to propose the main ideas in this report. So I am grateful to all the visiting scientists who came from all over the world to CIDD and presented their fantastic achievements. I feel very lucky to become a Churchill Fellow and to be a scientist working with great people.

EXECUTIVE SUMMARY

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Project description:

The increasing incidence of emerging infectious diseases poses great challenges for modern society. Understanding how pathogens evolved in the past may help us predict how new pathogens could emerge and evolve in humans, livestock and wildlife. Understanding the evolution of virulence requires measurement of the virulence of samples collected during outbreaks and the analysis of the genetic evolution of these pathogens. Two classic experiments in evolution of virulence happened when myxoma virus was released, first in Australia and later in Europe, during the 1950s as a biological control agent for European rabbits. This evolution is still ongoing. I used this model of myxoma virus and rabbits to understand the evolution of pathogens for better prediction of emerging diseases in the future.

Highlights of the places I went and the people I met:

The project was done at the Centre for Infectious Disease Dynamics (CIDD) of Pennsylvania State University (PSU) in the USA. This research centre hosts distinguished scientists working across the broad area of infectious agents and diseases: from genes and proteins of pathogens to disease dynamics, by integrating knowledge and skills from disciplines such as disease ecology, epidemiology, virology, evolutionary biology, genomics, immunology and mathematical modelling. The people I met were: Professor Andrew Read, Head of CIDD; Professor Peter Hudson, Director of Huck Institutes of the Life Sciences at PSU; Dr. Isabella Cattadori, Associate Professor of Biology at CIDD; Assistant Professor Matthew Ferrari at CIDD; Professor Grant McFadden, University of Florida.

What I learnt:

1. To design and perform large scale animal experiments, which is essential for study of infectious pathogens and diseases. To handle rabbits and clinically evaluate disease processes and to conduct autopsies and collect appropriate specimens. To process and analyse these samples to understand the evolution of viral tropism.
2. Myxoma virus evolved quickly in European rabbits and its genome is very flexible for mutation. As humans and most animals can't evolve as quickly as pathogens, we need to learn the principle of pathogen evolution and apply it for management of infectious diseases.
3. My visit coincided with the widespread Ebola outbreak in West Africa and this caused me to reflect on what I was doing and why. Two lessons from 2014 Ebola outbreak: 1) a leading agency to coordinate disease control at national level is important; 2) we need to change behaviours if necessary when there are outbreaks of infectious disease because we are the host species and our behaviours determine the disease dynamics to large extend.

How to disseminate and implement my learning in Australia:

1. Present my report to leaders in Government, industries and our society when possible.
2. Publish this report on the website of the Churchill Memorial Trust.
3. Circulate my report through Feral Flyer, the e-newsletter of Invasive Animals Cooperative Research Centre and within CSIRO, such as the Discovery Centre which is open to the general public.
4. Implement the animal experimental skills I learnt throughout my career in the research field of infectious diseases and share with other scientists and students.

PROGRAMME

The people I met at CIDD of PSU are listed in this table.

People	Title	Organization	Research interest	What I learnt from them
Dr. Andrew Read	Director of CIDD, Evan Pugh Professor of Biology and Entomology	Pennsylvania State University	Ecology and evolutionary genetics of pathogens	1) Pathogen evolution should be considered when we manage public health. 2) Essentials for my career development.
Dr. Grant McFadden	Professor of Department of Molecular Genetics and Microbiology	University of Florida	How viruses interact with the host immune system, development of new drugs	1) His passion to apply knowledge in therapy. 2) On the path of career aspiration, skills follow mindset.
Dr. Peter Hudson	Director of Huck Institutes of the Life Sciences, Willaman Professor of Biology	Pennsylvania State University	Ecology of wildlife diseases, including zoonoses	Animals, humans and environment, we are in the mess of infectious diseases together.
Dr. Isabella Cattadori	Associate Professor of Biology	Pennsylvania State University	Mechanisms of host-parasite interaction, how environmental conditions affect risk of infection	1) Rabbit experiment skills and knowledge about wild animal infection. 2) If I enjoy working, working hard is not hard anymore.
Dr. Nkuchia M'ikanatha	Adjunct Scholar of Centre for Clinical Epidemiology & Biostatistics	Pennsylvania University	Enhance infectious disease surveillance through efficient use of technology and workforce development	1) Effective surveillance for infectious disease needs collective efforts. 2) Communication between stakeholders is very important.
	Surveillance Epidemiologist	Pennsylvania Department of Health		
Dr. Matthew Ferrari	Assistant Professor of Biology	Pennsylvania State University	Understand patterns of disease incidence	1) Learn from Ebola, for now and for future. 2) Think globally, act locally. Start from what I am doing.
Dr. Firdaus Dhabhar	Director of Research, Stanford Centre on Stress & Health	Stanford University	The effects of stress on immunity and health	1) Management of public health is much more than medicine and hospital care. 2) Education on stress control may decrease our medical bills.

MAIN BODY:

From Myxoma Virus to Infectious Diseases:

Building a Strong Biosecurity Shield to protect our people

Part I. My Fellowship project on evolution of myxoma virus

My Churchill Fellowship project was done at Pennsylvania State University (PSU) in the USA from 16 September to 14 November 2014. The end of the trip was not the end of my fellowship, just the opposite, that trip was merely the beginning. Once a Churchill Fellow, I am always a Churchill Fellow. My trip as a Fellow will still be unfolding in the many years to come. As a scientist working in the research field of infectious disease, I am determined to develop my career in the biosecurity domain to protect the health of our people, the profits of our industries and the sustainability of our environment. In this sense, the Churchill Fellowship has been transformational for me as it has made me realise what I can aspire to achieve.

The aim of my project

The aim of my project was to understand emerging infectious diseases by using the biological control agent myxoma virus and rabbit as a model. Myxoma virus is one of the three famous poxviruses known to Australian society. The other two are variola virus and vaccinia virus. Variola virus causes smallpox and killed over 300 million people before it was eradicated by using vaccinia virus as a vaccine in humans. However, myxoma virus demonstrates a fascinating aspect of infectious agents: it does not kill American rabbits in which it evolved but it causes the fatal disease myxomatosis in European rabbits, which are a separate species. As a result, myxoma virus was introduced during the 1950s as a biological control agent to reduce the number of wild European rabbits, first in Australia and later in Europe [1, 2].

The release of myxoma virus into wild rabbit populations on two continents started a classic experiment in evolution of virulence in nature and the pioneering studies of Professor Frank Fenner in Australia provided a profound understanding of this host-pathogen co-evolution [3], showing what happens when an infectious agent jumps into a new species and causes a fatal disease. Species jump is the starting point of zoonoses such as Ebola and HIV-1 as well as influenza pandemics such as H1N1 swine flu in 2009. Zoonoses emerge when pathogens jump from animals into humans and establish in human populations, sometimes causing illness or death [4]. A survey showed that 60% of infectious diseases that emerged between 1940 and 2004 were zoonotic [5]. Although we have

increasing incidence of zoonoses now, it is still hard to study the disease dynamics and pathogen evolution over the long term in humans, because intervention to stop the disease is necessary and of course one cannot do experimental studies. This makes the ongoing myxoma virus and rabbit evolutionary arms race more valuable for us to study, even 65 years after its release. Nevertheless, investigation of other pathogens enriches our understanding about infectious diseases as well. Understanding how viruses evolved in the past may help us predict how new pathogens could emerge and evolve in humans, livestock and wildlife.

How to investigate the evolution of myxoma virus in my project

Investigating the evolution of virulence requires measurement of the virulence of samples collected during outbreaks and analysis of the genetic change in the pathogens. The strategy of my project was to use domestic rabbits to measure the virulence of myxoma virus strains isolated from wild rabbits during the past decades and determine the pathology they cause in rabbits. I was also involved in the larger experiments which were aimed at understanding novel means of immune suppression that the viruses have evolved. Meanwhile, the DNA sequences of the genomes of many strains of the virus were determined using next generation DNA sequencing techniques. This enables us to explore the relationship between the evolution of virulence and the mutations in the virus genome over time.

My research project at CSIRO is a part of a 5-year grant founded by National Institute of Health (NIH) of the USA. This grant supports scientists in the USA and Australia to work together on understanding the evolution of myxoma virus in wild rabbit populations in Australia and Europe. Driven by my passion for understanding infectious pathogens and diseases, I want to build collaboration with the top scientists in this field to develop big picture projects in the future. Luckily, I got the support from Churchill Trust in 2014 to carry out my project in the USA. My supervisor Dr. Peter Kerr is an expert working in CSIRO for 24 years on myxoma virus, rabbit calicivirus and rabbit control projects but he is planning to retire in a few years. He is delighted to pass his skills on animal experimentation to me.

How we carried out my project in the USA

There were two main components to the work I did. The first was animal studies involving detailed experiments aimed at understanding the virulence and pathogenesis of myxoma virus isolates, in particular the novel means of immune suppression that appears to have evolved both in Australia and in Europe. We also correlated the clinical observations with genomic analysis. What I learnt was: 1) how to conduct detailed clinical examinations to assess the condition and disease status of

individual animals; 2) detailed autopsy and pathology examinations to understand disease progression and how to sample tissues for further virological and pathological studies.

The second component was laboratory analysis of tissue samples in the Millennium Science Complex (Figure 1). The laboratory work included processing tissues and measuring virus level in each tissue to explore how the viruses were evolving and altering tissue tropism. I already had all the basic techniques in virology for the laboratory analysis but what I learnt was the power of quantitative measurement for understanding the interaction of these differently evolved viruses with the host immune system.

Figure 1. Millennium Science Complex at Pennsylvania State University, State College of the USA; the building I worked in during my project.

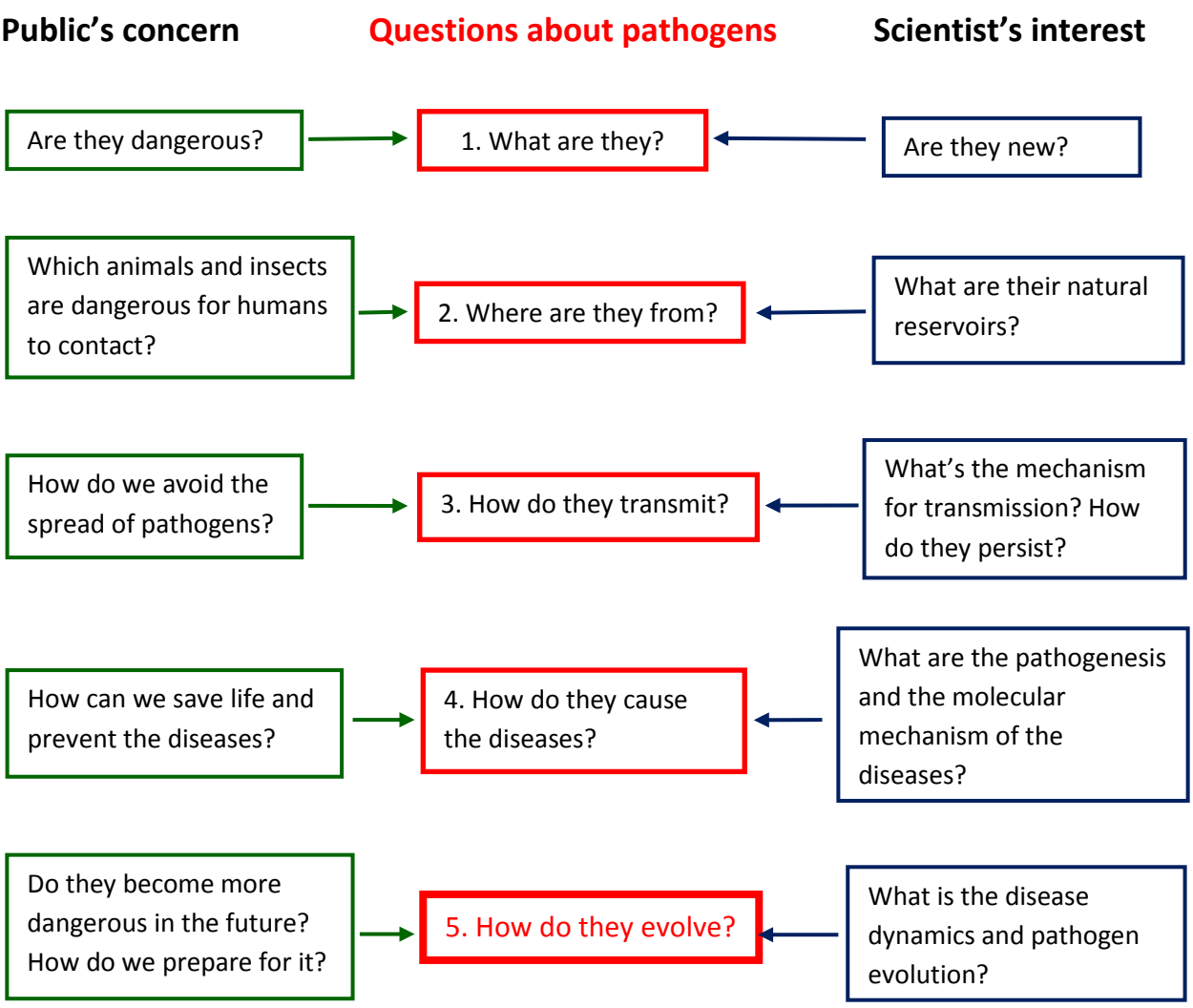
My experience at the Centre of infectious Disease Dynamics (CIDD) of PSU

During the trip, I found my passion for science has never been stronger. At the end of the trip, when I told Peter I did not want to leave CIDD, he said: “well, that is always my problem when I visit a university like this. The option is: we leave for now and we come back again when the next opportunity comes.” At that moment, I realized what kind of door was opened by the Churchill Fellowship for me, for my career, probably for the biosecurity shield in Australia as well. And, there is another option for staying in such an exciting academic environment. I will come to this later.

The building I worked in is a hotspot in the research field of infectious diseases. CIDD hosts distinguished scientists with broad research interests from infectious agents to vectors (insects transmitting diseases), from wild animal population dynamics to management of malaria resistance. The extra bonus for me being in the building was the access to several academic seminars every week. The speakers were from top-class universities, such as Harvard University, Stanford University, University of Florida, etc. The topics covered human pathogens, evolution of microbes, animal behaviour, immune system and community attitudes to vaccination. Inspired by the speakers, I started thinking about the big picture of the research field of infectious diseases.

Part II. A research centre to address the key questions in the field of infectious diseases

To support a strong biosecurity shield in Australia, we need a collaborative research centre which addresses at least the five essential questions in the field of infectious diseases (see below). The general public and scientists may focus on different aspects of the same question but the knowledge we can learn is useful for our common goal, fighting against infectious diseases. To explain the importance of each question, I give a brief introduction in following sections.



1. What are they?

We cannot see most of the pathogens without a microscope because they are so small. This is why, in many cases, we don't know of the existence of pathogens until they cause diseases. Usually, the emerging of infectious disease leads to investigation of the causative agent then a new organism is

"discovered" or an old one is identified as the cause of the disease. Once the pathogen is isolated, molecular and biochemical techniques can be used to analyse the components of the pathogen. Genome sequencing is used to decode the information from its genetic code. Usually, genomic information is enough to identify the pathogen. Once the identity of a putative pathogen is confirmed, we can infer some of its characteristics based on what is known about related species. If it is a new pathogen, we may need more investigation.

2. Where are the pathogens from?

The answer to this question is hard to determine because, often, the natural reservoir of a pathogen does not show obvious clinical signs of disease. The natural reservoir of vaccinia virus is still unknown, although we used this virus as a vaccine to eliminate smallpox. Most pathogens don't get our attention until they cause disease in humans and animals. Quite often, they come from wild animals. For example, the natural host of Severe Acute Respiratory Syndrome (SARS) Coronaviruses was originally thought to be the fruit civet but, years after the 2003 pandemic, more evidence suggested horseshoe bats as their natural reservoir [6]. The difficulty of investigating wild animals is obvious: not only they are hard to trace and sample, but also some of them are endangered species. When they get sick, they die quietly in the wild.

3. How do pathogens transmit?

The fact that the diseases caused by infectious agents are transmissible is frightening, especially in a world so well connected. There are only a few ways for pathogens to transmit between hosts: physical contact, via air or vectors such as insects. One way to investigate the method of transmission for human pathogens is to trace the contact history of patients during an outbreak and to check the distribution of pathogens in human tissues. It is much harder to find out the transmission route between animals, especially wild animals. Not only because they don't speak our languages, but also it is possible that more than one way and more than one species are involved in transmission. Another question is how pathogens persist in the environment over years. This question emphasizes the importance of our understanding about the ecosystem we live in: all the species (including humans, animals, microbes etc) in our environment and the relationships between them.

4. How can we treat or prevent infectious diseases?

If an infectious agent causes disease and death, the most important question people ask is how we treat or prevent the disease. Unfortunately, except for supportive treatment, we still don't have effective medicines to treat diseases caused by many pathogens, particularly viruses. Some scientists can develop new drugs in the lab and proceed to test the drugs in animal models. However, the

difference between model animals and humans varies and any conclusion based on model animal study has to be tested carefully in humans. So if the drug can pass the animal test, scientists can start looking for big funding to support phase I, II and III clinical trials, and the process of getting approval. As the whole picture of pathogenesis caused by many pathogens is not fully understood and the details of molecular mechanism in many cases are unknown, this poses a huge barrier for developing and marketing new drugs. This means prevention is paramount.

By using vaccines we have successfully controlled or eliminated some infectious diseases such as smallpox and measles. However, vaccines work only when they are administrated in advance of infection. This means that, ideally, vaccines should be developed before the start of endemic by anticipating the type of pathogens. Without understanding the evolution of infectious agents, anticipating the antigenicity of the next pathogen is only a guess.

5. How do pathogens evolve?

Understanding the evolution of pathogen and the disease dynamics in host populations are critical for control of infectious diseases. One way to study the evolution of pathogens is to observe it under laboratory conditions. For example, vaccinia virus rapidly acquired higher fitness through transient gene amplification which counteracted the selective pressure imposed by a human cell line [7]. The increase in genome size facilitated the subsequent gain of an adaptive amino acid substitution in the protein which defeated the immune defence of the cells. After the amino acid substitution became dominant in the virus population, the gene amplification reduced to offset the cost associated with the larger genome size [7]. This “gene-accordions” demonstrated beautifully how poxviruses can rapidly evolve to adapt under new selection pressure.

Another way of understanding pathogen evolution is to observe what happened in nature. As Dr. Kerr and colleagues wrote, “A massive biological experiment of emerging infectious agent jumped into its new host was repeated on two continents — this is the release of myxoma virus into wild rabbits in Australia and Europe. The shift in species, initial extreme virulence and subsequent host-pathogen co-evolution, in a species with prolific reproduction and short generation time, plus the ability to undertake experimental studies in the same host species, made myxomatosis the paradigm for what happens as an emerging pathogen adapts to a new host” [8]. This is what our 5-year research project on evolution of myxoma virus is about.

The main conclusions of the myxoma virus evolution project

1. Myxoma virus evolved quickly in its new host European rabbits. This is demonstrated by the change of its phenotype: the virus attenuated in a short period of time after its release in 1950s and the less

virulent virus strains became dominant in the rabbit populations. However, recent virus isolates appeared to have evolved novel means to suppress the host immune system and change tissue tropism, probably in response to genetic resistance in rabbit populations.

2. The genome of myxoma virus is very flexible: there are many ways at genomic level for virus to adapt to its host. We found that there is no common genetic mutation responsible for attenuation or enhanced virulence of different virus strains we have studied so far.

Manage drug-resistant pathogens from the evolutionary perspective

The understanding of pathogen evolution is also useful for management of drug-resistance of pathogens. After a pathogen infects a host, it replicates quickly to large numbers. The genomes of the pathogens in one host are not necessarily uniform because mutation happens during genome replication. After the host immune system is activated or drug administered, billions of individual pathogens may be cleared. However, the rare resistant mutants in the pathogen population can be pushed to a percentage high enough for transmission to next host. So the evolution of drug-resistant pathogen continues in the next host. Many specific drugs for treating infectious diseases can induce resistant pathogens readily because pathogens evolve or mutate quickly. If we don't manage the issue of drug resistance well, the speed the pathogens developing resistance can be faster than the pace we investigate, design, test, re-test and produce new drugs, leaving some infectious diseases incurable.

We cannot stop the *de novo* mutation of pathogens; neither can we avoid using drugs. The good news is there are ways to manage the development of drug resistance. The main collaborator of my project, Professor Andrew Read, is addressing this major challenge for 21st century medicine. His group use malaria and mouse as a model system to explore ways to better manage drug resistance developed by pathogens so as to extend the useful life span of drugs. "The key is to manage the rate of spread of high-resistant pathogens because this determines the useful life span of a drug [9]," he wrote. Smart management of pathogen resistance not only leads to economic benefit from available drugs on the market, but also give us time to develop new drugs before the evolution of pathogens override our solutions to infectious diseases.

The importance of establishing a leading research centre to address the key questions

To effectively control pathogens, it is obvious that we need to know what they are, where they are from and how they transmit between hosts. Treatment and prevention for infectious disease are important for human society as that is the fundamental goal of our efforts. We need to keep

accumulating knowledge about pathogens and disease pathogenesis and improving our skills to develop drugs and vaccines. At the same time, emerging and re-emerging diseases makes the investigation of evolution of pathogens and disease dynamics important. So we need to address all the key questions mentioned above because any loose end may lead to failure to protect our people from infectious diseases.

The public's main concern is how we can control or prevent the outbreak of infectious diseases. Although the outbreak of infectious diseases may be perceived as outbreak of fire, the fire extinguisher for infectious diseases is not always readily available because the pathogens and disease dynamics vary a lot, in particular when new diseases emerge. Ideally, we should have a constantly working alarm system and various tools for known and high risk infectious pathogens. To achieve this, we need to support research in the field of infectious diseases to continuously accumulate knowledge, improve technology and provide solutions for control and prevention of emerging and re-emerging infectious diseases for the long term.

Supporting research in the field of infectious disease is also like buying health insurance for our nation. A person who cares about his health takes his insurance as a priority. It does not work well if you only start it when you are seriously sick. The waiting period and the levy for not continuously investing will hurt you badly in the long term. The same rules apply for supporting research.

Furthermore, supporting research in this field is more than developing knowledge and providing solutions. It demonstrates a nation's confidence for its economy and its commitment to strive for a better life. The positive impacts can be transformed into political influence in the world and economic benefits from our industries.

With limited resources available, we need to optimize our strategy so we may get the best benefit/cost ratio from our investments. To achieve this goal, I think a Research Centre for Infectious Disease (RCID) should be established to lead the research in this field. This is not a novel suggestion. What is new is that I have realised that I can help to drive this idea rather than standing back and waiting for somebody else to do something.

What scientists in this field can contribute to for fighting against infectious diseases?

Scientists can contribute in many areas for fighting against infectious diseases, such as:

1) To develop methods or test established protocols for disease diagnosis;
2) To investigate the infectious agent for development of drugs and vaccines;
3) To contribute to setting up practical protocols for health care workers by investigating the transmission of the pathogen;

4) To study the pathogenesis of the disease to support medical workers for developing effective treatments;

5) To collaborate with government agencies to propose appropriate quarantine measures and disinfection procedures;

6) To monitor disease dynamics, collect first-hand data and report to the world;

7) To work with media experts to communicate important information with general public;

8) To help to train volunteers for sampling, lab diagnosis and other relevant activities if needed;

9) To contribute to seeking international support because they have connections with international funding agencies;

10) To summarize the lessons we learn and recommend solutions for a better biosecurity shield.

I hope the ten points can deliver a strong message that a long term strategy supporting research in the field of infectious diseases can benefit our nation in many ways.

Part III. Lessons I learnt from 2014 Ebola epidemic

The tragic 2014 Ebola outbreak in West Africa was first reported in March 2014, and has rapidly become the deadliest occurrence of the disease since its discovery in 1976. Up to 14 January 2015, 8,429 deaths had been reported from six countries and the total number of reported cases is more than 21,261. “This Ebola outbreak is unlike anything since the emergence of HIV/AIDS, and this is controllable and this was preventable.” Centres for Disease Control and Prevention (CDC) chief Thomas Frieden said (http://www.bbc.com/news/world-africa-29555849). I believe so, too. But it happened anyway and it is still ongoing! No matter who we blame, we have to admit that an infectious disease like Ebola is a huge challenge for any country in the world. After the first Ebola patient died at Texas of the USA, two health care workers from the hospital were tested positive for the virus. Complains about the hospital’s response to the first Ebola case appeared in the media and an investigation was initiated. As a Churchill Fellow, I could not help asking: “what should we learn and how can we do better in Australia?”

Lesson 1: A leading agency to coordinate the disease control at national level is important

An important factor for effective control of infectious disease is the executive power of a leading agency in each country. After the first Ebola patient died in Texas, some experts said the way the USA handles public health is not up to the challenge. "One of the things we have to understand is the federal, state and local public health relationships," says Dr. Michael Osterholm, director of the Centre for Infectious Disease Research and Policy at the University of Minnesota. "Public health is

the purview of the states in many countries. The state really is in charge of public health at the state and local level. The CDC can't just walk in on these cases (http://www.usatoday.com/story/news/nation/2014/10/12/examining-the-nations-ebola-response/17059283/)". This indicates that in the USA and other countries with similar health management system, the coordination for disease control at national level could be a challenge. However, this is a challenge we must address as disease can easily spread cross the border of states but our actions of disease control should not stop at the border of each state.

This challenge may be even harder to address for Australia as we don't have a national centre for disease control yet, as far as I know. No matter which agency each country chooses, we should have one leading agency influential and powerful enough to coordinate all the resources effectively at state and national level and adjust the control strategy and priorities according to the disease dynamics.

Lesson 2: Change social behaviours guided by rules established in emergency if necessary

Ideally, with all the knowledge we learnt from research and past outbreaks, we should be able to prevent or decrease incidences of infectious diseases. Or, if it happens, we can control it at the very early stage. However, there is one factor which is hard to guide: social behaviour of humans. We are the host species so how we behave determines largely the disease dynamics. As the situation in Africa demonstrated, just telling people what to do didn't work. As scientists we have to do better.

Based on the epidemiology and laboratory data, the transmissibility and the clinical course of infection of the 2014 virus are similar to those in 2007-2008 Ebola outbreaks [10], and genetic analyses of 99 Ebola virus genomes showed that the 2014 Ebola strains are closely related to viral strains from the two most recent Ebola outbreaks in Central Africa [11]. But there are a number of distinct genetic changes and it is unknown if these changes have an impact on transmissibility or disease severity [11]. The 2014 Ebola epidemic in West Africa is unprecedented in scale (http://www.cdc.gov/vhf/ebola/transmission/human-transmission.html). It is evolving in its new hosts but we don't know which evolutionary direction it is going. We are not sure if there is no chance for a new mutant of Ebola virus becomes transmissible before the onset of clinical symptoms during this epidemic.

In my opinion, we should consider how to change behaviours if necessary, in particular during the outbreak of infectious diseases. Such changes are never easy and require social scientists, biologists and medical researchers work together with policy makers in truly multidisciplinary environments. In

the light with this idea, I will start initiating conversations with the social scientists in CSIRO and discuss what we can do to address this challenge.

Final remarks

When I stand at the beginning of 2015, I am more confident than ever to say that: the best thing happened to me in 2014 was the award of Churchill Fellowship. But there is more to add now: the second best thing was the experiences at CIDD which include my meeting with Professor Andrew Read. The words from him were very powerful to motivate me so I have shared the details as a story in the appendix of this report.

Last but not the least important: I will never forget to acknowledge Churchill Trust for any positive impacts I may bring to Australian society in the next 20 years. Let me put it this way: I had enough snow and the Churchill Fellowship gave me the chance to make a snowball. I started rolling the snowball on my career track since then. In 20 years, if my snowball is big enough, you will find the following words on it: Churchill Trust supported me to start rolling this snowball.

CONCLUSIONS AND RECOMMENDATIONS (ESSENTIAL)

1. I achieved the main goal of my project: I have learnt essential skills for animal experiments in the field of infectious diseases. I performed detailed clinical examination to assess the condition and disease status of individual animals and carried out autopsies and pathology examinations to understand disease progression and sampling of tissues. These skills can be used in my long term career as a scientist and shared with other scientists and students in this field**. More important was the inspiration and confidence I gained to enable me to think about the big picture of infectious diseases and how determined I am to make a major contribution.**

2. I have built trusting relationship with key collaborators at CIDD of PSU and they welcome me to visit again in 2015. Their broad research interests in infectious diseases inspired me to develop big picture project in the future and collaborate broadly with scientist in Australia and around the world. The impacts of this overseas trip awarded by Churchill Trust are far beyond me and my career.

3. Myxoma virus evolved quickly in European rabbits and its genome is very flexible. There are different genetic changes responsible for attenuation of the virus to adapt to its new host. Unfortunately, humans and most animals can't evolve as fast as pathogens, so we need a different strategy to deal with infectious pathogens.

4. To control and prevent emerging and re-emerging infectious diseases for the long term, we need to continuously accumulate knowledge, improve technology and provide solutions with limited resources, guided by an optimized strategy to achieve best benefit/cost ratio for our investments. **I recommend a Research Centre for Infectious Disease should be established to lead and coordinate the research in Australia** to serve the purposes mentioned above. I believe the positive impacts of such a research centre in Australia addressing the challenge posed by pathogens on public health can be extended into industrial and political domains in our nation and in the world.

5. Learning from the 2014 Ebola epidemic, I recommend we should **start discussing the importance of a leading agency to coordinate the control of infectious diseases at national level**. As we are the host species of human pathogens, our behaviours determine largely the

disease spread and dynamics. What this epidemic has shown is how difficult it is to change people's behaviours. **This suggests that social research is as important as the biological and medical studies and that multidisciplinary approach is essential for effective controlling of infectious disease outbreaks.**

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Appendix

The meeting with Professor Andrew Read in the USA

Two things make my meeting with Professor Andrew Read a story. The first is: that was the first time for me, as an early career scientist, to try so hard to convince a world-famous scientist to have a one-to-one and face-to-face meeting with me, talking about things I want to discuss and learn from him. The second is: what I learnt in the meeting is worth sharing, especially with early career scientists in Australia and those who plan to take this career path.

As the head of CIDD and the leader of his research group, plus the other position he holds at Fogarty International Center, National Institutes of Health at Maryland, Andrew is always busy. I figured the best way for me to get into his busy schedule was to make this meeting his priority. I spent three days to prepare a long email, trying my best to convince him that it is worth putting one hour of his time for a meeting with me. In the email, I mentioned three things I wanted to discuss with him: 1) how to apply scientific discovery in the management of public health; 2) how I want to promote the research in infectious diseases field in Australia; 3) my intention to visit PSU again and get support from him.

I prepared the meeting carefully. First, I did some research about "applying scientific discovery in the management of public health". I listed some of the main components of this topic: the multi-discipline research team, the process of applying and managing public health with new policies, the benefits and risks, etc. I also had a few questions about promoting research in infectious disease field and career development.

After a few days, I got an email from him: "how about 1pm tomorrow, at my office?" At 1pm sharp on 11, November 2014, I was knocking the door of Andrew's office. There were one L-shaped table and two big computer screens in his office, with a sandwich in front of him. After the greetings, I started talking about my interest of applying knowledge in policy and public health management. He is keen to see development in this area but this is not the focus of his group for the moment. He recommended that I should talk to Dr Matt Ferrari who is working in this field.

I moved to the second topic quickly: "The Ecology and Evolution of infectious Disease Conference was held annual in the USA in the past 12 years. You are one of the main organizers. Could you please consider having the conference in Australia, for example, in Sydney, in the near future? I am keen to introduce this conference into Australia and promote the research in this field." "Unfortunately, it is very hard to do so because the main aim of this conference is to encourage PhD students and Postdocs in the USA to attend this conference and motivate them to develop career in this field. There is no problem for academic staff to travel to Australia, but there is no budget for the PhDs and

Postdocs to travel overseas annually." I was disappointed but I totally understood his concern. I was impressed by the efforts they put into educating students and promoting early career researchers. Thought for a few seconds, I said: "I want to establish a centre like CIDD in Australia and organize a conference for the research community if I have the opportunity. Give me 10 years." I did not know if he took my words seriously, but I did. And I still do now.

I started questions about my career development.

"I read your papers. I found your writing is very powerful and influential. Is that a natural gift for you?"

"No. I learned it along the way."

"How did you learn it?"

"By reading. I read a lot, even now. I worked with an editor for a while and learned a lot of writing skills from him. But the key thing is reading good papers and articles. The more you read, the easier you pick up and use the good skills in your writing. But you need to pay attention to the writing skills when you read."

"What should I read?"

"Read the short articles in the first part of the Science and Nature – the two august journals in academic world. There are good books too, such as Stephen King's "On Writing", the annual book "Best American Science and Nature writing". I made notes and bought the two books later. And I have been reading and learning from them since then.

"You have a very successful career as a scientist. Except for being very, very smart and working hard, what are the most important factors for your success?"

"Well, I don't know much about being smart. Work hard, yes. You need to work hard. Other than that, it is important to work with great people and collaborate with excellent scientists, such as your supervisor Peter."

"How do you know they are good?"

"I read their published papers and have dinner with them if I have the opportunity so I can know them better."

"What is the most difficult part in your career?"

"Getting funds for our research is very hard. Sometimes, I work on a research proposal for half a year and submit it. Then I get nothing. It is very frustrating." Sure it is. It is so hard for a leading scientist like Andrew – just picture what it is like for an early career scientist like June.

"Another problem is time. I don't have enough time to do all the things I want to do. Yes, I try to work more efficiently but there is a limit. When you get to that point, you just cannot do any more." "Yes, then it is about priority." I added. It is not about time, it is about priority, for him and for me, for

scientists. That's why I learned the skills of prioritization, time and energy management and stress control.

For the last question, I shared my concern about my "pushing" email: "I used a long email to persuade you for having this meeting because this is very important for me. This is the first time in my career I tried so hard to convince someone. I hope you don't feel uncomfortable about me doing this."

"No, not at all. It is my responsibility to support young scientists to develop their career in research. I am glad you are interested in infectious disease field."

"Well, this research centre (CIDD) is an exciting and inspiring place. I enjoyed very much working here. That's why I want to visit again next year." I gave him my feedback about the research centre he is leading.

"Good to know that. We'll work something out for your next trip."

I realized it was time to wrap up the meeting so I thanked him and left his office. When I closed the door of his office, I felt the meeting was worth all the efforts I put in. And the positive impact of his advice on my career development will be long lasting.

- The end -