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Legacy of the influenza pandemic 1918: Introduction

Siamon Gordon *

Graduate Institute of Biomedical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan
Exeter College Emeritus Fellow in Pathology, and Emeritus GlaxoWellcome Professor of Cellular Pathology, University of Oxford, UK

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Siamon Gordon, FRS, is an emeritus Glaxo Wellcome professor of cellular pathology at the Sir William Dunn School of pathology at the University of Oxford and a Visiting Professor at Chang Gung University in Taiwan. His research has dealt broadly with macrophage functions in infection and immunity. His group has characterized receptors that mediate entry and secretory responses to a range of pathogens, including flaviviruses, influenza and HIV.He is interested in the history of immunology, with particular reference to Elie Metchnikoff, and continues to sponsor an AIDS prevention education project in South Africa, his country of origin.

This guest edited issue contains the first group of reviews to mark the centennial of the influenza pandemic which swept the world in 1918, continuing into the following year. The outbreak was characterized by catastrophic mortality, illness, social and economic disruption, reminiscent of previous epidemics of smallpox, plague and cholera. It coincided with the termination of the Great War, which contributed to susceptibility and dissemination of infection, yet its role in the onset of the influenza pandemic is not entirely clear. The pandemic initiated a pattern of subsequent epidemics attributed to major genetic shifts in the viral strains and less severe seasonal mutations. The search for a universal vaccine and effective antiviral drugs continues, even though the original virus has been recovered and a great deal is known about the molecular and cellular mechanisms of infection and its spread in human populations and animal reservoirs. The viral-host response has been described in great detail, but much remains uncertain about the virulence of the original pandemic and the secondary infection by bacteria in the lung. The role of individual genetic susceptibility and of innate and adaptive immunity are only now beginning to be unraveled by genomic, molecular and cellular advances.

* Corresponding author. Graduate Institute of Biomedical Sciences, Chang Gung University, 259 Wenhua 1st Rd., Gueishan, Taoyuan 333, Taiwan.
E-mail address: siamon.gordon@mail.cgu.edu.tw.
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In this issue we present reviews by three researchers and their colleagues. Laura Denney and Ling-Pei Ho describe the features of the human respiratory epithelium which underlie the pathobiology of infection by the influenza virus;

Yu-Nong Gong, Rei-Lin Kuo, Guang-Wu Chen, and Shin-Ru Shih trace the viral evolution associated with the epidemiology of influenza outbreaks in Taiwan, and Andrew McMichael outlines milestones in T lymphocyte research, much driven by the need to understand the nature of acquired immunity to influenza. Further topics to be presented in early 2019, will consider host mechanisms of innate resistance and the initial response to infection and vaccines.

Our understanding of influenza virus–host interactions has catalyzed research into other emerging virus infections such as HIV and Ebola, as well as vaccination strategies for polio, measles and flaviviruses such as yellow fever and dengue. Yet, the development of effective antiviral treatment of acute life-threatening infections and their chronic sequelae remains elusive.

The following section provides brief personal background, perspectives and references provided by the three corresponding authors.

Ling-Pei Ho: Respiratory epithelium during influenza virus infection

The specific role of respiratory epithelium in the host defence against influenza has been less studied compared to the immune system as a whole, yet its coverage of the lungs is massive and it is the very first contact that the virus has with the host. Indeed it can be viewed as the first point in the innate immune machinery against influenza virus infection. Prof Ho and her team were originally interested in how the immune response in the lungs shaped lung immune-mediated lung diseases like sarcoidosis; particularly in how CD1d-restricted natural killer T cell (NKT) regulated lung immune responses [1]. They used influenza as a model to understand lung immune responses [2–4] and how non-conventional T cells like NKT and MAIT cells controlled anti-viral responses but soon found that myeloid cells are key to immunepathology during murine influenza virus infections [5,6]. During the recent pandemic, Prof Ho led an investigation into the immune correlates of severe disease in patients who had particularly poor outcome, a study that again implicated the monocyte-macrophage pathway in lung immunepathology during influenza infection [7]. Her team also contributed to studies which identified IFITM3 as a key anti-viral ISG in IAV infections [8,9]. Prof Ho is currently based at the MRC Human Immunology Unit, Oxford, and her group now focuses on how monocytes and macrophages contribute to injury and (dys) repair of the alveolar epithelium.

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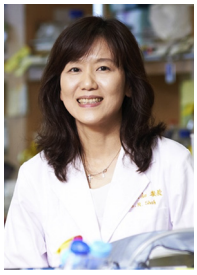
Shin-Ru Shih: Centennial review of influenza in Taiwan



Shin-Ru Shih obtained her bachelor degree in Medical Technology and master degree in Biochemistry from National Taiwan University and her Ph.D. in Biochemistry and Molecular Biology from Rutgers University, New Jersey, USA. She established a Molecular Virology Laboratory at Chang Gung University in 1996 and was appointed Medical Director in Clinical Virology Laboratory, Chang Gung Memorial Hospital in

1998. She also started the Research Center for Emerging Viral Infections at Chang Gung University in 2009 as centre director.

Dr. Shih began influenza virus research from her Ph.D. study under the supervision of Professor Robert M. Krug [1,2]. Her papers regarding influenza virus surveillance have been widely discussed in influenza control and surveillance [3,4]. Her team identified several therapeutic targets for development of antiviral strategies [5,6].

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Andrew J McMichael: Legacy of the influenza pandemic 1918: The host T cell response

The wealth of knowledge gained on the influenza virus, stimulated by the 1918 pandemic and subsequent discovery of the virus, stimulated research into the immunology of this infection. Early studies focused on the antibody response, how this might be optimized by vaccination and how antibodies contributed to antigenic drift and shift in the virus. Then in the 1970s Zinkernagel and Doherty made the major discovery that $CD8^+$ T cell recognition of virus infected cells was restricted by class I molecules of the major histocompatibility complex (MHC) [1]. The mechanisms behind this were revealed twelve years later when Townsend et al. showed that influenza specific T cells recognized peptides bound to class I MHC molecules [2], subsequently beautifully demonstrated in crystal structures by Pamela Bjorkman and colleagues [3]. These experiments showed that T cells could recognize internal proteins of virus infected cells, with profound implications for understanding cellular immunity to infections and cancers heralding the development of vaccines and novel therapies.

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