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Meeting Report

2017 international meeting of the Global Virus Network

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ABSTRACT

The Global Virus Network (GVN) was established in 2011 to strengthen research and responses to emerging viral causes of human disease and to prepare against new viral pandemics. There are now 40 GVN Centers of Excellence and 6 Affiliate laboratories in 24 countries. The 2017 meeting was held from September 25–27 in Melbourne, Australia, and was hosted by the Peter Doherty Institute for Infection and Immunity and the Institut Pasteur. This report highlights the recent accomplishments of GVN researchers in several important areas of medical virology, including the recent Zika epidemic, infections by human papillomavirus, influenza, HIV, hepatitis C, HTLV-1, and chikungunya viruses, and new and emerging viruses in the Australasia region. Plans for the 2018 meeting also are noted.

1. Introduction

The Global Virus Network (GVN) was established in 2011 to strengthen research in response to human viral diseases and to prepare for new viral pandemic threats (Mann, 2011). The GVN now has 40 Centers of Excellence and 6 Affiliate laboratories in 24 countries (Fig. 1). Network scientists meet annually to address research and collaborative priorities, learn about each member's current work and plan future programs. These international conferences have become critical platforms for the exchange of ideas.

The 2017 international GVN meeting was held from September 25–27 in Melbourne, Australia, in partnership with the Peter Doherty Institute for Infection and Immunity, and the Institut Pasteur. It brought together directors of GVN Centers and their colleagues for three days of scientific presentations and discussions of emerging and re-emerging viral threats. The Melbourne meeting was the first GVN event open to non-GVN scientists and students. Investigators, clinicians and students from area institutes and universities had the opportunity to attend scientific sessions and present ongoing student work at a poster session to expand opportunities for collaborative dialogue, particularly with young virologists. The main objectives of the meeting were to present and discuss current findings in medical virology, including advances in research on HIV vaccines; HTLV-1 infections among indigenous Australians; other important Australasian viruses; and address the GVN's annual strategy for continued development.

2. The Global Virus Network

The formation of the GVN and the rationale for its structure have been previously described (Akkina et al., 2017). Currently, the GVN consists of 40 Centers of Excellence and 6 Affiliate laboratories in 24 countries. GVN's mission is focused on strengthening medical research and responses to viral causes of human disease, and to preparing for new viral threats. That mission is achieved through basic research, public education, and advocacy.

3. The 2017 Robert C. Gallo Award

Diane Griffin, PhD, MD, University Distinguished Service Professor, and Alfred and Jill Sommer Chair of the W. Harry Feinstone Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health—a GVN Centre of Excellence—was presented with the Robert C. Gallo Award for Scientific Excellence and Leadership for her studies on measles and

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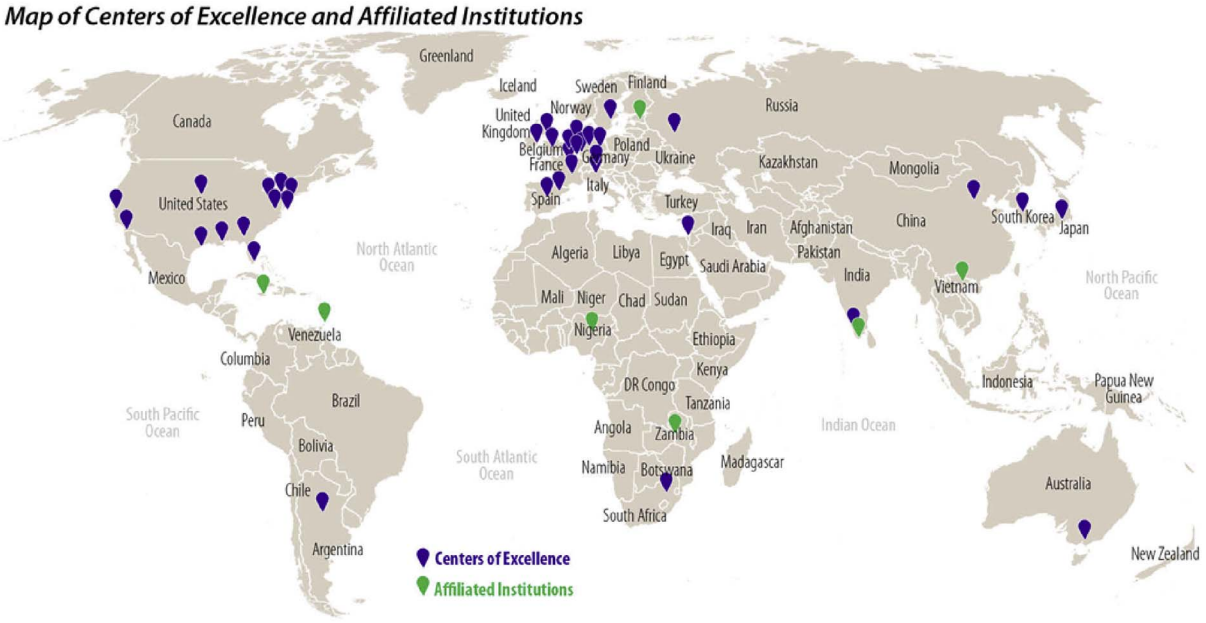

Centers of Excellence	
Argentina	IBBM – National University of La Plata
Australia	Peter Doherty Institute for Infection & Immunity, University of Melbourne
Belgium	Northern Europe Consortium, Gembloux Agro-Biotech; Rega Institute for Medical Research, University of Leuven
China	Chinese Consortium
France	Institut Pasteur; Mérieux Foundation
Germany	Robert Koch Institute Berlin; Technical University of Munich; Philipp University Marburg; University of Veterinary Medicine Hannover
India	Amrita Institute of Medical Sciences, Kerala; Rajiv Gandhi Biotechnology Centre
Ireland	University College Dublin
Israel	Tel Aviv University
Italy	Italian Consortium
Japan	National Institute of Infectious Diseases (NIID-Tokyo)
Netherlands	Erasmus University Hospital
Russia	Moscow Center for HIV/AIDS Prevention and Treatment
South Africa	National Institute for Communicable Diseases, Johannesburg
South Korea	International Vaccine Insitute
Spain	Centro de Biología Molecular Severo Ochoa (CBMSO), Madrid; Centre de Recerca en Sanitat Animal (CReSA), Barcelona
Sweden	Scandinavian-Baltic Consortium, Karolinska Institute
U.K.	MRC-University of Glasgow, Scotland; The Pirbright Institute, England
USA	University of California San Francisco; Scripps Research Institute; J. Craig Venter Institute; Colorado State University, Fort Collins; University of Miami; Emory University; Tulane University School of Medicine; Institute of Human Virology at the University of Maryland; Johns Hopkins Bloomberg School of Public Health; University of Michigan; Icahn School of Medicine at Mt. Sinai; University of Rochester Medical Center; University of Buffalo; University of Pittsburgh Cancer Institute; UTMB Galveston National Laboratory.

Affiliated Institutions	
Estonia	University of Tartu
Grenada, W.I.	St. George's University
India	Molecular Virology Laboratory Rajiv Gandhi Centre for Biotechnology
Jamaica	University of the West Indies, Mona
Nigeria	Institute of Human Virology-Nigeria
Vietnam	National Institute of Hygiene and Epidemiology, Hanoi
Zambia	Africa Center of Excellence for Infectious Diseases of Humans and Animals (ACEIDHA), School of Veterinary Medicine, University of Zambia

Fig. 1. GVN Centers of Excellence and associated laboratories. Each centre has a director who has made significant contributions to the literature; high productivity in terms of publications; has served as a regional resource for research, diagnostics and treatment; programs that interact with other centers in the region, and outreach programs with less developed countries. Current Centre Directors are listed at: http://gvn.org/gvn-centers.

alphavirus encephalomyelitis, which have delineated the role of host immune responses in virus clearance, vaccine-induced protection from infection, tissue damage and immune suppression. Dr. Griffin also was cited for her leadership role within the GVN's international conferences and virology training programs, for making important basic science contributions to medical virology.

The award is named for Robert C. Gallo, MD, co-founder and director, The Homer & Martha Gudelsky Distinguished Professor in Medicine, Institute of Human Virology, University of Maryland School of Medicine, and Co-Founder and Scientific Director of the GVN. Dr. Gallo and his co-workers discovered interleukin-2 (IL-2), followed by the discovery of the first human retroviruses, Human T-Cell Leukemia Virus-1 (HTLV-1) and HTLV-2. He and his colleagues co-discovered HIV as the cause of AIDS and developed the first HIV blood test.

4. Pre-meeting and public forum on HTLV-1 in remote indigenous Australians

While not part of the formal GVN meeting, there was a morning session on HTLV-1 infection chaired by Damian Purcell of the Peter Doherty Institute and a closing summary by Robert Gallo. Some of what was discussed has been published (Tagaya and Gallo, 2017; Gallo et al., 2017), and it is anticipated that additional publications by other speakers will be forthcoming.

5. Scientific presentations

5.1. Re-awaking to HTLV-1 in indigenous communities

Antoine Gessain (Institut Pasteur, Paris) reviewed the epidemiology, origin and genetic diversity of HTLV-1. In 2012, the EU Commission requested the European Centre for Disease Prevention and Control (ECDC) to construct a map indicating all the HTLV-1 high-prevalence areas in the world. By analyzing more than 1000 papers and hundreds of abstracts, Gessain and colleagues provided the first complete epidemiological data (maps and tables) for the 203 world's countries (ECDC, 2015). In most of the highly endemic areas, HTLV-1 is mainly disseminated and maintained in the human population through intra-familial transmission.

(mother-to-child and by sexual intercourse). More rarely, transmission may also occur by transfusion or intravenous drug use. HTLV-1 originated from a simian retrovirus called simian T-leukemia virus type 1 (STLV-1), which is widespread in Old World monkey and ape species. The idea that HTLV-1 originated from STLV-1 is mainly based on the very high sequence homology (African subtypes b, d, e, f) found between some STLV-1 strains and HTLV-1 found in individuals, including hunters, living in Central/West Africa. However, data concerning transmission of STLV-1 to humans *in natura* and modes of acquisition remain quite scarce. Gessain also reviewed reported cases of HTLV-3 and -4, and speculated on the future emergence of these viruses and Simian Foamy viruses (Gessain et al., 2013).

Lloyd Einsiedel (Baker Heart and Diabetes Institute, Australia) reported on HTLV-1 subtype C as a major cause of morbidity and mortality among indigenous Australians. The virus is highly endemic to central Australia where more than half of all indigenous adults residing in some remote communities are infected. Infection is associated with a rapidly progressive haematological malignancy (adult T-cell leukemia, ATL), inflammatory diseases involving various organ systems and an increased likelihood and severity of other infections, notably with *Strongyloides stercoralis*. In central Australia, each of the major HTLV-1-associated diseases has been described; however, in this setting HTLV-1 infection is most often associated with chronic respiratory disease, including life-threatening, severe bronchiectasis, and with invasive bacterial infections (Einsiedel et al., 2012). The region has the highest reported prevalence of adult bronchiectasis, and among the highest bloodstream infection incidence rates, worldwide. The risk of bronchiectasis and the extent of pulmonary injury are strongly associated with the HTLV-1 proviral load (pVL), which also predicts risk of invasive bacterial infection. The association between HTLV-1 pVL and these life-threatening conditions is consistent with recent findings that higher HTLV-1 pVL are associated with an increased risk of death in a large prospective cohort of Indigenous adults (Einsiedel et al., 2016). High rates of HTLV-1 infection and HTLV-1-associated diseases contribute substantially to the burden of ill health and early mortality among indigenous people in central Australia.

Charles R. M. Bangham (Imperial College, U.K.) noted that HTLV-1 causes disabling chronic inflammatory diseases or an aggressive, rapidly fatal malignancy, adult T-cell leukemia/lymphoma, in about 10% of infected people. In addition, HTLV-1 predisposes to and exacerbates infections with *Mycobacterium tuberculosis*, *Strongyloides stercoralis* and *Staphylococcus aureus*, with severe and sometimes fatal consequences. It has recently been shown that HTLV-1 also causes and exacerbates bronchiectasis, bronchitis and bronchiolitis. The risk of these HTLV-1-associated diseases is strongly correlated with the proviral load, which frequently exceeds 10% of peripheral blood mononuclear cells (PBMCs). The virus, which is non-cytolytic, drives proliferation of the infected $CD4^+$ T cell, and the high proviral load is limited by a strong, chronically activated cytotoxic T lymphocyte (CTL) response to HTLV-1. Until recently, it was believed that HTLV-1 persisted *in vivo* chiefly by continuous oligoclonal proliferation of about 100 clones of HTLV-1-infected $CD4^+$ T cells. However, Bangham and colleagues have shown that a typical individual carries between 10^4 and 10^5 clones, and the proviral load – the chief correlate of disease – is determined by the number of clones, not by oligoclonal proliferation. It was also believed that HTLV-1 was latent *in vivo*, but the existence of the persistently activated CTL response in virtually all hosts strongly argues that the virus is not latent but is frequently expressed. This suggests that the virus undergoes intermittent bursts of expression *in vivo*.

Bangham presented data from single-molecule RNA fluorescence *in situ* hybridization (smFISH) that the provirus indeed undergoes intermittent, intense bursts of expression. Work is under way to identify the factors that regulate the frequency, size and duration of these bursts. In addition, spontaneous reactivation of HTLV-1 from latency in fresh PBMCs is governed by the molecular oxygen availability and by glycolysis. Finally, he and colleagues discovered that HTLV-1 alters host chromatin structure in the infected cell, by binding the chromatin architectural protein CTCF, which regulates higher-order chromatin structure and gene expression in vertebrates. This observation implies that HTLV-1 does a remarkable experiment of nature, by changing the conformation of chromatin in tens of thousands of different ways in each infected host (Satou et al., 2016). Studies are under way to test the hypotheses that CTCF regulates HTLV-1 latency, and that the abnormal chromatin looping caused by CTCF can deregulate host gene expression and so may act as an oncogenic driver.

Fabiola Martin (University of Queensland, Australia; University of York, U.K.) discussed the clinical diagnosis and treatment of HTLV-1 diseases. The discovery of a cure for HTLV-1, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T-cell leukemia/lymphoma (ATLL) has been an ongoing process of refinement since the early 1980s. Martin presented summaries of more than 35 years of published and empirical intervention options, including HTLV prevention strategies as part of the international HTLV eradication efforts (Einsiedel et al., 2018).

Toshiki Watanabe (University of Tokyo, Japan) described recent government responses to HTLV-1 infection in Japan. Since the first report of ATL by Takatsuki's group in 1977, Japanese clinicians and researchers have made major contributions to understanding the virology of HTLV-1 and the pathophysiology of ATL, as well as identifying other HTLV-1-associated diseases such as HAM/TSP and HTLV-1 uveitis (HU). In the first decade of 2000, groups of Japanese patients with HTLV-1-associated diseases petitioned the government for improved health care and treatment, as well as continuous and strong support for

clinical and basic research. In 2010, the government organized a HTLV-1 Task Force composed of the Prime Minister and government officials, representatives of patient groups, and medical specialists. Subsequently, a nationwide campaign began in 2011 with screening for HTLV-1 antibody in all pregnant women to prevent new mother-to-child transmissions. Counseling also was initiated for HTLV-1 carriers and HAM/ATL patients. Some of the results of stepped-up government support for HTLV-1 research and care have been reported (Satake et al., 2016; Nosaka et al., 2017).

5.2. New and emerging viruses in Australasia and beyond

Linfa Wang (Duke-NUS Medical School, Singapore) presented a review of his 20 years of research on the importance of bats as natural reservoir of viruses. Specifically, he addressed three questions:

1. Are bats true reservoirs of emerging viruses? Since the discovery of rabies virus in bats more than 100 years ago, bats have been known to carry zoonotic viruses. But the field remained relatively "quiet" until the discovery of Hendra virus in Australian bats, which was responsible for lethal outbreaks in horses and humans. Since then, bats have been confirmed or suspected as reservoirs of several emerging viruses, including Nipah, SARS, MERS, Ebola and Marburg viruses. Although scientists working in this field still debate whether bats are the true reservoir of Ebola virus, for example, Wang pointed out that it took an international collaborative team more than ten years to obtain convincing evidence of the bat origin of the SARS coronavirus (Ge et al., 2013).
2. Are bats special in their ability to host viruses? There are two working hypotheses associated with this question. First, it is difficult to induce experimental infections in bats with many viruses lethal to humans and livestock. Second, bats can harbor more viruses on a per species basis and there is a greater genetic diversity of viruses in bats than in other mammals. Evidence has been gathered to support these hypotheses, although most of them are based on retrospective studies of past literature. The most significant study examined a database of 2805 mammal-virus associations and concluded that bats harbor a significantly higher proportion of zoonotic viruses than any other mammalian order (Olival et al., 2017).
3. What makes bats special? Wang noted that bats have a long lifespan and are less prone to cancer. He hypothesized that the evolutionary adaptation to flight has resulted in a unique immune system significantly different from terrestrial mammals. He presented genomic data indicating a more robust positive selection of genes responsible for DNA damage pathways (Zhang et al., 2013). The most recently data obtained from his group suggests that the overall dampening of inflammatory responses may be key to why bats can carry so many viruses, yet seldom develop symptomatic infections.

Alex Greenwood (Leibniz Institute for Zoo and Wildlife Research, Berlin, Germany) introduced the concept of exogenous and endogenous retroviruses. While it is known that the mammalian genome is composed of up to 11% endogenous retroviral elements (ERVs), most of them completed their invasion millions of years ago obscuring the changes in virus and host associated with them. The koala retrovirus (KoRV) is one of the few examples of a virus that is currently in the earliest stages of transitioning from an exogenous retrovirus to an ERV (Tarlinton et al., 2006). By going through a collection of archived samples of modern wild and zoo koalas dating back to 1891, Greenwood and his collaborators found crucial early events in endogenization involving recombination, often mediated by existing retroviral-like elements already resident in the host genome. These recombination events disable the exogenous retrovirus making it less potentially harmful to the host while at the same time, the ancient retroviral-like elements may re-establish themselves as actively propagating retroelements (Hobbs et al., 2017). In the context of trying to find the origin of KoRV, Greenwood, et al. confirmed its close relationship to the gibbon ape leukemia virus (GALV). Both are likely from recent interspecies transmissions.

Phylogenetically, two rodent viruses, *Melomys bertoni* retrovirus (MbRV) and *Melomys* woolly monkey-like virus (MelWMV) are the closest to the KoRV/GALV-like viruses identified to date (Alfano et al., 2016). Greenwood concluded that very close relatives of KoRV/GALV have been circulating in a variety of mammalian taxa within the Australo-Papuan region east of the Wallace Line.

Lorena Brown (University of Melbourne, Australia) presented a new concept in antiviral drug design. While most current antiviral strategies tend to target specific viral proteins and inhibit their function, Brown described antiviral drugs that are modular in structure, consisting of a viral attachment domain and an effector domain. In general, the attachment domain can be antibody or any domain or motif structure that binds the surface of a virus. An effector domain can vary from an enzyme to a charge cloud.

In collaboration with Aus Bio Ltd., the concept was tested against influenza virus. Entry of influenza virus into cells is by receptor-mediated endocytosis. As the environment of the endosome becomes more acidic, the viral hemagglutinin (HA) undergoes a conformational change to reveal a hydrophobic fusion region that penetrates the endosomal membrane, thus initiating the life cycle of virus replication inside the cell. Candidate drug molecules use an attachment domain that binds to HA, and an effector domain that provides a negatively-charged environment to trigger a premature conformational change in the neighbouring HA to prevent viral replication. Brown presented *in vivo* data on two drugs, MD185 and MD345, that provided better protection in mouse and ferret models than did zanamivir. These constructs appear to provide an extended therapeutic window until the adaptive immune system comes into play. The long-duration activity of the drugs suggests they may be useful in prophylaxis, especially in a pandemic context.

Soren Alexandersen, (Geelong Centre for Emerging Infectious Diseases, Australia), described outbreaks of severe infections among Australian infants caused by a recombinant strain of human parechovirus type 3. Human parechovirus types 1–16 (HPeV1-16) are positive-strand RNA viruses. Type 3 parechovirus (HPeV3) causes a severe disease in infants with mortality up to 6% and potential long-term sequelae. As this was a newly recognized disease of infants, there was no diagnostic test available in Australia until 2013.

During the investigation of a 2015 HPeV3 outbreak, it was found that the genome of the Australian viruses had undergone a major recombination event that took place between March 2012 and November 2013, followed by further virus evolution and possibly recombination. The phylogenetic and network analyses from the Geelong group support a temporal evolution from the first Australian recombinant virus sequence from November 2013 to March/April 2014 to the 2015 outbreak. Their data showed that the 2015 outbreak viruses are recombined from the Yamagata 2011 lineage and an as yet unknown virus (Nelson et al., 2017).

This unknown virus, the donor of the non-structural coding region, may come from a not-yet sequenced human parechovirus or alternatively, from a potential unknown animal source, as similar viruses do infect animals such as the recombinant HPeV4 detected in pigs in South America (Nix et al., 2013). Finally, Alexandersen observed that the HPeV3 outbreaks seem to follow a 2–3-year cycle, suggesting there may be another wave of HPeV3 outbreaks in Australia in 2017/8.

5.3. Pandemic and epidemic viruses

Nobel Laureate **Peter Doherty**, (Peter Doherty Institute for Infection and Immunity, Australia), provided a review of $CD8^+$ cytotoxic T lymphocyte contributions to antiviral immunity. The human family is constantly challenged by viruses, with epidemic/pandemic pathogens either emerging from wildlife or domestic animal reservoirs,

or as a consequence of "immune escape" mutations in strains that are circulating in us. Vaccines that promote long-term antibody-mediated immunity to "mop up" invaders can provide immediate protection though, of course, as Doherty noted, we have no such products when something new and unexpected hits. As our most intimate parasites, viruses grow only within living cells. As a consequence, part of the process of recovery requires the elimination of these cellular "factories" of pathogen production. The "hit man" of immunity that does this job is a circulating white blood cell, the virus-specific, $CD8^+$ "killer" T-cell, or cytotoxic T-lymphocyte (CTL) and the CTL is targeted to cell surfaces via recognition of viral peptide bound to self MHC class I glycoproteins. Some recent findings concerning HLA type and influenza prevention and susceptibility are of particular interest, especially with regard to the greater susceptibility of indigenous populations to influenza.

Maël Bessaud (Institut Pasteur, Paris), reviewed genetic recombination among positive-strand RNA viruses and suggested enteroviruses as a convenient model for *in vitro* studies of recombination. In particular, mostly non-homologous recombinant genomes were seen; that is, genomes with deletions or duplications, which can subsequently evolve into homologous recombinant genomes. Regions where recombination occurs more frequently have been identified. These hotspots bound genomic domains that can be considered as modules used to engender new mosaic genomes through recombination. These results illustrate how recombination is able to generate a wide genetic and phenotypic diversity and can promote the emergence of new viruses.

Joaquim Segales (Centre de Recerca en Sanitat Animal, Spain) described dromedary camels as models for Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) infection. Experimental intranasal inoculations with MERS-CoV produces only upper respiratory tract infection (URT) and mild clinical signs. Infectious virus is only detected in the trachea, large bronchi and tracheobronchial lymph nodes, while viral RNA is more widely detectable in the nose, the upper and lower respiratory tracts and in extrapulmonary lymphoid and visceral tissue. Nasal, tracheal and bronchial inflammation are present, without gross lesions. A similar clinical-pathological picture is seen after intranasal MERS-CoV inoculation of domestic new world camelids, producing either no clinical signs (alpacas) or mild mucus secretion (llamas), with MERS-CoV detectable in the URT (nasal swabs and trachea) of both species, and cleared from the URT 7–10 days post-infection, concomitant with antibody responses. Pigs also may be experimentally infected and show the presence of viral RNA in nasal swabs, trachea and bronchi until 7–10 days postinoculation. Only very limited transmission to direct contact mates is seen under experimental conditions. Experiments performed to date suggest that other large animal domestic species such as horse, sheep and goat are not susceptible to MERS-CoV infection.

Ramesh Akkina (Colorado State University, USA) described new and improved humanized mouse (hu-mouse) models that harbor a transplanted human immune system to study viral pathogenesis, evolution, latency, and human immune responses to HIV, dengue and Zika viruses (Schmitt et al., 2017). He outlined the use of Hu-mice as an alternative to *in vitro* viral outgrowth assays (qVOA), which are currently the gold standard for measuring latent HIV in cure research, but often fail to detect very low levels of replication-competent virus as evidenced by the "Boston patients (Hayden, 2013)." Akkina showed that Hu-mice also provide a potential animal model to study HIV-2, and for testing a three-drug formulation of anti-retrovirals (Hu et al., 2017). Hu-mice are susceptible to HIV-2 infection and show persistent viremia and CD4 T-cell loss, key hallmarks of AIDS pathogenesis.

Akkina also described how ideal animal models of human cell infections and human immune responses are lacking for the flaviviruses, dengue and Zika. In dengue pathogenesis studies, hu-mice were shown to be permissive for productive infection resulting in viremia lasting up to three weeks. Fever—characteristic of dengue—was noted with infected mice developing human neutralizing anti-dengue IgM and IgG antibodies. Recent experiments showed that hu-mice (BLT mice) are also susceptible to Zika virus with chronic viremia lasting more than 220 days. Virus-infected human monocytes/macrophages, B cells and hematopoietic stem cells were found in bone marrow (Schmitt et al., 2018) Human neutralizing antibodies are detected highlighting the use of this model for future vaccine testing.

5.4. Approaches to eliminating persistent viruses, part 1

Peter Revill (The Doherty Institute in Melbourne) described the International Coalition to Eliminate Hepatitis B Virus (ICE-HBV), which was established in 2016 to accelerate research on cures for hepatitis B infection. The vision of ICE-HBV is to develop an international, independent, research-based and patient-centered forum to coordinate, promote and foster collaborative partnerships working towards a cure for chronic hepatitis B (CHB). Over 250 million people worldwide are chronically infected with HBV, and even though a prophylactic vaccine and effective antiviral therapies are available, no post-infection cure exists. This is of concern in the Asia-Pacific region, where over 118 million people, including 239,000 Australians live with CHB.

Recent advances in the field, such as the identification of the NTCP receptor for viral entry and improved cell culture and animal models, are facilitating a new era in cure research worldwide (Watashi et al., 2014; Revill et al., 2016). Through its global network, ICE-HBV is working to promote research collaborations aimed at developing a cure as quickly as possible.

Liz Bannister (Royal Melbourne Hospital, Australia) noted that children in the world's poorest countries often are not vaccinated against HBV, including much of Africa, where 75 million people are chronically infected. With immigration of peoples from highly endemic regions, including sub-Saharan Africa, Australia's HBV prevalence continues to rise. Furthermore, African HBV genotypes and the natural history of African CHB remain poorly characterized, particularly in children. African CHB is associated with unique genotypes such as E and A1, although the prevalence of these genotypes outside Australia is poorly described.

Bannister and colleagues found that the HBV genotypes in African children and adults living in Melbourne largely reflected their country of origin, including genotypes associated with rapid progression to hepatocellular carcinoma, reduced vaccine efficacy, and recombinant viruses. Early e-antigen seroconversion was observed, and HBV variants that have previously been associated with more severe clinical disease progression were seen in around 40% of children before adulthood. *In vitro* studies of these genotypes showed differences in the way the African clones replicated and produced viral proteins, which may have implications for how these strains produce disease or can be treated. These findings have important ramifications for patient monitoring and treatment guidelines, particularly in the pediatric setting, in Australia.

Shyamasundaran Kottilil (Institute of Human Virology, USA) reported that chronic hepatitis C virus (HCV) infections affect approximately 71 million people worldwide and is a major cause of morbidity, liver cancer, liver transplantation and mortality. Currently, the goal of HCV therapy is to achieve a "functional cure," which is defined as a sustained virologic response (SVR) in which no detectable plasma HCV RNA is detected 12 weeks after therapy. Recently, oral direct-acting antiviral (DAA) therapy has been shown to be safe, tolerable and highly effective in achieving SVR without the use of interferon-alpha, which has been associated with adverse events, long duration, and modest SVR. This is a major milestone in the management of chronic hepatitis C. Still, most people infected with HCV are not aware of their status, only twenty percent are in care and less than ten percent are treated. Greater awareness among both providers and patients is required to optimize the care continuum. Approaches that enable increased patient screening, effective task-shifting of care, and development of point-of-care testing strategies for marginalized patients are critical to achieving elimination of hepatitis C infections (Mathur et al., 2017).

5.5. Approaches to eliminating persistent viruses, part 2

HIV and HCV are important global viral pathogens, for which the landscape of prevention by vaccination and cure through drug treatment is changing substantially.

Glenda Gray (South African Medical Research Council) provided an update on current HIV vaccine efficacy trials. Although anti-retroviral treatment (ART) is highly successful, it is expensive, can lead to drug resistance and is difficult to fully implement. Further, half of all HIV infections are transmitted by subjects within the first 5 months of their infection, often before they are aware of their infection. It is widely recognized that a HIV vaccine will be an essential tool in control of the HIV epidemic, especially in regions with high prevalence, such as Southern Africa. Over the last 20 years, HIV vaccine strategies have evolved from simple protein approaches or single vectors designed to induce cytotoxic T cells towards heterologous prime-boost regimens designed to induce broader immunity. The Thai RV 144 trial of a canarypox vector-gp120 protein prime boost vaccine regiment showed 31.2% efficacy (Rerks-Ngarm et al., 2009). The 5400 subject HVTN 702 trial is now under way, to see if it can improve upon this efficacy. At the time of the GVN meeting, 1600 subjects had already been enrolled. A two-stage follow-up of this trial is planned, to determine if any efficacy is durable.

Gray also reported that planning for a second prime-boost efficacy trial in southern Africa, the 2600-subject HVTN 705 trial using an adenovirus type 26 vector-gp140 boost regimen was well advanced. This regimen has showed significant efficacy in monkey trials (Barouch et al., 2015) and it has been announced subsequent to the GVN meeting that the trial is going ahead (www.nih.gov/news-events/news-releases/nih-partners-launch-hiv-vaccine-efficacy-study). Separate from the prime-boost vaccine efficacy trials, another efficacy trial of a passively transferred monoclonal neutralizing antibody (VRC01) is under way in both South Africa and North America (HVTN 703 and 704 studies). The VRC01 antibody is effective in preventing infection in monkey models and can reduce HIV levels in infected humans (Gray et al., 2016; Lynch et al., 2015).

Damian Purcell (The Doherty Institute/University of Melbourne) provided an update on approaches to an HIV cure. HIV remains latent despite ART, meaning that treatment must continue for life. Latent HIV can be reactivated with certain drugs that activate virus transcription, such as histone deacetylase inhibitors, with the hope that the reactivated virus will then be cleared (the so-called “shock and kill” strategy (Deeks, 2012)). However, recent clinical trials of these drugs show that their effect is modest and that effects on gene transcription can be non-specific and prolonged (Sogaard et al., 2015). Newer, more specific, more effective and less toxic alternatives are needed.

Purcell's group has developed assays to measure transcription of HIV mediated more specifically by HIV-1 Tat that lend themselves to high-throughput screens for inhibitors. He described a novel class of drugs, the amidothiazoles, that appear to specifically activate Tat-mediated HIV transcription in T-cell lines, with minimal toxicity. Their precise target mode of action is being studied, as is their ability to reactivate HIV from blood samples from infected people. This is a promising approach that should ultimately expand the armamentarium of potential HIV-cure drugs.

Margaret Hellard (Burnet Institute, Melbourne) presented the efforts of her group and collaborators to eliminate HCV transmission through multipronged efforts to cure large numbers of patients. The efficacy and simplicity of newer DAAs for hepatitis C provides a window to reduce transmission by reducing the numbers of viremic subjects. Modelling shows this should be a highly effective strategy, so long as sufficient numbers of people at risk of transmitting HCV can be treated. The cost of the newer drugs is coming down in many parts of the world and Australia's approach of universal access is facilitating larger scale treatment uptake. Increased rapid testing for HCV, assessment of liver fibrosis, and treatments administered to transmission networks in communities are likely to be required to achieve these goals (Pedrana et al., 2017).

5.6. Arboviruses

Arboviruses are some of the most widely distributed viral pathogens that also cause frequent episodes of epidemic disease. Many factors contribute to the emergence and spread of these viruses, including globalization, changes in vector competence, climate change, and spillover events affecting the vectors and the ensuing victims (Gould et al., 2017). This session provided research information ranging from mosquito control interventions to epidemiological understanding to vaccines and virus-host interactions.

Cameron Simmons (University of Melbourne, Australia) described past and present difficulties with controlling dengue virus (DENV) infections globally, and highlighted strategies that are currently being employed against mosquitoes to limit the replication and transmission of many arbovirus infections, including DENV. He detailed current approaches employed by the World Mosquito Program (WMP; previously known as Eliminate Dengue) to establish the intracellular bacterium, *Wolbachia,* in mosquito populations. *Wolbachia* is a bacterium with the intriguingly ability to limit virus replication in co-infected cells (Moreira et al., 2009). *Wolbachia*-harbouring mosquitoes have been successfully deployed around Cairns, Australia, and the WMP has initiated similar programs in DENV-endemic areas such as Indonesia, Brazil, Columbia, Vietnam and India. Simmons underlined some of the challenges of the WMP, including communication with the local population, the cost of large-scale implementation, measuring milestones and evidence-based outcomes, and developing methods to measure the impact of *Wolbachia* on disease incidence. Still, current results and projections look encouraging for this approach to limiting arbovirus infections.

Scott Weaver (University of Texas Medical Branch, Galveston, USA), Chair of the GVN task force on Zika virus (ZIKV), provided a timely update on the dramatic emergence of ZIKV in South and Central America in 2016, and a historical view on the spread of ZIKV from Africa to Asia to the South Pacific and now to the Americas (Aliota et al., 2017). Weaver described the manifestations of the disease in humans (Guillain-Barré syndrome and microcephaly) and the significant impact infection has on the unborn fetus in infected pregnant women. One of the most interesting recent observations is the precipitous decline in reported Zika cases in 2017. The reasons for this are currently unclear though increasing “herd immunity” may be a factor.

Weaver highlighted recent advances in ZIKV research, emphasising the large volume of research dedicated over the past few years, and culminating in numerous vaccine candidates under clinical trials and the development of nonhuman primate models to investigate pathogenesis. One of the most important considerations from these studies is the potential of cross-reactive flavivirus antibodies (particularly against either DENV or ZIKV) to enhance DENV/ZIKV disease in subsequent infection. He identified many of the research gaps that still remain, particularly in diagnosis, as many of the current diagnostic tests are cross-reactive but developments with a specific ZIKV anti-NS1 kit look encouraging. (GVN is supporting a ZIKV serum bank to aid in the development of better diagnostics). Additionally, the proposed herd immunity generated against ZIKV in the Caribbean and Latin America may hinder the development of vaccines, as it will be difficult to: 1) assess candidate vaccines in naïve populations, and 2) market vaccines in the absence of significant new cases (Ferguson et al., 2016). The principles that underlie the unique pathogenesis and transmission routes of ZIKV still remain unanswered.

Robert Garry (Tulane Medical School, USA) discussed the development of antibodies against Lassa fever virus (LASV) and Ebola virus (EBOV), and provided an overview of the history of these two viruses and efforts to coordinate and establish collaborative networks to provide outreach and education to affected African communities (Yozwiak

et al., 2016). He described the generation of human monoclonal antibody cocktails targeting the LASV glycoprotein and the technologies available to produce large quantities of highly specific human monoclonals, which have proven effective in nonhuman primate models (Mire et al., 2017). These developments and the construction of bivalent and trivalent vaccine candidates expressing stabilized LASV and EBOV glycoproteins are encouraging tools against lethal haemorrhagic fever viruses.

Marc Lecuit (Biology of Infection Unit, Institut Pasteur and Inserm, France) described the role of the cellular unfolded protein response (UPR) in the development of ZIKV disease. He presented evidence that the UPR contributes to neurogenesis and that upregulation of the UPR in neuronal progenitor cells can impact development, resulting in microcephaly in a mouse model. He showed compelling data indicating that ZIKV induces the UPR in neuronal progenitor cells; this was reflected in dysregulated neuronal development and reduced brain mass in ZIKV-infected fetal mice (Gladwyn-Ng et al., 2017). Therapeutic interventions alleviating the UPR reduced the presentation of microcephaly in ZIKV-infected mice, offering the possibility of therapeutic strategies in this area (Gladwyn-Ng et al., 2018).

5.7. Arboviruses and Ebola

John Fazakerley (The Peter Doherty Institute for Infection & Immunity, Australia) reported on the European Union-funded 'Integrating Chikungunya Research' (ICRES) Programme. ICRES consists of 14 international laboratories working to develop new molecular and cellular tools for the study of Chikungunya virus; further the understanding of the virus-vector relationship; develop new diagnostics, antivirals and a vaccine; and advance understanding of the pathogenesis of the disease and its sequelae. He also presented two studies of experimental animal models for investigating whether an alphavirus (Semliki Forest virus) that causes encephalitis can persist in the brain and whether an alphavirus (Chikungunya virus) that causes arthralgia can persist in joints.

Massimo Palmarini (GVN Centre Director at the MRC-University, Glasgow, Scotland) reported on the innate immune response mediated by type I interferon (IFN), and the resulting up-regulation of hundreds of IFN-stimulated genes (ISGs or the "interferome"), which provide an immediate barrier to virus infection. Studies on the type I IFN response have mainly been carried out at a single-species level, often lacking the comparative power necessary to understand key evolutionary features of this pathway. Palmarini and colleagues determined common and unique properties of the interferomes for multiple vertebrate species and developed an open access webserver to mine the dataset. They reported finding a "core" of 62 ISGs, including genes not previously associated with IFN, underscoring the ancestral functions associated with the type IFN response. They showed that gene expansion contributed to the evolution of the IFN system and that interferomes are shaped by lineage-specific pressures. Furthermore, an analysis of genes commonly down-regulated by IFN suggests that epigenetic regulation of transcription is a fundamental aspect of the IFN response.

Joshua Hayward (Burnet Institute, Australia) noted that viral infections of bats typically produce no signs of clinical disease, raising questions about what innate immune differences might exist between bats and other mammals. The APOBEC3 gene family encodes antiviral DNA cytosine deaminases, which are restriction factors with important roles in the suppression of diverse viruses and genomic parasites. Hayward and colleagues characterized the megabat (family *Pteropodidae*) APOBEC3 genes and show that pteropid bats possess the largest and most diverse array of APOBEC3 genes identified in any mammal reported to date. Several bat ABOEC3 proteins have been shown to be capable of restricting retroviral infectivity, using HIV-1 as a model. Hypermutation analysis of the endogenous retroviruses of *P. vampyrus* support a role for APOBEC3-mediated restriction of ancient bat retroviruses, and a molecular clock analysis indicates that the expansion of APOBEC3 genes coincided with the extinction of pteropid LINE-1 retroelements (Hayward et al., 2013). These findings reveal the first group of antiviral restriction factors identified in bats with extensive diversification and divergence relative to homologues of other mammals.

Didier Fontenille (Institut Pasteur du Cambodge) described the diversity of arbovirus vectors in Asia. More than 430, 220 and 240 different mosquito species have been identified in Thailand, Vietnam, and Cambodia, respectively. Little is known about ticks, however, and even less about sandflies and biting midges. Compared to the diversity of vectors, very few arboviruses have been identified beyond the "big four": dengue virus (serotypes 1–4); Japanese encephalitis virus; chikungunya virus; and more recently, Zika virus. Strategies for vector control in most Asian countries are few—with rare successes and numerous failures. There appear to be several reasons for the vector control stalemate, including a paucity of field research, as well as lack of interest and/or competency in research laboratories.

Fontenille posed a number of questions about the region and the emergence of new viruses, asking: How can we effectively control vectors? How can we assess the risk of emergence and outbreak within the frame of environmental, social and climate change? What do we know about the biology and evolution of mosquitoes (for example, *Ae. aegypti* vs *Ae. albopictus*), and mosquito-virus co-adaptation in Asia? Should Southeast Asia expect the emergence of Zika virus? Fontenille reviewed these issues and made recommendations for a more active, holistic research approach involving virologists, zoologists, ecologists, social scientists and the often-neglected entomologists (Roche et al., 2017).

5.8. Persistent viruses

Anthony L. Cunningham (University of Sydney, Australia) described the "find me" and "eat me" signals that attract human dermal dendritic cells (dDCs) to Langerhans cells (LCs) infected with herpes simplex virus (HSV), and facilitate recognition and uptake of apoptotic LCs (Botting et al., 2017). He and his colleagues assessed the expression of chemokines by HSV-infected LCs and corresponding chemokine receptors on dDC subsets, as well as apoptotic receptors that may recognize and facilitate their interactions. These studies help to define the mechanisms of uptake and viral antigen transfer between LCs and dDCs, leading to subsequent differential presentation to $CD4^+$ and $CD8^+$ T-cells, which may define potential dendritic cell targets for adjuvants in future mucosal or intradermal vaccines.

Zhiwei Chen (AIDS Institute and Department of Microbiology, Hong Kong SAR, China) reported on "HIV enteropathy" in acute HIV infection, which is characterized by diarrhea, gastrointestinal inflammation, increased intestinal permeability and malabsorption of nutrients. Inflammatory mediators such as infiltration and activation of $CD8^+$ T-cells, pro-inflammatory cytokines and CD4 T-cell depletion likely contribute to these changes in the intestine following local immune activation. Chen and colleagues have discovered that a subset of gamma-delta T-cells ($\Delta 42PD1 + V\delta 2$) also may contribute to innate immune activation and mucosal damage during acute HIV infection (Cheung et al., 2017). These cells may serve as targets for the investigation of diseases with mucosal inflammation, in addition to initial HIV infection at the mucosal surface.

Bonnie Howell (Merck, Boston, USA) described the importance of elucidating mechanisms of HIV-1 persistence and developing innovative strategies for treatment and a functional cure. A class of small molecules – histone deacetylase inhibitors (HDACis)—has been studied as latency-reversing agents, and clinical studies have shown that single and multiple administration results in induced viral RNA transcription and protein in $CD4^+$ T-cells from ART-suppressed HIV+ subjects (Wu et al., 2017). Furthermore, applying novel screening strategies for latency reversal agents in the presence of a sensitizing agent, such as a HDACi, can be a useful approach in identifying new mechanisms and

alternative therapies for latency intervention. Notably, the exploration of cure strategies targeting the latent HIV reservoir also highlights a need for new assays and research tools to quantify viral burden in tissue and various body fluids. The rare incidence of latently-infected cells, for which robust phenotypic markers are still needed presents a challenge to identifying these cells and measuring changes in viral expression, particularly after therapeutic intervention (Wu et al., 2017).

Sarah Palmer (Centre for Virus Research, University of Sydney, Australia) reported that full-length HIV sequencing techniques revealed the majority of persistent HIV provirus in cells is genetically defective during antiretroviral therapy (Hiener et al., 2017). However, the distribution of intact proviruses within memory $CD4^+$ T-cell subsets from participants who initiated therapy during either acute or chronic infection showed the proportion of intact provirus was significantly different across cell subsets. Cells expressing the HLA-DR activation marker and effector memory cells contained the highest proportion of intact HIV genomes. In addition, clonal expansions of intact proviruses were identified indicating that proliferating cells contribute to the latent reservoir. The HLA-DR marker identifies cells containing a high frequency of intact HIV genomes; therefore, assays quantifying the persistent HIV reservoir should include these cells. Determining the type of cells and cellular mechanisms contributing to persistent replication-competent HIV is crucial for future efforts aimed at HIV eradication.

5.9. Finale

Ricky Mentha (Baker Heart and Diabetes Research Institute, Australia) reported that Aboriginal populations residing in remote locations have limited general knowledge of infectious diseases, modes of transmission, and preventative public health measures. Exposure to an array of communicable diseases is prevalent, and morbidity and mortality are significant. Effective partnerships with local Aboriginal stakeholders are critical to improving knowledge of infectious diseases and developing preventative strategies derived from a well-thought-out research agenda. Mentha described many pressing needs, including: research grounded in the principles of social justice and equity; community consultations and partnerships; building capacity with Aboriginal researchers and community members; and translating findings into policy, practice and health promotion. There are many complexities to address in conducting communicable disease research in remote Aboriginal populations, but it can be done in ethical and culturally sensitive ways that contribute to reducing exposure to poverty-related infectious disease that impact on morbidity and mortality (Brown et al., 2016).

Kanta Subbarao (WHO Collaborating Centre for Reference and Research on Influenza, Australia) presented recent data on replication and viral properties governing the airborne transmission of influenza virus 2009 pandemic A/H1N1 in a ferret transmission model, and described some of the complex viral and host interactions that influence the transmissibility phenotype of influenza viruses (Sutton et al., 2017).

Frederick Kristensen (CEPI, Oslo, Norway) described the recently established Coalition for Epidemic Preparedness Innovations (CEPI). The organization was launched in January 2017 with an initial investment of more than $500 million provided by the governments of Norway, Japan and Germany, the Bill & Melinda Gates Foundation and the Wellcome Trust. In addition, the European Commission agreed to co-fund some CEPI projects with €200 million. Other funds will be available from Australia, Belgium and Canada. At its launch, CEPI issued a call for proposals to develop vaccines against three viral agents: MERS-coronavirus, Lassa and Nipah virus. A new call is planned for developing vaccine platforms.

6. The network in 2017

On October 1, 2017, Christian Bréchot, MD, PhD became the new GVN President (http://gvn.org/brechot/). He previously served as President of the Institut Pasteur in Paris. Dr. Bréchot held other leadership positions with the French National Institute of Health and Medical Research (Inserm), the Institut Mérieux, and the BIOASTER Technology Research Institute. He previously served as a university professor, hospital practitioner, and head of departments of hepatology and cell biology. In 1982, Dr. Bréchot received a Doctor of Medicine from Paris Descartes University (Paris VII) and a PhD in biochemistry from the Paris Descartes University. Throughout his career, his research has focused on HBV and HCV, particularly regarding their role in liver cancer and to the molecular mechanisms that drive liver regeneration and cancer. He is a member of numerous scientific committees and societies and has received a myriad of prestigious awards. Dr. Bréchot has authored more than 350 articles in medical and scientific journals.

While there are new changes to the GVN headquarters staff, several other activities have continued, including the collection of acute and convalescent sera from confirmed Zika patients to aid in developing new diagnostics. The serum bank is funded by a grant from the Allergan Foundation, and samples are stored at the University of Texas Medical Branch in Galveston, Texas. In addition, Shyamasundran Kottilil and colleagues at the Institute of Human Virology in Baltimore have continued a project with the GVN to expand a training model for health care providers using DAA treatment for hepatitis C patients in India (Mathur et al., 2017). The training program is funded by the Gilead Foundation. Similarly, a pilot study to develop an integrated clinical database to support community-based care of hepatitis B patients in Arunachal Pradesh, India also is under way, and is funded by the John C. Martin Foundation.

GVN's HTLV-1 task force members published a commentary recommending the current name for HTLV-1 be changed back to its original name (human T-cell leukemia virus-1), in keeping with its oncogenicity and pathogenesis (Gallo et al., 2017). Other GVN investigators published work on the oncogenicity of HTLV-1 (Tagaya and Gallo, 2017). Members of the GVN task force on Zika virus also published a major review on what has been learned about Zika in the first two years of the epidemic in the Americas, and what gaps remain (Aliota MT et al., 2017).

During 2017, the Network expanded the number of cooperating research centers by adding the Mérieux Foundation in Lyon, France, and the Rega Institute for Medical Research at the University of Leuven in Belgium (Fig. 1). These two new centers are expected to strengthen research on vaccines and collaborative activities in developing countries.

7. Plans for 2018

GVN staff will continue to solicit patient serum samples for the Zika serum bank in Galveston, Texas. Additionally, a project to sequence and conduct phylogenetic analyses of collected Zika virus isolates is continuing in cooperation with the World Reference Centre for Emerging Viruses and Arboviruses (WRCEVA), which is funded by the National Institute of Allergy and Infectious Diseases (USA).

The GVN will host the fifth annual Short Course on Medical Virology for young investigators in the summer of 2018. The Short Course attracts an international class of 15–20 postdoctoral students and fellows for five days of meetings and lectures with experts in medical virology research and clinical practice. Information about the course and registration is available online at http://gvn.org.

The 2018 international GVN meeting will be in Annecy, France during November 28–30. It will be co-hosted by the Research Centre for Emerging Infections and Zoonoses at the University of Veterinary Medicine in Hanover, Germany. The Scientific Organizing Committee includes: Christian Bréchot, GVN President, USA; Huber Endtz, Scientific Director at the Fondation Mérieux, France; Robert Gallo, Co-Founder & Scientific Director, GVN; William Hall, Co-Founder, GVN, University College Dublin, Ireland; Ab Osterhaus, Director of the

Research Centre for Emerging Infections and Zoonosis (RIZ), Germany; and Marc Lecuit, Director of the Biology of Infection Unit at Institut Pasteur, France.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.antiviral.2018.02.001.

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