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2019 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 52 GVN Centers of Excellence and 9 Affiliate laboratories in 32 countries. The 11th International GVN meeting was held from June 9–11, 2019 in Barcelona, Spain and was jointly organized with the Spanish Society of Virology. A common theme throughout the meeting was globalization and climate change. This report highlights the recent accomplishments of GVN researchers in several important areas of medical virology, including severe virus epidemics, anticipation and preparedness for changing disease dynamics, host-pathogen interactions, zoonotic virus infections, ethical preparedness for epidemics and pandemics, one health and antivirals.

1. Introduction to the GVN

The Global Virus Network (www.gvn.org) is a global coalition of leading virologists. Founded in 2011, the not-for-profit organization GVN has grown to 52 Centers of Excellence and 9 affiliate institutions in 32 countries throughout the world. The GVN mission is to strengthen research and response to current viral causes of human disease and to prepare for new viral pandemic threats through the collaboration of a global network of expert virologists. The GVN activities are mainly based on virology research, training and advocacy. The GVN International meetings is one way to support its mission, providing a framework where global junior and senior virologists can connect, discuss and establish new collaborations and advance the field.

Past GVN International meetings have taken place in Washington DC, USA and Dublin, Ireland (2011), Naples, Italy and Baltimore, MD, USA (2012), Munich, Germany and Moscow, Russia (2013), Beijing, China (2015), Sapporo, Japan (2016), Melbourne, Australia (2017), and France (2018). The 2019 GVN International meeting took place in Barcelona, Spain, June 9–12 and was jointly organized with the Spanish Society of Virology. The meeting had 311 delegates from 22 different countries. A common theme throughout the meeting was globalization and climate change. The 11th GVN International meeting gave participants an opportunity to discuss recent findings in virology, thus providing a platform for collaboration and networking, particularly for the high number of participating young Spanish virologists. The conference sessions are outlined in the present report.

In addition to plenary lectures and workshops that were held at the SEV-GVN joint meeting, contributions in the format of short oral presentations were arranged to include a wide spectrum of issues addressed by member-scientists of GVN. Poster sessions allowed an interesting discussion among essentially younger scientists from Spanish laboratories and participants from other countries. With this perspective for the first time GVN established travel grants that consisted of partial financial help to encourage participation of younger members of

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GVN centers. In contrast to previous GVN meetings (4–5 oral presentations on related subjects in each block) sessions were arranged as a series of talks that covered a quite diverse repertoire of issues of interest to virologists around the world.

2. The 2019 Robert C. Gallo award for scientific excellence and leadership

Criteria for the selection of this award include: 1. The candidate has published important scientific information on virology in the areas of interest to the GVN, including but not limited to: basic science, clinical aspects, pathogenesis, epidemiology, diagnostics, antivirals, and vaccine development. 2. The candidate has made a consequential and meaningful contribution to the GVN and has furthered the mission of the GVN, including but not limited to; development of the network of Centers of Excellence, participation in training programs, contributions to meetings and other GVN activities, and contributions to advocacy and public communication activities.

The 2019 Robert C. Gallo award for scientific excellence and leadership was awarded to Dr. William Hall, GVN Co-founder.

3. Scientific presentations

3.1. Anticipation and preparedness

Scott C Weaver (University of Texas Medical Branch Galveston, USA) gave an overview on the history and the distribution of Zika virus (ZIKV). He summarized the recent epidemic of ZIKV in the Americas and depicted the association between ZIKV and microcephaly that was established late in 2015. He then illustrated the reaction of GVN with the assembly of a global Zika Task Force that was established within three months after the association between ZIKV infection and microcephaly was recognized. This task force gathered experts on flaviviruses, arboviruses, and viral congenital diseases from 13 GVN centers from 13 countries.

Besides communication of the latest information on ZIKV and the distribution of expert reviews (Weaver et al., 2016) the task force, which was supported by a private donation, established the GVN ZIKV Serum Bank. This serum bank collected and characterized more the 100 sera from donors who had been exposed in different countries all across South and Latin America. They made this collection of highly characterized sera available to international expert labs by providing lyophilized aliquots. They further provided a collection of ZIKV strains, different virus antigens, and two cDNA infectious clones.

Weaver also reported on ZIKV vaccine strains that were attenuated through deletions in the 3′UTR. As a DNA-launched ZIKV live-attenuated vaccine, having a 20-nucleotide deletion, this mutant virus gave rise to high antibody titers after a single immunization and was highly protective in a ZIKV mouse model, as well as, in a rhesus macaque infection model (Zou et al., 2018).

Núria Busquets (Centre de Recerca en Sanitat Animal, Spain) highlighted the importance of arboviruses as pathogens and focused on the surveillance of vectors and animal reservoirs. She gave a short overview on the emergence of arboviruses which over the last 40 years has become an important global public health threat causing significant morbidity and mortality among humans and animals. While for Chikungunya, Dengue, and Zika virus carrying mosquitos easily can spread also other arboviruses, e.g. Rift Valley Fever virus (RVFV), and West Nile virus (WNV), there is a critical role for vertebrate hosts as animal reservoirs.

Dr. Busquets stressed that good surveillance data are the base for intervention strategies thus helping to protect public health and to save money. Thus, detailed knowledge on which mosquitoe species are competent hosts for the virus and where and when these mosquitoes are present, as well as, on which the vertebrate hosts are the reservoir and their presence are important. So is the knowledge on the kinetics of infection, viremia and virus shedding, the immune response and last but not least good, reliable, and rapid diagnostic tools. She pointed out that virus circulation in vectors and in animal reservoirs precedes human exposure and infection. During an arbovirus outbreak in humans, clinical signs might only be detected when the peak of an outbreak has already been passed. However, virus circulation in vectors and the animal reservoir will precede human infections (Reusken et al., 2018). Therefore, early detection in vectors and animal reservoir hosts can serve as an early warning system to mitigate economic and human health impact.

How important the interplay between different information sources is was demonstrated in 2015–2016 when the combination of weather forecast and syndromic animal surveillance during El Nino rains in Kenya resulted in an effective early warning for a major outbreak of RVFV, thus allowing precautions to prevent spill over to humans (Oyas et al., 2018).

As a second example she presented the WNV outbreak on the American continent starting in New York City in 1999 (CDC, 1999) and the emergence of WNV lineage 2 in Spain in 2017 (Napps et al., 2019). In both cases dead bird surveillance and identification of equine infections was an important for WNV surveillance as an early warning system. Dr. Busquets concluded that arbovirus surveillance provides a realistic picture of the epidemiological situation and allows for monitoring the effectiveness of intervention measures. Surveillance in vectors and in vertebrate hosts enables detection of arbovirus circulation before clinical onset in humans. However, countries need to adapt their surveillance scheme to their epidemiological situation, surveillance objectives and capacities. Effective early warning requires the interaction between multiple disciplines like entomologist, veterinarians, biologists, clinicians, epidemiologists, etc.

Masao Matsouka (Kumamoto University, Japan) gave a detailed insight into aspects of the strategy and pathogenesis of human T-cell leukemia virus type 1 (HTLV-1). In his presentation he focused on two viral proteins, the transactivator of viral gene expression (Tax) and the HTLV-1 bZIP factor (HBZ). HTLV-1 is the causal agent of adult T-cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in adults. It has close relatives in several non-human primates and is an important human pathogen with a global distribution of infection foci and an estimated 10 million people are infected (Sonoda et al., 2011). HTLV-1 is transmitted only through cell-to-cell contact passing the virus from mother to infant through breast milk and from male to female through semen. Therefore, living infected cells are essential for transmission and in order to enhance transmission the virus increases the number of infected cells.

While the cellular receptor for HTLV-1 is ubiquitous (Manel et al., 2003) the provirus is mainly detected in $CD4^+$ effector/memory T cells *in vivo*. However, it was not clear if HTLV-1 preferentially infects these cells or if infected precursor cells differentiate into these cells. Analyzing tax expression as a marker for viral replication in STLV-1 infected Japanese macaques as a model for HTLV-1 infection in humans, Matsouka and colleagues showed that elevated tax expression is mainly seen in the bone marrow suggesting *de novo* infection of hematopoietic stem cells (HSCs). Further, in HAM/TSP patients they detected identical integration sites of HTLV-1 proviruses in neutrophils, monocytes, B cells $CD8^+$ T cells and $CD4^+$ T cells indicating that these cells are all derived from HTLV-1 infected HSCs *in vivo*.

While Tax has an important role in the upregulation of anti-apoptotic genes and the maintenance of cell populations it is only expressed transiently, most likely because the Tax protein is highly immunogenic and a major target for CTL. In leukemic cells Tax is expressed only in a minor fraction of the cells and only for a short period of time (Mahgoub et al., 2018). Matsouka then concentrated on the important role of HBZ in HTLV-1 pathogenesis. HBZ is encoded on the antisense strand of the provirus and has a low immunogenicity. In contrast to Tax it is expressed constantly in all ATL cells. HBZ regulates several different pathways in infected cells, enable immune escape, trigger inflammation

through the induction of IFNg expression, and enable the infection to overcome immune suppressive effects. HBZ also induces expression of the chemokine receptor CCR4 allowing infiltration of infected T-cells into tissues. Seen that HTLV-1 is transmitted through cell-to-cell contact he suggested that HBZ-induced CCR4 expression enables HTLV-1 infected cells to migrate into breast milk and into semen, thus allowing efficient transmission of the virus between humans.

Marion Koopmans (Erasmus MC, Netherlands) elaborated in her presentation on the complex interplay between man-made disturbances of ecosystems and the resulting increase in number and amplitude of emerging viral disease outbreaks. She presented several examples to underline how changes in environmental conditions and in human behavior can create conditions that result in an increase of pathogen transmission, spill-over to new hosts, broad dissemination of infection, and changes in viral properties. The recent Ebola outbreak in West Africa and the ongoing outbreak in the Democratic Republic of Congo illustrate how demographical and political changes can affect spreading of diseases.

Dr. Koopmans emphasized the important role and the potential of surveillance by presenting preliminary results on arbovirus surveillance from the ARBO study and data from an influenza market surveillance in poultry in China (Bai et al., 2019). She also pointed out a potential role for co-circulation of different viruses, e.g. Zika and dengue for new pathogenesis pathways (Langerak et al., 2019).

Shifting the burden of disease detection from clinicians to early detection and forecasting of spillover through surveillance of reservoir hosts would mean a paradigm change in the surveillance of emerging infectious diseases from reactive to pro-active measures. Early detection allows timely control and thus mitigates the number of human cases (Karesh et al., 2012). Matching these surveillance data with data on demographic development, global travel and trade, and climate change might allow to predict potential international spread of pathogens. The utility of such approaches will very much depend on a switch from the detection of single pathogens to an “open view” surveillance with multiplex assays, broad antibody profiling, metagenomics approaches, and an efficient way of data sharing.

3.2. Host-pathogen interaction

Thomas Rasmussen, a Senior Researcher at the National Veterinary Institute of Virology in Australia, presented an update on the potential use of latency-reversing agents (LRAs) for HIV elimination. The great success of antiretroviral therapy (ART) for HIV Infection is tempered by the fact that treatment must be maintained for life. Rasmussen reviewed work showing that HIV can remain in a latent state where the immune system or ART cannot eliminate the virus. Rebound viremia occurs when ART is stopped even in individuals with no detectable virus in cells or plasma. An experimental approach to clear latent HIV and thus cure HIV infection has been dubbed “shock and kill.” LRAs are used to activate latent HIV allowing the reactivated cells to be targeted and killed by ART and/or the immune system. Administration of LRAs alone have thus far not demonstrated an effect on the frequency of latently infected cells or the time to virus rebound following interruption of ART (“shock, no kill”). For example, in the DIORR trial (Dolutegravir Intensification Effect On Residual virus Replication on ART) lead by Rasmussen there was no change in levels of HIV DNA or RNA. Negative results where mechanisms for failure are carefully examined are important because they can demonstrate which strategies will not work and provide guidance to strategies that do work. Elimination of latently infected cells (particularly those that are long-lived) may require HIV-specific $CD8^+$ T cell effector functions similar to those of so-called elite controllers of HIV-1 infection. Various strategies to boost anti-HIV immunity currently under development including therapeutic vaccines, toll-like receptor agonists, broadly neutralizing antibodies, immune checkpoint inhibitors, interferon-α and interleukin therapy should be investigated. Immune checkpoint blockade could also play a role in developing an HIV cure by re-invigorating exhausted T cells and potentially reversing HIV latency in $CD4^+$ T cells.

Infection by mosquito-borne viruses has increased over the past few decades due to globalization, increase in societal mobility and climate change. **Juana Diez** from the Universitat Pompeu Fabra in the lovely host city of Barcelona continued the session by exploring how viruses such as Chikungunya virus (CHIKV) are able to express their genomes at high levels in cells from diverse species. The four bases of the genetic code create 64 codons, of which 61 are translated into 20 amino acids and 3 are stop codons. Synonymous codons differ principally at the third base or wobble position. Different species, including mosquitoes and humans, vary widely in which codons are used for protein translation. Dr. Diaz and her team integrated subcellular fractionation and transcriptome-wide analyses of translation in human cells, to show that CHIKV infection induces a host adaptation to viral codon usage into the endoplasmic reticulum (ER), the preferred site of CHIKV protein expression. The tRNA modification enzyme methyltransferase 9 (KIAA1456) methylates uridine in the wobble position and enhances speed of translation of certain mRNAs, including CHIKV mRNAs. KIAA1456 mRNA is translationally activated up to 40-fold by CHIKV infection. Overexpression of KIAA1456 increases CHIKV replication and KIAA1456 mRNA silencing decreases replication. These findings demonstrate an unexpected interplay of viruses with the host tRNA epitranscriptome that favors viral protein expression. This mechanism appears to be conserved among viruses that replicate effectively in more than a single host species, which opens the intriguing possibility of future exploitation of a broad-spectrum antiviral target.

3.3. Ebola virus, viral protein corona and arboviruses

The ebolaviruses cause highly lethal disease with sporadic and unpredictable outbreaks. An ongoing outbreak in Democratic Republic of the Congo is the second largest in history. While the genome of Ebola virus encodes just seven proteins, the deleterious effects on the human body are immense causing severe pathology and fatalities. Thus, basic research is needed to understand the viral protein conformations and their role in viral replication.

Sara Lenderas Bueno from the Scripps Research Institute explained that several of these proteins are multifunctional in the viral cycle, and some of these are also multi-structural, adopting different forms at different times to mediate different, essential functions. Using crystallography, electron microscopy and biochemistry, it was found that two essential proteins in infection; the nucleoprotein NP and the matrix protein VP40 display different conformations. NP is involved in viral nucleocapsid formation and facilitates viral transcription and replication. To avoid premature self-polymerization and non-productive binding to cellular RNAs, NP is chaperoned by the viral phosphoprotein VP35. NP complexing with the amino-terminal portion of VP35 was delineated at 2.3 Å resolution and electron microscopy indicated the importance of this binding interaction to control NP polymerization. Structure-directed mutagenesis studies identified conserved critical residues in the NP-VP35 interface which could be targeted by broadly effective antivirals. With regard to the matrix protein VP40, another multi-structural protein, it rearranges into three alternative structures, each with its corresponding function at different stages of the life cycle. How these structural changes are triggered has remained unclear. New data revealed that the binding of the VP40 dimer to specific nucleotide sequences is enough to form the octameric structure/form responsible for regulation of viral RNA replication. These findings provide the molecular basis for the multifunctionality of these proteins and reveal attractive targets for therapeutic intervention.

Kariem Ezzat from Stockholm University presented tantalizing data on the role of viral protein corona in viral pathogenesis and amyloid aggregation. Viruses rely on the intracellular host machinery for replication, production of viral proteins and assembly. However, outside

cells, viruses share many biophysical properties with nanoparticles. Based on these features, viruses have the capacity to accumulate a host-derived protein corona layer in extracellular environments similar to nanoparticles. To evaluate this possibility and its implications, protein corona layers of respiratory syncytial virus (RSV) and herpes simplex virus 1 (HSV-1) in different biological fluids such as human plasma and bronchioalveolar lavage fluid were analyzed using proteomics, electron microscopy, infectivity, and dendritic cell activation assays. It was found that RSV and HSV-1 accumulate rich protein corona layers that are unique for each biological fluid and corona pre-coating differentially affects viral infectivity and immune cell activation. In addition, like nanoparticles, viruses should be able to function as nano-surface catalysts that enable accelerated extracellular amyloid protein aggregation.

The authors also showed that HSV-1, which has been implicated in Alzheimer's disease, catalyzes the nucleation and accumulation of the Aβ42 peptide both *in vitro* and *in vivo*. Results from Ezzat et al., (2019) showed that unlike the viral genome coded surface proteins, the viral protein corona is an acquired structural layer that is dependent on the viral microenvironment resulting in different viral identities based on the target tissue and the target organism. Additionally, the viral corona-driven heterogeneous nucleation of amyloids illustrates convergence between viral and amyloid pathologies suggesting a direct physical mechanistic link that warrants further investigation.

Ana Isabel Nunez from IRTA-CReSA, Barcelona, Spain, discussed novel findings on mosquito molecular responses to arbovirus infection, particularly related to Rift Valley fever phlebovirus (RVFV) and *Culex pipiens*. In the literature, the *Aedes aegypti*-Dengue virus (DENV) combination is the most studied in terms of gene expression. However, there is a general paucity of information on mosquito genes involved in vector competence and immune responses with regard to other important vector-virus interactions. RVFV causes an emerging significant public health zoonotic disease which is commonly transmitted mainly by the Culex and Aedes genus mosquitoes. In her talk, molecular responses of *Culex pipiens* to RVFV infection were presented, particularly those related to genes implicated in the innate immunity pathways (Toll, IMD, JAK/STAT) and RNAi. A total of 445 differentially expressed genes (DEG) were identified. The gene expression profiles varied at different days post infection. A total of 445 DEG were found wherein 42 DEG were immune function related. Among these genes, some are involved in innate immunity pathways; Cactus or Defensin-A in the Toll pathway or Piwi4 and Drosha in the RNAi pathway. Specifically, three immune pathways Toll, IMD and RNAi and apoptosis were affected by RVFV infection. Conversely, JAK/STAT pathway seems not to be involved in *Culex pipiens* response to RVFV. Toll and Imd pathways are suppressed after infectious blood feeding, for example AMP (Defensin-A) was down-regulated. The RNAi pathway was mainly down-regulated in the course of the RVFV infection. All these immune system responses would allow the establishment of the RVFV infection in *Culex pipiens* mosquitoes. These results form a basis for future in depth studies to better understand the functionality of immune related DEG in relation to vector competence to develop new strategies for vector control programs.

Ken Olson from Colorado State University reviewed the RNAi and arbovirus interactions. Such infections in *Aedes aegypti* allows transmission of yellow fever, dengue, Zika, and chikungunya viruses throughout the mosquito's lifetime. The mechanisms of viral persistence in mosquitoes, which involves the production of virus RNA-derived siRNAs and piRNAs, are not well understood. The RNA interference pathways involve double stranded RNAs that degrade target RNAs and mediate gene regulation. In his studies, siRNA and piRNA product depletion, small RNA sequencing, piRNA product expression profiles, immunoprecipitation, and arbovirus assays were used to dissect the viral and host-cell interactions. It was found that the Piwi-family protein Piwi4 has antiviral activity in *Aedes aegypti* Aag2 cells and in mosquitoes infected with arboviruses and insect-specific flaviviruses. Although these RNA viruses encode no reverse transcriptase, circular episomal DNA in arbovirus-infected *Aedes aegypti* cells consisting of hybrid sequences of arbovirus-derived cDNA (vDNA) and retrotransposable elements were found. These episomal DNAs appear to be acquired during reverse-transcription by a discriminatory process of vDNA recombination with retrotransposons. Transcripts from vDNA may serve as precursors for antiviral vpiRNAs. Integrated viral-derived (vDNA) can also be detected in the mosquito genome as endogenous viral elements (EVEs) that are often associated with piRNA clusters in the mosquito genome. EVEs are transcribed to produce piRNAs that associate preferentially with Piwi4. Importantly, EVE-derived piRNAs can inhibit the replication of a cognate virus. These findings suggest that the *Aedes aegypti* Piwi family of proteins and episomal vDNA, and EVEs provide a means of moderating viral load in mosquito cells and a potential mechanism for transgenerational virus tolerance in the mosquito.

Richard Zhao from the University of Maryland presented data on the virologic differences in severity between historical and epidemic Zika virus-mediated infection and neurocytotoxicity. The 2015 Zika virus (ZIKV) outbreak in the Americas have had a severe impact as it in Brazil alone left > 3000 babies with ZIKV-associated neurological disorders (ZAND) including microcephaly. Even though the causal relationship between the ZIKV and ZAND have been confirmed, the reasons why the ZIKV suddenly became so pathogenic and caused ZAND in humans remain largely unknown. To help answer this question, the virologic differences and the underlying molecular mechanisms between the representative historical African MR766 ZIKV strain and the epidemic Brazilian BR15 ZIKV strain were examined. Glioma SNB-19 cell line and 3-D neurospheres were used to evaluate both primary and chimeric viruses. Notable differences were found between strains with regard to viral attachment, permissiveness and replication, as well as, the induction of neurocytopathic effects in host neuronal cells.

Chimeric virus analyses suggested that the ZIKV E protein correlates with the viral attachment, and the C-prM region contributes to the permissiveness and ZIKV-induced cytopathic effects. Furthermore, the prM protein and its cleaved Pr product, but not the mature M protein, induces apoptotic cell death in the SNB-19 cells. The Pr region, which resides on the N-terminal side of prM protein, is responsible for prM-induced apoptotic cell death. Mutational analysis further identified four amino-acid residues that have an impact on the ability of prM to induce apoptosis. These findings suggest that functions of the structural prM-E proteins contribute in part to the difference in ZIKV-mediated viral pathogenicity between the historic and epidemic strains. Ongoing studies are likely to identify the role of other viral proteins with regard to neuropathogenesis.

Ramesh Akkina from Colorado State University reported on the ZIKV mediated pathology on human hematopoietic cells. While many previous studies have focused on ZIKV viral effects on the CNS, few have explored the viral effects on the human immune and hematopoietic system. Dr. Akkina presented both *in vitro* and *in vivo* studies conducted on human cells. *In vivo* studies involved humanized mice (hu-mice) that harbor a transplanted human immune system. These mice generate human T cells, B cells, NK cells, monocytes and macrophages, as well as, dendritic cells that orchestrate both humoral and cellular immune responses and thus are ideal models to examine viral effects and interactions with human immune cells (Akkina, 2013). Since the hu-mice also harbor human hematopoietic stem cells in the bone marrow, viral effects on these cells can also be ascertained. Recent studies (Schmitt et al., 2018) has shown that ZIKV infection of hu-mice can generate a human neutralizing antibody response to ZIKV and also that human B cells and CD34 HSC can be infected.

In studies presented at the meeting, further investigations were carried out on the ZIKV infection on human B cells *in vitro* and *in vivo* to determine any adverse effects such as cell death or cell dysfunction, as well as, viral persistence. Viral exposure of mature naïve B cells resulted in the loss of one subset and aberrant proliferation of another.

Upregulation of markers indicative of B cell progression into the plasmablast stage was seen in the expanding subset. *In vivo*, results from ZIKV infected hu-mice showed the presence of ZIKV + B cells in the periphery during acute infection and later in bone marrow during the chronic stage. It was also found that CD34 $^{+}$ HSC were susceptible to ZIKV infection *in vitro* and could be detected in the bone marrow of infected hu-mice. B cell loss can lead to delayed viral clearance, whereas aberrant B cell activation may have implications in the pathogenesis of autoimmune diseases such as Guillain-Barré syndrome. Infection of CD34 $^{+}$ HSC has implications for hematopoietic cell differentiation and viral persistence.

Currently several murine models of ZIKV neuropathogenesis exist. Since standard mice are not susceptible to ZIKV, mostly IFN deficient mice that lack an innate immune system and thus permitting ready viral infection are used. A significant drawback with these models is that viral infection leads to rapid fatalities, which is not a common feature with ZIKA. In the studies presented BALB/c RAG2$-/-\gamma c-/-$ mice (also known as BRG mice) with intact IFN pathway were used. Neonatal mice when exposed to ZIKV developed severe microcephaly and other important CZS features such as eye deformations and stunted growth. This model is likely to be useful as an experimental neonatal ZIKV infection model. With regard to human cell infections, these findings highlighted the utility of hu-mice as valuable human surrogate experimental system to directly assess ZIKV effects on these cells *in vivo*.

3.4. Preparedness for zoonotic infections, emerging infectious diseases and ethical review, and vaccine take in the elderly

Christopher Kratochvil, co-director of Global Center for Health Security (GCHS, University of Nebraska) presented the mission and resources of the center, which is an initiative of the University of Nebraska Medical Center (UNMC) with the purpose of leading US domestic and global preparedness for emerging infectious diseases (EIDs) (https://www.unmc.edu/iexcel/global-center/index.html). Since its foundation in 2017 it has become a primary biosecurity resource for training, education, research, and clinical care and for advancing international capacity and innovation to prevent and mitigate the effects of EIDs and other public health emergencies. The program's successes have been built upon a foundation of robust partnerships with diverse governmental and academic organizations (Ktatochvil et al., 2017; Eitzen et al., 2019).

The GCHS has numerous resources, including a clinical biocontainment unit, a quarantine unit, a training and simulation center which includes a simulated biocontainment unit, as well as, diverse laboratory and clinical resources from across the academic health center.

Strategic partnerships with the Assistant Secretary for Preparedness and Response (ASPR), the Centers for Disease Control and Prevention (CDC), the Department of Defense, and other academic health centers, have resulted in multiple collaborative initiatives. Examples include the National Ebola Training and Education Center (NETEC), the Special Pathogens Research Network, the U.S. Air Force C-STARS training program, the Federal Quarantine Center, a National Disaster Medical System training program, and a central institutional review board (IRB) specializing in preparedness, as well as, rapid response (NETEC, 2019). The center is open to global collaboration, which already includes Singapore, Germany, South Korea, and China. Among the relevant events Dr. Kratochvil mentioned recent workshops and training courses and the anticipated 2020 FDA Course “Achieving Data Quality and Integrity in Clinical Trials Involving High Consequence Pathogens” at the Davis Global Center.

Jordi Rodon (Food & Agriculture Science and Technology Center IRTA; Center for Animal Health Research CReSA, Barcelona, Spain) presented a suitable a new model to study early events of Middle East respiratory syndrome coronavirus (MERS-CoV) infections (van Boheemen et al., 2012; Cotton et al., 2014) MERS, a previously unreported zoonotic disease emerged in 2012. As of May 2019, World Health Organization has been informed of more than 2000 laboratory-confirmed human cases including almost 838 fatalities (Ramadan and Shaib, 2019). It is endemic in the Middle East and human cases have been reported in 27 countries. Symptoms range from asymptomatic to very severe pneumonia with acute respiratory distress syndrome (ARDS), septic shock and multiorgan failure. No vaccines are commercially available nor have specific treatments been developed.

Dromedaries are the natural reservoir, but alpacas have also been reported as potential hosts for MERS-CoV (Chan et al., 2014). Since handling dromedary camels is not an easy option, especially under biocointantment conditions, and based on preliminary data showing that alpacas is a valuable model to study early MERS-CoV infection events, the Catalan scientists set out to develop an *ex vivo* model derived from the latter animals. Dr. Rodon described the isolation of respiratory tissues to assess the early local immune events elicited upon infection. Isolated nasal mucosa and tracheal explants were maintained *in vitro* and infected with MERS-CoV/Qatar 2015. Samples obtained at different times from 0 to 96 h post-inoculation were used to quantify viral RNA by RT-qPCR, detect virus antigen localization by immunohistochemistry (IHC) and to isolate virus. This work indicated that nasal mucosa and tracheal explants from alpaca are suitable *ex vivo* models to study MERS-CoV replication and molecular mechanisms leading to viral infection and/or virus clearance. The researchers hope to further develop the system to explore antiviral therapeutic approaches (Stalin Raj et al., 2018).

Wendy K. Jo (RIZ, TiHo, Hannover, Germany) described a new flavivirus (genus *Pestivirus)* detected in a toothed whales from the North Sea harbor porpoise *Phocoena phocoena* (Tautz et al., 2015). High-throughput data obtained by using next generation sequencing (NGS) and analyzed using an *in-house* metagenomics pipeline, followed by *de novo* assembly and phylogenetic analyses, allowed the identification of a novel pestivirus in two out of three investigated harbor porpoises. The complete genome of 11,880 bp, were reconstructed by *de novo* assembly of sequence reads, and confirmed by Sanger sequencing of the full-length genome. Alignment of the complete genomes of pestivirus species showed that the newly identified virus is evolutionary closest to porcine LINDA virus and porcine Bungowannah virus with 60% homology at the amino acid level. *In situ* hybridization showed strong granular staining in the cytoplasm of multiple cell types. Based on the new sequence information RT-PCR screening of samples from more than 100 stranded harbor porpoises, collected from the North Sea indicated that about 9% of these animals were positive for the novel pestivirus. The identification of a novel pestivirus in harbor porpoises suggests that the host spectrum of pestiviruses extends to members of the order Cetacea (whales, dolphins, and porpoises), which are considered to have evolved from artiodactyls (even-toed ungulates) (Jo et al., 2019).

Elena García Sánchez (Center of Molecular Biology “Severo Ochoa”, Madrid, Spain) reported an outbreak of African swine fever (ASF) affecting wild boars and domestic pigs that started in the Caucasus in 2007 and spread across Russia and Eastern Europe. This more recent geographic expansion of ASF further increases the threat to the global swine industry (Karger et al., 2019). Dr. García Sánchez presented information on genes involved in immune evasion and those hypothetically involved in attenuation of virulence of the genotype I parental ASFV NH/P68. Based on the information obtained, the research team generated putative live attenuated vaccines (LAV) prototypes by constructing recombinant NH/P68 viruses lacking specific genes and containing markers for DIVA tests (Gallardo et al., 2018). A bottleneck for the production of live attenuated virus vaccines has been the lack of permanent cell lines able to sustain productive virus infection. In the studies presented, porcine alveolar macrophages (PAM) were used to propagate the viruses. The results showed that naturally attenuated ASFV NH/P68 strain induced full protection against both homologous (genotype I) Lisbon 60 (L60) and heterologous (genotype

II) Armenia07 virulent strains. The recombinant viruses carrying specific deletions were all fully protective against parental homologous (genotype I) Lisbon 60 (L60) strain but only slightly protective against the heterologous (genotype II) circulating Armenia07 strain. More studies are required to assess the basis for the lack of heterologous protection of the recombinant vaccine strain, which could be related to the cell line used to produce the vaccine (Sánchez et al., 2019).

Meagan Deming (Institute of Human Virology; Center for Vaccine Development and Global Health, Baltimore, United States) analyzed the response to hepatitis B vaccines in an aging population and its dependence on route of injection (Weinberger et al., 2008; Williams et al., 2012; de Lalla et al., 1988). Fifty-two healthy adults (65–82 years; mean age 72 years), seronegative for hepatitis B (HBV), were recruited and enrolled by the SENIEUR protocol to select a strictly healthy population (Ligthart et al., 1984). These seniors were randomized to receive an alum-adjuvanted recombinant HepB vaccine, either subcutaneous (SC) or intramuscular (IM) injection, with the inoculum site guided by Computerized Tomography (CT) imaging. The immunological response, expressed as anti-HBs antibody titers at day 210, demonstrated that volunteers who received their vaccinations IM were over three-times more likely to be responders to the HBV vaccine than volunteers receiving SC vaccinations (54% versus 16%, $P = 0.004$) (Ikeno D et al., 2010). The low seroconversion rate even in the IM group showed a progressive decline with increasing age of the cohort and was associated with significantly lower IgG2 and IgG1 isotypes suggesting a marked shift in Th1 responses. Moreover, the percentage of seniors that showed T-cell mediated responses was significantly reduced and also lower in intensity compared to young adults (Arnold et al., 2011). This study confirmed that SC inoculation sites markedly impair seroconversion rates probably related to the inoculation in the SC fat. These data show qualitative and quantitative deficits in B and T cell responses to alum adjuvanted protein antigens, even in strictly healthy elderly cohorts (Schillie et al., 2018).

Abigail Lowe (University of Nebraska Medical Center, United States) turned the attention to the institutional preparedness for ethical review in scenarios of outbreaks (WHO, 2014). Clinical research during epidemics is crucial to build an urgent response and, yet, requires thoughtful oversight by research ethics committees to ensure the protection of vulnerable subjects facing health uncertainties. To appropriately address the regulatory aspect should be cultivated in anticipation of epidemics and pandemics, rather than in response to them (Alirol et al., 2017). The University of Nebraska Medical Center (UNMC) institutional review board (IRB) response during the 2014–2015 Ebola epidemic provided an example of research ethics review under a rapid response model. This IRB provided rapid review of multiple protocols during the epidemic, typically with 24 h or less from submission to approval. Since then, UNMC has been developing a centralized IRB for two national networks, both focused on public health emergency research with a vision of establishing a rapid response resource for these networks (Busta et al., 2017).

A new model is being developed to adapt it for research networks in order to pave a way for clinical research including early drug development for novel pathogens that may emerge in future outbreaks. This review model will be tested for multi-site research within the US; however, there is also a need to explore models for international public health emergency research. This process is complex from regulatory, as well as, operational perspectives and will only succeed with close collaborations by broad stakeholders.

3.5. One health: fact or fiction

Jordi Figuerola (*Estación Biológica de Doñana* – CSIC, Spain), **Albert Osterhaus** (Research Center for Emerging Infections and Zoonoses (RIZ), University of Veterinary Medicine Hannover, Germany) and **Amelia Nieto** (*Centro Nacional de Biotecnología* – CSIC, Spain) presented their views on the One Health concept, taking into account the fields of wildlife, ecology, as well as, veterinary and medical infectious disease disciplines. Figuerola highlighted the fundamental contribution of wildlife and environment (including climate change) to emerging and re-emerging zoonotic diseases, including some examples on mosquito borne flaviviruses like West Nile virus (Rizzoli et al., 2015), as well as, non-infectious diseases. He emphasized the need to further research on how organisms interact and how they interact with their environment as a cornerstone to understand infectious disease dynamics. Osterhaus covered aspects of emerging diseases in wildlife, livestock and companion animals, and the role they play in emerging human infections. Subsequently he highlighted the need to prioritize syndrome surveillance and diagnostic platforms in humans and animals, as well as, the increasing role of novel molecular technologies in pathogen discovery (Kruppa et al., 2018). In addition, he stressed that these priorities must be coupled with platforms offering mathematical modelling capacity, animal models and pathogenesis studies for new infections. Moreover, all these aspects should be accompanied by investment in therapeutics discovery and preventive intervention strategies. He finally emphasized a key point of the One Health concept, which is communication among experts, politicians, stakeholders and society (Reperant et al., 2015). Nieto focused specifically on one of the most devastating zoonoses in human history: influenza. She presented recent results showing that the heart should be considered a new target of influenza A viruses in addition to lung, especially by strains of high pathogenicity. In addition, she discussed the need for novel developments of most effective, ideally universal, influenza vaccines, as well as, more effective antivirals with low escape potential.

After their presentations, the roundtable was open to all delegates and several interventions took place. Some focused on the issue of communication. Most contributors agreed that scientists in general are not the best advocates to communicate hazards associated with emerging and re-emerging diseases to animals and humans alike. Moreover, we are still in a reactive framework (acting once the disease is present) and should rather move towards a preventive and preparedness strategy, that ideally prevents interspecies transmission of pathogens to occur, and if not successful provide the tools for early detection and intervention strategies. Consequently, confronting emerging epidemics at the source and from the onset is paramount to control global infectious disease prevention and mitigation scenarios.

Availability of adequate resources in ‘peacetime’ was another hot topic, since investment in a preventive and preparedness scenario should be done in preparation for emerging infections, and not ‘when the house is on fire’. Unfortunately, both at national and the international levels, current reality shows a generally reactive rather than proactive willingness to invest in preventive and preparedness scenarios. The title of the roundtable (“One Health: fact or fiction?”) was intentionally provocative. The impact of deadly infectious diseases is far different when comparing developed and developing countries, which further emphasizes the lack of a global, coordinated and effective agenda on One Health. Interestingly, the concept One Health has been highlighted regularly in the scientific literature (more than 1800 peer-reviewed articles), but only few manuscripts propose methodologies to measure the true impact of the implementation of this concept. Moreover, only few suggested quantitative indicators to follow, but no common methodology proved to be available (Baum et al., 2017). Therefore, and concluding the round-table discussion, much effort is needed by scientists, administration, politicians, stakeholders and citizens to truly implement the One Health concept at a global level.

3.6. Antivirals

Johan Neyts, Rega Institute for Medical Research, University of Leuven, Belgium, started the session by giving an overview of the antiviral agents now available for the treatment of infections with HIV, HBV, HCV, influenza and RSV infections. Dr. Neyts pointed out that for many other viruses that cause life-threatening infections and many of

which are considered emerging and/or neglected pathogens, there are no drugs available. He then described the robotized lab-in-a-box automated platformed in a BSL3+ environment for high-throughput screening now installed at the Rega institute.

Dr. Neyts presented the current state of Rega Institute's development of potent antivirals against flaviviruses (such as dengue), alphaviruses (such as chikungunya) and enteroviruses as well as against noroviruses, the hepatitis E and the rabies virus. Several excellent molecular targets for the selective inhibition of viral replication (and that have remained largely unexplored) have been identified, such as the non-structural protein NS4B of flaviviruses, the capping machinery of alphaviruses and the 2C helicase of enteroviruses. The Rega Institute now has molecules that target the NSB4 of the dengue virus with pan-serotype antiviral activity in the low nM to pM range. Dr. Neyts also reported that the anti-flu compound Favipiravir (T705), also active against flavi-, arena-, bunya-, and filoviruses, protects mice from infection with chikungunya virus (CHIKV). A new class of CHIKV inhibitors, targeting viral capping active in the low microM range have now also been described (Delang et al., 2016; Gigante et al., 2014).

As for entero/rhinoviruses, besides the target for capsid binders like pocapavir (Thibout et al., 2012), the researchers at the Rega Institute have found a novel druggable pocket formed by the viral proteins VP1 and VP2 in the virus capsid and have now identified analogs targeting this pocket with broad spectrum activity (Abdelnabi et al., 2019). Also described was a novel class of tryptophan dendrimers targeting the capsid five-fold vertex were found to inhibit EV-A71 replication at low nanomolar to high picomolar concentrations *in vitro* (Sun et al., 2019). A lead compound in the series (MADAL385) prevented binding and internalization of the virus but did not, unlike classical capsid binders, stabilize the particle. Dr. Neyts stated that also potent inhibitors of the enterovirus virus helicase are under way. Other viruses for which antiviral substances are tested for at the Rega Institute include diarrhea causing viruses like human norovirus (for which zebra fish larvae has been found to be a replication model) and rota virus, rabies virus, and hepatitis E virus.

Raymond Schinazi of Emory University School of Medicine presented his recent efforts to develop HBV capsid effectors that may offer an option to aid in a combination therapy aimed at curing chronic hepatitis B virus (HBV) infections. This virus affects over 250 million people globally and causes 686,000 deaths worldwide per year. HBV persists due to the formation of covalently-closed circular DNA (cccDNA) – the viral minichromosome – in the nucleus of hepatocytes, and current nucleoside analogs and interferon therapies have a low rate of cccDNA clearance and require lifelong treatment (Schinazi et al., 2018; Schinazi and Asselah, 2017; Boucle et al., 2016). Dr. Schinazi's group has identified the compound GLP-26, a novel and potentially best-in-class glyoxamide derivative, affecting HBV nucleocapsid formation and replenishment of the cccDNA pool. The drug has an EC_{50} in the low nM range with a therapeutic index of > 10,000. In a humanized mouse model stably engrafted with human hepatocytes and infected with HBV, GLP-26 displayed a major effect on HBeAg secretion and HBsAg in addition to a promising pre-clinical profile. More interestingly, long term combination treatment with Entecavir (ETV) in this model induced a four ^{10}log decrease in viral loads and viral antigens reductions that were sustained for up to 12 weeks after ceasing treatment. Dr. Schinazi also briefly describe the activity of novel norovirus protease inhibitors which were also interestingly effective against certain enteroviruses at nM levels. Enterovirus protease has some similarity with norovirus and coxsackievirus protease.

María Jesús Pérez Pérez, Instituto de Química Médica (IQM) Consejo Superior de Investigaciones Científicas (CSIC), Spain argued that antiviral drug development has particular characteristics when compared to other therapeutic fields in drug discovery. As an example, it is indicated that phenotypic screening is still one of the main strategies do identify novel classes of antiviral agents while for other therapeutic areas target-based or fragment-based screening has often become more relevant (Murcko, J., 2018; Brown and Bostrom, 2014). Once a hit with antiviral properties has been identified, its optimization to become a lead is a multiparameter process, that can also be determined by the mechanism of action of the compound. Dr. Pérez Pérez' group's own experience in triazolopyrimidines as inhibitors of CHIKV replication was presented to illustrate how proactive and collaborative efforts among academic groups can lead to the identification and optimization of antivirals exploring a new mechanism of action (Gigante et al., 2014; Delang et al., 2016; Gigante et al., 2017; Gomez SanJuan et al., 2018).

Esteban Domingo, Centro de Bilogía Molecular Severo ochoa (CSIC-UAM), Spain, discussed the development of antiviral resistance. The evolution of viruses involves two major steps: (i) intra-host (short-term) and (ii) inter-host (long-term) evolution. Step (i) is influenced mainly by random genome variations and quasispecies dynamics, and its description is based on mutant spectrum analyses. Step (ii) is guided by the multifactorial epidemiological fitness and transmission-associated random drift of genomes, and its description is based on phylodynamic approaches (Geoghegan and Holmes, 2018; Domingo and Perales, 2019). How events in step (i) influence events in step (ii) is an open question. Selection of mutants resistant to antiviral agents, one of the major problems in antiviral therapy, occurs at step (i) and its consequences are felt in steps (i) and (ii).

Several mechanisms of selection of mutants resistant to antiviral agents have been identified including amino acid substitutions termed RAS (resistance-associated substitutions) at the viral protein targeted by the antiviral agent, and antiviral resistance mediated by high viral fitness, documented with hepatitis C virus (HCV). Both mechanisms affect standard inhibitors and mutagenic agents active in lethal mutagenesis (Perales et al., 2019). Intra-host selection of resistant mutants affects treatment efficacy and the choice of rescue treatments. Resistant mutants can acquire epidemiological relevance, therefore affecting step (ii) of virus evolution. Epidemiological dominance of resistant mutants may render ineffective the relevant antiviral agents, a problem with similarities to antibiotic resistance in bacteria. Possible approaches to minimize selection of escape mutants inspired in quasispecies dynamics will be suggested.

3.7. Respiratory viruses

Leo Poon, (The University of Hong Kong), reviewed the emerging influenza viruses like H5NX and H7N9 circulating in southeastern China. These viruses continue to reassort with different avian influenza viruses and spread to other geographical locations via wild birds. Dr. Poon reported on a study of 96 low pathogenic avian influenza virus genomes detected from wild bird samples collected from 2010 to 2017. Their phylogeographic analysis indicated several independent trans-regional reassortment events during the period. All of these reassorted viruses acquired at least one segment from avian influenza viruses found in North/South America.

Yungmee Jee (National Institute of Health, South Korea) reported on the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks in 2015 and 2018 in South Korea. She emphasized the lessons learned from their experience, which were as follows: A single, missed case may trigger a huge, nationwide outbreak. The first line of defense is not the thermal scanner at the airport, but doctors in the community clinics/hospitals. Superspreading events may occur in healthcare settings, especially at the emergency department. Early detection and isolation are critically important. Aggressive strategy for quarantine maybe necessary, especially when a large number of individuals are exposed in the health-care settings.

Enric Mateu (Department de Sanitat I Anatoia Animals, Universitat Autonoma de Barcelona, Spain), described the virulence of and immunity against Porcine reproductive and respiratory syndrome virus (PRRSV) as two sides of the same problem. He emphasized that the genetic basis for the differences in virulence is multigenic and is related

to (i) the damage caused by the virus, (ii) the damage caused by the immune response of the pig and, (iii) the interaction of the virus with the functionality of the immune system. Neutralizing antibodies, cell-mediated immunity, ability or disability to induce type I interferon from macrophage and plasmacytoid dendritic cells, make the complexity of the disease outcome.

3.8. Influenza surveillance in Cameroon, monitoring hepatitis B virus in rural districts of India, virus evolution, three-dimensional cell culture infection models and new targets for antiviral intervention

Dr. Richard Njouom (Centre Pasteur of Cameroon, Yaounde, Cameroon) showed data of influenza surveillance in Cameroon for the last 10 years. Although influenza virus strains circulate in the country all year round, larger prevalences were observed in the rainy season, with a major peak between September and December. Both types of influenza (A and B) were detected every year, although the A (H3N2) strain was the most prevalent when all data were considered. Unfortunately, the surveillance system revealed that in many seasons, the influenza vaccine compositions available were not a good match for the types and subtypes that circulated in Cameroon.

Dr. Shyam Kottilil (Institute of Human Virology, University of Maryland, Baltimore, USA) presented their impressive efforts in monitoring hepatitis B virus (HBV) in Western districts of Arunachal Pradesh (India). As part of this GVN-lead program, researchers interviewed > 11,800 patients and collected > 11,500 samples for HBV testing. They found high HBV seroprevalences in most of the studied communities (4.8–12.9%), particularly in the Nyishi and Miji tribes. An interesting observation was the abundance of C/D recombinant genotypes, which had been previously found only in the neighboring Tibet, probably a consequence of migration across the Chinese border.

Two studies on virus evolution were presented by Drs. **Dieter Hoffmann** (Technische Universität München, Munich, Germany) and **Richard Scheuermann** (J Craig Venter Institute, La Jolla, USA). **Dr. Hoffmann** and colleagues studied norovirus evolution in chronically infected patients using next-generation sequencing. They had previously shown that norovirus capsid gene sequences evolved quickly and accumulated non-synonymous mutations reflecting positive selection (Hoffmann et al., 2012). Sequentially appearing mutations correlated with structural changes that may lead to a decreased antibody binding. Interestingly, Dr. Hoffman's group has now reported that in infected individuals, progression of the infection associates with increased concentrations of capsid-specific antibodies.

The presentation by **Dr. Scheuermann** concentrated on enterovirus evolution. An enterovirus (EV) D68 outbreak in the summer of 2014 coincided with a spike in the number of cases of polio-like acute flaccid myelitis/paralysis (AFM). Subsequent outbreaks in 2016 and 2018 raised concerns about the possibility of EV D68 being a new public health threat. Comparative genomics analysis showed the emergence of new EV D68 lineages in recent years. Cell culture and animal studies revealed that these emerging viruses have acquired the ability to infect and kill neuronal cells (Brown et al., 2018) and cause paralysis in mice. Virion binding and cell entry limit the neuronal infectivity of older isolates.

Basic research was represented by the work of **Dr. Heinz Ellerbrok** (Robert Koch Institut, Berlin, Germany) who developed new three-dimensional cell culture infection models based on a biological extracellular matrix (decellularized equine pericardium) with primary human keratinocytes (Koban et al., 2018). Using these models for studying antiviral susceptibility in cowpox virus infection, Ellerbrok and colleagues showed that the inhibitory potency of host-directed epidermal growth factor receptor-blocking molecules such as gefitinib and cetuximab was considerably higher in three-dimensional cell culture models than in conventional two-dimensional models, suggesting that the classical monolayer cell cultures could underestimate the potential inhibitory effect of an undetermined number of antiviral drugs.

Dr. Luis Menéndez-Arias (Centro de Biología Molecular Severo Ochoa, Madrid, Spain) presented new data on how HIV-1 reverse transcriptase (RT) connection subdomain mutations and non-nucleoside RT inhibitors modulate polypurine tract (PPT) removal during initiation of plus-strand DNA synthesis (Betancor et al., 2015). Using different HIV-1 and HIV-2 RT variants, this study showed that major determinants defining the correct cleavage site at the PPT/U3 junction of the HIV genome reside at the connection subdomain between positions 342–351. These observations together with the fact that nevirapine, doravirine and efavirenz alter the efficiency of the PPT/U3 cleavage and impair the initiation of (+)-strand DNA synthesis, suggest that this step of reverse transcription could become a specific target for antiretroviral intervention.

4. The network in 2019

In 2019, GVN welcomed the following Centers and Affiliates: University of Wisconsin-Madison Global Health Institute, U.S. Food and Drug Administration's Office of Vaccine Research and Review, the Smorodintsev Research Institute of Influenza of the Ministry of Health of the Russian Federation, Manipal Institute of Virology, The Tropical Medicine Institute "Alexander von Humboldt" of the Universidad Peruana Cayetano Heredia, Research Institute of Virology Ministry of Health of the Republic of Uzbekistan, Korea National Institute of Health's Center for Infectious Diseases Research, Wyss Institute for Biologically Inspired Engineering at Harvard University, the Antiviral Pharmacology Laboratory and Clinical Trials Research Center Virology Program at the University of Zimbabwe.

The 6th GVN Short Course took place in Baltimore, July 29-August 2, training to date, a total of 90 junior scientists from every continent.

The GVN is currently developing the "GVN Academy" initiative, which is an investment in a small group of outstanding mid-career virologists. For our pilot program, the idea is to match a selected number of outstanding early and mid-career from low- and-middle-income countries virology researchers with our senior leaders in the field to provide a series of mentoring and networking opportunities.

The GVN is also working on the development of Regional GVN Chapters to shift towards a flexible, global organization. Although the GVN is headquartered in Baltimore, it is believed that GVN presence needs to be truly global and therefore each GVN center needs to meet specific geographic challenges found particularly in Southeast Asia, South America, and Africa. This year, GVN has established the Africa GVN Regional Unit, in a meeting co-Organized by Dr. Pontiano Kaleebu, Director, UVRI and Dr. Glenda Gray, President, MRC South Africa. The meeting took place in Entebbe, Uganda and helped delineate collaboration as well as plan for future joint training initiatives.

During 2019 GVN has continued to provide public education and expert perspectives on current topics, such as the Ebola outbreak in the DRC.

Under the Anticipation and Preparedness Task Force umbrella, several Virus Watch Groups have been established, meeting regularly to discuss recent advances and findings in the field, monitoring viruses and virus research to ensure its efficacy and reinforce the GVN capacity.

5. Plans for 2020

We are in the process of organizing the GVN's 12th International meeting in Medellin, Colombia. This will be a unique opportunity to increase collaborations between the South American Regional GVN and GVN centers from other parts of the globe.

Plans are underway for the South East Asia Regional GVN kickoff meeting. This is an effort lead by Drs. Sharon Lewin and Linfa Wang.

GVN will continue fostering collaborations among its members, for example through joint grant applications and implementing various activities from the Anticipation and Preparedness Task Force and well as the Virus Watch Groups.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.antiviral.2019.104645.

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