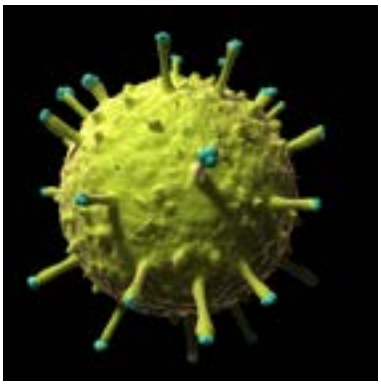
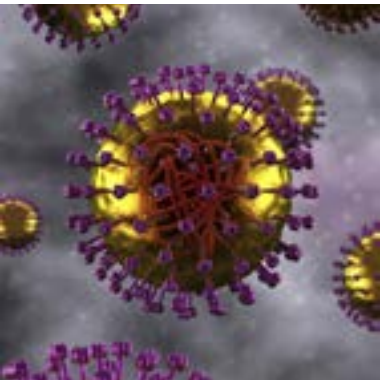
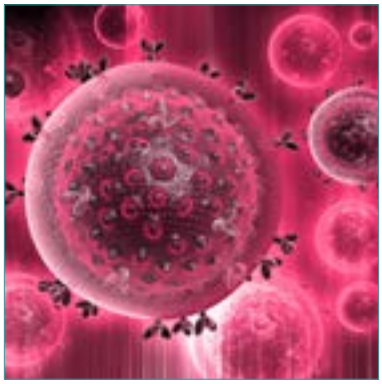
Keynote Forum
October 30, 2017

Virology Conference 2017







International Virology Conference

October 30-31, 2017 | Toronto, Canada

Veronique Barban

Sanofi Pasteur, France

A new dengue non-human primate protection model with improved translation to vaccine clinical efficacy

Recent data obtained with live-attenuated tetravalent dengue CYD-TDV vaccine showed moderate clinical efficacy to DENV-2 as compared to DENV-4, while high protection rates to both viruses were expected from previous non-human primate experiments. Viral loads observed in naturally-infected humans are generally much higher than those achievable in macaques by subcutaneous or intramuscular inoculation, which may contribute to levelling vaccine efficacy. More stringent conditions of infection resulting in about 100-fold increase of the viral load were established in cynomolgus macaques and subsequently applied to assess efficacy of CYD-TDV vaccine lots. Complete protection (i.e. undetectable viral RNA) against DENV-4 infection was achieved in 6/6 monkeys, while complete protection to DENV-2, or nearly (aborted RNAemia), was observed in only 6/18 animals. All other macaques (12/18) developed DENV-2 RNAemia curves, although below those of control animals. Viremia parameters were found inversely correlated to pre-challenge neutralizing antibody titers, emphasizing the key role of these antibodies in controlling DENV infection. Moreover, early detection of antibodies to CYD-TDV antigens in all animals and post-challenge induction of strong anamnestic responses suggested efficient vaccine priming, which likely contributed to restrict DENV-2 RNAemia. Collectively, these data are in better agreement with CYD-TDV clinical vaccine efficacy data reported against DENV-2 and DENV-4, and demonstrate the improved translatability of this new dengue NHP protection model.

Speaker Biography

Veronique Barban is a trained Molecular and Cellular Virologist, with 30 years of experience in Vaccine Research in Pharmaceutical Industry. She started her career as Research Scientist at Institut Merieux that later became Pasteur Merieux Connaught (PMC), then Sanofi Pasteur. She was Head for 20 years of a Virology group that worked on various human viral diseases and contributed 15 years to the development of the 1st dengue vaccine, licensed in 2015 (commercial name Dengvaxia™). Her current position at Sanofi Pasteur is Expert in Virology in the Global Scientific Office.

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Notes:

Lori Frappier

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Epstein-Barr virus manipulation of host responses

Epstein-Barr virus (EBV) is a common herpesvirus that is a causative factor in several types of lymphoma as well as gastric and nasopharyngeal carcinomas. In EBV latent infection, cells are immortalized as a result of expression of a small subset of proteins that always includes EBNA1. In addition to maintaining the EBV genomes, EBNA1 alters cells to promote survival and proliferation in part by inducing the degradation of promyelocytic leukemia (PML) tumour suppressor proteins. PML proteins and the nuclear bodies that they form have antiviral properties and are important for several cellular processes including apoptosis. We have shown that PML degradation by EBNA1 involves direct interactions of EBNA1 with CK2 kinase and the PML IV isoform, triggering PML phosphorylation and degradation, which promotes the survival of gastric and nasopharyngeal carcinoma cells. EBV can also switch to a lytic infectious cycle which involves the expression of ~80 proteins, and accumulating data suggests that lytic protein expression contributes to EBV-induced cancers. However, the functions of many of the lytic EBV proteins are poorly characterized or completely unknown. To gain insight into EBV lytic proteins that manipulate cellular pathways, we have screened a library of EBV proteins for those that affect a variety of cellular processes including the DNA damage response (DDR). Herpesviruses typically inhibit some aspects of the DDR to limit downstream consequences, including apoptosis. Our screen identified an uncharacterized EBV tegument protein as an inhibitor of the DDR. Further studies determined that the block in the DDR was at the step of histone ubiquitylation and that the EBV protein bound directly to histones. Furthermore, analysis of transcriptome data from EBV-positive gastric carcinomas showed that this EBV protein is expressed in these tumours. Together our results suggest mechanisms by which both EBV latent and lytic proteins contribute to oncogenesis.

Speaker Biography

Lori Frappier is a Professor of Molecular Genetics at the University of Toronto and a Tier 1 Canada Research Chair in Molecular Virology. Her lab is known for their work on understanding the structure, function and mechanisms of action of Epstein-Barr virus proteins, including EBNA1, as well as of cellular targets of EBNA1, including USP7. Their use of unbiased proteomics approaches has led to several discoveries of viral-host interactions, novel functions for viral and cellular proteins and new mechanisms of regulation of cellular pathways.

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