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Host-Specific Antiviral Responses to the Tick-Borne Flaviviruses: Powassan and TBEV

Currently Dr. Taylor's research focuses on the arthropod-transmitted members of the *Flaviviridae* family. Flaviviruses are globally significant human pathogens including dengue virus (DENV), West Nile virus (WNV) and the TBEV serocomplex of viruses. Select members of the TBEV serocomplex includes the highly pathogenic TBEV-Sofjin and Powassan virus (POWV) and require biosafety level (BSL)-4 and 3 facilities respectively. The group also includes the naturally attenuated Langat virus (LGTV), which greatly simplifies studies with TBEV under BSL-2 conditions. Viruses in the TBEV serocomplex span the clinical spectrum for flaviviruses. Symptoms range dramatically from asymptomatic infection to more severe encephalitis and hemorrhagic fevers with mortality rates exceeding 30%. Treatment of infection with these viruses is hindered by the lack of effective antiviral therapies and few available vaccines. The overwhelming morbidity, in addition to the risk of emerging viruses, highlights the need for better treatment options. Fresh insight for new antiviral treatments may come from studies of the classical IFN response. IFN treatment induces the expression of hundreds of genes (interferon stimulated genes or ISGs), many of which are antiviral molecules. Though flaviviruses are highly sensitive to the antiviral effects of IFN, viral antagonism of IFN

signal transduction prevents the expression of ISGs in infected cells. Thus, virus suppression of IFN signaling renders IFN ineffective as a medicinal therapy for flavivirus infections. Identifying ISGs with virus-specific antiviral activity may reveal new methods for treating flavivirus infections.

A major accomplishment of Dr. Taylor's work has been the identification of a previously unnamed mouse-specific tripartite motif (TRIM) protein (now designated TRIM79) that targets the nonstructural 5 protein (NS5) from TBEV to inhibit virus replication. NS5 is the major IFN antagonist for flaviviruses and is an essential component of the virus replication complex and as such is a prime candidate for antiviral drug design. Focus in the lab will characterize the TRIM79-NS5 interaction, and ultimately determine the importance of the antiviral molecule to host protection in a mouse model of TBEV infection. Additionally Dr. Taylor's lab is using various screening approaches including shRNA libraries and mass spectrometry to identify new virus-host interactions that can be targeted as part of a virus-specific immune therapy. Finally, viral proteins have evolved the capacity to perform many important functions during the virus life cycle. NS5, for instance is necessary for virus replication and immune evasion. Understanding how the virus protein can maintain different functions and protein interactions in distinct cellular regions may again lead to new therapeutic targets. Previous studies by Dr. Taylor have determined that NS5 is modified by the cellular ubiquitination machinery. Understanding the importance of this post-translational modification may provide insight into NS5 regulation and/or cellular mechanisms to interfere with NS5 function.

Dr. Taylor received his Ph.D. degree at the University of Texas Southwestern Medical Center at Dallas under the mentorship of Dr. Wade Bresnahan. He then completed his

postdoctoral training at the NIH Rocky Mountain Laboratories where he studied the biosafety level (BSL)-4 tick-borne flaviviruses in the laboratories of Drs. Marshall Bloom and Sonja Best. Dr. Taylor joined the Department of Medical Microbiology and Immunology in August of 2012.

Conference Lecture Summary

Tick-borne flaviviruses (TBFVs), including Powassan virus and tick-borne encephalitis virus cause encephalitis or hemorrhagic fevers in humans with case-fatality rates ranging from 1-30%. Despite severe disease in humans, TBFV infection of natural rodent hosts has little noticeable effect. Currently, the basis for resistance to disease is not known. We hypothesize that the coevolution of flaviviruses with their respective hosts has shaped the evolution of potent antiviral factors that suppress virus replication and protect the host from lethal infection. In the current study, we developed an *in vitro* model to study TBFV infection in a representative natural host, the white-footed mouse *Peromyscus leucopus*. By using this model, we determined that flaviviruses indeed can infect cells from a natural host, yet replication is severely impaired. Replication of vesicular stomatitis virus was equivalent in *P. leucopus* and *M. musculus* cells suggesting that restriction was flavivirus-specific. Furthermore, by knocking down *P. leucopus* genes involved in antiviral interferon (IFN) responses, restriction was relieved and TBFV replication was restored to levels observed in more susceptible cells. Collectively, this work demonstrates that the IFN response of P. leucopus imparts a strong and virus-specific barrier to flavivirus replication and indicates that resistance in the natural reservoir to TBFV is an active process of virus suppression and not a passive lack of proviral factors. Future identification of the IFN stimulated genes responsible for virus restriction specifically in *P. leucopus* will yield mechanistic insight into efficient control

of virus replication and may inform the development of antiviral therapeutics.