It is with a significant measure of regret that I write the introduction to the MMI newsletter one last time. Budget constraints this year dictated that we reduce the Department’s operating budget by 4%, and we have been told that we will have to find another 2% to cut for next year. We have decided to eliminate this newsletter. You may say, an electronic newsletter cannot cost very much, after all, the electrons are virtually free. Well, that’s true, but some one on our staff has to contact writers, assemble and edit the newsletter and maintain the email address list. Approximately 90% of the Department’s operating budget goes toward salary and fringes of faculty and staff with the remaining costs covering fixed costs. In order to achieve the 4% cut, we have eliminated all non-tenure track instructor positions and reduced appointments of administrative staff.

On behalf of my MMI colleagues I want to take this opportunity to thank Alicia Hamilton for her service as the MMI Newsletter editor. She has done a great job helping us communicate to our alumni, staff and friends.

~ Rodney Welch, Professor and Department Chair
Seeing is Believing for Influenza Virus Infections

Infections are dynamic events, yet much of our knowledge comes from static snapshots. This is especially true when studying influenza virus replication in animal models. Cohorts of animals are infected and euthanized, and viral load or immune responses are measured only at specific times in predetermined tissues. Given the inherent variability between animals, these approaches also routinely require large numbers of animals. We have not been able to serially measure viral replication dynamics in real time. Prior approaches thus created a major bottleneck in the study of influenza virus pathology and the development of anti-influenza treatments that require testing in animals.

Vy Tran and members of the Mehle lab have overcome these roadblocks by creating influenza reporter viruses that allow real-time in vivo detection of viral load and spread in the same animal over time. Creation of influenza reporter viruses is complicated by the complex architecture of the viral genome: (i) all of the viral genes are critical in vivo, precluding simple replacement with the reporter; (ii) the compact genome does not tolerate large insertions; (iii) most insertions attenuate the virus and limit its utility; and (iv) insertion of reporter genes can disrupt sequences necessary for packaging the genome into new virions. The Mehle lab created replicating reporter viruses by identifying key sites within the viral genome that would tolerate insertions. They inserted fluorescent proteins to visualize infections in culture (Fig. 1A). They also used a newly developed bioluminescent enzyme from Madison’s own Promega to create viruses suitable for non-invasive in vivo imaging (Fig. 1B). Cells, or even whole animals, infected by bioluminescent reporter viruses will emit light when given the appropriate substrate.

All of the reporter viruses have proven to be incredibly powerful tools to visualize infections in real time, probe steps throughout the viral life cycle, longitudinally monitor sites of replication and dissemination within animals, and to determine the impacts of therapeutic interventions. In collaboration with the Small Animal Imaging Facility on campus, they used these tools to simultaneously measure viral replication via bioluminescence and immune-mediated inflammation via PET/CT scanning (Fig. 1C). This multi-modal imaging showed that antiviral drugs not only suppress viral replication, but very rapidly reduce inflammation and associated lung damage.

The Mehle lab is currently expanding the utility of their reporter virus technology to monitor diverse strains of influenza virus and dissect viral genetics during animal infections. It is hoped that these new technologies and applications will dramatically accelerate in vitro and in vivo influenza virus studies as they are...
used to rapidly assess the properties of emerging viruses, test the sensitivity of virus to current therapies, and screen the efficacy of candidate vaccines or novel antivirals.

Figure 1: Real time imaging of influenza virus replication. (A) Cells infected with an influenza reporter virus expressing green fluorescent protein. (B) In vivo imaging of a mouse infected with a bioluminescent reporter virus. Non-invasive bioluminescent imaging shows replication in the trachea and both the right and left lobes of the lung. In subsequent serial measurement, imaging showed clearance of the virus and this animal survived the infection. (C) Bioluminescent imaging to measure replication was paired with PET/CT scanning to measure immune-mediated inflammation. The animal on the right was treated with Tamiflu (Oseltamivir), one of the few currently approved anti-influenza virus medications. Treatment with antiviral therapy completely suppressed viral replication in this animal and dramatically reduced inflammation.

~ Andrew Mehle, Assistant Professor

Lab Notes: Caitlin Pepperell

I started my lab in late 2011, after finishing up a post-doc at Stanford. We had a pretty unusual setup in the beginning: a biosafety level 3 lab for working with live cultures of *Mycobacterium tuberculosis*, and a computational ‘dry’ lab. There are hazards associated with computational work – most notably, carpal tunnel syndrome. *M. tuberculosis* is another story.

Since that time, we’ve expanded to include a biosafety level 2 lab. This addition allows us to work with some other bacteria, namely non-tuberculous mycobacteria, *Gardnerella vaginalis* and *Staphylococcus saprophyticus*. Those of you who are familiar with microbiology – I’m assuming there are a few among the readership of this newsletter – are probably thinking that this is a strange collection of organisms.

I ended up working on *S. saprophyticus* and *G. vaginalis* because some unique opportunities happened to come my way – this assemblage was not planned. However, it turns out there are interesting and instructive contrasts in the ecology and evolution of these organisms. For example, *M. tuberculosis* is essentially strictly clonal, whereas *G. vaginalis* recombines freely. *S. saprophyticus* is somewhere in between. Lateral gene transfer (LGT) is central to bacterial adaptation, and one of the theme areas we are pursuing. Beyond LGT, we are interested in other basic processes affecting bacterial pathogen adaptation, such as mutation rates, patterns of migration, demography, and natural selection. We mostly focus on analysis of genomic data from natural populations, complemented by experimental data from our own lab and that of collaborators. So far we seem to be keeping the carpal tunnel syndrome at bay.
30 Years of Virology in the Blink of an Eye: The Reminiscences of Robert Visalli

It’s hard for me to believe that next year is my 30th anniversary of starting graduate school in the Department of Medical Microbiology and Immunology at UW-Madison. I remember the final decision was between Penn and UW. I was originally from Pittsburgh, PA so Philly was not my favorite city. Madison seemed like a cool (in more ways than one) and comfortable college town. I remember receiving the acceptance letter from Dr. Byrne. I liked the red letterhead and felt at home in Madison during my visit. So in the summer of 1986 I made my way to Wisconsin. My graduate school experience was typical – mostly great times and a few not so great times. I could write a book on the topic but since my space is limited, I’ll hit some highlights.

I was Dr. Brandt’s first graduate student. He was a virologist, and I wanted to work on viruses. I was 22 and he was probably around 32 – we were both very young and driven. I wanted to get papers, and he wanted to get tenure. He loved heavy metal, and I enjoy alternative rock. I was so glad to be in a lab where I could crank tunes. I think it’s safe to say we worked day and night. It was probably not good for our health and we got on each other’s nerves, particularly the last few years. In the end, it was all worth it because I feel I was one of the last students from an era where we did everything from scratch – no kits! We ended up with 7 papers (again no kits!), I received multiple post-doc offers and he was awarded tenure. Mission accomplished.

My graduate cohort was made up of truly exceptional people who went on to be incredibly successful. My first roommate and brother in arms during the first year was Tom Wynn. We had some hilarious times particularly being thrown into teaching and having no idea what we were doing. Tim Uphoff was one smooth, mellow guy. I still hear from him every now and then. Margherita Cantorna, a fellow Italian, had her first child almost exactly the same time as my wife (Melissa). Speaking of my wife, she was a student in the undergraduate Immunology Laboratory course for which Tom and I were teaching assistants under Dr. (Judy) Manning. I said to Tom “see her, she’s the one” (Tom would confirm this). I managed to get Dr. Brandt to hire Melissa in the lab and then worked to prove that I wasn’t a science geek. It wasn’t easy, but tickets to see Sting and our shared interests in sports sealed the deal. She’s gone on to publish more papers than me over the past 30 years (oh, and without a PhD).

Virology has treated me pretty well. I don’t know what all of the complaining was about when I was younger. If you work hard, things tend to work. After my post-doc in Hershey, PA (I liked the smell of chocolate), I went on to work at Wyeth (now Pfizer) for 6 years, just outside of New York City. I did some of my best research during that stretch, patenting a potential HSV vaccine and discovering a novel class of small molecules that inhibited viral portal protein function. After 9/11 occurred just outside my front door, I decided to leave the
area for a fresh start. I returned to academics and was an assistant and then associate professor in the Indiana Purdue University system. I continued to study viral portal proteins and DNA encapsidation as novel antiviral targets. It was a good niche and I managed to secure back-to-back NIH R15 grants each on my first try. Talk about the right topic at the right time. After my daughter finished high school and went off to college on a DI golf scholarship, Melissa and I made our way south to Mercer University School of Medicine in Savannah, GA. We don’t care to see a single snow flake the rest of our lives. In recent years I’ve taught medical students and performed research at Mercer. Turning 50 has coincided with handling department chair duties, but I’m still doing virology, publishing, and writing grants.

Thirty years went by in a flash. Wasn’t I just sitting at the field house with Drs. Byrne, Brandt, Balish and Welch watching my Indiana University basketball team notch another win while they all gave me the stink eye? Luckily I got out of there before the tables completely turned! I have fond memories of Madison – the department, UW sports, the faculty, my graduate class peers, teaching, State Street, Dotty Dumplings and Dr. Brandt. Those of you that are currently there – enjoy every single second. I swear I just finished my first HSV growth curve yesterday

Dr. Visalli is an Associate Professor of Microbiology and Interim Chair of Biomedical Sciences, Mercer University School of Medicine-Savannah Campus. He received his BS in Microbiology from Indiana University-Bloomington (1986) and his PhD in Medical Microbiology and Immunology from the University of Wisconsin-Madison (1992). Dr. Visalli completed postdoctoral training at the Pennsylvania State University School of Medicine. He has held positions as assistant professor at the University of Evansville, adjunct assistant professor at Western Connecticut University and Mt. St. Mary’s college (NY), senior research scientist at Wyeth and Wyeth Vaccines, and assistant and associate professor at Indiana University Purdue University Fort Wayne. Dr. Visalli joined the faculty at Mercer University School of Medicine-Savannah Campus in May 2012. The Visalli laboratory uses Varicella-zoster virus as a model organism to understand the mechanism of viral genome (DNA) processing and packaging (i.e. encapsidation). He is interested in the function of protein that form the encapsidation machinery(i.e. the terminase and portal proteins), portal structure and association with the viral capsid, and the identification of antivirals that inhibit viral DNA cleavage and packaging. Dr. Visalli was the lead scientist involved in the identification of novel VZV encapsidation inhibitors and through studies with the VZV encapsidation and capsid proteins, seeks to define the mechanism of action of these inhibitors. Studies on novel antiviral compounds that specifically inhibit the encapsidation process may lead to new therapeutic strategies to treat herpesvirus infections. Equally important is Dr. Visalli’s dedication to productive student research opportunities, hands on mentoring and a genuine interest in exposing students to science early in their research careers.