Infectious Diseases

Powel H. Kazanjian, MD
Division Chief/Professor

Emeritus Faculty
F. Robert Fekety Jr, MD

Professor
N. Cary Engleberg, MD
Carol A. Kauffman, MD
David M. Markovitz, MD

Associate Professor
Suzanne F. Bradley, MD
Kathleen L. Collins, MD, PhD

Clinical Associate Professor
Carol E. Chenoweth, MD, MS

Assistant Professor
David M. Aronoff, MD
David J. Miller, MD, PhD

Clinical Assistant Professor
Sandro K. Cinti, MD
Daniel R. Kaul, MD
Preeti N. Malani, MD
James Riddell IV, MD

Clinical Lecturer
Mark H. Kaplan, MD
Anurag N. Malani, MD
Laraine L. Washer, MD
Viruses in Our Brains?

Every summer across America, the West Nile virus sneaks its way into thousands of people via a mosquito bite. Almost immediately, the virus inserts its genetic material into the bitten individual's cells, hijacks their inner workings, and begins to reproduce.

In most people, the immune system fights off the infection handily, perhaps causing a headache or mild fever. But in a few unlucky people, the virus travels to the brain and spinal cord, prompting a massive immune reaction called West Nile encephalitis and meningitis. The resulting effects on the nerve cells and tissues can kill or paralyze.

This kind of ‘overreaction’ by the immune system in the brain and spinal cord also occurs in many other diseases caused by arboviruses—the general name for viruses that are spread by mosquitoes and other insects.

In fact, the potentially deadly effects of brain-infecting arboviruses have even been harnessed for weapons in the past by the United States and other countries. And security experts fear that they could be used once again by terrorists.

Because of this dual threat of disease from naturally-occurring and weaponized arboviruses, and the lack of effective treatments, there’s an urgent need to understand exactly what happens when viruses enter brain and nerve cells.

That’s what drives the research of David J. Miller, MD, PhD (right), and his laboratory team. Together, they are making strides in uncovering what happens inside an infected cell, how those events interact with the immune system, and what drugs might work to counteract the virus.

Their work is a truly collaborative effort, drawing on several core research facilities of the University. The project is funded by the Great Lakes Regional Center of Excellence for Biodefense and Emerging Infectious Disease Research, of the National Institute of Allergy and Infectious Diseases.

The team works with the Western Equine Encephalitis virus, an arbovirus similar to West Nile virus, using human brain tumor cells that can be grown in the lab. Much of their work seeks to explain why arbovirus infection of central nervous system cells can be so damaging.

Brain and spine cells can’t regenerate like other types of cells, so they tend to have a very responsive mechanism for detecting and attacking invaders. This property is called innate immunity, and Miller and his team have made progress in tracking the specific steps in the battle between virus and cell.

Another key aspect of understanding the neurological effects of arboviruses is determining how they hijack the cell’s machinery. The Miller lab team is working to determine exactly how this happens inside brain and nerve cells.

All of this work is important not just for understanding these viruses, but also for developing new weapons against them. The Miller team is working with the Center for Chemical Genomics (CCG), part of the U-M Life Sciences Institute, to test a broad range of drugs and natural compounds. Using rapid drug-screening technology once available only to large drug companies, and cell cultures in various stages of viral infection, the Miller team is working with CCG director David Sherman, PhD, of the U-M College of Pharmacy, and associate director Richard Neubig, MD, PhD, of the Medical School’s Department of Pharmacology.

Soon, they hope to find compounds that could be effective antiviral agents for nipping an arbovirus infection in the bud—no matter how much the viruses’ RNA has mutated. This work, being done in collaboration with Sonja Gerrard, PhD in the U-M School of Public Health and with Richard Kuhn at Purdue University, is seeking antiviral agents that will work against a variety of arboviruses.

Meanwhile, using genetics and bioinformatics core facilities at the Medical School, and working together with Steve Qin, PhD, of the U-M Bioinformatics Program, they’re looking at the genetic factors that may influence a person’s vulnerability to arbovirus infection. For instance, the genes involved in cells’ interferon-based immune defense may play a role.
Viruses in our DNA?

Like a shadow of our ancient past, they lurk silently within our DNA, posing as useless “junk” scattered between the genes. But now, research at U-M and elsewhere is revealing their true nature.

“They” are human endogenous retroviruses, or HERVs, a family of ancient viruses handed down in our genome from millions of years ago. Like HIV, the virus that causes AIDS, these viruses can squirrel away copies of their genetic material inside the DNA of their host, then hijack that host’s own cellular machinery to reproduce.

Unknown until a few decades ago, HERVs have become a major focus in the past several years, ever since the human genome sequencing project was completed. Some studies have shown that their genetic remnants may actually be read by our own cells and used to make helpful products—explaining why they have survived millions of years of evolution.

But now, as research reveals more knowledge about their nature and their effect on the human body, HERVs are looking less like a shadow of our past and more like a sinister factor in modern diseases.

This year, a new faculty member brought his HERV research into full effect at Michigan, together with colleagues in the department and other parts of the Medical School. Mark Kaplan, MD (below), came to Michigan from the North Shore University Hospital on Long Island, New York, where he had spent several decades as a leader in AIDS treatment after taking part in the team that discovered that HIV causes AIDS.

Now, working with Rafael Contreras-Galindo, PhD, and David Markovitz, MD, he focuses on studying the group of HERVs known as HERV-K viruses—the kind with the most complete presence in our DNA, conserved for nearly 30 million years.

This year the U-M researchers and their colleagues showed that people infected with HIV have evidence of actively growing HERV-K virus particles circulating in their blood. By contrast, traces of HERV-K were only rarely found in the blood of people infected with hepatitis C virus, and healthy control subjects.

In other words, having AIDS appears to “stir up” the HERV-K machinery, causing the cell to make the various proteins that can be assembled into an actively replicating HERV-K virus.

Showing HERV-K activity is one thing. But showing that it is associated with, or may even help cause, a disease is quite another. The first disease Kaplan has examined is AIDS-related lymphoma, a blood cancer that strikes 10 to 15 percent of people with uncontrolled AIDS and can often hasten their deaths. Initial results suggest that the presence of HERV-K in AIDS patients’ blood is highly associated with their risk of developing lymphoma.

The ability to study HERVs in AIDS patients is important because of the severely reduced immunity that AIDS patients have. But he is also branching out into studies of HERV-K in lymphoma patients who do not have AIDS, working in cooperation with Scott Gitlin, MD, Hematology/Oncology.

Dr. Kaplan is also looking at HERVs in other diseases, including human breast cancer because of the similarities between HERV-K and a mouse virus known to be strongly associated with breast cancer in mice. Working with Daniel Hayes, MD, Hematology/Oncology, Kaplan is analyzing blood samples from U-M breast cancer patients to see if HERV-K is present and to see how its activity relates to estrogen levels.

At the same time, the lab team is looking at the influence of HERV-K on human gene expression. Early results from cell models suggest that HERV-K genetic fragments may be involved with protein splicing and cell immortality.

As this research continues, Kaplan and his colleagues have a sense that HERVs may be more important than anyone could have suspected. But exactly how important, only time and hard work will tell.
Infectious Diseases

The virus HERV-K HML2 seen by electron microscopy performed on a breast cancer cell line T47D.