Understanding HIV

More than 33 million people worldwide are infected with the human immunodeficiency virus, or HIV, which causes AIDS. Once diagnosed, treatment includes a lifelong course of antiviral medications. But one striking gap in these therapies is that, although they prevent the virus from infecting new cells, none targets already-infected cells to keep them from manufacturing more of the virus. Unlike many other viruses, HIV is able to successfully evade the immune system, and Kathleen Collins, MD, PhD (below), has had a long-standing drive to find out why.

While doing postdoctoral work at Massachusetts Institute of Technology in the laboratory of Nobel laureate David Baltimore, Dr. Collins and her colleagues made a remarkable discovery; HIV encodes a gene called Nef that, when expressed in cells infected with HIV, protects it from the host immune response. In work that was published this year in Nature the team showed that when the Nef gene was disabled in lab experiments, cytotoxic T lymphocytes, a type of host immune cell, was able to kill infected cells and clear the culture of infection.

Dr. Collins joined the U-M faculty in 1998 and since then her laboratory has made tremendous progress toward understanding the specific molecular mechanisms by which Nef operates to promote immune evasion. An important set of immune system proteins, encoded by major histocompatibility complex 1, or MHC-1, which are present in every mammalian cell type, present peptides, or pieces of the virus, on cell surfaces to signal to the immune system that there’s an invader inside. This triggers a cascade of events that leads to destruction of the infected cell. Dr. Collins’ group discovered that the HIV-1 Nef protein binds directly to the immune system proteins in HIV-infected cells, thwarting the MHC-1 proteins which never make it to the cell surface.

In fact, Nef also recruits two other cellular proteins and creates multi-protein complexes that signal the cell to direct MHC-1 proteins to the lysosomal compartment, the part of the cell responsible for processing waste. There, MHC-1 proteins are destroyed, eliminating any way for the host’s immune response to adequately respond to the infection.

Using siRNA techniques, Dr. Collins’ lab has identified both cellular proteins—AP-1 and β-COP—involved in directing the MHC-1 complex to the lysosome. Her group is the first to find these proteins and to identify the common pathway. “This gives us two clear targets for trying to develop inhibitors,” she says. The work was published in the journal PloS Pathogens.

Dr. Collins and colleagues recently have initiated high-throughput assay screening, which will allow her to explore a large number of drug-like compounds to see if they disrupt the Nef-initiated process. “If we can make inhibitors, we could potentially improve control of virus levels by targeting already-infected cells and, in combination with other drugs, we could get closer to a cure,” she says.

Seeking Latent HIV

Another important mechanism through which HIV can persist is latency, whereby the viral genome actually becomes part of an infected cell’s DNA. “Sometimes that genome is completely silent, and it doesn’t make any virus or viral proteins—it just sits,” says Dr. Collins. In that way, the virus is invisible to the host immune system because it’s not producing any antigens or abnormal proteins.

But under some circumstances the virus can be activated. “An important focus for us is to also understand latency and try to develop strategies to eradicate the latent pool,” Dr. Collins says. Investigators in her laboratory have discovered that HIV is able to infect certain cells in the bone marrow and achieve latency in those cells, something that wasn’t understood prior to her lab’s findings.

“This gives us a better perspective on the disease and why it’s so hard to eradicate even after years and years of therapy. It’s likely because of these very long-lived cells that have the viral genome and act as a potential reservoir of new infection when therapies are stopped,” says Dr. Collins, who is continuing work to decipher the molecular mechanisms at play.

Dr. Collins’ work has been funded by the National Institutes of Health and the Burroughs Wellcome Fund.
Antimicrobial Stewardship

Studies in recent decades have suggested that as much as 50% of antibiotic use is inappropriate. In the hospital setting, inappropriate use of antimicrobials can have a number of serious—as well as costly—consequences: toxicity; the emergence of resistant organisms and selection of dangerous organisms such as Clostridium difficile (C. diff), a bacterium that causes severe diarrhea and inflammation of the colon. An effective and comprehensive infection control program, along with antimicrobial management programs can put the brakes on the emergence and spread of drug-resistant infections as well as lower costs and improve patient safety. Tejal Gandhi, MD (below right), and Laraine Washer, MD (below far right), have partnered with infectious diseases pharmacists Curtis Collins, PharmD; Daryl DePestel, PharmD and Jerod Nagel, PharmD, to develop and launch a formalized and comprehensive, institution-wide stewardship effort over the past year.
"We developed the program with the goal of reducing inappropriate antimicrobial therapy and to optimize outcomes and safety by promoting appropriate use," says Dr. Gandhi. Appropriate use refers to the proper selection, dose and duration of antibiotics for each patient who requires such therapy.

Drs. Washer and Gandhi work closely with three infectious disease clinical pharmacists along with staff from the Department of Infection Control & Epidemiology and the Department of Microbiology & Immunology. They provide feedback and advice regarding antimicrobial selection to physicians, house officers and physician assistants. One of the first steps the multidisciplinary team took was to collaborate with general medicine physicians to institute computerized order entry sets for doctors that incorporate evidence-based treatment guidelines for several situations, including treating hospital and community acquired pneumonia and urinary tract infections.

The team also instituted a prior approval paging process for physicians wanting to prescribe restricted antibiotics. The program currently has 20 restricted agents, nine of which require prior approval before ordering the first dose. Particular target agents include broad-spectrum antimicrobials, which have the greatest potential to promote resistance, explains Dr. Washer. Now doctors can get immediate feedback and recommendations from an infectious diseases pharmacist or physician. The group reviews about 2,500 restricted agent requests annually.

Other initiatives in the program’s first year include education programs, working with the departments of Anesthesiology and Pharmacy Services on a weight-based dose optimization protocol for perioperative antibiotics and collaboration with infection control & epidemiology on C. diff control measures.

The outcomes are already encouraging: decreased overall utilization, with lower use of targeted restricted antimicrobials. Feedback has been encouraging too. “Doctors tell us they appreciate being able to have a discussion with an infectious diseases specialist about the best choices for their patients’ particular infections,” says Dr. Gandhi. “We hear very positive feedback.”

Plans for the near future include collaborating with the Department of Microbiology & Immunology to provide antibiograms, or antimicrobial resistance patterns, for individual intensive care units of the hospital.

“On several fronts,” says Dr. Gandhi, “we’re really trying to refine our ability to deter inappropriate antimicrobial use.”