In the dimness of an early 1900s laboratory, an immunologist peering into the lens of a microscope might be looking at a tuberculosis specimen squirming on the slide. Identified as the leading cause of death prior to the development of antibiotics, TB, as well as other outbreaks during the industrialization era including typhoid fever and dysentery, was closely linked to cramped living conditions and poor sanitation and hygiene. The Centers for Disease Control credits public health initiatives and modern miracles such as penicillin, chlorinated water, sewage disposal, and vaccinations, for bringing these diseases under control.

With a new multi-million dollar grant, a UVM group studies infectious agents that impact the health of millions of people worldwide.

Ralph Budd, M.D., Professor of Medicine and Director of the Center for Biomedical Research excellence in immunology and infectious diseases.
Though many major infectious agents were controlled by the 1950s, a cascade of new challenges have emerged over the past 20 years, among them bioterrorism, antibiotic resistance to microorganisms, and an increase in the incidence of certain autoimmune diseases. Research teams like a new interdisciplinary group led by Ralph Budd, M.D., professor of medicine and director of immunobiology, seek to address these crises and gain a better understanding of several Centers for Disease Control-designated “priority pathogens” and their related immune responses. In recognition of their well-established expertise in basic immunology and medically significant infectious agents such as bacteria, viruses and parasites, Budd and his colleagues recently received an $11.4 million National Institutes of Health Center of Biomedical Research Excellence (COBRE) award to fund the Vermont Center for Immunology and Infectious Diseases at the University of Vermont. Ten years ago the UVM immunobiology group needed a National Institutes of Health Program Project grant in order to really grow; but in NIH terms, they lacked the critical mass required to qualify for these larger grants. Determined to get funding, Budd made a creatively bold move. He initiated collaborations with the Trudeau Institute in Saranac Lake, N.Y., a world-renowned center with expertise in mouse models of basic immune mechanisms and infectious diseases. The new alliance clinched the deal; in 1999, the group applied for a program project grant and received it on the first try. In explaining his program’s collaborative approach, Budd says “We’ve done our best to recruit other immunologists here. They haven’t always been in our department, but we’ve always included them in the Immunobiology Program. That’s why it’s a program, not a division or a department.”

Over the past five years, faculty members with immunology expertise were recruited to the departments of medicine, surgery, and obstetrics and gynecology. All immunobiology researchers, regardless of department, were invited to join the weekly lab meeting. The lab meeting, Budd says, is a collaborative and fun exchange. “It works well, because I’m not everyone’s boss; faculty come because they want to.” The more the group met, the more they realized that they could now bring their research to the next level, so they teamed up with clinical and basic science infectious disease specialists and applied for a COBRE award. “COBRE grants are hard to get,” admits Budd. “But we thought we could be competitive, because we had a very strong theme.” Though the group didn’t succeed on their first try, they garnered strong support from UVM and College of Medicine administrators and their second application was successful. Led by Budd and co-principle investigator Gary Ward, Ph.D., professor of microbiology and molecular genetics, the COBRE grant funds the research of several junior faculty members chosen for their competitive expertise in immunology and infectious diseases. Each is mentored by two or more senior faculty members. In total, the grant involves faculty from six separate departments and four colleges at UVM and supports technology expansion in two of UVM’s core facilities — proteomics, which allows for high-level protein analysis, and microarray, which allows researchers to look at as many as 15,000 genes simultaneously and zero in on those genes that are critical to the disease process. The research projects concentrate on four infectious agents and the body’s immune response to them. The COBRE research will focus on how the two types of immune systems that humans possess function during different infections. Though they use different strategies, both systems are critical to combating infection. The innate immune system is the evolutionarily older one, and is the one that responds quicker. It is also the type of immune system found in other life forms, including insects and plants. It functions using a limited number of receptors that recognize a discrete repertoire of foreign material in microorganisms. The innate system is fast to respond, albeit rather limited in its scope.

The second category of immune response, known as adaptive immunity, is found only in vertebrate animals. It produces millions of different receptors that recognize myriad components of microorganisms. Budd describes the system as “genetically expensive and wasteful,” but adds that it ensures that the body has a good armament against a wide array of pathogens. It is slower to respond than the innate system, but becomes, over time, more fine-tuned to a specific infection.

Junior investigator Beth Kirkpatrick, M.D., associate professor of medicine, is conducting research on the body’s innate immune response to Cryptosporidium parvum, a water-borne parasite notably responsible for a 1993 outbreak in Milwaukee, Wisconsin that infected over 400,000 people. An infectious disease clinician who has an NIH Clinical Scientist Development Award, Kirkpatrick is being mentored by Budd, an expert in innate immunity, and Elizabeth Bonney, M.D., associate professor of obstetrics and gynecology, whose research interests include innate immunity at the maternal-fetal interface. Cryptosporidium parvum is considered a major global problem, yet it is poorly understood. It can trigger massive outbreaks of water-borne disease, and causes persistent and chronic diarrhea in children and immunocompromised individuals.

Innate immunity is also the focus of research by Jonathan Boyson, Ph.D., assistant professor of surgery. Boyson is examining T lymphocytes known as...
Natural Killer (NK) T cells. NK T cells play an important role in a variety of immune responses, including infectious disease, anti-tumor responses, autoimmunity, and inflammation. In particular, he is focusing on the molecular activity that controls NK T cell interactions with CD1d — a molecule expressed on the surface of cells involved in the activation of NK T cells. Boyson’s mentors on the project include Budd, Professor of Pathology Huber, Ph.D., who has expertise in the role of CD1 in Coxackie virus infection, and Bonney.

The third leading cause of parasitic death worldwide is Entamoeba histolytica. Through his COBRE project, Christopher Huston, M.D., hopes to gain a greater understanding of the mechanisms involved in infections by this intestinal-based bug. Huston is an assistant professor of medicine who currently works in infections by this intestinal-based bug. Huston is an assistant professor of medicine who currently spends most of his time in the lab, he has rheumatology clinic hours each Thursday afternoon and serves on call every three months for two weeks at a time. His vision includes getting access to clinical specimens for research, increasing the number of clinical studies.

Another parasite, Toxoplasma gondii, is the research project of Mariana Matrajt, Ph.D. This organism infects approximately one-third of the United States’ population and is the leading cause of neurological birth defects, affecting about 3000 babies each year. An assistant professor of microbiology and molecular genetics, Matrajt’s objective is to elucidate the genetic basis and mechanisms underlying the transition between the two infectious stages of Toxoplasma gondii, a dormant phase and an actively replicating stage. She hopes to define how this parasite interferes with immune response signaling. “We are trying to understand that process so in the future we can develop drugs against the parasite that would help manage the patient,” says Matrajt, whose mentors include Ward, a Toxoplasma gondii expert, and Associate Professor of Medicine Mercedes Rincon, Ph.D., who specializes in the specific type of immune response signaling Matrajt is studying.

“This COBRE is designed to launch these junior faculty and also allow us to immediately begin recruit-