

Backing Into EXCELLENCE

Renowned for his research in immunobiology, Ralph Budd, M.D., has also built a legacy of mentorships with the next generation of physicians and scientists.

“IT ISN’T ABOUT YOUR RESEARCH ... IT’S ABOUT HOW YOUR RESEARCH OVERLAPS WITH SOMEONE ELSE’S”

University Distinguished Professor Ralph Budd, M.D., fancies himself a late bloomer. He’s almost apologetic for not having considered studying medicine till he was well into his junior year of college, and for not settling on a specialty until the final rotation of his clinical year of medical school. In his research, he thinks he’s sometimes a little slower than he might be.

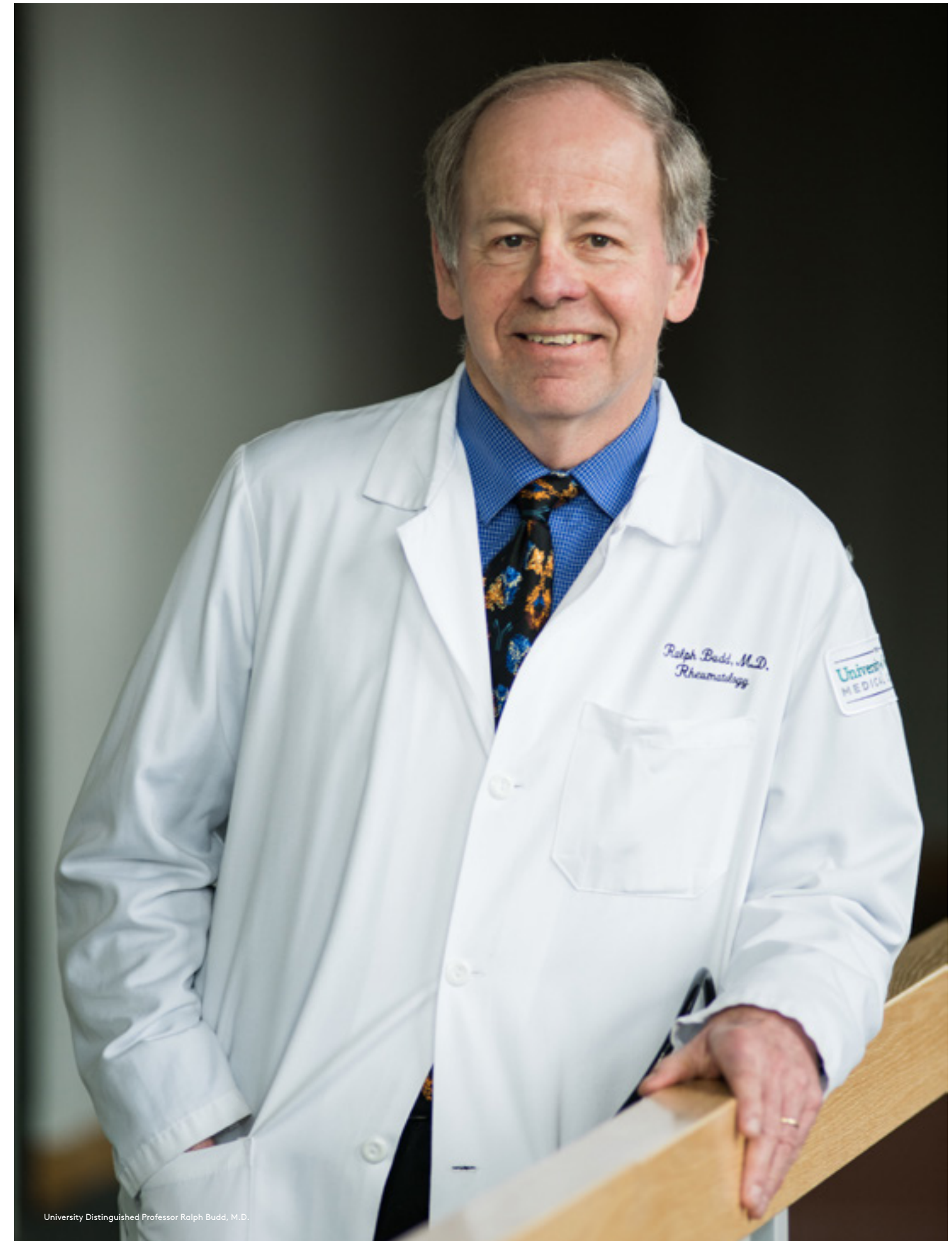
“It’s my whole career, backing into everything,” says Budd. Whether or not that’s an accurate description, he makes an effort to recognize and nurture those who, like him, need time and encouragement. Indeed, this much-lauded physician and scientist has made a science of helping others to find their way.

“He’s skilled at mentoring the whole spectrum of learner-faculty member-student,” says Beth Kirkpatrick, M.D., professor of medicine in the Division of Infectious Disease. “He can mentor the basic scientist, the translational scientist, the physician, the basic researcher. He knows the critical thinking skills that develop folks into independent scientists. That’s one of his real legacies in Vermont: how many people, and the broad spectrum of research strength they’ve had.”

Budd was the force behind the establishment of the Division of Immunobiology in the Department of Medicine. He is also the founder and director of the Vermont Center for Immunology and Infectious Diseases (VCIID), a multi-department partnership that brings together work in immunobiology and infectious diseases, with faculty from the Departments of Medicine, Microbiology and Molecular Genetics, Obstetrics and Gynecology, Animal Science, Surgery, and Pathology, as well as students from the Cellular, Molecular, and Biomedical Sciences graduate program. In ten years, the VCIID has grown to include 26 faculty members who have published more than 400 articles and garnered more than \$92 million in grant support. It is supported by a twice-renewed National Institutes of Health (NIH)-sponsored Centers of Biomedical Research Excellence (COBRE) grant.

In May of 2016, Budd, the only member of the Association of American Physicians at UVM, received University Distinguished Professor status. Last November he was named Research Laureate of the Larner College of Medicine at the inaugural Dean’s Excellence in Research Awards.

“He has done an enormous service within the College of Medicine in terms of building up the immunobiology program and then reaching out to and integrating the immunobiology research with the microbiology research going on around campus,” says Gary Ward, Ph.D., professor of microbiology and molecular genetics and co-Principal Investigator with Budd on the COBRE grant. The grant has supported the recruitment and development of a number of junior



University Distinguished Professor Ralph Budd, M.D.

faculty, including Kirkpatrick, who went on to start the University's Vaccine Testing Center and serves as its director; Christopher Huston, M.D., whose work on treatment of intestinal parasites caught the eye — and the funding — of the Bill & Melinda Gates Foundation; and Aimee Shen, Ph.D., whose work led to her being named a recipient of one of only 102 Presidential Early Career Awards for Scientists and Engineers as well as a prestigious Pew Scholar Award.

Budd has also made a point of encouraging undergraduates, including Katie Bashant, a former Goldwater Scholar, who graduated from UVM in 2016 and is now an NIH Cambridge Scholar using real-time deformability cytometry to characterize neutrophils within inflammatory disease states. She spent close to four years as an undergrad in Budd's lab, where she contributed to research on how necroptotic dendritic cells activate gamma delta T cells, and says it was his genuine support of and interest in her work that gave her the confidence to tackle the challenging research she's now engaged in — work that many people don't get to until they are well into their doctoral program.

"Even though I was just an undergraduate student, I saw Dr. Budd every week when I was there," says Bashant. "He's not one of those professors who's in his office and you don't see them unless you go seek them out. He actually comes into the lab and says, 'Hey, how are things going? Do you have some data to show me? Do you have any concerns?'"

Bashant is an example of how Budd nurtures independent learning, but at the same time, says Shen, now assistant professor of molecular biology and microbiology at Tufts, he has long "helped to initiate a lot of collaborations. Now that I'm in academia and trying to manage people, I appreciate how talented Ralph is at taking on these leadership roles and really helping to direct people. He's selfless in it and he's very, very good at it. He's always thinking about how to stimulate research and how to get people to work together."

It's an approach that begins with mentoring, for everyone from students to postdocs to junior faculty — with the latter having two or three senior faculty mentors each to help them learn grant writing, how to run a lab, and the finer points of publication. Thursdays mean research-in-progress meetings, and junior faculty members in particular are encouraged to present their work.

"We tear it apart," Budd says of the process, which is informally known by participants as a COBRoscopy. "We're rigorous because if we're not, they're going to get it when their work is put before an NIH study section. As a result, our success rate is better than most medical schools." Faculty also go on periodic retreats; Budd was particularly pleased with the outcome of the so-called challenge talks he initiated during one retreat early on in the COBRE grant. Individuals were asked to present their work, but not to enlighten their colleagues as to their research, since most already had at least some idea of what others were doing. Rather, they would show just one slide of a model, and explain how their research overlapped with the work of someone else in the group.

"So it isn't about *your* research," says Budd. "It's about how your research overlaps with someone else's — and it's also to challenge them." Some made better connections than others, he admits, adding that seed money was invested in those collaborations that showed the most promise.

If collaborating has been a theme for Budd as an administrator, its roots go back to his own early days as a researcher. After graduating from Cornell University Medical College, Budd began a residency in internal medicine at Dartmouth-Hitchcock Medical Center, with plans to go into private practice. But before that transpired, he met a rheumatologist who introduced him to the world of autoimmune diseases and the relatively new field of immunology.

"Clinically the diseases were fascinating because they'd present in all sorts of ways," says Budd, listing skin rashes, heart disease, neurologic disease, and joint disease as some of those presentations. The challenge of diagnosing and treating them was exciting, and Budd settled on a rheumatology fellowship. But by the end of his first of two years, he'd grown disheartened by the fact that the only "treatments" were essentially aspirin and steroids, and decided instead to spend time behind the scenes, in an immunology lab, to hopefully discover more treatments. Two years later, he began a postdoc fellowship from the Arthritis Foundation, that allowed him to go to the Ludwig Institute for Cancer Research in Lausanne, Switzerland. It was



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Ralph Budd, M.D., works in one of his two laboratory spaces in the Given Building.



THE BUDD FILE

Ralph Budd, M.D.

University of Vermont

2006–PRESENT Director, Vermont Center for Immunology and Infectious Diseases (VCIID), The University of Vermont

1997–PRESENT Professor of Medicine, Department of Medicine, UVM Larner College of Medicine

1995–PRESENT Associate Chair of Research Training, Department of Medicine, The University of Vermont College of Medicine

1995–PRESENT Director, Immunobiology Program, Department of Medicine, The University of Vermont College of Medicine

1992–1997 Associate Professor of Medicine, Department of Medicine, The University of Vermont College of Medicine

1989–1992 Assistant Professor of Medicine, Department of Medicine, The University of Vermont College of Medicine

1988–1989 Scientist, Division of Molecular Immunology, Genentech, Inc. Clinical Assistant Professor of Medicine, Stanford University School of Medicine

Education & Training

1973–1977 M.D., Cornell University Medical College, New York, N.Y.

1970–1973 B.A. (Biology), Cornell University, Ithaca, N.Y.

1969–1970 M.I.T., Cambridge, Mass.

2011–PRESENT

Member, Association of American Physicians

2016 University Distinguished Professor of Medicine and Microbiology & Molecular Genetics

2016 Research Laureate, Larner College of Medicine Dean's Excellence in Research Awards

Selected Honors

2013 University of Vermont Medical Group — Senior Researcher of the Year

2009–2010 University Scholar, University of Vermont

1998–1999 Fogarty International Fellow, Institute of Biochemistry, University of Lausanne, Lausanne, Switzerland

1994–PRESENT Member, American Society for Clinical Investigation

1990–1994 Pew Scholars Program Award in the Biomedical Sciences

1989–1992 RJR Nabisco Research Scholars Award in Immunology

1983–1986 Arthritis Foundation Postdoctoral Fellow Member

1974–1977 Joseph Collins Foundation Scholar, Cornell Medical College

a conscientious decision Budd and his wife, Lenore, a wildlife biologist, made to experience life outside the United States (“New country, new language, new baby, new laboratory — piece of cake!” he laughs). It turned out to be transformative, the one period of his life Budd would live over, if given the opportunity. It’s also where the groundwork for his focus on collaboration was laid.

“It taught me a lot about how to make science work,” he says of the Ludwig. “It was a fairly small institution — probably about half the size of UVM. I had been at big places before and I went to big places afterward, but that place taught me that with the right people you can do top-rate science with a small group if they get along and they talk to each other.”

And it was there that Budd began his research on a mouse model of lupus. Although it didn’t teach him much about autoimmunity at the time, because it had a single gene mutation in a death receptor, working with it transformed his thinking around the immune system, specifically the role of memory in the system. Though the idea that the immune system can “remember” is a concept as old as Jenner’s smallpox vaccine, Budd’s lab was able to locate the genetic marker that arose when lymphocytes were activated. They then found a minor subset that had the marker and demonstrated that those cells housed immune memory. When he came to Vermont after a couple of years at Stanford and Genentech, he brought the lupus mouse model with him. Like Lausanne, Budd says, UVM was a “smaller place with very talented people.” In addition, UVM would allow him to work across departments in a way that was harder at a larger university.

“What appealed to me was that by talking to people in different fields you can make a connection to versus talking to 20 immunologists all looking at T-cell development,” he says. “It’s thinking laterally as opposed to vertically. That’s what happened back in Lausanne. We had a small group of cancer biologists next to us, a small group of biochemists next to us, but we all talked all the time and found interactions.”

In Vermont, Budd continued to look at the death receptor defect. In addition to lupus, the mouse had enlarged lymph nodes, but it took a couple of false starts in understanding where all the extra cells came from before Budd and his team had their lightbulb moment.



Dr. Budd leads a Monday morning laboratory group meeting.

“The reason we’d missed it is because it’s very subtle and slow,” he says, likening the lymphocytes to an engine in a firehouse, perpetually running just in case the alarm goes off. Approximately 3 to 5 percent of the lymphocytes in a human body are turned over every day, which doesn’t sound like much until you take into consideration what that looks like after a month — or six — of the body not ridding itself of them. Through microarrays, they found upregulation of a lot of cytolytic molecules, which in turn could cause significant damage if they were so abundant that they invaded the wrong tissues. Then, using flow cytometry, they moved the mouse model to humans and found the same upregulation. That suggests “that this process of homeostatic proliferation is going on in all of us, but when it gets accelerated, as possibly in lupus, it may well contribute to the inflammation we see here,” says Budd. Those studies are ongoing.

They also looked at what makes lymphocytes sensitive to the death signal, and through a now famous “failed” experiment (“As I tell students: ‘never come in my office and say the experiment didn’t work — usually it did, and it’s trying to tell you something you didn’t expect.’”), they determined that by simultaneously stimulating growth and giving a death receptor signal, the cell not only did not die, it actually grew faster. The graduate student went on to show that one of the molecules in the death signaling pathway was also required for cell growth. That finding was not initially well received in the field, but was subsequently confirmed by several other labs.

More recently, Budd contributed to a study that appeared in *Science Signaling* in which he and his co-authors (who included Assistant Professors of Pathology and Laboratory Medicine Iwona Buskiewicz, Ph.D. and Andreas Koenig, Ph.D.) examined a pathway through which the immune system detects foreign viruses. They observed that in lupus patients this pathway is activated in the absence of viral infection, and this is likely driven by oxidative stress in cells. They further found that an antioxidant that specifically targets mitochondria may serve a therapeutic effect in people with lupus, potentially significant news, given that exactly one new drug to treat the disease has been developed in the last half-century.

Despite these findings, of late, Budd has had to maintain a near-exclusive focus on the VCIID and his students and postdocs and junior faculty, which steadily impinges on the amount of time he can spend on his own research. But he has no regrets.

“Are you going to go for your own career your whole life or are you going, at some point, to devote a little bit of your time to help the junior folks? And I just decided it’s the right thing to do, to get them going,” he says, adding that he is more than okay with fewer personal grants and a

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smaller lab. In life outside the lab Budd indulges in his love of chamber music. He is a former board member of the UVM Lane Series, and a pipe organist (he first studied it at college as a break from science, though until he convinces Lenore that there’s room in their house for an instrument, he’s making do with a piano).

The father of two and grandfather of one, Budd wouldn’t mind a little more down time. But not just yet. He’s keeping a window open for research and hoping that the antioxidant-related findings will lead to an adjuvant therapy for lupus.

“It would be fun, after all the years of research, to do one thing that really impacts human health,” says Budd. “So few people get to do that.” **VM**