

# BREATHING LIFE INTO TRANSLATIONAL RESEARCH

by Sarah Zobel

For physicians and scientists around the world, the **Vermont Lung Center** is a prime example of an institution that connects leading edge research to clinical needs.

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— Charles Irvin, Ph.D.



## Take a deep breath.

With luck, that felt good, maybe even a little relaxing. But if you’re one of the 25 million Americans living with asthma, or are among the more than 15 million who have chronic obstructive pulmonary disease (COPD), or the 221,000 who will be diagnosed with lung cancer this year alone, perhaps it didn’t.

You could even suffer from airway disease but not yet know it, due in part to the fact that 20 percent of the so-called “silent zone” of lung function can disappear before it becomes palpable. Researchers affiliated with the Vermont Lung Center (VLC) have been tracing those airways to their very ends — and beyond — and in so doing, have raised the Center to a level of national and, indeed, global distinction.

“Everybody knows the Vermont Lung Center — it’s internationally renowned for its expertise and leadership role in assessment of lung function,” says **Polly Parsons, M.D., E.L.** Amidon Professor and Chair of Medicine and a VLC member.

That’s a view reiterated by one of the more recent additions to the center, **David Chapman, Ph.D.**, a postdoctoral fellow who came to the Center from his native Australia upon the recommendation of his doctoral program director in order to research the physiology of asthma at a molecular level. “I studied lung functions in the lab and wanted to learn the animal

model side of things,” says Chapman. “My director said, ‘Vermont’s the place for you to go,’ since there aren’t many places that put the two together. And Charlie is exceptionally well-known.”

“Charlie” is **Charles Irvin, Ph.D.**, the Vermont Lung Center’s director and, some say, the very reason the center exists today. In 1988, Irvin was brought in from the National Jewish Hospital in Denver, the leading respiratory hospital in the United States, where he was the medical director of the largest lung-function lab in the country, and a professor at the University of Colorado Medical Center. But with his work divided equally between animal models and understanding basic mechanisms, he yearned to get involved in clinical research, which wasn’t possible in Denver. Former Denver colleagues who’d moved on to UVM helped draw Irvin to Burlington, where his charge was to set up an asthma center in the department of medicine.

At the time, there was no Vermont Lung Center *per se*, but there had been related funding, in the form of a Specialized Centers of Research (SCOR) grant to look at the biology and causes of fibrosis — more specifically, silicosis, an issue for many quarry workers — as well as a lung demonstration grant from what today is the UVM Office of Health Promotion Research. Both of those grants dated to the early 1970s, and by the time Irvin arrived, their funding had run



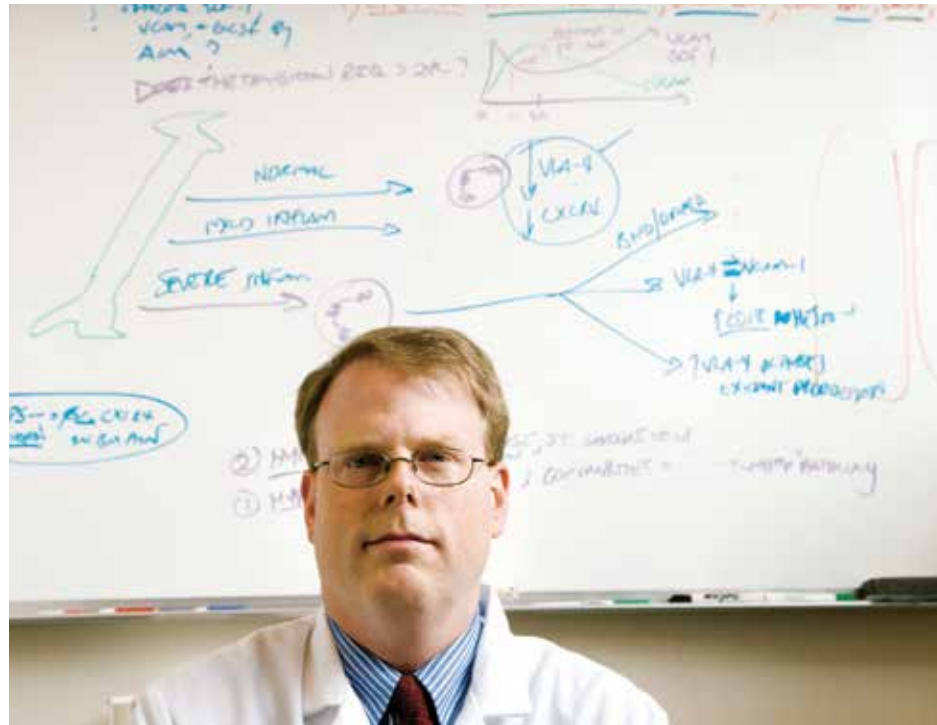
Professor of Medicine Charles Irvin, Ph.D., has directed the Vermont Lung Center since coming to the College of Medicine in 1999. Professor of Pathology Yvonne Janssen-Heininger, Ph.D., conducts research on chronic remodeling of lung airways.

out. Pretty much all that remained was a Vermont Lung Center logo on the wall.

“There was a history of excellence here, and an association with the medical school and the university,” says Irvin. “And that was basis enough to establish the Center.” Soon after he arrived, a new grant was announced: the American Lung Association-Asthma Clinical Research Center program.

“That really started the ball rolling,” Irvin says. “It was a highly competitive

Professor of Medicine Benjamin Suratt, M.D., at right, conducts clinical trials dealing with obesity and asthma; Associate Professor of Medicine Renee Stapleton, M.D., Ph.D., below right, focuses on nutrient and other supportive care interventions; postdoctoral fellow David Chapman, Ph.D., below, researches the molecular physiology of asthma.



national program, and we finished solidly in the middle of the pack of grantees, which I was very happy with. It was a home run the first time out." It also resulted in Irvin's being named division chief of pulmonary critical care and meant he could start adding faculty members to an intensive care unit that at the time included only a half-dozen lung physicians. But the following year, after being awarded a Centers of Biomedical Research Excellence (COBRE) grant from the National Institutes of Health, the Vermont Lung Center fully came to life. The first-cycle COBRE brought "serious money" — some \$40 million over a total of 15 years, with successful renewals at five-year intervals (with the VLC often earning the best score in the competition, says Irvin). The funding cycle was successfully completed this July and Irvin takes pride in the fact that the VLC was among the small number of COBRE grantees that qualified for all 15 years of funding. Faculty members continue to receive grants from a variety of sources, and he points to those as confirmation of the VLC's success. "There's a track record of outstanding excellence based on peer review," he says, "so when I say we have a

terrific center, I base it on this consistent high level of peer review." Those grants fund continually innovative research by an interdisciplinary faculty whose members collaborate across the departments of medicine, microbiology and molecular genetics, physiology, and pathology, and the College of Engineering and Mathematical Sciences. Their collective basic science, translational, and clinical research focuses on a range of lung-related issues including bacterial genetics and metabolism, cell therapy, cystic fibrosis, pulmonary fibrosis, critical care, obesity, and asthma. "That was a game-changer — when Charlie came on board and recruited all these fantastic people," says Professor of Pathology **Yvonne Janssen-Heininger, Ph.D.**, whose primary research interest is the biochemical processes underlying the chronic remodeling of airways in lung tissue, a problem that can't be combatted with steroids or beta agonists. So her lab is focusing on the molecular mechanisms that drive disease manifestations, and in particular, the role of epithelial cells and how their response to inhaled agonists, particulates, or viruses dictate whether the damage will be repaired or remain



chronically inflamed. She's also behind a partnership with Maastricht University Medical Center in the Netherlands, where she earned her Ph.D. "We have very complementary interests," she says of the two centers. "They have a strong clinical, translational rehabilitation program in chronic obstructive pulmonary disease, and they've had an interest in expanding it to encompass asthma and obesity, which are two up-and-coming areas of research here. Given that you have this wealth of patient records and clinical data, that

partnership is incredibly enabling in that it allows us to work much more effectively when it comes to clinical and translational research programs." In addition, graduate students and postdoctoral fellows go back and forth between the two centers, with a conjoint Ph.D. program recently approved. Asthma and obesity are indeed getting plenty of attention at the VLC — in fact, says **Benjamin Suratt, M.D.**, obese asthma is becoming its own category of asthma, and he and several colleagues have conducted several clinical trials and ancillary studies to comprehend the mechanics behind it, considering whether it's an inflammatory response, and what the best treatment might be. Suratt, professor of medicine and vice chair of medicine for academic affairs, has also looked at the effects of obesity on Acute Respiratory Distress Syndrome (ARDS), which is common to hospital intensive care units and kills roughly 30 percent of patients who have it. "Most of the work that's been done over the last 30 years has looked at cardiovascular and endocrine disease in obesity, so there's very little that's known about what obesity does to the lung, and how it modifies both the incidence of a disease like asthma, but also how it modifies the actual manifestation of the disease," says Suratt. Together with Professor of Medicine **Anne Dixon, M.D.**, Suratt coordinates a biannual conference on these issues; "Obesity and Metabolism: An Emerging Frontier in Lung Health and Disease" is slated to take place in October at UVM's Davis Center. He also frequently collaborates with Associate Professor of Medicine **Renee Stapleton, M.D., Ph.D.**, whose own research is largely clinically based and focuses on nutrient and other supportive care interventions in the ICU, as well as communication around treatment preferences in palliative care. "The great thing about the VLC for investigators is that it really brings together a diverse and multidisciplinary group of scientists that come from all areas of pulmonary investigation. It's a wonderful coalescence of clinical research and basic

## The "Connective Tissue" of Collaboration

"Interactome" is a term from the world of molecular biology that describes the whole set of molecular interactions in a cell. But the same approach to describing biological networks on the molecular scale works to show the impressive scale of interaction among the researchers at the Vermont Lung Center (VLC).

The interactome chart below was created from 523 publications co-authored by VLC faculty members covered by the center's T32 training grant from the National Heart, Lung, and Blood Institute. Each connecting strand represents a publication, with senior researchers in aqua and trainees in blue.

"The group is incredibly collaborative, as the interactome shows," says VLC Director Charles Irvin, Ph.D. "But most importantly it shows how much junior-to-junior faculty interaction we have, which suggests how well we can sustain our culture of collaboration within the center as we go forward."



## Planting a Seed

Sally and John Ouellette, M.D.'60 never envisioned themselves as philanthropists. Dr. Ouellette was raised on a 450-acre dairy farm in Tunbridge, Vt., and if everything had gone according to plan, he'd be a retired dairy farmer now. Instead, he's a retired allergist, a Wisconsin tree farmer of the year, and oh yes, he and his wife, Sally, are philanthropists.

A childhood bout of polio weakened John's body enough to make dairy farming with his family's 100-head herd of Jerseys impossible. Instead, he focused on academics. After earning his M.D., he completed his residency at the University of Wisconsin, where he met Sally, and following Army service at Walter Reed Medical Center, he began a busy practice in Wisconsin. His specialty was in allergies, specifically those associated with indoor air quality, and building science.

After John's retirement from the University of Wisconsin faculty in 2004, the Ouellettes focused on building their Dayton Ridge Tree Farm in Richland County, Wisc., where they grow red and white pine, chestnut, red oak, and black walnut trees. They estimate they have planted 40,000 trees and shrubs over the years, and they earned the state's 2010 Tree Farm of the Year award.

Along the way, they also discovered the joy that comes with giving. They have recently decided to give back to the UVM College of Medicine with a \$50,000 gift to establish the John, M.D. '60 and Sally Ouellette Endowed Lectureship for the Vermont Lung Center (VLC). The Ouellettes' gift will enable the VLC to maintain this vital speaker series in perpetuity. The Ouellettes will be present for the inaugural lecture in October of 2015, featuring a presentation by Charles Reed, M.D., a renowned allergist and one of Dr. Ouellette's mentors during his medical training at Wisconsin.

science and physiology that I think is very difficult to find at other institutions," says Stapleton. "Another thing VLC does incredibly well is manage both a very active, productive, successful basic science side as well as a very similarly active and productive clinical research side, two totally different skill sets."

Recently there's been engagement among VLC faculty in alternative, or complementary medicine: Professor of Medicine **David Kaminsky, M.D.**, is conducting a project on the effects of yoga breathing on Chronic Obstructive Pulmonary Disease (COPD), while Irvin is looking at the use of biofeedback on asthma with collaborators at Rutgers and in Denver. A recent VLC-member authored study in the *Journal of the American Medical Association* focused on the effect of soy supplements on lung function, while others are being published on the use of continuous positive airway pressure for sleep apnea and nondrug approaches to treating asthma.

"We're interested in projects that are going to have high impact, and high impact means affecting patient care," Irvin says of the group's broad research targets. Those also include work by **Matthew Wargo, Ph.D.**, assistant professor of microbiology



Assistant Professor of Microbiology and Molecular Genetics Matthew Wargo, Ph.D., works in his UVM lab.

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and molecular genetics, on bacterial lung infections and how various gram-negative opportunistic pathogens respond to surfactant when they get to the lung, as well as how they respond to damage to the host lung surfactant and cells and tissues and cause diseases including cystic fibrosis. Together with Suratt, Wargo is using a mouse model to determine changes in respiratory physiology during infections. The mouse model is a classic approach

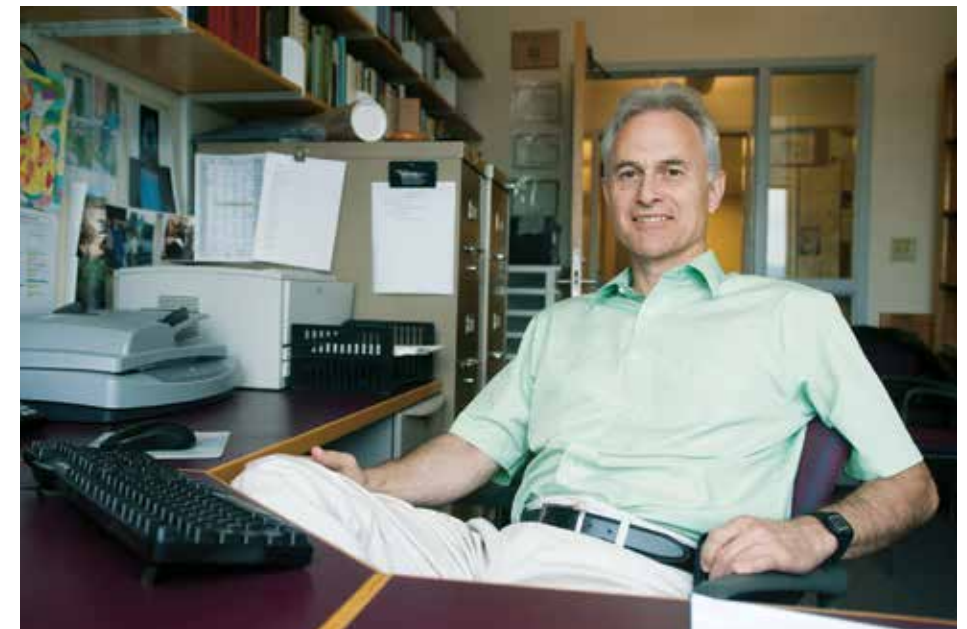
in studying the lung, and as at centers worldwide, they're using the flexiVent, a device that accurately measures lung function in small animals, which was created by the VLC's **Jason Bates, Ph.D.**, professor of medicine. Bates calls the flexiVent a "plug and play," but in fact it's now the industry-standard tool for measuring lung stiffness and airway resistance.

Bates, who has one foot in UVM's College of Mathematics and Engineering as well, serving as graduate coordinator for the new bioengineering Ph.D. program, wants to understand the physics of the lung: how big are the airways, how much pressure does it take to force the flow of air through, and how can the lungs be expanded? That applies to asthma, as well as to ARDS: "You have this delicate lung; how do you ventilate it in a way that minimizes the physical damage you do to it?" says Bates. He's also currently collaborating with **Matt Poynter, Ph.D.**, associate professor of medicine, to test hypotheses about allergic inflammation.

"My computational inclinations match up with his immunological knowledge, and we end up doing a lot of interesting work," says Bates. "It's always at the interface between different disciplines or different skill sets that the good stuff comes. The buzzword in research is *translational*, but here in the VLC it's a natural thing."

"I think we have a lot to be proud of, and we've got a very bright future, because we've got the one thing that matters, and that is fantastic people who get along and collaborate with each other."

— Charles Irvin, Ph.D.



At top, Professor of Medicine Jason Bates, Ph.D., has made important discoveries in measuring lung function; above, Associate Professor of Medicine Matt Poynter, Ph.D., researches allergic inflammation.

The Vermont Lung Center is supported by a National Heart, Lung and Blood Institute T32 training grant that funds four doctoral students and three postdoctoral fellows. Irvin says those trainees are an integral part of the Center's work, and are crucial to its progress.

"I've made it the hallmark that we hire outstanding trainees and faculty—and when you hire good people, good things will happen," says Irvin. "The group is incredibly collaborative. We've achieved what we set out to do, and

that was to develop a world-class center of lung biology and understand disease pathogenesis of the lung. I think we have a lot to be proud of, and we've got a very bright future, because we've got the one thing that matters, and that is fantastic people who get along and collaborate with each other."

As rates of lung cancer, COPD, and asthma continue to climb, that collaboration will be key not only to the health of the nation, but also the world. [VM](#)