



new approaches

FOR NEARLY 40 YEARS, THE VERMONT CANCER CENTER HAS BROUGHT TOGETHER PHYSICIANS AND SCIENTISTS WHO WORK TO UNDERSTAND AND TREAT THE DISEASE — THROUGH RESEARCH, CLINICAL INNOVATION, AND COMMUNITY PARTNERSHIP.

by Sarah Zobel | photographs by Raj Chawla

Nothing lets loose a shot of dread quite as quickly as the word “cancer.” One of three Americans will be diagnosed with cancer at some point in his or her lifetime; one of five will die from it. As the country’s population ages, the disease’s prevalence will only increase. At the Vermont Cancer Center, one of the primary goals is to develop approaches that will someday make cancer a fully treatable disease.

Down the road, I think it’s going to be a disease that one is going to treat on a continual basis,” says VCC co-director Gary Stein, Ph.D., “and that will be compatible with a high quality of life. The more we understand about the disease, the more we are becoming capable of addressing it using treatments that have more specificity and fewer ‘off-target’ effects.”

Stein, who is also chair of the College of Medicine’s Department of Biochemistry, arrived at the VCC in July, joining co-

director Claire Verschraegen, M.D., who had served as interim director since 2011. Their arrivals signaled a turning point for the center. Stein came from the University of Massachusetts Medical School’s cancer center; and Verschraegen, from the University of New Mexico’s. She is a native of Belgium who describes herself as a world citizen, at home anywhere, while he’s a Brooklynite who first moved to Vermont as a UVM undergrad, skis in hand. Already they’ve established what seems to the casual observer as an obvious easy rapport, often finishing each other’s sentences. Stein says they, in essence, recruited each other to the VCC.

“We represent a composite picture,” he says. “We have extensive combined experience in the development and implementation of clinical trials that are not confined to an institution, but regional expertise in investigation with cellular

VCC Co-Directors Claire Verschraegen, M.D., and Gary Stein, Ph.D., have shared leadership of the center since July. They consider themselves a “composite picture of the research and clinical elements of the center.”

molecular biochemical approaches that span test tube cells and animal models and into patients.” Summarizes Verschraegen: “Gary is the researcher and I’m the physician investigator, and we get along very well.”

The VCC, founded in 1974, is a matrix organization whose 135-plus members range from College of Medicine and University-wide faculty to students and fellows and health care providers. Its accessibility to residents of Vermont, New Hampshire, and northern New York means patients don’t have to travel out of state for treatment, which would only add to the physical and mental stresses of treatment.

Stein is a 25-year cancer survivor himself and, while he would have preferred not to go through that experience, he recognizes it as an unparalleled learning opportunity.

“Why shouldn’t Vermonters have state-of-the-art opportunities to be treated?” asks Stein rhetorically. “Why should they have to go out of state?” Here “state-of-the-art” includes genomic analysis, including massively parallel signature sequencing, something for which the University is nationally recognized. Stein is confident that in the not-so-distant future, molecular diagnostics will be the most effective and most widely used form of diagnosis.

The VCC has also established a specific laboratory for translation research, which allows the kinds of partnerships it supports to flourish in a mentored environment. “It’s not just for people initiating their careers,”



Associate Professor of Pharmacology Alan Howe, Ph.D., focuses his research on early detection of cancer.

says Stein. “It’s for somebody who has an established career treating cancer patients or an established career working on cell division in the laboratory, and they’ll be able to partner and bridge what is coming out of both those disciplines.”

Stein and Verschraegen keep translation at the forefront of their work together, defining it as a continuum that reaches all patients, from children through geriatrics, on issues ranging from prevention and early detection through survivorship.

“I ENVISION A DAY WHERE, IF A PERSON HAD OTHER PREDISPOSING FACTORS OR SYMPTOMS, WE WOULD HAVE A BETTER WAY TO EXAMINE THEM... THEN WE’D BE ABLE TO FIND OUT WHETHER THEY HAD CANCER MUCH EARLIER.”

— Alan Howe, Ph.D., Associate Professor of Pharmacology

The majority of cancer-related deaths are due to metastasis rather than the primary tumor, and VCC member Alan Howe, Ph.D. wants to understand the mechanisms behind metastasis. Specifically, he is focused on examining how cancer cells respond to cues in their microenvironments, how these cues promote cancer metastasis, and how the cues might be exploited for early detection of tumors. His laboratory studies how the microenvironment outside cancer cells controls the structural scaffolding inside cells — the cytoskeleton — to effect changes in cell shape, movement, and invasion.

Howe is extrapolating from the model of what happens in breast cancer, where healthy cells around a tumor will respond with a reaction that attempts to kill the tumor, or at least keep it contained. There’s frequently a physical rearrangement of the architecture around the tumor — what Howe describes as a basket of tightly-woven fibers that are pulled together by the surrounding normal cells. Unfortunately, says Howe, “cancer is clever and insidious,” and instead of being contained, it responds to those signals by multiplying more

rapidly and pulling on those fibers to invade more efficiently. Howe is focusing on how this rearrangement might contribute to ovarian cancer, whose most significant problem is its difficulty of detection: in 75 percent of cases, by the time cancer is discovered it has already metastasized, a stage at which the five-year survival rate is less than 20 percent. Howe is studying the changes that occur between ovarian cancer and its microenvironment, and how these changes affect the invasive behavior of ovarian cancer cells, in the hope that these changes can one day be used as a target for therapy or as screening tool in women who are predisposed to ovarian cancer.

“This new dialogue between tumor and host presents not only a whole new avenue for understanding why the cancer is getting worse,” says Howe, “because now the disease is not limited to factors that are inherent to the tumor cells, but also a new opportunity to understand how the body may be reacting. This may help you detect cancer in new ways — you’re not just looking for evidence of the tumor, you might be looking for evidence of changes in surrounding stromal tissue that have come up in reaction to the tumor.” This means doctors would have new, physical ways to look for cancer, including functional MRIs, second-harmonic imaging, and nonlinear optical imaging. Howe thinks that this may be a first step in routine physical screening for ovarian cancer, and that it’s possible that this approach will eventually be applicable to other cancers as well.

“I envision a day where, if a person had other predisposing factors or symptoms,” he says, “we would have a better way to examine them through novel imaging methods or by looking in their blood for specific markers of cancer-induced stromal reactions or changes. Then we’d be able to find out whether they had cancer much earlier.”

Both Verschraegen and Stein want to make the VCC a “one-stop shopping” model for cancer early detection and treatment, but at the same time, both recognize the benefits

“WE’RE PLAYING A CATALYTIC ROLE IN BRINGING THE REGION TOGETHER ... IT’S THE ONLY EFFECTIVE WAY TO PROVIDE OPTIMAL PATIENT CARE AND MOVE SCIENCE FORWARD.”

— Gary Stein, Ph.D., VCC Co-Director

to be gained from working with other regional centers. They’ve already established a regional collaboration with two other cancer centers that are also practicing what is essentially rural medicine: the Norris Cotton Cancer Center at Dartmouth, N.H., and UMass Medical School Cancer Center. Initially meeting in Grafton, Vermont, the leadership of the three centers put together a series of funded initiatives to facilitate the establishment of programs in basic cancer biology translation investigation and clinical studies by their collective scientists and physicians.

“We took a dual approach where we encouraged people to start working together so we can show the track record,” says Verschraegen, “and on the other hand we’re basically remodeling infrastructure to make it more palatable for the researcher to do the work.”

The efforts have already seen measurable success: a total of six collaboration grants were funded. In June, a one-day symposium was held at UVM for grantees to present the progress of the first year’s projects, the basis for continuing into a second year of funding.

“The unanimous opinion of the leadership from the three cancer centers was that it exceeded everybody’s expectations,” says Stein. “The Vermont Cancer Center is playing a catalytic role in bringing the region together, and even the initial successes, I think, are a real indication that this is going to be how we operate in future. In a contracting economy, it’s the only effective way to provide optimal patient care and move science forward.”

The success of this initiative has reached other institutions; additional regional centers beyond Vermont have since contacted Stein and Verschraegen to inquire into potential collaboration.

One UVM researcher who has taken advantage of the opportunity for inter-institutional collaboration is Kim Dittus, M.D., Ph.D. Dittus received a pilot grant from the VCC to expand to Dartmouth and UMass an online behavioral weight loss program for cancer patients. Because it’s known that a inactivity and obesity can have negative impacts on cancer outcomes through higher levels of recurrence and overall mortality, Dittus, who is also a nutritionist, piloted a weight-loss intervention program for area breast cancer survivors with Professor of Nutrition Sciences Jean Harvey-Berino, Ph.D., R.D. Patients lost almost as much weight as the general population but they didn’t exercise enough. In expanding to a multi-site program with rolling entry, then, Dittus has made some modifications to enhance the exercise including using pedometers and online methods to track activity.

“Here in Vermont, I’m not going to prove the overall survival benefit of weight loss,” says Dittus. “Our population is too small. But we can look at some of those people who’ve lost weight and try to understand what’s changed. We can look for the biologically plausible mechanisms that might explain why women who are overweight are more likely to have their cancer come back.”



With cardiologist Philip Ades, M.D. and Patricia O'Brien, M.D., Dittus has now established an oncology rehabilitation program that will allow cancer survivors access to an athletic trainer for aerobic and resistance training two days a week. While the patients are gaining the benefits of regular exercise (they're encouraged to exercise on their own as well), Dittus is collecting data on physiologic functioning; strength; anxiety and depression; and two of the common lingering effects of cancer: fatigue and sleep disturbance.

"Oncology rehabilitation can serve as a platform for translational research," says Dittus, explaining that one approved study will look at the etiology behind post-therapy fatigue and shortness of breath. "You'd like people to be exercising through therapy, as much as they can. It helps with fatigue, and people feel better and have a sense of control." Her goal is to expand oncology rehab so it moves with the patient through each phase of treatment and beyond.



Karen Lounsbury, Ph.D., and Chris Francklyn, Ph.D., are an example of an intra-institutional collaboration. "One thing the VCC does a really good job with, is bringing people together and getting them to talk," says Lounsbury. The two are looking at a potential connection between angiogenesis (the growth of blood vessels), metastasis (the proliferation of cancer cells) and the inhibition of an enzyme, threonyl-tRNA synthetase (TARS) by an antibiotic, BC194 (a derivative of the naturally occurring compound borrelidin). Lounsbury's specialty is vascular biology, so Francklyn, a biochemist, invited her to collaborate to determine whether BC194 influences gene expression in cancer cells. Lounsbury's initial experiments highlighted a connection to vascular endothelial growth factor (VEGF), but an even greater surprise occurred when Lounsbury's post-doctoral fellow Tamara Williams showed that the TARS protein itself has an unexpected function, which is to promote blood vessel development. Apparently, in a bit



Above: Steven Ades, M.D. focuses his research on treatment of clots, and nausea/vomiting caused by radiation. Opposite page: Kim Dittus, M.D., Ph.D., talks to an oncology rehabilitation patient.

“WE CAN LOOK FOR THE BIOLOGICALLY PLAUSIBLE MECHANISMS THAT MIGHT EXPLAIN WHY WOMEN WHO ARE OVERWEIGHT ARE MORE LIKELY TO HAVE THEIR CANCER COME BACK.”

— Kim Dittus, M.D., Ph.D., Assistant Professor of Medicine

of moonlighting, the TARS protein was promoting the ability of the endothelial cells to grow and migrate, and BC194 blocked this function. Furthermore, in looking at stained tissue slices from ovarian and prostate cancer patients, Francklyn and Lounsbury were able to see that the protein was overexpressed in the tumor environment of both cancers.

In future work, Francklyn and Lounsbury will investigate in both human patients and animal models to determine whether the TARS protein can be used as a diagnostic, measurable in the bloodstream — not unlike the currently used PSA test. Inhibitors of TARS might be potential cancer therapeutics, though Francklyn admits that's a ways off. One promising sign is the ability of borrelidin to inhibit tumor metastasis in

a mouse model of melanoma. Discovering new anti-cancer lead compounds remains a strategic goal of the VCC.

"While devising a complete cancer cure would be a huge breakthrough, many people think the more achievable goal is to make life with cancer livable, as it apparently is with HIV," says Francklyn.



It's the very question of patient quality of life that intrigues Steven Ades, M.D., whose work with Mary Cushman, M.D., and Steven Grunberg, M.D. centers on treatment of clots and nausea and vomiting in response to gastrointestinal cancer radiation, respectively.

"We want to impact patients' ability to live and thrive, not just exist," says Ades.



Top: Professor of Pharmacology Karen Lounsbury, Ph.D.; bottom: Professor of Biochemistry Christopher Francklyn, Ph.D.

“WHILE DEVISING A COMPLETE CANCER CURE WOULD BE A HUGE BREAKTHROUGH, MANY PEOPLE THINK THE MORE ACHIEVABLE GOAL IS TO MAKE LIFE WITH CANCER LIVABLE.”

— Christopher Francklyn, Ph.D., Professor of Biochemistry

Clots are a significant concern to advanced cancer patients — roughly one-fifth to one-quarter of them will develop a venous thrombosis or pulmonary embolism during treatment. There are any number of potential causes: the

thickening of the blood that’s associated with cancer, chemotherapeutic or other drugs, underlying cancers, the insertion of a catheter, or the fact that cancer patients as a group are less active than the general population. Regardless, the result is a

“WE WANT TO IMPACT PATIENTS’ ABILITY TO LIVE AND THRIVE, NOT JUST EXIST.”

— Steven Ades, M.D.,
Associate Professor of Medicine

dangerous cycle, says Ades: “Cancer begets blood clots, and clots help cancer spread.”

The standard clot treatment, blood thinners, is not optimal since it tends to result in heavy bleeding. Statins, however, have been shown in the literature to lower the risk of clots without that side effect. So Ades and his colleagues are conducting a randomized phase II crossover study that includes one month each of rosuvastatin, a placebo, and no treatment.

With Grunberg, Ades is examining a relatively new class of antiemetic drugs that target a different receptor, neurokinin 1, in patients receiving radiation therapy to the abdomen. The hope is that they’ll be able to change the current standard of care and find a drug that can safely be administered over an extended period of time during radiotherapy. Though the study opened in collaboration with the Mayo Clinic and Wake Forest School of Medicine’s comprehensive cancer center, Dartmouth and U-Mass Memorial are now also coming on board.


“These are two examples of how collaboration is really important, both within the institution and outside it,” says Ades, adding, “It’s easy to get excited about being here, because I’m around people who are passionate about what they do.”

In addition to diagnosis and treatment, the VCC provides community awareness and support. Its most prominent community event is the annual Breast Cancer Conference, held every October for the last 15 years, which is free and open to both the public and healthcare professionals.

The conference goals are to educate attendees on lifestyle choices that will prevent cancer or its recurrence; there’s also an advocacy piece for high quality breast health care in the region. In addition, the VCC collaborates with the Cancer Patient Support Program, which provides funds for patient transport, lodging, childcare, and other expenses that arise during treatment. Evening Song, a gala that has brought in more than one million dollars to date, helps fundraise for this program.

Outside the center proper, Stein and Verschraegen serve on the advisory board of Vermonters Taking Action Against Cancer, and the VCC collaborated with the American Cancer Society and a number of dermatologists to help Vermont become the second state to enact legislation banning teenagers from tanning salons. The VCC also sponsors educational outreach programs, including one for students in kindergarten through high school that uses cancer as a mechanism for teaching science. Stein and Verschraegen are engaging the community to hear what Vermonters need most from the VCC. Along with Kim Luebbers, the VCC Administrative Director, they are expanding the capabilities of the VCC, as a destination center for cancer care and a resource for cancer research locally, regionally, and internationally.

When asked about meeting the translational expectations required by the NCI Verschraegen replied, “When I came here, I realized that all the elements are in place to translate discovery to clinical practice. We are bringing all the mechanisms that we can together so that infrastructure on which we rely — whether it’s in the lab or the clinical trial arena — is really simplified and unified.”

Referring to her co-director and herself, Verschraegen says, “Our goal is to succeed and success is not *us*. We’re focused on maximizing translation of discoveries into cancer prevention, early detection, treatment, and survivorship, and we’re also proud of the integration of the region. We want everyone to understand that it’s a greater good.” 

Jeff Clarke



The midday research poster session was held in the College’s Given Courtyard.

MAKING CONNECTIONS

A key element of the Vermont Cancer Center (VCC) mission is the encouragement of collaborations and the development of effective processes to foster clinical and translational research avenues. One recent example of this was the recent free day-long Annual Clinical and Translational Science Research Symposium, titled “Exercise, Nutrition, and Cancer.”

Hosted at the Davis Auditorium in the Medical Education Center in Fletcher Allen’s Ambulatory Care Center on November 16, 2012, the symposium featured a special presentation — the J. Walter Juckett Distinguished Lecture — titled “Exercise Therapy for Cardiovascular Injury and Tumor Progression in Cancer,” which was delivered by Lee Jones, Ph.D., associate professor and scientific director of the Duke Center for Cancer Survivorship in the Department of Radiation Oncology within the Duke Cancer Institute.

Co-chaired by Susan Lakoski, M.D., UVM assistant professor of medicine and director of cardiovascular prevention, and Kim Dittus, M.D., Ph.D., assistant professor of medicine and oncologist, the symposium’s presentations focused on clinical and translational research at the VCC and other cancer research institutions with a particular emphasis on exercise, nutrition, and their overall effect on cancer risks and outcomes.

In addition to a welcome provided by VCC co-director and director of hematology/oncology Claire Verschraegen, M.D., UVM presenters at the symposium included: Michael Toth, Ph.D., associate professor of medicine; Jean Harvey-Berino, Ph.D., R.D., professor and chair of nutrition and food sciences and associate professor of medicine; Lakoski; and Dittus.

The Lake Champlain Cancer Research Organization has for many years provided support for the Juckett Lecture and the annual symposium.



Juckett Lecturer Lee Jones, Ph.D.