DYNAMIC DUOS

When clinicians and basic science researchers team up, new approaches to fighting cancer reach patients faster. Through “bench-to-bedside” collaborations, UVM Cancer Center researchers accelerate the translation of laboratory discoveries into clinical practice.

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“WE’VE STARTED TO HAVE A STRONGER MINI-GROUP AROUND NOT ONLY Glioblastoma, BUT BRAIN TUMORS, AND THAT’S GOOD FOR EVERYBODY.”
— DELPHINE QUENET, PH.D.

PICTURE, IF YOU WILL, A CANCER CELL. ALONE, IT IS JUST A HARMLESS ANOMALY. BUT FREE TO DIVIDE EXPONENTIALLY, THE CELLS EXPLODE TO TAKE OVER AN ORGAN.

THERE’S NOTHING LIKE CANCER TO SHOW THE SHEER POWER OF MULTIPLICATION.

Now imagine that instead of cancer cells, you have two UVM Cancer Center members, a basic researcher and a clinician, each working away in their own areas. The two decide to collaborate, combining the researcher’s lab work and the physician’s knowledge of the patient care dimension of the disease. With this doubled-up approach, they are able to tackle with their own focused and multiplex power some of the biggest questions in cancer today. This, in essence, is the heart of what is known as “translational research.”

“We developed the UVM Cancer Center to be able to support those types of relationships,” says Director Gary Stein, Ph.D. “Collaboration is really the fabric of this Cancer Center, and what we have done—and it’s by design, not just by happenstance—is to try to accelerate the transition from discovery to clinical application.” At present, more than a dozen translational teams are working at the UVM Cancer Center with new partnerships emerging each year among the Center’s more than 200 members. Many of those partnerships evolved naturally, over coffee and conversations about current projects. Others were encouraged by the Cancer Center’s leadership team, themselves representing multiple basic and clinical research areas, including Stein, who is as likely to match junior researcher with senior clinician as he is to introduce two peers. It’s a model whose focus is on not only cancer treatment, but also prevention and screening.

“You’re really thinking about both ends of the spectrum: What is the science involved, and what is the clinical outcome you want?” says the center’s associate director for clinical and translational research, Chris Holmes, M.D., Ph.D. “Research is a long process that starts at the platform of the patient and patient needs, and then moves forward toward identification of a biomarker, or an actual new treatment, or a treatment approach.” In some instances, it’s all of the above, because in cancer research, it seems, for every answer there are two more questions. Although such partnerships are not unique to UVM, they thrive here thanks, in part, to the university’s size and structure. For starters, unlike many larger cancer centers, where bench scientists are housed miles from their hospitals, here, clinicians and researchers often find their offices are but a five-minute walk apart. In addition, Holmes says the work is facilitated by UVM’s large cancer control and population health group.

“The goal is to have the University of Vermont Cancer Center optimally contribute to cancer cures, cancer prevention, and survivorship issues,” Holmes says. “We think this is a somewhat unique way to do that, and it certainly leverages our strength in a collegial way.”

Vermont Health Commissioner Mark Levine, M.D., concurs. “This is pivotal, essential work. One does not need to be one of the big-name research institutions in the country to do this kind of work effectively—it can be done on the scale that we do it here in Vermont. So much research in this decade is truly collaborative across states and sometimes across nations, so the fact that we’re playing a role is highly appropriate and will continue to be very valuable.”

6 glioblastoma is rare among cancers—Vermont’s registry shows only 30 cases of it annually (if it sounds familiar, that’s because it made news as the cause of death for senators Ted Kennedy and John McCain). Despite its relatively low numbers, it has piqued the interest of researchers, partly because of its aggressiveness.

“Glioblastoma is a very invasive cancer, so you can never get a clean surgery with nice margins,” says Alissa Thomas, M.D. “It has tentacles that grow deep into portions of the brain, so you can’t treat it surgically. It’s a cancer that tends to acquire a lot of different mutations, so it develops resistances to radiation and chemotherapy relatively quickly. And it grows fast, so most of the time patients show up with a couple weeks’ worth of symptoms at most; the survival average is somewhere between one and two years.” Standard treatment combines surgery, radiation, and chemotherapy with temozolomide (Temodar®), but recurrence is largely anticipated. Because there is no cure and no effective salvage therapy for glioblastoma, Thomas, a neurologist and neuro-oncologist, and Delphine Quenet, Ph.D., a basic science researcher and assistant professor in the department of biochemistry, are exploring whether a specific Poly (ADP-ribose) polymerase (PARP) inhibitor could serve as an adjuvant to standard chemotherapy. They recognize the likelihood is slim that every patient would benefit from it, but hope to find those who will. To be able to offer such personalized therapy, says Quenet, is their “dream goal.” The two acknowledge that theirs is not the standard approach to research, this quest for a one-size-fits-some therapy.
“One of our frustrations in clinical trials for glioblastoma is that once you get to a big enough clinical trial, most treatments fail. That’s because we set this benchmark that 80 percent of patients have to respond for this to be a successful trial. But with a lot of these trials, five percent of patients respond and that’s not good enough to get the drug approved or make this the standard of care. Figuring out who those five percent are so that these patients do this trial and not a different one—that would have a huge impact,” says Thomas.

Quenet’s lab has been focused on the effect of PARP inhibitors on the metabolism and biology of glioblastoma cell lines, specifically PTEN, which is an enzyme that acts as a tumor suppressor and is often mutated or deleted in patients.

“We would like to know if patients who are mutated for this tumor suppressor benefit more from the PARP inhibition or not, due to a concept called synthetic lethality, which has been developed these last 20 years in the PARP field,” she says. In essence, synthetic lethality occurs when two genes with mutations are expressed simultaneously, leading to cell death. A familiar example is BRCA-related cancers, where PARP inhibitors have enhanced the benefits of radiotherapy and chemotherapy. Quenet and Thomas are hopeful that PTEN—which, like BRCA—is involved in double-strand break repairs—will similarly respond to a PARP inhibitor. Working with established cell lines from as far back as the 1960s, coupled with fresh samples donated by UVM Medical Center patients that must be examined in real time, before cell death begins, Quenet’s lab uses biochemical, molecular, and immunohistochemical approaches to understand how proteins are expressed in the cells. When there are several, they look at the subtypes to find any that might be more sensitive to therapy.

“If we see that one of Delphine’s cell lines is responding really well to treatment she’s doing in the lab, we can also look and see if this was a patient who did particularly well or not well with the kinds of treatments we have available now. It gives us some real control, and gives us a lot of power,” says Thomas. The current treatment, temozolomide, works by attaching a methyl group to the backbone of DNA, which keeps the DNA from cross-linking and replicating itself. Conversely, having a good DNA repair mechanism generally interferes with a patient’s ability to respond well to the chemotherapy. PARP is a DNA repair pathway that Quenet and Thomas think may be influencing sensitivity to the chemotherapy.

“Patients often relapse, and one potential reason is because some cells are more resistant to the current treatment. Maybe they will be more sensitive to PARP inhibitor and that’s what we need to address,” says Quenet. The two have also been building a small tissue bank they hope will allow them to undertake different kinds of research in the future, ideally with enough fresh tissue for them to follow their own cell lines. They note the tremendous support they’ve had from patients in allowing use of tumor samples. The pair has been inspired by the desire of patients to play a role in advancing treatment for this disease. With initial support from the UVM Cancer Center through an American Cancer Society Institutional Research Grant, their team has further evolved and is even more fully transdisciplinary; it now includes pathologist John Dewitt, M.D., Ph.D., and neuroscientist James Stafford, Ph.D. Neuroscientist Diane Jaworski, Ph.D., has mentored Quenet and Thomas as they’ve applied for studies and grants—even helping Quenet by blinding her first samples.

“We’ve started to have a stronger mini-group around not only glioblastoma, but brain tumors, and that’s good for everybody,” says Quenet.

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Jason Stumpff, Ph.D., came to Vermont from a large medical center whose size precluded him from having routine interactions with clinicians. But here, Stumpff was assigned to an office suite with another basic science researcher and two medical oncologists.

“Putting clinicians and basic scientists together is really never easy because you don’t talk the same language,” says Marie Wood, M.D., Ph.D., associate director for cancer control and population health science for the Cancer Center, and one of those scientists. “Basic scientists spend so much time thinking about this little part of the world, whether it’s a mitochondrion or an endoplasmic reticulum or a piece of DNA, and physicians focus on the bigger picture as they deal with patients. To bring both the clinicians diving deeper into the cellular layers, and the laboratory people up a little bit more to look outside the weeds is so helpful.”

For Stumpff, an associate professor of molecular physiology and biophysics, and Wood, meeting in the middle evolved after repeated chats about cell division around the office coffeemaker. Stumpff had been studying the organization and division of chromosomes and “stumbled onto” an observation that a particular molecule involved in that process is required for cancer cells—but not normal cells—to divide. Wood was intrigued, because most chemotherapeutics operate by keeping cells from dividing, but make no distinction between cancer and normal cells.

“We talked about how to package that into a proposal so we could explore the question of which cancer cells are sensitive to the loss of this particular cell division protein and try to understand why that would be happening, with the idea of developing a potential new therapeutic strategy,” says Stumpff. They decided to focus on triple negative breast cancer because it has so few targeted treatment options. Compared to other kinds of breast cancer, TNBC (the term for breast cancer that lacks the three receptors most commonly associated with breast cancer—estrogen, progesterone, and the human epidermal growth factor receptor 2) tends to occur in younger women, is more likely to recur, and has a greater ability to metastasize. Stumpff received a Susan G. Komen career development grant. Wood was named one of the members of the mentoring committee.

Wood’s daughter, Lisa, worked in Stumpff’s lab as an undergraduate, so Wood naturally stayed informed about how the research was progressing. As Stumpff tracked down the two patient advocates the Komen grant required (Carol Vallier and Marion Thurnauer became important members of the team), Wood and Stumpff designed a “journal club” to focus on translational science. The goal, according to Wood, was to “try and teach the basic scientists a little bit more clinical focus.”

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“We’re rigorously testing the idea that one particular molecule is required for cancer cell divisions and not normal cell division,” he says. Further noting preliminary findings that suggest there are weaknesses in the "molecular machinery" TNBC cells need to divide—specifically, in the mitotic spindle structures. In addition, molecular composition varies among the tumors. Using cell-based models, Stumpff is testing this idea in different subtypes of TNBC; he’s currently testing "molecular machinery" TNBC cells need that suggest there are weaknesses in the cell division. "Then, I look at gene expression, says van der Velden. The organoid's response will reflect the actual tumor's response. "That’s huge, because it lets you manipulate tumors, that’s a lot easier if you can do it in these dishes with these organoids. You can manipulate tumors and find out what the immunocompetent tumor immune checkpoint inhibitors," he says. With the trial application of ezatiostat immune checkpoint inhibitors," he says. With the trial application of ezatiostat for his success in the lab. Stein remarks, "I think we've been fortunate to have folks who come together in that way."