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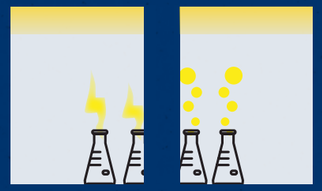
WHEN CLINICIANS AND BASIC SCIENCE RESEARCHERS TEAM UP, NEW APPROACHES TO FIGHTING CANCER REACH PATIENTS FASTER. THROUGH "BENCH-TO-BEDSIDE" COLLABORATIONS, UVM CANCER CENTER RESEARCHERS ACCELERATE THE TRANSLATION OF LABORATORY DISCOVERIES INTO CLINICAL PRACTICE.



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Delphine Quenet, Ph.D., and Alissa Thomas, M.D., review their work on glioblastoma in the Given Building laboratory.

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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 multiplied 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 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 as a smaller community where a lot of the silos are broken down and we know each other, and we can move science forward 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."

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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.

Marie Wood, M.D., and Jason Stumpff, Ph.D., in Dr. Stumpff's laboratory in the Health Sciences Research Facility.

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"IT DOES TAKE EFFORT ON BOTH PARTS TO MAKE THOSE COLLABORATIONS WORK, BUT IT BRINGS YOU TO THE MIDDLE FROM YOUR OPPOSING WORLDS, AND THAT CAN BENEFIT THE NEXT GENERATION OF LEARNERS."
— MARIE WOOD, M.D.

"One of our frustrations in clinical trials for glioblastoma is that once you get to a big enough clinical trial, most treatments fail. They fail because we set this benchmark that X 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-life correlation," 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., , associate director for cancer control and population health science for the Cancer Center, and one of those suitemates. "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 (so named because it 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, and indeed, their collaboration has evolved as a mentorship.

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 Vallett 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." She also invited Stumpff to sit in on tumor boards, where he heard cases presented by oncologists, including treatment options. Stumpff says that opportunity in particular provided a context that helps him understand which questions are worth addressing in the lab.

"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 also compared the effects among various cancers. He and his lab members found that while, for example, colorectal cancers only sometimes responded to the molecule, all of the TNBC cells they tested consistently did so. A plus: preliminary data also showed it had minimal effects on normal cells, meaning there's less likelihood of toxic side effects. Going forward, Stumpff will examine why some cells are sensitive to the loss of this regulator, and then, with luck, determine whether there's a drug that can be developed. As important as learning which patients would respond is figuring out which would not.

The Komen grant was not Stumpff's first for this work; that came in the form of support through the UVM Cancer Center's American Cancer Society Institutional Research Grant, which provides competitive pilot project funding to UVM Cancer Center members and incentivizes translational partnerships. It was awarded to Stumpff and Christopher Anker, M.D., a radiation oncologist and associate professor of radiation oncology.

Jos van der Velden, Ph.D., and Matthew Kinsey, M.D., M.P.H., in the UVM Medical Center.

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"MATT'S REALLY GOOD AT CORRELATING PATIENT CHARACTERISTICS, AND THEN I LOOK AT GENE EXPRESSION AND WE PUT THAT TOGETHER."
— JOS VAN DER VELDEN, Ph.D.

"I think that has gotten people to think about 'How could I test my question using patient samples that come from the hospital or a unique bank of patient samples?'" says Stumpff of the support. And again, what's key is the welcome opportunity to make unexpected connections, with Stumpff noting that he currently has a clinical fellow from OB/GYN, Jessica Ryniec, M.D., in his lab, a first for him. For Wood, the opportunity to teach others is an imperative: "It does take effort on both parts to make those collaborations work, but it brings you to the middle from your opposing worlds, and that can benefit the next generation of learners. As I think about what my role is now, it's as an older, more seasoned person who's going to help the next group of people get inspired, but also learn right."

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One of the cruel ironies of cancer is that it never grows where you want it to.

"It's one of these stunning problems that we can't get cancer to stop growing—particularly lung cancer—in the body, but as soon as you take it out and try to put it on a dish, it dies," says interventional pulmonologist Matthew Kinsey, M.D., M.P.H. There's little point in applying potential therapeutic treatments to cells that are no longer living, of course. Fortunately, Kinsey found an answer and a counterpoint in a partnership with Jos van der Velden, Ph.D., an assistant professor in the Department of Pathology and Laboratory Medicine, who had a grant to study lung cancer but little access to patient samples.

"There are no good models to study lung cancer," says van der Velden. "We have some mouse models, we have cell lines, but in the age of personalized medicine, it's going to be very interesting if you can study a biopsy in the lab to come up with a suitable therapy." The lung does not lend itself to casual study: with more than 40 different cell types, it's challenging enough, but add in the heterogeneity of cancers in that organ, and things get even trickier. Thanks to prodding from Stein and Claire Verschraegen, M.D., then the co-directors of the Cancer Center, and pilot funding through the Cancer Center, Kinsey and van der Velden undertook a collaboration to explore targeted therapies to treat lung cancer, the most lethal and intractable of all the common cancers—its five-year survival rate in the mid-teens is virtually unchanged since the 1970s.

Kinsey procured samples from his patients ("People are really amazing" in their willingness to participate in research, he says), and van der Velden began to grow cultures. When too many of the cells died off before they could be useful, he suggested growing them into three-dimensional tumor organoids instead. It's a process that has only recently gained traction in cancer research—van der Velden says a team at Stanford demonstrated earlier this year that properly grown organoids can represent not only the tumor cells but their inflammatory environment as well—and the difference between looking at a pen-and-paper sketch of a house and peeking inside a scale model of a Victorian made of wood.

"It's a way to resemble the organ—or in this case the tumor—as closely as possible to how it was in the patient," including gene expression, says van der Velden. The organoid's response will reflect the actual tumor's response. "That's huge, because if you can manipulate tumors, that's a lot easier if you can do it in these dishes with these organoids. You can manipulate tumor cells so they become responsive to these immune checkpoint inhibitors," he says. With the trial application of ezatiostat hydrochloride (Telintra, TLK199), an oral agent, supported by patient characteristics provided by Kinsey for each, it makes for truly personalized medicine.

In late March, the two enrolled their one-hundredth patient, a number that once seemed an unattainable goal. The collaboration has already proven fruitful: since they began working together, Kinsey has received an NIH K-series grant and van der Velden has received a five-year NIH R01 grant, which, he says, has about a 10 percent funding rate. They agree that the translational nature of their work made the grant applications more attractive to the NIH, and are already talking about the next one.

"Matt's really good at correlating patient characteristics, and then I look at gene expression and we put that together," says van der Velden. Using organoids has also allowed the pair to explore an interest of Kinsey's, the link between chronic obstructive pulmonary disease (COPD) and cancer, and to consider why a tumor in an area of COPD reacts differently to treatment than a tumor elsewhere. Both are perhaps most energized about plans to use organoids to determine whether it's feasible to inject chemotherapeutics directly into tumors. Today, they are working to increase the number of lung cancer patients who respond dramatically to immunotherapy from 20 percent. Someday, they say, the process may work on any kind of tumor. It will mean figuring out the composition of a tumor and then putting it through single-cell RNA sequencing; says van der Velden, "In terms of personalized medicine, that's really the future."

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Gary Stein gauges the level of success of Cancer Center-affiliated translational partnerships by the multi-year duration of many of the teams, and by their ability to glean extensive extramural funding and to repeatedly publish multi-author articles in peer-reviewed journals. But the secret ingredient may be compatibility. When Stein and his leadership team propose a collaboration, they look for people who have not only complementary interests and skillsets, but complementary personalities as well. Quenet and Thomas meet regularly just to chat, and say every time they do so, more ideas bubble up. Stumpff and Wood play off each other like a couple of vaudeville performers, but there's clearly deep respect. Kinsey says van der Velden is a "friend as well as a collaborator," while van der Velden points to the pair's work as one of the major reasons for his success in the lab.

"If you really want a partnership to work, you need to make certain the individuals make contributions that are going to be more than what either one can do by themselves," says Stein. "I think we've been fortunate to have folks who come together in that way." VM

WEB EXTRA: THE RESEARCH TEAMS DISCUSS HOW THEIR SKILLS AND PERSONALITIES COMPLEMENT EACH OTHER IN THREE VIDEO VIGNETTES: MED.UVM.EDU/VTMEDICINE/WEB-EXTRAS