RESEARCH

Researchers at the College of Medicine are driven by the need to discover, and the need to apply those discoveries. In all their efforts, they seek to understand the basic sciences, use their findings to improve care for patients, and translate those discoveries into further improvements in the years ahead.

Professor of Medicine Mercedes Rincon, Ph.D., presents on UVM's initiative at the first SPARK International Conference in Taipei, Taiwan.

SPARK-VT Spurs Research Innovation at UVM

With proposals ranging from low-cost ground-penetrating radar to a lung sealant derived from seaweed, six research teams from the University of Vermont pitched their ideas to a panel of experts at the first university-wide SPARK-VT session in June 2015, all hoping to receive a seed grant to help move their innovative work one step closer to the marketplace.

Launched in 2013 by the Department of Medicine, SPARK-VT aims to support researchers as they navigate the tricky terrain between developing an idea for a new device or therapy and making it a reality. Its premise hinges on feedback from outside of the university: A panel of 12 leaders from biotech, pharmaceutical, business, engineering, finance, and legal fields are invited to listen to presentations from top researchers. Panel members ask questions, challenge presenters on the details of their plans and ultimately offer suggestions for next steps. All participants get tips and suggestions, but the winners receive seed funding from UVM's Office of the Vice President for Research.

SPARK is part of a global initiative. Professor of Medicine **Mercedes Rincon, Ph.D.,** represented the UVM SPARK-VT program at the first SPARK International Conference in Taipei, Taiwan, in August of 2015. She was invited to give a talk along with seven other representatives from SPARK programs around the world, with a goal to share information and create a global SPARK program that supports researchers as they move their work from bench to bedside.

This year, after two successful years at the College of Medicine, UVM's Provost and Office of the Vice-President for Research broadened the program's reach, resulting in 13 teams from a variety of UVM colleges submitting proposals. After a selection process, the six teams invited to present this year included faculty from the UVM College of Medicine, the College of Engineering and Mathematical Sciences, and the College of Arts and Sciences.

Courtesy Mercedes Rincon

Among the four successful proposals were two initiatives involving College of Medicine faculty:

- An innovative easy-to-use, non-toxic, lung sealant patch/band-aid that could be used for lung surgeries or other emergency sealant needs developed by Assistant Professor of Mechanical Engineering **Rachael Oldinski, Ph.D.,** and Professor of Medicine **Daniel Weiss, M.D., Ph.D.** SPARK-VT funds will aid the team in testing the long-term durability and reliability of the innovative alginate material in animal models, before later moving on to humans.

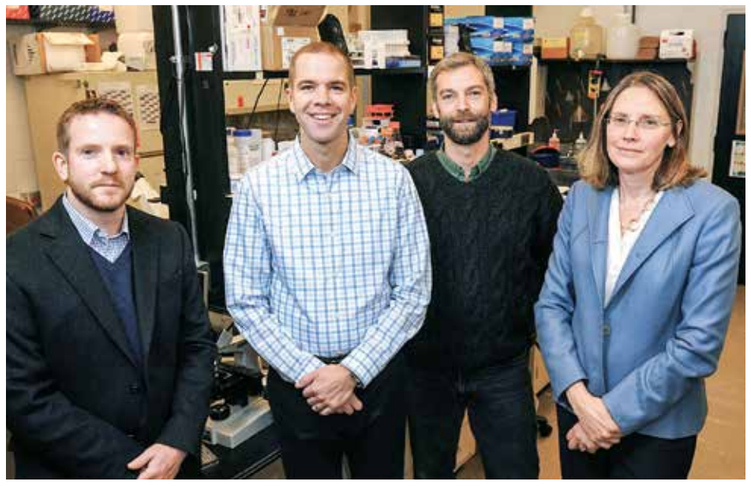
- A proposal by **Jon Ramsey, Ph.D.,** a research associate in the Department of Biochemistry, Professor of Medicine **Claire Verschraegen, M.D.,** and Professor Emeritus of Chemistry **William Geiger, Ph.D.,** regarding a new family of compounds called cymanquines that disrupt autophagy, a process cancer cells use to develop drug resistance. The SPARK-VT funds will be used to test a cymanquine compound in animal models of metastatic melanoma, as well as in other cancers.

Vaccine Testing Center Works to Prevent Dengue Fever

No matter whether it is the "dog days" of summer or the frozen depths of winter, mosquitoes, and — more accurately — the diseases they can transmit, are on the minds of College of Medicine vaccine researchers **Sean Diehl, Ph.D.,** and **Beth Kirkpatrick, M.D.,** of the UVM Vaccine Testing Center (VTC). They and UVM colleagues **Jon Boyson, Ph.D.,** and **Jason Botten, Ph.D.,** received a three-year, $2.2 million grant this year from the Bill and Melinda Gates Foundation to study the immunological basis of protection from dengue fever, a mosquito-borne viral disease that affects as many as 400 million people annually.

A reported 40 percent of the world's population — 2.5 billion people — are at risk for dengue infection, with a rising number of home-grown cases occurring in the U.S over the past decade. However, no directed therapeutic options or licensed vaccines exist, says Diehl, an assistant professor of medicine. Currently there is no dengue virus circulating in Vermont.

In addition to UVM VTC investigators, the team includes researchers from the Johns Hopkins Bloomberg School of Public Health, the National Institute of Allergy and Infectious Disease (NIAID), the La Jolla Institute for Allergy and Immunology, the University of North Carolina, and Atreca, Inc.



Left to right: Sean Diehl, Ph.D., Jason Botten, Ph.D., Jon Boyson, Ph.D., and Beth Kirkpatrick, M.D. of the UVM Vaccine Testing Center.

David Seaver

Kirkpatrick, a UVM professor of medicine and VTC director, Diehl, and their colleagues are conducting and coordinating research that examines how the immune system recognizes dengue virus in an effort to confirm the protective effects of new vaccines in development. The new award builds on nine years of collaboration between the team at the UVM VTC and Johns Hopkins' Center for Immunization Research, led by Associate Professor of International Health **Anna Durbin, M.D.,** and the National Institute of Allergy and Infectious Diseases' **Stephen Whitehead, Ph.D.,** to test new candidate dengue vaccines. Whitehead designed the vaccine candidates.

Dengue infection is caused by any of four related viruses and can cause fever, headache, intense joint and muscle pain, and rash. Although some infections are asymptomatic, severe infections can cause hemorrhagic fever and dengue shock syndrome, and have a higher risk of complications and death.

Like all infections, dengue activates the immune system and that's the goal for the dengue vaccines as well: to build up the body's immunity to completely prevent the disease. A major focus of this new study is the antibodies and T-cell responses produced in the blood in response to the dengue.

"We are so excited to have this wonderful group of collaborators," says Durbin, who adds that the focus of the new study originated from an idea she, Diehl, and Kirkpatrick developed. "We are well positioned to tackle these questions about dengue immunology and hope that by gaining a greater understanding of dengue, we can help develop the most effective vaccines possible."

UVM's effort to understand the dengue immune response will be bolstered by Botten, an assistant professor of medicine, and Boyson, an associate professor of surgery, who will investigate the role of T cells, another type of immune cell, with colleagues from the La Jolla Institute for Allergy and Immunology.

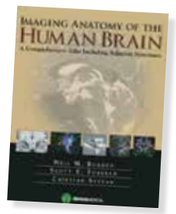
"This work will help fill important knowledge gaps that will help drive vaccine development and implementation and will advance diagnostics for both dengue disease and to gauge vaccine effectiveness," Diehl says.

Borden Creates "Atlas" of the Human Brain

One wall of **Neil Borden's** office at the University of Vermont Medical Center is lined with dozens of books showing images of the brain. Some show cerebral slices. Others contain unlabeled images, but none is a comprehensive, all-encompassing reference of a full variety of cranial views.

During his more than 30 years of practice, Borden, a UVM associate professor of radiology and former endovascular neurosurgeon, came to realize that no single book illustrated the brain in its entirety or provided the encyclopedic breadth of everything from the hippocampus to the vascular structure. So he decided to publish one himself.

Titled *Imaging Anatomy of the Human Brain: A Comprehensive Atlas Including Adjacent Structures,* Borden's book was released by Demos Medical Publishing in 2015. He calls it "a very detailed anatomic atlas of the brain."



"This is something I've wanted to do for a long time," says Borden, who started outlining the project with two colleagues (his coauthors) while still at the Medical College of Georgia. It wasn't until he arrived at the College of Medicine in early 2013 that he began the arduous process of pulling together all the images for the book.

With the help of Associate Professor of Radiology **Richard Watts, Ph.D.,** director of the MRI Center for Biomedical Imaging, and Scott Hipko, a senior research technologist, he was able to assemble images taken by the UVM research magnet. **Alastair Moore, M.D.,** a radiology resident, provided 3-D modeling for the book.

Board-certified in diagnostic radiology and neuroradiology, Borden has published two other textbooks in the field of neuroradiology, including *3D Angiographic Atlas of Neurovascular Anatomy and Pathology* (Cambridge University Press, 2006), *Pattern Recognition Neuroradiology* (Cambridge University Press, 2011). With this latest volume, he applied his decades of experience to give students and future radiologists exactly what they'll need to know in practice. Borden completed another book later in the year titled *Imaging Anatomy of the Human Spine,* which was released in December.

Study Finds Blood Type and Memory Loss Link

People with blood type AB may be more likely to develop memory loss in later years than people with other blood types, according to a study published in *Neurology,* the medical journal of the American Academy of Neurology, by **Kristine Alexander, Ph.D.,** postdoctoral fellow in medicine, **Mary Cushman, M.D., M.Sc.,** professor of medicine, and their colleagues.

AB is the least common blood type, found in only about four percent of the U.S. population. The study found that people with AB blood were 82 percent more likely to develop the thinking and memory problems that can lead to dementia than people with other blood types. Previous studies have shown that people with type O blood have a lower risk of heart disease and stroke, factors that can increase the risk of memory loss and dementia.

The study was part of a larger study (the REasons for Geographic And Racial Differences in Stroke, or REGARDS Study) of more than 30,000 people followed for an average of 3.4 years.

"Our study looks at blood type and risk of cognitive impairment, but several studies have shown that factors such as high blood pressure, high cholesterol and diabetes increase the risk of cognitive impairment and dementia," says Alexander.

Postdoctoral fellow in medicine Kristine Alexander, Ph.D., was first author of the study linking blood type and memory loss.

"Blood type is also related to other vascular conditions like stroke, so the findings highlight the connections between vascular issues and brain health. More research is needed to confirm these results."

In the *Neurology* study, researchers also looked at blood levels of factor VIII, a protein that helps blood to clot. High levels of factor VIII were related to higher risk of cognitive impairment. People in this study with higher levels of factor VIII were 24 percent more likely to develop thinking and memory problems than people with lower levels of the protein. People with AB blood had a higher average level of factor VIII than people with other blood types.

Another recent study that also looked at this association was published in the *Journal of Thrombosis and Haemostasis* by **Neil Zakai, M.D.,** associate professor of medicine, and colleagues including Cushman. Also using the REGARDS study, those researchers reported that blood type AB was associated with increased stroke risk.

Medical Student is First Author of Mesothelioma Treatment Study

University of Vermont College of Medicine student **Mutlay Sayan '16** was first author this year on a study that takes an important step forward in understanding and developing a potential therapy for malignant mesothelioma (MM), a type

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Medical student Mutlay Sayan '16 led a study that points toward new therapy for mesothelioma.

of lung cancer that has been notoriously difficult to treat.

MM, caused by exposure to asbestos or similar carcinogens, is relatively rare but carries a high mortality rate. According to the American Cancer Society, about 3,000 new cases are diagnosed in the U.S. annually, with a five-year survival rate of between five and 10 percent. Sayan and a team of co-authors in the Department of Pathology and Laboratory Medicine studied human cell lines from two histological forms of MM: epithelioid (HMESO), the most common type of MM, and sarcomatoid (H2373), the most aggressive form of the cancer and the most resistant to treatment. Their paper, published online in the *American Journal of Respiratory Cell and Molecular Biology,* identifies two novel cell survival/resistance pathways — ERK5, and cAMP response element binding protein (CREB) — that are inhibited by a combination of two therapies.

This is the first time these pathways have been shown to interact with these drugs in a way that reduces the proliferation of MM cells, Sayan says, noting that the initial goal was to "come up with different drug combinations to tackle this disease." This novel finding may be an alternative approach to treat MM.

Next steps will include applying this work done with human cell lines to animal models, with the eventual goal of conducting clinical trials. A recent increase in the number of mesothelioma deaths in Sayan's home country of Turkey adds extra urgency to this work. The high number of cases — about 600 to 800 times higher than the world average, according to some reports — in the Cappadocia region is believed to be caused by a mineral native to rock in the area that has been used in construction.

Sayan's work in the lab pre-dates his entrance to medical school; he has been conducting research in the lab of UVM Distinguished Professor of Pathology **Brooke Mossman, Ph.D.'77,** a co-author on the study, since his undergraduate years at UVM. "It has been a privilege to work with her," Sayan says, as Mossman is one of the pre-eminent researchers in the MM field. Second author of the study is Associate Professor of Pathology **Arti Shukla, Ph.D.,** who is well known for her work on CREB pathway, and has been a great contributor in this project, Sayan says. Other co-authors include **Maximillian Brian MacPherson; Sherrill L. Macura, Ph.D.; Jedd M. Hillegass, Ph.D.; Timothy N. Perkins, Ph.D.; Joyce K. Thompson; Stacie L. Beuschel;** and **Jill M. Miller, M.D.** — all affiliated with the UVM Department of Pathology.

Scholarly Projects Showcase Breadth of Research from Class of 2015

When do emergency first responders in Vermont decide to turn on lights and sirens? Can narrative medicine help curb physician burnout? How do disadvantaged students fare during the admissions process for medical school? These are just some of the questions explored by fourth-year students at the College of Medicine through their scholarly projects. Students work with a faculty mentor to identify a topic and carry out the research.

Tyler Lemay, M.D.'15, a Vermont native with extensive experience as an Emergency Medical Technician, focused his scholarly project on the use of lights and sirens during ambulance transport. Since there's growing consensus about the dangers of using them when not necessary — and no established protocol in Vermont regarding their use — it's an issue ripe for further study.

Lemay partnered with **Kalev Freeman, M.D., Ph.D.,** assistant professor of surgery and emergency medicine specialist, and a team of undergraduates enrolled in a surgery course Freeman teaches for the Institutional Review Board-approved study. The students, whose course participation includes staffing the UVM Medical Center Emergency Department in shifts 16 hours per day, asked emergency first responders to complete a survey related to when they turn on lights and sirens. Their responses have provided a nuanced look at how Emergency Medical Technicians in Vermont make decisions about transport.

"What we're hoping is that it will identify targets to reduce the use of lights and sirens," Lemay says. "Nobody has really looked at why they're being used."

Elyse Goveia '15 presents her scholarly project during a poster session in May.

Sally McCay; COM Design & Photography