Working to Fine-Tune the Immune System

EYAL AMIEL, PH.D., ASSISTANT PROFESSOR OF MEDICAL LABORATORY AND RADIATION SCIENCES

Microbiologist Eyal Amiel, Ph.D., didn't think he wanted to study immunology, let alone make a career of it. But as co-author of a paper recently published in the journal *Nature Immunology,* Amiel is at the forefront of research that could eventually lead to changes in vaccine design, along with new approaches to treating immune-related diseases.

Amiel's research focuses on dendritic cells, which are critical to the immune system; their function is to process antibody-generating materials, or antigens, and present them to T cells, which then shape the immune response. His study considers the cellular upregulation of glucose, which maintains a cell's energy but also creates fatty acids that are secreted by the cell as part of its immune activity. Together with his colleagues, Amiel determined that the early consumption of glucose is vital to the activation of cells, in terms of the production and secretion of proteins that are essential to the cells' immune function. Amiel is already bringing these findings from mouse to human, having spearheaded a memorandum of understanding with the Champlain Valley Physicians' Hospital in Plattsburgh, N.Y., which will provide his lab with human blood cell filters, a waste product. The lab will reverse flush the white blood cells out and fill them with cultures, allowing them to make new observations about the innate immune response in humans.

Amiel's graduate work at Dartmouth, where he earned a doctorate in microbiology and immunology, focused on the two categories of receptors and the relationship between them — signaling cells, essentially the "on" switch to the cell's immune protection program, and recognition molecules that facilitate the engulfment of bacteria — and how they cooperate to bring bacteria to the surface. He found that if you take away some of the interactions between the two, you can push that fine balance of the immune system into problem areas like sepsis.

At New York's Saranac Lake-based Trudeau Institute, Amiel undertook a postdoctoral project, in which he studied the metabolic regulation of dendritic cell activity. When dendritic cells are activated, they undergo fundamental changes in their use of nutrients, increasing dependence on sugar consumption. Specifically, he wanted to gain an understanding of why cells change their metabolism when they're activated, whether that is necessary for their activation and what happens if it is modulated. By understanding the metabolic switch in both directions, Amiel hypothesizes we could increase immune activity where we might want to — in vaccines, for instance — or we could dampen it where that would be advantageous, as in autoimmune disease or hyper-inflammatory conditions.

In February 2014, Amiel received a patent for a method of producing activated antigen presenting cells and potential methods of using them in anti-cancer vaccines. He's looked at the application of dendritic cells on a melanoma model in mice, and his lab is beginning research into glutamine, which shares many properties with glucose, but may be more important in governing what cells do. One finding Amiel's lab has made is that the activation of dendritic cells means a shortening of their lifespan, which they've determined is metabolically linked. By manipulating key metabolic pathways, Amiel says, they can toy with their activation and cell survival, something that could result in dendritic cells that have both longer lives and bigger immune responses than their normal counterparts, and would therefore be beneficial in mounting an immune response to a tumor.

"The immune system is constantly riding that fine line between how much protection we can have without too much collateral damage," Amiel says, noting that the system is based on being toxic to the non-self. "It's really that fine line that makes immunology so interesting."

Eyal Amiel, Ph.D., studies the function of the immune system's critical dendritic cells.

"THE IMMUNE SYSTEM IS CONSTANTLY RIDING THAT FINE LINE BETWEEN HOW MUCH PROTECTION WE CAN HAVE WITHOUT TOO MUCH COLLATERAL DAMAGE … IT'S REALLY THAT FINE LINE THAT MAKES IMMUNOLOGY SO INTERESTING."

— Eyal Amiel, Ph.D.

From Bacteria to Biofuels: Understanding Cellular Survival

MARY DUNLOP, PH.D., ASSISTANT PROFESSOR OF COMPUTER SCIENCE

Mary Dunlop, Ph.D., is looking into how organisms respond to changing environments, and in doing so, she's crossing disciplines, using synthetic and systems biology to research natural and manufactured cellular processes. Dunlop, assistant professor in the School of Engineering and associate faculty member in the Vermont Complex Systems Center, was the recipient of the National Science Foundation's CAREER Award, the Outstanding Junior Faculty Award from UVM's College of Engineering and Mathematical Sciences, and the U.S. Department of Energy's Early Career Award. She's interested in studying how microscopic organisms — bacteria — handle macroscopic phenomena — antibiotic resistance and biofuel production.

"My lab takes two different perspectives," says Dunlop. "One is trying to understand natural examples of how cells can deal with changing environments. The other is exactly the opposite direction, where we try to build completely novel feedback systems that don't exist in nature."

That work begins with the basic knowledge that bacteria, though single-celled, have a complexity and a level of individuality that renders them useful models of more intricate biological systems. Through studying E. coli, Dunlop and her team of five graduate students and one undergraduate have found that even cells that are genetically identical can take on different phenotypes, or characteristics, allowing them to "hedge against uncertainties in the future." That may translate to a microbe's ability to evade antibiotics, for example, by turning on an efflux pump that will force the drugs away or at the very least make the organism more tolerant of them; another reaction might be a change in its cell membrane composition. Regardless of the response, if it were shared by an entire colony that could be costly — especially if there's little likelihood of an antibiotic encounter. Instead, such a task is generally relegated to a smaller subset of the population, which, says Dunlop, serves as an insurance policy. That way, if something were to happen to the responsive subgroup, the surviving cells would still be able to regenerate. Although she and her colleagues focus on E. coli, the mechanisms are common to a variety of different microbes, Dunlop says, including pathogens.

Their research is focused on why the changes happen, but Dunlop says it's not impossible that one outcome down the road would be a finding that when cells diversify their responses, they trade off which cells in a given population are antibiotic resistant and for how long. That may be important from a clinical perspective because knowing how long that transient resistance lasts may affect length of treatment. For the most part, however, they remain focused on costs and benefits of the different cellular approaches to survival — that bet hedging within the cells: some might survive while others do not, but even so they have collectively diversified their responses. Dunlop uses time-lapse microscopy — basic time-lapse photography under a microscope — with fluorescent colors to assess changes and establish quantitative histories of the cells over time.

On a somewhat larger scale, Dunlop's lab is researching the creation of transportation biofuels from cellulosic — plant-matter — sources. While most biofuel is currently made from corn and sugar cane, Dunlop is looking at the end process of converting recycled material — debris from forests, grass clippings, and the like. Likening it to making beer, in which the level of alcohol is naturally self-limiting to avoid yeast die-off, Dunlop says cells that are converted to biofuels suffer from the same toxicity concerns.

Mary Dunlop, Ph.D., researches optimizing the environments for long-term cell survival, which has major implications for such fields as biofuel production.

"That's a real problem for making biofuel," says Dunlop. "You want to make a lot of fuel to be efficient and cost effective, but after a certain point, the cells start to die." In an effort to make microbes more robust, Dunlop is studying their tolerance mechanisms, using organisms that exist in harsh environments, such as areas around natural oil seepages in the ocean, or near oil rigs or spills. Such microbes, whose primary purpose is to eat hydrocarbons, have developed a tolerance to high quantities of biofuel-like compounds; Dunlop hopes to find which genes are responsible and eventually crossbreed them with E. coli to create a more durable cell.

"MY LAB TAKES TWO DIFFERENT PERSPECTIVES … ONE IS TRYING TO UNDERSTAND NATURAL EXAMPLES OF HOW CELLS CAN DEAL WITH CHANGING ENVIRONMENTS. THE OTHER IS EXACTLY THE OPPOSITE DIRECTION, WHERE WE TRY TO BUILD COMPLETELY NOVEL FEEDBACK SYSTEMS THAT DON'T EXIST IN NATURE."

—Mary Dunlop, Ph.D.

Calculating the Benefits of Nature

TAYLOR RICKETTS, PH.D., GUND PROFESSOR OF ECOLOGICAL ECONOMICS AND DIRECTOR OF THE GUND INSTITUTE

When Professor Taylor Ricketts talks about making advancements in global conservation efforts, he isn't so much worried about fuzzy little creatures necessarily, unless they're native bees. Ricketts is interested in "ecosystem services" — the economic benefits nature provides — and in calculating their value in terms of finances, but also in their financial, cultural, and health-related value.

"There's a whole mess of things that native ecosystems and the species in them do that confer serious value to us," says Ricketts. "It's just that we're pretty bad at understanding and accounting for them and including them in our decision making."

Food is an obvious benefit, but Ricketts is most concerned with how wetlands purify water for drinking downstream, for example, and how they controlled floods — or didn't — during 2011's Tropical Storm Irene, how forests are able to capture carbon and slow climate change, and the importance of wild bees in crop pollination.

Seventy percent of the world's major commodities need to be pollinated in order to fully set fruit, and Ricketts is working to determine how much less a farmer would earn if this "free service" weren't available. He spent time on a coffee farm in Costa Rica and calculated the farm would produce about 20 percent less coffee, which translates to an annual loss of roughly $60,000 in income. He's currently investigating the same question on Vermont blueberry farms, and notes it's already clear that blueberry farmers need bees, and that many of those bee species are declining.

The decrease in the native bee population can be blamed on increased pesticide use, as well as the tilling of soil, which is where many of them nest. A standard response is to truck in boxes of honeybees and hope they'll do the work of the wild bees, but Ricketts says that's like owning one stock rather than an entire portfolio, and trusting that you'll still make money. Diversity — in nature, as in investing — is essential to stable returns. Although honeybees can help, they're often not specialized and efficient enough to fully replace native bees.

"It's heartening that farmers are thinking about other strategies," says Ricketts of the effort to make habitats welcoming to wild bees. He's currently taking part in a five-year USDA-funded study to conduct experiments on pollinator strips, which are growing in popularity worldwide. Large areas of wildflowers that flower all summer have been purposefully planted near crops where they serve as an enticing buffet for the bees, which will stay around to enjoy them even after the crops themselves have finished flowering.

Ricketts also co-founded the Natural Capital Project, a partnership among UVM, Stanford University, the University of Minnesota, the World Wildlife Fund, and the Nature Conservancy, that's working to quantify the role of nature in sustainable investment and policy decisions. He's working with Vermont's State Agency for Natural Resources to determine the flow of economic benefits of Vermont's conservation investments — parks, land trusts and the like. He notes the project wouldn't have been possible 10 years ago, because scientists have only recently gotten good at putting a dollar value on such things in a credible way.

Fitting in time to teach undergraduate and graduate courses in landscape ecology and ecosystems services, Ricketts is also working internationally to help governments and NGOs determine how changing natural conditions affect people's health. So he's looked at whether pollinator declines result in poorer diets and more nutritional disease in developing countries, and how conservation of watersheds around the world can reduce water-borne diseases like diarrhea in children. The message for health ministries is that investing in conservation efforts can be a cost-effective public health strategy for their own citizens.

"That's putting nature and our decisions to destroy it or keep it in really concrete health terms," says Ricketts. As with all of his projects, the overarching goal is to make conservation more central to decision making, for individuals and governments.

Professor of Environment and Natural Resources Taylor Ricketts, Ph.D., is an expert on the benefits of bees, and is part of a USDA-funded grant to study "pollinator strips."

"THERE'S A WHOLE MESS OF THINGS THAT NATIVE ECOSYSTEMS AND THE SPECIES IN THEM DO THAT CONFER SERIOUS VALUE TO US. IT'S JUST THAT WE'RE PRETTY BAD AT UNDERSTANDING AND ACCOUNTING FOR THEM AND INCLUDING THEM IN OUR DECISION MAKING."

— Taylor Ricketts, Ph.D.

DISCOVERY. INNOVATION. IMPACT.

The 2014 Research Report of the University of Vermont is a publication of the Office of the Provost and the Office of the Vice President for Research.

David V. Rosowsky, Ph.D.
Provost and Senior Vice President

John N. Evans, Ph.D.
Interim Vice President for Research

EDITORS

Carole Whitaker
Assistant Dean for
Medical Communications

Edward Neuert
Creative Director
Medical Communications

Jeff Wakefield
Associate Director
University Communications

ART DIRECTOR

Steve Wetherby
Wetherby Design

OFFICE OF THE VICE PRESIDENT FOR RESEARCH

Melody Burkins, Ph.D.
Corine Farewell, D.V.M.
M. Jennifer Gagnon
Dan Harvey

OFFICE OF THE PROVOST

Kerry Castano, M.F.A.

OFFICE OF UNIVERSITY RELATIONS

Wendy Koenig, J.D.
Joseph Speidel

CONTRIBUTING WRITERS

Joshua Brown
Lee Ann Cox
Cheryl Dorschner
Sarah Keblin
Meredith Woodward King
Jennifer Nachbur
Erin Post
Jon Reidel
Amanda Waite
Sarah Zobel

CONTRIBUTING PHOTOGRAPHERS

Mike Bradley
Joshua Brown
Raj Chawla
Jeff Clarke
Andy Duback
Bob Handleman
Jamie Lent
Sally McCay
Mario Morgado
Alison Nihart
Erin Post

Recycled
Supporting responsible use of forest resources
FSC
www.fsc.org Cert no. SW-COC-2000
© 1996 Forest Stewardship Council

100%

PRINTING: Printed by Queen City Printers, Inc. Environmentally certified to the Forest Stewardship Council Standard.

PAPER: Printed on paper manufactured using 100% post-consumer recycled fiber, Process Chlorine-Free, and certified by Green Seal and SmartWood to the Forest Stewardship Council Standard.

Copyright © 2014 University of Vermont