

With \$1.6M award, biochemist tackles diabetes

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PROVIDENCE – **WOLFGANG PETI**, a biochemist who studies the structure, motions, and interactions of proteins at the atomic scale, has won a five-year, \$1.625-million New to Diabetes Research Accelerator Award announced January 9 by the American Diabetes Association. Peti is one of only five researchers around the country to win.

interactions can now be fully analyzed with advanced techniques such as nuclear magnetic resonance spectroscopy and X-ray crystallography.

Last year, when Brown acquired a powerful new NMR magnet, Peti gained a rare degree of capability to study the dynamic motions of these proteins and the timing of their interactions, as well as their basic structure.

Peti's ambitious goal is to enable the development of medicines that improve on the status quo so greatly that insulin injections might no longer be necessary.

"The easiest thing would be if you have type 2 diabetes instead of injecting insulin, you'd just take a tablet," he said. "If you can control the insulin-signaling pathway with a drug, that would make your life much easier."

Three targets

Peti still sees the insulin-signaling pathway as rife with potential new leads. He plans to look in novel ways and in novel places at the interactions of three main proteins in particular.

One target is the binding between insulin and the insulin receptor. That step activates the "TK" domain, or section, of the receptor, kicking off the cascade of protein signaling that leads

to the metabolism of glucose. This may seem like an obvious place to start, but the complexity comes from trying to observe the movements of the TK domain and the specific timing that may be going awry in type 2 diabetes.

Peti and his colleagues have been able to model it all in *E. coli* bacteria, which will allow them to observe it precisely with NMR. That will allow Peti see how the TK domain reshapes and moves, how quickly and when. That could yield a clear understanding of whether a drug could block or slow a key movement that is happening too soon or too quickly.

Peti also plans to work with fellow Brown biologist Marc Tatar to take the ideas into the fruit fly where they can investigate the differences made by known genetic mutations.

Another target is an enzyme called PTP1B, which can shut off insulin signaling. Because the goal in treating type 2 diabetes is to improve insulin function, Peti wants to stop PTP1B.



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Brown's powerful new NMR magnet will allow Wolfgang Peti to study the motion and timing of protein interactions, advancing the effort to understand and possibly to improve insulin signaling in people with type 2 diabetes.

His goal is to help develop drugs to improve the body's insulin signaling so that injections become unnecessary. As it is for millions of people around the world, the pervasive condition is personal for Peti. His grandmother battled it for decades.

"It affected her ability to see, her ability to walk through the mountains of Austria, and her ability to eat all the traditional foods she grew up eating and cooking," Peti said. "And while she successfully battled the disease for many years, eventually the doctors had to amputate both of her legs (first at age 80, second at age 88) and she was confined to a wheelchair for the last eight years of her life."

Although he hasn't focused specifically on diabetes before, decades of research have given him a deep expertise in the atomic structure and behavior of some of the key proteins of insulin signaling. He and his collaborators have refined these proteins in the lab to the degree that they and their

PTP1B has proven time and again to be tough to block without unintended consequences, but Peti hopes a less direct approach than others have taken will make a difference. Rather than targeting the main catalytic parts of the enzyme directly, he's looking at the behavior of a more peripheral but nevertheless influential structure called the "c-terminal segment." It's an underexplored region that could be targeted very specifically, likely with a combination of surgical strikes on more than one area. A key requirement of any drug is that it only affects insulin signaling and not other interactions by similar enzymes.

Sure enough, along with colleague Nicholas Tonks at the Cold Spring Harbor Laboratory, Peti has begun to characterize a drug that works in this area. They plan to use NMR to improve the understanding of the drug's workings further and use that knowledge to improve its abilities.

Peti's third approach under the ADA award is more

traditional in that it depends "simply" on characterizing the structure of a complex of proteins, together known as GM:PP1. That complex controls the balance between storing glucose in the form of a larger "glycogen" molecule and breaking glycogen down into glucose. GM:PP1 accomplishes the latter by turning on an enzyme called glycogen phosphorylase.

Peti's idea is to figure out how a drug could inhibit GM:PP1's recognition of glycogen phosphorylase so that it doesn't break down glycogen into glucose so readily. Peti already knows where he wants to look on the proteins to try the idea and has developed a means of screening drugs that might interact with those areas.

Success with any of the three approaches is hardly guaranteed, but if there is a chance he can save anyone else from the kind of difficulty his grandmother endured, Peti is eager to try. ❖

NIH awards URI pharmacy professor \$1.3M grant to fight cancer with nanoparticles

KINGSTON — The National Institutes of Health have awarded a University of Rhode Island pharmacy professor a \$1.3 million grant to further study a new class of inorganic nanoparticles that target primary cancer, and help control the disease's spread (metastases) and recurrence.

WEI LU, assistant professor of biomedical and pharmaceutical sciences in the College of Pharmacy, has discovered in his preliminary research that hollow copper sulfide nanoparticles are effective in delivering chemotherapy and heat through a laser that can burn the tumor.

The Kingston resident will be using the four-year NIH grant to further his laboratory study with a focus on breast cancer, the second most frequently diagnosed malignancy in women worldwide.

"We are developing a novel cancer therapeutic technology that has several innovative features: biodegradability, multimodality and simplicity," said Lu, who is teaming with Pharmacy Professor Bingfang Yan, a specialist in genetic and environmental factors that combine to regulate the expression of

genes involved in drug response and the cellular switches related to tumor formation.

"One nanoparticle can carry hundreds or even thousands of drug molecules to a target like a tumor cell," Lu said.

He wants to enhance photothermal ablation therapy, a process that uses lasers in cancer treatment.

"As is the case with surgical removal of a tumor, getting all of the cancer is critical," Lu said. "The new nanoparticles provide a three-way punch to the tumor: a more widespread ability in a tumor to distribute heat and burn the tumor, a more efficient and comprehensive way to deliver chemotherapy, and better use of heat to activate the chemotherapeutic agents and immunotherapeutic agents. The new nanotechnology offers promise in tumor eradication.

"Such nanoparticles are introduced intravenously and are absorbed into a tumor," Lu said. "This study is using near-infrared laser light instead of ultraviolet light or visible light because it penetrates tumor tissue better and has much lower side effects. In addition, these particles are readily



URI PHOTO BY JOE GILILIN

Wei Lu, assistant professor of biomedical and pharmaceutical sciences in URI's College of Pharmacy, in his lab conducting research on novel nanoparticles to battle metastatic breast cancer.

degradable in the body, minimizing potential organ toxicity."

Lu, who came to the University in 2010, said he could not have competed for the NIH award if it weren't for the support of the Idea Network of Biomedical Research Excellence, a \$45 million initiative funded by NIH and headed by URI to increase research capacity among biomedical faculty in Rhode Island. ❖