Researcher examines immunology in kidneys

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University of Virginia undergraduate researcher Kristen Whalen is exploring kidney cells to see if they can protect themselves, which could be a breakthrough in assisting kidneys in surviving injury and the side effects of treatments for diseases elsewhere in the body.

Whalen, 21, of Suffolk, a fourth-year biology major, received a Harrison Undergraduate Research Grant to explore the mechanisms of acute kidney injury, specifically the role of "programmed death 1," or PD-1, and PD-1 ligands, cell surface molecules that interact with PD-1 on tubular epithelial cells.

"We are investigating the mechanisms in which kidney cells interact with immune system cells," Whelan said. "Once we figure out the specific mechanisms, we hope to manipulate these interactions to protect the kidney cells from acute kidney injury."

Acute kidney injury is a common complication, affecting about one in five hospital patients. It often increases their length of stay, morbidity and mortality. There are currently no FDA-approved drugs that prevent acute kidney injury. Her lab's long-term goal is to develop novel therapeutic agents that prevent and treat the condition.

The Harrison Undergraduate Research Awards program funds undergraduate research projects for one year. Approximately 40 awards of up to $3,000 each are granted on a competitive basis to first-, second- and third-year undergraduate students. Students who receive the awards work closely with a faculty mentor on their research.

"Our lab hypothesizes that these cell surface proteins protect the kidney from toxic drugs and a lack of oxygen by sending out pro-survival signals into tubular epithelial cells of the kidney," Whalen said. "If PD-1 and PD-1 ligands provide kidney cells with pro-survival signals, this would open up new lines of investigation into different ways to promote this pathway in vivo to protect against acute kidney injury."

Whalen's faculty mentor, Gilbert R. Kinsey, an assistant professor in the School of Medicine's Division of Nephrology and the Center for Immunity, Inflammation and Regenerative Medicine, said the laboratory identified a protein, PD-L1, that plays a protective role in kidney injury.

"The way the PD-L1 works to protect the kidney is currently unknown and forms the basis of Kristen's project," Kinsey said. "We know that kidney cells express PD-L1 at a low level under normal conditions and that they up-regulate PD-L1 expression during stress. Kristen is working with Kasia Jobin, a research assistant in the lab, to engineer kidney cells that express different amounts of PD-L1 on their surface – none, intermediate and very high levels of PD-L1 – so that we can investigate the differences in these cells' responses to the types of stress that lead to kidney failure."

Whalen's research has practical applications in taking steps to protect kidneys from acute injury or nephrotoxic drugs, such as Cisplatin, used in cancer treatment, and to help in the search to find new therapeutic strategies to prevent patients from developing acute kidney injury.

"Cisplatin is a chemotherapeutic agent that is limited in use due to its destructive side-effects on kidneys," Whalen said. "If the PD-1 pathway could be induced in vivo, kidney damage could be limited in people taking Cisplatin as a cancer therapy."

But, as with much scientific research, the results have not been as clear

as she had hoped.

"I have become unsure of the role that PD-1 plays in the kidney," Whalen said. "While we originally hypothesized PD-1 is protective when up-regulated, recent results have proven the opposite. Although we are certain that PD-1 is an important player in acute kidney injury, we need to determine its exact role."

The lab is also working to understand what PD-1 does to immune cells that accumulate in the kidney during acute kidney injury.

"We know that PD-1 on immune cells is important to help the kidney resist acute kidney injury, but the way this works is currently unknown," Kinsey said.

"In order to determine the pathway that best protects the kidney from damage, more detailed experiments regarding the connection of PD-1 and inflammation are necessary," she said.

Whelan works 10 to 15 hours a week in the lab, in addition to a 12-credit courseload and community service. But the research has expanded Whalen's knowledge of the field.

"I have learned a lot about kidney function and structure, which provided necessary background for my project," Whalen said. "Beyond this, I now have an intricate understanding of the immunologic characteristics of the kidney, such as key cell markers and cell-cell interactions. I have also learned how to perform important laboratory techniques such as polymerase chain reaction, enzyme-linked immunosorbent assay, and flow cytometry."

Kinsey said, "She has learned numerous techniques, including primary and immortalized cell culture, in vitro toxicity assays, microscopic

analysis of hematoxylin and eosin stained kidney sections and generation of stable cell lines."

Whalen said she became fascinated with immunology after taking an Introduction to Immunology with David Kittlesen, a lecturer in the Department of Biology as a second-year student.

"Kidney immunology was especially appealing to me because of its complexity," she said. "I wanted to expand my knowledge of nephrology and immunology with this project."

Whalen's academic adviser, George Bloom, recommended that she pursue independent research.

"I could receive credit for my major, while working on a research project alongside a knowledgeable mentor," Whalen said. "I was able to conduct research in the School of Medicine because I reached out to principal investigators whose research interests aligned with my own."

Whalen, a member of Alpha Phi sorority, an Alternative Spring Break participant, a Madison House medical volunteer and sports volunteer and Physicians for Peace President, and Membership Chair of Order of Omega, plans a career in medicine and says the research will help her with her further education.

"I have developed analytical and problem-solving skills that are necessary in the medical field," she said. "I have also learned the value of perseverance. Even though research is oftentimes slow, frustrating and unpredictable, it is important to not get discouraged. At first, I would get upset if an experiment did not produce the results I expected, but I learned to be flexible and open-minded."

Provided by University of Virginia