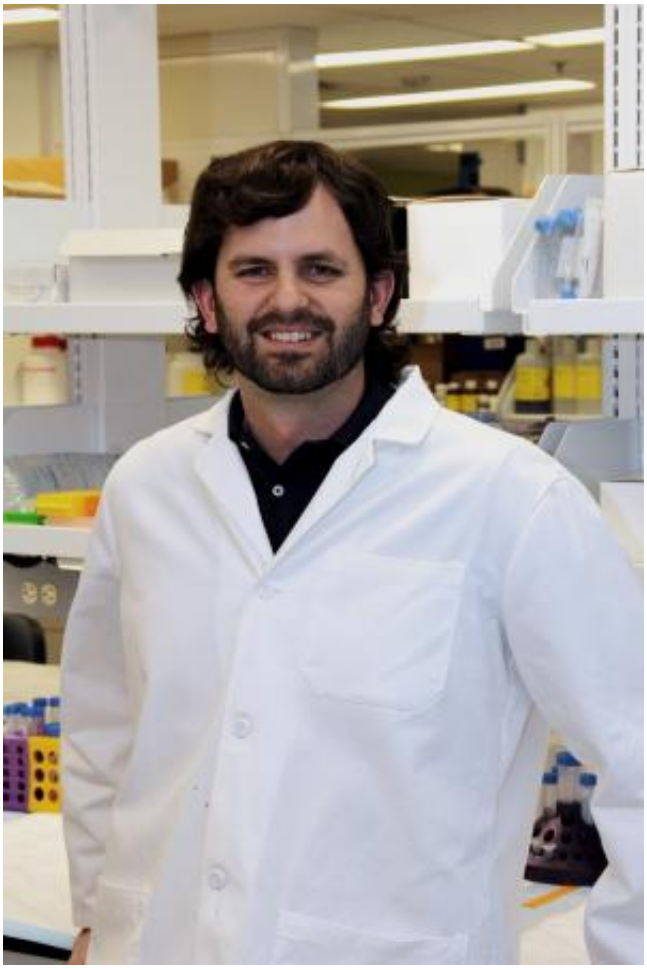
Doctoral student develops a new cross-disciplinary therapy for pancreatic cancer

May 9 2014, by John Wallace



David Durrant, doctoral candidate in the Department of Biochemistry and Molecular Biology

(Medical Xpress)—David Durrant is a doctoral candidate in the

Department of Biochemistry and Molecular Biology at the Virginia Commonwealth University School of Medicine. He conducts research in the lab of Rakesh Kukreja, Ph.D., Eric Lipman Professor in Cardiology at the VCU Pauley Heart Center and a member of the Developmental Therapeutics research program at VCU Massey Cancer Center. While Kukreja is renowned in the field of cardiology, Durrant's focus is on cancer. With Kukreja's guidance, he is making significant progress testing a new combination therapy for pancreatic cancer, and many in the field of pharmacology are taking notice.

The novel therapy combines the widely used chemotherapy agent doxorubicin with an experimental drug known as BEZ235. Durrant presented his research at the American Society for Pharmacology and Experimental Therapeutics (ASPET) conference in April in San Diego, and he has also been awarded a travel grant to attend the World Congress of Basic and Clinical Pharmacology (WCP) in Cape Town, South Africa in July.

Below, Durrant discusses his research, his upcoming travels and how he got into the field of cancer research.

Working in the lab of a cardiologist, how did you get the idea to combine these two drugs to treat cancer?

Doxorubicin has been used to treat a variety of cancers for quite some time. However, shortly after it was introduced it became apparent that it had the potential to damage cardiac tissue. Dr. Kukreja's research involves finding new ways to prevent heart damage from cancer therapies, and he has studied the effects of doxorubicin. Unfortunately, tumors often develop a resistance to doxorubicin, and the benefits of increasing the dosage are outweighed by the potential for heart damage.

Cancer cells often initiate several key survival mechanisms to counteract the deadly effects of doxorubicin. These mechanisms are carried out through signaling pathways, which are groups of molecules that work together to control cellular functions. When exposed to doxorubicin, cancer cells activate the PI3K/AKT/mTOR signaling pathway, which has been shown to promote cell growth and survival. Additionally, proteins known as ATP-binding cassette transporters literally pump doxorubicin out of the cancer cells.

In 2006, a drug named BEZ235 was the first PI3K inhibitor to enter clinical trials. BEZ235 works by blocking signaling through the PI3K/AKT/mTOR pathway. When I first entered the Ph.D. program, Dr. Kukreja wanted to study different kinase inhibitors, like BEZ235, in combination with doxorubicin. While we knew there was the possibility for heart damage, we thought it might be possible to make doxorubicin more effective.

What kind of results are you seeing?

So far, we've tested the therapy on human pancreatic cancer cells grown in the lab and in some basic animal models. The results have been very encouraging. The combination of doxorubicin and BEZ235 caused significantly more cancer cell death than treatment with doxorubicin alone. Not only did we find that the cells were undergoing apoptosis, a form of cell suicide, the results showed that there was a significantly higher amount of doxorubicin in the cancer cells. These results were surprising because they demonstrated that, in addition to blocking survival mechanisms through the PI3K/AKT/mTOR pathway, BEZ235 was disrupting the cell's ability to get rid of the doxorubicin.

Why did you decide to focus on pancreatic cancer?

Originally, we were working with breast cancer since doxorubicin is such a widely used treatment. We actually started looking into pancreatic cancer after the death of Steve Jobs. Sadly, pancreatic cancer has the lowest overall survival rate of all major cancers while being the fourth-leading cause of cancer death. Because most cases are diagnosed in later stages, it is often impossible to surgically remove the entire tumor. There have been very few improvements in patient outcomes in the past few decades, so there is a major need for new therapies and treatment options.

What do you see as the next steps?

I'm really hoping we will be able to translate our findings to a clinical trial and potentially bring a new therapy to pancreatic cancer patients. We will continue to perform experiments using cell lines to document how the therapy works. We will also develop more advanced animal models to better test the therapy's effectiveness. If the results are promising enough, I'm hopeful that we can find a clinical partner and start a phase 1 trial. Since doxorubicin is already approved for the treatment of a variety of cancers and BEZ235 is currently being tested in clinical trials, I'm optimistic that we could get the trial approved if our experiments are successful enough.

What most excites you about your upcoming travels?

I've been to a few conferences already, and the most interesting part for me is always meeting new people and being able to exchange ideas. These events are amazing opportunities to learn about cutting-edge research in a variety of fields.

WCP in South Africa is a very prestigious conference that only happens every four years. I'm extremely honored to take part in it. Dr. Kukreja

encouraged me to apply for the travel grant, and I was shocked to receive it. Honestly, just traveling to South Africa is something I never thought I would be able to do, so I'm really looking forward to the experience. I can't wait to meet people from all over the world and be exposed to their perspectives.

Where do you see your career taking you, and do you have any advice for students looking to enter the field of cancer research?

As far as what's next for me, I literally ask myself that question every day. I'm not going to rule out any options. I will likely complete at least one postdoctoral fellowship. Ideally, I would like to continue in academic research, preferably in Richmond, but I know that may not be an option since the funding environment is so competitive.

I think those most suited to this type of research have to be naturally curious. It takes a different sort of mind, and it's certainly not for everyone. Those who excel typically have a desire to figure things out and will work through challenges. While the basic knowledge is important, much of the required skills can't be taught in a book. My best advice is to confront challenges by applying yourself and making sure you understand exactly what you're trying to accomplish. Sometimes the most important discoveries are found in analyzing failures.

Provided by Virginia Commonwealth University