News Release

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TTUHSC Researchers Publish Preclinical Data on New Drug Combination to Treat Neuroblastoma

Neuroblastoma is the most common cancer outside of the brain in infants and young children and often fails to respond to therapy. Though it can appear in several areas of the body, it commonly develops as a solid tumor most frequently found in or adjacent to the adrenal glands, which sit atop the kidneys.

Patients diagnosed with high-risk neuroblastoma typically undergo intensive treatments that can include surgery, radiation therapy, chemotherapy and myeloablative chemotherapy, which is chemotherapy followed by a bone marrow or stem cell transplant. Regardless of which treatment is used, the five-year overall survival rate for these young patients is approximately 50%, and 50%-60% will experience a relapse.

To help improve the treatment outcomes for neuroblastoma patients, C. Patrick Reynolds, M.D., Ph.D., director of

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used for various functions in a normal cell, but cancer cells use the protein to help defeat cancer therapy. Some of these cancer cells, including several types of neuroblastoma, have a tendency to overexpress BCL-2 in order to survive and grow.

“The idea is to inhibit those molecules that defeat the chemotherapy with the venetoclax because it specifically targets the BCL-2 molecules,” Reynolds said. “The drug actually worked against lymphomas in adults and was registered and approved for use by the FDA.”

The Reynolds lab had previously worked with drugs from AbbVie that targeted multiple BCL-2 families, but venetoclax targeted very specific BCL-2 molecules without producing some of the toxicities that often occur in patients.

“One of the goals in this study was to find out if venetoclax, which is now in routine use for a type of leukemia and lymphoma, would enhance the fenretinide as we had seen before with similar drugs,” Reynolds said. “And in fact, that was the case.”

Nguyen, an M.D./Ph.D. student who was the study’s lead author, conducted additional cell culture work that demonstrated the fenretinide-venetoclax combination was very effective against the neuroblastoma cells.

Using xenografts, which are cancer cells taken from humans and grown in mice, Nguyen saw that fenretinide produces a significant number of unstable molecules that contain oxygen and easily react with other cell molecules. This process, known as reactive oxygen species, is one way by which fenretinide kills cancer cells.

However, this reaction also upregulated, or activated, a pair of transcription factors, which proteins help to turn on or turn off specific genes by binding to nearby DNA. In this case, the transcription factors were increasing the amount of NOXA. NOXA blocks MCL-1, a protein that can replace BCL-2 and help cancer cells survive. Thus, NOXA is a protein that overcomes a key mechanism of resistance to venetoclax, causing cancer cell death.

“What is happening is we are taking out the BCL-2 in the cell with venetoclax, but the cell defends itself by upregulating MCL-1,” Reynolds said. “Then the fenretinide comes in and triggers the upregulation of NOXA, which in turn takes out the MCL-1. That's why the combination of these drugs was so lethal for the cancer cells and really not that toxic at all for nord ̓ ll for nord ̓ ll ♂ ¯ ḥ