Lay Audience Summary:

Many human cancers are driven by defective genes inside the tumor cells. Some genes might be turned on too high, or overexpressed, and others may be turned off when they should be on. These on/off dials may also be controlled by defective proteins.

We (Dr. Rui Zhao, a structural biologist/biochemist, and Dr. Qinghong Zhang, a cancer/molecular biologist), have found that a protein called CtBP is abnormally overexpressed in several human cancers, including more than 50% of primary lung tumors and 90% of metastatic lung cancer lesions. We have also found frequent CtBP overexpression in breast and head/neck cancer, kidney cancer and melanoma.

CtBP is a protein that turns off expression of many important genes, and it is not expressed in most adult tissues. We have found that when CtBP is overexpressed in cancer cells, it turns off genes that are critical for cell death, which in turn leads to cancer development.

Moreover, we found that reducing CtBP expression in mouse models of human lung cancer started the cell death process and stopped tumors from growing, two hallmarks of a “good thing” in cancer treatment.

Based on these findings, we hypothesize that an anticancer agent that decreases CtBP’s function could be an attractive new therapy for many cancer types, likely with minimal side effects because the therapy will not affect normal cells (which don’t express CtBP). The novel agent would probably be a class of drug called a “small molecule inhibitor,” which goes inside the cell to switch on or off a specific protein or gene.

CtBP has never been a target for clinical treatment. We have done detailed biochemical and structural studies that show it is possible to use small molecule inhibitors to turn off CtBP. Our goal is to lay the foundation for developing a novel agent that will inhibit both tumor cell proliferation (multiplying) and metastasis (spread beyond the site of origin) while sparing normal cells.

We are experts in using high-tech tools, including rational drug design and complementary high throughput screening, to identify small molecule inhibitors that work on those targets. With funding from GAC and AMC Cancer Fund, we will use these tools from multiple angles to identify small molecule inihibitors of the CtPB complex.

The data we generate from this work will enable us to apply for a multi-PI grant from NIH to further identify and develop anti-CtBP drugs that can potentially serve as efficient anticancer agents.