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News Release

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TTUHSC Researcher Receives NIH Grant to Study Vulnerabilities in Specific Cancer Types

The National Cancer Institute, part of the National Institutes of Health, recently awarded a five-year, $ $1.9 million grant to C. Patrick Reynolds, M.D., Ph.D., director for the School of Medicine Cancer Center at the Texas Tech University Health Sciences Center. The grant, "Targeting Shared Vulnerabilities in Alternate Telomere Lengthening (ALT) Cancers," will allow Reynolds and his team to investigate their theory that certain types of cancers share common mechanisms that help them resist standard therapies, and certain vulnerabilities that may be exploited for therapy.

To survive and multiply, cancer cells must maintain their telomeres, which are DNA strands located at the end of their chromosomes. If they are not maintained by telomere maintenance mechanisms (TMM), telomeres will begin to erode and the cancer cell will die. The most common TMM uses a cell enzyme known as telomerase that has the ability to add DNA to the ends of chromosomes. However, there are some cancers that continue to grow by using a non-telomerase mechanism known as alternate lengthening of telomeres (ALT). These are known as ALT positive, or ALT+ cancers.

ALT+ tumors contain specific and sensitive ALT biomarkers known as C-circles. By employing the C-circle assay, Reynolds and his team have evaluated a variety of childhood and adult cancers and found 11 whose histology (microscopic tissue structure) with ALT-positivity ranges from 10% to 74%, and five other cancers with an ALT+ histology between 1% and 5%.

"ALT cancers have a poor clinical outcome," Reynolds said. "Regardless of their histology, ALT+ cancer cell lines manifest high resistance to DNA damaging agents relative to telomerase-positive cancers. ALT cancers have dysfunctional telomeres, which provides unique vulnerabilities that can serve as novel therapeutic targets."

The Reynolds team recently demonstrated that the enzyme ATM kinase is a driver of ALT. They also found that ALT+ cancers are addicted to ATM, which is a protein kinase that adds a group of phosphates to several other key proteins. This in turn triggers activation of the cell's DNA damage checkpoint, which leads to cell cycle arrest, DNA repair or cell death. They also demonstrated that this process can be reversed with a clinical-stage ATM inhibitor known as AZD0156.

For this study, the Reynolds team will evaluate a large panel of patient-derived cell lines (PDCLs) and patient-derived xenografts (PDXs) from ALT+ cancers. This will advance their overall study of ALT+ cancer biology, increase the chances of identifying and validating novel therapeutic targets, and enable the comparison of ALT+ cancers across a range of histologies.

They also will compare the ALT+ results to those of several PDCLs and PDXs that are positive for telemerase. These include pediatric cancers such as neuroblastoma, rhabdomyosarcoma and osteosarcoma, and adult cancers such as triple negative breast cancer, colon cancer and soft tissue sarcomas.

Using this unique panel of patient-derived models, Reynolds said his team will demonstrate that ATM kinase activation resulting from telomere dysfunction is a common feature of ALT+ cancers, regardless of histology.

To survive having high ATM, cancer cells must inactivate a tumor protein known as p53. Reynolds said many ALT+ cancers have mutant p53. This is an inherent vulnerability for ALT cancers because high ATM activation required by ALT cells makes ALT cancer cells highly sensitive to active p53.

“We are focusing on further development of ATM kinase inhibitors for ALT+ cancers, as well as leveraging the ATM kinase activation that ALT cancers are addicted to, which requires that they have inactivated p53, often by mutation,” Reynolds explained. “Thus, a major component of the grant is testing the ability of the p53 reactivating drug APR-246 against ALT cancers, and then developing optimal drug combinations to use with APR-246. “

For cell lines and xenografts of selected histologies, Reynolds said his team will evaluate whether or not AZD1390 can reverse resistance to irinotecan. They hypothesize that ALT+ cancers tolerate ATM activation due to dysfunctional p53, and that p53 restored to functionality by APR-246 will be activated by ATM.

“We will demonstrate that APR-246, alone or in combination with irinotecan, especially as the new nanoliposomal irinotecan formulation, will be selectively cytotoxic to ALT+ relative to telomerase+ cancer cell lines and xenografts,” Reynolds said. “This project will demonstrate that the unique vulnerability conferred by the dependence of ALT+ cancers cells on ATM kinase is common to ALT+ cancers across a range of cancer histologies found in adults and children.”

Reynolds said data from this project will aid in the development of clinical trials seeking to enroll patients with ALT+ cancers that are readily identifiable with a robust tumor biomarker.

“We hypothesize that ALT+ cancers have common mechanisms of resistance to chemotherapy, and also common sensitivity to novel drugs,” Reynolds added. “Therefore, we will test both standard drugs and novel investigational drugs against ALT+ cancer models to inform future clinical trials.”

- 30 -