Targeting Protein Homeostasis Holds Potential to Treat Solid Tumors and Blood Cancers

Burlingame, Calif. - The success of proteasome inhibitors such as VELCADE® (bortezomib) and Kyprolis® (carfilzomib) for the treatment of multiple myeloma has shown that protein homeostasis, which is how cells maintain a balance of protein synthesis and degradation, is a valid pathway for developing drugs to treat cancer. However, attacking the proteasome in solid tumors has not worked to date. New research published in the journals Cancer Cell and the Journal of Medicinal Chemistry highlights a novel approach to target protein homeostasis by inhibiting the protein p97 in both solid tumors and blood cancers. Preclinical data to be presented at the 57th ASH Annual Meeting & Exposition show specifically that targeting p97 induces disease regression in the blood cancer acute myeloid leukemia (AML).

Cancer cells often produce an overabundance of proteins, particularly misfolded proteins that are toxic to cells. Therefore, cancer cells rely upon the ubiquitin proteasome system (UPS), which is responsible in both healthy and tumor cells for eliminating surplus, misfolded and mutant proteins. The hyper-active UPS in tumor cells is critical for their survival. Without it, toxic proteins accumulate, and the tumor cells die.

p97 is a key mediator of several protein homeostasis processes. Among them, p97 mediates the extraction of cellular proteins destined for destruction by the UPS from organelles, chromatin and protein complexes. Scientists from Cleave Biosciences published in the Journal of Medicinal Chemistry the discovery and optimization of an orally bioavailable small molecule called CB-5083 that inhibits p97. In the paper published in Cancer Cell, the same researchers demonstrated that CB-5083 had antitumor activity in cancer cell lines and in various mouse tumor models, indicating its potential as a drug candidate.

“Researchers over the years have identified multiple inhibitors of p97, but until now those compounds have not successfully inhibited tumor growth in vivo,” said Mark Rolfe, Ph.D., senior author on the paper and President and Chief Scientific Officer at Cleave Biosciences. “If we can successfully translate this to treat both solid tumors and blood cancers, we could have a very powerful strategy for treating patients with these life-threatening diseases.”

CB-5083 has the potential to provide a completely new way to combat solid tumors such as colon, lung or breast cancer, as well as a number of different blood cancers. Despite the success of the proteasome inhibitors in treating multiple myeloma, the majority of other blood cancers are not responsive to such agents. AML, the most common acute leukemia in adults, is an aggressive disease with very poor outcomes – only a quarter of patients survive five years. However, the treatment paradigm has remained relatively unchanged for over 40 years. Targeting protein homeostasis with CB-5083 has the potential to achieve clinical benefit in patients with AML that historically have had few options.

In data generated from a collaboration between scientists at Cleave Biosciences, the University of Southern California, the University of Texas, San Antonio, and the Cleveland Clinic that will be presented
at ASH, CB-5083 demonstrated its potential in both established AML cell lines as well as primary AML cells. Treatment with CB-5083 in seven unique AML cell lines and 10 specimens of AML cells derived directly from patients demonstrated reduced cell line survival and increased cell death. In addition, CB-5083 was highly active in three different AML cell lines that are resistant to conventional AML treatments. In vivo, treatment with CB-5083 in two different mouse models was well tolerated and induced disease regression.

“It is important to note that in AML, both established cell lines as well as cells that came directly from patients, also known as primary cells, showed similar sensitivity to CB-5083,” noted Dr. Rolfe. “Typically, primary cells show reduced sensitivity to both conventional and experimental drugs in AML, indicating that CB-5083 could be a powerful tool against AML, especially in patients who have relapsed or refractory disease.”

Cleave Biosciences is studying CB-5083 in a Phase 1 trial in patients with advanced solid tumors with no available standard of care. Additionally, CB-5083 has been granted Orphan Drug Designation by the U.S. Food and Drug Administration for the treatment of multiple myeloma.

About Cleave Biosciences
Biopharmaceutical company Cleave Biosciences is a pioneer in the discovery and development of drugs that target protein homeostasis systems and have the potential to transform the treatment of people with difficult to treat solid tumors and hematologic malignancies. The company is privately held and located in Burlingame, California. For additional information, visit www.cleavebio.com.

Publication Citations

# # #