Abstract:

#800 Synergistic Effects of CBL0137 and Gemcitabine Against Non-Small Cell Lung and Pancreatic Cancer Xenografts

Catherine Burkhart1, Rachael Kohn2, Loretta Gawron3, Brittany Walker1, David Meyer4, Katerina Gurova3, Elizabeth Repasky3, Andrei Urmal1,4 and Andrei Gudkov3,4
1Buffalo Biolabs, LLC (Buffalo, NY, USA), 2Cleveland BioLabs, Inc (Buffalo, NY, USA), 3Roswell Park Cancer Institute (Buffalo, NY, USA), 4Incuron, LLC (Buffalo, NY, USA)

CBL0137 represents a novel class of small molecules that simultaneously activate p53 and inhibit cancer-associated stress response pathways, such as NF-κB and HIF-1α. The effects of CBL0137, culminating in tumor cell death, are mediated by the inhibition of FACT, a transcription and replication factor complex composed of SSRP1 and SPT16 subunits, that is involved in the transcription of genes with highly ordered chromatin structure, replication, and mitosis. FACT is expressed during early embryogenesis and in undifferentiated progenitors and stem cells of adult tissues while protein levels of both FACT subunits are almost undetectable in differentiated cells and tissues. FACT is expressed in several tumor types compared to equivalent normal tissues. In particular, SSRP1 is expressed in a high proportion of lung and pancreatic cancers (~45-63%). FACT positive tumors are associated with an aggressive malignant phenotype (high grade, metastatic disease, worse overall survival). Therefore, FACT represents a potentially important target for cancer therapy. We investigated the effect of CBL0137 and its combination with gemcitabine, a nucleoside analog used in treatment of non-small lung cancer (NSCLC) and pancreatic ductal adenocarcinoma (PDA). We found that CBL0137 had significant antitumor activity against a H1975 NSCLC xenograft model (89.6% growth inhibition) as well as a patient-derived PDA (PDA#46) model (70.4% growth inhibition). Furthermore, CBL0137 acted synergistically with gemcitabine against both tumor types as evidenced by increased median survival time compared to each drug administered as a single agent (increase in survival time: H1975: +47 days combination vs 24 days CBL0137 only, 32.5 days gemcitabine only; PDA: +42 days combination vs 28 days CBL0137 only, 30.5 days gemcitabine only). Preliminary investigation into the mechanism underlying the synergy of this combination suggest that CBL0137 may enhance gemcitabine activity in part by abrogating the expression of modulators of gemcitabine response, such as cytidine deaminase and ribonucleotide reductase. Together, these data indicate that CBL0137 may provide a clinical benefit for the treatment of both NSCLC and PDA when combined with standard agent gemcitabine.

Methods:

• Efficacy studies: H1975 and A549 human NSCLC cell lines were obtained from ATCC. All animal experiments were conducted in accordance with an approved IACUC protocol. Patient derived tumors were obtained under an approved IRB protocol. For PDA studies, 5 mice per experimental group were inoculated with a cell suspension (5 x 106 cells) mixed 1:1 with Matrigel. For both sets of studies, treatment commenced when tumors reached 50-200 mm3.

• Efficacy studies: Tumor volumes were normalized to Day 1 of treatment to follow fold tumor growth is determined by expressing the tumor volume on Day X relative to Day 1. Error bars represent the standard error of the means. EOT end of treatment.

• Efficacy studies: Dose-response studies of CBL0137 ± Gemcitabine on NSCLC and PDA xenografts derived from human cancer cell lines and patient-derived tumors. CBL0137 acts synergetically with gemcitabine with a dramatic increase in the time required for tumor growth to resume following completion of treatment. CBL0137 may enhance the antitumor activity of gemcitabine by downregulating genes/proteins involved in controlling gemcitabine sensitivity/resistance (e.g. cytidine deaminase, ribonucleotide reductase subunits).

Conclusions:

• FACT represents a potential new target for the treatment of NSCLC and pancreatic cancer due to higher levels in tumor than corresponding normal tissues.

• CBL0137, which targets FACT, has demonstrated antitumor activity against both xenografts derived from human cancer cell lines and patient-derived tumor xenografts. CBL0137 may enhance the antitumor activity of gemcitabine by downregulating genes/proteins involved in controlling gemcitabine sensitivity/resistance (e.g. cytidine deaminase, ribonucleotide reductase subunits).

Acknowledgments:

This work was funded by an NCI SBIR Phase II Contract R44CA169424 (2014-2017), NCI Phase I STRP R43CA195657-01A1 (KAG, CAB).

References: