Abstract:
Primary hepatocellular carcinoma (HCC) is the 6th most common malignancy diagnosed worldwide with an incidence that continues to rise. Even with the use of the current standard of care drug sorafenib, survival of patients remains at ~10-11 months and sorafenib toxicity results in dose interruptions and delays. Therefore, tolerable, effective therapies against HCC are greatly needed. CBL0137 represents a novel class of small molecules that simultaneously activate p30 and inhibit cancer-associated stress response pathways, such as NF-κB and HSF-1, and has demonstrated broad antitumor activity against pre-clinical tumor models. The effects of CBL0137 are mediated by the inhibition of the NF-κB activity. Furthermore, the combination of CBL0137 and sorafenib has potent antitumor activity against two HCC xenograft models. Treatment of tumor bearing mice intravenously with CBL0137, 10 mg/kg, every 4 days resulted in ~48-57% tumor growth inhibition in both models, including tumor regression in 60-80% of tumors during the course of treatment. Furthermore, combination of suboptimal doses of CBL0137 with sorafenib had greater efficacy compared to either drug alone (tumor growth inhibition: HepG2: 87.4% combination vs 74.4% CBL0137 only (P<0.016), 75.7% sorafenib only (P=0.0006)). HepB-2: 76.7% combination vs 32.2% CBL0137 only (P<0.003). Although the mechanism resulting in the combination of 51.4% sorafenib only (P=0.020). Although the mechanism resulting in the combination of 51.4% sorafenib only (P=0.020). Due to the unknown, in vitro analysis of markers of CBL0137 and sorafenib activity revealed that both drugs caused a marked decrease in the basal and induced expression of NF-κB target genes (IL-8 and TNF). Furthermore, the combination of CBL0137 and sorafenib almost completely abolished the expression of these genes in both HCC cell lines, suggesting that the combination effect may be mediated part in part by inhibition of the NF-κB pathway. Together, these data indicate that CBL0137 may provide a clinical benefit for the treatment of HCC both alone and in combination with sorafenib.

Methods:
- **SSRP1 and Spt16 levels in HCC**: Data were extracted from publically available databases using Oncomine (Compendia BioScience, Inc).
- **Efficacy Studies**: HepG2 and Hep3B human HCC cell lines were obtained from ATCC. All animal experiments were performed using an approved IACUC protocol. In these studies, athymic nude mice (nu/nu) b10-12 mice in each group were inoculated with ~2x2x2 mm non-necrotic pieces of HepG2 or Hep3B tumor pieces. When tumors reached 50-100 mm3 (n=9-10 mice/group were inoculated in each flank with ~2x2x2 mm non-necrotic pieces of HepG2 or Hep3B tumor pieces. The effects of CBL0137 on the growth of HepG2 and Hep3B HCC xenograft models. Treatment of tumor-bearing mice intravenously with CBL0137, 10 mg/kg, every 4 days resulted in ~48-57% tumor growth inhibition in both models, including tumor regression in 60-80% of tumors during the course of treatment. Comparisons were made across groups using a GraphPad Prism 6.

Conclusions:
- **FACT** represents a potential new target for the treatment of HCC due to higher levels in tumor than normal liver tissue.
- **CBL0137**, which targets FACT, has potent antitumor activity against two independent HCC xenograft models of diverse phenotypes (HepG2, p53wt, normal levels NF-κB; HepB-2 p53null, constitutively active NF-κB, HepB-2 sensitive).
- Sub-optimal doses of CBL0137 act synergistically with sorafenib to enhance the antitumor effect against HCC tumors compared to either drug administered as monotherapy.
- The synergistic effect between CBL0137 and sorafenib appears to be, in part, due to the engagement of the NF-κB pathway.

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References:

Cleveland BioLabs