cells) and was reversed by tyrosine phosphatase inhibitors orthovanadate and dephostatin. In addition, TLK199 potentiated the granulocytic cytodifferentiation of HL60 cells induced by all trans retinoic acid. KO mice for GSTpi had higher myeloproliferative indices and circulating white blood cells than wild type animals. TLK199 was also able to stimulate myeloproliferation in wild type mice but not in GSTpi KO animals. The mechanism of action of GSTpi and TLK199 in myeloproliferation is still unknown. We have observed that GST* interacts with JAK1 and JAK2, two proteins involved and required for normal hematopoiesis. We are currently studying the effect of cytokines (G-CSF and GM-CSF) and TLK199 on the interaction between JAK proteins and GSTpi and the involvement of this enzyme in cytokine signaling pathways. Taken together, these results show a potential role of GST* expression and modulation in myeloproliferation and myelodifferentiation.

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Phase I and pharmacokinetic study of LY293111, an orally available small molecule known to be an LTB4 receptor antagonist, 5-lipoxygenase inhibitor and peroxisome proliferator activated receptor-gamma agonist (PPAR gamma)

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Purpose: LY293111 has antineoplastic activity in a variety of preclinical models. LY293111 was demonstrated to have activity consistent with PPARg agonism in the ZDF rat diabetes model (ED50 for glucose reduction = 33 mg/kg, Css = 0.61μM). The EC50 for adipocyte differentiation in 3T3L1 cells was 0.5 μM. These values are consistent with concentrations required to inhibit tumor growth *in vivo*. We studied the tolerability and pharmacokinetics of LY293111 administered continuously, PO, twice daily (BID) for repeat cycles of 21 days.
Patients and Methods: Thirty-three patients with advanced solid tumors have been treated at five dose levels (200 to 800 mg BID) for a total of 89 cycles.
Results: The most common toxicities were diarrhea, abdominal pain and nausea. One patient at 600 mg BID (n=6) and 2 at 800 mg BID (n=9), experienced grade 3 diarrhea. At 600 mg BID, 1 patient experienced grade 1 abdominal pain and 1 patient experienced grade 1 nausea. At 800 mg BID, 1 patient had grade 1/2 abdominal pain and 3 had grade 1/2 nausea. Two patients with progressive chondrosarcoma and melanoma attained stable disease lasting approximately 16 and 8 cycles, respectively. Dose reductions/delays were infrequent. Increases in steady-state Cpeak and area-under-the-curve 0-10 hours were roughly dose-proportional over this 4-fold dose range. The interpatient variability in PK parameters was approximately 60% (CV %). Steady-state plasma levels in patients at 600 mg BID and above exceed levels in:i) rats treated with the ED50 for glucose reduction in the ZDF model and ii) the efficacious dose in the mouse tumor xenograft model.
Conclusions: LY293111 can be safely administered by continuous oral therapy. The toxicities observed to date are mild and manageable. Steady-state concentrations in humans exceed relevant levels observed in preclinical models. LY293111 will be evaluated in future Phase II studies.

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Phase I and pharmacokinetic trial of ILY293111 in combination with gemcitabine

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LY293111 is an orally available small molecule known to be an LTB4 receptor antagonist, 5-lipoxygenase inhibitor and an agonist of the peroxisome proliferator activated receptor-gamma (PPAR-g). In a single agent dose escalation trial, the maximally tolerated dose (MTD) of LY293111 was determined to be 600 mg BID with a dose limiting toxicity of Gr. 3 diarrhea(1). Combinations of LY293111 and gemcitabine (Gem) have activity in preclinical models of non-small cell lung and pancreatic cancers. We performed a trial of LY293111 in combination with Gem in which LY293111 (100 to 800 mg) was administered continuously, PO, twice daily (BID) in combination with a fixed dose of Gem (1000 mg/m^2 IV, 3 of 4 weeks) for repeat cycles of 28 days. 35 patients with a range of solid tumors were accrued to five dose levels of LY293111. Median age and ECOG performance status were 59 (24-83) and 1, respectively. All but 1 patient had received prior chemotherapy (16 with prior RT as well). The median number of treatment cycles was 2 (range 1 to 12). Toxicity was mild to moderate in general, and included diarrhea, fatigue, myalgias and nausea. One patient treated at 100mg BID experienced Gr. 3 elevation of transaminases: dose-modification of Gem eliminated this problem; and the patient went on to receive 12 cycles of therapy. LY293111-related Gr. 3 toxicity (diarrhea) was observed in one patient at the 800 mg BID dose. Sporadic myelosuppression was unrelated to LY293111 dose. Mild to moderate edema typical of Gem was cumulative. Four patients have had a partial response: 1 with pancreatic cancer previously treated with Gem, 1 with pancreatic cancer previously treated with 5-FU and radiation, 1 with non small cell lung cancer (1 prior regimen), and 1 with anaplastic thyroid carcinoma (2 prior regimens). Preliminary data suggest that Gem does not interact with the pharmacokinetics of LY293111. Analysis of PMN's for induction of genes regulated by PPAR-g is planned. Thus, full dose Gem can be safely combined with the single-agent MTD of LY293111. Phase II studies in combination with Gem will be conducted using a dose of 600 mg/bid. (1)See Abstract entitled -Phase I and Pharmacokinetic Study of LY293111, an orally available small molecule known to be an LTB4 receptor antagonist, 5-lipoxygenase inhibitor and peroxisome proliferator activated receptor-gamma agonist (PPAR g) [Budman et al., 14th EORTC-NCI-AACR submitted abstract].

New drug targets

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Telomestatin has a mixed type of binding modes with G-quadruplexes: intercalation between G-tetrads and end-stacking in the loop regions of intramolecular G-quadruplexes

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Telomestatin is the first natural product shown to be a telomerase inhibitor by virtue of its ability to interact quite specifically and strongly with the human telomeric intramolecular G-quadruplex (Kim et al., J. Am. Chem. Soc., 2002, 124, 2098). Previously, using a simulated annealing docking approach, we found that the minimized binding energy was found to be lower when two telomestatins were bound per one G-quadruplex than when one telomestatin was bound. Now we provide the experimental evidence for the stoichiometry of the reaction between telomestatin and the human telomeric intramolecular G-quadruplex structure. Further we provide evidence for the mixed binding modes of telomestatin in this complex. A novel modified filtration method was used to determine the stoichiometry of the reaction for telomestatin binding to the G-quadruplex structure which is formed with an oligomer containing four repeats of human telomeric sequence. When telomestatin was titrated against 0.2 mM of the oligomer, 0.4 mM of telomestatin was needed to saturate all the binding sites, while 0.6 mM of telomestatin was needed to saturate the oligomer at 0.3 mM concentration. These results are consistent with two telomestatin molecules binding per one human telomeric intramolecular G-quadruplex and this is in good agreement with the results from the aforementioned modeling study. In order to characterize the binding mode(s) of telomestatin in the G-quadruplex-drug complex, the stoichiometry of this reaction was determined using modified G-quadruplex structures, which have either an increased number of bases in the two loop regions or an increased number of G-tetrads. The stoichiometry of the reaction was unchanged regardless of the modifications made to the number of bases at each of the loop regions. However, more telomestatin molecules were needed to saturate the binding sites of mutated G-quadruplexes that have additional G-tetrads in their structures. The stoichiometry of these reactions between telomestatin and G-quadruplexes was found to be 2:1 (for G4 with 3 G-tetrads), 4:1 (for G4 with 4 G-tetrads), and 6:1 (for G4 with 6 G-tetrads). The results of these studies suggest that telomestatin intercalates between G-tetrads of intramolecular G-quadruplex structures as well as binds in the loop regions via end-stacking mode.