and 6 MHI). Following a single dose of E: M C_{max} 1.16 (0.620–1.87) vs 1.28 (0.241–2.35) μg/mL, T_{max} 2 (1–6) vs 6 (2–8) hours, M AUC_{0-inf} 30.9 (21.0−79.5) vs 41.5 (4.71−80.5) μg hr/mL, and M clearance 4.86 (1.89–7.15) vs 3.88 (1.86−31.9) L/hr in the AHF and MHI cohorts respectively. Plasma PB data available for 10 pts (7 AFH and 3 MHI) shows the percent of E bound is 97.3 (96.6−98.2) in AHF vs 97.2 (96.2−98.0) in MHI. Clinical data are available for 22 pts (16 AHF and 6 MHI). One MHI pt discontinued study prior to starting drug and is not included in the safety discussion. Common grade 1–2 adverse events related to E include diarrhea [4 (25%) vs 1 (17%)], nausea [6 (38%) vs 2 (33%)], acneiform rash [3 (19%) vs 2 (33%)], anorexia [4 (25%) vs 1 (17%)] and fatigue [4 (25%) vs 0 (0%)] in the AHF and MHI cohorts respectively. In the AHF cohort, 3 pts (19%) experienced tx related to E, including 1 pt (6%) with grade 3 diarrhea and 2 pts (13%) with grade 3 acneiform rash. No grade 3 related tx have been reported in the MHI cohort. There have been no grade 4 tx or serious adverse events related to E reported in either cohort. Preliminary data suggests that MHI may increase systemic exposure to E with no effect on plasma PB and drug-related tx. Enrollment into the MHI cohort is ongoing. Updated information will be presented.

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Discovery and characterization of a series of Axl kinase inhibitors using the CLIMB process

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Axl is a unique receptor tyrosine kinase, which has been implicated in inhibition of apoptosis, especially through counteraction of the pro-apoptotic activities of E1A, and is emerging as a viable target for a number of human malignancies, both solid and hematological. This protection is believed to operate through the action of Src and PI3K (via the Akt pathway), which are known proto-oncogenes themselves. Expression of Axl and its substrate, Gas6, has been implicated in defense against apoptosis in a variety of tumor subtypes. Overexpression of Axl in cells of the myeloid lineage also leads to a non-insulin dependent diabetes mellitus-like, or Type II diabetes phenotype. For these reasons, it is clear that there is an unfilled need for small molecule inhibitors of Axl kinase in the clinic, and we have set out to create such an entity. We have developed a proprietary drug discovery process, called CLIMB™, which we utilized for the identification of novel Axl modulating compounds with therapeutic potential. In traditional small molecule screening, as many as several million compounds may be tested in order to identify the few that interact selectively with a disease-related protein target. CLIMB™ can achieve similar results by screening as few as several hundred computationally selected compounds. CLIMB™ screening is based on the clustering of representative chemical structures and pharmacophores that embody our large virtual library of nearly 50 million compound structures. A homology model for Axl kinase was built using the known crystal structures for insulin-like growth factor-1 receptor and c-Met tyrosine kinases, and subjected to docking with an expansive virtual library of in-house and commercially available compounds. After passage through a series of in silico filters designed to predict pharmacological and physicochemical parameters, the “most drug-like” candidates with favorable predicted binding energies were selected for further biological and biochemical testing. Several compounds resulting from the computational screen bore significant activity (low micromolar to nanomolar) against recombinant Axl protein in an in vitro assay, validating the effectiveness of the CLIMB™ process in reducing time and cost of early lead identification. These compounds also demonstrate potent cell-based activity in a variety of tumor cell lines and in xenograft animal models, making them promising anti-cancer therapeutic leads.

414 POSTER

Discovery and characterization of a small molecule inhibitor for pim-1 kinase

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The Pim-1 serine/threonine kinase is known to be involved in a number of cytokine signaling pathways as a downstream effector. Once activated, Pim-1 kinase causes progression of the cell cycle, inhibition of apoptosis, and modulation of other signal transduction pathways, including its own. Pim-1 kinase is also shown to effect activation of transcription factors like NFAT, p100, c-Myb, and Pap-1 and inhibition of others such as HP1. Normal expression of Pim-1 kinase is seen in cells of hematopoietic origin, such as fetal liver, thymus, spleen, and bone marrow, additionally expression is also seen in prostate and oral epithelial cells. Pim-1 kinase is believed to be involved in the initiation or progression of malignant transformation leading to malignancies including Burkitt’s lymphoma, prostate cancer, oral cancer, and diffuse large cell lymphomas, among others. We have identified a series of Pim-1 kinase inhibitors, based on a heretofore-unexploited pharmacophore, using our proprietary CLIMB™ drug discovery process. Through the use of CLIMB™, the published Pim-1 kinase crystal structure was used as a substrate for docking of a very large virtual library, composed of in-house and commercially available small molecules, to generate a subset of leads based on calculated binding energies. These leads were then screened using a number of in silico physicochemical and ADMET prediction algorithms to determine “druggable” leads which were most likely to be successful in a biological context. Lead candidates were initially screened using biochemical enzyme-based or cell-based assays. Cell-based activity was determined in Panc-1 (pancreas), A549 (non-small cell lung), and PC-3 (prostate) cancer cell lines. At an initial concentration of 100 micromolar numerous candidates inhibited cell growth by over 60% compared to untreated controls in a preliminary screen. In the Pim-1 in vitro kinase assay two candidates exhibited inhibitory activity with IC_{50} concentrations in the low micromolar range. The lead candidates for pim-1 kinase inhibitors discovered through the CLIMB™ process have shown good biochemical and biological activity, based off of physical screening of less than 100 compounds, chosen from a library of millions, each of which show activity at a considerable level. Based off of the two most promising lead candidates a series of analog candidates are currently being produced to refine inhibitory activity and pharmacokinetic characteristics.

415 POSTER

Discovery and characterization of novel small molecule inhibitors of polo-like kinase-1, using a computational development process

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Polo-like kinases belong to a family of well-conserved kinases found throughout the eukaryotes. In humans, high levels of polo-like kinase-1 (Plk1) have been associated with poor prognosis in numerous cancer types including breast, colon, non-small cell lung cancer, and the difficult-to-treat pancreatic cancer, along with others, and has been validated as a target in these tumor types. Polo-like kinase-1 is a mitotic serine-threonine kinase which plays a very important role in the processes of centrosome separation, spindle formation and sister chromatid segregation. As well, it drives progression through the G2/M checkpoint by virtue of phosphorylation of Cdc25c, leading to an active Cdk1/CyclinB1 complex. RNA interference has shown that disruption of Plk-1 leads to such effects as mitotic arrest, cytokinetic failure and induction of apoptosis. Using our proprietary CLIMB™ drug discovery process, we have identified and synthesized a series of polo-like kinase-1 inhibitors. Using the Cdk1 crystal structure as a backbone, a homology model of polo-like kinase-1 was built and subjected to virtual docking algorithms in the context of a large in-house virtual collection of small molecules from a diversity of sources. Through the employment of several in silico predictors, compounds with strong binding interactions were ranked according to calculated ADMET properties and chemical characteristics (including solubility, partition coefficient, expected permeabilities and physical properties) before any in vitro assays were undertaken. This has allowed us to remove “non-druggable” leads before time and resources are wasted on development of undesirable compounds. Screening of lead candidates for inhibitory activity using the Z′-LYTE biochemical assay, which measures phosphorylation of a serine or threonine residue on a synthetic FRET-peptide by recombinant polo-like kinase-1, demonstrated that multiple lead candidates exhibited IC_{50} activities below 10 μM for the inhibition of polo-like kinase-1. This is significant, given that relatively few (less than 75) compounds from the computational screens have been tested, and all bear activity to some extent against the recombinant target. Cell-based testing on tumor cells also revealed considerable activity in cell culture. Analogs of these initial leads have been synthesized to improve their activity and specificity, giving way to a series of preclinical candidates for the treatment of a variety of cancer diseases.

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Identification of molecular targets in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the major histological type of primary liver cancer. HCC is the fifth most common cancer and the third leading cancer killer worldwide, and is responsible for about half million new cases and almost as many deaths per year. Surgical resection in the form of partial hepatectomy or liver transplantation is the mainstay for curative treatment. However, only 20% of all patients are eligible for surgery because the majority of patients are diagnosed at advanced stage with intra- and/or extra-hepatic metastasis. Nonetheless, recurrence is still common after curative surgery with approximately 50% at 5-year. Prognosis