which greatly increases drug selectivity toward cancer cells and also might allow by-passing drug cell resistance, when this is generated by mechanism of drug internalization or drug export. Moreover, modularity of drug-armed NT4 allows tailoring of drug-armed peptides on the basis of sensitivity of cancer cells to different drugs.
NT4 armed with 5-fluoro-deoxyuridine was used for *in vivo* experiments in HT-29-xenografted mice and produced a 50% reduction of tumor growth with respect to animals treated with equal amount of the un-conjugated drug.
In vitro and *in vivo* results indicated that branched peptides are valuable tools for tumor selective targeting.

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Potential clinical application of a novel Heat Shock Protein 90 inhibitor CH5164840: preclinical efficacy in mono therapy and combination therapy

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Background: HSP90 is a molecular chaperone and plays an important role in protein folding and stability. In tumor cells, HSP90 is activated by forming super chaperone complexes with co-chaperones. Inhibition of HSP90 function leads to degradation of multiple oncogenic client proteins, resulting in loss of signal transduction, growth inhibition, cell death, and anti-angiogenesis. This unique feature is expected to overcome the problem of resistance to TKIs. Thus, targeting HSP90 is considered to be an attractive strategy for anticancer therapy.
Results: We have identified CH5164840 as an HSP90 inhibitor with a novel chemical structure through virtual screening based on 3D-structure. CH5164840 binds to an ATP-binding pocket of HSP90 comparable to that of ansamycins, 17-AAG and 17-DMAG. Treatment with CH5164840 showed marked degradation of multiple clients in a dose- and time-dependent manner. Consistent with its selective binding to HSP90 in the super chaperone complex, longer pharmacodynamic duration and tumor retention profiles, CH5164840 shows tumor-selective degradation in vivo and therefore exhibits potent antitumor efficacy with a wider therapeutic range in NCI-N87, a Her2 positive gastric cancer model. Further extended efficacy studies with oral daily administration of CH5164840 in many xenograft models revealed that CH5164840 is sensitive to RTK-addicted tumors that occur when EGFR and HER2 are mutated or dysregulated. Moreover in combination therapy, CH5164840 enhances the anti-tumor efficacy with current standard RTK inhibitors.
Conclusion: CH5164840 is a novel, orally available, synthetic HSP90 inhibitor and shows highly potent antitumor efficacy in mono- and combination-therapies with standard-of care-agents. These profiles support the clinical development of CH5164840 for the treatment of RTK-addicted tumors, including tumors with overexpression and mutation of RTKs whose growth and survival depend on HSP90.

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Pharmacokinetic–pharmacodynamic modeling of the effect of GDC-0152, a selective antagonist of the inhibitor of apoptosis (IAP) proteins, on monocyte chemotactic protein-1 (MCP-1) indicates species differences in MCP-1 response

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Inhibitor of apoptosis (IAP) proteins are believed to suppress apoptosis and are overexpressed in a variety of cancers. GDC-0152 is a potent and selective antagonist of the IAP proteins that was developed as a potential treatment of tumors that are resistant to chemotherapies or radiotherapy. Monocyte chemotactic protein-1 (MCP-1) is a chemokine that is expressed during an inflammatory response. Based upon preclinical studies, antagonism of IAP proteins has been shown to induce MCP-1 expression via cIAP degradation and activation of NF-kB signaling. The objective of this study was to investigate species differences in MCP-1 response to GDC-0152 in rats, dog, and humans using pharmacokinetic/pharmacodynamic (PKPD) modeling. Briefly, dogs (n = 40) and rats (n = 20) were given intravenous (IV) doses of GDC-0152 ranging from 0.3 to 15 mg/kg and 20 to 120 mg/kg, respectively. A two compartment model was used to characterize the pharmacokinetics of GDC-0152 in both dogs and rats. A semi-mechanistic population PKPD model incorporating transit compartments was used to characterize the MCP-1 response to GDC-0152. Estimated parameters from the described model indicate that lower concentrations of GDC-0152 are required to trigger an increase in MCP-1 plasma levels in dogs when compared to rats. Simulations were performed with pharmacodynamic (PD) parameters estimated from rat and dog using human pharmacokinetic parameters and select doses. In simulations performed using dog PD parameters, an approximately 4-fold increase in MCP-1 plasma concentration was estimated at a dose of 0.76 mg/kg. In contrast, similar simulations using rat PD parameters suggest little or no change in MCP-1. Humans given intravenous doses $\geqslant$0.76 mg/kg showed no evidence of MCP-1 increase. Thus, the dog appears to be more sensitive to GDC-0152 (in terms of MCP-1 increase) when compared to rats and humans.

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Effect of TG02, a kinase inhibitor targeting Erk5, on triple negative breast cancer cells

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Background: Breast cancer is the most common neoplasia in women. Mitogen-activated protein kinases (MAPK) play important roles in tumorigenesis. Formerly, we reported that one of them, Erk5, is linked to the proliferation of breast cancer cells in vitro, is commonly overexpressed in primary breast tumors, and that its overexpression is an independent negative prognostic marker for disease-free survival. In addition, inhibition of Erk5 sensitized cells to treatments commonly used in the breast cancer clinic. Therefore, Erk5 may represent a novel therapeutic target in breast cancer.
Here we studied the effect of TG02 (a multikinase inhibitor that targets Erk5) on a panel of cell lines representing the basal-like or triple negative subtype of human breast cancer (TNBC).
Materials and Methods: The expression of Erk5 in a panel of TNBC cell lines and the mechanism of action of TG02 on Erk5 were analyzed by immunoprecipitation and Western blotting, using antibodies directed against Erk5. Effects on cell proliferation were determined by MTT assay and cell cycle and apoptosis analyses were performed by propidium iodide DNA staining and FACS analysis. In vitro drug synergies were explored using a caspase 3/7 ELISA and the in vivo activity of TG02 was tested in nude mice bearing established MDA-MB-231 xenografts.
Results: The TNBC cell lines analyzed showed high levels of Erk5 expression, and Erk5 was active under resting conditions in some cases. Cell proliferation studies indicated that the TNBC cells were very sensitive to the action of TG02 at low concentrations (IC_{50} $\leqslant$100 nM) and short exposure times (24−48 hrs). TG02 also induced cell cycle arrest at the G2/M transition leading to apoptotic cell death.
As Erk5 is a target of TG02, we explored whether Erk5 activity was affected by drug treatment. The kinase activity of Erk5 was compromised even though TG02 did not affect the Erk5 upstream activating kinase Mek5, or other upstream activating kinases. In vivo studies indicated that TG02 exerted strong antitumor activity in mice bearing MDA-MB-231 xenografts as a single agent and synergized with the standard of care drug doxorubicin.
Conclusions: TNBC cells are very sensitive to TG02, both in vitro and in vivo. TG02 induced cell cycle arrest at the G2/M transition, causing cell death alone and in synergy with doxorubicin, perhaps via inhibition of Erk5. These preclinical studies establish the bases for the clinical development of this compound for the treatment of TNBC.

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Identifying statins and dipyridamole as a novel drug combination showing efficacy in multiple myeloma and acute myelogenous leukemia

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Statins are drugs that have been utilized for years to treat hyperlipidemia via inhibition of the rate-limiting enzyme of the mevalonate (MVA) pathway, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR). Preclinical