GSK1120212 is a result of the potent and selective inhibition of MEK1/2, and support its advancement for the treatment of cancer in humans.

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Design, synthesis, biochemical and biological evaluations of novel and potent small-molecule inhibitors of STAT3

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Constitutive activation of the Signal Transducers and Activators of Transcription 3 (STAT3) is frequently detected in human cancer specimens from patients with advanced diseases and cancer cell lines, but not in normal epithelial cells. Persistent activation of STAT3 signaling has been demonstrated to directly contribute to oncogenesis by stimulating cell proliferation and preventing apoptosis in human cancer cells. STAT3 activation may not only provide a growth advantage, allowing accumulation of tumor cells, but also confer resistance to conventional therapies that rely on apoptotic machinery to eliminate tumor cells. STAT3 represents an important and specific molecular target for designing an entirely new molecularly targeted therapy for human cancer with constitutively active STAT3 with potentially low toxicity to the normal cells without constitutive STAT3 signaling.
STAT3 is recruited from cytosol and makes specific interactions through its SH2 domain with different cytokine receptor with phosphotyrosine docking sites on the receptors. STAT3 then becomes phosphorylated on a carbonyl terminal tyrosine (Tyr705). Tyrosine physphorylation of STAT3 causes it to dimerize and translocate to the nucleus and bind to specific promoter sequences on its target genes. Dimerization of STAT3 is a decisive event for its activation. Thereby, blocking the dimerization of STAT3 using a small molecule antagonist is a very attractive therapeutic approach for developing a molecularly targeted therapy for the treatment of human cancer in which STAT3 is constitutively activated. Herein, we wish to report the design, synthesis, biochemical and biological evaluations of novel and potent small-molecule inhibitors of STAT3. Our most potent inhibitors bind to Stat3 with low nanomolar affinities and display excellent selectivity over Stat1 and Stat5. These compounds are excellent biochemical and pharmacological tools to further elucidate the role of Stat3 in cancer and promising lead compounds for the development of potent and specific Stat3 inhibitors for the treatment of human cancer.

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Enhanced drug delivery to brain tumors with a new paclitaxel-peptide conjugate

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Background: The main limiting factor in the treatment of brain tumors or metastasis is the low accessibility of the central nervous system (CNS) to drugs due to the blood–brain barrier. In the present study, the utilization of a new strategy based on a peptidic vector (Angiopep) capable of delivering drugs into the CNS in non-invasive manner was evaluated. Paclitaxel which accumulation into the CNS is hindered due to the P-glycoprotein efflux pump, was conjugated to the peptidic vector. The in-vitro and in-vivo properties of this conjugate (ANG1005) were characterized using different approaches.
Material and Methods: The sensitivity of a panel of cancer cell lines to ANG1005 was evaluated in vitro. The pharmacokinetic behavior of ANG1005 in plasma after IP, IV injection or IV infusion and its toxicity were determined in vivo on healthy Nude rats. The antitumor activity of ANG1005 was evaluated by MRI in a model of Nude rats bearing NCI H460 lung tumor implanted in the brain.
Results: Among all tumor cell lines tested in vitro, ANG1005 displayed an IC50 (concentration inducing a 50% cell death) in the nanomolar range for the NCI H460 and U 87 MG cell lines. These IC50 were of the same order of magnitude than for paclitaxel. Toxicity experiments showed that the maximal total treatment dose (MTTD) using a Q3Dx5 schedule was 6 mg/kg/inj when ANG1005 was injected IV. With the same schedule, IV infusion enabled to increase treatment doses as the MTTD reached 15 mg/kg. Pharmacokinetic studies indicated that maximal ANG1005 plasma concentrations were similar after a single IV injection at 11.25 mg/kg or an IV infusion at 15 mg/kg. However, the area under the time-concentration curve (AUC) was slightly higher for rats receiving ANG1005 via IV infusion as compared to rats dosed via IV injection. After a single IP injection at 75 mg/kg, ANG1005 plasma concentrations and AUC remained lower. A preliminary in vivo experiment was performed in a model of Nude rats bearing NCI H460 tumors. Magnetic resonance imaging revealed a reduction of tumor growth early after the start of treatments for rats treated IP with ANG1005 at 75 mg/kg as compared to rats receiving the vehicle or paclitaxel.
Conclusions: These results demonstrate that ANG1005 delivers paclitaxel into the CNS and enhances its activity in an aggressive model. ANG1005 is currently under evaluation in phase I clinical trials for the treatment of glioma and brain metastases in human.

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Macrolactone based inhibitors of Heat Shock Protein 90

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Heat shock protein 90 (Hsp90) is an ATP-dependent molecular chaperone for many overexpresed or mutant oncogenic proteins. This enzyme has become an attractive target for chemotherapeutic agents, since its inhibition will disrupt multiple cancer causing pathways simultaneously and hence may address the six hallmarks of cancer. Radicicol (**1**) is a potent natural product inhibitor of Hsp90 in vitro, but does not have any substantial in vivo activity. It has been suggested that this is due to the reactivity and metabolic lability of both the enone and epoxide functionalities. To address this problem, a series of macrocyclic lactones based on radicicol **1** was made in our laboratory. This led to the discovery of compound NP-261 (**2**) which lacks the unwanted functionality present in radicicol **1** but retains nanomolar biochemical activity.
In order to further improve the cellular activity of NP261 **2**, a second generation of analogues was designed **3**–**4**. It was reasoned that cellular activity might be enhanced by increasing the molecular rigidity of the macrocyclic ring. Our strategy was to investigate a number of key analogues which set to achieve this goal. This included a series of triazoles with varying ring sizes **3**, macrolactams and altering the substituents on the macrocyclic ring **4**. We report the synthetic challenges and biological evaluation of these new analogues.

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Design and synthesis of novel indole derivatives as selective apoptosis-inducers

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Evasion of apoptosis is one of the hallmarks of cancer [1]. Although the apoptotic pathway contributes to the cytotoxic effect of most cancer chemotherapeutics, selective induction of apoptosis in cancer cells would confer advantages over conventional therapy in terms of efficacy, toxicity and drug resistance.
Different small libraries of novel indole-based heterocyclic systems were designed to act as selective pro-apoptotic agents in cancer cells. Twenty-two compounds of the 5-(2-indolyl)-3-substituted-1,2,4-oxadiazole class were designed, based on a previously reported series of selective proapoptotic 3,5-diaryl-1,2,4-oxadiazoles [2]. The new compounds were prepared from the corresponding indole-2-carboxylate ester and different amidoximes in moderate yields with simple reaction workup. Another library of ten compounds of indole-based 3,5-disubstituted isoxazoles with different indole orientations was prepared by dipolar cycloaddition between terminal alkynes and aldoximes in excellent yields. A third series was designed to act as Bcl-2 inhibitors, based on a series flexible heteroarotenoids [3] with urea or thiourea linkers reported to affect the level of antiapoptotic Bcl-2 proteins in cancer cell lines and have selective apoptosis-inducing activity. Docking of these Flex-Hets at the Bcl-2 surface pocket showed good interaction suggesting the possibility of acting as Bcl-2 inhibitors, but the presence of a deep hydrophobic groove that is not utilized by these Flex-Hets suggested that incorporation of a larger side chain could result in better inhibitors. Further docking studies have revealed possibilities for extension of the Flex-Hets structure to probe further binding interactions with the Bcl-2 domain potentially leading to more potent pro-apoptotic molecules.
Examination of the in vitro cytotoxic effect of the newly prepared compounds of the 1,2,4-oxadiazole series on a panel of human cancer cell lines showed that the COLO 320 (colon) and MIA PaCa-2 (pancreas) were the most chemosensitive cell lines with IC50 mean values in the micromolar range. Moreover, potency and efficacy of compound 21 (5.7 μM and 75.9%, respectively) on the poorly differentiated pancreatic cancer cell line MIA PaCa-2 were almost superimposable to those observed for 5-fluorouracil.
Different novel series of indole-based compounds were designed and synthesized to act as selective pro-apoptotic agents with different molecular