compared to control. 10 μM CH-1 slightly induced apoptosis at 72 hr. All chalcone derivatives inhibit proliferation of PBMCs dose-dependently. The IC_{50} values of these derivatives on PBMCs were 0.7–16.3 μM.
Conclusion: Our results suggest that some methoxy- and/or fluoro-chalcone derivatives have anti-melanoma cell efficacy with less suppression against human immune system. The data also suggest that the molecular mechanisms of the chalcone derivatives on the human melanoma cells involve the induction of apoptosis and blockade of cell cycle. These chalcone derivatives may be useful as lead molecules for developing new anti-melanoma agents.

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Eph receptor A2 modulation in human glioma cell lines by the natural product, Schweinfurthin A

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Eph kinases, the largest group of transmembrane receptor tyrosine kinases, bind to ephrin ligands and initiate bidirectional signaling impacting a wide variety of cellular processes including actin cytoskeletal organization, cell shape, motility, adhesion, growth, survival, and differentiation. The EphA2 receptor has been reported to be overexpressed in multiple cancers, including glioblastoma and astrocytomas, and is an attractive target for the treatment of brain tumors. Schweinfurthin A (SA) is a small molecule natural product isolated from a tree in Cameroon, Africa with a unique growth inhibitory fingerprint in the NCI 60 cell-lines, and potent activity against the CNS subpanel. COMPARE analysis of the pattern of toxicity of this highly active agent was unable to identify any putative mechanism of action. In an effort to understand the underlying molecular mechanism for the CNS specificity, microarray studies in the drug sensitive glioma cell line, SF-295, were used to identify candidate genes linked to the activity of the molecule. A group of SA-regulated genes were identified, including several related to the cytoskeleton, which was in accord with a dynamic change in the actin cytoskeleton observed in SA-treated sensitive cells. In particular, we identified changes in EPHA2 and EFA1 genes which code for the EphA2 receptor tyrosine kinase and its cognate ligand EphrinA1 respectively. In SF295, SA treatment led to down regulation of the receptor concurrent with an increase in the expression of the ligand, and these results were confirmed using PCR, Western Blotting and immunofluorescence. When RNAi was used to knock down EPHA2 receptor expression in the human glioma cell line U251 the consequences on phenotype, morphology and actin organization were similar to those observed following SA treatment. As EphA2 has been identified as a potential chemotherapeutic target, and as an important marker and determinant of aggressive, metastatic gliomas, functional studies are ongoing to confirm an SA-mediated effect on ephrin signaling and phenotypes such as migration and invasion.
Funded by NCI contract N01-CO-12400

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Phase I study of the novel anti-cancer drug PM00104 as a 1-hour weekly infusion resting every fourth week in patients with advanced solid tumors or lymphoma

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Background: PM00104 (ZALYPSIS®) is a novel synthetic alkaloid related to the marine compounds jorumycin and renieramycins. Preliminary analyses point to changes in cell cycle and DNA binding properties, as well as to transcriptional inhibition as main mechanisms of action. ZALYPSIS® has shown anti-tumor activity in vitro ($IC50 \leqslant 10^{-8}$ M) and in xenografts models, and an acceptable toxicological profile.
Methods: Patients (pts) with advanced cancers or lymphoma were enrolled to determine the safety, tolerability, maximum tolerated dose (MTD), recommended dose (RD), pharmacokinetics (PK), relationship between PK and pharmacodynamics (PD) and anti-tumor activity of ZALYPSIS® administered as a 1-hour i.v. infusion weekly and resting every fourth week. Sequential cohorts of 3−6 pts have received the following doses: 75, 150, 300, 600, 900, 1350, 2025, 2500 and 3037 μg/m^2.
Results: Thirty seven pts have been treated (22M; median age: 57, range: 36−73; ECOG PS $\leqslant$ 2). Six dose-limiting toxicities (DLT) have been reported, two at 3037 μg/m^2, three at 2500 μg/m^2 and one at 2025 μg/m^2, respectively. The DLTs were grade 3−4 asthenia, grade 3 nausea and grade 3−4 hematological toxicity (neutropenia, thrombocytopenia and anemia), delay in the administration of the dose due to hematological toxicity, and reversible grade 4 lipase increase. The MTD was reached at 2500 μg/m^2 and the RD at 2025 μg/m^2. At the RD nine more pts have been included in order to evaluate the safety and the anti-tumor activity. Other toxicities were the majority of grade $\leqslant$2 and included: transaminase increases, anorexia, diarrhea, constipation, asthenia and nausea, and vomiting (that augmented at doses >600 μg/m^2). Seven pts have had stable disease (SD) lasting >3 months, two of them with pleural mesothelioma. PD analysis is being performed in tumor samples in pts treated at 2500 μg/m^2. PK of ZALYPSIS® in this study is been characterized by a half life of 30−40 hours at the RD, wide volume of distribution (around 800 L) and a moderate to high inter-patient variability. The dose proportionality is been maintained in terms of Cmax and AUC. The presence of DLT has been found to be more related to total AUC than to Cmax.
Conclusions: this trial has shown an acceptable tolerability profile for ZALYPSIS® with limited anti-tumor efficacy. The usefulness of ZALYPSIS® in combination with other anti-tumor compounds shall be explored.

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The novel taxane derivative, IDN6140, crosses the Blood Brain Barrier and has a promising activity in CNS tumors

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Background: IDN6140 is a new paclitaxel (PTX) analogue derived from 14-β-hydroxy-10-deacetylbaccatin III, that was selected for further preclinical evaluation based on its high cytotoxic activity in human tumor cell lines, being about 40 fold more potent than PTX. Previous pharmacokinetic studies indicate that IDN6140 is characterized by good and rapid absorption, high distribution and long half-life allowing to achieve and maintain for long time plasma concentrations higher than the IC50 values (Marangon et al., Abstract No C140, 2007 AACR-NCI-EORTC Annual Meeting San Francisco).
The aims of this study were to evaluate the brain distribution of IDN 6140 and its antitumor activity against an orthotopically growing human glioma in nude mice.
Methods: The U-87 MG human glioma cell line was xenografted into the brain of CD1-nude mice. IDN 6140 was administered i.v. three times every fourth day at the dose of 5.4 mg/kg, and antitumor efficacy was assessed by examining mouse survival time and by MRI. Pharmacokinetic study was conducted on CD1 mice treated with single i.v. or oral dose of IDN 6140, 5.4 mg/kg. Drug levels in plasma and brain were determined according to HPLC/MS/MS method.
Results: IDN6140 was effective in increasing the survival time of mice orthotopically injected with U-87 MG cells achieving 53% ILS ($P < 0.05$ vs controls). The results were supported by the pharmacokinetic data where, after both oral or i.v. administration, IDN 6140 was rapidly distributed to mouse brain (Tmax $\leqslant$2 hr), achieving Cmax of 0.14 and 4.00 μg/mL, respectively. After both treatments, the compound disappeared from brain with a higher half-life (more than 30 hours) than the half-life determined in plasma (about 20 hours), causing accumulation in brain tissue. The ratios brain-AUC/plasma-AUC were 1.1 and 3.7 after oral and i.v. administration respectively, indicating high distribution of the compound in the organ.
Conclusions: The study provides evidence of good pharmacological properties of IDN 6140, i.e. high and prolonged brain distribution, which was reflected in the ability to affect the growth of intracranial tumors. These data suggest that IDN6140 deserves further investigations as a potential new drug for the therapy of CNS tumors and metastases.

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Evaluation of the marine compound PM02734 against a pediatric tumor cell line panel by ITCC preclinical drug evaluation program

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Background: The Innovative Therapies for Children with Cancer (ITCC) European consortium aims to develop new drugs for the treatment of