structures and to stabilize them. The very promising strategy of studies focuses on telomerase, which is responsible for cancer cells longevity. It was shown that telomerase is detected in over 90% of cancer cells while it is generally inactive in most normal cells.
The aim of the study was to estimate the influence of two ligands (1 and 2), papaverine oxidation products, on cells viability and DNA-quadruplexes stabilization and thus, inhibition of telomerase activity. The two ligands were shown to have high affinity to guanine quadruplexes (G-4 DNA) in vitro, which suggests that they could be able to block DNA-telomerase interactions.
The cytotoxicity of ligands was measured in Cell Proliferation MTT Kit and the influence of the compounds on Telomerase activity was assessed by Telo TAGGG Telomerase PCR ELISA Plus assay.
Cytotoxicity tests showed that both ligands inhibit cell viability with their IC50 values for ligand 1 and ligand 2 respectively, at 72 h incubation time in HL60 cells: 0.15 and 0.19 μM; in HL60AR cells: 46.21 and 16.48 μM; in MCF-7 cells: 1.16 and 0.42 μM; in MDA-MB-231 cells: 16.55 and 5.1 μM. Moreover, it was also reported that ligand 1, showing fluorescence at 365/397 (exc./emis.), binds the growing cells permanently, persisting even through a few cell passages what was observed in a fluorescence microscopy.
Telomerase activity assay showed that both ligands significantly inhibit telomerase activity at the concentration of 0.1 μM. However, the action of both ligands resulted also in Polymerase activity inhibition, which might suggest interactions specific not only to quadruplexes but also to DNA helix or maybe even enzyme structure.
It is suggested that both studied ligands could be strong and selective cancer cells growth inhibitors that results from their telomerase inhibition specific action. It is also possible that the studied compounds could be new promising fluorescent probes for DNA detection and labeling, however further studies concerning their specificity and sensitivity are required.

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Non-clinical pharmacokinetics, distribution and excretion of SNS-314, a novel, selective aurora kinase inhibitor

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Background: The Aurora kinase family is comprised of three proteins, Auroras A, B and C that function as key regulators of cell progression through mitosis and cytokinesis and may be important targets in anti-cancer therapy. SNS-314 is a novel small molecule that potently inhibits all three Aurora proteins in the low-nanomolar range. SNS-314 has robust anti-tumor activity in a wide range of human xenograft tumor models in mice using an intermittent dosing schedule. SNS-314 currently is being investigated in a Phase 1 trial to evaluate its safety and pharmacokinetic properties in humans.
Methods: Pharmacokinetic studies were conducted in mice, rats and dogs dosed with SNS-314 or [14C]SNS-314. Blood, tissue, bile, and urine were collected between 0−48 hours and analyzed via LC/MS/MS. Pharmacokinetic parameters were estimated using WinNonLin. Quantitative whole body autoradiography was used to measure tissue distribution in rats.
Results: Pharmacokinetic studies were conducted in mice, rats and dogs after single and repeated administration. In rising dose pharmacokinetic studies, SNS-314 displays non-linear systemic exposure; the area under the concentration curve increases more than dose linearly. This is most pronounced in rats and mice and occurs to a lesser extent in dogs. Sex-related differences in pharmacokinetic parameters are observed in rodents and to a much lesser extent in dogs. Female rats had 1.3 to 2 fold greater plasma AUC than male rats. SNS-314 is rapidly and extensively distributed in both mice and rats when dosed IV, IP, or PO. Administration at 170 mg/kg to tumor bearing mice shows drug levels persisting in the tumor for more than 96 hours post-dose (T1/2 = 7.5 hr), even though plasma levels were not measurable beyond 40 hours post-dose (T1/2 = 4.7 hr). Whole-body autoradiography indicates [14C]SNS-314 related radioactivity is widely distributed in tissues after an IV bolus dose with maximum concentrations observed 1 hour post dose. Approximately 70% of SNS-314 is eliminated through biliary excretion 48 hours post dose.
Conclusion: The favorable pharmacokinetic properties of SNS-314 including elevated tumor over plasma drug levels support clinical investigation of this oncology agent.

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Relationship between expression of CXCR4 and histological type in adenoid cystic carcinoma of the head and neck

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Background: Adenoid cystic carcinoma (ACC) is one of the most common malignant tumors of the salivary glands characterized by multiple recurrences and distant metastasis resulting in significantly worsening prognosis. CXCR4/CXCL12, a representative chemokine receptor and its ligand, has been reported to be involved in cancer metastasis, especially in breast cancer metastasis. In order to investigate the high invasive and metastatic potentials of ACC, CXCR4 expression in ACC was examined, and analyzed the relation to clinicopathological features and histological type.
Methods: We analyzed immunohistochemical expression of CXCR4 surgical specimen of ACC. We also used two established human tumor lines, ACCY and ACCI, in nude mice derived from ACC of the oral floor. The expression levels of protein and mRNA of CXCR4 in these tumor lines were examined by western blot and RT-PCR.
Results: Patients expressed CXCR4 at high levels showed lung metastasis, regional lymph nodes metastases, and poor prognosis. The solid type and cribriform type with distant metastases showed intense CXCR4 staining, while tubular type and cribriform type with no metastasis were weakly positive. In vivo model, ACCY tumor showed an increased growth rate as the passage levels proceeded, and the histological feature has been changed from a cribriform pattern to a solid one. CXCR4 was highly expressed in 15th passage level than in initial level of ACCY. ACCI tumor in nude mice developed spontaneous metastasis to the neck, and the histological feature changed from a cribriform pattern of ACC to undifferentiated carcinoma. This metastatic tumor (ACCIM) caused spontaneous metastasis to the lung at high incidence when transplanted subcutaneously in nude mice. Expressions of CXCR4 in ACCIM were higher than ACCI, and lung metastatic area was strongly positive immunohistochemically. Both ACCI and ACCIM had high levels of mRNA for human CXCR4 by RT-PCR.
Conclusions: Our results indicate that there is a close relationship between CXCR4 and histological type of ACC, and CXCR4 may play important roles in the process of metastasis and biological behavior of ACC.

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Association of miR-21, miR-31, miR-143, miR-145 and let-7a-1 levels with histopathologic features of colorectal cancer

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Background: MicroRNAs (miRNAs) are endogenously expressed short non-coding RNAs, that repress protein translation through binding to target mRNAs. Although the number of verified human miRNA is still expanding, only few have been functionally described. However, emerging evidences suggest the involvement of altered regulation of miRNA in pathogenesis of cancers and these genes are thought to function as both tumours suppressor and oncogenes. Previous studies, mainly based on microarrays technology applied on colorectal cancer cell lines, showed altered expression levels of several miRNAs in colorectal cancer (CRC).
Materials and Methods: In our study, we examined by Real-Time PCR expression levels of miR-21, miR-31, miR-143, miR-145 and let-7a-1 in bioptic samples of 29 colorectal cancer patients including 3 cases of IUCC Stage I, 11 of Stage II, 6 of Stage III, 9 of Stage IV. For 6 cases of CRC samples also adjacent non-tumor tissue was analyzed. MiRNAs expression levels were correlated with tumor stage, grade, size, anatomical localization, serum CEA levels and p53 protein expression in tumors. For data normalization we tried different approaches (18S rRNA, GAPDH, let-7a-1). Finally, variability of let-7a-1 expression was shown to be the lowest. P values were calculated using Mann-Whitney U test.
Results: Expression levels of all analyzed miRNAs significantly differ in tumor and normal mucosa, miR-21 ($p = 0.0001$) and miR-31 ($p = 0.0006$) were up-regulated and miR-143 ($p = 0.013$) and miR-145 ($p = 0.018$) were down-regulated in tumors. MiR-21 was also correlated with CRC stage. Although the highest levels of miR-143 and miR-145 were in normal mucosa, we identified positive correlation of tumor stage and their expression suggesting altered tumor suppressor function of these miRNAs in early events of colorectal carcinogenesis. Distal CRC showed significant