2	2,2,2-trifluoro-N-(6-(2-fluoro-4-(trifluoromethyl)benzoyl)imidazo-[1,2-a]pyridin-2- yl)acetamide
3	2,2,2-trifluoro-N-(6-(3-fluoro-4-methylbenzoyl)imidazo-[1,2-a]pyridin-2-yl)acetamide.
4	2,2,2-trifluoro-N-(6-(1-methyl-1H-indole-3-carbonyl)imidazo-[1,2-a]pyridin-2-yl)acetamide
5	2,2,2-trifluoro-N-(6-(thiazole-2-carbonyl)imidazo-[1,2-a]pyridin-2-yl)acetamide.
6	2,2,2-trifluoro-N-(6-(1-methyl-1H-imidazole-2-carbonyl)imidazo-[1,2-a]pyridin-2-yl)acetamide
7	diethyl 4-(imidazo[1,2-a]pyridin-2-ylamino)benzylphosphonate
8	6-(imidazo[1,2-a]pyridin-2-ylamino)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione.
9	N-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyridin-2-amine.

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Effect of some bis-mannich bases and corresponding piperidinols on DNA topoisomerase I as a possible mechanism of their cytotoxic actions

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Some acetophenone-derived bis-Mannich bases, bis-(3-aryl-3-oxo-propyl)-methylamine hydrochlorides (B1 through B5) and their structural isomers, piperidinols 4-aryl-3-arylcarbonyl-1-methl-4-piperidinol hydrochlorides (C1, C2 and C5) were synthesized and their effects on mammalian DNA topoisomerase I was tested. Chemical structures of the compounds were confirmed by UV, IR, 1H NMR, 13C NMR, ESI-MS spectra and elemental analysis. Among the compounds, all bis-Mannich bases, and 4-(2-thienyl)-3-(2-thienylcarbonyl)-1-methyl-4-piperidinol hydrochloride were found to inhibit DNA topo isomerase I at varying degrees. The compounds B1-B5 and C5 manifested an average of 46%, 20%, 40%, 22%, 24% and 22%, inhibition on topoisomerase I, respectively, which might suggest the cytotoxic actions of these compounds, previously reported by our laboratory, might be linked to DNA topoisomerase I inhibition. These compounds can be considered as the potential candidates for further studies in developing new cytotoxic and anticancer agents.

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Selection of high-affinity human monoclonal antibodies specific to the constant domain of versican as tools for tumor targeting

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Conventional cytotoxic therapies of cancer often suffer from a lack of specificity, leading to a poor therapeutic index and considerable toxicities to normal organs.One of the most promising new avenues for the development of more specific and efficacious cancer therapies relies on the selective delivery of therapeutics to the tumor site by conjugation with specific antibodies against tumor-associated markers. Markers expressed on the tumor's vasculature represent particularly attractive targets for site-specific drug delivery due to their accessibility for blood-borne agents and the various therapeutic options that they allow.In a study recently published in collaboration with our group1 a pool of tumor associated antigens that could be suitable targets for antibody-based anticancer therapy was identified. Among these potential tumor markers, versican was chosen for further studies. Versican is a member of the large aggregating chondroitin sulphate proteoglycan (CSPG) family. Structurally, versican is composed of a N-terminal G1 domain, two glycosaminoglycan (GAG) attachment regions and a C-terminal G3 domain. Alternative splicing generates at least four isoforms of versican, named V0, V1, V2 and V3. Versican is highly expressed in the early stages of tissue developments, during wound repair and tumor growth, this expression pattern of versican was proven to be a reliable prognostic factor and a good tumor marker in a number of publications.The aim of this work is to express recombinant forms of a constant domain of versican in different mammalian cell expression systems and use these recombinant proteins as target for selection of human monoclonal antibody in the scFv format from a large synthetic human antibody phage display library cloned in our lab2. The versican specific antibodies will be validated in vitro and in vivo before being used as building block for the development of antibody-based targeted anti-cancer therapeutics. (1) Castronovo, V.; Waltregny, D.; Kischel, P.; Roesli, C.; Elia, G.; Rybak, J. N.; Neri, D. Mol Cell Proteomics 2006, 5, 2083-91. (2) Silacci, M.; Brack, S.; Schirru, G.; Marlind, J.; Ettorre, A.; Merlo, A.; Viti, F.; Neri, D. Proteomics 2005, 5, 2340-50.

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Toxicological evaluation in non human primates of the mAb h-R3, used in the treatment of the cancer

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The humanized monoclonal antibody (mAb h-R3) is a product that will be dedicated to the treatment in the human, for intravenous route, of the neoplasic of transformed cells that they on-express the receiver of the Factor of Epidermal Growth in head and neck. The objective was to evaluate the toxicity for intravenous route of the mAb h-R3 in two studies to dose repeated respectively in monkeys Cercopithecus aethiops of 14 days and 26 weeks, three experimental groups conformed by group control, treated low and high dose of 2.85 and 28.57 (mg/Kg) respectively. Deaths were not observed, the body weight had a significant increase for weeks, toxic effects were not observed in the hematological and sanguine chemistry parameters. In the electrocardiography registrations, it was observed a I increase fast of the heart frequency in animals treaties, There were neither neurotoxic effects on the studied variables nor macro and microscopic lesions in the skin.

POSTER SESSION

Signalling pathways 3

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Butyrate simultaneously activates extrinsic and intrinsic apoptosis in colon adenoma andcarcinoma cell lines

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It is an accepted fact that butyrate, a product of bacterial fermentation of dietary fibre in the colon, induces apoptosis in colon cancer cells and may therefore be important in secondary chemoprevention of colorectal cancer. Since controversial results are available concerning the molecular mechanisms of butyrate-induced apoptosis, we analyzed how butyrate influenced molecular parameters of extrinsic and intrinsic apoptosis, respectively, and compared the effects in a human colon adenoma (LT97) and a colon carcinoma cell line (HT29). Effects of butyrate on caspase (-2, -3, -8 and -9) activity was analysed using ApoAlert® caspase activity profiling plates (Clontech). Protein activation of Bid was investigated using Western Blotting and mRNA expression of Bid, TRAIL, DR4 and DR5 was examined by real-time RT-PCR.Butyrate increased activity of caspase-2, -3, -8 and -9 in both HT29 and LT97 cells, with LT97 cells being more susceptible to the treatment. Simultaneous activation of caspase -8 and -9 is a hint that extrinsic as well as intrinsic apoptosis signaling was turned on by butyrate. Consequently, the BH3-only protein Bid, a member of the Bcl-2 protein family which connects extrinsic and intrinsic apoptosis, was activated by butyrate treatment in both cell lines as shown by Western Blotting using specific antibodies against Bid. On the mRNA level, however, Bid was not modulated by butyrate in either cell line, indicating the involvement of post-translational mechanisms. Activation of Bid was more pronounced in LT97 cells, demonstrating again an increased sensitivity of LT97 adenoma cells towards butyrate treatment. Gene expression of TRAIL receptors DR4 and DR5 was induced by butyrate in both cell lines, with LT97 cells showing a greater induction than HT29 cells. Gene expression of the ligand TRAIL, on the other hand was only increased in HT29 cells. Thus, different mechanisms may be involved in activation of apoptosis in HT29 and LT97 cells. In conclusion, extrinsic and intrinsic apoptosis is simultaneously activated by butyrate in colon cancer cells and this activation is mediated by increased Bid protein activity and increased mRNA levels of death receptors. The importance of butyrate in secondary chemoprevention of colorectal cancers is highlighted by the fact that LT97 adenoma cells, were more sensitive towards butyrate than HT29 carcinoma cells. Therefore butyrate may inhibit the formation of malignant tumors by killing early stage adenoma cells.

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ILEI, an essential cytokine for tumor progression - how does it act?

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ILEI (Interleukin-like EMT Inducer) is essential for tumor formation and progression in a murine mammary epithelial cell model. Stable expression