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<th>Chairman</th>
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## Program at a glance

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<tr>
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<td>Registration</td>
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<td>09:40-10:00</td>
<td>Coffe break</td>
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<td>10:00-10:20</td>
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<tr>
<td>Time</td>
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<td><strong>Nanomedicine (Moderators: Dr. Toru Kondo &amp; Nikolay Klassen)</strong></td>
<td>“Nanomedicine - targeted cancer therapy with magnetic nanoparticles” Dr. Christoph Alexiou (Germany)</td>
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<td>14:10-14:30</td>
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<td>“Water-soluble Quantum Dot Bioconjugates for Cancer Detection and Treatment: A “Bright” Future Ahead” Dr. Herman Mansur (Brazil)</td>
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<td>14:30-14:50</td>
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<td>“The AuNPs and AuNPs-Lanreotide conjugate in the inhibition of proliferation MCF-7 and B16 cells in vitro for treatment in cancer “ Dr. Eva Maria Molina Trinidad (Mexico)</td>
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<tr>
<td>15:10-15:30</td>
<td><strong>Cancer Stem Cells (Moderators: Dr. Toru Kondo &amp; Nikolay Klassen)</strong></td>
<td>“Investigation of miRNAs involved in gliomagenesis” Dr. Toru Kondo (Japan)</td>
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<td>15:30-15:50</td>
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<td>“Notch pathway as new therapeutic target in Neuroblastoma” Dr. Maurizio Memo (Italy)</td>
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<td>15:50-16:10</td>
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<td>“Cisplatin induces differentiation of breast cancer cells” Dr. Praseetha Prabhakaran (Australia)</td>
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<td>P1</td>
<td>“Chemotherapy for Cancer Stem Cells” (Yoshinori Kawazoe &amp; Daisuke Uemura (Japan))</td>
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<td>P2</td>
<td>“Biomodulation of H$_2$O$_2$ genotoxicity by phytochemicals from Armoratia rusticana” Dr. Eva Miadokova (Slovak Republic)</td>
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<tr>
<td>P3</td>
<td>“The pro-apoptotic effect of photoactivated hypericin A549 cell line” Eliska Galova Miadokova (Slovak Republic)</td>
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<td>P4</td>
<td>“Genetic polymorphism of five genes associated with growth traits in goat” Saleha Y. M. Alakilli (Saudi Arabia)</td>
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<td>“Ugonin K induces human skin cancer cells apoptosis by reactive oxygen species-mediated signal pathway” Dr. Chia-Hua Liang (Taiwan)</td>
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<td>P6</td>
<td>“New treatments for leukemia in Mexico” Villegas Balderas Nora Mayte (Mexico)</td>
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<td>P7</td>
<td>“Acute Taxol Toxicity: the Effects on Bone Marrow Mitotic Index and the Histology of Mice Hepatocytes” Samar omar Abdullah Rabah (Saudi Arabia)</td>
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<td>P8</td>
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<td>08:15-09:00</td>
<td>Cytoxicity of Apatone in vitro and in vivo xenotransplants: urologic and ovarian tumors Prof. Jacques Gilloteaux (UK)</td>
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<tr>
<td>09:00-09:20</td>
<td>Personalized medicine in chronic lymphocytic leukemia Dr. Malgorzata Rogalinska (Poland)</td>
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<td>10:40-11:00</td>
<td>Anticancer, antioxidant and antiobesity effects of some newly synthesized simple chalcone derivatives and their metal complexes Dr. Mohamed Aly (Egypt/Saudi Arabia)</td>
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<tr>
<td>11:40-12:00</td>
<td>“Interaction between Trastuzumab and ErbB2 analyzed by molecular dynamics simulation” Victor Cruz (Spain)</td>
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<tr>
<td>09:00-09:20</td>
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<td>09:20-09:40</td>
<td>Mutagenicity of topoisoerase targeting anticancer agents Dr. Sabry M. Attia (Saudi Arabia)</td>
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<td>09:40-10:00</td>
<td>“Are osteomimetic properties of cancer cells hoaxed or inherent cellular characteristics?” Henning M. Schramm (Switzerland)</td>
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<td>10:00-10:20</td>
<td>Coffee Break</td>
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<td>10:20-10:40</td>
<td>“Live yeast cells as a model for locating intracellular targets of fluorescenting anticancer drugs” Dr. Evgeny Puchkov (Russia)</td>
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<td>10:40-11:00</td>
<td>Anticancer, antioxidant and antiobesity effects of some newly synthesized simple chalcone derivatives and their metal complexes Dr. Mohamed Aly (Egypt/Saudi Arabia)</td>
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<tr>
<td>11:00-11:20</td>
<td>“The Two Faces of Hypercin” Dr. Eliska Galova (Slovak Republic)</td>
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<td>11:20-11:40</td>
<td>“About the communication of cancer cells” Dr. Konstantin Meyl (Germany)</td>
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<td>12:00-13:30</td>
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<tr>
<td>13:30-13:50</td>
<td>Natural Products &amp; Production of Anticancer Compounds (Moderators: Dr. Rodney Smith &amp; Professor Bertha Schwartz)</td>
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<tr>
<td>13:50-14:10</td>
<td>“A recombinant fungal compound Ostreolysin, induces anti-proliferative and pro-apoptotic effects on colon cancer cells” Professor Bertha Schwartz (Israel)</td>
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<tr>
<td>14:00-14:30</td>
<td>“Marine Natural Products as Drug-leads” Dr. Daisuke Uemura (Japan)</td>
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<td>14:30-14:50</td>
<td>“Synthesis and Characterization and Biological Activity of Metallocefepeime and Metallocephradine Complexes.”</td>
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<td>14:50-15:10</td>
<td>Coffee Break</td>
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<tr>
<td>15:10-15:30</td>
<td>Immunotherapy (Moderators: Dr. Rodney Smith &amp; Professor Bertha Schwartz)</td>
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<td>15:30-15:50</td>
<td>“Role of Vitamin D Binding Protein-derived Macrophage Activating Factor (GcMAF) in the immunotherapy of cancer” Dr. Rodney Smith (UK)</td>
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<td>15:50-16:10</td>
<td>“Interaction between Trastuzumab and ErbB2 analyzed by molecular dynamics simulation” Victor Cruz (Spain)</td>
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<td>16:10-16:30</td>
<td>“Using GlycoExpress to produce glycooptimized antibodies for cancer treatment” Dr. Steffen Goletz (Germany)</td>
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<td>16:30-17:00</td>
<td>Closing lecture</td>
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<td>17:00-18:00</td>
<td>Free Time/mingling</td>
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<tr>
<td>18:00-20:00</td>
<td>Farewell dinner</td>
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ORAL PRESENTATIONS
O1. Nanomedicine – targeted cancer therapy with magnetic nanoparticles

AUTHORS: Alexiou, Christoph MD

AFFILIATIONS: Division for Experimental Oncology and Nanomedicine at the ENT-Clinic, Else Kröner-Fresenius-Stiftung-Professorship, Universitätsklinikum Erlangen, Waldstr. 1, 91054 Erlangen, Germany

CORRESPONDING AUTHOR: Christoph Alexiou, Head Division for Experimental Oncology and Nanomedicine at the ENT-Clinic, Else Kröner-Fresenius-Stiftung-Professorship, Universitätsklinikum Erlangen, Waldstr. 1, 91054 Erlangen, Germany, Tel.: ++49-9131-85-34769, Fax.: ++49-9131-85-34828, E-mail: C.Alexiou@web.de

KEYWORDS: Cancer -Targeted Therapy - Nanoparticles

ABSTRACT Nanotechnology can be applied in a variety of biomedical and bioengineering proceedings and is called Nanomedicine. Magnetic nanoparticles of different sizes with tailored surface chemistry are used in vitro in a routine setting for cell separation and in vivo as magnetic resonance imaging contrast agents, hyperthermia and drug delivery. For in vivo application these particles are coated by different materials to receive biocompatibility. One major hurdle that underlies the use of nanoparticles in the treatment of diseases (i.e. cancer) is the problem of getting the particles to a specific body compartment. A potential benefit of using these particles is the application of external magnetic fields/gradients to focus the particles to the particular site in the body and to hold them until the therapy is complete. All these efforts point to an aim in which drugs are only delivered to specific sites and at therapeutic levels. Magnetic drug targeting, in which magnetic nanoparticles bound to a chemotherapeutic agent and concentrated in a tumor region by an external magnetic field after intraarterial injection, could be a promising tool in cancer therapy.

This abstract was selected as “Best Oral Presentation”
O2. Sapphire capillary needles and scalpels for anticancer drug delivery, online diagnostics and surgery

AUTHORS: Klassen, Nikolay, PhD¹, Kurlov, Vladimir, Dr.Sci¹, Shikunova, Irina, PhD¹, Shmyt’ko, Ivan, Dr.Sci¹, Strjukov, Dmitryi, post-graduate¹, Ryzhenkov, Anton, post-graduate¹, Loschenov, Victor, DrSci ²

AFFILIATIONS: ¹ Institute of Solid State Physics, Russian Academy of Sciences, Chernogolovka; ² Institute for General Physics, Russian Academy of Sciences, Moscow

CORRESPONDING AUTHOR: Nikolay Klassen, Institute of Solid State Physics, Russian Academy of Sciences, 142432, Chernogolovka, Moscow Region, Russia, Phone: +7 (903)7161631. Fax:+(7(496) 5228160. E-mail: klassen@issp.ac.ru

KEYWORDS: Cancer diagnostics, cancer surgery, cancer therapy, sapphire capillary, addressed drug delivery, point radiation therapy

ABSTRACT Sapphire capillary needles and scalpels developed in the Institute of Solid State Physics provide anticancer activities with new facilities for address drug delivery, express in vivo diagnostics and point therapy as well as for surgery with immediate information about the state of a tissue under the scalpel and instantaneous stopping of bleeding. Besides several capillaries connecting the spikes of the needles and scalpels with external ends these new facilities are based on three advantages of the tools: inertness of sapphire in contacts with biological tissues and liquids, good optical transparency in a wide spectral range and atomic smoothness of as-grown surfaces. Optical transparency of sapphire and possibility to have several micro-capillaries along the axis of a needle or scalpel provide in vivo application of a wide range of optical methods which are developed for analysis of tumors and other pathologies of living bodies (luminescence, Raman scattering, light absorption spectroscopy, etc.). For example, one of the capillaries can be used for the delivery of probing laser radiation to the point under examination, another – for collection and spectral analysis of the scattered and luminescence light whereas the transparent lateral surfaces will test the absorption spectrum of the tissue around the tool due to the effect of disturbed total internal reflection. In the case of sapphire scalpel the computer processing of the spectra thus obtained will supply the surgeon with immediate information about the state of the tissue being cut (cancer or healthy, etc.). Moreover one of the scalper capillaries can be used for immediate stopping of bleeding by means of laser light leading to coagulation of destroyed vessels. The diagnostics abilities of the sapphire needles can be improved essentially with especially functionalized luminescent nanoparticles. These nanoparticles are the main components of bio-chips which are used for spectroscopic analysis of biopsy probes. These nanoparticles fixed around the spoke of the sapphire needle can eliminate necessity of taking biopsy and provide fulfilling of this analysis of pathologies in vivo and instantaneously (if the needle be inserted into the patient body up to the contact with the suspicious point). Hence the bio-chip will be delivered to the pathology instead of delivering the part of the pathology tissue to the bio-chip. When the nature of the pathology will be determined by means of the procedure described above the microcapillaries in sapphire needles and scalpers can be used for addressed delivery of liquid drugs and suspensions of functionalized nanoparticles directly to the pathology. It should be emphasized that due to its chemical inertness the needles can be left inside the body contacting with the pathology for unlimited time duration. So it can be used for continuous optical analysis of the interaction of the drugs with cancer cells and other constituents of the pathology. On the other hand the microcapillaries due to softness of their internal surfaces can be used for point and effective delivery of X-ray and other radiations destructing the pathology without harmful treatment of healthy cells around it. This selectivity of radiation treatment can be enhanced by preliminary introduction of nanoparticles absorbing X-rays via the microcapillary into the pathology. Secondary electrons re-emitted by the particles will destroy pathological cells but will not touch healthy cells placed at distances longer than the electrons penetration depth. This depth can be regulated by adequate choice of the energy of the initial X-rays. On the other hand luminescent nanoparticles provide development of wide aperture X-Ray detectors with microscopic resolution capable to reveal cancer and other pathologies at the early stage of their growth.

AUTHORS: Mansur, Herman, PhD; Mansur, Alexandra, PhD

AFFILIATIONS: Center of Nanoscience, Nanotechnology and Innovation-CeNano\textsuperscript{1}, Federal University of Minas Gerais/UFGM, Brazil.

CORRESPONDING AUTHOR: Prof. Herman S Mansur, Department Center of Nanoscience, Nanotechnology and Innovation, Department of Metallurgical and Materials Engineering, Federal University of Minas Gerais, School of Engineering, Belo Horizonte-MG, Brazil (31901.270). Phone: +55 31 34091843 Fax: +55 31 34091815. E-mail: hmansur@deret.ufmg.br

KEYWORDS: Diagnosis of Cancer – Fluorescent Bioprobe – Bioconjugate.

ABSTRACT. Cancer is a global health problem causing more than 7 million deaths accounting to nearly 13% of all deaths worldwide. The burden of cancer is increasing globally, with an expected 20 million new cases per year in 2020, half of which will be in the low-and middle-income countries. Thus, the benefits of screening in terms of cancer prevention and early detection may bring about improvements in the treatment and a more satisfactory outcome. Nonetheless, screening for cancer is controversial in cases when it is not yet known if the test actually saves lives. Screening can lead to substantial false positive result and subsequent invasive procedures. Quantum dots (QDs) are ultra-small fluorescent semiconductor nanocrystals that have recently emerged as a novel class of nanomaterials due to their innumerable potential biomedical applications. QDs possess unique optical and electronic properties with narrow emission bands, high photo-stability associated with resistance to photo-bleaching surpassing organic dyes as biomarker and bioprobes for labeling and targeting cells, tissues and organs. Thus, the synthesis of biocompatible QDs with strong and stable photoluminescence in the visible region of electromagnetic spectrum is essential for developing advanced of QDs conjugates towards diagnosis, targeting and imaging cancer cells. However, to date, the large majority of luminescent QDs are based on highly toxic heavy metal “cores” (Cd, Pb, Hg) which are surface-functionalized with biocompatible “shells” using polymers and biomolecules raising some concerns regarding to their biological, medical and pharmaceutical applications as the long-term impact in humans is practically unknown. In the last 5-10 years, our research group has focused on designing and synthesizing novel water-soluble QDs via colloidal chemistry using facile, reproducible and economical processing methods by bio-conjugating with polymers, carbohydrates, amino acids, proteins and enzymes. Additionally, the QD-conjugates are luminescent and chemically modified towards offering affinity groups for targeting and detecting cell sites and other binding molecules. These nano-hybrid fluorescent systems offer suitable alternative to the techniques currently employed for cancer diagnostic such as medical imaging, tissue biopsy and bioanalytical assay of body fluids by enzyme-linked immunoassays which are often insufficiently sensitive and non-specific to detect most types of early-stage cancers. Moreover, these assays are labor intensive, time consuming, and quite expensive limiting their use as feasible screening methods for early cancer detection. In summary, in this study it is presented an approach for specifically designing water-dispersible QD conjugated to various biomolecules such as antibodies, peptides, polymers, saccharides and other ligands for potential use as luminescent bioprobes in the diagnosis and treatment of cancer.
O4. The AuNPs and AuNPs-Lanreotide conjugate in the inhibition of proliferation MCF-7 and B16 cells in vitro for treatment in cancer

AUTHORS: Molina-Trinidad, EM PhD¹; Estévez-Hernández, O³,⁴; Reguera Ruiz, E³; Santiago Jacinto, P⁵; Sánchez Morán, C⁶; Jiménez-Orozco, A⁶; De Ita-Gutiérrez, S.L.¹; Hernández-Ortiz, E¹; Garduño Villalobos O¹; Cruz-López S.¹


CORRESPONDING AUTHOR: Eva María Molina Trinidad. ICSa-UAEH. Tel: (01771) 71 72000 Ext. 5105, Fax; (01771) 71 72000 Ext. 5111. E-mail: mariaeva_molina@yahoo.com.mx

KEYWORDS: AuNPs; AuNPs-LAN; MCF-7 and B16 cells

ABSTRACT: Lanreotide (LAN) capped gold nanoparticles (AuNPs) conjugate (AuNPs-LAN) was prepared by a two-step aqueous synthesis: a variation of Turkevich method to prepare the colloidal gold nanoparticles followed of capping reaction with LAN. LAN is identified by spectrophotometry UV-Vis, Zeta-potential data and High-Resolution Transmission Electron Microscopy. The aim of this study was to develop a means of Capillary Zone Electrophoresis (CZE) to determine AuNPs-Lanreotide in vitro. Reduction HAuCl₄ was made with trisodium citrate, based on the synthesis of Turkevich-Frens for Au colloid to a boil. The UV-Vis detection was at a wavelength 530 nm at prolongation was observed migration times and peak broadening with the conjugate. We describe here the use of gold nanoparticles to manipulate the selectivity in Capillary Electrophoresis. In conclusion, the CZE has a greater sensitivity to determine AuNPs and AuNP-lanreotide, resulting in a good method to analysis making so reference spectrophotometric method and HRTEM used for study of AuNPs and the conjugate for study of biodistribution and pharmacokinetics. Also, check the inhibition proliferation cells of breast cancer MCF-7 and melanoma cells mice B16 with of AuNPs-LAN conjugate. Finally we are show results in relation with the nanoparticles elimination for use in biomedicine.
O5. Investigation of miRNAs involved in gliomagenesis

AUTHORS: Toru Kondo

AFFILIATIONS: Division of Stem Cell Biology, Institute for Genetic Medicine, Hokkaido University, JAPAN

CORRESPONDING AUTHOR: Dr. Toru Kondo. Division of Stem Cell Biology, Institute for Genetic Medicine, Hokkaido University. Kita-15, Nishi-7, Kita-ku, Sapporo 060-0815, JAPAN. Tel: +81-11-706-6082, Fax: +81-11-706-7870. E-mail: tkondo@igm.hokudai.ac.jp. http://www.igm.hokudai.ac.jp/stemcell/

KEYWORDS: miRNA, glioma, cancer stem cells, cancer-initiating cells

ABSTRACT Since it has demonstrated that malignant brain tumors, including glioblastoma multiforme (GBM), contain cancer-initiating cells (CICs; also known as cancer stem cells and cancer propagating cells), which self-renew and are malignant, a number of genes have been shown to be involved in the functions of CICs. However, it remains elusive to analyze functions of non-coding RNAs, including microRNA (miRNA). To identify miRNAs that increase and decrease in glioma-initiating cells (GICs), we used our induced mouse GIC lines, which form GBM even when ten of the cells are injected into brains of nude mouse, and human glioma sphere lines, which form glioma in brain of immunodeficient mouse. DNA microarray analysis revealed several miRNAs that increase and decrease in both mouse and human GICs, compared with their control cells. We focused on miRNA uncharacterized in glioma and found that the miRNA targets plasminogen activator network in GICs and induces cell cycle arrest and senescence. I will present details of our progress in the meeting.
O6. Notch pathway as new therapeutic target in Neuroblastoma

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KEYWORDS: Notch pathway, Neuroblastoma, Neuronal differentiation

ABSTRACT The Notch family proteins are a group of transmembrane receptors assigned to the control of cell fate during embryonic development. Notch pathway is involved in several type of cancers including Neuroblastoma, the most common extracranial solid tumor in childhood. The clinical and histological heterogeneity of Neuroblastoma seems to be the basis of the unsatisfactory response to classical therapies, leading to the search of new molecular pathways useful as a therapeutic targets. We identified that Notch pathway activation is responsible for increased proliferation of NB cells. On the contrary Notch pathway down regulation by gamma-secretase inhibitors, causes proliferation arrest and cell differentiation, and increases the 13-cis retinoic acid action. Furthermore, Notch pathway stimulation induces the Neuroblastoma cell resistance to retinoic acid differentiation. To better understand the role of Notch pathway in the onset and progression of Nb we studied the specific contribution of each pathway component, five ligands and four receptors, in cell lines with different malignancy degree.Dll1 ligand was identified as the Notch pathway component more expressed in high malignant neuroblastoma cells, and significantly inhibited by the component of microRNA 34 family, negative post-transcriptional regulators implicated in cancer control. In particular we found that miR-34 b induces Dll1 mRNA down regulation. Overall these data suggest that Notch pathway is an emerging therapeutics target in Neuroblastoma and Dll1-target therapy could be useful to arrest Neuroblastoma progression and prevent relapses.
O7. Cisplatin induces differentiation of breast cancer cells

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ABSTRACT  Breast tumours comprise cells with stem cell properties and more differentiated cells. This heterogeneity is reflected into the molecular breast cancer subtypes. Recent efforts are focusing on identifying treatments that may shift breast cancer stem cells (CSCs) towards a more differentiated phenotype, making them more susceptible to chemotherapy. We examined whether cisplatin, a metal-based anti-cancer drug induces differentiation in breast cancer cells that represent different breast cancer subtypes. Three cell lines representing triple-negative breast cancers, BT-549 and MDA-MB-231 (claudin-low) and MDA-MB-468 (basal-like), along with oestrogen and progesterone receptor positive MCF-7 cells (luminal) were used. Cell viability and proliferation were measured at 2.5, 5, 10 and 20 \textmu M cisplatin, using MTS and BrdU assays, respectively. The effect of cisplatin on the cellular hierarchy was examined by flow cytometry, immunofluorescence and qRT-PCR. Cisplatin treatment of 10 and 20 \textmu M reduced cell viability by 36-51\% and proliferation capacity by 36-67\%. Treatment with cisplatin resulted in 12-67\% down-regulation of stem cell markers and 10-130\% up-regulation of differentiation markers. These findings suggest that cisplatin induces differentiation of stem/progenitor cell subpopulations within breast cancer cell lines in addition to the reduction in cell survival. These effects indicate the potential of this drug to target specific chemotherapy-resistant cells within a tumour.
O8. Cytotoxicity of Apatone in vitro and in vivo xenotransplants: urologic and ovarian tumors

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KEYWORDS: Ascorbate:menadione - Apatone - tumor - chemotherapy - cell death

Oxidative stress induced in vitro (cancer cell lines) and in vivo (xenotransplants) demonstrated a new tumor cell damage developing into a new form of cell death named autoschizis. Morphological and biomolecular techniques showed that this novel cell death differs from necrosis, apoptosis or necroptosis and can be induced by ascorbate (VC) and menadione (VK3) treatment administered in a ratio of 100:1; those vitamins exhibiting synergistic antitumor activity. Morphology showed superficial and internal tumor cell cell alterations characterized by cytoskeletal damage and progressive nuclear irreversible changes, pieces of organelle-free cytoplasm are self-excised by tumor cells. During this process, mitochondria have lost ATP production and initiate signal for cell death but without caspase-3 activation while altering their matrices. Treatment induces intracellular Ca²⁺ levels, G₀/S and G₂/M blocks, diminishes DNA synthesis increases ROS production and decreases cellular thiol levels. These effects can be prevented by the addition of catalase to scavenge the peroxidative toxicity. Remaining organelles are clustered in a tight perikaryal area while altered nuclei displayed karyorrhexis and karyolysis and undergone progressive, extreme chromatolysis. Electrophoretic analyses of DNA have confirmed reactivation of DNases and RNases and DNA is cut randomly resulting in a smear pattern, like in necrosis. Ultimately tumor cells reduced their size with further self-excisions and the remainder nucleus burst along with its content. The xenotransplants treated by the same technique as in vitro demonstrated that the main cell death is through autoschizis with a few rare apoptotic cell deaths in the carcinomas allowing a significant tumor shrinking. More importantly mice treated by the combined vitamins outlived their Sham-treated without any significant toxicity. The technique has also been used in early clinical trials with success and on individual cases against at least several breast and ovarian cancers.

TRAMP autoschizis (in vitro - prostate tumor cells) Xenotransplanted DU145 human prostate carcinomas in SCID mice

Control After 1day treatment
O9. Personalized medicine in chronic lymphocytic leukemia

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KEYWORDS: CLL, personalized therapy, purine analogs, alkilator, monoclonal antibody

ABSTRACT In the last decade the big progress in a large number of disease therapies occurred. Despite that, to the date many cancers are still incurable. Chronic lymphocytic leukemia (CLL) is a common type of leukemia affecting most frequently older individuals, but with the growing number of younger cases around age of 40. A distinct disease progression, deregulated apoptosis and differences in response to therapy are currently main problems in the curing of this type of leukemia. Therefore, the choosing in in vitro conditions, the most effective type of treatment of CLL cell exposure to anticancer drug(s) could increase effective leukemia therapy options and avoid potential drug resistance in vivo.

The aim of our in vitro studies was to examine induction and progress of apoptosis in leukemia peripheral blood mononuclear cells (PBMCs) exposed to anti-cancer agents, i.e. combinations of drugs used in hematooncology: purine analogs applied with mafosfamide, an active form of cyclophosphamide, CM (cladribine + mafosfamide), FM (fludarabine + mafosfamide), and additionally to CM combined with monoclonal antibody, rituximab – RitCM. Moreover, purine analogs with anticancer potential: kinetin riboside (RK) and R-roscovitine (Rosc), were also tested. The CLL cell viability and rate of apoptosis were evaluated using Vybrant Apoptosis Assay #4. The changes in morphology of CLL cells exposed to anticancer agent(s) were observed by fluorescence microscopy (Hoechst 33258, IP).

The differences in CLL cell sensitivity in vitro exposed to anticancer agent(s) was noticed. The decrease of leukemic PBMC viability was observed. Moreover, the increase of apoptotic cell numbers were accompanied by the decrease (or even loss) of transition at 95±5°C in DSC of nuclear fraction preparations (chromatin remodeling). The proteolytic cleavage of apoptotic marker – PARP-1 was seen. These results were also confirmed by the changes in cell morphology after leukemia cell exposure to anticancer agent(s). For some cases, we observed the personal differences in the polarization of mitochondrial membrane and evaluate by fluorescent microplate method and a fluorescent carbocyanine dye JC-10. Usually, the collapse of ΔΨm after 48h of CLL cells exposition with agent(s) was correlated with programmed cell death course.

The obtained data revealed that CLL cell viability measurement, the changes in chromatin structure detected by DSC, as well as proteolytic cleavage of PARP-1 could be useful in the choosing and/or monitoring of anti-leukemic activity potential of anticancer agent(s).
O10. Mutagenicity of topoisomerase targeting anticancer agents

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KEYWORDS: DNA topoisomerases - mutagenicity - secondary tumours - abnormal reproductive outcomes

ABSTRACT Among the anticancer drugs currently used in the treatment of human malignancies, as well as several new series of drugs under development, are targeted at topoisomerase enzymes. Besides of inducing cell death due to both ‘mitotic catastrophe’ and the induction of apoptosis, topoisomerase-targeted drugs can increase the frequency of cells bearing mutations. These cells can develop resistance to the therapeutic agents or may lead to the development of secondary tumours and abnormal reproductive outcomes. This talk focuses on the mutagenic properties of the topoisomerase inhibitors, which are front-line therapies for a variety of malignancies. In addition, the topoisomerase catalytic inhibitors that are in clinical trials as anticancer agents will be discussed. An understanding of the mechanisms of mutagenicity is important not only in advancing our understanding of the action of mutagens but also in terms of improving cancer chemotherapy. This will, in turn, help us to design and bring safer drugs to the market. The demonstrated mutagenicity profile of topoisomerase inhibitors may support further development of effective topoisomerase inhibitors with less mutagenicity because such genomic alterations might result in an increased risk of birth defects, genetic disease or cancer in the children of cancer survivors.
**O11. Anticancer, antioxidant and antiobesity effects of some newly synthesized simple chalcone derivatives and their metal complexes**

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**KEYWORDS:** Chalcones – anticancer – antioxidant – antiobesity.

**ABSTRACT** A series of modified chalcone derivatives were prepared for anticancer, antioxidant and antiobesity screening. Chalcones with basic chelating or non chelating grafts at ring A were as active as Doxorubicin in prostate cancer cell line *in vitro*. The activity was reduced or at least in only one case retained upon Cu²⁺ and Zn²⁺ chelation. Chalcones with p-oleylamido residues at ring A (oleoyl esterone analogues) showed potential antiobesity activity with some derivatives being more active than a trade mark drug Orlistat in rat model *in vivo*. All synthesized chalcones were inactive as antioxidants either *in vivo* or *in vitro*.

![Chemical structures](image-url)
O12. Live yeast cells as a model for locating intracellular targets of fluorescing anticancer drugs

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KEYWORDS: Yeast – anticancer drug – doxorubicin – fluorescence microscopy – computer image analysis

ABSTRACT Yeast cells of Saccharomyces cerevisiae are widely used as a model for high eukaryotic cells in many studies of basic and applied cell biology. This is owing to the high degree of conservation in terms of DNA sequence similarity and function along with ease of genetic manipulation and handling. To test if the live yeast cells of S. cerevisiae can be used as a model for locating intracellular targets of fluorescing anticancer drugs, a methodology was developed called “single cell pseudospectral image analysis” based on fluorescence microscopy, color digital photography and computer image analysis (ImageJ software, NIH, USA). Intracellular distributions of the anticancer drug doxorubicin (DR) and nucleic acid dyes 4’,6-diamidino-2-phenylindole (DAPI) and ethidium (E) bromide were investigated. By visual inspection, it was observed that yeast cell culture was heterogeneous in stainability by DAPI, DR and E. There were different dynamics of staining by each dye. It was explained by the specifics of permeability of the cell envelopes for each substance, resulting from combination of at least two factors. The first one is the diffusion barrier of the cell wall and plasma membrane, the second is associated with the system of nonspecific drug resistance, providing energy-dependent excretion of cationic organic molecules from the cell. The fluorescence of DAPI in the cells made a clear pattern of “spots & dots”. The spots and dots corresponded to the nuclear and the mitochondrial DNA, respectively. A different pattern of fluorescence was seen for DR and E. While large spots, most probably representing nuclei, were well discerned, the entire region of mitochondria exhibited diffuse uniform glow. Upon joint treatment of cells with DAPI + DR or DAPI + E, both patterns were seen. To characterize further DR and E location, the following algorithm of ImageJ application for image analysis was developed. In the selected regions of interest (ROI “Oval Selection”) of the cell images, red, green and blue components of the fluorescence intensity were quantitatively assessed using “Analyze” plugin (“Measure RGB” option) in relative units of an 8-bit scale. The obtained data (pseudospectra) roughly corresponded to real spectra of the compounds measured by spectrofluorimetry in solution. The pseudospectra of DAPI and E were practically the same in nuclei and in the mitochondrial region. The red component of the DR pseudospectrum in nuclei was more pronounced than in mitochondria. These data could be interpreted supposing that some DR molecules were bound to mitochondrial membranes. This also explained the diffuse fluorescence of DR as distinct from the dot staining of mitochondria by DAPI. An essential distinction of the pseudospectrum of DAPI from those of DR and E was the lack of a red component and a more pronounced blue component. This allowed assessing the joint localization of DAPI with DR or E in the cells. Upon simultaneous addition of DAPI and DR, in the DAPI locations both in nuclei and in mitochondria the red component was greater as compared with DAPI alone, though smaller than with DR alone. If the cells were first incubated with DR and then DAPI was added, the qualitative pattern did not change but in total the red component was somewhat higher than upon their simultaneous addition. In both cases of DAPI + DR, the blue component almost did not change. Similar results were obtained for DAPI + E, with the difference that the intensity of the red component did not depend on the order of addition, while the blue component was somewhat lower when E was added before DAPI. Thus, pseudospectral analysis has revealed colocalization DAPI with DR or E in the DNA regions in nuclei and mitochondria. At the sites of colocalization of DR or E with DAPI the red component was markedly lower than when they were applied without DAPI. This result indicated potential competition of DAPI with DR and E for binding sites on DNA. In conclusion, with the approach presented herein, the yeast cells of S. cerevisiae can be used as a model for locating intracellular sites of the fluorescing anticancer drugs. This model may be of help in designing new DNA-targeted drugs and in preliminary studies of their interaction with eukaryotic cells.
O13. Are osteomimetic properties of cancer cells hoaxed or inherent cellular characteristics?

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KEYWORDS: mesenchymal - osteomimetic properties – metastasis- progenitor -

ABSTRACT Multiple publications describe the osteomimetic and mesenchymal properties of cancer cells and relate this to their tendency to metastasize to bone. Cancer cells are thought to originate from epithelial cells in the epithelium, and the question arises how cancer cells of epithelial origin can adopt osteomimetic properties. If we study osteomimetic properties in greater detail, we find that cancer cells of the primary tumour site already show osteomimetic features even in those cancer cells or types that seldom metastasize to the bone. Most known human carcinomas show an increased expression of osteopontin, osteocalcin and sialoprotein, which are bone-specific proteins. Thus the expression of bone-specific proteins by primary tumour cells is not just restricted to cancer cells metastasizing to bone but a general feature of the malignant phenotype. Moreover, cancer cells in the primary tumour site express various enzymes commonly expressed by osteoclasts too, such as TRAP, MMP-9 Cath-K and carbonic anhydrase, and the vacuolar H+-ATPase. These features do not accord with the assumed epithelial character of cancer cells in the primary site.

Preosteoclast-like behaviour is also reflected in the functional properties of cancer cells, that is: matrix-resolving properties, hormone and neuronal dependence, coupling with mesenchymal cells, migrating and transmigrating properties, neurogenetic properties, trafficking to the bone, immune deviation, sensitivity to antireumatics, bisphosphonates, polyphenols and steroids. When preosteoclasts fuse to osteoclasts they 'over-express certain intracellular signalling pathways which are likewise over-expressed in cancer cells during their proliferation.

When we compare the surface markers of cancer cells with those of osteoclasts and their myeloid lineage progenitors, we detect multiple correspondences. The following clusters of differentiation commonly expressed by myeloid, including pre- and osteoclast cells, are surface markers of various cancer cells as well: CD9, CD10, CD11b, CD13, CD14, CD24, CD26, CD31, CD34, CD35, CD36, CD37, CD40, CD44, CD46, CD47, CD49, CD51, CD53, CD54, CD55, CD56, CD59, CD61, CD63, CD68, CD71, CD73, CD75, CD80/86, CD81, CD87, CD90, CD97, CD98, CD105, CD115, CD117, CD151, CD133, CD147, CD163, CD164, CD166, CD184, CD200.

Beside the above cited clusters of differentiation expressed by both cancer and myeloid lineage cells, a multiplicity of other surface markers exist, of which we will name only the following: TLRs, RANK, ADAM, DAP12, OSCAR, MAC387, DC-STAMP, NK1 receptor, BMP receptor, Protease activated receptor-1 TRAF-6 and calcitonin receptors. The calcitonin receptors along with TRAP are specific osteoclast markers. These surface markers are not expressed by epithelial cells, demonstrating that cancer cells, even in their primary site, are more closely related to the various stages of myeloid cells. i.e. passing from stem cells to monocyte progenitor cells, dendritic cells, macrophages through to osteoclasts.

Due to epithelial markers, cancer cells seem likely to be of epithelial origin. But certain cells of the myeloid lineage, the Langerhans cells, usually adopt epithelial markers as well. Langerhans cells show a high level of epithelial surface markers CD326 (EpCAM), CD227(Mucin1) and E-Cadherin in the epidermis, through which they are connected with keratinocytes. Whether they may also adopt a local cytokeitin scaffold has not so far been ascertained to our knowledge.

MTA transgenic mice offer further evidence that myeloid lineage cells in the epidermis, rather than epithelial cells, are required for carcinogenesis. The mice are deficient in MHC-II positive cells in the epidermis, and Langerhans cells or any other myeloid cells are therefore completely absent in the epidermis. These mice are resistant to squamous cell carcinoma induction in the skin, which can be explained by the hypothesis that cells of myeloid origin, rather than epithelial cells alone, are a prerequisite for carcinogenesis. On the basis of phenotypic features, functional characteristics and intracellular signalling-specific activities, we hypothesize that cancer cells originate from the myeloid lineage. Cancer cells can be seen as different stages of the myeloid lineage, from bone marrow stem cells through monocytes to pre- and osteoclasts with the additional feature of malignancy. We can conclude that the osteomimetic properties of cancer cells are inherent properties of these cells and consequently cannot be interpreted as an epiphenomenon or as opportunistic features for the sole purpose of metastasis in the bone. Whether the fusogenic properties of macrophages and preosteoclasts or their plasticity allow them to adopt local cytokeatin characteristics, and how these aspects may be connected with their malignancy, is currently the subject of intense research undertaken by various research groups. If there is a transition between the different phenotypes of cancer cells, it is more a epithelial-myeloid transition and less a epithelial-mesenchymal transition.
O14. The Two Faces of Hypericin

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KEYWORDS: H. perforatum L. – hypericin – photodynamic therapy

ABSTRACT Hypericin a photosensitive pigment occurs in the plant Hypericum perforatum L. It is a substance which, thanks to its exceptionally good properties, has attracted for the decades interest of experts in the field of biology and medicine. Attention is given to its anti-retroviral, antidepressant, anti-inflammatory, antineoplastic, and antibacterial effects. Nowadays, however, scientists are mainly interested in the hypericin-mediated photodynamic therapy (PDT) as a promising anticancer therapy. The only comprehensive genotoxicological study, aimed at the detection of non-photoactivated hypericin genotoxicity assessment was accomplished in our laboratory on different genetic model systems. Previously we compared the potential genotoxic effect of non-photoactivated and photoactivated hypericin and their potential DNA protective effects. It was proved that non-photoactivated hypericin did not exhibit genotoxic or antigennotoxic effects. Moreover, our research was aimed at evaluation of the photoactivated hypericin induction damages to DNA using selected test systems enabling to assess growth inhibition, viability and apoptosis of selected cancer, non-cancer and stem cells in vitro. This work was supported by the grant APVV-0040-10, VEGA 1/0025/11.
O15. About the communication of cancer cells

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ABSTRACT The author has published derivations of a field theoretical model about the communication of cells and how to read and write the DNA by so called magnetic scalar waves (2012). On the other hand he has developed a scalar wave device for learning more about the new and unknown properties of these longitudinal waves. Actually at several scientific laboratories experiments take place with the aim, to prove the communication of cells by use of the scalar wave device. Some tentative results like killing cancer cells over a distance of more than 2 meters will be presented at the conference. The research is still going on but has to be reproduced by other laboratories. The idea is, to separate cancer cells, still connected by a scalar wave. If one sample is killed i.e. by 1% NaN3 and the “death information” is transported to the second sample by use of the scalar wave as a carrier wave switched on only few minutes, after 12 hours the cells at the receiver side are dead as well, whereas control samples are still alive. The practical research has been done only with cell cultures, not with cancer patients. This is why further developments by other, neutral institutes are required. More basic research has been done just proving the concept of cell communication by magnetic waves. It will be reported how yeast is slowed down in growth by Canesten, wherein the medicament is transferred via scalar wave. In another experiment, the expulsion of green peas seeds is increased by the growth hormone gibberelic acid over 4 m by modulating the 7 MHz-carrier wave. These experiments and many more descriptions about the practical use and the results of scalar waves may be found in the German book: “Skalarwellentechnik”, INDEL Verlag 2013, in the shop of www.meyl.eu. To be prepared about the used concept and the theoretical model of scalar waves the English written book “DNA and Cell Resonance” will be helpful or in a short form some published papers such as: Meyl, K.: “DNA and Cell Resonance: Magnetic Waves Enable Cell Communication”, DNA and Cell Biology. April 2012, 31(4): pp: 422-426. doi:10.1089/dna.2011.1415. A free access to this paper published in the Cell Biology is i.e.: http://www.kmeyl.de/go/Primaerliteratur/Magnetic_Waves-Enable-Cell_Communication.pdf
O16. A recombinant fungal compound Ostreolysin, induces anti-proliferative and pro-apoptotic effects on colon cancer cells

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KEYWORDS: Ostreolysin – cancer – apoptosis.

ABSTRACT Ostreolysin (Oly) is a protein found in the Pleurotus ostreatus mushroom (also called the oyster mushroom). It is a 15-kDa cytolytic protein expressed during fruiting bodies formation. This protein interacts with cholesterol-enriched raft-like membrane domains and forms trans-membrane pores. This unique ability enables it to exert hemolytic and cytotoxic activities specifically against cells rich in cholesterol-enriched domains (‘lipid rafts’). Since cancer cells contain high levels of lipid rafts in their membranes, we tested what could be the functional changes, induced by Oly, in colon cancer cells.

We obtained a recombinant version of Oly (rOly) by expressing the protein in E. coli using compatible expression vectors. Previous studies reported that the native Oly is equally hemolytic to human, bovine and sheep erythrocytes. Surprisingly, our recombinant version of Oly demonstrated no hemolytic activity. This fact is highly significant since this feature of rOly will probably prevent the lysis of other tissue cells.

We found that rOly is able to promote apoptotic death of HCT-116 colon cancer cells in a concentration of 125 μg/ml after 4 hours of exposure. A significant effect is observed when cancer cell viability is reduced to 50% after 8 hours only. Interestingly, rOly's effect on normal epithelial cells from the small intestine (FHs 74 Int) demonstrated a significantly reduced cytotoxic effect as compared to colon cancer cells.

Cells, including tumor cells, constantly face the decision of whether to survive and proliferate or to undergo programmed cell death (apoptosis). Therefore, identifying the pathways that are pro-apoptotic or anti-apoptotic has important implications for controlling tumor cell growth. Another interesting fact is that we have shown for the first time, that following treatment of cancer cells with rOly, Oly is able to penetrate through the cell membrane, which enters to the cytosol and accumulates in these cells. In addition, we also observed that rOly enhances cav-1 reorganization in clusters in lipid rafts on the plasma membrane.

We additionally tested the effect of rOly on HM-7 clones; HM-7 clone that expresses high levels of the protein cav-1 (#15) and HM-7 clone that does not expresses cav-1 (#1). The HM-7 clone expressing high cav-1 is sensitive to Oly as compared to HM-7 clone with no cav-1 expression. This effect was observed after treatment with rOly at a concentration of 62.5 μg/ml for 4 hours only. The cytotoxic effect of rOly on HM-7 clones is greater after 8 and 24 hours. However, rOly did not alter cav-1 expression in these clones and HCT-116 cells. Therefore, we concluded that the cytotoxic effect induced by rOly on colon cancer cells may be mediated by other lipid raft associated proteins, a case in point and the flotillins.

We demonstrate that control HM-7 cells (clone #1 and #15) lysates exhibit a double band when immunoblotted with anti flot-1 antibody, suggesting that the expression of the phosphorylated version of flot-1 is evidenced in these cells. Exposure of HM-7 cells to rOly completely inhibited the expression of this flot-1 putative phosphorylated species. The significance of these findings deserves further investigation.

In conclusion, this study represents a first effort to functionally characterize rOly as a potential pro-apoptotic drug and provide an innovative scientific evidence for its contribution in promoting death of cancer cells via apoptosis. This novel recombinant version of Oly exerts unique qualities such as cytotoxicity specifically against colon cancer cells and not against normal cells. Additionally rOly does not induce hemolysis as compared to the native Ostreolysin.
O17. Marine Natural Products as Drug-leads

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ABSTRACT. Many compounds with extraordinary chemical structures and brilliant bioactivities have been identified from marine organisms. I will illustrate the fascinating natural products as anti cancer drugs I have been investigating. My presentation consists of two topics.

1) Development of eribulin from halichondrin B.
2) Identification and characterization of novel antitumor natural products, lyngbyacycloamides.

Halichondrin B was isolated from the black sponge, Halichondria okadai, in 1986. Interestingly, this polyether macrolide exhibited antitumor activity both in vitro and in vivo. The mechanism of action of halichondrin B was shown to be a novel one that disrupts the polymerization dynamics of tublin, which makes this natural product an interesting candidate for the treatment of cancer. However, the difficulty of collecting sufficient material (only 12.5 mg from 600 kg of sponge) impaired studies for its development. The complete synthesis of halichondrin B in 1992 represented a breakthrough. The total synthesis also facilitated the structure-activity relationship study, and which revealed that the activity resides in the macrocyclic lactone C1-C38 moiety. Ultimately, the moiety derivative was approved for the treatment of breast cancer in several countries and is now available on the market as the anti-cancer drug Halaven.

Cyanobacteria are photosynthetic prokaryotes and that are widely distributed throughout marine and terrestrial environments. Members of the marine cyanobacteria genus Lyngbya are known to synthesize structurally interesting and biologically active secondary metabolites. Recently, my research group has purified new compounds lyngbyacyclamides A and B. The biological activities of these cyclic peptides are quite unique, since they show toxicity against B16 melanoma cells. And our study revealed that these compounds inhibit the ERK (Extracellular signal-regulated kinase) activity. Efforts to synthesize these molecules are currently in progress so that we can elucidate the mechanism of action in more detail.
O18. Synthesis and Characterization and Biological Activity of Metallocefepime and Metallocephradine Complexes.

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KEYWORDS: cefpime, cephradine, complexes.

ABSTRACT: Eighteen metal complexes of cefpime and cephradine were synthesized and analyzed. The complexes were characterized by physicochemical and spectroscopic methods gathered with magnetic measurements to be of different stoichiometries. The thermal analysis of the complexes was studied by TGA and DTA techniques to give more information on the structure of the investigated materials. The thermodynamic parameters of the decomposition reaction were evaluated and discussed. The change of entropy values, ΔS#, showed that the transition states are more ordered than the reacting complexes. The antimicrobial activities of the prepared complexes were screened in vitro against a Gram positive, a Gram negative bacterium and some fungi.
O19. Role of Vitamin D Binding Protein-derived Macrophage Activating Factor (GcMAF) in the immunotherapy of cancer

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ABSTRACT There has been much recent interest in the role of the vitamin D axis in the immunotherapy of cancer. The vitamin D axis includes vitamin D, vitamin D receptor (VDR) and vitamin D-binding protein (VDBP; also known as Gcglobulin) that is the precursor of the Gcglobulin-derived Macrophage Activating Factor (GcMAF) a protein that proved effective as an anticancer agent in a variety of experimental and spontaneous tumours (Oncol Lett. 2011 Jul;2(4):685-691). The interest for administering GcMAF to humans derives from the observation that different chronic pathologies such as cancer, HIV infection and systemic lupus erythematosus show elevated level of serum alpha-N-acetylgalactosaminidase (Nagalase), an enzyme that degrades VDBP resulting in the loss of MAF precursor activity with consequent impaired immune response (J Med Virol. 2009 Jan;81(1):16-26). Consequently, MAF precursor activity and serum Nagalase activity have been used as diagnostic indices for a variety of cancer patients and as prognostic indices during radiation therapy, surgical resection of tumours and GcMAF therapy of tumour bearing mice (Int J Oncol. 2004 Mar;24(3):521-8).

The well demonstrated anti-cancer efficacy of GcMAF can be attributed to different biological properties of the molecule that include activation of tumoricidal macrophages, inhibition of tumour-induced angiogenesis and direct inhibition of cancer cell proliferation, migration and metastatic potential (Anticancer Res. 2012 Jan;32(1):45-52). In the present study, we demonstrate that GcMAF-activated macrophages induce the apoptosis of human breast cancer cells and inhibit their proliferation in vitro. Macrophages (cell line Raw 264.7, HPA Culture Collection) were activated by culturing them in the presence of 100 ng/ml GcMAF (Immuno Biotech Ltd) for 72 h prior to addition to the human breast cancer cell culture (cell line MCF-7, HPA Culture Collection). Cell cultures were fixed and stained with Haematoxylin Eosin or with Papanicolaou staining after 18 and 40 h of co-incubation. It could be observed that GcMAF-activated macrophages surrounded MCF-7 cells and emitted pseudopods that appeared to “search for” contact with the cancer cells. MCF-7 cells in contact with activated macrophages showed a significantly altered morphology with large and irregular cytoplasm and with nuclei where the chromatin appeared fragmented as if the cells were undergoing apoptosis. In many fields the GcMAF-activated macrophages appeared to disaggregate the MCF-7 cytoplasm. These results are consistent with the recent observation that underlines the therapeutic potential of manipulating macrophage activation in breast cancer (Breast Cancer Res Treat. 2012 Sep;135(2):539-48), and provide a rationale to suggest clinical trials exploiting the potential of GcMAF in the immunotherapy of human cancer.
O20. Interaction between Trastuzumab and ErbB2 analyzed by molecular dynamics simulation

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ABSTRACT: Human epidermal growth factor receptor 2 (ErbB2) is a transmembrane oncoprotein that is over expressed in breast cancer. A successful therapeutic treatment is a monoclonal antibody called Trastuzumab which interacts with the ErbB2 extracellular domain (ErbB2-ECD). A better understanding of the detailed structure of the receptor-antibody interaction is indeed of prime interest for the design of more effective anticancer therapies. For this purpose, we have used molecular dynamics simulation (MD) at the atomistic and coarse grained scales. These methodologies can provide fine details about the molecular interactions between these proteins and give useful information to understand its biological action. The atomistic scale simulations were performed on the ECD / Trastuzumab Fab complex. In addition to the well established interaction between the Trastuzumab Fab and the ErbB2 domain IV epitope, a nascent interaction between domain II and the constant fragments of the Fab antibody is observed. This additional interaction is facilitated by a genuine hinge movement at the domain III/domain IV interface¹ (see the schematic representation on the left).

On the other hand, the coarse grained simulations were performed on the full ErbB2 receptor including the lipid bilayer. Starting from the Bagossi’s model², built using experimental information and homology modeling, a structural analysis of the influence exerted by the monoclonal antibody on the full receptor was carried out. Several multimicrosecond simulations arrived to structures of the protein complexes compatible with experimental observations. The ErbB2 ectodomain as well as the intracellular domain approached the bilayer surface, as can be observed on the two molecular representations (antibody-free system on the center and Fab including system on the right). However, the Trastuzumab Fab hindered the approximation of the ECD to the membrane, whereas the antibody effect is less notorious on the cytoplasmic domain, where the signaling cascade starts (the Fab molecule is represented in green). These findings support the idea that the main bioactive action of Trastuzumab is on the extracellular fragment, at least on the ErbB2 monomer.

References:
O21. Immunomodulatory and tumoricidal effects of grifola gargal, novel medicinal mushroom


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KEYWORDS:

ABSTRACT BACKGROUND: Antitumor activities of medicinal mushrooms appeared to be attributable to an immunomodulating action of their polysaccharides and polysaccharides-related complex in immune system. These polysaccharide-related compounds demonstrate their potent and unique properties as biological response modifiers (BRM).

OBJECTIVE: It is considered that immunomodulating polysaccharides from edible and medicinal mushrooms could augment or complement a desired immune system to maintain a health condition in a host. Cytokines play important roles in a regulation of immune responses via cytokine networks and signaling pathways. Then, normal immune responses could contribute to preventing from cancer and immunodeficiency diseases. In this study, we examined an immunomodulating action of polysaccharide fractions from novel medicinal mushroom, *Grifola gargal*, which is known as an edible mushroom in south region in Chile, against macrophages, and their tumoricidal effects.

MATERIALS & METHODS: The fruiting bodies of *G. gargal* cultivated at Iwade Research Institute of Mycology Co. Ltd. (Japan), was used. The lyophilized sample was extracted with hot water, and then a crude extract was obtained, and then it was separated by Sephacryl® gel permeation chromatography. The monocyte cell-line, THP-1 (Riken Cell Bank, Japan) was induced differentiation to a macrophage by PMA, and then stimulated with various concentrations of each fraction. After incubation, cytokine proteins and mRNAs produced in the macrophages were examined by western blotting and qRT-PCR, respectively. Moreover, after HeLa cells were co-cultivated with the stimulated cells, a tumoricidal effect was examined.

RESULTS: A crude extract of *G. gargal* induced to activate a macrophage. And then, it was shown that a growth of HeLa was inhibited by co-cultivation with it. We obtained three fractions from a crude extract. A polysaccharide fraction (Mw > 400 kDa) showed the strongest immunomodulating effect on cytokines productions. These cytokines were recognized as type 1, inflammatory, cytokine, such as TNF-α, IL-1β, IL-6, and IL-12. Moreover, we also elucidate that other polysaccharide-related complex (Mw < 20 kDa) played as a same immunomodulator.

CONCLUSION: It was shown that a hot water extract from *G. gargal* possessed a tumoricidal activity against HeLa. And, polysaccharide and polysaccharide-related complex fraction from it showed an immunomodulating effect on inflammatory cytokine production from stimulated macrophages. These results suggested that *G. gargal* induced a tumoricidal action of macrophages via type 1 cytokines network. It can be considered that *G. gargal* become a source of a novel medicinal material.
O22. Using GlycoExpress to produce glycooptimized antibodies for cancer treatment

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ABSTRACT Glycosylation is one of the major post-translational modifications of biotherapeutics that depends on the cell line used for production. By establishment of the GlycoExpress toolbox (GEX) we have generated a set of glycoengineered human cell lines for the high yield production of fully human glycoproteins to optimize the glycosylation of antibodies and non antibody biotherapeutics. Among other non antibody molecules three glycooptimized antibodies are presently in clinical development and further in the pipeline. Two of these are Biobetter antibody molecules directed against approved targets and glycooptimized with respect to manifold improvement of anti-cancer activity, half-life elongation, removal of immunogenic components and broadening of the patient and indication coverage.

The clinical outcome of the antibodies Cetuximab and Trastuzumab is largely depending on the FcyRIIIa allotypes where only less than 20% of the patients which are homozygous for the Valin allotype on position aa158 (V/V) show a drastically better clinical outcome than patients where the Phenylalanin (F) is present either heterozygous (F/V) or homozygous (F/F). The receptor is present on natural killer cells (NK cells) which are involved in antibody dependent cellular anti tumor cytotoxicity (ADCC) and are thought to be the main effector cells for cancer cell killing.

Based on glycooptimization by production in GlycoExpress the ADCC activity of CetuGEX, which is an improved 2nd generation GEX-glycooptimized antibody of Erbitux®, is improved by ~10-fold for patients carrying the V/V allotype and up to 250 fold for the other allotypes (>80% of patients). Thereby all allotypes reach an anti tumor activity about 10-fold higher than that of the V/V allotype with conventional non-GEX-glycooptimized antibodies. Therefore an improved anti-tumor activity and clinical outcome is expected for all patients as well as a broadening of the patient spectra. In addition, CetuGEX revealed a ~1.5-2 fold improvement of serum half live in PK studies within cynomolgus monkeys due to the optimization of its sialylation. The mean terminal serum elimination half-life of CetuGEX was 110 hours while the terminal half-life of Erbitux® was 67.5 hours, respectively, resulting in an improved area under the curve for the CetuGEX molecule. Furthermore, while Erbitux® induces severe hypersensitivity reactions that are caused by its non-human foreign Gallili epitope (Gal-Gal carbohydrate structures due to the production in mouse myeloma cells) CetuGEX will not since these structures are not present on CetuGEX.

TrasGEX is a Trastuzumab similarly GEX-glycooptimized as CetuGEX with a 10- 140 fold improved ADCC suitable for all patient ADCC receptor allotypes.

PankoMab-GEX is a highly potent anti-tumor antibody for up to 100% of the patients of Ovarian, Breast NSCLC and other endometrial cancers. It is directed against a combined carbohydrate-protein epitope specific for tumors combining high tumor-specificity towards the de novo carbohydrate tumor antigen and high affinity towards the protein part.

All these antibodies are in Phase I/II clinical development and preliminary data from Phase I indicate high clinical potency of the drugs.

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KEYWORDS: glioma, cancer stemness, stem cells, senescence, relapse, translational oncology

ABSTRACT: In contrast to the classical stem cell theory that proposes that there is a small subpopulation of cancer cells with stem cell properties, we have proposed the stemness phenotype model (SPM) as an alternative model. The SPM proposes that all cancer cells have stem cell properties and thus all of cancer stem cells are potentially tumorigenic. Therefore, to cure cancer, all cancer cells should be eliminated at once. Following this hypothesis, we developed in vitro a two phase treatment (2PT) where in the first phase cells are exposed to conventional anticancer drugs, followed by a second phase treatment with salinomycin. Our result showed that several conventional anticancer drugs eliminate the bulk of cancer cells but there is fraction of surviving cells that adopt a senescence-like state. Regarding gliomas, we found that glioma cells resistant to the clinically useful anticancer drugs temozolomide (TMZ), carmustine (BCNU), and lomustine (CCNU) survive and adopt a senescent-like state. In the second phase, a low concentration (0.5 uM) of salinomycin prevented the regrowth and partially eliminated these surviving cells. All together, the SPM and the 2PT may provide the basis for a more rational approach to develop effective anticancer therapies for gliomas and perhaps this strategy can be extrapolated to other tumors.
POSTER PRESENTATIONS
P1. Chemotherapy for Cancer Stem Cells

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KEYWORDS: cancer stem cells – small organic molecules – transcription factor

ABSTRACT Cancer stem cells (CSCs) usually stay in the stationary phase so that they are resistant against the ordinal chemotherapies because these treatments are effective to growing cells. Upon some stimuli or environmental alterations, the CSCs are activated and induced proliferation, then finally form secondary cancer cells. If we could modulate stem cell-like properties of CSCs by small organic molecule, it is expected that we could eliminate cancers from human body.

According to the recent studies, stem cells possess a molecular mechanism that guarantees undifferentiated state while they can proliferate well. One of the key factors related to this mechanism is transcription factor, Hairy and Enhancer of Split 1 (Hes1). This helix-loop-helix type transcriptional repressor is expressed in almost all undifferentiated cells, and inhibits differentiation [Kageyama et al., Exp.Cell Res, 2005]. For example, forced expression of Hes1 in fibroblasts results in the resistance to myogenesis, which in turn, repression of Hes1 expression facilitates differentiation. In the case of cancer cells, it was shown that expression level of Hes1 is 5~50 times higher in all the cell lines of rhabdomyosarcoma or cancer cells derived from patients [Sang et al. Science, 2008]. Thus, it is expected that Hes1 inhibitor could take stem cell-like property away from CSCs through induction of their differentiation.

Hes1 functions through association with a co-repressor, Grocho/transducing-like Enhancer of Split (Gro/TLE) family of proteins. The most important thing is that a Trp-Arg-Pro-Trp (WRPW) motif of C-terminus of Hes1 is required and sufficient for the binding to Gro/TLE. We speculated a WRPW motif mimicking compound binds to Hes1 binding site of Gro/TLE, interfere the association between Hes1 and Gro/TLE, and then inhibit Hes1 function. We take some advantages in this idea for three reasons: the motif is 1) only four amino acids long, 2) composed of characteristic amino acids, and 3) shown to be turn conformation at Pro residue. These features prompted us to design, synthesis, and evaluate the WRPW motif mimic.

For our initial study, we selected benzodiazepine scaffold to mimic the turn structure, and prepared 10 compounds. To evaluate the efficacy of these compounds, we can employ a luciferase reporter assay because Hes1 is a transcription factor. Briefly, introduction of Hes1 expression vector into the cells results in decrease of Luc activity because of transcriptional repression activity of Hes1 when using Luc plasmid containing actin promoter and Hes1 binding site, N-Box. In the presence of active compound, Luc activity should be restored by inhibiting the interaction between Hes1 and Gro/TLE.

We tested 10 compounds by luciferase assay, and found that one of the compound exhibited the activity. Docking study between the compound and Gro/TLE suggested several improvement points to increase activity. According to this, synthesis of second-generatin compounds is now in progress.
P2. Biomodulation of H2O2 genotoxicity by phytochemicals from Armoracia rusticana

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KEYWORDS: Chemoprevention –antioxidant – DNA damage modulation.

ABSTRACT In the recent years the research on various natural compounds has attracted extensive attention of scientists due to their potential usefulness in chemoprevention and treatment of cancer and some degenerative diseases. Because the prevention is better than cure, an emphasis has been given to find and chemically and biologically describe the new potential natural compounds which could help mostly in the chemoprevention. Therefore, a study of the influence of the plant extracts on human body is of great importance. In the following research the modulatory effects of the aqueous extract from Armoracia rusticana (horseradish) (AE) was studied. This perennial herb belongs to Brassicaceae family and it is widely used across the Europe. Firstly, we studied the molecular mechanisms underlying a potential antioxidant activity of AE using four assays: the DPPH assay, OH radicals scavenging assay, DNA-nicking assay and the Reducing power assay. Secondly, we aimed at the antigenotoxic/modulatory effect of an aqueous extract from A. rusticana, by the pre-treatment and post-treatment of H2O2-treated human lymphocytes. We focused on pre-treatment and post-treatment by AE as a way of hydrogen peroxide-induced oxidative DNA damages modulation using the alkaline Comet assay. It was proved that pre-treatment caused a significant reduction of the DNA damages, and AE acted as a desmutagen due to its antioxidant activities. This work was supported with the grants VEGA 1/0025/11, SK-BG-0006-10, BG/SK/206, APVV-0040-10.
P3. The pro-apoptotic effect of photoactivated hypericin A549 cell line

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KEYWORDS: Hypericin – photodynamic therapy – apoptosis.

ABSTRACT Hypericin is a substance isolated from Hypericum perforatum L. It is mainly known for its beneficial effects on human body such as antibacterial, anti-inflammatory, anti-depressant effects. Recently researchers have shown an increasing interest in hypericin mediated photodynamic therapy which is known for its tumour-seeking ability and minimal toxicity in dark. Our objective was to determine the effect of different concentrations of photoactivated hypericin to inhibit the growth of the A549 cell line and also to determine the mechanism inducing this effect. Our results show that the growth inhibition of hypericin treated and subsequently photoactivated A549 tumor cells is dependent on the concentration of hypericin and is caused by reduced viability and increased apoptosis of monitored cells. This work was supported with the grant APVV-0040-10.
**P4. Genetic polymorphism of five genes associated with growth traits in goat**

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**KEYWORDS:** Goats, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), GH, IGF-1, POUIF1, MSTN, BMP-15.

**ABSTRACT** Genetic polymorphism studies in domestic animals aim at evaluating genetic variations within and across breeds mainly for conservation purposes. In this study, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to detect polymorphisms of five candidate genes in four Egyptian and Saudi goat breeds (Barki, Zaribi, Ardi and Masri), to detect the genotype of GH, IGF1, POUIF1, MSTN and BMP15 genes in the goat breeds and their allele frequencies. Results of GH gene which encloses a Haelll endonuclease restriction site show four unique PCR-RFLP banding patterns (genotypes AA, AB, CC and CD). The frequencies of the A allele in the samples from the goat breeds varied from 0.410 to 0.620. While IGF-1gene revealed three fragments after digestion with Haelll with genotype AA, AB and BB and the frequencies of allele A varied from 0.432 to 0.731. Furthermore, PCR-RFLP of POUIF1 gene showed two fragments after digestion by PstI endonuclease with genotype TT and CC and the frequencies of allele T varied from 0.250 to 0.840. The MSTN gene revealed three fragments after digestion with Dral with genotype AA, BB and AB and the frequencies of allele A varied from 0.240 to 0.630. Meanwhile, the BMP15 gene revealed one fragments of 112 bp for AA after digestion with Hinfl enzyme.
P5. Ugonin K induces human skin cancer cells apoptosis by reactive oxygen species-mediated signal pathway

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KEYWORDS: Ugonin K – skin cancer cells – apoptosis

ABSTRACT. Skin cancer is divided into two groups by histological features – nonmelanoma skin cancers (NMSC) and melanomas. Cutaneous basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of NMSC are almost 75% among human skin malignancy cancer. Ugonin K isolated from Helminthostachys zeylanica, inhibited the growth of human skin cancer cells, especially in the case of treatment of SCC25 and BCC. The cytotoxicity results show that ugonin K expressed less toxic to human keratinocytes (HaCaT cells) and human skin fibroblasts (Hs68 cells) than BCC cells, suggesting that ugonin K may have potential to be developed effective drugs for skin cancer cells without damaging skin normal cells. After treatment with ugonin K in BCC cells, cell cycle arrested in S-G2/M phase with a markedly increased apoptotic sub-G1 peak, the expression of p53 and p21 revealed a more significant increased than the untreated control. In addition, ugonin K was found to increase reactive oxygen species generation on SCC25 and BCC cells. In this study, we expected ugonin K has potential for an effective and specific drug to cancer cell, can minimize the damage to normal cell and provide a better therapeutic method to skin carcinoma.
P6. Acute Taxol Toxicity: the Effects on Bone Marrow Mitotic Index and the Histology of Mice Hepatocytes


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KEYWORDS: Taxol, toxicity,

Hepatotoxic effects of acute intraperitoneal administration of 3 doses; MTD (Maximum tolerated dose) 1.7, ID (Intermediate dose) 1.15 and MD (Medical dose) 0.6 mg/kg Taxol were histologically studied. Mitotic index in bone marrow cells was used to test the drug effect on cell cycle. Vascular congestion, dilation and bile ducts dilatation was observed in liver. Hepatocytes became ballooned and the cytoplasm appeared vacuolated. Apoptotic cells were frequently encountered in all samples. Ultrastructure changes included degeneration of hepatocytes cellular organelles such as endoplasmic reticulum and mitochondria, lipid accumulation and cytoplasmic vacuolation. A significant decrease in mitotic index values in bone marrow cells was observed with higher doses after 24, 48 h. The frequencies of MicroNucleated Polychromatic Erythrocytes (MN-PCEs) were significantly higher in the Taxol treated mice after 24 and 48 h with all doses. This study indicated eneugenic and apoptotic potential of Taxol in mice.

This abstract was selected as “Best poster Presentation”
P7. Anti-adhesive effect of bergamot juice: a novel drug against metastases?

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KEYWORDS: Bergamot juice – cell adhesion – metastases

ABSTRACT Citrus bergamia Risso & Poiteau, a small tree belonging to the Rutaceae family, is cultivated almost exclusively along the southern coast of Calabria region (Italy). Bergamot fruit is mostly used for the extraction of essential oil from the peel, widely used in perfume industry. Instead, bergamot juice (BJ), which is obtained from the endocarp, is considered just as a secondary and discarded product. Over the past few years BJ attracted large attention as a result of its remarkable content of flavonoids, known for their beneficial effects. Based on the growing deal of data concerning the biological activity of flavonoid-rich natural products, the aim of the present study was to explore the anti-adhesive effect of BJ both in vitro and in vivo. Recently, we have documented the antiproliferative effects of BJ in vitro, shedding light on the mechanism through which exerts its anti-tumoral activity [1].

Here we show that BJ reduced neuroblastoma (NB) cell adhesiveness, invasiveness and migration capability in several in vitro models. The inhibition of adhesive capacity of SH-SY5Y, SK-N-SH and LAN-1 cells on different physiologic substrates and on endothelial cells monolayer were correlated with impairment of actin filaments, reduction in the expression of the active form of focal adhesion kinase (FAK) that in turn caused inhibition of cell migration. In parallel, BJ seems to hinder the association between the neural cell adhesion molecule (NCAM) and FAK.

Moreover, BJ exhibit slight anti-metastatic activity in a spontaneous metastatic NB xenograft model in vivo, showing some ability to reduce lung metastases in both LAN-1 and SK-N-SH-SCID mice.

Our data suggest a mechanisms through which BJ can inhibit important molecular pathways related to cancer-associated aggressive phenotype and suggest that the slight inhibitory effects on lung metastasis colonization in vivo may be due to impairment of NB cell adhesiveness, migration and invasion observed in vitro.

Finally, lack of any apparent sign of systemic toxicities suggest a promising role of BJ in oncologic field and offer new suggestions for further studies on the role of BJ in cancer treatment.

P8. NEWS TREATMENTS FOR LEUKEMIA IN MEXICO

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ABSTRACT Leukemia is the general term for some different types of blood cancer. There are four main types of leukemia called: Acute lymphoblastic (lymphocytic) leukemia (ALL), Acute myeloid (myelogenous) leukemia (AML), Chronic lymphocytic leukemia (CLL), Chronic myeloid (myelogenous) leukemia (CML).

It is important to know that patients are affected and treated differently for each type of leukemia. These four types of leukemia do have one thing in common – they begin in a cell in the bone marrow. The cell undergoes a change and becomes a type of leukemia cell.

The marrow has two main jobs. The first job is to form myeloid cells. Myeloid leukemia can begin in these cells. The second job is to form lymphocytes, which are a part of the immune system. Lymphocytic leukemia can arise in these cells. The leukemia is called lymphocytic or lymphoblastic if the cancerous change takes place in a type of marrow cell that forms lymphocytes. The leukemia is called myelogenous or myeloid if the cell change takes place in a type of marrow cell that normally goes on to form red cells, some kinds of white cells and platelets. For each type of leukemia, patients are affected and treated differently.

ALL and AML (acute leukemias) are each composed of young cells, known as lymphoblasts or myeloblasts. These cells are sometimes called blasts. Acute leukemias progress rapidly without treatment.

Patients who relapse after treatment and Patients who continue treatment after remission (maintenance). A carefully conducted clinical trial may provide the best available therapy.

Mexico is estimated that there are ten thousand new patients with leukemia and related diseases that are diagnosed each year, and in Mexico, for historical reasons, this is a cancer that is not treated by oncologists, hematologists treat it, said Dr. David Gomez Almaguer, president of the Mexican Association for the Study of Hematology. Under the National Day Leukemia specialists as the president of the College Jalisco Hematology, Charles Best Aguilera, the Doctor, Julio Kassack Ipiña General Hospital of Mexico, said in a press conference that although the innovative therapeutic options currently exist that allow patients with chronic myeloid leukemia (CML), the 6000 Mexican adults with the disease many are anymore they have and others do not have access to the latest therapies. Currently, there are new drugs called "molecular targeted therapies, which increase life expectancy and quality of life of patients, such as Imatinib (Glivec) and Nilotinib (Tasigna) that directly attack the malignant cells without harming healthy ones with this treatment, patients no longer suffer the aggressive therapies with traditional treatments such as radiotherapy and chemotherapy, allowing patients to continue with their daily activities while enjoying a good health with good quality of life. The chronic myeloid leukemia (CML) is a malignant disease of the blood and bone marrow progressive and slow that occurs in middle age, with the highest incidence between 35 and 55 years of age.
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