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Poster Sessions

Day 2

Yhun Y Sheen, J Clin Exp Pathol 2018, Volume 8
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Vactosertib, ALK5 inhibitor combinatorial treatment with radiation inhibits lung metastasis in syngeneic breast mouse models

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Radio-resistance and relapse after chemotherapy is a life-threatening problem for breast cancer patients. We identified the molecular signatures of the recurrent breast cancer patients after radiotherapy, which showed the up-regulation of TGF-β signaling and the epithelial-to-mesenchymal transition (EMT). In order to find the potential therapeutic strategies to improve radiation therapy, we conducted gene set enrichment analysis, a computational method that determines whether an a priori defined gene set shows statistically significant between two phenotypes, using the breast cancer clinical data with Servant cohort (GSE30682). Since we have proved that EW-7197 showed the inhibitory effect *in vivo* in various breast cancer mouse models previously, we carried out experiments that might test if combinatorial treatment of EW-7197 improves radiation therapy using two syngeneic mouse models. Met 1 cell, which are derived from primary tumors of the FVB/N transgenic mouse with mammary tumor-polyoma virus middle T antigen (MMTV-PyVmt), were injected to fourth inguinal fat pads of FVB/N mice. 4T1 cells, which are derived from primary tumors of Balb/c mice, were injected as same way into Balb/c mice. Mice were treated with the fractionated-radiation (total dose 12 Gy, 4 Gy X3) with or without the combinatorial treatment of EW-7197 (2.5 mg/kg). Conclusion & Significance: Vactosertib (EW-7197), ALK5 inhibitor combinatorial treatment with radiation inhibits tumor growth and metastasis in syngeneic breast mouse models. This effect of Vactosertib (EW-7197), ALK5 inhibitor combinatorial treatment with radiation inhibits tumor growth and metastasis in syngeneic breast mouse models. Vactosertib (EW-7197) maybe related to the breast cancer stem-like phenotype, which is increased by 4Gy irradiation *in vitro*. We need to further study to conclude the therapeutic mechanisms of EW-7197 on improving radiation therapy. This work was supported by the National Research Foundation of Korea grant funded by the Korea government (NRF-2015M2A2A7A01041499) and (NRF-2014R1A1A2005644).

Biography

Yhun Sheen has her research interest in developing new anti-cancer drug. She had participated in the development of TEW-7197 which is currently under clinical trial in USA (NCT02160106).

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Notes:

M Alasmari et al., J Clin Exp Pathol 2018, Volume 8
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Study the effects of capsaicin on triple negative breast cancer cells

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Triple negative breast cancer (TNBC) is one of the most aggressive types of breast cancer. It accounts for 12% of breast cancer cases. It lacks of estrogen receptor (ER), progesterone receptor (PR), and human epidermal receptor 2 (HER-2) which limits its treatment options and enhances its ability to metastasize and raises the risk of recurrence. Patients with TNBC are not responsive to conventional targeted breast cancer therapies. Capsaicin (CAP) is the most abundant and potent capsaicinoid produced in chili pepper fruits. Capsaicin has been used for its analgesic and anti-inflammatory effects. Moreover, several studies have shown that capsaicin has anti-carcinogenic properties in various types of human cancers. The aim of this study is to investigate the effects of capsaicin in human TNBC by using the BT-20 cell line. The results showed that capsaicin demonstrated concentration and time-dependent inhibitory activity on BT-20 cell viability as determined by MTS assay. Capsaicin produced cell viability inhibition at concentrations 150 and 250 μM at 24 and 48 h while at 72h it caused inhibition on cell viability at concentrations of 100, 150 and 250 μM. Capsaicin showed significant 5 fold increase in cytochrome C release at 250 μM as well as significant 1.6 fold increase in caspase 3/7 activity at 250 μM. Which are markers of apoptotic activation. In conclusion, capsaicin showed an inhibitory effect on cell growth and enhance apoptosis. These results will provide useful information regarding the development of a new therapy that can help in treating TNBC.

Biography

Moudi Alasmari is a PhD candidate in pharmacology at Massachusetts College of Pharmacy and Health Sciences University (MCPHS University, Boston, USA). She completed her MS in pharmacology in 2014 from MCPHS University. She is a Pharm D graduate from King Abdulaziz University (KAU, Jeddah, KSA) in 2009. She has experience in neuroscience research. She did 3 poster presentations and wrote 1 article under submission in this field. Also, she has been working in breast cancer research and she did one poster presentation about the anticancer activity of *annona muricata* extract on triple negative breast cancer cells and isolation/charcterization of active compounds.

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Knowledge modification in a group of Cuban women at risk of breast cancer

Priscilla Akua Agyapong and **Wilson Selorm Gobah**
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Statement of the Problem: Breast cancer is the most frequent malignant lesion in women, and the first cause of death by cancer in most developed countries. Cuba, though a developing country is not an exception to this negative trend, due to a high number of risk factors. Addiction to cigarette, and other illegal drugs is a major world-wide risk factor and health concern for breast cancer development. Cuba, one of the world's largest producer's tobacco has registered a significant increase in breast cancer cases in the last decade, due to tourism and the false perception of expressing friendship and recreation through the smoking of tobacco and other illegal drugs. In spite of efforts of reducing mortality rates through the use of modern methods that complement breast cancer diagnosis once the lesion is detected, results have not been that satisfactory, which prompted the organization of a national sub-program for pre-clinic and early breast cancer diagnosis.

Findings: An analytical study of cases and controls was realized in the province of Camaguey in Cuba, between January and September 2017, with the objective of identifying some of its risk factors. By establishing certain parameters the case and control groups were constituted by 90 women, who were selected at random. It was realized after the survey that the case group women had certain risk factors that are associated with a high possibility of developing breast cancer such as, family and personal history of breast cancer, toxic habits such as the smoking of cigarettes, age (50 to 65 years), early menarche and late menopause, first child birth after 30 years of age. It can be seen from the table 1. that 65(72.2%) of the case group women were addicted to the toxic habit of smoking cigarettes, compared to 21(23.3%) of the control group women, which signifies that, the practice of this toxic habit increases 8 times the possibility of developing the disease.

Conclusion & Significance: Health measures should geared towards preventing the modifiable risk factors of the disease, through education and health programs. Self-breast examination should be encouraged amongst women which can play a role in early diagnosis, thereby helping decrease significantly the rate of breast cancer in Cuba and the world as a whole.

Biography

Priscilla Akua Agyapong is a focused Ghanaian young lady, with the passion of improving health and wellbeing within and outside Africa. She is currently a 5th year medical student at the University Of Medical Sciences Of Havana. "Manuel Fajardo Faculty". Havana, Cuba. Before her current medical degree which is scholarship program, sponsored by the government of Ghana, she was pursuing her nursing degree at the Valley View University College, Accra, Ghana.

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The link between hormonal replacement therapy (HRT) use and breast cancer risk

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Statement of the Problem: Over 2200 of new breast cancer cases are diagnosed annually in Cuba, and it is estimated that 1 in 14 women will develop the disease. The highest incidence occurs among women between 45-65 years of age, and is the second leading cause of death in women. Hormonal replacement therapy (HRT) is any form of hormone therapy wherein the patient, in course of treatment receives hormones either to supplement lack of naturally occurring hormones or to substitute them. There are two main types of HRT: Combination HRT which contains the hormones estrogen and progesterone, and estrogen-only HRT, both of which have been linked to different effects on breast cancer risk. Combination HRT increases breast cancer risk by about 75% even when used for only a short time, whiles the estrogen-only HRT increases risk when used for more than 10 years. Current or recent past users of hormonal replacement therapy have a higher risk of being diagnosed with breast cancer. Before the link between HRT use and breast cancer link was established, many postmenopausal women took HRT for many years to ease menopausal symptoms such as hot flashes and fatigue and to reduce bone loss. Cuba is not an exception to the significant drop in the number of women taking HRT, since 2002 when research linked the therapy to the risk of developing breast cancer.

Findings: By establishing certain parameters a survey was conducted for a period of time to study the impact of the hormonal in a group of 22 Cuban women above 40 years who were in use of the therapy. It was realized after the intervention that most of the women surveyed were all oblivious of the risk of developing breast cancer through the use HRT, which helped increase their knowledge significantly, with as high as 90.9% of the participants acquiring adequate knowledge about the risk of developing breast cancer through the use of HRT after the survey relative to 13.6% before the intervention program as shown in table.1

Conclusion & Significance: This intervention has been found to be a useful avenue to address this topic, therefore recommendations made for future researches to throw more light on the topic since very little research has been done on it. Recommendations are also so made for early diagnosis, alternative and safer forms of treatment to reduce breast cancer incidence and mortality, since most women have had a positive attitude towards HRT use based on empirical data.

Biography

Wilson Selorm Gobah is from Ghana, and he is very passionate about improving the quality and delivery of healthcare in African. He is currently at 5th year medical student at the University Medical Sciences of Havana, Cuba that is sponsored by a Ghana Government Scholarship program. He was a Participant at the "10th Global Summit on Toxicology an Applied Pharmacology" held during July 20-22, 2017 in Chicago, USA. After the completion of his bachelor's degree program in chemistry from the Kwame Nkrumah University of Science and Technology, Kumasi, Ghana, He had the opportunity to work on several scientific researches with the center for scientific and industrial research, Ghana (CSIR). He draws on all these and other experiences, especially, the interaction with patients to shape his perspective on some of the novel ways the standards on healthcare and delivery can be improved.

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Notes:

Xiu-Mei Fu et al, J Clin Exp Pathol 2018, Volume 8
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The status and potential of Chinese marine materia medica resources

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Chinese marine materia medica (CMMM) is a vital part of traditional Chinese medicine (TCM). Compared with terrestrial TCM, the CMMM derived from specific marine habitats possesses peculiar chemical components with unique structures reflecting as potent pharmacological activities, distinct drug properties, and functions. Nowadays, CMMM appears to be especially effective in treating such difficult diseases as cancers, diabetes, cardio-cerebrovascular diseases, immunodeficiency diseases and senile dementia and therefore has become an important medicinal resource for the research and development of new drugs. In recent years, such development has attracted wide attention in the medical field. In this study, the CMMM resources in China were systematically investigated and evaluated. It was found that the historical experiences of Chinese people using CMMM have continuously accumulated over a period of more than 3,600 years and that the achievements of the research on modern CMMM are especially outstanding. By June 2015, 725 kinds of CMMMs from Chinese coastal sea areas have been identified and recorded, covering 1,552 species of organisms and minerals. More than 3,100 traditional prescriptions containing CMMS have been imparted and inherited. However, the number of CMMS is less than terrestrial TCM, which contains 8188 kinds of terrestrial TCM, concerning more than 12100 species of medicinal terrestrial plants, animals, and minerals. In the future, the research and development of CMMM should focus on the channel entries (TCM drug properties), compatibility, effective ingredients, acting mechanisms, drug metabolism as well as quality standard. Our study reveals that the potential of CMMM development is worth expecting.

Biography

Xiu-Mei Fu received his Ph.D. degree in marine medicinal bioresources from Ocean University of China, Qingdao in 2008. From 2000 to 2002, she studied for environment and resource science as a visiting scholar at University of Duesseldorf, Germany. Since 2006, she is an associate professor of marine medicinal bioresources at Ocean University of China. She is a member of the Commission of Shandong Oceanology and Limnology Special Committee, China. She has published more than 40 papers in reputed journals and 3 monographs.

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Cindy Yeoh, J Clin Exp Pathol 2018, Volume 8
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Hyperhomocysteinemia and Anesthesia

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57year old female with a history of uterine and breast cancer s/p chemoradiation presented for cervical LEEP/cone biopsy/D&C. Her medical history was complicated by elevated LFTs with recent hyperhomocysteinemia. She was seen by a hematologist prior to presenting for surgery. It was concluded that elevated homocystein levels were due to cancer therapy and alcohol consumption. The procedure was performed under monitored anesthesia care. The patient was sedated with 2mg of Midazolam, 50mcg of Fentanyl, and a bolus of 70mg of Propofol followed by a steady infusion of 150mcg/kg/min. Causes of hyperhomocysteinemia include genetic predisposition, acquired deficiencies (folate, B6, B12), malignancies, and renal disease. Elevated homocystein levels result in thromboembolic complications by causing endothelial dysfunction, increasing procoagulant activity, and decreasing antithrombotic effect. Challenges of patients with hyperhomocysteinemia undergoing anesthesia are related mainly to the procoagulant state and efforts should be focused on thromboprophylaxis and maintenance of hemodynamics and euvolemia. Patients with co-morbidities that include coronary artery disease, peripheral vascular disease, and cerebrovascular disease are at increased risk for peri-operative thrombotic events and post-operative complications. This risk is amplified for high-risk procedures under general anesthesia. In this case, the patient presented for a low-risk procedure. She did not have a history of coronary or cerebrovascular disease, but had risk factors (surgery, age>50yrs, malignancy, cancer therapy) in addition to a hypercoagulable state (due to elevated homocystein levels) that posed increased peri-operative risk for thrombotic events such as deep venous thrombosis and pulmonary embolus. The decision was made to proceed with MAC over general anesthesia to avoid fluctuations in hemodynamics and decrease the risk of venous stasis.The procedure took approximately 45 minutes and the patient recovered uneventfully and was discharged home the same day.

Biography

Yeoh received her Medical Degree from Washington University School of Medicine in St. Louis, USA. She completed 4 years of General Surgery residency before entering a residency in Anesthesiology at St. Vincent's Hospital/New York Medical College, USA. She currently practices at Memorial Sloan Kettering Cancer Center in New York. She is part of the Quality Assurance Committee and chairs the RISQ committee (Reporting to Improve Safety and Quality).

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Synthesis and evaluation of antidiabetic tmpa derivatives via Ir(iii)-catalyzed C−H alkylation

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Antidiabetic medication has revolutionized the treatment of metabolic disorders derived from high blood sugar level. In particular, the use of antidiabetics such as glucagon-like peptide (GLP) agonists, KATP channel inhibitors, AMP-activated protein kinase (AMPK) signaling activators, α-glucosidase inhibitors, and PPAR-γ inhibitors, has received considerable attention as potential medical agents because of their interesting pharmacological effects. Recently, natural antidiabetic octaketide metabolites, cytosporones A and B, have been isolated by Clardy in 2000. Notably, cytosporone B has been demonstrated to bind to the ligand-biding domain of nuclear orphan receptor 77 (Nur77) and stimulate the control of LKB1-mediated AMPK activation. Additionally, unnatural TMPA (ethyl 2-[2,3,4-trimethoxy-6-(1-octanoyl) phenyl]acetate) was also found to enhance AMPKα phosphorylation through reducing the NUR77–LKB1 interaction. Despite of the potent antidiabetic activity and relatively simple structure of TMPA, the single synthetic strategy has been reported for the preparation of TMPA derivatives. However, this strategy presents intrinsic drawbacks, namely, the multi-step synthesis (longest linear 7 steps) and harsh reaction conditions including Friedel–Craft intramolecular acylation, OsO4-mediated dihydroxylation and Pinick oxidation. We herein disclose the ketone-directed Ir(III)- and Rh(III)-catalyzed ortho-C–H alkylation of acetophenones with Meldrum's diazo esters. As results, this protocol may be beneficial to guide the design a variety of antidiabetic TMPA derivatives, and represents a catalytic alternative to transcend the barriers imposed by previous multi-step synthetic approach.

Biography

Saegun Kim is currently pursuing PhD from Sungkyunkwan University, Suwon, Republic of Korea.

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Design, synthesis and biological evaluation of novel celastrol derivatives as potent and selective cytotoxic compounds

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[3]Biocant - Parque Tecnológico de Cantanhede, Portugal
[4]University of Barcelona, Spain

Triterpenoids comprise a large and structurally diverse class of natural products. Among these, celastrol is one of the most active antitumour compounds. It has been reported to be highly active against a wide variety of tumours and to affect multiple cellular pathways. Therefore, celastrol is an ideal candidate for designing lead compounds for the development of new anticancer agents. In this communication we report the synthesis of novel celastrol derivatives as potent and selective cytotoxic compounds. Celastrol analogues, including carbamate derivatives, were designed and synthesised, and their anticancer activity was evaluated using different human cancer cell lines. Moreover, these new compounds were subjected to a preliminary structure–activity relationship study. The best derivatives were selected considering their best activity on malignant cell viability, combined with the highest selectivity between cancer cells and non-malignant fibroblasts. It was performed preliminary mechanistic studies with the best compound, which indicated a important cytotoxic effect on SKOV-3 human ovarian cancer cells (IC50 = 0.54 μM). Additionally, the results suggested that this compound presented an antiapoptotic activity, mediated mainly through activation of extrinsic apoptotic pathway. Furthermore, our results demonstrated the potential of this derivative as a new agent for combinatorial drug therapy for ovarian cancer.

Biography

Jorge A R Salvador has a degree in Pharmaceutical Sciences, a Master degree in Organic & Tecnological Chemistry, and a Ph.D. in Pharmaceutical Chemistry from the University of Coimbra in collaboration with the University of York, UK. He has a position as Full Professor at Faculty of Pharmacy of the University of Coimbra – Portugal. Author and co-author of over 90 publications in peer-review journals, 10 book chapters and 10 patents, two of them have been granted in US. Co-founder of the company CHEM4PHARMA, Lda, https://www.chem4pharma.com/.

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Design and synthesis of 1,3,4-oxadiazole derivatives as a new kappa opioid receptor ligands

Tabatabai S Abbas and **Masoumeh Behnami**
Shaheed Beheshti University, Iran

Introduction: Selective agonists of kappa opioid receptors are potent analgesics without causing complications such as euphoria, mental and physical dependency, usually occur during administration.In the current study, Tifluadom, a known agonist of kappa-receptors was used as a lead compound to design and synthesis 1,3,4-oxadiazole derivatives (a,b) as kappa selective agonists.

Methods and Materials: Compound d was synthesized from 2,4-dichlorobenzoic acid (c) through Aromatic Nucleophilic Substitution mechanism and estherified afterwards. Then the esther reacted with Hydrazine hydrate to form the related Hydrazine acid. From the reaction between Hydrazine acid and chloroacetyl chloride the intermediate compound, Benzoyl hydrazine, was synthesized. In the next step the oxadiazol ring was formed and compound e produced. Eventually, compound d was obtained throughout the Nucleophilic Substitution SN2 mechanism from compound e.

Results: Molecular structures of Target compounds were characterized by Mass, H-NMR and IR spectroscopic methods. The conformational optimization of the obtained compounds was studied by MM +force field method and conformations were exactly optimized by semi empirical method, AMI.

Discussion: First step of synthesis (figure1) was the most challenging part of this study due to the naturally low yield rate of Aromatic Nucleophilic Substitution reactions. Nonetheless, with carrying out modifications to reaction condition, it is accomplished to synthesis compound d with significantly high yield (75%). Furthermore, Tifluadom has antagonistic activity against CCK-B receptors therefore the superimposition of compounds a-b on L-365260, a known antagonist of CCK-B receptors, was studied as well as Tifluadom. The results of conformational analysis indicated that well-superimposition existed between pharmacophors of compounds a-b and the lead compounds. Accordingly, the obtained compounds are expected to be selective agonists of kappa receptors and antagonizing CCK-B receptors may contribute to their analgesic activity.

Biography

Masoumeh Behnami was graduated from School of pharmacy, Shaheed Beheshti University of Medical Sciences and Health Services with PharmD degree. She found her interest in designing compounds with novel structure resulting in unique pharmacologic properties. She has been active in scientific fields other than medicinal chemistry and published papers in reputed domestic journals.

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Notes:

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Correction of a scientific error in lippincott illustrated reviews pharmacology (anticancer drugs, p 605, Mechanism of action *of tamoxifen)*

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Kurdistan Institute for Strategic Studies and Scientific Research-Cancer, Iraq

Tamoxifen is one of the selective estrogen receptor modulators (SERM) with tissue-specific activities for the treatment and prevention of estrogen receptor positive breast cancer. Tamoxifen acts as an anti-estrogen (inhibiting agent) in the mammary tissue, but as an estrogen (stimulating agent) in cholesterol metabolism, bone density, and cell proliferation in the endometrium.

Mechanism of Action: Tamoxifen is a nonsteroidal agent that binds to estrogen receptors (ER), inducing a conformational change in the receptor. This results in a blockage or change in the expression of estrogen dependent genes. The prolonged binding of tamoxifen to the nuclear chromatin of these results in reduced DNA polymerase activity, impaired thymidine utilization, blockade of estradiol uptake, and decreased estrogen response. It is likely that tamoxifen interacts with other coactivators or corepressors in the tissue and binds with different estrogen receptors, ER-alpha or ER-beta, producing both estrogenic and antiestrogenic effects.

The illustration on the mechanism of action of tamoxifen in the book as follow:

B. Tamoxifen: Tamoxifen [tah-MOX-ih-fen] is an estrogen antagonist with some estrogenic activity, and it is classified as a selective estrogen receptor modulator (SERM). It is used for first-line therapy in the treatment of estrogen receptor–positive breast cancer. It also finds use prophylactically in reducing breast cancer occurrence in women who are at high risk. However, because of possible stimulation of premalignant lesions due to its estrogenic properties, patients should be closely monitored during therapy.

Mechanism of action: Tamoxifen binds to estrogen receptors in the breast tissue, but the complex is unable to translocate into the nucleus for its action of initiating transcriptions. That is, the complex fails to induce estrogen-responsive genes, and RNA synthesis does not ensue (Figure 46.26B). The result is a depletion (down-regulation) of estrogen receptors, and the growth-promoting.

The error is highlighted with yellow color, the correction is as follow:

Tamoxifen binds to estrogen receptors in the breast tissue, but the complex not productive, the complex fails to induce estrogen-responsive genes and RNA synthesis does not ensue. That is mean, the complex enter the nucleus, while its action block on the gene and prevent the translation effects of estrogen.

Biography

Hussein Albarazanchi born in Iraq, 1977, has M.Sc. cancer pharmacology from university of Bradford-institute of cancer therapeutics, and also has Bachelor degree in veterinary medicine and surgery from college of veterinary medicine-university of sulaimani-Kurdistan of Iraq. Currently he is working as a researcher in Kurdistan institute for strategic studies and scientific research-cancer research Dept., Kurdistan of Iraq; and as a lecturer of anticancer drugs in college of pharmacy university of sulaimani.

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Accepted Abstracts

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Effects of aluminium salts and cyclic volatile methylsiloxanes on DNA damage and DNA repair in immortalised non-transformed human breast epithelial cells

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Dermal absorption of components of underarm cosmetics may be a contributory factor in breast cancer development. Aluminium (Al) salts are added as the active antiperspirant agent, and cyclic volatile methylsiloxanes (cVMS) are used for purposes of conditioning and spreading. Al has been measured in human breast tissue, breast cyst fluid, nipple aspirate fluid and milk: Al levels in breast tissue have been recently reported to be a risk factor for breast cancer in young women. cVMS have been measured in human milk. The objectives of this study were to investigate any genotoxic effects of exposure to the antiperspirant salts Al chloride and Al chlorohydrate, and to the cVMS hexamethylcyclotrisiloxane (D3), octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5) in immortalised non-transformed human breast epithelial cells. All these compounds enabled a dose-dependent growth of the non-transformed cells in suspension culture, which is an established marker of transformation. DNA damage was demonstrated using a comet assay. Long term (≥20 weeks) exposure to these compounds also resulted in loss of expression (mRNA and protein) of the breast cancer susceptibility gene BRCA1 which is a key gene in repair of DNA in breast cells. Alterations to expression of other DNA repair genes at an mRNA level will be presented. If these compounds can both damage DNA and compromise DNA repair systems, then there is the potential for breast carcinogenesis.

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Breast pathology, proof of principle studies, and drug development

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Human Epidermal Growth Factor Receptor 2 (HER2), also known as ERBB-2, is a 185-kDa member of the erbB family of protein kinase receptors that is widely expressed in breast tissue. Binding with the epidermal growth factor like ligands (EGF-like ligands) will activate downstream signal transduction cascades as the MAPK, Akt, JNK, and JAK2/STAT3 pathways leading to cellular differentiation, mobility, proliferation, and survival. Several cancers are associated with HER2 overexpression including 25-30% of breast cancer invasive ductal carcinoma subtype. The role of histopathology in stage IV metastatic breast cancer has gone beyond diagnosis. Breast pathology biomarkers act as important prognostic and predictive tools to treatment response. Phase I and phase II proof of principle studies involved in the drug development process of anti- HER2 monoclonal antibodies, Tyrosine Kinase Inhibitors (TKIs), and Antibody-Drug Conjugates (ADCs) use breast pathology biomarkers as endpoints.

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Unraveling intricate molecular interactions of drug resistance pathways in neoadjuvant chemotherapy of TNBC patients: Exploring the design of individualized treatment strategies

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Neoadjuvant (NAC) and adjuvant chemotherapies are effective at least in the early clinical course of triple-negative breast cancer (TNBC) patients but most eventually chemoresistance occur. Therefore, in this study, we assessed the panel of KI67, TopoIIα, Bcl2, p53, PTEN, vimentin, ABCC1/MRP1, ABCB1/MDR1, ABCG1/BCRP1, β-catenin, all reported to be involved in drug resistance and tumor progression, in surgical pathology specimens before and after NAC in 148 cases of Japanese TNBC patients using immunohistochemistry, in order to explore the potential mechanisms of chemoresistance in these patients. TNBC patients harboring a low proliferative KI67 labeling index tended to be less likely to respond to the neoadjuvant treatment Anthracycline-Taxanes-based (pathologic complete response: p=0.009), but there were no significant differences of eventual clinical outcome of these patients after the treatment (Overall Survival: p=0.07). Drug efflux pumps (ABCC1/MRP1 and ABCB1/MDR1) have been reported to play a pivotal role in the development of therapeutic resistance and, in our present study the profiles of those above did predict neoadjuvant treatment response (pathologic complete response-ABCC1/MRP1: p=0.057; clinical treatment response-ABCG1/BCRP1: p=0.017), and the up-regulation of the above mentioned multidrug resistance proteins after treatment also did predict local (Disease Free Survival: p=0.055; p=0.03) and distant relapse (p=0.0.36; p=0.037) in the univariate analysis and, the down-regulation of the tumor suppressor PTEN was significantly associated with relapse (p=0.038). We also assessed the correlation among these factors and significant correlations were observed among ATP-binding cassette proteins (ABCG2/BCRP1 with ABCC1/MRP1 p=0.001, p=0.013; and ABCB1/MDR1 p<0.0001, p=0.024), and with Bcl2 (ABCG2/BCRP1 p=0.027; ABCC1/MRP1 p<0.0001; p=0.006), vimentin (ABCC1/MRP1 p=0.065, p=0.046), and β-catenin (ABCG2/BCRP1 p<0.001, p=0.029; ABCC1/MRP1 p<0.0001, p=0.006) in the biopsy or surgery specimens respectively, as well as between vimentin and β-catenin (p=0.004) or Bcl2 (p=0.007) in the surgery specimens. These immunohistochemical results above all indicated the presence of "stemness" phenotype in these carcinoma cells in the primary tumors, which persisted following NAC. Of particular interest, the status of TopoIIα was significantly positively correlated with that of ABCG2/BCRP1 (p<0.0001, p=0.006) and β-catenin (p=0.001, p=0.005) in both biopsy and surgery specimens of NAC and with PTEN (p=0.003) in the surgical specimens. These results above did highlight the intricate relationship among the putative mechanisms such as epithelial-mesenchymal transition, wnt/β-catenin pathway, apoptosis and drug-efflux in the process of development of chemoresistance in TNBC patients. In summary, we studied the potential cellular mechanisms related to the regulation of the tumor cell proliferation and cellular availability of chemotherapeutic agents, involved in developing chemoresistance and relapse in NAC-treated TNBC patients. In addition, the "stemness" phenotype in the residual tumor cells of these patients following NAC could be responsible for chemoresistance and recurrence as well, leading to those cellular features as the potential targets in overcoming therapeutic resistance in these patients. The results above also indicated that not a single but multiple markers assessment should be incorporated to achieve the best therapeutic outcome in TNBC patients.

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Comparision of serum prolactin level in persons with and without endometrial cancer

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Introduction: Endometrial carcinoma is the most common gynecological malignancy in the developed countries. The early detection of this disease can change that to a disease which can mostly be cured. Recently Prolactin has been known as a Hormone,Cytocine that has an increased level in some malignancies,The aim of this study is Comparision of serum prolactin level in persons with and without endometrial cancer.

Methods: In comparative-descriptive study,we studied 50 women in the form of two 25 cases groups(first group, 25 patient with endometrial cancer,and the second group 25 cases without endometrial cancer) refferring to Tabriz Alzahra and Taleghani hospitals durin the 2011 after achieving the inclusion criteria. Demographic data was recorded for all patients mserum Prolactin levels was assessed for all patients using Elisa method. All the information was comapred and analyzed using SPSS software.

Results: The mean age of subjects with disease was 54.84±6.66 years, and the mean age of healthy subjects was 52.64±5.47 years,the difference in two groups was not statistically significant($p=0.433$). The two groups was matched for marital status and occupational status($P=1$ and $P=0.856$ respectively).The mean serum prolactin levels in group with endometrail cancer was 525.72±290.86 ng/ml and in the group without endometrial cancer was 258.16±113.28 ng/ml which was significantly higher in the patients group($p<0.001$).

Conclusion: With regard to the findings of this study we can conclude that serum prolactin levels in patients with endometrial cancer is significantly higher that the level of this hormone in healthy subjects,we can use this hormone measurment for forecasting the incidence of this disease in high risk popualtion, identification of the specificity and sensitivity of this marker is recommended using multicenter studies.

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Differential expression of rage, EGFR and Ki-67 in primary tumors and lymph node deposits of breast carcinoma

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Background: Breast cancer is a complex disease that results from the inheritance of a number of susceptible genes. Intensive search wok was conducted world-wide on molecular bases of breast cancer in order to achieve the best therapeutic modalities; however, breast cancer still remains a challengeable task. It is very important to determine if the biological parameters in metastatic regional lymph nodes are similar to that in the primary breast cancer because therapy is indicated for patients with synchronous metastatic regional lymph nodes of breast cancer. Difference in therapeutic response in cases of breast cancer may be assumed partially to variability in the biological behavior of tumor tissue in primary breast cancer and lymph node metastasis.

Aim: Our aim is to evaluate any variability in the expression of three types of tissue markers in both the primary breast tumors and corresponding axillary lymph nodes in order to expect the targeted therapeutic effect on both sites.

Material & Methods: Three markers from different categories; RAGE, EGFR and Ki-67 were immunohistochemicalyl studied for their expression in biopsy specimens from primary breast tumors and their corresponding axillary lymph nodes.

Results: There was a statistically significant difference in the expression of these markers between benign and malignant breast lesions.Although we found some differences in the expression of the three studied markers between primary breast cancer and corresponding axillary lymph nodes, yet these variations were mostly not statistically significant.

Conclusion: Our findings support the validity of anti-RAGE and anti-EGFR therapy for treatment of both primary and nodal metastatic breast cancer in immunopositive cases.

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Knowledge based analytical development

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The recent (and ongoing advancements in analytical techniques and methodologies have resulted in a resurgence in the application of analytical test methods to analysis of molecules (both chemical and biological). This presentation will present a well-established systematic way of developing a robust analytical strategy that is compliant with both ICH Q6B requirements and with the molecule requirements. This knowledge-based approach can be best described as orthogonal/multi dimensional enabling components attributes and performance attributes to be established following a theoretical and practical approach.

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Development registration of biosimilars to global regulatory standards

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Outlining the importance of biosimilars, the current legislation, commercial and technical/scientific status of biosimilars in the EU this presentation outlines the growing potential of products within this market. There will be examples of currently approved biosimilars, the basis of their approval and details of the developmental pathway differences between innovator products and biosimilars. The process for the determination of biosimilarity and details of the approaches used successfully will be shared. A knowledge-based approach to biologics testing is described that uses analytical, bioassays, and preclinical tests to minimise the need for extensive clinical evaluation therefore reducing the cost of development. Some of the limitations including regulatory, scientific, and quality concerns will be highlighted with particular emphasis on interchangeability and an overview of the requirements for on-going comparability and conformance.

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Synthesis and biological evaluation of new a-ring modified asiatic acid derivatives as anticancer agents

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Cancer is one of the leading causes of mortality and morbidity worldwide. Despite major advances in diagnostics and therapeutics of cancer, the the outcome for many patients remains limited. Thus, there is a constant demand for the search of new, safer and effective pharmacological treatments to fight cancer. Asiatic acid (AA) is an pentacyclic triterpenoid that exhibited promising anticancer effects in both *in vitro* and *in vivo* studies. In addition, this compound exhibited a relatively safe profile, and is readily availability in nature, which support the contention that AA is an interesting compound for the design of new leads aimed at the development of new anticancer agents. Hence, in the present work, a series of new lactol and A-nor AA derivatives were prepared, and their antiproliferative activities were evaluated against several human cancer cell lines. Among all the derivatives tested, compound 1 exhibited the best antiproliferative profile, with IC50 values ranging from 0.11 μM to 0.65 μM for cancer cells. The results of the preliminary mechanistic studies suggest that compound 1 induced cell cycle arrest at G0/G1 phase and apoptotic HeLa cell death. In light of this results, compound 1 might represent a promising drug candidate for the development of new anticancer agents.

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Design, synthesis and cytotoxic evaluation of novel a-ring cleaved ursolic acid derivatives in human non-small cell lung cancer cells

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Lung cancer is a leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for 80 to 85% off all lung cancer diagnosis. Despite advances in diagnostics and therapeutics, the outcome for patients with lung cancer remains poor. Therefore, novel anti-lung cancer agents are greatly needed. Ursolic acid (UA) is a pentacyclic triterpenoid with recognized anticancer properties, and could be used as a starting-point for the development of more potent anticancer drugs. Hence, in this study we designed and synthetized a series of new A-ring cleaved UA derivatives and evaluated their cytotoxic activity in NSCLC cell lines using 2D and 3D culture models. Compound 1, bearing a cleaved A-ring with a secondary amide at C3, was found to be the most active compound, with potency in 2D and 3D culture models systems. The preliminary study on the molecular mechanism showed that compound 1 induced apoptosis via activation of caspases-8 and -7 and via decrease of Bcl-2. Futhermore, induction of autophagy was also detected with increased levels of Beclin-1 and LC3A/B-II, and decreased levels of mTOR and p62. Given its activity and mechanism of action, compound 1 might be potential lead candidate for further development for NSCLC treatment.

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Conventional and computational investigation of the newly synthesized organotin (IV) complexes derived from o-vanillin and 3-nitro-o-phenylenediamine

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Novel Schiff base with general formula H2L was derived from condensation of o-vanillin and 3-nitro-o-phenylenediamine. This Schiff base was used for the synthesis of organotin(IV) complexes with general formula R2SnL [R=Phenyl or Me] using equimolar quantities. Elemental analysis UV-Vis, FTIR and multinuclear spectroscopic techniques (1H, 13Cand119Sn) NMR were carried out for the characterization of the synthesized complexes. These complexes were coloured and soluble in polar solvents. Computational studies have been performed to obtain the details of the geometry and electronic structures of ligand as well as complexes. Geometry of the ligands and complexes have been optimized at the level of Density Functional Theory with B3LYP/6-311G (d,p) and B3LYP/MPW1PW91 respectively followed by vibrational frequency analysis using Gaussian 09. Observed 119Sn NMR chemical shifts of one of the synthesized complexes showed tetrahedral geometry around Tin atom which is also confirmed by DFT. HOMO-LUMO energy distribution was calculated. FTIR, 1HNMR and 13CNMR spectra were also obtained theoretically using DFT. Further IRC calculations were employed to determine the transition state for the reaction and to get the theoretical information about the reaction pathway. Moreover molecular docking studies can be explored to ensure the anticancer activity of the newly synthesized organotin(IV) complexes.

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