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DAY-1

MONDAY, AUGUST 6, 2018

Keynote Presentation

The Proton Preparation NSC-631570 (UKRAIN) and its Selective Effect

Techn. Wassil Nowicky

"Nowicky Pharma"/ Ukrainian Anti-Cancer Institute, Austria

Abstract

First indications on the selective effect of NSC-631570 on the cancer cells were provided in an early study when different oxygen consumption by normal liver cells and Ehrlich's tumor ascitic cells after the incubation with NSC-631570 was revealed. In the tests on the Jurkat lymphoma model, NSC-631570 has been proven to be a strong apoptosis inductor. Profound research showed NSC-631570 brought about the depolarization of mitochondrial membranes and consequently the activation of caspases. NSC-631570 induced apoptosis in a panel of cancer cell lines (cervical cancer HeLa, HeKB, HeKS32, HeBcl3, HeNFR and HeIKK, human colon cancer SW480, human renal carcinoma HEK293, human osteosarcoma MG-63) by activating the caspases of the intrinsic cell death pathway. Interestingly, non-transformed fibroblasts (hTERT) cell line was insensitive to the drug. In the tests on human cervix carcinoma cells HeLa, squamous carcinoma cells WHCO5, normal kidney cell line Graham 293, and transformed kidney cell line Vero from African green monkey, NSC-631570 inhibited the tubulin polymerization and caused a metaphase block in cancer cells which is characterized by abnormal chromosomal distribution, and results in the formation of micronuclei and in apoptosis.

The effects of NSC-631570 on cell survival, alteration of the cell cycle and induction of apoptosis without and in combination with ionising radiation (IR) were investigated on the exponentially growing human tumor cells MDA-MB-231 (breast), PA-TU-8902 (pancreas), CCL-221 (colon), U-138MG (glioblastoma), and human skin and lung fibroblasts HSF1, HSF2 and CCD32-LU. Without IR, NSC-631570 exerted a time- and dose-dependent cytotoxic effect, more pronounced against the cancer cells. The combination of NSC-631570 plus IR enhanced toxicity in CCL-221 and U-138MG cells with their accumulation in the G2/M phase, but not in MDA-MB-231 and PA-TU-8902 cells. A radio protective effect was found in normal human fibroblasts.

NSC-631570 caused the accumulation of prostate cancer cells as well as epidermoid carcinoma cells in the G2/M phase, however, not of normal cells. The cytotoxic effects of NSC-631570 were evaluated in primary pancreatic cancer cell lines (PPTCC), fibroblasts derived from pancreatic ductal adenocarcinoma specimens (F-PDAC), and an immortalized epithelial ductal pancreatic cell line HPNE. Cytotoxic effects of NSC-631570 in PPTCCs were significantly higher than those observed in F-PDAC and HPNE cells. Furthermore, it was revealed that PPTCCs cells consumed more drug than F-PDAC and HPNE cells. This selective effect of NSC-631570 in PPTCCs may be related to a different transport system or higher metabolism of the drug in PDAC. Altogether, in comparative studies NSC-631570 has been tested on 18 cancer and 12 benign cell lines at identical conditions so far. In all these experiments the selective effect of NSC-631570 against cancer cells was confirmed. This selective effect of NSC-631570 against cancer cells explains its good tolerability in clinical use.

Biography

Dr. Wassil Nowicky — Dipl. Ing., Dr. Techn., DDDr. h. c., is the Director of "Nowicky Pharma" and President of the Ukrainian Anti-Cancer Institute (Vienna, Austria). Dr. Wassil Nowicky Has finished his study at the Radiotechnical Faculty of the Technical University of Lviv (Ukraine) with the end of 1955 with graduation to "Diplomingeniueur" in 1960 which title was nostrificated in Austria in 1975. Inventor of the anticancer preparation on basis of celandine alkaloids "NSC-631570". Author of over 300 scientific articles dedicated to cancer research. Dr. Wassil Nowicky is a real member of the New York Academy of Sciences, member of the European Union for applied immunology and of the American Association for scientific progress, honorary doctor of the Janka Kupala University in Hrodno, doctor "honoris causa" of the Open international university on complex medicine in Colombo, honorary member of the Austrian Society of a name of Albert Schweizer. He has received the award for merits of National guild of pharmacists of America. He won the award of Austrian Society of sanitary, hygiene and public health services and others.

Resistance to Tyrosine Kinase-Targeted Therapy in Lung Cancer: Autophagy and Metabolic Changes

Olivier E Pardo[2*], Hongde Li[1], William B Stokes[2], Emily Chater[2], Ewa Rupniewska[2], Rajat Roy[2], Francesco A Mauri[2], Xinxue Liu[2], Maciej Kaliszczak[2], Julian Downward[3], Eric Aboagye[2], Huiru Tang[1], Yulan Wang[1] and Michael J Seckl[2]

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[2]Department of Surgery and Cancer, Imperial College, London, UK

[3]Signal Transduction laboratory, CRUK-LIF, London, UK

Abstract

Lung cancer is the commonest cancer killer worldwide. Tyrosine-kinase inhibitors (TKI) are novel agents in the treatment of this cancer. However, their efficacy is impaired by the rapid development of drug-resistance through a variety of mechanisms. Here, we will discuss resistance to the first-generation EGFR inhibitors (Eg: Erlotinib) and SRC inhibitors (Eg: Dasatinib).

The principal mechanism of resistance to first-generation EGFR inhibitors is the appearance of the T790M receptor mutation. While the reason for resistance was proposed to be changes in affinity of the receptor for ATP, our metabolomics analysis additionally revealed that resistance is associated with decreased cellular levels of glutathione (GSH), a direct consequence of the T790M mutation. This occurred because of decreased SQSTM1/NRF2-mediated transcription of GSH synthesising enzymes in cell lines and clinical samples with T790M-EGFR. We demonstrate that increasing GSH levels in resistant cells re-sensitises these to first-generation EGFR inhibitors in vitro and in vivo. As compounds exist in the clinic to achieve this, our finding may have profound therapeutic and economic consequences.

Src family kinases (SFK) are commonly overexpressed or hyperactivated in lung cancer cell lines and clinical samples. However, despite their on-target efficacy, SRC inhibitors have failed to prevent tumour growth and improve patients' survival in multiple clinical trial. Here we show that this failure is associated with the induction of autophagy in treated cells that prevents these compounds from triggering apoptosis cell death. Targeting autophagy, either genetically or using our novel small-molecule inhibitor, C1A, sensitises lung cancer cell lines to Dasatinib both in vitro and in vivo by unlocking the apoptotic response. These findings propose new combinational therapeutic strategies that could resurrect the use of SRC inhibitors in the treatment of lung cancer.

Role of Mtor in the Tumor Endothelium

Olivier Dormond
CHUV, Switzerland

Abstract

Tumor endothelium plays a complex role in tumor biology, from delivering oxygen and nutrients to recruiting immune cells in the tumor microenvironment. Hence, therapeutic opportunities exist to shape tumor endothelial cells in order to slow down tumor progression. Several signaling pathways have been identified that play a central role in endothelial cells. Among them, the mechanistic target of rapamycin (mTOR) and its two complexes named mTORC1 and mTORC2, contribute to the formation of a vascular network that favors tumor growth. Hence, it is important to identify cellular processes that are regulated by mTOR in endothelial cells. Here, the role of mTOR in tumor endothelium will be presented based on results that were obtained in different tumor mouse models. The consequences of targeting mTOR in tumor endothelium will be described and future challenges of such therapies will further be detailed.

Pancreatic Cancer Dictates an Inflammatory Mediated Tumorigenesis in the Host Microenvironment

Myron R. Szewczuk
Queen's University, ON, Canada

Abstract

Stromal cells and growth factors play important roles during tumor initiation and progression. Growth factors not only mediate normal biological processes such as development and tissue repair but also tumorigenesis by contributing to proliferation and transformation in neoplastic cells. This study investigated the host angiogeneic and pro-inflammatory cytokines during tumor initiation and progression in heterotopic xenografts of eGFP-MiaPaCa-2 tumors growing in RAGxCγ double mutant mice. The time-to-tumor progression revealed significant host cytokine responses initiated by the cancer cells in order for them to establish neo-vasculture for tumor growth. Here, cancer cells manoeuvre multiple host circulating angiogeneic and pro-inflammatory cytokines by significantly reducing host angiostatic and pro-inflammatory cytokines that restrain tumor development and increasing those that are needed. Oseltamivir phosphate (OP) monotherapy when tumor volume reached 100-200mm3 revealed a reversal in some of the anti-angiogeneic and pro-inflammatory cytokines in preventing tumor growth. The data signify several important cytokines as potential biomarkers for therapy. The findings identify for the first time how cancer cells surreptitiously use multiple host cytokines for tumor initiation and progression, all of which can be targeted by OP monotherapy.

Biography

For the past 37 years, Dr. Szewczuk is full Professor of Immunology and Medicine, Queen's University, Kingston, Ontario, Canada. Dr. Szewczuk's recent research has focused on the role of glycosylation in receptor activation with a particular focus of TOLL-like, nerve growth factor Trk, EGFR and insulin receptors. He has discovered a novel receptor-signaling platform and its targeted translation in multistage tumorigenesis.

Biology of Cell-Free Nucleic Acids and their Role in Initiation, Progression and Metastasis of Cancer

Professor Indraneel (Neel) Mittra

Tata Memorial Centre, Advanced Centre for Treatment, Research & Education in Cancer (ACTREC), MH, India

Abstract

Several hundred billion to a trillion cells die in the adult human body daily, and a considerable quantity of fragmented extra-nuclear cell-free chromatin (cfCh) from dying cells are released into the circulation. Our research has shown that circulating cfCh can freely enter into healthy cells, accumulate in their nuclei, trigger a DNA damage repair response (DDR) and integrate into host cell genomes by an unique mechanism; Similarly, at the tissue level, locally generated cfCh from dying cells can be taken-up by healthy bystander cells to induce DDR that facilitates their integration into recipient cell genomes. Genomic integration of cfCh leads to dsDNA breaks, inflammation, chromosomal instability, senescence and apoptosis of recipient cells cfCh from cancerous cells can cause oncogenic transformation of NIH3T3 cells which are tumourigenic in immune-deficient mice. These findings raise a new hypothesis of cancer metastasis which posits that metastasis arises from *de novo* oncogenic transformation of cells of target organs induced by cfCh arising from apoptotic circulating tumour cells (CTCs). This hypothesis challenges the current dogma that metastasis are produced by growth of CTCs that are lodged in distant organs.

Biography

Professor Mittra obtained his medical degree from University of Delhi and is a Fellow of the Royal College of Surgeons of England and holds a PhD degree from University of London. He did his post-doctoral training with Dr Renato Dulbecco, Nobel Laureate, at the Imperial Cancer Research Laboratories in London. Professor Mittra is a multi-faceted personality. He is a breast cancer surgeon and is also deeply involved in public health and basic research in cancer. Professor Mittra's current research interests lie in the area of biology of extracellular nucleic acids and their role in ageing, inflammation, degenerative disorders and cancer.

Effects of Far-Infrared & Terahertz Onnetsu Therapy on Rheumatoid Arthritis and Various Cancers

Kazuko Tatsumura
OMD Director, Gaia Holistic Health, NY, USA

Abstract

Onnetsu means comfortable heat. Onnetsu Therapy invented by Dr. Kazuko Tatsumura emits from a special patented ceramic; 1) Heat 2) Precise 8-10μ of vibration of Far Infrared SunRay 3) Vibration of Terahertz, Dr. Tatsumura is the first in the world to incorporate Terahertz minerals using from active volcanos from Japan to medical use (Worldwide Patent pending).

When Onnetsuki is slid over the skin, healthy areas are comfortable, but IF deep tissue is cold, unhealthy or degenerated, "hot spot" is detected by the sensation reported from the patient. The Onnetsu Therapy is both a diagnostic and therapeutic. When this hot spot is effectively treated with Onnetsu Therapy, (Far-Infrared & Terahertz vibrations, and Heat) the hot sensation subsides, the Disease Conditions improve through vibrating water molecules of our deep tissue. Dr Kazuko's Onnetsu Therapy is based on four historical and scientific facts. Traditional Japanese Concept of the significance of Body Temperature. Hippocrates also has left quotes on Heat. NASA's finding regarding Far-Infrared vibration from Sun light 8-10μ only. Also, added is the specific Terahertz vibration of earth minerals from volcanos of our deep planet. Immunology by Dr. Toru Abo, balancing autonomic nervous system to improve condition of white cells; Raising Immunity. Promoting four flows of Energy through acupuncture technique. Dr. Kazuko has taught Onnetsu Therapy to MDs and health practitioners over past decades. Some countries (Peru, Cuba, and Mexico) are practicing it in the hospitals and clinics. Clinical Trials have shown improvements on many diseases: such as asthma, brain, ear & eye problems, cancers, diabetes, rheumatoid arthritis, tuberculosis and various pain conditions. Clinical studies from Cuba and Peru will be presented.

Biography

Dr. Kazuko Tatsumura Graduated from Toho Academy of Music in Tokyo, as a pianist and composer, invited by the Boston Symphony, she came to the USA in 1961 as one of the first Japanese women. She then received Master of Art from New York University and finished her Ph.D. credits in Philosophy in 1965. In 1967, Dr. Tatsumura then turned to an independent career and became the top International Classical and Cultural Impresario/producer. Until 1992, she produced an average of 2,000 cultural events each year, traveling to more than 140 countries. She was presented with numerous honors for her work, many for humanitarian causes. She studied Oriental Traditional Medicine of Japan, Korea, Taiwan and China. In 2,000 she received her PHD and OMD from the International Academy of Education in Tokyo. She established the Oki-Do Holistic Health Center in 1994 in NY and at the wake of 9/11 Tragedy in 2001, the GAIA Holistic Center (501C3 nonprofit organization), for body mind and spirit, aiming for the noninvasive natural healing methods based on the wisdom of the East.

Dr. Kazuko Tatsumura wrote numerous articles and several books: FE "Overcoming Cancer and Other Diseases in a Holistic Way", "Your Immune Revolution & Healing Your Healing Power "(with Toru Abo, M.D.) Dr. Tatsumura has been invited as a speaker at many International Conferences.

YAP1 as a Therapeutic Target: Novel Regulatory Mechanisms in Tumor Angiogenesis

Chellappan Srikumar

Department of Tumor Biology, H. Lee Moffitt Cancer Center and Research Institute, FL, USA

Abstract

Non-small cell lung cancer (NSCLC) is the leading cause of cancer related death worldwide. In this study, we show that transcriptional co-activator YAP1, the oncogenic component of the Hippo pathway, contributes to the progression of NSCLC by supporting tumor angiogenesis and vascular mimicry of cancer stem-like cells (CSCs). NSCLC CSCs were found to have higher expression of *VEGF receptor II (KDR)* and *Angiopoietin-2 (AngPT-2)* mRNA; depletion of YAP1 inhibited the promoter activity as well as the expression of *VEGF*, *KDR* and *AngPT-2*, with a corresponding reduction in vascular mimicry as well as tumor growth in a mouse xenograft model. These results suggest a possible mechanism by which YAP1 regulates tumor angiogenesis.

A role for YAP1 in tumor angiogenesis was further supported by the finding that that NSCLC cells grown in hypoxic conditions have higher levels of YAP1. Elevated YAP1 was found to associate with HIF1α under hypoxic conditions and enhance its transcriptional activity; YAP1 could enhance HIF1α-mediated induction of the VEGF promoter. Elevated levels of YAP1 and HIF1α interaction was detected in lung tumor tissues compared to normal lung tissue, as detected by proximity ligation assay (PLA), suggesting that the elevated interaction and resulting transcriptional activity might have contributed to tumor growth.

An examination of the mechanism by which YAP1 levels are elevated under hypoxic conditions revealed a novel regulation of YAP1 protein by prolyl hydroxylase PHD2 and E3 ubiquitin ligase VHL, which are mainly known to regulate HIF1α under normoxia. PHD2 was found to hydroxylate proline residue(s) of YAP1 between aa 283 to aa 288 as seen by mutational studies. YAP1 was found to directly associate with PHD2 as well as with VHL; depletion of PHD2 or treatment with DMOG, which is an inhibitor of prolyl hydroxylases, reduced YAP1 association with VHL ligase. This further elevated YAP1 levels in the nucleus. Interestingly, disruption of the YAP1-PHD2 interaction using a domain specific peptide enhanced the angiogenic tubule formation by endothelial cells. Our data therefore identifies a novel non-canonical pathway of regulation of YAP1 in that supports angiogenesis and tumor growth. Strategies for targeting YAP1 as a therapeutic target will be discussed.

Biography

Dr. Srikumar Chellappan obtained his Ph.D. in Biochemistry from Indian Institute of Science, Bangalore in 1987. After a highly productive post-doctoral stint at Duke University Medical Center, he started his independent laboratory at Columbia University in 1992 and continued to work on the links between cell surface signaling and transcriptional regulation in cancer. He moved to H. Lee Moffitt Cancer Center and Research Institute in 2001, where he is currently a Moffitt Distinguished Scholar and Chair of the Department of Tumor Biology. Dr. Chellappan works on smoking related cancers, with an emphasis on the molecular mechanisms underlying EMT, stemness, angiogenesis and metastasis.

Specimens, Standards, and Signatures: Keys to the Vision of Precision Medicine

Carolyn Compton
Arizona State University, AZ, USA

Abstract

The future of medicine depends on the development of molecular biomarkers that provide more precise diagnosis and patient stratification, detect early disease, elucidate risk of disease predict disease outcome, response to therapy, and therapeutic toxicities, and permit monitoring of therapeutic management. Rigorous adherence to standards that are consistent and consistently applied across the development process is required to achieve the reproducibility that is currently lacking in the process. Of primary importance is the quality of the starting materials – the biospecimens used for analysis. Development of complex biomarkers approaches cannot be achieved without the assurance of the provenance of the specimens being analyzed as well as their associated data and consents. The pre-analytical variation to which biospecimens are subjected can dramatically alter their molecular quality and composition artefactually. Pre-analytical artefact may abrogate any ability to define biological effects of interest or distinguish biological signatures of importance in patient samples. This is especially consequential when the biomarker assay is a companion diagnostic and the gateway to access to a therapy. Neither false positive nor false negative tests are tolerable in that circumstance. Biospecimens for biomarker analysis must be systematically collected, processed, stabilized, transported and stored according to standards that render the samples fit for the analytic approach and platform. Regulatory approval of new biomarker assays also is focused on specimen quality as it relates to the quality of the data on which regulatory approvals are based. The biomarker qualification program of the US FDA and the EMA emphasize the need to document the biospecimen quality of diagnostic biomarkers used for either drug or device (assay) development. It is imperative that the entire biomedical community address the need for standardized processes and fit-for-purpose biospecimens to accelerate the delivery of accurate, reproducible, clinically relevant molecular diagnostics for precision medicine.

Biography

Dr. Carolyn Compton, MD, PhD, is an academic pathologist who is Professor of Life Sciences at Arizona State University, Professor of Laboratory Medicine and Pathology at the Mayo Clinic School of Medicine, and adjunct Professor of Pathology at the Johns Hopkins Medical School. She is the Chief Medical Officer of the National Biomarker Development Alliance and the Complex Adaptive Systems Initiative. She is a former Professor of Pathology at Harvard Medical School and Massachusetts General Hospital and former Pathologist-in-Chief at McGill University. More recently she was the Director of the Office of Biorepositories and Biospecimen Research at the National Cancer Institute.

IL-1-Activated Signaling Pathways Induce Resistance to Cisplatin through ΔNP63 in Breast Cancer Cells

Isaura Meza[1*], Mónica G Mendoza-Rodríguez[1], Eloy A Pérez-Yepez[2], Jorge T Ayala-Sumuano[3] and María C Domínguez-Robles[1]

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[3]Universidad Politécnica de Huatusco, Huatusco 94100, Veracruz, Mexico

Abstract

The inflammatory cytokine IL-1β induces, in breast cancer cells, the expression of markers associated with an aggressive phenotype. The resistance to anti-cancer drugs is one of the markers for malignancy in tumors. Cisplatin is a selective drug used in the treatment of breast cancer by causing DNA damage and apoptosis. It is well known that resistance to cisplatin is associated with the expression of genes that code for proteins participating in the regulation of cell survival and inhibition of apoptosis in cancerous cells. One of these proteins is ΔNP63α, an oncoprotein coded from the gene *TP63* associated with drug resistance. However, the inducer of the over-expression of this gene remains unknown. In this work we demonstrate that IL-1β is an inducer of the resistance to cisplatin via a signaling pathway that up-regulates the expression of ΔNP63α.Under the effect of the inflammatory cytokine ΔNP63α activates the expression of EGFR and Wip1, two proteins involved in cell survival and evasion of apoptosis, respectively. The changes in the expression of Wip1 correlate with decrease in the expression of ATM, a protein involved in DNA damage response, elicited by the effect of cisplatin. These data establish a clear link between the inflammatory cytokine IL-1β and the induction of resistance to cisplatin, enhancing tumor cell survival and a poor prognosis.

Biography

Dr. Isaura Meza is a Professor in the Department of Molecular Biomedicine in the prestigious research institute CINVESTAV in Mexico City, Mexico. After obtaining her Doctorate in the University of California, Berkeley and a postdoctoral stay in the University of Geneva, Switzerland, she returned to Mexico where she has worked in structural, biochemical and molecular aspects of cell motility. Her most recent work with breast cancer cells has described signaling pathways and mechanisms induced by the inflammatory cytokine IL-1beta that lead to EMT and drug resistance of the invasive cells.

Targeting Transcription-Associated CDKs is an Effective Strategy to Combat Glioblastoma and Medulloblastoma with Minimal Effect on Primary Neurons

Jaya Padmanabhan

Dept. of Molecular Medicine, University of South Florida, FL, USA

Dept. of Tumor Biology, Moffitt Cancer Center and Research Institute, FL, USA

Abstract

Glioblastoma multiforme (GBM) is the most prevalent and malignant brain tumor in adults. Currently there are no effective therapies to manage the disease efficiently. Medulloblastoma is the most common type of pediatric tumor and accounts for approximately 15% of all pediatric brain tumors. We aimed to determine if targeting the transcription-associated cyclin-dependent kinases, cdk7 and cdk9, using specific inhibitors, could interfere with the growth and metastatic properties of glioblastoma and medulloblastoma cell lines. We tested the effectiveness of Flavopiridol, a known inhibitor of cdk4, cdk6, pTEFb and cdk9; THZ1, a cdk7 inhibitor; and SNS032, which is shown to inhibit cdk2, cdk7 and cdk9, on U87 and SNB19 glioblastoma, H4 neuroglioma and Daoy medullobastoma cells. Treatment with these pharmacological agents showed very strong cytotoxic effects on these cancer cells as measured by MTT (3-(4, 5-dimethylthiazol-2yl)-2, 5-diphenyl tetrazolium bromide) assay. Among these agents the cdk7 inhibitor was most effective and showed efficacy at nanomolar concentrations. Additionally, the inhibitors interfered with the cancer cell migration, as measured by wound healing assay, and anchorage independent growth, as measured by soft agar colony formation. In stark contrast, the inhibitors had no cytotoxic effects on primary neurons. Mechanistically, western blot analysis showed that the tumor cells treated with the inhibitors had reduced levels of Pol II C-terminal domain phosphorylation, indicative of its inhibition and suppression of transcription. Furthermore, inhibitor treatment resulted in a significant reduction in p70S6 kinase phosphorylation, suggesting that in addition to the transcriptional machinery, the translational machinery is also affected upon treatment with the aforementioned cdk inhibitors. Immunostaining analysis of the cells showed a marked reduction in the levels of P-Pol II and P-p70S6 kinase upon inhibitor treatment, confirming that the cdk inhibitors indeed interfere with both transcription and translation. These inhibitors appear to be working in a p53-dependent fashion. These novel findings shed light on potential mechanisms that can be targeted to combat both glioblastoma and medulloblastoma effectively. More specifically, our studies imply that cdk7 and cdk9 inhibitors may serve as potential therapies for effective management of brain tumor.

Biography

Dr. Jaya Padmanabhan obtained her Ph.D. in Biochemistry from the University of Kerala, India, in 1988. After successful post-doctoral training at Duke University Medical Center and Columbia University, she joined the University of South Florida. She became an Assistant Professor in the Dept. of Molecular Medicine in 2010. She currently works at the Moffitt Cancer Center, with a joint appointment in the University of South Florida. Her work focuses on the common molecular events that drive neurodegeneration and cancer, with an emphasis on targeting cell cycle regulatory pathways to combat cancer as well as certain neurodegenerative diseases.

Towards Personalized Medicine for Patients with Recurrent Malignant Brain Tumours

Ella L. Kim
Johannes Gutenberg University Medical Center, Germany

Abstract

Glioblastoma WHO°IV (GB) is the most common and most aggressive form of brain malignancy in adults. The complex biology, limited effectiveness of current treatments, high treatment costs and inapplicability of prevention strategies make GB one the most challenging human cancers today. The current standard of care for GB is based on the "one-treatment-for-all" principle and consists of surgical de-bulking followed by combined therapy with ionizing radiation (IR) and DNA alkylating agent temozolomide (TMZ). Although regarded as the "gold standard" for GB treatment, non-targeted therapy offers only a modest survival advantage compared to RT alone (median survival 14,6 vs 12,2 months, respectively). The recurrence of GB is inevitable. Lack of effective therapeutic options for recurrent GB (recGB) is the main obstacle to improving therapeutic outcomes in GB. There has been a growing realization that recGBs comprise a molecularly distinct subgroup of tumours that differ from newly diagnosed GBs in the mutation spectrum, frequency of genomic rearrangements and gene expression patterns. Furthermore, it appears that cytotoxic treatments used for GB treatment pro-actively promote the emergence of new genomic alterations/gene expression patterns in recGBs. Clinical experience accumulated over the past decades calls for rethinking the prospects of the "one-treatment-fits-all" approach for GB. There has been a growing realization of the limitations of traditional low-throughput diagnostics, which does not consider the impact of intratumoral heterogeneity and dynamics of molecular changes during tumor progression. Conceptual and methodological challenges to implementing high through-put diagnostics and personalized treatment of GB in both first diagnosis and recurrence settings will be discussed.

Biography

Ella L. Kim has completed her PhD in molecular biology at the Institute of Molecular Biology and Genetics (Kiew, Ukraine). After her postdoctoral studies at the Barrow Neurological Institute (Phoenix, AZ USA) Dr. Kim moved to Germany as a Postdoctoral Fellow supported by the European Molecular Biology Organization (EMBO). Since 2006 Dr. Kim is directing the Translational Neurooncology Research Group and Laboratory of Experimental Neurooncology first at the University Medical Centre Göttingen (Germany) and currently at the Johannes Gutenberg University Medical Center Mainz (Germany).

DAY-1

Posters

Poster Presentation

Synthesis and Bio-Applications of Luminescent Transition-Metal Complexes

Hai-tao Wang [1*], Qian-ling Zhang [3], Xun-jin Zhu [1] and Wai-Yeung Wong[1,2]

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[2]*Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong*

[3]*College of Chemistry and Environmental Engineering, Shenzhen University, Shenzhen, P. R. China*

Abstract

In the last two decades, various metal complexes such as ruthenium, rhodium and platinum complexes have been extensively synthesized to probe DNA with spectroscopic assays and to light up the cells. Ir(III) complexes have been widely applied in the design and preparation of light-emitting diodes due to their excellent photochemical and photophysical properties. However, iridium complexes are not frequently reported on the DNA binding and other biological applications. Recently, the iridium complexes have shown luminescence in DNA binding and cell imaging thus triggered the promising field of bio-applications of irdium complexes.

Six series of iridium complexes were synthesized and characterized. The HOMO and LUMO energy levels and energy gaps of complexes are calculated based on cyclic voltammetry (CV). The DNA-binding and quenching constants were acquired from spectra of absorption and photoluminescence. Stokes shifts in those complexes also matched well with the differences of those HOMO and LUMO energy gaps. The bio-application experiments were carried out in cell morphology, proliferation, cellular uptake and distribution. The typical characteristics of cell apoptosis were obviously observed by Fluorescence Inverse Microscope (FIM) and confocal laser scanning microscopy (CLSM) under the incubation of those complexes.

Biography

Mr. Haitao Wang has obtained his B.Sc., and M.Sc., from Shenzhen University. He is pursuing his Ph.D. Candidate from Hong Kong Baptist University under the Supervision of Prof. Wai-Yeung Wong, Dr. Xun-jin Zhu.

Prognostic Variables and their Potential Roles in the Development of Autoimmune Thyroid Disorders in Breast Cancer

Arif Malik[1*], Muhammad Abdul Basit Ashraf[1], Sulayman Waqar[1] and Siew Hua Gan[2,3]

[1]*Institute of Molecular Biology and Biotechnology (IMBB), University of Lahore, Pakistan*

[2]*School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia*

[3]*School of Pharmacy, Monash University Malaysia, Selangor, Malaysia*

Abstract

Background: Breast cancer is most common type of tumor in females. Increased incidents of cancer are often related with oxidative stress. Decrease in the level of serum vitamins and hypothyroidism result in hyperhomocystinemia. Therefore, breast cancer is correlated with the autoimmune thyroid disorders (AITDs).

Methodology: Hundred (n=100) breast cancer patients (stage III) and hundred (n=100) clinically healthy individuals were included. Levels of antioxidants i.e., GSH, CAT, SOD, vitamins, amino acid and thyroid antibodies were estimated by their respective methods.

Results: The levels of MDA, NO, GPx, homocysteine, cysteine were higher in patients (3.90±0.56 nmol/ml, 55.43±4.231 pg/ml, 55.43±4.231 µmol/L, 17.61±2.26 **µmol/L**, 207.39±5.70 µmol/L) as compared to healthy individuals. Moreover, levels of thyroid antibodies (TgAb, TPOAb and TSHrAb) were increased in the cancer patients. While, level of antioxidants and vitamins were lower in breast cancer patient. Higher serum levels of prolactin (35.09±4.76) and estrogen (10.47±1.67 pg/ml) were also observed in breast cancer patients as compared to controls.

Conclusion: Results of the current study concludes that oxidative stress plays significant role in the proliferation of cells. Cancer patients are often observed with the increased levels of thyroid antibodies. Hence, it may be stated as dietary deficiency of antioxidants coupled with thyroid hormone dysfunction is responsible for breast cancer progression.

Biography

Prof Arif Malik works as Biochemistry Professor at University of Lahore, Pakistan. His research interests include: Biochemistry and Physiology of stress tolerance. Prof Malik work ranges from basic pathological basis to explore new circulating biochemical markers to redesign etiologies of different diseases under stress to education, medical community, policy-makers, and the public. Scientific communication includes frequent interaction with peer review journals. The other research interest is to use genomics, biochemical, computational models to elucidate the mechanisms involved in abiotic/biotic stress tolerance and designing of new drugs for different diseases from natural sources. He specially focuses on Hepatitis, different types of cancers, diabetes and complicated pregnancies.

Primary Hepatic Perivascular Epithelioid Cell Tumor (PEComa) -Dilemmas in Diagnosis & Treatment

Aminder Singh*, HRS Gir, Neena Sood, Bhavna Garg, Harpreet Puri and Harish Kamboj

Department of Pathology & Liver Transplant Unit, Dayanand Medical College & Hospital, India

Abstract

Brief Introduction: Perivascular epithelioid cell tumor (PEComa) is a rare mesenchymal tumor. Preoperative diagnosis is difficult as they mimic other hepatic neoplasms and data about diagnosis and management is limited. Here we are presenting an interesting case of incidentally detected primary hepatic PEComa.

Case History: A 58-year old male with type 2 diabetes mellitus was incidentally found to have a mass lesion in liver on ultrasonography whilst undergoing cardiac work up for his triple vessel disease. Fine needle aspiration cytology revealed possibility of HCC. Positron emission tomography scan revealed no abnormal 18F-fluorodeoxyglucose activity elsewhere besides in liver. Contrast enhanced multi-detector computed tomography of the abdomen showed a large well defined encapsulated lesion in segment VIII/V. A radiological diagnosis of De-novo HCC was made. Laboratory investigations revealed mildly deranged AST, ALT with high Alpha fetoprotein levels. Patient underwent triple coronary bypass and 6 weeks later, right hemihepatectomy was performed in February 2017. Grossly, the specimen was weighing 1120 grams. A solitary well circumscribed firm greyish white tumour identified in right lobe measured 7.5x7x6 centimetres which was 4 mm away from the surgically resected margins. Initial histopathology was suggestive of poorly differentiated malignancy while subsequent immunohistochemistry confirmed the diagnosis of PEComa. Human Melanoma Black-45, CD117 (focal positive), Smooth muscle actin & Vimentin were positive while Cytokeratin, S-100, CD34, Desmin, Myogenin, Hep-par1, Epithelial membrane antigen, Chromogranin A, CD68 & Discovered on GIST-1 (DOG-1) were negative. Proliferation index was low (Ki-67<2%). Follow-up visits till date after a period of 1.4 years were unremarkable without any evidence of systemic or local recurrence. No chemotherapy or radiotherapy was given.

Discussion: PEComa was first classified by the World Health Organization in 20021. Diagnosis is based on histopathology with immunohistochemical evidence of both melanocytic and smooth muscle markers. Few authors2-3 defined certain criteria to classify malignant PEComa. Surgical resection with an adequate margin remains the gold standard for the treatment of hepatic PEComa particularly in malignant cases2,4,5. Hemi-hepatectomies were usually performed in those who were misdiagnosed with hepatocellular carcinoma prior to the surgical intervention. At present, chemotherapy & radiotherapy does not indicate an improved survival. However, some studies2,4,6 have shown promising results, including a study of rapamycin, a mTOR inhibitor. On follow up, some patients succumbed to death due to recurrence2,7. Thus, the prognosis of PEComa remains unpredictable; management is on a case by case basis by specialised multidisciplinary teams in each hospital and it is necessary to perform long-term follow-up studies for every case.

Biography

Dr. Aminder Singh is an Assistant Professor, Department of Pathology, Dayanand Medical College & Hospital, Ludhiana, Punjab India. He is histopathologist with special interest in liver pathologies.

Gestational Trophoblastic Diseases: A Seven-Year Observational Study in the City Of Duhok – Iraq

Eleane Ayou
Azadi Teaching Hospital, Duhok, Iraq

Abstract

Background: Although Gestational trophoblastic disease (GTD) is mostly a benign condition, malignant transformation may occur. It is the most curable disease among all the gynecological malignancies especially when early diagnosis is made. Despite that, there is paucity of local data regarding the burden of this condition, its management and outcome.

Objectives: The study aims to assess the data for the prevalence, treatment protocols and outcome of GTD in cases admitted to Azadi teaching hospital, Duhok- Iraq.

Methods: A retrospective and prospective analysis of cases documented during the period from February 2011- July 2017. Ninety-six cases were included. Retrospective data were retrieved from patients' medical records and GTD special registry while prospective data were recorded in patients' record at Gynecology Clinic and were updated with each visit. Human chorionic gonadotropin hormone level was the main investigation we based on for diagnosis and follow up.

Results: Seventy (72.9%) cases were multigravida, forty-three (44.8%) were between the age 21-30 years. All patients had vaginal bleeding at presentation. Only five (5.2%) cases had extra uterine metastasis, two (2%) patients had history of previous GTD, Four (4.2%) patients ended with hysterectomy. 23(23.9%). Patients were solely treated with dilatation and curettage without need for any chemotherapy, 62(64.8%) patients were treated successfully with single agent chemotherapy while 11(11.6%) patients needed multi-agent's chemotherapy.

Conclusion: No patient died from GTD during this period. Among patients who needed chemotherapy most of our cases had good response to Single agent chemotherapy.

Biography

Dr. Eleane Ayou has completed her bachelor's degree in general medicine and surgery at the age of 23 from Duhok University / College of Medicine and currently she is 4th year trainee toward specialty in obstetrics and gynecology. She is one of the senior registrars at both Duhok Maternity Hospital and Azadi Teaching Hospital in the city of Duhok -Iraq. Dr. Ayou is responsible for managing and follow up of patients who have been diagnosed with gestational trophoblastic disease under the supervision of head of Department of Obstetrics & Gynecology at Azadi Teaching Hospital.

Is Lymphadenectomy Essential in Early Stage Endometrium Cancer?

Tijen Atacag* and Cemal Yenen M
Dr. Suat Günsel Kyrenia University Medical Faculty, Turkey

Abstract

Cancer of the endometrium is the most common gynecologic malignancy in developed countries and the second most common in developing countries. Endometrioid carcinoma is the common site and histologic subtype of endometrial carcinoma and of uterine cancer overall. Endometrioid tumors tend to have a favorable prognosis and typically present at an early stage with abnormal uterine bleeding. More than two-thirds of patients with endometrial cancer are diagnosed at early stage and have a good prognosis (with a 5-year survival rate of 89.6%). The need for lymphadenectomy in endometrial cancer management is still a subject of debate. Removal of all pelvic and paraaortic lymph nodes (lymphadenectomy) is absolutely recommended in the first operation, and pelvic and para-aortic lymphadenectomy remains a part of the FIGO (International Federation of Gynecology and Obstetrics) staging system for endometrial cancer. This recommendation is based on data from studies that are not randomized controlled trials (RCTs), and treatment of pelvic lymph nodes may not confer a direct therapeutic benefit, other than allocating women to poorer prognosis groups. No evidence is found that lymphadenectomy decreases the risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. Women who received lymphadenectomy had a significantly higher risk of surgically related systemic morbidity and

lymphoedema/lymphocyst formation than those who had no lymphadenectomy. A renewal assessment must be done for the necessity of lymphadenectomy in early stage endometrial cancer.

Biography

Dr. Tijen Atacag after graduating from Ankara University Medical Faculty, completed gynecology specialization in Dr. Zekai Tahir Burak Womens Hospital, Ankara. From 2011 working at Near East University Medical Faculty, giving lectures, and from 2016 working at Dr Suat Günsel Kyrenia University Medical Faculty.

Polyphenols Act Synergistically with Doxorubicin and Etoposide in Leukemia Cell Lines

Mahbub AA[1], Le Maitre CL[2], Haywood-Small SL[2], Cross NA[2] and Jordan-Mahy N[2]

[1]Faculty of Applied Medical Sciences – Department of Laboratory Medicine and Pathology, Umm Al Qura University, Makkah, KSA

[2]Biomolecular Sciences Research Centre - Cancer Research, Sheffield Hallam University, Howard Street, Sheffield, UK

Abstract

The study aimed to assess the effects of polyphenols when used in combination with doxorubicin and etoposide, and to determine whether polyphenols sensitised leukaemia cells, causing induction of apoptosis. Quercetin, apigenin, emodin, rhein and cis-stilbene were investigated alone and in combination with etoposide and doxorubicin in two lymphoid and two myeloid leukaemia cells lines. Measurements were made of ATP levels using CellTiter - Glo assay as an indication of total cell number, cell cycle progression using PI staining and flow cytometry, and apoptosis by NucView caspase 3 assay and Hoechst 33342/PI staining. Effects of combination treatments on caspases 3, 8 and 9 activity were determined using Glo luminescent assays, glutathione levels were measured using the GSH-Glo Glutathione Assay and DNA damage determined by anti-γH2AX staining. Doxorubicin and etoposide in combination with polyphenols synergistically reduced ATP levels, induced apoptosis and arrested S and/or G2/M phases in lymphoid cell lines. However, in the myeloid cell lines the effects of the combination treatments varied; doxorubicin had a synergistic or additive effect when combined with quercetin, apigenin, emodin, and cis-stilbene, but had an antagonistic effect when combined with rhein. Combination treatment caused a synergistic downregulation of glutathione levels and increased DNA damage, driving apoptosis via caspase 8 and 9 activation. However, in myeloid cells where antagonistic effects were observed, this was associated with increased glutathione levels and a reduction in DNA damage and apoptosis. In conclusion, doxorubicin and etoposide activity can be enhanced by polyphenols, particularly in lymphoid leukaemia cells, although effects were strongly dependent on type of cell line, with some interactions were antagonistic in myeloid cell lines.

Biography

Dr. Amani Mahbub had completed his MSc of Biomedical Basis of Disease in 2010 and PhD of Anti-Cancer Potential of Polyphenols in Treatment of Leukemia in 2015 at the Sheffield Hallam University of Biomedical Research Centre – Cancer Research, Sheffield, UK. He is interested in investigating the biological effects of a number of nutraceutical compounds such as polyphenols alone and in combination with chemotherapies on the induction of apoptosis, reduced cel proliferation and signalling pathways that involved in the pathogenesis of leukaemias.He has four published papers in: the Journal of Pathology (2012), the Journal of Anti-cancer Agents in Medicinal Chemistry (2013) and recently Two in Nature (2015). In addition, I was awarded three prizes: (1) The Alastair Currie prize for the best poster and presentation at the Pathological Society of Great Britain & Ireland Conference in 2012, Sheffield, UK; (2) Best poster prize for research entitled: Polyphenols Act Synergistically with Doxorubicin and Etoposide in leukaemia cell lines at t the 4th International Conference on Blood Malignancies and Treatment: 18th -19th April (2016), Dubai –UAE; (3) Best poster award for research entitled: Polyphenols Act Synergistically with Doxorubicin and Etoposide in Leukaemia cell lines at the 14th World Cancer and Anti-Cancer Therapy Convention and that held in Nov 21-23, 2016 in Dubai, UAE. Currently, He is Assistant Professor in Pathology and the Vice Head of Laboratory Medicine Department in Faculty Applied of Medical Sciences– Umm Al-Qura University, Makkah, KSA.

Rational Design of a Novel Anti-Angiogenic Antibody Targeting CLEC14a

Mira Kim* and Jihye Jang
Scripps Korea Antibody Institute, South Korea

Abstract

Antibody design is a key challenge for the successful development of therapeutic antibodies. Antibody design has been hampered by a poor understanding of the complex structural architecture of antibodies and the lack of computational design tools. Here, we develop a new strategy to improve the quality of antibody attributes using the example of a parental human antibody specific for the C-type lectin-like domain (CTLD) of the C-type lectin-like 14a protein (CLEC14a-CTLD). We used in silico techniques to perform complementarity determining region (CDR) grafting and consecutive deglycosylation, and we subsequently generated an antibody with improved stability and homogeneity. The optimized antibody specifically suppressed vascular endothelial growth factor (VEGF)-dependent angiogenesis and tumor angiogenesis in vivo similarly to bevacizumab treatment. The optimized anti-angiogenic antibody exhibited a novel mode of action, which involved direct inhibition of CLEC14a-CTLD-mediated endothelial cell-to-cell contact, and this mechanism was distinct from the mechanism of action of bevacizumab. Collectively, our results demonstrate an effective strategy for antibody optimization and offer an optimized antibody that may potentially function as a novel anti-angiogenic antibody for the suppression of CLEC14a-mediated pathological angiogenesis.

Human Antibodies Targeting the C-Type Lectin Domain of the Tumor Endothelial Cell Marker Clec14a Regulate Angiogenic Properties *in vitro*

Jihye Jang*, Mira Kim*, Min-kyoung Ki, Mee Hyun Jeoung and Sukmook Lee
Scripps Korea Antibody Institute, Korea

Abstract

It has been suggested that clec14a may be involved in tumor angiogenesis. However, a molecular mechanism has not been clearly identified. In this study, we show for the first time that C-type lectin-like domain (CTLD) of clec14a may be important for regulating cell migration and filopodium formation. Using phage display technology, recombinant human antibodies specific to the CTLDs of human and mouse clec14a (clec14a-CTLD IgG) were selected. Functional assays using the antibodies showed that clec14a-CTLD IgGs specifically blocked endothelial cell migration and tube formation without affecting cell viability or activation. Further, clec14a-CTLD IgGs inhibited clec14a-mediated cell-cell contact by blocking interaction between CTLDs. Finally, clec14a cross-linking by the clec14a-CTLD IgGs significantly down-regulated clec14a expression on the surface of endothelial cells. These results strongly suggest that the clec14a-CTLD may be a key domain in angiogenesis, and that clec14a-CTLD IgGs specifically inhibit angiogenesis by modulating CTLD-mediated cell interactions and clec14a expression on the surface of endothelial cells. Human clec14a-CTLD IgGs may have therapeutic value in clec14a-mediated cancer progression.

DAY-2

TUESDAY, AUGUST 7, 2018

Speaker Presentation

Targeting Caspase-8-Dependent Apoptosis in Cancer Cells to Enhance Immunotherapy

Thomas J. Sayers[1,3*], Alan D. Brooks[1,3], Curtis J. Henrich[2,3], Ya-Ming Xu[4], E.M. Kithsiri Wijeratne[4], A.A. Leslie Gunatilaka[4] and Poonam Tewary[1,3]

[1]CIP, [2]MTL, NCI Frederick and [3]Basic Research Program, Leidos Biomedical Research Inc., FNLCR Frederick, Frederick, MD, USA

[4]School of Natural Resources and the Environment, University of Arizona, Tucson, AZ, USA

Abstract

We previously identified Withanolide E, a steroidal lactone from *Physalis peruviana*, as a selective and novel sensitizer of cancer cells to apoptosis in response to the TNF family member TRAIL. Further testing of >150 analogues identified some that were 8-16-fold more active than WE. All active analogues were 17beta-hydroxywithanolides (17-BHWs). Structure activity relationship (SAR) analysis suggested that the enone moiety in ring A, acetoxylation at C18, an alpha orientation of the lactone ring and the double bond at C24(25) all played important roles in promoting caspase-8-dependent apoptosis. Active 17-BHWs promoted caspase-8-dependent apoptosis in human renal carcinoma and melanoma cells not only in response to TRAIL, but also the TLR3 ligand and viral mimetic poly (I:C). In both cases the major molecular mechanism of action of the 17-BHWs appeared to be due to a dramatic reduction in the levels of the anti-apoptotic $cFLIP_L$ and $cFLIP_S$ proteins. This reduction by 17-BHWs was post transcriptional. Furthermore, reduction of either $cFLIP_L$ or $cFLIP_S$ using siRNA sensitized both renal carcinoma and melanoma cells to apoptosis, demonstrating that cFLIP reduction alone could be sufficient for apoptosis sensitization. Intratumor administration of the combination of an active 17-BHW and poly (I:C) in a human melanoma xenograft model (M14) or the mouse B16.F10 melanoma demonstrated that the combination provided an improved therapeutic effect when compared to the controls. Future studies using the more potent 17-BHWs could lead to the identification of novel cellular therapeutic targets involved in controlling cancer cell apoptosis by reducing levels of the anti-apoptotic cFLIP proteins.

Biography

The Molecular Immunotherapy Section of Dr. Sayers at NCI Frederick is interested in characterizing molecular mechanisms by which cells of the immune system destroy cancer cells, particularly when using the pro-apoptotic tumor necrosis factor (TNF) family proteins. A critical role for the anti-apoptotic protein cFLIP in protecting cancer cells has been established, and high-throughput screening has identified several natural products that can target cFLIP and promote the degradation of the protein. These compounds may be useful in enhancing cancer immunotherapy by increasing the susceptibility of cancer cells to immune-mediated destruction.

Cancer Immune-Monitoring; Challenges of Big Data Management

Shahram Kordasti

Senior Lecturer in Applied Cancer Immunopathology, KHP-CRUK Cancer Centre, Guy's Hospital, King's College London, London, UK

Abstract

Novel technologies provide new opportunities to define novel immune-signature(s) for predicting response to immunomodulatory drugs. However, the "big data" management could be challenging. Using mass cytometry (aka CyTOF or Cytom) and multidimensional data analysis, we have identified two distinct sub-population of regulatory T cells (Tregs) (Treg A and Treg B) with distinct phenotypes, gene-expression, expandability and function. In patients with aplastic anaemia (AA), Non-responders to immunosuppressive therapy (IST) were more likely to have higher Treg A compared to non-responders, whereas responders had higher Treg B numbers compared to HDs. Treg B subpopulation characterized by a more "activated/memory" phenotype and functional GEP analysis revealed marked enrichment of Treg B subpopulation with G2M checkpoint and mitosis related genes suggesting that Tregs B are more prone to enter cell-cycle.

In patients with MDS however, an increase in Treg B cells is correlated with disease progression toward AML. This approach also identifies an immune signature that predicts for response to immunotherapy at time of diagnosis of AA and MDS, and which may allow a more patient specific approach to future treatment decision-making.

Biography

Following graduation from medical school and clinical training in Internal Medicine/ Haematology, Dr Kordasti received his MSc in Medical Immunology and PhD in Cancer studies from King's College London. He established the role of Tregs in MDS and their effects on disease progression and response to treatment. He continued his work at King's College London as a senior lecturer to study the immunobiology of bone marrow failure syndromes, in particular AA and MDS. He has been appointed as senior lecturer and group leader in applied cancer immunopathology at KHP-CRUK Cancer Centre (Guy's Hospital) since April 2018.

Immunotherapy of Cancer: Triumphs and Challenges and the Impact of Immunosenescence

Graham Pawelec
University of Tuebingen Center for Medical Research (ZMF), Germany
Second Department of Internal Medicine, Tübingen University, Tübingen, Germany
Health Sciences North Research Institute, Sudbury, ON, Canada
John van Geest Cancer Research Centre, Nottingham Trent University, Nottingham, UK

Abstract

Geriatric oncology, important for the ever-increasing numbers of elderly cancer patients, has thus far focused primarily on tolerance to chemotherapy. With the advent of breakthrough immunomodulatory antibody treatments relying on the patient´s own immune system to control the tumor, the issue of immunosenescence becomes extremely important. There is increasingly a valid concern that anti-cancer immunity may be compromised in the elderly due to i) their low amounts of naïve T-cells (potentially leading to holes in the repertoire for neoantigens), ii) "exhaustion" of potentially tumor-specific memory T-cells, and iii) accumulations of suppressive T-cells and myeloid cells. Despite there being no clinical trials specially addressing the issue in the elderly, happily, accumulating clinical data suggest that advanced age does not result in decreased responses to checkpoint blockade or increased toxicity. However, the fraction of patients experiencing clinical benefit is often still low and stratifying patients for multiple factors may reveal an influence of age in non-responders. As newer agents are licensed, broader and more detailed studies focusing on the age question are required.

In our own work, we have established prognostic phenotypic and functional "immune signatures" using peripheral blood from younger melanoma and breast cancer patients, which comprise phenotypic T-cell and myeloid-derived suppressor cell quantification and measurement of pro- and anti-inflammatory CD4+ and CD8+ T-cell responses to shared tumor antigens such as NY-ESO-1 and Her2 in vitro using intracytoplasmic flow cytometry to detect 6 cytokines simultaneously. We found that these peripheral immune signatures were equally prognostic for overall survival (OS) in older patients (>80 years of age). We therefore conclude that immunosenescence should not be a barrier to anti-tumor immunity in elderly people treated with immunomodulatory antibodies, at least for responses targeting shared tumor antigens. It remains to be established whether responses to tumor neoantigens are compromised by immunosenescence, which seems *a priori* more likely, given that responses to shared antigens are memory responses whereas neoantigen-specific immunity would require naïve T cells. Given the current emphasis on neoantigen responsiveness, immunosenescence remains an unexplored concern.

Furthermore, in a recent series of 128 melanoma patients from 3 different centers, we have observed that benefit of anti-PD1 therapy, as assessed by OS, is influenced not by the age but by whether the patient was infected with Cytomegalovirus (CMV). While age itself had no significant impact (taking 70 years of age as the cutoff for stratification), patients who were CMV-infected tended to have superior OS (and the proportion of CMV-infected individuals in industrialized countries increases with age, confounding any age effect *per se*). This survival difference became statistically significant when patients were stratified according to relative percentages of natural killer cells and CD8+ effector memory cells, together with their CMV serostatus. Thus, greater proportions of these cells in CMV-seropositive, but not CMV-seronegative, patients were associated with superior OS. Given the associations of CMV infection with markers of "immunosenescence" in humans, this finding is of great practical and theoretical interest.

Biography

Dr. Graham Pawelec received an MA in Natural Sciences in 1978 and a PhD in Transplantation Immunology in 1982 from the University of Cambridge, UK, and the Dr. Habil and Venia Legendi from the University of Tübingen, Germany, where he became Professor of Experimental Immunology in 1997. From 1999 to 2017 he led the Tübingen Ageing and Tumour Immunology (TATI) group within the Second Department of Internal Medicine, University of Tübingen Hospitals System. He remains affiliated part-time with the department at the Center for Medical Research, University of Tübingen. He is currently affiliated with the Cancer Solutions Program, Health Sciences North Research Institute of Canada, Sudbury, ON, and is a Visiting Professor at Nottingham Trent University, UK, King´s College London, London, UK, and is an Honorary Professor at Manchester University, UK. He is Co-Editor-in Chief of Cancer Immunology Immunotherapy, and is Deputy or Associate Editor in several other journals. He has authored or co-authored 270 peer-reviewed original articles from a total of 486 PubMed-listed publications, has edited 3 books and co-edited several others (citations 22763, H-index 85). He has coordinated three European Union collaborative programs on immunosenescence (EUCAMBIS, ImAginE and T-CIA) and two on cancer vaccine research (EUCAPS, ESTDAB). He was a member of the Sanofi-Pasteur-MSD and Sanofi-Aventis Advisory Boards on Immunosenescence and Vaccination, and of the WHO Initiative for Vaccine Research Advisory Board on the Impact of Ageing on Vaccination. His research interests remain centered on vaccination, cancer immunology, immunotherapy and immunogerontology.

Inactivation of Type I Interferon Pathway as a Critical Determinant of Immune Suppressive Tumor Microenvironment

Serge Y. Fuchs
Department of Biomedical Sciences, University of Pennsylvania, PA, USA

Abstract

Understanding the mechanisms by which solid tumors suppress anti-tumor immunity is critical for success of immune therapies. Refractoriness of solid tumors including colorectal cancers (CRC) to immunotherapies is attributed to the immunosuppressive tumor microenvironment that protects malignant cells from cytotoxic T lymphocytes (CTL). We found that downregulation of the type I interferon receptor chain IFNAR1 occurs in human CRC and mouse models of CRC. Tumor microenvironment factors-induced downregulation of type I interferon receptor IFNAR1 appears to function as a central mechanism underlying the ability of tumor microenvironment to undermine viability of cytotoxic T cells and to generate intra-tumoral immune privileged niches devoid of these cells. Means preventing the loss of IFNAR1 eliminated these niches and inhibit tumor growth. Downregulation of IFNAR1 in tumor stroma stimulated CRC development and growth, played a key role in formation of the immune privileged niche and predicted poor prognosis in human CRC patients. Genetic stabilization of IFNAR1 improved CTL survival and increased the efficacy of the chimeric antigen receptor T cell transfer and PD-1 inhibition. Likewise, pharmacologic stabilization of IFNAR1 suppressed tumor growth. These findings delineate a mechanism of localized intra-tumoral immune suppression and prompt the development of IFNAR1-stabilizing agents for their use in anti-cancer immune therapies.

Biography

Dr. Serge Y. Fuchs, MD/PhD, got his post-doc training in the US and then joined the University of Pennsylvania where he developed a research program focused on the molecular mechanisms underlying ubiquitination and downregulation of signaling cytokine receptors and the role of these mechanisms in cancer, immunity, infectious and autoimmune diseases. The resulting paradigm of "eliminative signaling" (i.e. the signaling pathways re-shaping the repertoire of cell surface cytokine receptors and thereby dictating cellular responses to the cytokine stimuli) has been instrumental in subsequent studies on inflammatory tissue damage and defenses against tumor development, progression and metastasis.

Cancer Immunotherapy with Low-Level Whole-Body Exposures to Ionizing Radiation

Marek K. Janiak* Aneta Cheda and Ewa M. Nowosielska

Dept. of Radiobiology and Radiation Protection, Military Institute of Hygiene and Epidemiology, Warsaw, Poland

Abstract

Evidence amassed over the last several decades from epidemiological, experimental, and clinical studies indicates that whole-body exposures at low doses (i.e., ≤100 mGy delivered over a short time) of low-LET ionizing radiation inhibit the development and/or progression of various neoplasms. The primary mechanism of such effects is thought to be stimulation of both the innate and adaptive arms of anti-cancer immunity. Indeed, the immune system is regarded as the most potent guardian of the organism against neoplastic disease. However, as defined by the recently accepted cancer immunoediting hypothesis the system protects the host against the incipient cancer at the early stages of carcinogenesis, but later 'edits' the immunogenicity of the extant neoplastic cells and supports remodelling of the tumour microenvironment towards the immunosuppressive and pro-neoplastic state. The presentation will review immunosuppressive mechanisms induced by growing tumours as well as immunomodulatory effects of whole-body low-dose exposures to X or gamma rays directly or likely associated with cancer-inhibiting outcomes of such exposures. Suggestions will be provided how such exposures can possibly restore and/or stimulate effective anti-tumour immunity during the more advanced stages of carcinogenesis. Finally, we will postulate that, based on epidemiological and experimental data accumulated over the last few decades, whole or half-body exposures to low-dose low-LET radiation should be viewed and further examined as a viable immunotherapeutic treatment option for patients with systemic and metastatic cancer.

Biography

Dr. Marek K. JANIAK, MD, PhD, Professor in medical sciences, head of Dept. of Radiobiology and Radiation Protection, Military Institute of Hygiene and Epidemiology, Warsaw, Poland. Dr. Janiak has been President of the Polish Radiation Research Society during the period of 2007-2013. A member of the European Society for Cancer Research and European Radiation Research Society; representative of Poland to the UN Scientific Committee for the Effects of Atomic Radiation. Author of 115 publications in radiobiology, immunology, radiation hygiene, and epidemiology. Co-editor of a monograph "Medicine of Radiation Hazards" (2005; in Polish) and "Pathology of Injuries and Diseases Caused by Contemporary Weapons during a War and Acts of Terrorism" (2010; in Polish).

Co-Inhibitory Immune Signaling Generates the Splicing of an Immunophilin which Marks a Tregs Subset Associated with Immunotherapy Response of Melanoma Patients

Maria Fiammetta Romano

Department of Molecular Medicine and Medical Biotechnology, University Federico II, Naples, Italy

Abstract

Cancer immunotherapy has shown surprising efficacy in several types of advanced and incurable tumors, particularly, malignant melanoma. There are several immunotherapeutic strategies aimed at enhancing immunological defenses against tumor. Among these, monoclonal antibodies against the so-called "immune checkpoint inhibitors", that counteract tumor-induced immune-disarming pathways, have shown the best outcomes. Regulatory T lymphocytes or Tregs are a subset of lymphocytes involved in immune-surveillance and maintenance of self-tolerance. Tumor often exploits Tregs to allow tolerance to its own antigens and avoid immune system attack. Tregs are usually increased in melanoma patients. It is noticeable that Tregs is a heterogeneous population with respect to their immunosuppressive capability. Lymphocytes are particularly rich in FKBP51 (FKBP5 gene), an immunophilin better known as the intracellular receptor for FK506 and rapamycin. Melanoma aberrantly expresses this immunophilin, which supports cancer resistance and invasion. Recently, our group has shown that melanoma interaction with immune cells, through PD-L1/PD1, bidirectionally generated the splicing of FKBP5 gene inducing a lower molecular weight form of FKBP51, termed FKBP51s, in both melanoma and lymphocyte. A study performed on PBMC of 64 patients with advanced melanoma (stage III/IV) showed that FKBP51s marks a Treg subset which was correlated, as an independent variable, to anti-CTLA4 (ipilimumab) response. More precisely, a low

frequency of Treg FKBP51s^{pos} (≤1% of total CD3/CD4 lymphocytes) was associated with unresponsiveness to ipilimumab (Chi-square=9.916, p=0.002). *In vitro* iTreg generation suggested that FKBP51s was associated with CD25^{high}, Ki67^{high} and p70S6k^{high} iTregs, corresponding to a highly metabolically active profile associated with strong suppressive capability. FKBP51s silencing by siRNA attenuated the suppressive phenotype of such iTregs. A study performed on a different cohort of patients receiving anti-PD1 reinforced the hypothesis that melanoma patients that benefit from immune checkpoint targeted therapy are recognizable by an expansion of FKBP51s^{+}Treg subset which may be involved in de-activation of stimulatory co-signalling pathways, in support of tumor immune evasion.

Biography

Dr. Maria Fiammetta Romano MD, presently an associate professor of Biochemistry. Her present research activity is in the field of molecular and translational oncology, especially focused on the elucidation of FK506 binding proteins (FKBP) role in cancer. She has won several awards at AACR and EORTC CLTF meetings for relevant scientific contributions in the field of glioma, melanoma and lymphoma. Dr.Romano studies demonstrated the crucial role of FKBP51 in NF-κB activation and stimulation of TGF-β pro-tumour activity, responsible for resistance and metastasis. She identified for the first time an isoform generated by alternative splicing of FKBP5 gene, essential for regulation of PD-L1 at the post-translational level. This spliced isoform marks a Treg subset with highly suppressive potential which is correlated to melanoma immunotherapy response.

Tumour Infiltrating Lymphocyte Therapy; Melanoma and Beyond

Gray Kueberuwa[1*], Milena Kalaitsidou[1], Gemma Owens[1], Chitra Sethuraman[2], Edmund Cheesman[2], Ian Kamaly-Asl[2], John-Paul Kilday[2] and Robert E Hawkins[1]

[1]University of Manchester, UK

[2]Royal Manchester Children's Hospital, UK

Abstract

The presence of tumour infiltrating lymphocytes (TILs) signify the presence of an on-going immune response against tumour cells. Endogenous immune responses are generally insufficient to eradicate established tumours or indeed prevent disease progression due to a range of mechanisms employed by cancer cells to evade, escape and suppress immune attack. However, the crucial impact of immune responses against tumours is evidenced by the correlation of TIL presence with improved prognosis in a long and growing list of cancers.

TIL therapy involves harnessing endogenous immune response; this is achieved by extracting TILs from surgically removed tumours and expanding them *ex vivo* away from the immune suppressive environment of the tumour. Expansion *ex vivo* not only allows TILs to be "switched back on", but dramatically increases their total number. TILs are then re-infused into lymphodepleted patients where there increased number and activation status can lead to tumour remissions.

Clinical trials evaluating TIL therapy against metastatic melanoma by us and others have seen some dramatic and long term tumour remissions. Our research group is now investigating the prospect of applying TIL therapy to other cancer indications.

Our research group has shown that TILs can be extracted and grown from ovarian, breast, colorectal, renal and high-grade brain tumor samples. In all these indications, in a high proportion of samples, extracted TILs display tumour reactivity. Characterization of TILs across tumour types will be discussed, as well as using these results to shape future research.

Biography

Dr. Gray Kueberuwa received a DPhil in Oncology from the University of Oxford, UK, in 2012.Since 2014 he has worked in the Clinical and Experimental Immunology Group within the Department of Cancer Sciences at the University of Manchester, UK. His research interests include chimeric antigen receptor (CAR) T cell therapy of cancer, tumour infiltrating lymphocyte (TIL) therapy of cancer and the production of immune regulatory agents from within therapeutic cells.

Synergistic Interaction of Cancer-Reductive and Anti-Tumor Driven Immunotherapeutic Activity of a New Class of Oxazaphosphorine Cytostatics

Georg Voelcker

Institute of Biochemistry II, Goethe University Frankfurt Medical School, Frankfurt, Germany

Abstract

Aldophosphamide the pharmacologically active metabolite of oxazaphosphorine cytostatics (OX), in vivo is cleaved enzymatically into the alkylating phosphoramide mustard (PAM) and 3-hydroxypropanal (HPA). HPA is a strong pro apoptotic aldehyde. The cytotoxic event of OX is p53 mediated apoptosis of cells the DNA of which is damaged by PAM. To investigate how the kind of DNA damage - easily repairable or poorly repairable - influences the anti-tumor efficacy of OX, the substances IAP and SUM-IAP which spontaneously hydrolyze to Aldo-Ifosfamide derivatives were synthesized and tested in advanced growing P388 mouse tumors. The alkylating function of the IAP molecule contains two 2-chloroethyl group which generate easily repairable inter strand crosslinks. In SUM-IAP one 2-chloroethyl group is substituted by a mesyl-ethyl group which generates poorly repairable intra strand cross links.

Given equimolar dosages only a marginal increase in life span (ILS) of 11% was measured in therapy experiments with IAP while in the experiments with SUM-IAP ILS was measured to be 280%. Further experiments showed that the well-known anti-tumor driven immunological effect of OX, caused by apoptosis of regulatory T cells (Treg) is greatly enhanced by SUM-IAP. When SUM-IAP was injected 6 days apart, there was an excessive increase in number of leucocytes and all animals survived (ILS >800%). Thus SUM-IAP combines two mechanisms of action: Induction of HPA-supported apoptosis and - due to suppression of Treg - immunological eradication of resistant tumor cells by anti-tumor driven $CD8^+$ T-cells.

Biography

Dr. Habil Georg Voelcker is a graduate biochemist, born in 1938 having a research and teaching experience since 1972. He is an associate member of the Institute of Biochemistry 2, Medical School Frankfurt Germany. Dr. Voelcker has experience in the biochemistry of the metabolism of oxazaphosphorine zytostatics. He is also co-author of the textbook: *Müller-Esterl "Biochemistry" 2nd edition*, He was and been corresponding and first author of more than 50 publications in peer reviewed journals.

Polyol Pathway as a Novel Therapeutic Target for Aggressive Tumors

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Abstract

Cancer cells alter their metabolism to support their malignant properties. A transcriptomic analysis on NCI60 datasets conducted to identify metabolic genes correlated with the epithelial-to-mesenchymal-transition (EMT) revealed a glucose-transforming enzyme belonging to the polyol pathway (PP): the aldo-keto-reductase family 1-member B1 (AKR1B1). AKR1B1 expression was found 7-fold higher in mesenchymal-like cancer cells. IHC on samples from an EMT-driven colon cancer mouse model with p53 deletion showed higher AKR1B1 in invasive tumors from $p53^{\Delta IEC}$ (KO in intestinal epithelial cells) mice compared to both non-invasive or wildtype tumors. Moreover, AKR1B1 staining of cancer tissues from lung cancer patients confirmed a significant correlation with EMT and a negative prognostic value. *In vitro*, shRNA-mediated knockdown of AKR1B1 in lung, ovarian and colon cancer cells lead to EMT reversal, diminished cancer stem cells, and suppressed EMT induced by TGF-β or by excess glucose. Besides reduced migration, AKR1B1-deficient cells displayed decreased proliferation rate and colony-formation ability. The phenotype observed with AKR1B1 knockdown could be observed by targeting sorbitol dehydrogenase (SORD), the second and last enzyme of the PP.

Comparative RNA sequencing profiling confirmed a profound alteration of EMT in PP-deficient cells, revealing a strong repression of TGF-β signature genes. Mechanistically, excess glucose was found to promote EMT through autocrine TGF-β stimulation, while PP-deficient cells were refractory to glucose-induced EMT. This study provides novel mechanistic insights on the metabolic control of cancer differentiation, defining the role of a glucose-transforming pathway in TGF-β-driven EMT. PP represents a novel therapeutic target for the treatment of aggressive tumors.

Biography

Dr. Paolo Ceppi is a junior group leader at the Interdisciplinary Center of Clinical Research (IZKF) of the FAU University of Erlangen Nuremberg in Germany since 2015. The team focuses on the mechanisms that regulate cancer plasticity and at studying the epithelial-to-mesenchymal transition, the cancer stem cells and the association between cancer differentiation and sensitivity to chemotherapy. His mentored and independent research has been published in international journals like *Nature Communications*, *Cell Reports*, *Journal of Pathology*, *Oncogene, Cancer Research* and many others, and received funding from agencies like the US DOD, DFG, IASLC and others.

Building Better and Safer NSAIDS: Development and Therapeutic Potential of Hybrids that Release Nitric Oxide and Hydrogen Sulfide

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) in general and aspirin are chemo preventive, but their long-term use may lead to significant gastrointestinal (GI), cardiovascular (CV) and renal side effects. In our search for a "better NSAID", we developed NOSH-NSAIDs. These are regular NSAIDs such as aspirin, naproxen, sulindac, etc., to which nitric oxide (NO) and hydrogen sulfide (H_2S) releasing moieties have been covalently attached. Both NO and H_2S are gaseous signaling molecules of biological relevance. The rationale for their use was based on the observations that both have some of the same properties as prostaglandins within the gastric mucosa, thus modulating some components of the local mucosal defense systems, leading to reduced gastrointestinal toxicity. Also, these gas transmitters have protective roles in the CV and renal systems. To date we have reported on the synthesis and some general characterizations of NOSH-aspirin

(NBS-1120), NOSH-naproxen (AVT-219), and NOSH-sulindac (AVT-18A). All three have enhanced GI safety profiles yet retain all the basic pharmacological activities of their respective native NSAID. They have potent anti-inflammatory characteristics coupled with anti-pyretic, analgesic, and anti-platelet properties. Furthermore, they are orders of magnitude more potent than their corresponding NSAID in inhibiting the growth of adenomatous, epithelial, and lymphocytic cancer cell lines but have minimal effects on normal cell. In vivo, NOSH-aspirin exhibited chemo-preventive properties that were superior to aspirin and NOSH-naproxen was shown to have chemotherapeutic properties. Of interest, NOSH-aspirin showed synergistic activity with 5-flurouracil in inhibiting colon cancer cell growth. Mechanistically, these agents a) reduced proliferation, b) caused G_0/G_1 cell cycle arrest, c) increased apoptosis, d) reduced NF-kB, FoxM1, and b-catenin expressions in tumors, e) activated caspase-3 enzyme activity, f) increased reactive oxygen species, and g) increased p53 expression in tumors. Some of these proteins were modified through *S*-nitrosylation (S-NO) and *S*-sulfhydration (S-SH). Our studies provide a rationale for the potent anti-cancer effects of these unique compounds.

Biography

Dr. Khosrow Kashfi is an associate medical Professor of Pharmacology at the City University of New York School of Medicine and is a Fellow of the Royal Society of Chemistry. His research is currently focused on the molecular targets of NOSH-NSAIDs in cancer. He is the co-inventor of this class of compounds and holds patents in this general area. He has setup a company around this technology, Avicenna Pharmaceuticals Inc. and is working towards taking some of these compounds to the clinic.

Selective Anti-Cancer Drug NSC631570 Re-Educates Alternatively Activated Phagocytes

Larysa Skivka[1]*, Mariia Rudyk[1], Ievgeniia Hurmach[1], Niccola Funel[2], Ascold Nowicky[3] and Wassil Nowicky[3]

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[2]*University of Pisa, Italy*

[3]*Ukrainian Anticancer Institute, Austria*

Abstract

NSC-631570 is an anticancer agent created based on alkaloids from *Chelidonium majus*. It has the ability to accumulate selectively in cancer cells and induce apoptosis in malignant but not normal cells. The activation of antitumor immune responses is additional effect of the drug. Phagocytes are important players in antitumor immunity. In tumor growth, phagocytes undergo polarized activation to promote tumor growth and metastasizing. Our comprehensive research was aimed to study the effect of NSC-631570 on resting and alternatively polarized phagocytes of different populations. For this purpose, we have used circulating human monocytes and granulocytes, and tissue resident phagocytes (rat peritoneal macrophages and microglial cells). Alternative phagocyte activation was reached by hypoxia exposure *in vitro*. Phagocyte metabolic profile was characterized by arginine metabolism, ROS generation, phagocytic activity, HMGB1 release as well as CD80/86, CD206, CD14 expression. NSC-631570 causes M1 (N1) shift of circulating phagocytes after *in vivo* introduction. Modulatory effect of the drug on circulating phagocytes was abrogated by moderate physical activity. NSC-631570 restored M1 metabolic profile of hypoxia-polarized M2 peritoneal macrophages with enhanced NO synthesis *in vitro*. The drug promoted transition of hypoxic microglial cells to the state of mature pro-inflammatory antigen-presenting cells with up—regulated CD80/86 and CD14 expression along with decreased CD206 level. Overall, our data highlight phagocytes as important determinants of NSC-631570 therapeutic effect and provide experimental evidence that the drug can cause pro-inflammatory metabolic activation of resting phagocytes and re-educate alternatively polarized phagocytes to restore their immunogenic properties.

Biography

Dr. Larysa Skivka – PhD, ScD, has completed her PhD at the age of 28 years from R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, NAS of Ukraine and postdoctoral studies from Taras Shevchenko National University of Kyiv. Currently she is a Professor of the Educational and Scientific Centre "Institute of Biology and Medicine" of Taras Shevchenko National University of Kyiv (Ukraine), Head of the Department of Microbiology and Immunology. Dr.Skivka research interests and activities are immunomodulation as a component of adjuvant cancer therapy, metabolic polarization of phagocytes in the pathogenesis of inflammatory diseases.

Therapeutic Resistance in Cancer: Role of Quercetin

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Abstract

Cancer is one of the leading causes of death worldwide and despite the chemotherapy is central to clinical management of cancer, failure in chemotherapy is very common mainly due to the dose-limiting toxicities and drug resistance. Drug resistance in cancer is generally classified into two categories: intrinsic and acquired. Whichever kind of resistance the cancer cells have this resistance is one of the major problems during chemotherapy, thus the drug resistance mechanisms of cancer cells have been comprehensively investigated, and novel therapeutic strategies against resistance have been tried to be developed especially by using natural products. A number of natural products have been widely used for therapeutic resistance in cancer over several action of anti-apoptotic mechanisms such as necroptosis, autophagy, oncosis, and methuosis to overcome this resistance. Throughout these natural products quercetins is one of the outstanding compounds which might be derived from different natural products such as turmeric and have been studied by even by clinical trials to cope with the therapeutic resistance in cancer. This presentation will mainly focus on the use of quercetin in several cancer types for drug resistance including the studies that our group is conducting against temolozolamide resistance in microglioma.

Biography

Dr. Mukerrem Betul Yerer- Aycan is the Head of the Pharmaceutical Sciences Division, and Dept of Pharmacology in Erciyes University, Faculty of Pharmacy. She has nearly 20 years of experience in the research and discovery of medications aimed to treat cancer and neurological disorders. She is a pharmacist graduated from Hacettepe University, Turkiye and gained her doctorate degree in Erciyes University in 2006. She made her thesis in collaboration with the Dept. of Molecular Biology and Biochemistry in University of Balearic Islands, Mallorka, Spain. She has been in Switzerland to make post doc on neurodegenerative diseases in the Neuro-psychoparmacology dept of Basel University, Medical Faculty. Then she has been to University of Colorado to the Dept. of Pharmaceutical sciences to conduct a collaborative study. She has several national and international grants and she has been the member of several scientific societies. Previously, Dr. Yerer- Aycan served as the Associate Dean of The Faculty of Pharmacy for 8 years. Notably, she has authored more than 30 manuscripts and she is also in the editorial board of several journals including Current Pharmacogenomics and Personalized Medicine, Journal of Cellular Biotechnology and Journal of Natural Products for Cancer Prevention and Therapy. She is also the faculty member who gives pathophysiology and pharmacology classes in Erciyes University, Faculty of Pharmacy and Faculty of Dentistry for more than 15 years.

Second Generation Proteasome Inhibitors: Side Effects and Potency in Cancer Therapy

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[2]Department of Toxicology, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey
[3]Department of Genetics and Bioengineering, Engineering Faculty, Okan University, Istanbul, Turkey
[4]Department of Chemistry - BMC, Analytical Chemistry, Uppsala University, Uppsala, Sweden
[5]Department of Molecular Toxicology, German Institute of Human Nutrition Potsdam-Rehbrücke, Germany

Abstract

Proteasomal system is a crucial target in cancer therapy. The main reason is the high proteasome activity of several cancer cells following several types of treatments. As also shown by our group, proteasome activity increases almost 10-fold in cancer cells than normal healthy cells in stress conditions. This increase in the proteasome activity leads chemotherapy resistance via degradation of damaged proteins. On the other hand, proteasome plays role in the regulation of many transcription factors and therefore it is involved in cell cycle, cell proliferation, apoptosis and metastasis.

Proteasomal system has been focused as a chemotherapeutic agent since 1999. Bortezomib is the first-generation proteasome inhibitor approved by FDA in 2003 for treatment of multiple myeloma and in 2006 for mantle cell lymphoma. Following the approval, bortezomib has been used in the clinic for a large group of hematologic cancer patients as adjuvant therapy. But recent years, a discussion arose among clinicians about dose reduction and abandoning it because of its side effects. Bortezomib, due to its less specificity against proteasome, causes neurotoxicity and cardiotoxicity besides many other side effects. As a solution to this crucial problem, second-generation proteasome inhibitors have been developed. Among others carfilzomib is the first clinically approved one.

In our laboratory, we are comparing the efficiency of carfilzomib with bortezomib in different cancer cell lines. Additionally, we are testing the mechanisms and severity of neuropathy side effects on different type of neural cells. We are mostly using the co-culture cell systems to be able to mimic the interactions in between cancer and healthy cells.

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Biography

Dr. Betul Karademir graduated from Faculty of Pharmacy, University of Istanbul, Turkey in 2003. She obtained her Ph.D. degree from Institute of Biological Chemistry and Nutrition, University of Hohenheim in 2009. She has a position as an associated professor in the Department of Medicinal Biochemistry, University of Marmara. She is an author and co-author of several research articles in journals with 1645 citations. She has contributed in two book chapters and a book. She has received Loreal Turkey 2012 Young Scientist Award and Catherine Pasquier award 2016. She has been a member of Society of Free Radical Research-Europe. Recently she is working about the proteasome inhibitors and side effects in cancer. She also has publications on the role of heat shock proteins in proteasomal degradation.

New Inhibitors of the Tyrosine Kinase ACK1/TNK2 Active in Prostate and Breast Cancer

Harshani R. Lawrence[1,2*], Shuai Meng[1], Yunting Luo[1], Daniel Zhang[1], Steven Gunawan[1], Yuliya Marysuk[1], Kiran Mahajan[1,2], Nupam Mahajan[1,2] and Nicholas J. Lawrence [1,2]

[1] H. Lee Moffitt Cancer Center and Research Institute, FL, USA

[2]University of South Florida, FL, USA

Abstract

ACK1, is a non-receptor tyrosine kinase that is aberrantly activated, over expressed or mutated in many cancer cell types. It interacts with several important ligand-activated receptor tyrosine kinases (RTKs), for example, EGFR, MerTK, HER2, PDGFR and insulin receptor to initiate intracellular signaling cascades. ACK1 activation has been reported in various cancers including prostate, breast and pancreatic tumors. We have shown that the androgen receptor (AR) and AKT are two major downstream effectors of ACK1. ACK1 directly phosphorylates AKT at Tyr176 resulting in AKT membrane localization and activation. Further, we have shown that a 5,6-biaryl-furo[2,3-d]pyrimidine inhibitor of ACK1 (AIM-100) inhibits ACK1 activation and suppresses pTyr267-AR phosphorylation and AKT Tyr176-phosphorylation, inhibiting AR and AKT activity. These findings indicate that ACK1 is prognostic of progression of castration resistant prostate, breast and pancreatic cancer.

We will discuss the development of new potent ACK1 inhibitors by fragment-recombination and structure-based design. Focused chemical libraries were developed and structure activity relationships will be described. The study has produced compounds capable of inhibiting ACK1 in vitro at low nanomolar concentrations. We used an ELISA based assay that measures the ability of ACK1 to phosphorylate an AKT derived peptide as a primary screen. ACK1 inhibition of hits was confirmed in the 33P ATP "Hotspot" assay platform. Selected compounds from the library have been shown to inhibit ACK1 autophosphorylation and the phosphorylation of AR at Tyr267, a surrogate for ACK1 inhibition in vivo. Furthermore our work shows that ACK1 is a promising drug target for cancer therapy.

Biography

Dr. Harshani Lawrence is the Scientific Director of the Chemical Biology Core at the Moffitt Cancer Center and has recently been awarded an R50 NCI research specialist grant. Dr Lawrence has a broad background in synthetic organic chemistry with specific expertise in medicinal chemistry to carry out cancer research in the chemical biology field. Dr.

Lawrence leads several collaborative projects at Moffitt requiring the design and synthesis of chemical probes for target validation studies, focused chemical library design for drug discovery and multi-gram synthesis of key compounds for animal studies.

Dual Targeting of BET Bromodomains and JAK2 Kinase as a New Anticancer Therapeutic Strategy

Nicholas J. Lawrence [1,2*], Steven Gunawan[1], Muhammad Ayaz[1], Pradeep Nareddy[1], Sang Yang[1], Stuart Ember[1], Jin-Yi Zhu[1], Rezaul Karim[1], Rebecca Jacobsen[1], Norbert Berndt[1], Que T. Lambert[1], Gary W. Reuther[1], Harshani R. Lawrence[1,2] and Ernst Schonbrunn[1]

[1]H. Lee Moffitt Cancer Center and Research Institute, FL, USA

[2]University of South Florida, FL, USA

Abstract

Bromodomain (BRD)-containing proteins are essential for the recognition of acetylated lysine (KAc) residues of histones during transcriptional activation. Targeting BRD4 [a member of bromodomain and extra-terminal (BET) protein family] represents a new way to treat prostate and breast cancer, acute myeloid leukemia (AML), and melanoma. We hypothesize that dual inhibition of BRD4 (which regulates oncogenes e.g. c-Myc) and oncogenic kinases will improve anticancer responses. Several kinase inhibitors that also inhibit BRD4 were identified by co-crystallization screening and serve as starting points for this study.

We report the design, synthesis, structural and preliminary biological analysis of next-generation nanomolar BET-selective and nanomolar dual-activity BET-JAK2 inhibitors. Structure-activity relationships were developed using differential scanning fluorimetry (DSF) and co-crystallization of the inhibitors with BRD4. Several potent BRD4-JAK2 inhibitors have higher BRD4 activity compared to the widely used BRD4 inhibitor JQ1. Additionally, MM.1S cell survival by MTT assay showed good activity with cellular IC50 of < 100 nM. Screening against a large panel of cancer cell lines revealed differential growth inhibitory potential, with high activity against bone and blood cancers. Lead compounds exhibit good solubility, high stability in human plasma (t½ > 24 h) and are being assessed for other drug properties and activity in multiple myeloma mouse models. The dual acting agents have the potential for the treatment of cancers with resistance to single activity kinase or BET inhibitors. We will discuss the advantages of dual targeting agent's vs combination therapy of targeted drugs.

Biography

Dr. Nicholas Lawrence is a Senior Member of the Moffitt Cancer Center in the Drug Discovery Department and Professor at the University of South Florida. Dr. Lawrence earned his MA (Natural Sciences) and PhD (Chemistry) at the University of Cambridge. After faculty positions at the University of Manchester and Cardiff University he joined Moffitt in 2004. His laboratory focuses on the design and synthesis of new anticancer agents. Dr. Lawrence has published over 110 peer reviewed papers and 13 issued patents. These include patents protecting several anticancer small molecule technologies licensed to pharmaceutical and biotech companies.

T Cell Co-Stimulation Vulnerable to Breach by Cancer Cells in the Tumor Microenvironment

Per Thor Straten

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Abstract

T cells are capable of recognizing and killing cancer cells by specifically recognizing antigens expressed by cancer cells in the context of HLA molecules. Over the past few years the capacity of T cells to kill cancer cells has been successfully exploited, and immunotherapy of cancer – largely based on T cell killing of cancer cells – extends the lifespan or even cures cancer patients with metastatic disease. However, T cells are carefully regulated by signals from the environment, either soluble factors interacting with surface receptors on T cells or via receptor-ligand interactions e.g., directly allowing cancer cells to block or inhibit functionality of T cells in the tumor. We have characterized a novel co-stimulatory pathway in CD8 T cells. The stimulatory signal goes via activation induced surface expression of both the receptor as well as the soluble ligand. Importantly, increased signaling via this pathway lead to increased cytokine release and proliferation, whereas blocking of the pathways by mono-clonal antibody or siRNA technology leads to diminished production of TNF-α and INF-γ, as well as and reduced proliferation. Using the xCelligence technology we could further demonstrate that blocking of the pathway in tumor specific T cells led to reduced capacity to control cancer cell growth. Interestingly, cancer cells as well as cells of the innate immune system, e.g., macrophages express the same receptor on the surface which implies that cancer cells may hijack the ligand and thereby convert a co-stimulatory signal for the T cells into oncogenic signaling in the cancer cells. We believe this pathway plays an important role in suppression of CD8 T cell responses in the tumor microenvironment, which could be subject to therapeutic intervention.

Gene Master Regulators and the Personalized Timely Cancer Gene Therapy

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Abstract

In previous publications we have defined the gene master regulators (GMRs) as genes whose highly protected expression levels by the cellular homeostatic mechanisms control major functional pathways. Because of their high protection, GMRs are the last genes to be regulated by disease and therefore not selectable as biomarkers whose most frequent regulation in large population is seen as indicative for the cancer transcriptomic signature. Here, we prove that cancer nodules and surrounding normal tissue are governed by distinct Gene Master Regulators (GMR) and that smart manipulation of a GMR's expression selectively affects cancer cells. The method, consistent with our Genomic Fabric Paradigm [1], relies on an original mathematical algorithm that establishes the gene hierarchy from the transcriptomic profiles of tumor biopsies based on their Gene Commanding Height (GCH). GCH is a composite measure of gene expression control and coordination with major functional pathways. We present validation of the approach using microarray data obtained in our NYMC laboratory by profiling human kidney [2], thyroid [3] and prostate cancer samples (in revision). The GMR approach provides the most legitimate targets for cancer gene therapy. It is also personalized and time-sensitive because the GMR hierarchy is unique for each patients and changes slowly during cancer development.

Anti-angiogenesis in Cancer Therapy – Signaling and Gene Expression Mechanisms of ECM Derived Endogenous Angio-Inhibitor Hexastain and its Sub-Fragment Molecules

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[2] Centre for Chemical Biology Division, CSIR-*IICT, TS, India*

Abstract

Angiogenesis is key process in the developing tissue whether it is benign or malignant tissue. If the balance between proangiogenic and antiangiogenic signals is impaired, the pathological condition occurs to counter signaling mechanism. In the course of deregulated signaling, typically angiogenesis signaling favors the proangiogenic pathway and that promotes vigorous malignant tumors. ECM derived endogenous type IV collagen metabolites have been shown to inhibit neovascularization towards growing tumor. These endogenous cryptic domains, when degraded by MMPs, elevate the antiangiogenic signaling pathway coupled with apoptotic signaling. In the present study we developed a novel method of coding sequence construction from the genomic DNA that does not require RNA. This method circumvents the limitations in tissue specific or condition specific RNA expression during gene isolation for cloning and also useful to construct the fusion proteins. We cloned the NC protein fragments in pLATE31 cloning and expression vector that does not require the ligation and restriction digestion to prepare the recombinant molecules. Functional assays of angiogenesis assays on HUVECs and chick embryo proved the antiangiogenic effect of the α6(IV)NC1, α6S2(IV)NC1, and α6S3(IV)NC1 molecules. Signaling and 14 gene expression studies suggested the p53 mediated apoptosis and PTEN mediated cell survival pathway inhibition. *In-silico* analysis inferred the sequence and structure conservation in the VBM proteins and NC domains. We observed the α6S2(IV)NC1 and α6S3(IV)NC1 similar angio-inhibitory effect and explained the reason by structural alignment analysis. Protein-protein docking results demonstrated the RGD independent binding of NC fragments to the integrins during angio-inhibition.

Biography

Dr. Smita C. Pawar is currently the Head and Associate Professor in the Department of Genetics at Osmania University and has been a faculty member here since 2004. She is recipient of prestigious awards and scholarships like State Best Young Teacher Award (2016), DST BOYSCAST FELLOWSHIP-2012, Young Investigator Award, Telangana Science Academy Associate Fellow, etc. She presently has ongoing major research projects from SERB, ICMR and UGC-UPE and has published her research work in international journals of repute. Her research specialization is in the field of Cancer Genetics and therapeutics. Currently five research scholars are pursuing theirs PhD under her supervision and one ICMR Women scientist is carrying her post-doctoral research in her mentorship.

Anti-TACE Antibody Drug Development for the Treatment of Cancer

Hang Fai Kwok[1*] and Gillian Murphy[2]

[1]Faculty of Health Sciences, University of Macau, Avenida de Universidade, Macau SAR [2]Department of Oncology, CRUK Cambridge Institute, University of Cambridge, UK

Abstract

TNF-Alpha Converting Enzyme (TACE) is a membrane-bound zinc metalloprotease (MP) that may play a significant role in tumour biology, notably by the conversion of many inactive cell-surface ligands into active soluble ligands. Moreover, TACE can stimulate local inflammation by solubilising TNF-Alpha, and aid immunological evasion by removing tumour cell surface MICA. Due to the homology between MP active sites, the development of small molecule TACE inhibitors has been plagued with unwanted non-specific MP activity. Recently, our group has successfully developed an inhibitory TACE antibody [A9(B8)] and showed the effective inhibition of both human and mouse TACE. In this study, we evaluated the anti-tumour efficacy of A9(B8) -- the first specific 'Human and Mouse Cross-Reactive' anti-ADAM17 inhibitory IgG antibody with a mouse model of pancreatic ductal adenocarcinoma (PDA). It has been demonstrated that ADAM17 is required for Kras-driven tumorigenesis in PDA mouse models. Here, we show that intraperitoneal injection of A9(B8) effectively attenuates high grade pancreatic intraepithelial neoplasia (PanIN) formation in Pdx1Cre; KrasG12D; Trp53fl/+ mice. Thus, A9(B8) has anti-ADAM17 activity in vivo, inhibits pancreatic tumorigenesis and has potential for the use in ADAM17-

dependent tumours. For the extend of this drug development programme, we also studied the A9(B8) in combination with FDA approved EGFR inhibitor (Erlotinib) for the treatment of lung cancer (NSCLC). It demonstrated that A9(B8) *in vitro* enhanced sensitivity of lung cancer cell line (NCI-H1975) to the anti-cancer therapy of EGFR-TKis and also augmented the p-ERK suppression by EGFR-TKis under PMA stimulation. Currently, we are further investigating whether A9(B8) has an additive effect on anti-tumour when combined with Erlotinib in NCI-H1975 in *in vivo* xenograft model and planned to perform *Ex vivo* studies by using xenograft's tumour samples in order to dissect the combinatory anti-cancer mechanism.

Biography

Currently, Dr. Hang Fai (Henry) is Assistant Professor and also the Histopathology Core consultant in the Faculty of Health Sciences at University of Macau. He is also the visiting scientist in the CRUK Cambridge Institute University of Cambridge. Henry procured BSc (Hons) degree and PhD in Biomedical Sciences in UK in 2003. He then awarded a *knowledge transfer partnerships fellow* as a post-doctoral researcher in the UK No. 1 Pharmacy School at the Queen's University Belfast. After 4 years of the postdoctoral training, he moved to the pharmaceutical industry as a senior scientist from 2007 to 2011, then returned to academia as a senior research fellow in the department of oncology at University of Cambridge, working with Prof Gillian Murphy at the Cancer Research UK Cambridge Institute and bringing together his interests in protease biochemistry research with biologics development to pursue novel therapeutic and prognostic approaches in the treatment of cancer. Apart from protease and antibody research, Henry also interested in the discovery and characterization of novel bioactive molecules from sources in nature including amphibian defensive skin secretions, reptile, scorpion and insect venoms for exploiting their anti-cancer therapeutic potential.

Postmastectomy Chest Wall Reirradiation with Proton Therapy for Breast Cancer

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Mayo Clinic Arizona, AZ, USA

Northwestern Medicine Chicago Proton Center, IL , USA

Abstract

Purpose: Assess toxicity in breast cancer patients receiving post-mastectomy chest wall (PMCW) reirradiation (reRT) with proton therapy (PT).

Methods and Materials: From 2012-2016, 22 breast cancer patients received PMCW reRT with PT. Median PT dose was 50.51 (45.1-76.31) GyE Initial RT characteristics include the following: 40 Gy mantle field for Hodgkin Lymphoma (N=1), intact breast (N=18) or breast/CW plus supraclavicular fossa for breast cancer (N=2) and partial breast (N=1). Median initial RT dose was 60 Gy (10-70 Gy). Median time interval between courses of RT was 12 years (3-36 years).Toxicity was assessed prospectively per CTCAE v. 4.0 at baseline. Cosmesis was retrospectively graded according to the Harvard/NSABP/RTOG grading scale.

Results: Median follow-up was 15 months (3-39 months). At the time of last follow-up, all patients had locoregional control. One patient developed distant metastases 17 months following PT. Acute skin toxicity occurred in all patients; grade 1 (N=5), grade 2 (N=15) and grade 3 (N=2). Acute grade 2 esophagitis occurred in 7 patients. Acute grade 2 chest wall pain occurred in 10 patients; grade 3 in 1 patient. Toxicities at last follow-up include the following: rib fracture (N=3), grade 2 lymphedema (N=3), pneumonitis requiring steroids (N=1), delayed wound healing in the reRT treatment field (N=3); one of which required hyperbaric oxygen. Cosmetic outcomes at the time of last follow-up were grade 1 (N=1), grade 2 (N=9) grade 3 (N=11) and grade 4 (N=1). All patients experienced CW fibrosis; grade 1 (N=14), grade 2 (N=6) and grade 3 (N=2).

Conclusions: ReRT with PT in breast cancer patients appears to have acceptable toxicity.

Biography

Dr. McGee is an Assistant Professor in the Department of Radiation Oncology at Mayo Clinic Arizona. She subspecializes in the treatment of breast cancer and head and neck malignancies.

DAY-3

WEDNESDAY, AUGUST 8, 2018

Metformin Reduces the Risk of Biliary Tract Cancer in Patients with Type 2 Diabetes

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Division of Environmental Health and Occupational Medicine of the National Health Research Institutes, Zhunan, Taiwan

Abstract

This study evaluated whether metformin use in patients with type 2 diabetes mellitus might reduce the risk of biliary tract cancer (BTC). New-onset type 2 diabetes patients aged 25-75 years during 1999-2005 were enrolled from the Taiwan's National Health Insurance and followed up until December 31, 2011. A total of 287,995 ever users and 16,229 never users were identified (unmatched original cohort) and a 1:1 matched pairs of 16,229 ever users and 16,229 never users based on propensity score (PS) were created (matched cohort). Hazard ratios were estimated by three Cox regression models: 1) adjusted for PS; 2) incorporated with the inverse probability of treatment weighting using PS; and 3) all covariates treated as independent variables. Results showed that in the unmatched cohort, 73 never users and 523 ever users developed BTC, with respective incidence of 100.36 and 38.06 per 100,000 person-years. An overall risk reduction was observed in metformin users in all three regression models with respective hazard ratio (95% confidence interval) of 0.442 (0.344-0.568), 0.377 (0.295-0.481) and 0.477 (0.370-0.615). The tertile analyses showed a dose-response pattern with a neutral effect in the first tertile when metformin use was <2 years and a significant risk reduction in the second and third tertiles. Findings in the matched cohort were consistent with those observed in the unmatched cohort. In conclusions, metformin significantly reduces the overall risk of BTC by 50%-60%. A dose-response effect is observed and users of more than 2 years show significantly reduced risk.

The Tumour Suppressor OPCML Prevents AXL-Mediated EMT and Motility in Ovarian Cancer Cells

Chiara Recchi
Imperial College London, London, UK

Abstract

Ovarian cancer is a lethal gynaecological malignancy with a very poor prognosis. OPCML is a tumour suppressor gene that is silenced by methylation in over 80% of ovarian cancer patients but also in other cancers such as lung, colon and breast. OPCML is a GPI-anchored protein and it inhibits tumour cell growth in vitro and in vivo by interacting directly with a spectrum of Receptor Tyrosine Kinases (RTKs) and inducing their degradation. AXL, a member of the TAM family of RTKs, promotes metastasis in ovarian cancer by stimulating Epithelial to Mesenchymal Transition (EMT) upon binding to its ligand Gas6. We recently discovered that OPCML interacts with AXL and that this interaction is promoted by the activation of AXL by Gas6. Upon binding, OPCML recruits and concentrates AXL in detergent resistant membranes, where AXL is dephosphorylated by a local resident phosphatase, PTPRG. So, after an initial activation of the ERK1/2 pathway upon Gas6 stimulation, in the presence of OPCML AXL phosphorylation is lost and the whole downstream signalling pathway, including the sustained phosphorylation of ERK1/2, is inhibited. As a result, the EMT transcriptional regulator Slug is not transcribed and the cells show a strongly reduced motility in both single and collective cell migration assays and in a 3D invasion assay. The recruitment of AXL to detergent resistant membranes is key, as depletion of cholesterol does not disrupt AXL-OPCML interaction but alts completely the interaction of AXL with the phosphatase. Furthermore, OPCML synergizes with the AXL inhibitor R428 in vitro and in vivo, thus making it a promising clinical therapeutic agent.

Biography

After graduating in molecular biology in Italy, Chiara Recchi obtained her PhD in microbiology at the Pasteur Institute in Paris, working on Mycobacterium tuberculosis virulence factors. She then focused her interest to cancer cell biology as a

post-doc in Philippe Chavrier's lab, at the Curie Institute, investigating intracellular trafficking in breast cancer cells. In 2007 she moved to Imperial College London, continuing and expanding her studies on metastatic cancer cells in Miguel Seabra's lab. In 2013 she was appointed as research fellow in Hani Gabra's group, successfully leading the functional characterisation of the tumour suppressor OPCML in ovarian cancer models.

Aspirin, Oseltamivir Phosphate and Metformin Sensitize 3D Triple-Negative Breast Cancer Spheroids to Tamoxifen Treatment

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Abstract

Triple-negative breast cancer (TNBC) is a highly aggressive, chemoresistant, and metastatic subtype of breast cancer that accounts for approximately 12.5-15% of all breast cancer cases. TNBC patients exhibit poor prognoses, widespread metastatic growth, as well as frequent relapses, and are commonly treated with combinations of generic chemotherapies. Currently, there are no targeted treatments for TNBC. Tamoxifen is a standard breast cancer chemotherapy that has displayed modest anti-tumor effects in TNBC. Tamoxifen-sensitizing agents may prove useful in the treatment of TNBC. We investigated whether acetylsalicylic acid (ASA), more commonly known as aspirin, oseltamivir phosphate (OP), and metformin can independently produce anti-tumor effects. With the growing use of MCTS to study complex interactions in the tumor microenvironment, triple-negative breast cancer spheroids (MDA-MB-231 spheroids) constitute a good three-dimensional model for investigating anti-tumor drug combinations. MCTS can be generated from the MDA-MB-231 cell line using the cyclo-RGDfK (TPP) peptide, a novel method that enables rapid, inexpensive and true spheroid formation. We have successfully generated 3D spheroids from the MDA-MB-231 TNBC cell line and shown that aspirin, OP, and metformin can independently and additively decrease volume and cell viability in non-resistant MDA-MB-231 spheroids. Additionally, we have shown that Aspirin, OP, and metformin can independently and additively sensitize tamoxifen-resistant MDA-MB231 spheroids to tamoxifen treatment. These findings give rise to the possibility of using aspirin, OP, and metformin as tamoxifen adjuvants in tamoxifen-resistant triple-negative breast cancer.

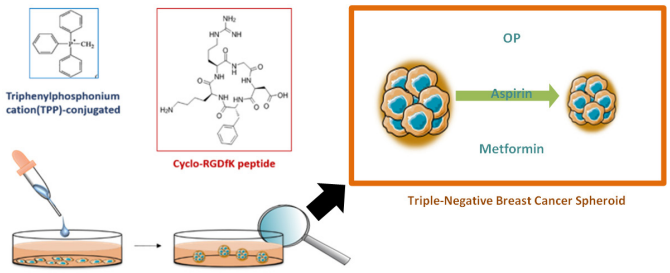

Figure: Experimental process for prostasphere MCTS formation using the cyclo-RGDfK(TPP) method. The top two images depict the chemical structure of the peptide used to generate spheroids. The bottom images depict the simple method by which spheroids are produced. The image on the right depicts the formation of smaller triple-negative breast cancer spheroids with decreased cell viability after treatment with aspirin, OP and metformin. In brief, a previously established concentration of the peptide is added to cells in monolayers. After seven days, 3D spheroids are generated without the addition of any mechanical or gravitational force or changes in the components.

Biography

Regina-Veronicka (Nicka) is a trainee in the laboratory of Prof. Dr. Myron R Szewczuk. She has special interest in optimizing the multicellular tumor spheroid (MTS) model developed by her colleagues. Her research explores how different types of glycosylation may be contributing to prostasphere tumor formation. She has shown that prostate cancer cells are highly fucosylated and that blocking core fucosylation in prostaspheres results in the formation of spheroids with a reduced volume. In addition to her work with MTS, Nicka is also investigating whether fucosylation may be involved in metastasis in pancreatic cancer.

Association of Ring Box-1 Protein Overexpression with Clinicopathologic Prognostic Parameters in Prostate Carcinoma

Zeliha Esin Celik[1*], Mehmet Kaynar[2], Fatma Dobur[1], Pınar Karabagli[1] and Serdar Goktas[2]
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Abstract

Aim: To determine the expression of Ring Box-1 (RBX-1) protein in prostate carcinoma (PCa) and the association between RBX-1 expression and clinicopathologic prognostic parameters.

Material & Methods: Relevant data such as age, preoperative serum PSA values, and tumor stage were obtained from 51 PCa patients' records who underwent radical prostatectomy between January 2010 and March 2014. Hematoxylin-eosin stained pathology slides were evaluated by two pathologists blinded to patients' data in order to determine Gleason grade groups, tumor stage, tumor volume, capsule invasion, lymphovascular invasion, perineural invasion, and seminal vesicle invasion. Immunoreactivity scoring system (IRS) was used to determine RBX-1 expressions.

Results: A statistically significant difference was determined in terms of RBX-1 expression between non-tumoral prostate tissue, high grade prostatic intraepithelial neoplasia (H-PIN) and carcinoma foci (p=0,001). RBX-1 expression in the Gleason pattern 4 was higher than the Gleason pattern 3 and H-PIN foci as well as non-tumoral prostate tissue. Likewise, in cases with PSA levels of >10, 1 ng/ml, RBX-1 expression was higher than those ≤10 ng/ml. Moreover, RBX-1 expression of stage II cases was higher than stage I (p=0,019), RBX-1 expression of stage III higher than stage I cases (p=0,044). However, RBX-1 expression was not related with clinicopathologic parameters including patient age, tumor volume, lymphovascular invasion, perineural invasion, seminal vesicle invasion, or capsule invasion.

Conclusions: RBX-1 protein is overexpressed in PCa and associated with clinicopathologic prognostic parameters related with biological potential of the aggressive disease. This study also provides the basis for future investigations of RBX-1 as a potential therapeutic target in PCa.

Biography

Zeliha Esin Celik has graduated from Selcuk University Faculty of Medicine in 2011. She has been working as a pathologist and lecturer at the same institute since 2013. She has investigations on molecular markers on prostate and bladder carcinomas. She is a member of Uropathology Working Group, Federation of Turkish Pathology Societies.

Targeting Neuraminidase-1 with Multi-Modal Therapy to Sensitize Pancreatic Cancer to Chemotherapy and Moderate the Inflammatory Microenvironment

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[2]*ENCYT Technologies, Inc., Membertou, Nova Scotia, Canada*

Abstract

Pancreatic cancer represents the fourth leading cause of cancer-related deaths, attributed to the advent of metastases, rendering curative surgery an option in less than 25% of patients at diagnosis. The highly inflammatory microenvironment characteristic of pancreatic cancer contributes to the already dense extracellular matrix (ECM) to further exacerbate resistance to chemotherapy and other therapeutic agents. We have previously reported that neuraminidase-1 (Neu-1) cleaves a-2,3 sialic acid residues on receptor tyrosine kinases (RTKs) including the epidermal growth factor receptor (EGFR), insulin receptor (IR) and TOLL-like receptors (TLRs). We have shown that anti-viral oseltamivir phosphate (OP) inhibits the activity of Neu-1 ultimately shutting down a novel signaling paradigm implicated in tumorigenesis. Recent reports describing the overlapping effects and mechanisms of action of anti-diabetic metformin and non-steroidal anti-inflammatory drug acetylsalicylic acid (aspirin) led us to incorporate these drugs in our drug cocktail. Enzyme activity assays on live PANC-1 cells have revealed that aspirin works similarly to OP to target Neu-1 activity, an effect that has not been previously reported

on. These findings have led us to optimize this multimodal therapy to target effectively target multistage tumorigenesis. We propose that the combination of OP, metformin and aspirin will work synergistically to sensitize pancreatic cancer cells to Gemcitabine chemotherapy, prevent metastasis, neovascularization and tumor growth.

Biography

Bessi Qorri is a trainee in Prof. Dr. Myron R. Szewczuk's lab. She is interested in optimizing the drug combination consisting of oseltamivir phosphate, aspirin and metformin to target multistage tumorigenesis in pancreatic cancer. She has shown that these drugs act synergistically to inhibit malignant cell proliferation, as well as discovered a novel role of aspirin within our signaling paradigm implicated in tumorigenesis.

Cancer Vaccines and the Impact of Irradiation on the Induction of Bystander Killing by Genetically Engineered Ovarian Tumor Cells: Implications for Clinical Use

Jehad Zweiri* and Stephen Christmas

Tumour Immunology and Cancer Vaccines, University of Liverpool Medical School, London, UK

Abstract

Cellular based therapeutic approaches for cancer rely on careful consideration of finding the optimal cell to execute the cellular goal of cancer treatment. Cell lines and primary cell cultures have been used in some studies to compare the *in vitro* and *in vivo* efficacy of autologous vs allogeneic tumour cell vaccines. This study examines the effect of g-irradiation on a range of tumor cell lines in conjunction with suicide gene therapy of cancer. To determine the efficacy of this modality, a series of *in vitro* and *in vivo* experiments were conducted using genetically modified and unmodified tumor cell lines. Following co-culture of HSV-TK modified tumor cells and unmodified tumor cells both *in vitro* and *in vivo* we observed that the PA-STK ovarian tumor cells were sensitive to g-irradiation, completely abolishing their ability to induce bystander killing of unmodified tumor cells. In contrast, TK-modified human and mouse mesothelioma cells were found to retain their *in vitro* and *in vivo* bystander killing effect after g-irradiation. Characterisation of tumor cell death showed that PA-STK cells underwent pyknosis (necrosis) after g-irradiation. These results suggest that PA-STK cells are not suitable for clinical application of suicide gene therapy of cancer, as lethal g-irradiation (100Gy) interferes with their bystander killing activity. However, the human mesothelioma cell line CRL-5830-TK retained its bystander killing potential after exposure to similarly lethal g-irradiation (100Gy). CRL-5830 may therefore be a suitable vehicle for HSV-TK suicide gene therapy. This study highlights the diversity among tumor cell lines and the careful considerations needed to find the optimal tumor cell line for this type of whole cell tumour vaccination.

Biography

Dr Jehad Zweiri, lecturer in cancer studies at the University of Liverpool Medical School, born and grew up in Jordan and received his Bachelor's degree from the University of Jordan in 1990. He obtained his master degree from London School of Hygiene and Tropical Medicine/University of London, and then obtained his PhD degree in 2000 from Kings College Medical School/University of London, in the field of Immune Gene Therapy of Cancer under the supervision of Professor Farzin Farzaneh. He then started his work as Postdoctoral Associate at the department of Immunology and Medicine at the University of Liverpool in 2002. In 2010 he was appointed as a lecturer in the university of Liverpool medical school and he is currently fellow of the British Higher Education Academy since 2012.

CDK 4/6 Inhibitors Beyond Estrogen Receptor Positive Breast Cancer: Synergistic Effect of PI3K and CDK4/6 in Triple Negative Breast Cancer

Yuan Yuan[1*], Wei Wen[2], Susan E. Yost[1], Quanhua Xing[2], Jin Yan[2], Ernest S. Han[3], Joanne Mortimer[1] and John H. Yim[2]

[1]*Department of Medical Oncology & Molecular Therapeutics, Duarte, CA, USA*

[2]*Division of Surgical Oncology, Duarte, CA, USA*

[3]*Division of Gynecologic Oncology, City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA*

Abstract

Triple negative breast cancer (TNBC) is an aggressive form of breast cancer with multiple distinctive molecular subtypes. Despite PI3K/AKT/mTOR being one of the most commonly altered pathways in TNBC, single agent inhibitors have not shown marked efficacy. CDK 4/6 inhibitor has been currently FDA approved for treatment of metastatic estrogen receptor positive breast cancer. In this study, we investigate the efficacy of PI3K-α inhibitor, BYL719 (alpelisib), either alone or in combination with CDK4/6 inhibitor Lee011 (Ribociclib), in TNBC. Our results showed that targeting PI3K-α pathway alone with BYL719 had limited activity in TNBC cells. While strong inhibition of p-RB and p-S6 was found in the BYL719 sensitive cell line, T47D, less inhibition of p-RB and p-S6 was observed in TNBC cells. Addition of the CDK4/6 inhibitor, LEE011 (ribociclib) to BYL719 led to increased inhibition of p-RB and p-S6 in TNBC. This synergistic inhibition of cell survival in an RB-dependent and subtype-dependent manner was observed both *in vitro* and in a PDX model of TNBC. These findings suggest that inhibition of p-RB and p-S6 is important for an effective response to the treatment of TNBC and points to a potential role for combination therapy with BYL719 and LEE011 in the treatment of RB-intact TNBCs. These result suggest the combination of BYL719 and LEE011 could be an effective therapy in treatment of TNBC and the combination should be further tested in clinical trials.

Biography

Dr. Yuan Yuan MD PhD completed her Hematology and Oncology Fellowship at New York University. She is an Associate Professor at the Department of Medical Oncology and Molecular Therapeutics, City of Hope National Cancer Center. Her main research interests are developing novel therapeutics for treatment resistant breast cancer, especially triple negative breast cancers. She recently completed a 4-year NIH K-12 training in 2017. She is experienced in pre-clinical, translational, and clinical application of novel combination therapy. She is currently PI for multiple investigator-initiated clinical trials including the following studies: a phase I/IB clinical trial studying eribulin plus everolimus in patients with metastatic TNBC (NCT02120469); a phase II trial androgen receptor (AR) targeted therapy GTx-024 in combination with pembrolizumab in patients with metastatic AR+ TNBC.

Biomarker Identification and Neuromodulation as Treatment for Chronic Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Sarah Prinsloo[1*], Diane Novy[1], Larry Driver[1], Lois Ramondetta[1], Cathy Eng[1], Gabriel Lopez[1], Randall Lyle[2] and Lorenzo Cohen[1]

[1]*The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

[2]*Mt. Mercy University, Cedar Rapids, IA, USA*

Abstract

Background: CIPN is a common side effect of chemotherapy, leading to impairment in daily activities and diminished quality of life. Neurofeedback (NF) is a brain-computer interface that induces neuroplasticity to modulate brain activity and therefore may improve CIPN symptoms.

Methods: Seventy-one (62 female; mean age=63; 52 breast, 8 gynecologic, 11 others; average length of symptoms=24 mos) cancer survivors ≥3 months from completing chemotherapy who reported ≥3 on a neuropathy rating scale, were randomized to NF (35) and underwent 20 sessions of EEG NF or a wait-list control group (WL=36). We used quantitative electroencephalography (qEEG) neural imaging to determine EEG patterns unique to CIPN and then provided NF to change aberrant brain signatures. The Brief Pain Inventory (BPI), the Pain Quality Assessment Scale (PQAS), and EEG

were collected at baseline and after 10 weeks. EEG analysis was done using qEEG and Low Intensity Electromagnetic Tomography (LORETA) imaging

Results: 100% of participants who started NF completed treatment. qEEG patterns showed elevated cortical activity in parietal and frontal sites compared to a normal population. NF significantly reduced pain (NF=3.5 vs WL=5.7, p=.003), numbness (NF=2.9 vs WL=5.6, p=.001), intensity (NF=3.5 vs WL=5.3, p=.003), and unpleasantness (NF=3.4 vs WL=6.0, p=.001). EEG analyses showed increased alpha and decreased beta power after NF, where protocols were based on increasing alpha and decreasing beta, with no changes noted in the WL group. **Conclusion:** NF clinically and significantly reduced pain and other symptoms associated with CIPN. Patients with CIPN exhibited specific and predictable EEG signatures that changed with NF.

Biography

Dr. Prinsloo`s laboratory is the first lab at MD Anderson to establish non-invasive neuromodulation as a treatment modality for side effects of cancer therapies and to publish specific EEG correlates of physical and psychological neuropathic symptoms, and resolution of neuropathic symptoms by a targeted, non-invasive technique. Her expertise is in applied neuroscience, specifically the integration of electroencephalographic (EEG) neuroimaging and non-invasive neuromodulation techniques. Dr. Prinsloo primary research interest is in the utilization of neuroscientific methods to explore the efficacy and mechanisms of non-conventional medicine. Currently, she focused on the determination of central nervous system effects of chemotherapy, the association with patient perception of peripheral neuropathy, and the effects of neuromodulatory techniques on pain conditions. In separate studies, she is examining neurofeedback to treat neuropathy resulting from breast cancer treatment, repetitive transcranial magnetic stimulation to treat oxaliplatin-related neuropathy, neural correlates of acute head and neck pain from radiotherapy and neurofeedback to augment management of acute pain, neural mechanisms of meditation for cognitive dysfunction after chemotherapy, neural mechanisms of acupuncture to treat xerostomia in head and neck radiation patients, neural mechanism of hypnosedation in breast surgical patients, and neurophysiological effects of chronic stress and tumor proliferation.

Glutathione is Key to the Synergistic Enhancement of Doxorubicin and Etoposide by Polyphenols in Leukemia Cell Lines

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[1]Faculty of Applied Medical Sciences - Department of Laboratory Medicine and Pathology, Umm Al Qura University, Saudi Arabia

[2]Biomolecular Sciences Research Centre - Cancer Research, Sheffield Hallam University, UK

Abstract

Recently published in Nature: Cell Death and Discovery, Mahbub et al 2015 have demonstrated that polyphenols can synergistically enhance the action of the topoisomerase II inhibitors: doxorubicin and etoposide in leukemia cells. A reduction of glutathione (GSH) was strongly associated with sensitizing cells to the pro-apoptotic effects of polyphenols when used in combination with doxorubicin or etoposide. Importantly, when polyphenols and topoisomerase II inhibitors were combined, it was possible to induce a synergistic decrease in cell proliferation (measured as ATP levels), cell-cycle arrest and induction of apoptosis in leukemia cell lines (Mahbub et al, 2015). Five polyphenols that had been previously shown to induce apoptosis in leukemia cells (quercetin, apigenin, emodin, Rhein and cis-stilbene) (Mahbub et al, 2013) were combined with doxorubicin or etoposide in two lymphoid (CCRF- CEM and Jurkat) and two myeloid (THP-1 and KG1a) cell lines. These cell lines were selected as they had been identified as the most sensitive and most resistant to polyphenol-induced apoptosis; (Mahbub et al, 2013) in addition, two non-tumor control haemopoietic stem cells (HSCs) (CD133+ and CD34+) were investigated. The results of Mahbub et al (2015), raise the possibility of a similar effect in myeloid malignancies treated with topoisomerase II inhibitors, in that dietary polyphenols may prevent etoposide/doxorubicin-induced anti-tumor activity. The mechanism of action of polyphenol-mediated antagonism of topoisomerase II inhibitors is unclear. However, it is known that GSH is contra-indicated for other chemotherapy agents, such as for cisplatin, where GSH supplementation inhibits the action of cisplatin. However, GSH-mediated depletion appears unrelated to cisplatin insensitivity in myeloid leukemia cell Lines (Amran et al, 2005). This is, however, in contrast to most other tumor models, suggesting that alternate multi-drug resistance mechanisms may be a feature of myeloid leukemia cell lines. Similarly, recent

work has shown that antioxidants can increase the metastasis of melanoma in mice, (Le Gal et al, 2015) which raises the possibility that in some cancer types, polyphenols other antioxidants could be detrimental. Thus, it is fundamental to tailor any treatment, be it with novel anti-tumor agents such as polyphenols or standard chemotherapy, to the specific cancer types and investigate any possible treatment interactions.

Biography

Mr. Amani Mahbub completed MSc of Biomedical Basis of Disease in 2010 and PhD of Anti-Cancer Potential of Polyphenols in Treatment of Leukemia in 2015 at Sheffield Hallam University of Biomedical Research Centre – Cancer Research, Sheffield, UK. Dr. Mahbub is interested in investigating the biological effects of several nutraceutical compounds such as polyphenols alone and in combination with chemotherapies on the induction of apoptosis, reduced cell proliferation and signaling pathways that involved in the pathogenesis of leukemias. He published four papers in: the Journal of Pathology (2012), the Journal of Anti-cancer Agents in Medicinal Chemistry (2013) and recently Two in Nature (2015) and was awarded three prizes: (1) The Alastair Currie prize for the best poster and presentation at the Pathological Society of Great Britain & Ireland Conference in 2012, Sheffield, UK; (2) Best poster prize for research entitled: Polyphenols Act Synergistically with Doxorubicin and Etoposide in leukemia cell lines at t the 4th International Conference on Blood Malignancies and Treatment: 18th -19th April (2016), Dubai –UAE; (3) Best poster award for research entitled: Polyphenols Act Synergistically with Doxorubicin and Etoposide in Leukemia cell lines at the 14th World Cancer and Anti-Cancer Therapy Convention and that held in Nov 21-23, 2016 in Dubai, UAE. Currently, Dr. Mahbub is working as Assistant Professor in Pathology and the Vice Head of Laboratory Medicine Department in Faculty Applied of Medical Sciences– Umm Al-Qura University, Makkah, KSA.

Lymphoma: at a Single Institution Experience Running title: Surgery of Gastrointestinal Diffuse Large B-Cell Lymphoma

Dae Ro Lim*, Jung Kul Kuk, Taehyung Kim and Eung Jin Shin

Division of Colon and Rectal Surgery, Department of Surgery, Soonchunhyang University College of Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, South Korea

Abstract

Propose: The study aimed to analyze peri/postoperative outcomes and long-term oncologic outcomes after surgical management for primary gastrointestinal diffuse large B-cell lymphoma (DLBL).

Material and Method: Between January 2001 and December 2013, 19 patients who underwent surgery for primary gastrointestinal DLBL were retrieved from a retrospective database.

Results: With a median follow up of 49.2 months, the most common tumor locations were the terminal ileum and cecum (n= 14, 73.7%) and stomach (n=4, 21.1%). The most common clinical symptoms were abdominal pain (n=15, 78.9%) and intussusceptions (n=5, 26.3%). None of the patients had B symptoms. Emergency surgery was undertaken in 36.8% (n=7) of the patients. Mean mass size was 8.4cm; 4 patients (21.1%) had a bulky mass (>10cm). The International Prognostic Index (IPI) scores were low (n=11, 57.9%), low-intermittent (n=7, 36.8%), and high-intermittent (n=1, 5.3%). Patients` staging was IE (n=9, 47.4%), IIE (n=8, 42.1%), and IVE (n=2, 10.5%) based on the Ann Arbor staging system, and I (n=2, 10.5%), II1 (n=5, 26.4%), IIE (n=10, 52.6%), and IV (n=2, 10.5%) based on the Lugano staging system. B-lymphocyte antigen CD20 was positive in most patients (n=17, 89.5%) and Ki-67 was high (>70%) in 12 patients (63.2%). Two types of chemotherapy were administered: CHOP (n=5, 26.3%), R-CHOP (n=13, 68.4%). The 5-year disease-free survival rate was 94.4% and the 5-year overall survival rate was 89.5%.

Conclusion: Surgery for primary gastrointestinal DLBL is feasible and acceptable. Low staging of primary gastrointestinal DLBL has good prognosis.

Biography

Assistant Professor Dae Ro Lim obtained his medical degree from University of Yonsei and is a colorectal Fellow of the Yonsei University Hospital. He is now working at Soonchunhyang University Bucheon Hospital. He is a colorectal surgeon and is also deeply involved in public health and basic research in cancer. Dr. Lim is the member of Korean Surgical Society, Korean Society of Coloproctology, Korean Society of Endoscopic Laparoscopic Surgery, Korean Society of Surgical Oncology. Assistant Professor Dae Ro Lim's current research interests lie in the area of surgical oncology of cancer.

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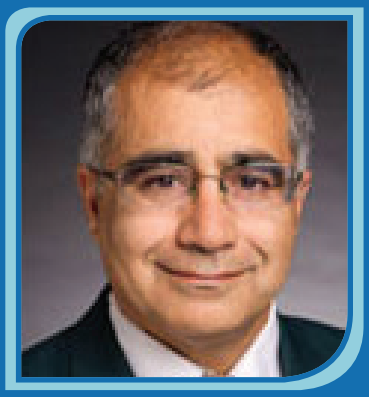

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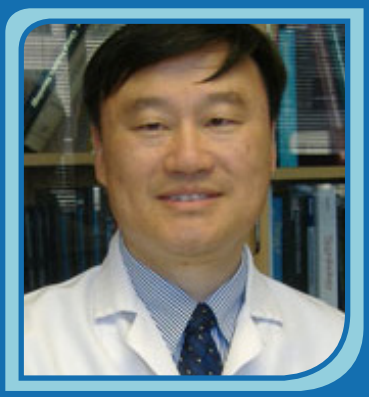

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