International Conference on
Disease Biomarkers and Precision Medicine

Date
October 22-24 2018

Venue
DoubleTree by Hilton
Houston Intercontinental Airport
15747 John F. Kennedy Blvd.
Houston, TX 77032 USA
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Development of Automated Companion Diagnostic Immunoassays in Collaboration with Therapeutic Partners

Philip Hemken
Abbott Diagnostics, IL, USA

Abstract
Abbott partnered to develop two automated diagnostic immunoassays as potential future companion diagnostic tests to identify patients with severe asthma who would most likely benefit from an investigational anti-IL-13 immunotherapy. Abbott developed tests to measure the serum levels of the proteins periostin and DPP4 (dipeptidyl peptidase-4), which have potential to be predictive biomarkers for up-regulated IL-13 in patients with severe asthma.

Biography
Dr. Phil Hemken has worked at Abbott in the Diagnostics Division for 21.5 years. He has for the last 15 years been involved with numerous assay development projects for the automated immunoassay instrument ARCHITECT including companion diagnostics. He received his BS in Microbiology from Iowa State University, MA in Biotechnology from Washington University in St. Louis and his PhD in Molecular, Cellular and Developmental Biology from Iowa State University in Ames, Iowa under the direction of Dr. Richard M Robson in the Muscle Biology Group.
Involvement of the Bufodienolides in the Diagnosis and Management of Traumatic Brain Injury (TBI) and Post-traumatic Stress Disorder (PTSD)

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*Baylor University, Waco, TX, USA*

**Abstract**

The bufodienolides are members of the group of compounds referred to as the cardiac glycosides or cardiotonic steroids. They are synthesized in the adrenal cortex, the placenta, and, perhaps, also in the brain. Dr. Puschett and his colleagues have studied their activities in traumatic brain injury (TBI) as well as other disorders. A substance called marinobufagenin (MBG) can detect the inflammatory injury in TBI at an early stage of the inflammatory process. Another compound, called resibufagenin (RBG), serves as an antagonist of MBG. RBG is able to reduce the lesions produced by MBG, resulting in a fall in the MBG level in serum and urine and either a reduction in the brain inflammatory lesion or a reversal of that process along with the decrement in blood and urine. In studies performed in head traumatized animals (rats), RBG reduced or resolved the inflammatory reaction noted in the brain tissue and lowered the level of MBG to that of control rats. MBG levels are elevated early in the traumatic process in animals and human subjects. When RBG is administered, it lowers MBG levels to normal and dramatically reduces the inflammatory lesions. We propose that RBG will also effectively treat TBI and PTSD in affected human patients. Studies of the utility of RBG as a therapy of both TBI and PTSD are planned pending governmental approval. Finally, we have confirmed involvement of the bufodienolides in 2 other disorders: preeclampsia, and the acute respiratory distress syndrome (ARDS).

**Biography**

Dr. Puschett is a Research Professor at the Texas A&M College of Medicine in Temple, Texas, and an Adjunct Professor in the Department of Chemistry and Biochemistry, at the Baylor University in Waco, Texas. He is the author and/or coauthor of 400 abstracts and articles in the medical literature. He is a graduate of the University of Pennsylvania School of Medicine and a former Chief of the Renal/Electrolyte Division at the University of Pittsburgh Medical School and served for 15 years as the Chairman of the Department of Medicine at the Tulane University School of Medicine in New Orleans, Louisiana.
Simultaneously Attenuating Multiple Krebs Cycle Enzymes for Cancer Treatment

Benyi Li
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**Abstract**

We recently demonstrated that the natural compound Alternol exerts a cancer-specific killing effect with very limited effect benign prostate cells through an oxidative stress-dependent mechanism. To elucidating the mechanism underlying Alternol-induced oxidative stress and apoptosis in prostate cancer cells, we identified four Krebs cycle enzymes as Alternol-interacting protein targets. These enzymes are dihydrolipoamide acetyltransferase (DLAT) as an E2 enzyme in pyruvate dehydrogenase complex (PDHC), dihydrolipoamide S-succinyltransferase (DLST) as an E2 enzyme in a-ketoglutarate dehydrogenase complex (KGDHC), fumarate hydratase (FH) and malate dehydrogenase-2 (MDH2). Our data revealed that at the basal level, PDHC and KGDHC activities were significantly higher in prostate cancer cells compared to benign BPH1 cells. Alternol treatment reduced their activities to the levels close to BPH1 cells. Although FH and MDH2 activities were comparable among multiple malignant and benign cells, their activities were enhanced by Alternol in malignant cells. Metabolomic analysis revealed that Alternol treatment remarkably reduced major Krebs cycle intermediates and attenuated mitochondrial respiration rate. Alternol treatment also drastically reduced ATP contents in PC-3 cells in vitro and in PC-3 cell-derived xenograft tissues but not in BPH1 cells or in mouse liver tissues. These results suggest that Alternol interacts with and attenuates the functions of multiple Krebs cycle enzymes, disrupts mitochondrial respiration activities, resulting in reduced energy production in malignant cells and xenograft tissues. As the authors aware, Alternol is the first natural compound reported targeting multiple Krebs cycle enzymes in cancer cells.
The Gene Master Regulators Approach Provides the Best Targets for the Personalized Cancer Gene Therapy

Dumitru A Iacobas and Sanda Iacobas

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Abstract

We prove that cancer nodules and surrounding normal tissue are governed by distinct Gene Master Regulators (GMR) and that smart manipulation of the GMR expression selectively destroys cancer cells. The method relies on an original mathematical algorithm that establishes the gene hierarchy from the transcriptomic profiles of tumor biopsies based on their Gene Commanding Height, a composite measure of gene expression control and coordination. The experimental protocol and the method principle are illustrated with our own transcriptomic data on human samples and standard cell lines from prostate, thyroid (doi: 10.18632/oncotarget.23417), blood and kidney (DOI: 10.13189/cor.2017.050301) cancers.

Biography

Dr. Dumitru Iacobas is a systems biologist with over 100 genomic publications who developed the Genomic Fabric Paradigm and advanced computational tools to analyze the organizational principles of the transcriptome. He and Dr. Sanda Iacobas, a molecular biologist has standardized the experimental protocol, proposed and tested the GMR approach.

Butyrylcholinesterase and BCHE Gene: A Druggable Target and Prognostics Biomarker in Cancer

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2Department of Pediatrics, Division of Hematology / Oncology, University of Nebraska Medical Center, NE, USA

Abstract

BCHE gene is emerging as an important survival biomarker in cancer. The product of this gene is butyrylcholinesterase (BChE, EC 3.1.1.8), an enzyme in the family of serine esterases that hydrolyzes esters of choline. BChE was first described in 1940s. Today, nearly eighty years later, the function of BChE in malignancy remains unknown. The existing paradigm considers BChE as a nonessential protein with the physiological function limited to its esterase activities.

We have identified BChE as an important druggable target in several cancers and developed a series of drugs targeting this protein. For example, we have analyzed 5-year overall survival (OS) of patients with serous ovarian cancers with low and high BCHE gene and BChE protein expression. The median OS was estimated at 50.7 months and 40.0 months, respectively. BCHE gene was identified as one of the 12 genes amplified in ovarian cancer that are associated with poor outcomes suggesting that BChE protein may be a valid prognostic biomarker as well as therapeutic target in the treatment of ovarian cancer. High BCHE
gene levels in head and neck cancer are also associated with unfavorable prognosis. The five-year survival for high BCHE is 39% compared to 55% for low BCHE expression. In neuroblastoma cell lines, BChE protein levels are directly proportional to the MYCN amplification.

We will present our experimental data that illustrate BChE’s role in malignancy with specific examples of BChE protein and BCHE gene in ovarian and head and neck cancers as well as neuroblastoma and glioblastoma.

Biography

Dr. Janina Baranowska-Kortylewicz earned her MSc from Politechnika Wrocławska and her doctorate from University of Kentucky. She continued her postgraduate research at Albert B. Chandler Medical Center and Harvard Medical School. She is currently a professor at UNMC.

Molecular Insights into Immune Targets of Patients with Prostate Cancer: Implications for Health Disparities, Metastasis and Chemoresistance

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Abstract

Prostate cancer (PCa) is the most commonly diagnosed cancer and second leading cause of cancer-related death in American men. African American (AA) men are more likely to be diagnosed with aggressive PCa at a younger age and twice as likely to die from the disease as European Americans (EA). Despite racial disparities, studies profiling sera for autoantibodies to tumor antigens have overwhelmingly used patients with European ancestry. In order to reduce PCa mortality, there is a critical need to identify and target pathways that drive molecular processes responsible for PCa aggressiveness. The immune system offers a minimally invasive tool to delineate PCa tumorigenesis in a given patient. Cancer uses the glycolysis pathway for rapid glucose metabolism, ATP production, and plasminogen activation for metastasis by degrading extracellular fibrin networks during tissue invasion. The glycolytic enzyme alpha-enolase (ENO1) plays a dual role in energy metabolism and plasminogen activation, and was the target of autoantibodies in PCa patients. In a cohort of PCa (N=157) and non-PCa (N=183) sera from ethnically diverse men, we saw a higher frequency of antibodies to ENO1 in PCa patients (p<0.05). Surprisingly, when we probed a panel of non-PCa and PCa cell lines with anti-ENO1 positive sera, AA patients had increased immunoreactivity to ENO1 in metastatic PCa cells. In contrast, the anti-ENO1 EA-PCa sera showed uniform immunoreactivity across the same panel of cell lines. Targeting ENO1 with immunotherapy impaired proliferation in metastatic cells and re-sensitized chemo-resistant cells to docetaxel suggesting ENO1 is a viable target for aggressive PCa.
Phenolic Compounds in Dark Sweet Cherry (Prunus avium L.) Help to Prevent Breast Cancer Tumor Growth and Invasion in MDA-MB-453 Cells Through Regulation of Mitogen-activated Protein Kinases (MAPK) Signaling Pathway and Induction of Apoptosis

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³Federal University of Ouro Preto, Brazil

Abstract

About 30% of fatal breast cancer cases are driven by the overexpression of human epidermal growth factor receptor 2 (HER2) that leads to invasion and metastasis. Dark sweet cherry (DSC), a rich source of phenolics reported to exert breast cancer chemo-preventive effects have not been previously investigated for their potential against this type of breast cancer.

DSC phenolics extract (WE) or isolated fractions of anthocyanins (ACN) and proanthocyanidin (PCN) were assessed for their anti-proliferative and anti-invasive potential on HER2+ MDA-MB-453 cells. Results showed cell viability was suppressed by WE, ACN, and PCN with similar order of potency (IC50 = 83±33ug/mL, 70±14ug/mL, and 45±7ug/mL, respectively) (p<0.05). This was mediated, at least in part, by induction of apoptosis as shown by PARP, caspase 3 and caspase 9 cleavage. Also, cell invasion was inhibited significantly by ACN (60.1%), WE (48.8%), and PCN (32.3%), and motility by WE (80%), PCN (67.2%) and ACN (57.7%) (p<0.05). Interestingly, DSC extracts induced the phosphorylation of the MAPK ERK 1/2 and p-38. ERK 1/2 (U0126) and p-38 (SB203580) inhibitors abrogated the effect of WE and PCN on cell invasion and motility without effect on cell growth. Western blots results confirmed that WE and PCN exert their anti-invasive potential through activation of the MAPK proteins ERK 1/2 and p-38 cell signaling pathway, while the tumor growth suppression seem to be mediated by extrinsic apoptosis mechanisms.

Biography

Ms. Marjorie Anne Layosa is a master's student at the University of the Philippines Los Baños and currently a research visiting scholar at Texas A&M University. Her research interests include nutrigenomics specifically exploration of bioactive components against different diseases.
CSF3R Mutations are Highly Concomitant with Transcription Factor Genes Abnormalities in Acute Myeloid Leukemia

Yang Zhang¹, Fang Wang¹, Xue Chen¹, Yu Zhang¹, Mingyu Wang¹, Hong Liu¹, Panxiang Cao¹, Xiaoli Ma¹, Tong Wang¹, Jianping Zhang¹, Xian Zhang¹, Daopei Lu¹, Peihua Lu¹, Xiaosu Zhou¹,² and Hongxing Liu¹,²*

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Abstract

Mutations in CSF3R gene occur frequently in chronic neutrophilic leukemia (CNL), providing important molecular diagnosis indications and may be targeted therapeutically. In this study, we analyzed 1152 acute leukemia patients and assessed the association of CSF3R mutations with other potentially collaborating genetic changes. Amplicon-targeted next generation sequencing of 58 genes known to be frequently mutated in hematologic malignancies was carried out retrospectively for 587 acute myeloid leukemia (AML) and 565 acute lymphoblastic leukemia (ALL) patients. RT-PCR was carried out to detect 35 leukemia-specific gene fusions in the patient cohorts. CSF3R mutations (totally 26 cases) were detected in 3.6% (13/364), 4.6% (8/175), and 8.3% (4/48) of de novo, relapse, and secondary AMLs; and 0.2% (1/565) of ALL. A total of 9 distinct CSF3R mutations were detected. Membrane-proximal missense mutations and cytoplasmic truncations were found to be mutually exclusive. The proportion of FAB M2 and M4 in the CSF3R-mutated group was significantly higher than in the CSF3R-wild-type group for both de novo (92.3% VS 46.7%, P=0.001) and relapse AML cohorts (87.5% VS 43.1%, P=0.024). All de novo and relapse AMLs with CSF3R mutations were associated with genetic alterations in transcription factors including RUNX1-RUNX1T1, CBFB-MYH11, double mutated CEBPA (CEBPAdm), and NPM1 (a transcription cofactor gene) mutations. In this study, we find that CSF3R mutations are uncommon in AML, and rare in ALL. When present, they often occur in association with CBF abnormalities and CEBPAdm in AML and provide a clue for possible targeted therapy and more refined classification of the diseases.

Biography

Dr. Hongxing Liu is the Vice President of Lu Daopei Institute of Hematology and director of Pathology & Laboratory Medicine Division, Lu Daopei Hospital, China. He is dedicated to the research and clinical application of molecular hematology and has issued more than 100,000 molecular diagnosis reports. He has published more than 40 academic papers as the first/corresponding author.
Aurora Kinase A Localises 1 to Mitochondria to Control Organelle Dynamics and Energy Production : Implication for Cancer Cells overexpressing Aurora-A

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Abstract

Many epithelial cancers show cell cycle dysfunction tightly correlated with the overexpression of the serine/threonine kinase Aurora A (AURKA). Its role in mitotic progression has been extensively characterised, and evidence for new AURKA functions emerges. Here, we reveal that AURKA is located and imported in mitochondria in several human cancer cell lines. Mitochondrial AURKA impacts on two organelle functions: mitochondrial dynamics and energy production. When AURKA is expressed at endogenous levels during interphase, it induces mitochondrial fragmentation independently from RALA. Conversely, AURKA enhances mitochondrial fusion and ATP production when it is over-expressed. We demonstrate that AURKA directly regulates mitochondrial functions and that AURKA over-expression promotes metabolic reprogramming by increasing mitochondrial interconnectivity. Our work paves the way to anti-cancer therapeutics based on the simultaneous targeting of mitochondrial functions and AURKA inhibition.

Translational Research with Nanosecond Pulse Stimulation for Immuno-Oncology Applications

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Abstract

Nano-Pulse Stimulation (NPS) is based on pulsed power physics, used for decades in high-powered physics and military applications. Electrical energy is stored and released in nanosecond bursts, producing high power, non-thermal energy. Because biological cells have not experienced such impacts in evolutionary history, their responses are of interest. NPS strategy for cancer treatment uses 100 ns pulse durations and electric field strengths up to 65 kV/cm. When orthotopic 4T1 mouse mammary and rat N1-S1 hepatocellular carcinoma tumors are eliminated, animals are protected by an immune-mediated, vaccine-like effect against exposure to the same cancer. Dynamic immune responses include induction of regulated cell death (RCD) for primary tumor elimination. This is accompanied by activation of CD8+ natural killer (NK) cells and NKT-cells expressing the NKG2D and CD161 activation receptors. Activated dendritic cells (DCs) induce cytotoxic T-cells expressing adaptive memory phenotypes. Decreases in immunosuppressive cells in the tumor microenvironment and blood serve as diagnostic indicators. In the mouse model, an abscopal effect occurs including reduced spontaneous distant metastases. Studies with humanized NSG mice carrying triple negative breast cancer are in progress.
Non-lethal NPS attenuates respiration in DCs by affecting complexes I and IV in the electron transport chain and increasing reactive oxygen species in mitochondria. DCs are activated as indicated by expression of activation markers and cytokine secretion. Lethal NPS opens the mitochondrial permeability transition pore and induces RCD. How these and other intracellular NPS-induced mechanisms lead to ablation-induced immune responses are under investigation.

Biography

Dr. Stephen J Beebe, received his PhD (1982) in Medical Sciences (Pharmacology) from the Medical College of Ohio, now University of Toledo College of Medicine. He was a post-doctoral fellow at the HHMI, Department of Molecular Physiology and Biophysics, Vanderbilt and a Fulbright and Marshal Scholar in Oslo. He served as an Assistant and Associate Professor in the Jones Institute for Reproductive Medicine, Center for Pediatric Research and Department of Physiological Sciences at Eastern Virginia Medical School, Norfolk. He is now a Professor in the Frank Reidy Research Center for Bioelectrics, Old Dominion University, Norfolk VA USA.

Epigenetic Drivers in Pediatric Medulloblastoma

Jennifer L. Stripay* and Martine F. Roussel
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Abstract

Epigenetics is the process by which gene expression is regulated by events other than alterations of the genome. DNA methylation, chromatin remodeling, and histone modifications regulate the chromatin and access of transcription factors to DNA and in turn gene transcription. Alteration of chromatin is now recognized to be deregulated in many cancers. Medulloblastoma (MB), an embryonal tumor of the cerebellum, is the most common malignant brain tumor in children. Medulloblastoma is characterized by four molecularly and histo-pathologically distinct groups with different prognosis: Wingless (WNT), Sonic hedgehog (SHH), Group 3, and Group 4, that, except for WNT, are each now subdivided in several subtypes. Gene expression array, next-generation sequencing, and methylation profiling of several hundred primary tumors by several consortia including the St. Jude-Wash U. Pediatric Cancer Genome Project revealed that medulloblastomas harbor a paucity of mutations, many of which occur in epigenetic regulators. Remarkably, some tumors have no reported mutations, suggesting that some genes required for oncogenesis might be regulated by epigenetic mechanisms which are still to be uncovered and validated. Despite being overexpressed in Group 3 MBs, our laboratory showed that deletion of EZH2, the catalytic enzyme of the PRC2 complex, via gene editing accelerates tumor development and progression. These data have important therapeutic implications and suggest the need for functional evaluation of epigenetic regulators in different contexts. We are currently using unbiased screening approaches and integrative analysis to identify and functionally validate epigenetic regulators in MB.

Biography

Dr. Jennifer L. Stripay is a second-year postdoctoral fellow in the laboratory of Dr. Martine Roussel at St. Jude Children's Research Hospital. She received her PhD in Neuroscience from the University of Rochester School of Medicine and Dentistry in 2016 where she was supported by an NIH/NCI F31 Predoctoral Fellowship. She has focused her research efforts in cancers of the central nervous system, exploring molecular mechanisms of pathogenesis and novel therapeutic development. In Dr. Roussel’s laboratory, she is involved with several projects related to medulloblastoma modeling, epigenetic regulation, and preclinical evaluation.
Radiomic Features of Pretreatment MRI Could Identify T Stage in Patients with Rectal Cancer: Preliminary Findings

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Abstract

Recent studies have shown magnetic resonance radiomic analysis is feasible and has some value in identifying tumor characteristics, but there are few data regarding the role of MR-based radiomic features in rectal cancer. This study aimed to determine whether radiomic features extracted from T2-weighted imaging can identify pathological features in rectal cancer. A cohort of 119 rectal cancer patients underwent surgery between January 2015 and November 2016 were enrolled. Patients were classified according to pathological features such as T stage, N stage, perineural invasion, histological grade, lymph-vascular invasion, tumor deposits, and circumferential resection margin (CRM). All patients had MR imaging with 3.0T, axial high-resolution T2-weighted turbo spin echo (TSE) sequence and the whole tumor volume was distinguished and segments by a radiologist. These volumes were used for radiomic analysis. A total of 256 radiomic features were extracted. To achieve reliable results, cluster analysis and least absolute shrinkage and selection operator (LASSO) were implemented. In the cluster analysis, the patients were divided into two groups, and chi-square tests were performed to investigate the relationship between the pathological features and the radiomic-based clusters. The area under the curve (AUC) was calculated to evaluate the predictability of the model in the LASSO analysis. The cluster results revealed that patients could be stratified into two groups, and the chi-square test results indicated that the pT stage was correlated with the radiomic feature cluster results (p=0.002). The prediction model AUC for the diagnostic T stage was 0.852 (95% confidence interval: 0.677–1; sensitivity: 79.0%, specificity: 82.0%).

Biography

Dr. Weigang Hu is an associate professor, Chief physics and vice director of Department of Radiation Oncology. He had medical physics research training in UCSF from 2009-2010. He obtained his PhD from Fudan University in 2015. He has been a member of AAPM. His researches focus on radiomic, deep learning based automatic treatment planning and machine QA, organ motion and treatment optimization. He is an author on more than 60 peer-reviewed publications, a co-inventor on 5 issued and pending patents.
DISC1 Pathway Rare Variants for Psychiatric Disorders

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Abstract

Psychiatric disorders, including schizophrenia, bipolar disorder and major depression, are common complex disorders that affect 1.1 billion people worldwide. The genetics risk factors of these diseases are incompletely understood, and discovering the genomic biomarkers associated with mental disorders is a research priority. Recent sequencing studies showed that rare variations have large effects on the risk for schizophrenia, which indicates that rare variants account for much of the missing heritability in the development of mental disorders. Disrupted in schizophrenia 1 (DISC1) gene is a well-researched target for developing psychiatric disorders. The molecular studies have shown that DISC1 functions as scaffold protein in brain functions through a large complex pathway. We applied targeted resequencing to sequence 213 DISC1 pathway genes in 1543 individuals. We observed an enrichment of rare disruptive variants in schizophrenia patients, and the increased burden of damaging mutations could reduce cognitive measures. We applied sequence-based machine learning methods to predict the effects of the rare disease-causing mutations on protein function, protein stability and post translational modification. we utilized structure-based methods to quantitatively assess the effects of rare mutations on protein stability and protein-protein interaction. We showed that the rare missense mutations could significantly affect the protein structures and functions. The findings improve our understanding of the roles of rare variations in DISC1 pathway in susceptibility to psychiatric disorders and offer the genomic biomarkers for developing more precise mental illness treatments for individuals with psychiatric disorders.

Biography

Dr. Shaolei Teng is an Assistant Professor of the Department of Biology at Howard University. He received his PhD in Biochemistry and Molecular Biology from Clemson University, and completed his postdoctoral training in Bioinformatics and Genomics at Cold Spring Harbor Laboratory. His research interests are to develop and apply bioinformatics approaches for analyzing the genetic variations associated with diseases. His group at Howard University is currently focused on machine learning, next-generation sequencing and protein structure modeling. He has published more than twenty papers in the peer-reviewed journals such as Molecular Psychiatry, BMC Genomics, Amino Acids and Biophysical Journal.

Adipose Stromal Cells as a Disease Marker and Therapy Target

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Abstract

Obesity underlies metabolic and cardiovascular disease as well as cancer progression. Our studies have demonstrated that white adipose tissue (WAT) overgrown in obesity is at least partly responsible for this link. We have shown that perivascular adipocyte progenitors, termed adipose stromal cells (ASC), become mobilized in cancer patients. Circulating ASC have been revealed as a biomarker of obesity and cancer in our clinical studies. ASC are similar to bone marrow-derived mesenchymal stromal cells that have potent trophic, vasculogenic, and immunomodulatory functions that can be hijacked by tumors. Using animal models, we have demonstrated that ASC populate tumors where they engage in carcinogenic signaling. We have also demonstrated that tumor-associated adipocytes serve as a source of lipids utilized by cancer cells. Our results indicate that both of these cell populations support cancer progression in obesity. Our
group is a leader in developing new-generation targeted peptide-based therapeutics. We have a unique expertise in screening combinatorial libraries for peptides binding to receptors selectively expressed on the surface of cell populations of interest. It is based on combination of in vivo phage display technology with FACS and high throughput approaches. Library-derived cell-targeted peptides that we isolate can be used as delivery vehicles in therapy targeting applications. In a number of reports by our group, ‘hunter-killer’ peptides, composed of a cell-targeted domain and a cytotoxic domain, have been developed and used for targeted ablation of various cell types. Experimental drugs developed by our group include BMTP-11, a peptide targeting cancer cells through binding to IL-11 Receptor, and Adipotide, a peptide targeting adipose endothelial cells and adipocytes through binding to cell surface Prohibitin. Both compounds, have shown promising results in phase I clinical trials (NCT01262664 and NCT00872157). We are now developing peptide-based therapeutics targeting ASC for obesity and cancer applications. We have identified a peptide that specifically targets ASC and used it to design a hunter-killer peptide ablating ASC in vivo. We have reported that in mice this compound suppresses growth of WAT and inhibits tumor growth. Finally, we have developed a hunter-killer peptide targeting the vasculature of brown adipose tissue (BAT) that can be used for BAT inactivation in hypermetabolic conditions. This presentation will cover recent data on the physiological effects of these peptides on metabolism and discuss their clinical potential.

Statistical Methods for Analyzing Longitudinal Biomarker Data with Missing and Censored Values

MinJae Lee
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Abstract

In patient-based studies, biomarker data are often subject to left censoring due to the detection limits, or to incomplete sample or data collection. In the context of longitudinal regression analysis, inappropriate handling of these issues could lead to biased parameter estimates. Likelihood-based approaches that assume multivariate normal distributions have been proposed to account for the left-censoring problem; however, biomarker data are often highly skewed even after transformation. Quantile regression is increasingly used in biomarker analysis for non-normal or heteroscedastic data. We developed a statistical analysis strategy based on weighted censored quantile regression (CQR) that not only accounts for censoring, but also missing data at follow-up visits. We assessed through simulation studies the performances of developed statistical approach by considering various scenarios of covariance structures of longitudinal data and levels of censoring. Our findings from simulation studies indicated that the proposed method performs better and is not sensitive to the choice of covariance structure, as compared to other traditional methods that assume normality of biomarker data. The proposed method offers a more valid statistical approach to evaluate a biomarker of disease longitudinally in the presence of both issues with censoring and missing data in follow-up visits. We also illustrated the application of the proposed method to the real data.

Biography

Dr. MinJae Lee received her Ph.D. degree in Biostatistics from University of Pittsburgh. She has considerable experience working at academic medical centers, collaborating with clinicians of various specialties to provide her expertise in study design, data management and statistical analysis. Since 2012, she has served as an Assistant Professor of Biostatistics. She is familiar with the different types of statistical methodological issues and challenges related to missing or censored data, especially in longitudinal biomarker data analysis. Her areas of expertise include modeling for informative missing data in longitudinal studies, quantile regression, imputation, and semi-parametric modeling for survival data.
Red Cell Distribution Width as a Predictor of Persistent Pulmonary Hypertension of the Newborn

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Abstract

Objective: Persistent pulmonary hypertension of the newborn (PPHN) is a critical condition with high mortality and morbidity rates in neonatal intensive care unit (NICU) admitted neonates due to severe hypoxemia. The aim of this study was to evaluate red cell distribution width (RDW) as a biomarker of hypoxemia and determine the optimal cutoff point of RDW for identifying neonates with PPHN.

Study Design: All PPHN diagnosed, NICU admitted term infants with hypoxemia after birth from May 2014 to September 2016 were enrolled as case control and healthy term infants with non-hemolytic jaundice who were admitted for phototherapy on the second or third day of birth were the control group. Blood samples were collected. Multiple logistic regression modeling was used to examine the association between PPHN and RDW.

Results: Receiver-operating characteristics (ROC) curve analysis was used to determine the optimal cutoff point of RDW for identifying neonates with PPHN. RDW was higher in the PPHN group compared to the control group (p < 0.001). Significant predictors of PPHN were mother’s underlying disease (p < 0.01) and RDW (p < 0.001). The optimal RDW cut point for prediction of PPHN by the ROC curve analysis was 17.9 (sensitivity 85.71%). RDW’s area under the curve was 0.9197 (p < 0.001).

Conclusion: RDW may be a simple, valuable, accessible marker for predicting PPHN before performing echocardiography in hypoxemic NICU admitted neonates.

Blood Glycated CD59 (GCD59): A Novel Biomarker for Gestational Diabetes

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Abstract

Clinical and experimental evidence supports a role of complement and the complement regulator CD59 in the pathogenesis of diabetes complications. Also, glycated CD59 (GCD59) is an emerging biomarker in diabetes: GCD59 levels are higher in individuals with T2 diabetes and independently predict the response to oral glucose tolerance testing. We hypothesized that GCD59 could be a sensitive biomarker for screening and diagnosis of gestational diabetes (GDM).

We conducted a prospective nested case-control study of 1,000 pregnant women receiving standard prenatal care. Using a highly sensitive and specific ELISA developed in our laboratory we measured plasma levels of GCD59 (pGCD59) at gestational weeks 24-28 in 500 “control” women with a normal 50-gram glucose load screening test (GCT) and in 500 “cases” defined as women who failed the GCT. We assessed the sensitivity and specificity of pGCD59 to predict the results of GCT screening test, of the diagnostic 100-gram glucose tolerance test (OGTT), and the association of pGCD59 with large for gestational age (LGA) newborns.

pGCD59 1) distinguished cases from controls with high sensitivity and specificity (ROCAUC: 0.92); 2) identified cases who met OGTT criteria for GDM (ROCAUC: 0.92; LR+ 38), and 3) was positively associated with the prevalence of LGA. The prevalence of LGA was 4.3% in the lowest and 14% in the
highest quartile of pGCD59 values.

We conclude that a single pGCD59 value in late second trimester classifies pregnancy-induced glucose intolerance and GDM with high sensitivity and specificity and may identify pregnancies at higher risk of LGA.

Biography

Dr. Jose Halperin is an Associate Professor of Medicine at Harvard Medical School and Director of the Laboratory for Translational Research at Brigham and Women's Hospital. A physician-scientist, he originally described the role of complement and glycation-inactivation of CD59 in the complications of human diabetes. His research on this topic included molecular biology, in vitro and in vivo experiments in molecular engineered mice as well as human studies. More recently, he has developed an assay to measure blood levels of glycated CD59, and conducted human studies indicating that glycated CD59 represents a novel and promising biomarker in diabetes.

Identification of Plectin as a Cancer Stem Cell (CSC) Biomarker and Potential Drug Target in Non-small Cell Lung Cancer (NSCLC)

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2Cancer Systems Imaging, MD Anderson Cancer Center, TX, USA
3Hamon Cancer Center, UT-Southwestern Medical Center, TX, USA

Abstract

A small subset of highly proliferative cancer cells, termed cancer stem cells (CSC) resist traditional treatments, and drive both relapse and metastasis. Cancer treatments that target CSCs directly are essential to fully eliminating cancer. CSC-targeting strategies face challenges: (I) due to the paucity of true known CSC biomarkers, and (II) not having proper CSC drug-lead identification tools, as the conventional drug development approach first needs to identify the biomarkers important for the disease state and then develop targeted drugs. We applied our unique “unbiased” On-Bead Two-color peptoid combinatorial cell screen on CSCs sorted from H358 lung cancer cells and identified peptoid-PCS2 as high CSC specific ligand. Through cross-link and pull-down techniques, we identified Plectin as the target of PCS2 in these cells. Plectin is a ubiquitously expressed cytosolic protein found in normal cells as a cytoskeletal scaffolding unit, but has been reported to be localized to the cell surface in metastatic cancer cells. We confirmed the presence of plectin on CSC surface and plectin activity correlations with CSC phenotypes. Through gene-targeted knockdown and PCS2-based treatment, we identified plectin as a regulator of NSCLC culture growth and cell migration. Plectin therefore can be considered as a putative CSC biomarker with PCS2 having therapeutic potential.

Biography

Dr. Gomika Udugamasooriya is a chemical biologist, exploring peptoids to identify and target new cancer biomarkers. The development of a unique on-bead two-color (OBTC) combinatorial cell screen to identify new cell surface biomarkers and highest specificity ligands to target those biomarkers is one of the major milestones in his career. By applying this OBTC methodology, his group successfully identified and validated peptoid compounds for: (I) VEGFR2, (II) T-cell receptors, (III) Fibulin-5, (IV) lipid-phosphatidylinerine, and (V) Plectin - cancer stem cells, and taken a majority of these compounds all the way to pre-clinical studies on both therapeutic and imaging applications.
Detection of Disease Markers in Human Breath with Laser Absorption Spectroscopy

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²Institute of Optoelectronics, Military University of Technology, Poland

Abstract

Number of trace compounds (called biomarkers), which occur in human breath, contain an information about individual feature of the body as well as on state of its health. By now the biomarkers are mainly detected using gas chromatography methods, which are time consuming and expensive. Novel human breath analyzers might be constructed due to progress in laser spectroscopy and optoelectronics. These devices are cheap, sensitive and simple for maintaining. Non-invasiveness and real time measurements are the main advantages of breath analysis.

We present the results of experiments about detection of certain biomarkers using laser absorption spectroscopy methods of high sensitivity. Multipass spectroscopy with laser wavelength modulation as well as the cavity ring down spectroscopy was applied. High detection limits and good selectivity sensors of nitrogen oxide, carbon oxide, carbonyl sulphide, ammonia, ethane methane, formaldehyde and other VOC’s were elaborated. We will present the way of the approaches selection depending on individual properties of the biomarker. We will also show the methods of spectrum analysis from the point of view of optimal detectability. The influence of various interferents contained in exhaled air will be also considered. These table top sensors providing the results within the minutes might be useful for screening in the future.

Biography

Dr. Tadeusz Stacewicz completed his M.Sc. studies in 1976 and Ph.D. in 1982 at Faculty of Physics of University of Warsaw. Since that time, he works in Optics Division of the Institute of Experimental Physics at this faculty, where he has got the position of professor in 2000. His scope of interest concerns laser spectroscopy, cold plasma physics, as well as the investigation of atmospheric aerosol with multiwavelength lidars. Presently he mainly works about detection of disease biomarkers in breath with laser techniques. His list of publications contains 5 books, about 100 scientific articles and about 200 other scientific papers.

Diagnostic Evaluation of Various Biomarkers in Non Alcoholic Fatty Liver Disease

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Abstract

The precise etiology of Non-Alcoholic Fatty Liver Disease (NAFLD) is unknown. However, there are strong associations with obesity, metabolic/insulin resistance syndrome & dyslipidemias. Ultrasonography is an easily available, safe, radiation free & cost-effective tool for assessing fatty infiltration of liver. BMI and waist/hip ratio are also useful biomarkers for the assessment of diagnosis of NAFLD. A recent clinical study has suggested that periostin, a matricellular protein, can be used as a potential novel biomarker in the management of NAFLD since it plays an important role in the progression of steatohepatitis, inflammation & fibrosis. Further, decreased adiponectin levels, increased TNF-α and IL-6, proinflammatory cytokines also play a pivotal role in the pathogenesis of NAFLD. Furthermore, liver fibrosis assessment could also be done using NAFLD fibrosis score & BARD score.

NAFLD could interfere with life activities & quality of life (QOL). Chronic liver disease questionnaire (CLDQ) also correlates QOL with severity of liver disease.
Biography

Dr. Uma Bhandari is a Professor in the Department of Pharmacology, School of Pharmaceutical Education & Research (SPER), Jamia Hamdard, having 30 years of teaching and research experience. Her field of research interest include obesity, atherosclerosis and related metabolic disorders. She has presented her research outcome in various international and national conferences.

Intelligent Cellulose-Based Protease Sensors & Modulating Materials for Potential Point-of-Care Detection and Treatment of Chronic Wounds

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Abstract

Despite advances in biosensor technology some diseases present a challenge for point of care (POC) diagnostic approaches. This is especially the case with chronic wounds, a major clinical problem with an estimated 40 million people suffering worldwide. Although treatment and sensor technologies are available, understanding when and how to effectively apply POC biomarker detection to guide wound treatment is mostly the subject of translation research. One approach is to develop intelligent dressings, which may be defined as materials that respond to specific changes in the wound environment i.e. exudate volume, and harmful protease levels. In this regard the chronic wound proteases Human Neutrophil Elastase (HNE) and Matrix Metalloprotease, which are biomarkers for a wide range of disease states and tend to perpetuate the stalled inflammatory stage characteristic of chronic wounds. Here we present a series of modified nano-cellulosic and cellulosic materials as transducer surfaces for colorimetric and fluorescent protease sensors. We also demonstrate that these materials have protease sequestrant activity. Cellulosic nanomaterials with high surface area and biocompatible properties are good transducer surfaces for protease sensors. The sensor is a fluorescent or colorimetric peptide-cellulose conjugate interchangeable on the surface of different semi-occlusive dressing motifs and sensitive to protease levels found in chronic wounds. The protease modulation activity of the dressing is based on the degree of surface zeta potential required on the material surface to remove excess wound protease levels. As a highly crystalline biopolymer with a hydrophilic, high surface area, cellulose possesses reactive hydroxyls that can be derivatized to covalently append a wide range of biologically active molecules. Peptide analog substrates of Human neutrophil elastase (HNE) were attached to nano-cellulosic substrates. Here we show how HNE is detectable either with fluorescence or colorimetric assessment utilizing 2 milligrams of peptide-nanocellulose conjugate at levels commensurate with HNE activity found in the chronic wound (< 0.05 Units HNE/mL). Since the ultimate goal of point of care protease sensors is to make them compatible with protease modulating wound dressings the cellulosic and nano-cellulosic materials of this study were characterized for suitable chronic wound interface, HNE detection sensitivity and protease modulating activity.
Type A Aortic Dissection Complicated by Pheochromocytoma

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The Jewish Hospital of Cincinnati, CN, USA

Abstract

Type A aortic dissection is a surgical emergency characterized by a tear in the ascending aortic intima allowing blood to travel along the length of the aorta, compromising perfusion to its various branches [1]. It can be rapidly lethal if not diagnosed and treated emergently, with mortality steadily increasing with delayed treatment. Major risk factors include poorly controlled hypertension, smoking, male sex, age, connective tissue diseases, trauma and use of intravenous drugs [2]. Aortic dissections and their management can be further complicated by the presence of a pheochromocytoma, a neuroendocrine tumor that can release high amounts of catecholamines, contributing to uncontrolled hypertension. We present one case, in which aortic dissection was the patient’s initial presentation of an undiagnosed pheochromocytoma.

Case Presentation: This case describes a 36-year-old who presented with substernal chest pressure and abdominal pain. On CT, the patient was found to have a type A aortic dissection and incidentally, a 3.6 cm left adrenal mass. Patient underwent surgical repair and subsequent workup for secondary causes of hypertension. Elevated catecholamine levels were diagnostic of pheochromocytoma and patient underwent left adrenalectomy and pheochromocytoma resection.

Conclusion: Type A aortic dissection caused by uncontrolled hypertension secondary to pheochromocytoma is a rare entity. This can complicate surgical planning and blood pressure control. It is important to pursue surgical repair of the aortic dissection due to increasing mortality as time passes. Although rare it is important to consider pheochromocytoma in the differential for uncontrolled hypertension in the setting of type A aortic dissections.

Biography

Ms. Brianne Runyan is a second-year general surgery resident at The Jewish Hospital of Cincinnati. She graduated from St. George’s School of Medicine in Grenada. Prior to medical school, she obtained her Master’s in Public Health from Medical College of Wisconsin and her Bachelor of Science in Microbiology from the University of Wisconsin. She is originally from Milwaukee, Wisconsin.

Usefulness of NT-proBNP as Analytical Marker of Left Ventricular Hypertrophy in Dialytic Patients

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Abstract

Natriuretic peptides are molecular compounds closely linked to maintaining hydrolelectrolytic homeostasis, specially sodium. Both the Brain Natriuretic Peptide and its precursor - NT-proBNP – are associated to heart failure and left ventricular hypertrophy. Serum NT-proBNP levels were studied as an indicator of left ventricular hypertrophy in dialytic patients. 47 adult patients with chronic renal failure in dialysis were studied from July 2012 to December 2013. Of the 47 patients recruited in this 18-month period, 22 were female (46.8%), and 25 were male (53.2%) with a mean age of 64.6 ± 9.9 (age range: 46 – 83). A complete blood count (CBC) was made - sodium, potassium, total protein, albumin, phosphorus, calcium, phosphocalcic product, parathyroid hormone, NT-proBNP, creatinine, urea, and ureic nitrogen. Creatinine clearance was obtained from a 24-hour urine collection. An echocardiogram
measuring ventricular heart mass, left ventricular telesystolic and telediastolic diameters, circumferential ejection fraction and fractional shortening was performed. Statistical analysis showed a highly significant connection between NT-proBNP and left ventricular hypertrophy (p = 0.0001). No significant differences between NT-proBNP and the rest of the parameters in study were found. It was concluded that the increase in serum NT-proBNP is a useful biomarker that reveals the underlying presence of left ventricular hypertrophy in dialytic patients. Values above 10,000 pg/ml might identify a particular group of patients in dialysis with increased risk of dying.

Biography

Dr. Gabriel Aranalde attended ‘Universidad Nacional de Rosario’ A Postdoctoral Scholar in Postdoctoral Research Projects, he has received the City Council Award. He became a specialist in Nephrology, Accident and Emergency Medicine, and Internal Medicine. Chief of Hospital Stay and Clinical Emergency Services at HECA (Emergency Hospital), he is also a distinguished member of the Medicine Doctoral Commission, the Postdoctoral Program Commission, and the Interdisciplinary Teaching and Research Committee. In addition, he is an associate professor of Human Physiology. He has several published books, ‘Cálculos Scores y Abordajes en Medicina Interna’; ‘Fisiología Renal’; and ‘Alteraciones hidroeletrolíticas y del estado ácido-base’.

Placental Biomarkers for the Diagnosis of Fetal Growth Restriction

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2 Fundación de Investigación HM Hospitales, Madrid, Spain
3 Department of Obstetrics and Gynecology, Texas Children’s Hospital, Baylor College of Medicine, Houston, TX, USA.

Abstract

The placenta is a key organ in pregnancy because during this period supports normal fetal growth and development. It is responsible in nutrient and oxygen transport to the fetus, and also secretes several hormones and growth factors important for fetal development, such as activin, human chorionic gonadotropin (hCG), placental lactogen (pL), placental growth hormone (pGH), IGF-1, IGF-2, inhibin A, pregnancy-associated plasma protein A (PAPP-A), progesterone, prolactin, and placental vascular endothelial growth factor (pVEGF).

An alteration in placental function or development could lead to pregnancy disorders (preeclampsia, fetal growth restriction -FGR-, miscarriage, fetal alcohol syndrome and gestational diabetes, among others), all of them with increasing worldwide prevalence.

It is known that the placenta alters the expression levels of several placental biomarkers differently during pregnancy. For example, through the first trimester of pregnancy, levels of IGF-2, progesterone, soluble VEGF receptor 1 (sVEGFR-1) and β-hCG are increased, while at term or during labour levels of activin A, β-hCG and progesterone are augmented, respectively. However, there are several hormone levels that are constant or increase during pregnancy, i.e. IGF-1, inhibin A and PAPP-A. This distinctive placental biomarker expression would allow the study of such concentrations as prognostic factors and/or therapeutic targets of the aforementioned pregnancy disorders.

Until now, although different placental biomarkers have been associated with pregnancy syndromes (e.g. PAPP-A, AFP, unconjugated estriol, hCG, inhibin A, free subunit β-hCG, estriol, pL, pGH, IGF-1, IGFBP-1 are associated with FGR), no biomarker has been effectively used in clinical practice to diagnose and predict such diseases.
Analysis of Small Fragment Deletions of the APC Gene in Chinese Patients with Familial Adenomatous Polyposis

Senqing Chen, Qingwei Chen, Xiaomei Zhang, Jiannong Zhou, Xin Zhou, Guojian Ma, Ming Zhu, Yuanying Zhang, Jun Yu and Jifeng Feng
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Abstract

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease mainly caused by mutations of APC gene with almost complete penetrance. These colorectal polyps are precancerous lesions that will inevitably develop into colorectal cancer at the median age of 40-year old if total proctocolectomy is not performed. So identification of APC germline mutations has great implications for genetic counseling and management of FAP patients. In this study, we screened APC germline mutations to find novel mutations and the APC gene germline mutation characteristics of Chinese FAP patients. Then patients peripheral blood samples were collected, and genomic DNA was extracted. The mutation analysis of the APC gene was conducted by direct DNA sequencing for micromutations and MLPA for large duplications and/or deletions. We found 6 micromutations out of 14 FAP pedigrees, while there were no large duplications and/or deletions found. These germline mutations are all deletion mutations resulted in a premature stop codon. At the same time, we found c.3921_3924delAAAA and two c.3926_3930delAAAAG are located in AAAAG short tandem repeats, c3184_3187delCAAA is located in the CAAA interrupted direct repeats, and c4127_4128 del AT is located in the 5’-CCTGAACA-3’,3’-ACAAGTCC-5’ palindromes (inverted repeats) of the APC gene. Furthermore, deletion mutations are mostly located at codon 1309. Though there were no novel mutations found as the pathogenic gene of FAP in this study, we found nucleotide sequence containing short tandem repeats and palindromes (inverted repeats), especially the 5 bp base deletion at codon 1309, are mutations in high incidence area in APC gene.

Biography

Dr. Senqing Chen has completed his PhD in 2008 from Nanjing Medical University. He is now the director of Laboratory of Genetics and Molecular Biology, Jiangsu Institute of Cancer Research. He has published more than 60 papers in reputed journals, including 15 SCI papers.
for subject-level neural decoding. First, for MR-based biomarker detection, I developed a probabilistic graphical model-based method, called Graphical-Model-based Multivariate Analysis (GAMMA), for joint dimension reduction and model construction. GAMMA groups voxels into brain regions based on their probabilistic association; and generates a stable model using ensemble learning. GAMMA is used in detecting MR biomarker for Alzheimer’s disease and stroke. Second, I proposed a network-based neural decoding method called predictive dynamic network modeling (PDNM). PDNM generates a dynamic Bayesian network model for each group. Such network represents complex spatiotemporal interactions among brain regions. Then PDNM calculates a score representing that subject’s deviation from expected network patterns. This network-derived score is used to construct predictive models. PDNM can classify Alzheimer’s disease patients and controls with accuracy 0.86, based on longitudinal structural MRI data.

Biography

Dr. Chen’s research focuses on leveraging machine learning, deep learning, and computational modeling to understand the relationship between brain and behavior, leading to novel therapeutic concepts for brain disorders and brain-inspired AI. He has 20 years of experience in advanced modeling, algorithm, and software development and published about 60 peer-reviewed research articles. He has released two open-source biomedical data mining software packages on NITRC: the GAMMA suite and Advanced Connectivity Analysis. He is a senior member of IEEE. He is an editorial member of Frontier of computational neuroscience, Frontiers of neurorobotics, and the Open Neuroimaging journal.

Protein Tyrosine Kinase 7 Promotes Cancer Stemness in Head and Neck Cancer and Acts as Biomarker

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Abstract

Head and neck squamous cell carcinoma (HNSCC) is one of the most popular cancer that badly affect the health and living quality of humans. Therefore, there is still an urgent need to determine the cellular and molecular mechanisms of HNSCC and develop the biomarkers for prediction of metastasis, chemo recurrence, and prognosis. Protein tyrosine kinase 7 (PTK7) and cancer-associated fibroblasts (CAFs) play important roles in cancer stemness and tumor progression. However, little is known about the interaction between CAFs and PTK7 in human head and neck squamous cell carcinoma (HNSCC). Our results revealed that PTK7 was correlated with aggressive clinicopathologic features in HNSCC tissues and was related to chemoresistance and lung metastasis in vivo. In addition, POSTN secreted by CAFs was found to be an upstream ligand of PTK7 and promoted the cancer stem cell (CSC)-like phenotype and the proliferation and invasion of HNSCC cells only in the presence of PTK7. Furthermore, we demonstrated that POSTN enhanced Wnt/β-Catenin signaling via PTK7. We concluded that POSTN interacted with PTK7 in HNSCC and promoted HNSCC cell stemness and progression, suggesting that POSTN and PTK7 are potential and effective prognostic and diagnostic biomarkers for HNSCCs. The study is supported by National Program on Key Research Project of China (NO. 2016YFC0902700) and Shanghai Science and Technology Research and Development Platform Project (18DZ2291500).

Biography

Dr. Wantao Chen has completed his Ph.D from Shanghai Jiao Tong University School of Medicine, Shanghai China and visiting professor from M.D Anderson Cancer Center, TX, USA. He is the director of Shanghai Institute of Stomatology, the vice chairman of Department of Oral and Maxillofacial Head and Neck Oncology, the director of Oral Oncology and Biology Laboratory. He has acquired 9 grants from the National Natural Science Foundation and the National Program on Key Research Project of China. He has published more than 126 papers in reputed journals and has been serving as nine editorial board members of repute.
Differences in Immunomodulatory Properties Between Venlafaxine and Paroxetine in Patients with Major Depressive Disorder

Chun-Yen Chen¹,², Yi-Wei Yeh³, Shin-Chang Kuo¹,² and San-Yuan Huang
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²Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

Abstract

Inflammatory processes play a crucial role in the pathophysiology of depression, and identifying the specific cytokines targeted by different antidepressants is important for personalized treatment. The aims of this study were to examine whether venlafaxine and paroxetine cause different immunomodulatory effects when used to treat patients with major depression and to clarify the relationships between plasma cytokine levels and the therapeutic effectiveness of these drugs. A total of 91 Han Chinese patients with major depression completed the 8-week paroxetine or venlafaxine treatment and 90 healthy controls were recruited. A multiplex assay was used to measure cytokines levels in patients with major depression before and after an 8-week venlafaxine and paroxetine treatment. Cytokine levels were measured in healthy controls at the baseline. The 21-item Hamilton Depression Rating Scale was used to assess the changes in psychopathological symptoms from the baseline to the end point in each patient. Venlafaxine treatment caused greater decreases in the levels of interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin 4 (IL-4), IL-5, IL-1β, and IL-8 than did paroxetine. Paroxetine treatment increased the levels of proinflammatory cytokines IFN-γ, TNF-α, and IL-6 and decreased Th2 cytokine levels. After paroxetine treatment, IL-6 levels increased more in the non-remitter group than in the remitter group. In the remitter group, IL-4 and IL-5 levels decreased to values seen in the healthy controls. After venlafaxine treatment in both the remitter and non-remitter groups, IL-1β levels decreased to values seen in the healthy controls. Our results suggest that venlafaxine and paroxetine have different immunomodulatory properties and that venlafaxine has greater anti-inflammatory effects than paroxetine.

Biography

Dr. Chun-Yen Chen is a psychiatrist and works for Tri-Service General Hospital, Taipei, Taiwan. His current research interests focus on the link between genetics, clinical psychopathology, therapeutic effectiveness and neuroinflammation in patients with psychiatric disorder and substance use disorders.
Myasthenogenic Markers in Different Types of Self-tolerance Loss in Patients with Myasthenia Gravis

Elena Klimova¹*, Anatoly Bozhkov², Yury Avdosyev¹, Larissa Drozdova¹, Elena Lavinskaya¹ and Valery Boyko¹
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²Research Institute of Biology, V.N. Karazin Kharkov National University, Kharkov, Ukraine

Abstract

There is an increase in incidence of myasthenia gravis, which is characterized by progressive muscular weakness on the background of structural disorders of the thymus. Myasthenia gravis is a multifactorial autoimmune disease, it has a pronounced clinical heterogeneity, and therefore the standard diagnostic and treatment protocol is effective, but not always. To substantiate an individual approach to the treatment of various clinical forms of myasthenia mechanisms and markers of loss of central and peripheral self-tolerance in thymus-independent (M) and thymus-dependent myasthenia gravis with thymic hyperplasia (MH) and thymoma (MT) were studied. By means of spectrophotometry, flow cytometry, enzyme immunoassay, and bioindication with the help of a cellular test system cytotoxic myasthenogenic factors were identified. In patients with MH on the background of lymphofollikular hyperplasia of the thymus, pronounced humoral sensitization was revealed in comparison with the reference values: an increase in the content of the C4 component of the complement, C-reactive protein, concentration of circulating immune complexes and initiation of the mediated autoimmune reaction – a reliable increase in autoantibodies (AAbs) to the α₁ subunit of nicotinic receptors (nAChR), a twofold increase in AAbs to the α₇ subunit nAChR, a triple increase in IgE concentration, and 7 times increase in the integral cytotoxicity index in the bioindicator test. In MT group a double increase in AAbs to the α₁ subunit of nAChR, IL-2, IL-6 and sixfold increase of cytotoxicity index was detected. In M and MT groups a high similar titer of AAbs to other epitopes was revealed: to DNA, β₂-glycoprotein, membranes of intestinal and stomach cells, lung, liver, kidney cells. In the MT group a pronounced blast-transforming response to the presence of the mitogen PHA was revealed. In M group a three-fold decrease in the content of CD4⁺CD28⁺ co-stimulatory molecules were detected, fivefold increase of cytotoxicity coefficient, and in MT – fourfold decrease in CD4⁺CD25⁺ Treg lymphocytes was found.

Individual methods for correcting the loss of self-tolerance were justified taking into account the use of diet and immunosuppression, the use of specific viral-neutralizing immunoglobulins and massive IgG immunoglobulin therapy, and the application of anti-inflammatory recombinant interleukins.
October 24
WEDNESDAY
Precision Diagnosis of Clostridioides difficile Infection Using a Systems-Based Approach

Qinglong Wu*, Aiswarya Aravamudhan Ramanujam¹, Kathleen Hoch¹, Joe Haidacher¹, Nazli Yalcinkaya¹, Numan Oezguen¹, Anthony Haag¹, Kevin Garey² and Tor Savidge¹

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Abstract

Clostridioides difficile infection (CDI) is listed by the CDC as an urgent threat to public health. Early CDI diagnosis is crucial for optimal clinical management and improved prognosis. Due to the rapid turn-around and cost effectiveness, many hospitals utilize nucleic acid amplification tests to diagnose CDI. However, such sensitive molecular testing is widely recognized to misdiagnosis up to 30% of CDI cases. A major reason for this misdiagnosis is that a positive stool test cannot differentiate C. difficile colonization from symptomatic disease. Underscoring the importance of this assay deficiency, other factors including younger age and non-responsiveness to CDI therapy positively correlate with higher rates of alternative diagnoses e.g. functional gastrointestinal disorders (FGIDs). Given the urgent need to generate a robust CDI diagnostic assay, we used a systems-based approach to identify microbiota and host biomarkers that differentiate CDI cases from antibiotic-associated diarrhea (AAD) and FGIDs. We developed supervised learning classifiers based on systems data generated from >2,500 fecal microbiome (16S rDNA), metaproteome and metabolome profiles from adult and pediatric cases with CDI, AAD or FGID, and control subjects without GI disease. CDI-classification based on fecal 16S microbiome data only provided >90% diagnostic accuracy, whereas classification accuracy improved to >99% when adding metaproteome and metabolite biomarkers. Importantly, these improved classifiers confidently distinguishing CDI from potential AAD and FGID misdiagnosis. In summary, supervised learning classification of systems-based metadata offers precision diagnosis of CDI versus non-infectious enteric disease at a population scale level.

Biography

Dr. Qinglong Wu received his B.Eng. (2012) and Ph.D. (2016) in the field of food microbiology. He has studied GABA-producing lactic acid bacteria during his graduate study at The University of Hong Kong, and later moved to Savidge Laboratory in Texas Children’s Microbiome Center as Postdoctoral Associate for studying GABA-producing gut commensals that exacerbate Clostridioides difficile infection. His current major focus are characterization of disease-associated gut commensals and analysis pipeline development for gut microbiota data.
Serological Signatures of Clinical Cure Following Successful Treatment with Sodium Stibogluconate in Ethiopian Visceral Leishmaniasis

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³Amhara Regional State Referral, and Research Laboratory, Bahir Dar, Ethiopia
⁴University of Lübeck, Lübeck, Germany

Abstract

In Ethiopia, visceral leishmaniasis (VL) is a growing public health threat. Among the key challenges in VL control in Ethiopia is lack of test of cure. The recommended test of cure is parasite detection. As, sterile cure is not expected with the currently widely used drugs, the value of parasite detection as test of cure is questionable. Moreover, the sampling is invasive, requires well-equipped facility and highly skilled personnel, which are hardly found in our set-ups.

Objective: Our aim was to assess value of sCD40L, MMP9 and IL- as signature biomarkers of clinical cure in VL cases from Ethiopia.

Methods: A total of 45 VL cases before and after treatment and endemic health controls were included in the study. Sandwich ELISA was used to measured serum level of sCD40L, MMP9 and IL-10.

Result: The mean sCD40L, MMP9 and IL-10 serum levels changed significantly at clinical cure. At individual cases level sCD40L and MMP9 showed an increasing trend. Yet, the degree of increase in serum level of MMP9 seem to be affected by nutritional status of the individual VL case. The mean IL-10 serum level was significantly reduced at clinical cure. Looking at it on cases by case, all demonstrated a dealing trend but two VL cases had had high IL level at clinical cure.

Conclusion: Our result is suggestive of the possibility of developing signature biomarkers to monitor VL treatment in Ethiopia considering one or combination.

Understanding and Overcoming Acquired Resistance to Third Generation EGFR Inhibitors

Shi-Yong Sun

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Abstract

Targeting epidermal growth factor receptor (EGFR) activating mutations, 90% of which present as an exon 19 deletion (Del19) or exon 21 point mutation (L858R), with first generation EGFR tyrosine kinase inhibitors (EGFR-TKIs; e.g., erlotinib and gefitinib) and T790M resistant mutation with third generation EGFR-TKIs (e.g., AZD9291 or osimertinib) has provided significant clinical benefit in patients with non-small cell lung cancer (NSCLC) with these mutations.

AZD9291 (osimertinib) selectively and irreversibly inhibits EGFR activating and T790M mutants while sparing wild-type EGFR. This agent is now an approved therapeutic option for NSCLC patients with activating EGFR mutations (first-line) or those who have become resistant to the 1st generation EGFR-TKIs through the T790M mutation (second-line). Unfortunately, all patients eventually relapsed and developed resistance to AZD9291 treatment. Hence the effective strategies that can overcome the resistance are urgently needed in the clinic.
Development of new resistant EGFR mutation (e.g., C797S) is an important AZD9291 resistance mechanism (~30%). Beyond, MET gene amplification/protein hyperactivation is a common resistance mechanism for both 1st and 3rd generation EGFR-TKIs. Hence, AZD9291 combined with a MET inhibitor is an effective strategy against MET-caused resistance. Moreover, we have recently demonstrated that modulation of MEK/ERK-dependent Bim and Mcl-1 degradation critically mediates sensitivity and resistance of EGFR-mutant NSCLC cells to AZD9291. Accordingly, co-targeting MEK is an effective strategy for overcoming AZD9291 resistance irrespectively of the underlying resistance mechanisms. Therefore, fully understanding the resistance mechanisms to AZD9291 or other 3rd generation EGFR-TKIs warrants development of effective strategies for overcoming acquired resistance to 3rd generation EGFR-TKIs.

Biography

Dr. Shi-Yong Sun is a tenured Professor in Department of Hematology and Medical Oncology at Emory University School of Medicine and Winship Cancer Institute in Atlanta, Georgia, USA. He is also a Georgia Research Alliance Distinguished Cancer Scientist and Halpern Research Scholar. He has been working on the biology and targeted therapy of lung cancer by primarily focusing on: 1) regulation of death receptors, particularly TRAIL receptors, in cancer therapy; 2) understanding mTOR signaling in cancer and targeting this signaling axis for cancer therapy; and 3) understanding and overcoming acquired resistance to third generation EGFR inhibitors.

Precision Magnetic Resonance Imaging

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Department of Diagnostic and Interventional Imaging, McGovern Medical School, University of Texas Health Science Center at Houston, USA

Abstract

Magnetic resonance imaging (MRI) is a powerful diagnostic and prognostic tool and is an indispensable tool in modern healthcare. Generally, patients are scanned using a generic MRI protocol that is appropriate for one category. This one-shoe-fits-all approach, though sufficiently sensitive for gross abnormalities, can miss subtle pathologic differences which can be potentially critical for patient care. This presentation focuses on the development and implementation of MRI protocols that are automatically customized for each individual patient in order to assure optimal image quality and maximize the diagnostic content. This is conceptually similar to "Precision Medicine". Measuring the MRI-based physiological parameters in pseudo real time and providing this information to the MRI scanner is the heart of this customized or precision scanning. The proposed framework comprises of an adaptive scanning engine that dynamically customizes the MR exam based on the output from a scanner-integrated real-time image analysis pipeline to optimize the image quality and/or an objective criterion derived from the goals of the study. Our personalized imaging framework provides numerous advantages over standard imaging methods such as in-session preview of the quantitative results, inspection of data quality while the patient is still in the scanner, and assisting the radiologists in the interpretation of the image. The performance of patient-adaptive MRI is demonstrated through a few examples that show subtle pathology in Multiple Sclerosis (MS) patients that is not apparent on conventional protocols.

Biography

Dr. Ponnada Narayana, DABR is a Professor, Vice Chair for Research, and Director of Magnetic Resonance Research in the Department of Diagnostic and Interventional Imaging, McGovern Medical School. He is also holds an Endowed Chair in Bioengineering. Professor Narayana is nationally and internationally recognized for his research in MRI novel MRI pulse sequences and quantitative MRI and their application to Multiple Sclerosis, Neurotrauma, and Substance Abuse. He received numerous honors that include Presidential Scholar (UT-Houston), Elected Fellow, International Society of Magnetic
Resonance in Medicine, Distinguished Academy of Radiology Researcher (2013). He is a Diplomate of the American Board of Radiology.

**Shrinking the Psoriasis Assessment Gap: Early Gene-Expression Profiling Accurately Predicts Response to Long-Term Treatment**

Lewis E Tomalin¹, Joel Correa da Rosa² and Mayte Suarez-Farinas³

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²LEO Pharmaceuticals, Denmark

**Abstract**

In many immunological diseases, there is an “assessment gap” between the moment a patient’s response to treatment is biologically determined and when a response can actually be determined clinically. Patients’ biochemical profiles are a major determinant of clinical outcome for a given treatment. It is therefore feasible that molecular-level patient information could be used to decrease the assessment gap. Thanks to clinically accessible biopsy samples, high-quality molecular data for psoriasis patients are widely available; also, many therapeutic options are in use or under development, with varying degree of efficacy. Psoriasis is therefore an excellent disease for testing the prospect of predicting treatment outcome from molecular data. We have mined data from expression profiles, obtained during proof of concept studies using biologics for the treatment of psoriasis, and use machine learning algorithms to develop precision medicine models. Our study shows that gene-expression profiles of psoriasis skin lesions, taken in the first 4 weeks of treatment, can be used to accurately predict (>80% AUC) the clinical endpoint at 12 weeks. This could decrease the psoriasis assessment gap by 2 months. We show that key biomarkers are associated with responses to drugs and doses and thus provide insight into the biology of pathogenesis reversion. Taking skin samples is relatively invasive, thus we performed a follow-up analysis using less invasive blood proteomic profiles, but predictive performance was weaker than the skin data. These analyses demonstrate the potential of machine learning to predict treatment responses to established psoriasis treatments, possibly using minimally invasive blood sampling.

**Biography**

Dr Lewis E Tomalin is an Assistant Prof at the Icahn School of Medicine at Mt Sinai Hospital (NY), with an extensive background in Biomedical Science, Molecular Biology and Systems Biology. His current research focuses on analysis of longitudinal transcriptomic/proteomic data to study disease pathogenesis and reversion, particularly for inflammatory and dermatological diseases. This includes the use of machine learning to develop precision-medicine strategies for the treatment of psoriasis.

**Genomic Strategies to Sub-phenotype Patients with Sarcoidosis**

Nancy G. Casanova¹, Manuel Gonzalez-Garay and Joe G.N. Garcia

Department of Medicine, University of Arizona, AZ, USA

**Abstract**

Sarcoidosis is a systemic granulomatous disease of unknown etiology commonly affecting the lung. Most patients achieve full remission but a significant proportion experience progressive lung involvement and sometimes cardiac or neurological involvement. The diagnostic of sarcoidosis is challenging due to the unspecific symptomatology associated and the absence of a diagnostic test clearly differentiating it from other granulomatous diseases.

Despite limitations, the use of biomarkers to support diagnosis and predict disease activity remains a focal point in clinical care. Advances in genomic research strongly associates sarcoidosis as an immune-
mediated disease, with an interestingly overlapping immunity with other diseases. Identified altered genes and regions are associated to functional implication such as cell surface immune receptors and cytokines involved in the granuloma formation and disease progression.

Relevant and promising approaches explored recently by our research group, include blood-based molecular gene-based signatures predicting complicated sarcoidosis, identification of disease-relevant transcripts in granulomatous tissues to sub-phenotype sarcoidosis, dysregulated blood cell gene expression secondary to cytokine stimulation and the identification of single nucleotide polymorphisms associated to disease-risk and sarcoidosis severity. All these elements provide the opportunity to translate basic research into innovative diagnostic tools, and genome-based biomarkers to monitor disease progression and implement personalized innovative-targeted therapies.

Biography

Dr. Nancy G. Casanova is working as research assistant professor at University of Arizona, AZ, USA. As a physician-scientist her research interest is in translational research to develop novel molecular-based biomarkers and potential molecular therapeutic targets in sarcoidosis. She is interested in studying the genetic and non-genetic factors that contribute to sarcoidosis disparities, identifying patient-specific risk factors that underlie differential disease course and molecular markers that define therapeutic response that will guide a personalized approach to the management of sarcoidosis.

MicroRNA Expression in Advanced Breast Cancer

Lei Huo*
The University of Texas, USA

Abstract

Inflammatory breast cancer is the most aggressive form of breast cancer, comprising 1-5% of newly diagnosed breast cancers in the United States. It is characterized by clinical hallmarks of diffuse erythema and edema and rapid progression from the onset. Recent advances have implicated the role of microRNAs as oncogenes or tumor suppressor genes in tumorigenesis, metastasis and response to treatment in various cancer types including breast cancer. We studied microRNA expression profiling of human advanced breast cancer including inflammatory breast cancer using a previously validated microRNA microarray assay. Molecules that were differentially expressed in cancer compared to normal breast tissue, as well as in inflammatory breast cancer compared to non-inflammatory locally advanced breast cancer, were selected. Further validation was performed by quantitative reverse transcription real-time PCR and in situ hybridization. There was distinct segregation between tumor and normal breast tissue in microRNA expression profiles. In contrast, between inflammatory breast cancer and non-inflammatory breast cancer, distinct clustering was not readily identified in the microarray analysis. However, several microRNAs were differentially expressed in inflammatory breast cancer. For example, miR-26b expression was decreased in inflammatory breast cancer compared to non-inflammatory breast cancer in both the array analysis and by quantitative real-time PCR. Lower expression of miR-26b was associated with worse distant metastasis-free survival and overall survival. MicroRNAs may serve as therapeutic targets in advanced breast cancer.

Biography

Dr. Lei Huo is a practicing breast pathologist in The University of Texas MD Anderson Cancer Center. She is actively involved in clinical and translational research in the field of breast cancer. Her research interests include molecular and immunohistochemical markers in tumorigenesis, diagnosis and treatment of breast cancer, among others.
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Abstract

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Pharmacogenomic and Pharmacokinetic Determinants of Imatinib Toxicity in Gastrointestinal Stromal Tumor Patients

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7State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine Sun Yat-sen University Cancer Center, PR China
8Institute of Clinical Pharmacology, School of Pharmaceutical Sciences, Sun Yat-Sen University, PR China

Abstract

Purpose: To evaluate the pharmacokinetic and pharmacogenomic determinants of toxicities of Imatinib mesylate (IM), the first approved selective tyrosine kinase inhibitor.
**Patients and Methods:** A prospective clinical study of 154 GIST patients was performed. Detailed toxicity and epidemiological characteristics were recorded. 33 candidate single-nucleotide polymorphisms of IM’s molecular targets, metabolic enzymes, transporters and chemokines were genotyped by matrix-assisted laser desorption/ionization time-of-flight platform. IM and its metabolite N-demethyl-IM (NDI) were determined.

**Results:** Skin rash and edema were not IM-concentration dependent. However, myelosuppression was correlated with the concentration of IM ($C_{IM}$) and NDI ($C_{NDI}$). Variability in the extent of myelosuppression was best explained by a multivariate logistic regression model incorporating $C_{NDI}$ (OR=1.46, $P=0.051$) and FLT1 rs9554314, a 3’-UTR polymorphism (OR=3.042, $P=0.009$), while some mutations in the signaling pathway of molecular targets, such as FLT1, MAPK1, SHC1 and $C_{IM}$ contribute to the occurrence of myelosuppression. EGFR 3’-UTR polymorphism was correlated with the occurrence of skin rash ($P=0.027$, OR=0.033), while variability in the extent of skin rash was associated with two genetic polymorphisms in chemokines CCL5 and CXCL14 (OR=8.542 and 13.504, respectively). Gender and PDGFRB rs55712339 were found to be associated with the occurrence of peripheral edema ($P=0.025$, OR=2.647; $P=0.026$, OR=3.547).

**Conclusion:** This combined pharmacokinetic and pharmacogenomic model identified the primary determinants of myelosuppression, skin rash and edema of IM. These findings help to design clinical trials targeting a particular toxicity and modify dosing regimen in patients experiencing dose-limiting toxicities of IM, thereby benefiting patients on long-term IM treatment.

**Biography**

Dr. Xueding Wang is an Associate professor. Her research interests are pharmacogenomics, drug metabolism and pharmacokinetics, drug–drug interactions. She has received 3 grants from the National science foundation of China and some important grants from other organizations. She has conducted the Validation and qualification of some biomarkers for Gefitinib, Imatinib, thiopurines and FK506. She has published more than 50 papers in the recent 10 years. She was honored with the Servicer – Chinese pharmacological Society annual awards for Yong pharmacologists, which was the uppermost honorable prize for Chinese youth pharmacologists, in 2010.
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