3rd Annual Meeting of the
International Ovarian Cancer
Consortium
in conjunction with the
International Symposium on Tumor
Microenvironment and Therapy
Resistance

August 28-30, 2016

Sheraton Oklahoma City Downtown Hotel
1 North Broadway Avenue
Oklahoma City, OK 73102
Funding support by the NIH-COBRE (P20 GM103639) and the Symposium Grant from the Presbyterian Health Foundation, Oklahoma City, OK, USA.
INSTITUTIONAL PARTNERS

Thank you to our sponsors for their support.
Dear Colleagues,

Welcome to the 3rd Annual Meeting of the International Ovarian Cancer Consortium in conjunction with the International Symposium on Tumor Microenvironment and Therapy Resistance, hosted by the Stephenson Cancer Center. On behalf of the international organizers and the organizing committee, it is my great pleasure to welcome you to Oklahoma City, Oklahoma.

The 2016 meeting has been organized to provide a comprehensive overview of clinical challenges, research breakthroughs, and therapeutic innovations in two major thematic areas of cancer research, namely ovarian cancer and tumor microenvironment. We have more than thirty distinguished speakers from Canada, China, Italy, Japan, Korea, and USA with expertise in cancer biology, cancer genomics, targeted therapy, therapy resistance, personalized medicine, and cancer bioinformatics joining this meeting. Highly insightful papers will be presented in the form of keynote address, plenary lectures, thematic sessions, and posters.

We thank the sponsoring institutions for their willingness to participate. In addition, we gratefully acknowledge the funding support to the meeting by the Presbyterian Health Foundation of Oklahoma and the NIH COBRE program. We would also like to thank the dedicated staff at the Stephenson Cancer Center for their assistance in planning and organizing this meeting.

We hope that you will enjoy the meeting and this venue will continue to facilitate the exchange of ideas for forging successful collaborations towards the development of novel diagnostic, prognostic, and therapeutic strategies for the treatment of cancer.

Thank you,

Danny N. Dhanasekaran, Ph.D.
Professor and Samuel Roberts Noble Foundation Endowed Chair in Cancer Research
Director, SCC COBRE & Center for Basic Cancer Research
Deputy Director for Basic Sciences
Stephenson Cancer Center
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ORGANIZERS

Danny N. Dhanasekaran, PhD
Director, Stephenson-COBRE and Center for Basic Cancer Research
Deputy Director for Basic Research
Stephenson Cancer Center
Professor and The Samuel Roberts Noble Foundation
Endowed Chair in Cancer Research
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Chairman, Graduate School of Cancer Biology
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Seoul, Republic of Korea

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Director and Professor, Tumor Microenvironment Global Core Research Center
College of Pharmacy
Seoul National University
Seoul, Republic of Korea
ORGANIZING COMMITTEE

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Stephenson Cancer Center
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Milwaukee, WI, USA

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Associate Professor, Department of Cell Biology
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Program Leader, Preclinical Cancer Translational Cancer Research
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Priyabrata Mukherjee, PhD
Oklahoma TSET Cancer Research Scholar
Professor and Director of Nanomedicine Laboratory
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Professor, Department of Pathology
University of Oklahoma Health Sciences Center
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ORGANIZING COMMITTEE

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Oklahoma City, OK, USA

Joe Zhao, PhD
Stephenson Cancer Center
Alfred M. Shideler Professor of Pathology
Professor, Department of Pathology
University of Oklahoma Health Sciences Center
AGENDA AT A GLANCE

Sunday, August 28
Sheraton Downtown Oklahoma City Hotel
All Sessions—Plaza Ballroom

4:00-5:30  Registration
          Sheraton Hotel, 2nd Floor Foyer
4:30-5:30  Reception
          Sheraton Hotel, Mezzanine
5:30-5:45  Welcome Address
5:45-6:30  Keynote Address
6:30-7:30  Session I: Clinical Challenges and New Frontiers
7:30-9:00  Dinner
          Sheraton Hotel, One Broadway Ballroom

Monday, August 29
Sheraton Downtown Oklahoma City Hotel
All Sessions—Plaza Ballroom

7:45-8:30  Breakfast and Registration
          Breakfast—18th Century Ballroom
          Registration—2nd Floor Foyer
8:30-10:10 Session II: Therapeutic Strategies I
10:10-10:25 Coffee Break
            Foyer
10:30-12:10 Session III: Ovarian Cancer: Target Discovery I
12:10-1:30  Lunch
            18th Century Ballroom
1:30-2:30  Poster Session
2:30-3:15  Stephenson Cancer Center-COBRE Distinguished
          Plenary Lecture
3:20-4:20  Session IV: Ovarian Cancer: Target Discovery II
4:20-4:35  Coffee Break
          Foyer
4:35-5:55  Session V: Therapeutic Strategies II
Tuesday, August 30
Sheraton Downtown Oklahoma City Hotel
All Sessions—Plaza Ballroom

7:45-8:30  Breakfast and Registration
            Breakfast—Foyer/Plaza Ballroom
            Registration—Foyer

8:30-10:10  Session VI: Tumor Microenvironment: Biology and
            Therapeutic Targets

10:10-10:25  Coffee Break
            Foyer

10:30-12:10  Session VII: Cancer Target Discovery and Pathway
            Analysis

12:10-1:15  Lunch
            Foyer/Plaza Ballroom

1:15-2:10  Session VIII: Cancer Target Discovery and
            Validation

2:15-2:30  Closing Remarks
DETAILED AGENDA

Sunday, August 28
Sheraton Downtown Oklahoma City Hotel
All Sessions-Plaza Ballroom

4:00-5:00  Registration
2nd Floor Foyer

4:30-5:45  Reception & Welcome Address
Mezzanine

5:45-6:30  Keynote Address
Earlier Detection and More Effective Treatment for Patients with Epithelial Ovarian Cancer
Robert Bast, Jr., MD

6:30-7:30  Session I: Clinical Challenges and New Frontiers
Session Chair: Yong Sang Song, MD

6:30-6:50  Limitation in the Prevention and Treatment of Epithelial Ovarian Cancer: Where are Science and Medicine Failing to Meet?
Katherine Moxley, MD

6:50-7:10  Identification of Novel Tumor-Suppressor Micro-RNAs and Their Application for Cancer Diagnosis and Therapeutics
Johji Inazawa, MD, PhD

7:10-7:30  Next-Generation Cancer Research with Artificial Intelligence
Satoru Miyano, PhD

7:30-9:00  Dinner
One Broadway Ballroom

Monday, August 29
Sheraton Downtown Oklahoma City Hotel
All Sessions-Plaza Ballroom

7:45-8:30  Registration and Breakfast
2nd Floor Foyer and 18th Century Ballroom

8:30-10:10  Session II: Therapeutics Strategies I
Session Chairs: Ciro Isidoro, MD, DSc
Ralf Janknecht, PhD
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<td>Application of Machine Learning to Optimized Ovarian Cancer Therapy</td>
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<td>John McDonald, PhD</td>
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<td>8:50-9:10</td>
<td>Two Potential Weapons Defeating Ovarian Cancer: Circulating Tumor Cells and HOX</td>
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<td>Yong Beom Kim, MD</td>
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<td>9:10-9:30</td>
<td>Targeting the Unfolded Protein Response to Overcome Therapeutic Resistance in Cancer</td>
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<td>Hari Koul, PhD, MSc, FACN, FASN</td>
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<tr>
<td>9:30-9:50</td>
<td>Exploiting Therapeutic Vulnerabilities in Ovarian Cancer by Targeting Unfolded</td>
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<td>Protein Response Pathway</td>
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<td>Jeremy Chien, PhD</td>
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<td>High Intensity Focused Ultrasound Ablation for the Treatment of Solid Tumors with</td>
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<td>Benjamin Tsang, PhD</td>
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<td>PGC1a Induced by Reactive Oxygen Species in Tumor Spheres and Patient-Derived</td>
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<td>Ascites Cells Confers Chemoresistance to Ovarian Cancer</td>
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<td>Yong Sang Song, MD</td>
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<td>10:50-11:10</td>
<td>Hypoxic Signaling in Ovarian Tumor Metastasis: Molecular Mechanisms and Targeted</td>
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<td>Erin Naik, PhD</td>
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<td>Mechanism and Therapeutic Efficacy of a Novel Inhibitor of BMI-1 Function in Ovarian</td>
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<td>Resham Bhattacharya. PhD</td>
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<td>11:30-11:50</td>
<td>Anti-HGF Antibody as a Therapeutic Agent for Ovarian Cancer</td>
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<td>Junho Chung, MD</td>
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<td>11:50-12:10</td>
<td>Probing Cellular Processes using Engineered Nanomaterials</td>
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<td>Priyabrata Mukherjee, PhD</td>
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1:30-2:30  **Poster Session**  
2nd Floor Foyer

2:30-3:15  **Stephenson Cancer Center-COBRE Distinguished Plenary Lecture**  
The PI3KCA-mTOR Signaling Circuitry and Cancer: New Precision Therapies and Prevention Strategies  
J. Silvio Gutkind, PhD

3:20-4:20  **Session IV: Ovarian Cancer: Target Discovery II**  
Session Chairs: Yong Beom Kim, MD  
Jie Wu, PhD

3:20-3:40  Role of Hexokinase II in the Regulation of Aerobic Glycolysis and Cisplatin Sensitivity in Ovarian Cancer Cells  
Benjamin Tsang, PhD

3:40-4:00  Copy Number Variations and MicroRNA Aberrations in Ovarian Cancer  
Pradeep Chaluvally-Raghavan, PhD

4:00-4:20  Long Non-coding RNA Targets in Ovarian Cancer Biology and Therapy  
Danny Dhanasekaran, PhD

4:20-4:35  Coffee / Snack Break  
2nd Floor Foyer

4:35-5:55  **Session V: Therapeutic Strategies II**  
Session Chairs: Priyabrata Mukherjee, PhD  
Joe Zhao, PhD

4:35-4:55  Resveratrol Counteracts LPA-Induced Epithelial-to-Mesenchymal Transition in Ovarian Cancer Cells by Inhibiting BMI-1 and Inducing Autophagy  
Ciro Isidoro, MD, DSc

4:55-5:15  Targeting Ribosome Biogenesis in Cancer  
Lawrence Rothblum, PhD

5:15-5:35  Biology and Therapeutic Targeting of PAKs in Cancer  
Rakesh Kumar, PhD

5:35-5:55  Targeted Nano-Therapeutics for Drug Resistant Tumors  
Mansoor Amiji, PhD
Tuesday, August 30
Sheraton Downtown Oklahoma City Hotel
All Sessions—Plaza Ballroom

7:45-8:30  Registration and Breakfast
2nd Floor Foyer/Plaza Ballroom

8:30-10:10  Session VI: Tumor Microenvironment: Biology and Therapeutic Targets
Session Chairs: Min Li, PhD
                Xin Zhang, PhD

8:30-8:50  Notch4 as an Oncogenic Signal in Pancreatic Tumorigenesis
Gloria Su, PhD

8:50-9:10  Targeting the TGF-b Signaling Pathway for Oncology
Rosemary Akhurst, PhD

9:10-9:30  Therapeutic Strategy TGF-b-Smad3 Signaling in Metastatic Cancers
Jinah Park, PhD

9:30-9:50  Ephrin-A Ligands Regulate Cutaneous Tumor Etiology and Metastasis through Cell Autonomous and Non-Autonomous Mechanisms
Bingcheng Wang, PhD

9:50-10:10  Astrocytes in the Microenvironment Influences Metastasis
Ramani Ramchandran, PhD

10:10-10:25  Coffee / Snack Break
2nd Floor Foyer

10:30-12:10  Session VII: Cancer Target Discovery and Pathway Analysis
Session Chairs: Junho Chung, MD, PhD
                Resham Bhattacharya, PhD

10:30-10:50  Mechanism Based Repurposing of Neurodegenerative Disease Drugs for Breast Cancer Treatment
Ajay Rana, PhD

10:50-11:10  Novel Anti-Glioma Therapies Assessed in Pre-Clinical Models
Rheal Towner, PhD

11:10-11:30  Histone Demethylase JMJD2A in Prostate Cancer
Ralf Janknecht, PhD
11:30-11:50  Roles and Mechanisms of JAK1/JAK2 Genetic Deficiencies in Cancer
Jie Wu, PhD

11:50-12:10  A Systems Biology Application in Cancer: Pathome-Web
Taesung Park, PhD

12:10-1:15  Lunch
2nd Floor Foyer/Plaza Ballroom

1:15-2:15  **Session VIII: Cancer Target Discovery and Validation**
Session Chairs: Gloria Su, PhD
Rajagopal Ramesh, PhD

1:15-1:35  Characterization of a Natural Product that Effectively Suppresses Myeloproliferative Neoplasm Phenotypes in Mice
Joe Zhao, PhD

1:35-1:55  Role of HDAC- in RD3-Loss Dependent Evolution of MYCN-Non-Amplified Neuroblastoma
Natarajan Aravindan, PhD

1:55-2:15  Targeting Tumor Stem Cell Marker Doublecortin-Like Kinase in Cancers
Naushad Ali, PhD

2:15-2:30  **Closing Remarks:**
Yong Sang Song, MD
Ciro Isidoro, MD, DSc
Danny Dhanasekaran, PhD
Robert C. Bast, Jr., MD
Vice President for Translational Research, Internist and Professor of Medicine, Department of Experimental Therapeutics, Division of Cancer Medicine, Harry Carothers Wiess Distinguished University Chair for Cancer Research, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

KEYNOTE ADDRESS

EARLIER DETECTION AND MORE EFFECTIVE TREATMENT FOR PATIENTS WITH EPITHELIAL OVARIAN CANCER

While five year survival has improved, the cure rate for patients with epithelial ovarian cancer has changed little over the last three decades. Poor outcomes relate, in large part, to late detection and to the persistence of dormant drug resistant cells following cytoreductive surgery and chemotherapy with carboplatin and paclitaxel.

When diagnosed in stage I or II, 70-90% of ovarian cancer patients can be cured with currently available therapy, but only 20% are detected in early stage (I-II). Given the prevalence of ovarian cancer in postmenopausal women at normal risk (1:2500), effective screening strategies require high sensitivity for asymptomatic early stage disease (>75%) and very high specificity (99.6%) to achieve a positive predictive value of 10%, i.e. 10 operations for each case of ovarian cancer detected. To date, two-stage strategies have been most promising, where rising CA125, judged by a computer algorithm, triggers transvaginal sonography (TVS) and, if abnormal, possible surgery. The NROSS trial coordinated by MD Anderson and the UKCTOCS coordinated by University College London have demonstrated high specificity with no more than 3-4 operations required for each case of ovarian cancer detected. The NROSS trial in ~5,000 women over 15 years performed 18 operations to detect 12 cases of ovarian cancer with 9 in stage I or II. The UKCTOCS trial in ~200,000 women over the same interval detected ~40% of ovarian cancers in Stage I-II. Excluding prevalent cases and primary peritoneal disease, a 20% reduction in mortality was observed (P=0.021) in the CA125/TVS arm, albeit with broad confidence limits that will require further follow-up to narrow. There is room for improvement in both stages of this two-stage strategy. We have evaluated >110 biomarkers to identify a panel including CA125, HE4, and CA72-4 that detects 18% of patients missed with CA125 alone. Recently, autoantibodies
against TP53 have been detected in 20% of ovarian cancer patients in the UKCTOCS trial with a mean lead time of 13.5 months prior to elevation of CA125 and 32 months prior to diagnosis in CA125 negative cases. Statistical techniques are being developed that will permit use of multiple markers to improve sensitivity without sacrificing specificity. In collaboration with Rice University, NanoBiochip assays have been developed to permit prompt point of service assays in screening clinics. With John Hazel at MD Anderson, we are evaluating Superconducting Quantum Interference Detection (SQUID) to measure Magnetic Relaxation (MRX) using ferritin nanoparticles coated with anti-CA125 antibody to detect ovarian cancers with substantially greater sensitivity than TVS.

Most ovarian cancer patients receive a combination of carboplatin and paclitaxel chemotherapy during primary therapy, but only 42% respond to paclitaxel as a single agent. Little attention has been given to improving outcomes by enhancing the primary response to paclitaxel. Knockdown of kinases that enhance microtubule stability of ovarian cancer cells enhances sensitivity to paclitaxel. Salt induced kinase 2 (SIK2) encodes an AMP-like kinase that is overexpressed in 30% of ovarian cancers, associated with decreased survival. Knockdown of (SIK2) prevents centrosome splitting, induces polyploidy, inhibits PI3K signaling, inhibits growth of ovarian cancer cell lines and xenografts and enhances sensitivity to paclitaxel. In collaboration with Arrien Pharmaceuticals we have evaluated specific low molecular weight inhibitors of SIK2, one of which will enter a phase I trial within the next year. Synergistic interaction between a SIK2 inhibitor and the PARP-inhibitor olaparib has been found in multiple ovarian cancer cell lines.

Dormant, drug resistant cancer cells remain after primary therapy in more than half of ovarian cancer patients. We have identified an imprinted tumor suppressor gene that regulates tumor dormancy and that is upregulated in >80% of residual ovarian cancers found at positive second look operations, associated with evidence of active autophagy. ARHI (DIRAS3) encodes a 26Kd GTPase with 50-60% homology to the Ras family of onco genes, but with an opposite function mediated by a 34 amino acid N-terminal extension. ARHI is downregulated by multiple mechanisms in 60% of ovarian cancers. Re-expression of ARHI blocks cell growth, inhibits motility, induces autophagy and establishes tumor dormancy. By re-expressing ARHI from a doxycycline inducible promoter in human ovarian cancer xenografts in nu/nu mice, our group has developed the first inducible model for tumor dormancy in ovarian cancer, permitting evaluation of novel anti-autophagic therapy to eliminate dormant ovarian cancer cells. Functional inhibition of autophagy with chloroquine in dormant ovarian cancer cells substantially delayed outgrowth of xenografts when dormancy was interrupted, suggesting for the first
time that autophagy can sustain dormant ovarian cancer cells in a nutrient poor environment. Conversely, excessive autophagy can proceed to autophagic cell death. When ARHI is induced in xenografts, dormant ovarian cancer cells can survive for weeks and grow promptly when ARHI is down-regulated. When ARHI is induced in cell culture, autophagic ovarian cancer cells die within 72 hrs. Survival factors detected in xenografts, including VEGF, IL-8 and IGF can rescue autophagic ovarian cancer cells in culture and this rescue can be reversed with specific monoclonal antibodies against VEGF, IL-8 and IGFR. Treatment of mice with dormant xenografts with these 3 antibodies can cure a majority of the mice when dormancy is interrupted. A clinical trial has been planned to treat patients with positive second looks using bevacizumab as a first step toward translating results with the dormant xenograft model.
**BRIEF CURRICULUM VITAE**

**Education:**
B.A. Wesleyan University, Middletown, CT  
M.D. Harvard Medical School, Boston, MA, USA

**Representative Careers:**
Asst. / Assoc. Professor Dana Farber Cancer Institute, - Harvard Medical School, Boston, MA, US  
Prof. and Co-Director Hematology/Oncology, Duke University Medical Center, NC, US  
Director Duke Comprehensive Cancer Center, NC, US  
Head Division of Medicine, MD Anderson Cancer Center, Houston, TX, US  
Vice President Translational Research, MD Anderson Cancer Center, Houston, TX, US

**Interesting Research Areas:**
Cell growth regulation of ovarian and breast carcinomas; Imprinted tumor suppressor genes; Autophagy and tumor dormancy; Early detection and prevention of ovarian cancer; Modulation of taxane sensitivity

**Selected Publications:**


**Representative Awards:**
Shashikant Lele Lecture, Roswell Park Cancer Institute, 2014

Claudia Cohen Award, Gynecological Cancer Foundation, Society of Gynecologic Oncology, 2013

Emil Frei III Award for Excellence in Translational Research, Division of Cancer Medicine, MD Anderson Cancer Center, 2011

Hero Award, Cattlemen for Cancer Research, 2011
SESSION I: CLINICAL CHALLENGES AND NEW FRONTIERS
SESSION CHAIRS: Yong Sang Song, MD, PhD

Limitation in the Prevention and Treatment of Epithelial Ovarian Cancer: Where are Science and Medicine Failing to Meet?
Katherine Moxley, MD

Identification of Novel Tumor-Suppressor Micro-RNAs and Their Application for Cancer Diagnosis and Therapeutics
Johji Inazawa, MD, PhD

Next-Generation Cancer Research with Artificial Intelligence
Satoru Miyano, PhD

The Genetics of Early-Stage High Grade Serous Ovarian Cancer and its Progression: Evidence for Early Peritoneal Metastases that Precede Ovarian Carcinomas
Jeremy Chien, PhD

IncRNAs: New Links in Ovarian Cancer Pathobiology
Danny Dhanasekaran, PhD
SESSION I: CLINICAL CHALLENGES AND NEW FRONTIERS

LIMITATION IN THE PREVENTION AND TREATMENT OF EPITHELIAL OVARIAN CANCER: WHERE ARE SCIENCE AND MEDICINE FAILING TO MEET?

Epithelial ovarian cancer remains the leading cause of gynecologic cancer morbidity and mortality worldwide (WHO cancer statistics, 2016). Despite improvements in therapy, the majority of patients develop disease recurrence and succumb to their cancer. With the introduction of platinum-based chemotherapy in the 1970’s, significant improvements in overall survival time have been observed. However, despite initial chemosensitivity demonstrated by high rates of remission following first-line chemotherapy, more than 80% of patients recur with incurable disease (Konstantinopoulos et al, 2015). Response rates to chemotherapy following recurrence are dependent upon both the observed response to initial treatment and the time that has elapsed from completion of first-line therapy and disease recurrence, known as the “platinum-free interval.” Despite the addition of new cytotoxic and biologic therapies, overall survival in EOC remains dismal with a 5-yr survival of only 30%. Of more concern is the observation that this survival has changed minimally over the last 10-15 years despite an increase in our knowledge of both drug resistance mechanisms and the cancer genome (Seigel et al, 2015). An improved understanding of tumor escape, inherent and acquired drug resistance and amolecularily-based alternative treatment strategies are urgently needed to improve outcomes for women with this incurable disease.
BRIEF CURRICULUM VITAE

Education:
M.D. University of Oklahoma, Oklahoma City, OK, US

Representative Careers:
Assistant Professor University of Oklahoma Health Sciences Center, Stephenson Cancer Center, Oklahoma City, OK, US

Interesting Research Areas:
Mechanisms underlying acquired chemoresistance as well as the identification of therapeutic targets for reversing drug resistance; Utility of liquid biopsy in the prediction of disease specific outcomes; Molecular mechanisms underlying drug class specific toxicities in patients undergoing targeted therapy

Selected Publications:


Representative Awards:
Top Clinical Trial Enroller, Stephenson Cancer Center (Received), 2014
Johji Inazawa, MD, PhD
Director and Professor, Bioresource Research Center, Department of Molecular Cytogenetics, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan

SESSION I: CLINICAL CHALLENGES AND NEW FRONTIERS

IDENTIFICATION OF NOVEL TUMOR-SUPPRESSOR MICRO-RNAs AND THEIR APPLICATION FOR CANCER DIAGNOSIS AND THERAPEUTICS

MicroRNAs (miRNAs) are endogenous small non-coding RNAs that regulate gene expression by interfering with the translation or stability of target transcripts via binding to the 3'-UTR, and function as a “fine-tuner” of numerous biological processes. Down-regulation of several tumor-suppressor miRNAs (TS-miRs) has been shown to be associated with cell proliferation, epithelial and mesenchymal transition (EMT), invasion/metastasis, and chemoresistance. In the last decade, using a method of reporter-coupled miRNA library screen, we identified more than 20 novel TS-miRs in various types of cancer. Among them, some TS-miRNAs were found to simultaneously target multiple cancer-related genes, and may be useful as a therapeutic agent for cancer therapy. Recently, we isolated exosomes from highly metastatic human oral cancer cell line, HOC313-LM, and identified two oncogenic miRNAs highly expressed in exosomes. These miRNAs were transferred to low metastatic cells by exosomes, resulting in increased cell motility and invasive ability. Our findings signify the metastatic role of exosomal miRNAs, underlining their application in miRNA-based therapeutics in cancer.
BRIEF CURRICULUM VITAE

Education:
M.D. Kyoto Prefectural University of Medicine, Kyoto, JP
Ph.D. Kyoto Prefectural University of Medicine, Kyoto, JP

Representative Careers:
Associate Professor Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo, JP
Professor Medical Research Institute, Tokyo Medical and Dental University, Graduate School of Comprehensive Medical and Dental Science, Tokyo, JP
Director Bioresource Research Center, Tokyo Medical and Dental University, Tokyo, JP
Deputy Director Research, Tokyo Medical and Dental University, Tokyo, JP

Interesting Research Areas:
cancer omics, medical genetics

Selected Publications:
Yanaka Y, Muramatsu T, Uetake H, Kozaki K, Inazawa J: miR-544a induces epithelial-mesenchymal transition through the activation of WNT signaling pathway in gastric cancer. Carcinogenesis. 36:1363-71. 2015

Representative Awards:
JCA – Mauvernay Award, Japan Cancer Association, 2006
Prizes for Science and Technology (Research Category), The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, Japan, 2008
SESSION I: CLINICAL CHALLENGES AND NEW FRONTIERS

NEXT-GENERATION CANCER RESEARCH WITH ARTIFICIAL INTELLIGENCE

Integrative systems understanding of cancer based on personal omics data and their interpretation/translation into therapeutics are the most important issues in cancer research. While the cost for human genome sequence is drastically decreasing but the cost of data analysis is getting higher. In this talk, we will not focus on ovarian cancer but all aspects of cancer that we will face with commonly. First, we figure our current situation in genome and cancer research from the viewpoint of digitalized data explosion. The amount of genome sequence data is estimated to exceed 2 EB by 2018. More than 200,000 papers on cancer were published only in 2015. PubMed compiles more than 25 million publication abstracts. If printed, it exceeds 4km (higher than Mt. Fuji) and, by 2050 it will reach 100km. All are digitalized data. Therefore, computers can read and understand natural languages make reasoning/learning with the current AI technologies. Further, recently studies unraveled that cancer evolves in years and acquires unbelievably complex tempo-special heterogeneity. Even for a single gene, say, BRCA1, JAMA (2015) reported that 365 mutations have been known. From 19,591 female people with mutation(s) in BRCA1, breast cancer 9,052 (46%), ovarian cancer 2,317 (12%), both 1,041 (5%), but no cancer 7,171 (37%) until age 70. It is not easy to understand even a single exon 11. Retrieving COSMIC (Catalogue of Somatic Mutations in Cancer) is exhausting out our limited time. Whole genome sequence data, even exome data, threw us in chaos. We have only investigated 1.5% of whole genome while some non-coding RNAs (70% transcribed from whole genome) have been shown to have “functions” in cancer, too. We have to confess that we are “a big fish in a little barrel.” How can we interpret/translate clinically/biologically? This issue is obviously beyond human abilities. The second part is about “Genomon” on super-computers: a suite of bioinformatics tools for analyzing cancer genomes and RNA sequencing data that realizes a very large-scale and very high-precision data analysis. We present how important results came out
through this platform. Finally, we present the clinical sequence system and practice running at our institute based on whole genome sequence, whole exome sequence and cancer panel for hematopoietic tumor and colorectal cancer. This platform is also extendable to other types of cancer. The supercomputer system of our Human Genome Center and the system of next-generation sequencers are systematically controlled by Clarity LIMS system in order to provide secure and traceable data analysis pipelines, computational systems biology tools, and a documentation system. In July 2015, IBM Watson Genomic Analytics (currently named Watson for Genomics) trained at New York Genome Center was introduced in our system and started learning. We show how it changed our clinical sequence and how it will contribute to basic cancer research.
BRIEF CURRICULUM VITAE

Education:
B.S. Kyushu University, JP
M.S. Kyushu University, JP
Ph.D. Kyushu University, JP

Representative Careers:
Professor Research Institute of Fundamental Information Science, Kyushu University, JP
Professor Human Genome Center, Institute of Medical Science, The University of Tokyo, JP
Director Human Genome Center, Institute of Medical Science, The University of Tokyo, JP
President (Adjunct) Kanagawa Cancer Center

Interesting Research Areas:
Personalized Cancer Clinical Sequence, Cancer Systems Biology, Bioinformatics

Selected Publications:


Representative Awards:
Fellow, International Society for Computational Biology, 2013
SESSION II: THERAPEUTIC STRATEGIES I
SESSION CHAIRS: Ciro Isidoro, MD, DSc
Ralf Janknecht, PhD

Application of Machine Learning to Optimized Ovarian Cancer Therapy
John McDonald, PhD

Two Potential Weapons Defeating Ovarian Cancer: Circulating Tumor Cells and HOX
Yong Beom Kim, MD

Targeting the Unfolded Protein Response to Overcome Therapeutic Resistance in Cancer
Hari Koul, PhD, MSc, FACN, FASN

Exploiting Therapeutic Vulnerabilities in Ovarian Cancer by Targeting Unfolded Protein Response Pathway
Jeremy Chien, PhD

High Intensity Focused Ultrasound Ablation for the Treatment of Solid Tumors with Therapeutic Resistance
Lian Zhang, MD
SESSION II: THERAPEUTIC STRATEGIES I

APPLICATION OF MACHINE LEARNING TO OPTIMIZED OVARIAN CANCER THERAPY

One important goal of precision cancer medicine is the accurate prediction of optimal drug therapies from the genomic profiles of individual patient tumors. Machine learning (ML) is a computational method that systematically extracts sub-sets of informative features from large datasets in order to build optimal predictive models. I report on the development of a ML-based method to accurately link gene expression profiles to drug responsiveness. The algorithm predicts the responsiveness of a diversity of human cancer cell lines to a variety of cancer drugs with 80-93% accuracy. The results of preliminary studies using the algorithm to retrospectively and prospectively predict the responsiveness of ovarian cancer patients to first line cancer therapies will be presented.
BRIEF CURRICULUM VITAE

Education:
Ph.D. University of California – Davis, CA, US
Post-doc University of California – San Diego, CA, US

Representative Careers:
Head Dept. of Genetics, University of Georgia, GA, US
CEO Ovarian Cancer Institute, Atlanta, GA, US
Chair School of Biology, Georgia Institute of
Technology, Atlanta, GA, US
Associate Dean Georgia Institute of Technology, GA, US
Director Integrated Cancer Research Center, Georgia
Institute of Technology, Atlanta, GA, US

Interesting Research Areas:
analysis of metabolomic/genomic data by machine learning algorithms to
develop more accurate cancer diagnostics and personalized therapeutics;
development of small non-encoding RNAs as therapeutic agents and the
use of functionalized nanoparticles for their targeted delivery to cancer
cells; exploring the significance of mRNA splice variants in the onset and
progression of cancer

Selected Publications:
Gaul DA, Mezencev R, Long TQ, Jones CM, Benigno BB, Gray A, Fernandez
FM, McDonald JF. 2015. Highly-accurate metabolomics detection of early-
stage ovarian cancer. Sci Reports (Nature pub) Nov 17; 5:16351. Doi
10.1038/srep16351

Mittal, V.K. and McDonald, J.F. 2015.Integrated sequence and expression
analysis of ovarian cancer structural variants underscores the importance

Ectopic over-expression of miR-429 induces mesenchymal-to-epithelial
transition (MET) and increased drug sensitivity in metastasizing ovarian
cancer cells. Gyn Oncol 134:96-103.

Representative Awards:
Elected Fellow, American Assoc. for the Advancement of Science, 2005
Yong Beom Kim, MD  
Director and Chair, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology  
Seoul National University Bundang Hospital  
Seongnam, Korea

SESSION II: THERAPEUTIC STRATEGIES I

TWO POTENTIAL WEAPONS DEFEATING OVARIAN CANCER: CIRCULATING TUMOR CELLS AND HOX

Current standard treatment of ovarian cancer is complete cytoreductive surgery followed by adjuvant chemotherapy with or without targeted agent, for example, bevacizumab. Despite the tremendous effort in achieving durable treatment response, most patients experience recurrence in the end and die of disease. Survival rate is still very poor. There are two major obstacles to remarkable survival improvement.

One is the absence of effective diagnostic tools for early detection as well as differential diagnosis of ovarian mass. Circulating tumor cells (CTCs), isolated tumor cells disseminated from the site of disease in metastatic and/or primary tumors that can be identified in the peripheral blood, have shown prognostic value in breast, colorectal, prostate, and ovarian cancer. CTCs from peripheral blood are convenient and non-invasive method for disease monitoring. Therefore, CTCs could be a good blood biomarker for early detection and differential diagnosis of indeterminate adnexal mass.

The other obstacle is the absence of tumor-specific tailored therapy. Although ovarian cancer is a group of heterogeneous tumors with various histologic types and different molecular genetic characteristics, there is no treatment strategy that considers those differences. HOX genes, known as developmental genes which code for proteins that function as critical master regulatory transcription factors during embryogenesis, were also involved in the development of various cancers including ovarian cancer. HOX genes are usually not expressed in normal ovarian surface epithelium, however, they became overexpressed during the development of cancer, such as HOXA7, HOXA9, HOXA10, and HOXA11. There were multiple lines of evidence suggesting various kinds of HOX genes were aberrantly overexpressed in ovarian cancer cells and contributed to some oncogenic properties such as invasion and migration.

We herein presented clinical aspects of the two potential weapons for surmounting the major obstacles to survival improvement in ovarian can-
BRIEF CURRICULUM VITAE

Education:
M.D. Seoul National University College of Medicine, Seoul, KR
Diploma Korean Board of Obstetrics and Gynecology

Representative Careers:
Clinical Professor Chungbuk National University Hospital, KR
Clinical Professor Seoul National University Hospital, Seoul, KR
Professor Seoul National University Hospital, Seoul, KR
Visiting Professor Ovarian Cancer Research Institute, MD Anderson Cancer Center, Houston, TX, USA
Visiting Doctor Memorial Sloan Kettering Cancer Center, New York, NY, USA

Interesting Research Areas:
management of gynecology cancer; early detection of gynecologic cancer; molecular biologic study in gynecologic cancer; minimally invasive surgery

Selected Publications:


SESSION II: THERAPEUTIC STRATEGIES I

TARGETING THE UNFOLDED PROTEIN RESPONSE TO OVERCOME THERAPEUTIC RESISTANCE IN CANCER

In 2016 over half a million men and women will die of cancer in US, mostly due to therapeutic resistant disease. While current therapies appear to produce high rates of cure for many malignancies diagnosed early and localized at the time of detection, we appear to have a limited success in treating solid malignancies that have spread beyond the original location. Moreover, solid tumors in general respond poorly to current chemotherapeutic regimens. There is urgent, yet unmet, need for identification and characterization of new targets that can be explored for therapeutic intervention. In a quest to preserve their proliferative potential, the cancer cells incur a lot of stress due to nutritional deprivation, hypoxia etc. As a result, tumor microenvironment becomes limiting and cancer cells up-regulate survival pathways to continue cell growth and evade apoptosis. Treatment resistant tumors frequently acquire mutations in KRAS and loss of function of PTEN (as a result of loss of expression of PTEN or mutations in PTEN). This signaling pathway is generally associated with cell survival, cell growth and cell cycle progression. For example, PI3K-Akt pathway increases the expression of oncogenes by raising their protein synthesis that further speeds up the cell cycle. Thus it is no surprise that KRAS and PI3-Akt have been actively targeted, albeit unsuccessfully, for therapeutic intervention.

Second Cancer cells in solid tumors in general are under extreme hypoxia which puts them under a constant ER stress thus, they need UPR to maintain their protein folding quality control. Moreover, aggressive cancer cells have very high demand for protein synthesis, as such protein synthetic machinery is highly active in cancer cells. The newly synthesized proteins need to be properly folded, and sorted for them to function properly. UPR is a collection of signaling pathways elicited in response to accumulation of unfolded proteins in the ER lumen whose downstream effectors are responsible for alleviating ER stress. It should also be mentioned that UPR can also tip the balance to cell death if ER stress is beyond remedy. Thus we believe that pushing the ER stress to its limit may offer an additional opportunity to overcome therapeutic resistance. Based on these consider-
ations we hypothesize that dual targeting PI3-Akt and UPR could offer a novel way to overcome therapy resistance in general and in solid tumors in particular.
BRIEF CURRICULUM VITAE

Education:
B.Sc. Kashmir University, Srinagar, IN
M.Sc. Kashmir University, Srinagar, IN
Ph.D. Post Graduate Institute of Medical Education and Research, Chandigarh, IN
Post-doc Fellowship University of Massachusetts Medical School, Worcester, MA, US

Representative Careers:
Sr. Staff Scientist Henry Ford Health Center, Detroit, MI, US
Director and Professor University of Colorado Cancer Center, Colorado University – Denver School of Medicine, Aurora, CO, US
Research Biologist VA Medical Systems
Director Basic and Translational Research, Feist Weiller Cancer Center, Louisiana State University Health Sciences Center, Shreveport, LA, US
Endowed Chair Carroll W. Feist Endowed Chair, School of Medicine, Louisiana State University Health Sciences Center, Shreveport, LA, US

Interesting Research Areas:
Prostate cancer biology and development of therapeutic resistance; understanding the interplay between ROS activated signaling cascades and cancer progression; characterizing mechanisms of action of a small molecule that inhibits growth and proliferation in castrate resistant prostate cancer cells and Gemcitabine Resistant Pancreatic Cancer Cells

Selected Publications:

Koul HK, Pal M and Koul S. Role of p38 MAP kinase Signal Transduction in Solid Tumors. Genes and Cancer 2013:4(9-10) 342-359
**SESSION II: THERAPEUTIC STRATEGIES I**

**EXPLOITING THERAPEUTIC VULNERABILITIES IN OVARIAN CANCER BY TARGETING UNFOLDED PROTEIN RESPONSE PATHWAY**

Valosin-containing protein (VCP) or p97, a member of AAA-ATPase protein family, has been linked to several cellular functions including endoplasmic reticulum associated degradation (ERAD), cell division, golgi-membrane reassembly and autophagy. Recent studies have indicated VCP as one of the vulnerabilities in ovarian cancer. Here, we show that treatment with CB-5083, an orally bioavailable compound derived from previously identified quinazoline scaffold-based VCP inhibitor ML240, contributes to cytotoxicity in high-grade serous or clear cell ovarian cancer cell lines. CB-5083 treatment results in increased unfolded protein response (UPR), accumulation of cell cycle proteins as a result of inhibition of proteosomal degradation, cell cycle arrest at G1, and subsequent cell death mediated by both intrinsic and extrinsic apoptotic pathways. These results support an emerging concept that ER stress pathway can be therapeutically targeted in ovarian cancer.

Since CB-5083 induces CHOP-dependent apoptosis, we tested the extent to which VCP inhibitors act synergistically with salubrinal, a compound that inhibits GADD34 and enhances eIF2a phosphorylation and transcriptional activation of CHOP. Results from Sulforadamine B and clonogenic assays indicate that VCP inhibitors and salubrinal act synergistically across various concentrations of drug combination. Based recent studies indicating that mifepristone, a steroidal antagonist to progesterone and glucocorticoid, induce ER stress and subsequent cell death, we also tested the potential drug synergies between VCP inhibitors and mifepristone. Our results indicate these drugs act synergistically across various concentrations in ovarian cancer cells. Analysis of TCGA RNA-sequencing datasets indicate VCP expression is down-regulated in cisplatin-resistant tumor samples compared to cisplatin-sensitive cancer. This data is consistent with the fact that tumors with lower expression of VCP shows significant association with poor progression-free survival and overall survivor. Finally, our results indicate that cells with lower expression of VCP are more sensitive to VCP inhibitors than those with higher expression. Considering that cisplatin-resistant tumor
samples have lower expression of VCP, VCP inhibitors may serve as an effective therapeutic candidate to treat cisplatin-resistant ovarian cancer. Collectively, our results provide evidence that VCP inhibitors can be used as a single agent and can be synergized with compounds that induce ER stress in ovarian cancer.
BRIEF CURRICULUM VITAE

Education:
B.S. Pittsburg State University, Pittsburg, PA, US
Ph.D. University of Kansas Medical Center, Kansas City, KS, US
Post-doc Fellowship Mayo Clinic, Rochester, MN, US

Representative Careers:
Assistant Professor Mayo Clinic, Rochester, MN, US
Associate Consultant Mayo Clinic, Rochester, MN, US
Assistant Professor University of Kansas Medical Center, Kansas City, KS, US

Interesting Research Areas:
Cancer Genomics, Functional Genomics, Molecular Diagnostics, Cancer Progression, Molecular Cancer Therapeutics, Synthetic Lethal Drug Targets, TP53-FoxM axis

Selected Publications:

Sarah Munchel, Yen Hoang, Yue Zhao, Joseph Cottrell, Brandy Klotzle, Andrew K. Godwin, Devin Koestler, Peter Beyerlein, Jian-Bing Fan, Marina Bibikova, and Chien J. Targeted or whole genome sequencing of formalin fixed tissue samples: potential applications in cancer genomics. *Oncotarget*. Accepted on June 24, 2015.


Representative Awards:
American Cancer Society Research Scholar

Department of Defense, Ovarian Cancer Academy

Lis Tilberis Scholar, Ovarian Cancer Research Dund

Helen Harris Memorial Trust Travel Fellowship
SESSION II: THERAPEUTIC STRATEGIES I

HIGH-INTENSITY FOCUSED ULTRASOUND ABLATION FOR THE TREATMENT OF SOLID TUMORS WITH THERAPEUTIC RESISTANCE

High-intensity focused ultrasound (HIFU) is a non-invasive technique meant to destroy tissue deep within the body selectively and without harming overlying and adjacent structures within the path of the beam. HIFU uses a transducer (acoustic lens) to generate ultrasound beams, and then concentrates these ultrasound beams on a target to ablate tumors by thermal or mechanical effects. After HIFU treatment, the treated tumor tissue gradually shrinks or disappears. The possibility that focused ultrasound therapy might be developed as a result of controlling local heating phenomena was introduced by Lynn et al. in the 1940s, but the technique was not developed at that time because of inadequate targeting methods. With the progress in diagnostic imaging, the HIFU technique has received considerable international attention in 1980s. Diagnostic ultrasound was the first imaging modality used for guiding HIFU ablation. In 1997, a patient with osteosarcoma was first successfully treated with ultrasound imaging-guided HIFU in Chongqing, China. Since then, several HIFU clinical projects have been conducted by various research groups, indicating that HIFU ablation is safe, effective, and feasible in clinical application. Over the last decade, thousands of patients with uterine fibroids, liver cancer, breast cancer, pancreatic cancer, bone tumors, and renal cancer have been treated with ultrasound imaging-guided HIFU. In addition to the potential for curative treatment and the extension of life expectancy, HIFU has been demonstrated to reduce or eliminate tumor related pain and thus improve the quality of life for patients with advanced carcinoma. Furthermore, this novel technique has been used to treat tumors with therapeutic resistance and has shown promising results. Based on several research groups’ reports, as well as our ten-year clinical experience, we conclude that this technique is safe and effective in treating human solid tumors. Most importantly, HIFU offers patients another alternative when those patients have no other treatments available.
BRIEF CURRICULUM VITAE

Education:
M.D. Medicine, Chongqing Medical University, China
M.A. Gastroenterology, Chongqing Medical University, China

Representative Careers:
Assistant Professor Chongqing Medical University, China
Postgraduate Research University of California, San Diego, CA, US
Scientist
Professor, Chief Chongqing Medical University, China
Professor Chongqing Medical University, China

Interesting Research Areas:
High intensity focused ultrasound for the treatment of solid tumors

Selected Publications:


Representative Awards:
The 2nd class of the national science and technology progress award of China, 2010
SESSION III: OVARIAN CANCER: TARGET DISCOVERY I
SESSION CHAIRS: Kathleen Moore, MD
Benjamin Tsang, PhD

PGC1α Induced by Reactive Oxygen Species in Tumor Spheres and Patient-Derived Ascites Cells Confers Chemo resistance to Ovarian Cancer
Yong Sang Song, MD

Hypoxic Signaling in Ovarian Tumor Metastasis: Molecular Mechanisms and Targeted Therapy
Erinn Rankin, PhD

Mechanism and Therapeutic Efficacy of a Novel Inhibitor of BMI-1 Function in Ovarian Cancer
Resham Bhattacharya, PhD

Anti-HGF Antibody as a Therapeutic Agent for Ovarian Cancer
Junho Chung, MD, PhD

Probing Cellular Processes using Engineered Nanomaterials
Priyabrata Mukherjee, PhD
SESSIOIII: OVARIAN CANCER: TARGET DISCOVERY I

PGC1α INDUCED BY REACTIVE OXYGEN SPECIES IN TUMOR SPHERES AND PATIENT-DERIVED ASCITES CELLS CONFRS CHEMORESISTANCE TO OVARIAN CANCER

Due to altered metabolism, malignant cells suffer from oxidative stress by a high level of reactive oxygen species (ROS). To relieve the stress, they activate antioxidant mechanisms, resulting in resistance to chemothera- peutic agents. Here, we found that PGC1α, a key molecule facilitating mitochondrial biogenesis and activating antioxidant enzymes, enhances chemoresistance in response to ROS generated under the sphere-forming culture condition of ovarian cancer cells. Spheres exhibited stem cell-like phenotypes, such as a high activity of aldehyde dehydrogenase (ALDH) and expression of stemness-related genes with the drug-resistant phenotype. Intriguingly, scavenging ROS using N-acetyl-cysteine diminished ALDH-positive population and inhibited proliferation of spheres. Production of ROS triggered expression of PGC1α, which in turn resulted in enriched mitochondrial biogenesis and reduced mitochondrial activity in spheres. The drug-resistant phenotype was observed in both spheres and PGC1α-overexpressed cells but not in parent cells. Knocking down of PGC1α by siRNA, however, sensitized spheres to cisplatin. Similarly, patient-derived malignant cells floating in ascites had ALDH-positive population and displayed the tendency of a positive correlation between chemoresistence and PGC1α. This is the first article suggesting that PGC1α induced by ROS mediates drug resistance, and provides a potential as a new therapeutic target to overcome chemoresistance in ovarian cancer.
BRIEF CURRICULUM VITAE

Education:
Residency  Seoul National University Hospital, Seoul, KR
Fellowship  Seoul National University Hospital, Seoul, KR
Research Fellowship  University of Wyoming, Laramie, WY

Representative Careers:
Professor  College of Medicine, Seoul National University
Honorary Professor  Guangdong Medical College, China
Adjunct Professor  Human Medicine College, Michigan State University, MI, US
Hon. Prof. and Chair  Henan University, China

Interesting Research Areas:
Ovarian cancer, Cancer stem cell, Organoid, Cancer Microenvironment, Metabolism

Selected Publications:


Representative Awards:
Academic Award International Conference on Ovarian Cancer, 2006

Professor of Superiority in Academy, Seoul National University, 2008

Academy Award, Clinical Research Institute, Seoul National University Hospital, 2010

President Award on Prevention, Korea Government, 2014
Erinn B. Rankin, Ph.D.
Assistant Professor, Department of Radiation Oncology, Department of Obstetrics and Gynecology, Stanford University
Stanford, California, United States

SESSION III: OVARIAN CANCER: TARGET DISCOVERY I

THE HYPOXIC MICROENVIRONMENT OF OVARIAN CANCER PROMOTES METASTASIS THROUGH THE RECEPTOR TYROSINE KINASE AXL

Ovarian cancer is a leading cause of cancer related deaths world-wide. Despite current surgical and cytotoxic therapies, 80% of patients diagnosed with advanced epithelial ovarian cancer develop recurrent disease and only 30% of patients survive 5 years following diagnosis. Therefore, there is a significant unmet clinical need for the development of novel therapeutic agents for the treatment of ovarian cancer.

Hypoxia within the ovarian cancer tumor microenvironment promotes tumor progression, drug resistance, and poor survival. However, therapeutic strategies to target the hypoxic microenvironment in ovarian cancer progression remain to be identified. Here we sought to identify the mechanisms by which hypoxia promotes the resistant and metastatic behavior of ovarian tumor epithelial cells. We utilized chromatin immunoprecipitation and gene expression arrays to identify novel hypoxia induced HIF targets in tumor epithelial cells. We then used cellular, molecular and functional assays to identify novel HIF targets involved in ovarian drug resistance and metastasis. Here we identify the receptor tyrosine kinase, AXL, as a direct target of the hypoxic signaling pathway in ovarian tumor epithelial cells. In ovarian cancer, AXL is a key factor promoting the mesenchymal phenotype, mesothelial cell clearance, invasion, and metastasis. Most importantly, therapeutic inhibition of AXL using a soluble AXL decoy approach is sufficient to improve the therapeutic index of current standard of care chemotherapies in preclinical models of advanced ovarian cancer. Our data identify AXL as a key factor driving ovarian cancer tumor progression. Our data indicate that anti-AXL therapy may be an effective therapeutic strategy for the treatment of advanced ovarian cancer.
BRIEF CURRICULUM VITAE

Education:
Ph.D. University of Pennsylvania, Philadelphia, PA, US

Interesting Research Areas:
Hypoxia, the tumor microenvironment, metastasis, resistance, ovarian cancer

Selected Publications:


Representative Awards:
DOD Ovarian Cancer Academy Early Career Investigator
SESSION III: OVARIAN CANCER: TARGET DISCOVERY I

MECHANISM AND THERAPEUTIC EFFICACY OF A NOVEL INHIBITOR OF BMI-1 FUNCTION IN OVARIAN CANCER

Therapy resistance is responsible for cancer relapse and poses a major clinical challenge. This is exemplified by high grade serous ovarian cancer (HGSOC) where ~70% of advanced stage patients relapse and eventually succumb to recurrent disease. Decades of intensive research on a handful of potential targets have not yielded any major advances. Hence there is a compelling need to identify new molecular targets.

BMI-1, a polycomb group protein that confers self-renewal property to normal and cancer stem cells has emerged as an important therapeutic target in several malignancies. Realizing the pathological significance, PTC-209, a small molecule that inhibits translation of BMI-1 was first described in 2014. More recently, PTC-028 was developed with optimized pharmaceutical properties. It is orally bioavailable and decreases BMI-1 by post-translational modification.

Here we show that PTC-028 significantly inhibits clonal growth and viability of HGSOC cells by specifically decreasing the levels of BMI-1 through hyper-phosphorylation mediated depletion, while normal ovarian cells with minimal expression of BMI-1 remain unaffected. At a lower concentration than required for PTC-209, PTC-028 induces faster depletion of BMI-1 and potentiates caspase-dependent apoptosis through generation of mitochondrial reactive oxygen species (ROS). Importantly, orally administered PTC-028 exhibits significant single agent antitumor activity similar to that of the standard of care cisplatin/ paclitaxel, administered by the intraperitoneal route in an orthotopic mouse model of ovarian cancer.

Thus, PTC-028 has the potential to be used as an effective therapeutic in patients with HGSOC, where treatment options are limited.
BRIEF CURRICULUM VITAE

Education:
B.Sc. University of Calcutta, IN
M.Sc. University of Calcutta, IN
Ph.D. Bowling Green State University, OH, US

Representative Careers:
Post-Doc Fellow Mayo Clinic, Rochester, MN, US
Instructor Mayo Clinic, Rochester, MN, US
Assistant Professor Mayo Clinic, Rochester, MN, US
Assistant Professor University of Oklahoma Health Sciences Center, Oklahoma City, OK, US

Interesting Research Areas:
Role of Bmi-1, a chromatin modifying epigenetic repressor, in promoting ovarian cancer stemness, chemotherapy resistance and metastasis; microRNA based systems biology approaches are utilized to identify novel therapeutic targets in chemoresistant high grade serous ovarian cancer

Selected Publications:


SESSION III: OVARIAN CANCER: TARGET DISCOVERY I

ANTI-HGF ANTIBODY AS A THERAPEUTIC AGENT FOR OVARIAN CANCER

*Purpose:* The hepatocyte growth factor (HGF) and its receptor cMet play a critical role in cell proliferation, angiogenesis and invasion in a wide variety of cancers. We examined the anti-tumor activity of an HGF-neutralizing humanized monoclonal antibody (YYB101) in mouse model and determined pharmacokinetics, toxicokinetics and tissue cross-reactivity to support clinical development.

*Methods:* HGF neutralizing assays, Erk1/2 phosphorylation and scattering assay, were performed by treating YYB101 to HGF expressing cell lines *in vitro*. Anti-tumor efficacy of HGF mAb was assessed in various tumor mouse models including ovarian cancer. Tissues from human and cynomolgus monkey were stained with HGF mAb to test tissue cross-reactivity. Preclinical pharmacokinetics and toxicokinetics of HGF mAb were evaluated in cynomolgus monkeys.

*Results:* YYB101 successfully inhibited HGF mediated cMet signaling *in vitro* and tumor growth in mouse model. In tissue cross-reactivity study, there was no specific positive staining in the tissues from human and cynomolgus monkey. The terminal elimination half-life (*t*₁/₂) was 21.7 days.

*Conclusions:* In *in vitro* and *in vivo* studies YYB101 showed a potent HGF-neutralizing ant anti-tumor efficacy. The preclinical data including pharmacokinetics, toxicokinetics and tissue cross-reactivity enabled clinical development of HGF mAb for advanced cancer.

*Keywords:* Hepatocyte growth factor (HGF), humanized monoclonal antibody, preclinical study
BRIEF CURRICULUM VITAE

Education:
M.D. Seoul National University College of Medicine, Seoul, KR
Ph.D. Seoul National University College of Medicine, Seoul, KR

Representative Careers:
Professor & Chairman Dept. of Microchemistry & Molecular Biology, Seoul National University College of Medicine, Seoul, KR
Principal Investigator Div. of Molecular Oncology, Dept. of Basic Sciences, National Cancer Center Research Institute

Interesting Research Areas:
Antibody engineering, therapeutic antibody development

Selected Publications:


Koo MY, Park J, Lim JM, Joo SY, Shin SP, Shim HB, Chung J, Kang D, Woo HA, Rhee SG. Selective inhibition of the function of tyrosine-phosphorylated STAT3 with a phosphorylation site-specific intrabody.
SESSION III: OVARIAN CANCER: TARGET DISCOVERY I

PROBING CELLULAR PROCESSES USING ENGINEERED NANOMATERIALS

Although biomedical applications of nanotechnology, which typically involve functionalized nanoparticles, have taken significant strides mostly pertaining to detection, diagnosis and therapy, use of surface engineered nanomaterials to understand cellular processes is under represented. In this talk, I will discuss how surface engineered nanoparticles could be utilized to probe cellular processes to understand the biology of tumor growth and drug resistance.
BRIEF CURRICULUM VITAE

Education:
B.Sc. University of Burdwan, IN
M.Sc. University of Burdwan, IN
Ph.D. University of Burdwan, IN

Representative Careers:
Research Assistant Mayo Clinic, Rochester, MN, US
Assistant Professor Mayo Clinic, Rochester, MN, US
Professor University of Oklahoma Health Sciences Center, Oklahoma City, OK, US

Interesting Research Areas:
Nanomedicine and its application in both Ovarian and Pancreatic Cancers

Selected Publications:


Representative Awards:
Chartered Member, Biotechnology and Surgical Sciences Study Section at National Institute of Health (Received), 2015 - Present

Peggy and Charles Stephenson Endowed Chair in Cancer Laboratory Research, University of Oklahoma (Received), 2013 - Present
J. Silvio Gutkind, PhD
Professor and Associate Director of Basic Science, Department of Pharmacology, University of California – San Diego Moores Cancer Center, La Jolla, California, United States

Stephenson Cancer Center-COBRE DISTINGUISHED PLENARY LECTURE

THE PIK3CA-MTOR SIGNALING CIRCUITRY AND CANCER: NEW MOLECULAR-TARGETED THERAPIES AND PREVENTIVE STRATEGIES

With approximately 500,000 new cases annually, squamous cell carcinomas of the head and neck (HNSCC), represent one of the six most common cancers in the world. This disease, which includes malignant lesions arising in the oral cavity, larynx and pharynx, results in nearly ~11,000 deaths each year in the United States alone. The five-year survival rate after diagnosis for HNSCC remains low, approximately 50%, which is lower than that for other frequent cancers types, such as colorectal, prostate, and breast cancer. This poor prognosis is largely due to the advanced nature of the disease at the time of diagnosis, and the limited response to currently available treatment options. There is an urgent need to develop new therapeutic strategies to prevent and treat HNSCC. A striking finding from the recent deep sequencing of the HNSCC genomic landscape was the remarkable multiplicity and diversity of genetic alterations in this malignancy. The emerging picture, however, is that most fall within only a few major driver biological processes, including mitogenic signaling with particular emphasis on aberrant activation of the PI3K/mTOR pathway. Among them, PIK3CA, encoding the PI3Kα catalytic subunit, is the most commonly mutated oncogene in HNSCC (~20%), with a significant enrichment in (HPV)-associated tumors (25%). Our team has focused on the study of oncogenic signaling circuitries driving HNSCC initiation and progression, aimed at identifying novel druggable targets for HNSCC prevention and treatment. These efforts led to our early discovery that the persistent activation of the PI3K/mTOR signaling circuitry is the most frequent dysregulated signaling mechanism in OSCC, and that PI3K/mTOR inhibition exerts potent antitumor activity in a large series of genetically-defined and chemically-induced HNSCC models, including those involving HPV-associated HNSCC. These findings provided the rationale for launching a multi-institutional Phase II clinical trial (NCT01195922), targeting mTOR in HNSCC, which was recently completed and achieved encouraging results. Emerging results from this trial and the molecular mechanisms underlying
the remarkable effects of mTOR inhibitors in HNSCC and other cancer types will be discussed. A recently initiated clinical trial for HNSCC prevention using metformin, which decreases mTOR activity in oral premalignant lesions and their cancer initiating cells will be also presented.
BRIEF CURRICULUM VITAE

Education:
Ph.D. University of Buenos Aires, Buenos Aires, AR

Representative Careers:
Chief Oral and Pharyngeal Cancer Branch, NIDCR, NIH
Professor University of California – San Diego Moores Cancer Center, La Jolla, CA, US
Associate Director Basic Science, University of California – San Diego Moores Cancer Center, La Jolla, CA, US

Interesting Research Areas:
The goal of our research program is to exploit the emerging information on dysregulated signaling circuitries and individual genomic and molecular alterations to identify new therapeutic options to prevent and treat cancer.

Selected Publications:


Representative Awards:
Pharmaceutical Research and Manufacturers America (PhRMA), Research & Hope Award for “Excellence in Academic Research”, 2015

Honorary Professor, West China School of Stomatology, Sichuan University, Chengdu, China, 2014
SESSION IV: OVARIAN CANCER: TARGET DISCOVERY II
SESSION CHAIRS: Yong Beom Kim, MD
Jie Wu, PhD

Role of Hexokinase II in the Regulation of Aerobic Glycolysis and Cisplatin Sensitivity in Ovarian Cancer Cells
Benjamin Tsang, PhD

Copy Number Variations and MicroRNA Aberrations in Ovarian Cancer
Pradeep Chaluvally-Raghavan, PhD

Long Non-coding RNA Targets in Ovarian Cancer Biology and Therapy
Danny Dhanasekaran, PhD
SESSION IV: OVARIAN CANCER: TARGET DISCOVERY II

ROLE AND REGULATION OF HEXOKINASE II IN AEROBIC GLUCOLYSIS AND CISPLATIN SENSITIVITY IN OVARIAN CANCER CELLS

Ovarian cancer (OVCA) is the 5th leading cause of cancer death in women, mainly due to late diagnosis and chemoresistance. Cisplatin (CDDP) resistance is a major hurdle to successful therapy. Cancer cells preferably obtain energy via aerobic glycolysis (Warburg effect). The key glycolytic enzyme, Hexokinase II (HKII) converts glucose to glucose-6-phosphate and is highly associated with tumorigenesis. We have previously shown that p53 is required for overcoming of chemoresistance in OVCA and is a critical determinant for induction of apoptotic response to CDDP. However, it remains unknown if HKII plays an etiologic role in chemoresistance, and whether and how HKII-mediated aerobic glycolysis may be involved.

We hypothesize that HKII plays an important role in cell survival in chemoresistant OVCA. To investigate the role and regulatory mechanism of HKII-mediated aerobic glycolysis in chemoresistance, we used paired CDDP sensitive cell line (A2780s) and its resistant counterpart (A2780cp) as well as multiple chemoresistant OVCA cells with varied p53 status. Despite no significant differences in basal HKII protein levels of between the chemosensitive and chemoresistant cells, CDDP down-regulated HKII mRNA abundance and protein content in chemosensitive cells, but not in chemoresistant cells, suggesting that CDDP-mediated HKII responsiveness is the determinant factor for chemosensitivity. P53 is a transcriptional regulator of HKII expression and its promoter binding activity is compromised in chemoresistant OVCA cells. While silencing p53 markedly enhanced HKII mRNA and protein levels, HKII down-regulation (siRNA or 2-DG) sensitized p53-wt (but not p53-deficient) chemoresistant cells to CDDP-induced apoptosis. CDDP treatment resulted in the P-p53-mediated translocation of HKII from the mitochondria to the nucleus and decreased HKII enzymatic activity in chemosensitive but not in chemoresistant cells.

Taken together, these findings demonstrate the novel regulatory mechanism of HKII in OVCA cells and suggest that HKII-mediated aerobic glycoly-
sis can be a therapeutic target in treatment of chemo-resistant OVCA (supported by a grant from the Canadian Institutes of Health Research).
BRIEF CURRICULUM VITAE

Education:
B.S. Bemidji State University, Bemidji, MN
M.S. University of Iowa, Iowa City, IA
Ph.D. University of Ottawa, Canada

Representative Careers:
Senior Research Scientist Columbia Research Laboratories, Madison, WI, US
Director, Reproductive University of Ottawa, CA
Professor Seoul National University, KR
Honorary Professor Nanjing Medical University, Nanjing, China

Interesting Research Areas:
Ovarian Function and Female Infertility; Ovarian Cancer Biology; Chemoresistance

Selected Publications:


Representative Awards:
Angel Award, 2012
OCRI Research Award, Ottawa Centre for Research and Innovation, 2011
Award of Excellence in Reproductive Medicine, Canadian Fertility and Andrology Society, 2008
SESSiON IV: oVARIAN CAncER: TaRGEt DISCOV ery II
COPY NUMBEr VARIATION MEDIATED microRNA ABERRATIONS IN OVARIAN CANCER

The 3q26.2 locus is highly amplified in high-grade serous ovarian cancer (HGSOC). We have previously demonstrated that the 3q26.2 amplicon contains several oncogenes including PIK3CA, PKCl and MECOM. Recently we identified two microRNAs, miR569 and miR551b are located in the 3q26 amplicon. While the functions of coding genes and proteins are well characterized, non-coding genes represent understudied tumor drivers in ovarian cancer. Herein our studies provide novel mechanism of actions of microRNAs promote ovarian tumor growth and metastasis.

Using high-resolution SNP-based copy number analysis of 533 high-grade serous ovarian cancer samples, we have demonstrated that miR551b and miR569 are highly amplified in ~35% of HGSOC patients’ samples. Analysis using the miR expression data from the TCGA and our own sample sets, we have confirmed that 3q26.2 amplification leads to the increased expression of mature miR551b and miR569, relative to the non-amplified tumor samples.

Employing reverse phase protein array (RPPA), mRNA array and AGO-CLIP assays; we have identified the targets of miR551b and miR569. Briefly, our results identified the key proteins regulates cell proliferation, survival and apoptosis such as TP53INP1, STAT3, KIT and IGFR1 were deregulated by 3q26.2 miRs. In compliment to the targets identified, 3q26.2 miRs contribute to resistance to apoptosis and increased survival and proliferation of cancer cells in vitro and in vivo. Furthermore, miR551b and miR569 expressions are associated with poor outcome in high-grade serous ovarian cancer patients. In compatible with TCGA and other clinical datasets, our results demonstrated that 3q26.2 miRs and their targets could be used as a promising candidate biomarker and therapeutic targets in ovarian cancer.
BRIEF CURRICULUM VITAE

Education:
Ph.D. Beaton Institute for Cancer Research, Glasgow, UK
Post-doc Fellow Weizmann Institute of Science
Post-doc Fellow University of Texas MD Anderson Cancer Center, Houston, TX, US

Representative Careers:
Instructor University of Texas MD Anderson Cancer Center, Houston, TX, US
Assistant Professor The Medical College of Wisconsin, Milwaukee, WI, US

Interesting Research Areas:
Non-coding RNA, ceRNA, RNA activation, EGF Receptor Family and Notch Family genes

Selected Publications:


Representative Awards:
Scientific Scholar Award, Marsha Rivkin Center Foundation for Ovarian Cancer Research, 2014
AACR-Millennium Scholar in Training Award, American Association of Cancer Research Annual Symposium, 2013
Ann Schreiber Program of Excellence Fellowship Award, Ovarian Cancer Research Fund (OCRF), USA, 2013
SESSION IV: OVARIAN CANCER: TARGET DISCOVERY II

LONG NON-CODING RNA TARGETS IN OVARIAN CANCER BIOLOGY AND THERAPY

Long non-coding RNAs are emerging as critical factors involved in the genesis and progression of many cancers. With a focus on defining the role of IncRNAs in ovarian cancer, we have identified the overexpression of several IncRNAs in ovarian cancer. Narrowing our focus on UCA1, an overexpressed oncogenic IncRNA in ovarian cancer cells and tissues, we demonstrate that its expression is regulated by G-protein coupled receptor pathway involving the putative gep oncogene. Functional analysis of UCA1 indicates that it acts as a pleotropic modulator of different facets oncogenic phenotype. Ectopic expression of UCA1 induces cell proliferation as well as invasive cell migration through the stimulation of both proliferation- and EMT-specific genes. Furthermore, the knockdown of UCA1 sensitizes cisplatin-resistant ovarian cancer cells to cisplatin. More significantly, analysis of ovarian cancer tissue-microarray from 126 patients indicates that the increased expression of UCA1 correlates with disease recurrence and poor overall survival in ovarian cancer patients. More significantly, intratumoral injection of UCA1-siRNA inhibits ovarian cancer growth in a xenograft mouse model, thus validating the therapeutic potential of targeting UCA1 in ovarian cancer. In addition to providing the first evidence for a G-protein-regulated IncRNA and its role in ovarian cancer pathobiology, our results point to UCA1 as an attractive candidate for RNA-targeted ovarian cancer therapies.
BRIEF CURRICULUM VITAE

Education:
Ph.D. Indian Institute of Science
Post-doc Research Assoc. University of Wisconsin, Madison, WI, US
Post-doc Research Assoc. National Jewish Center for Respiratory Medicine and Immunology, Denver, CO, US

Representative Careers:
Assistant Scientist University of Wisconsin, Madison, WI, US
Professor Fels Institute for Cancer Research, Temple University
Prof. / Deputy Director Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, US
Director NIH-Center of Excellence in Biomedical Research and Center for Basic Cancer Research, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, US

Interesting Research Areas:
Oncogenes, Ovarian Cancer, Pancreatic Cancer, Tumor Microenvironment, Metastasis, Biomarkers, Drug Resistance and Therapy

Selected Publications:

DN. Hax-1 is required for Rac1-Cortactin interaction and ovarian carcinoma cell migration. Genes Cancer. 2014; 5:84-99. PMID: 25053987

SESSION V: THERAPEUTIC STRATEGIES II
SESSION CHAIRS: Priyabrata Mukherjee, PhD
Joe Zhao, PhD

Resveratrol Counteracts LPA-Induced Epithelial-to-
Mesenchymal Transition in Ovarian Cancer Cells by Inhib-
it ing BMI-1 and Inducing Autophagy
Ciro Isidoro, MD, DSc

Targeting Ribosome Biogenesis in Cancer
Lawrence Rothblum, PhD

Biology and Therapeutic Targeting of PAKs in Cancer
Rakesh Kumar, PhD

Targeted Nano-Therapeutics for Drug Resistant
Tumors
Mansoor Amiji, PhD
Ciro Isidoro, MD, DSc
Associate Professor, General Pathology, Universita
del Piemonte Orientale, Novara, Italy

SESSION V: THERAPEUTIC STRATEGIES II

RESVERATROL COUNTERACTS LPA-INDUCED EPITHELIAL-TO-
MESENCHYMAL TRANSITION IN OVARIAN CANCER CELLS BY
INHIBITING BMI-1 AND INDUCING AUTOPHagy

Ovarian cancer has the highest mortality ratio among gynecologic malignancies, essentially because often it is diagnosed at a very late stage (when the tumor has spread out the ovary) and because of metastatic re-lapse. Lysophosphatidic acid (LPA), a biological signalling mediator that strongly promote cell proliferation and cell motility, is found at high concentrations (1–80 μM) in ascites from ovarian cancer patients. LPA is known to signal through G-coupled receptor. In ovarian cancer cells, LPA promotes the Epithelial-to-Mesenchymal (EMT) transition along with increased expression of the Slug (Snail2) transcription factor, which reportedly represses the expression of E-cadherin. Bmi-1, a Polycomb G (PcG) transcription repressor downstream of the Hedgehog (HH) pathway, acts as an oncogene that promotes stemness and EMT in association with increased activity of the Snail and Twist pathways. Here, we show that LPA stimulates ovarian cancer cell motility through induction of the Bmi-1 - Twist pathway. Interestingly, LPA also inhibited autophagy, a macromolecular degradation process known to oppose to cell migration. Cyclopamine-mediated inhibition of the HH pathway or si-RNA silencing of Bmi-1 inhibited EMT and cell migration, down-regulated Twist, and restored autophagy and E-cadherin expression. These same effects were elicited by Resveratrol (RV), a bioactive dietary polyphenol that inhibits the AKT pathway and promotes the epigenetic inhibition of cell migration. RV could counteract the LPA pro-invasive effects through down-regulation of Bmi-1 and hyper-induction of autophagy.
BRIEF CURRICULUM VITAE

Education:
D.Sc. Universita di Torino, IT
MD Universita del Piemonte Orientale, Novara, IT

Representative Careers:
Visiting Professor Siriraj Faculty of Medicine, Mahidol University of Bangkok; Chulalongkorn University of Bangkok, TH
Professor Honoris Causa Universite de la Franche – Comte of Besancon, France
Scientific Board Member Integrative Cancer Research Center of the Georgia Institute of Technology, Georgia Tech University, Atlanta, GA, USA
Executive Vice-President International Association of Traditional and Complementary Medicine

Interesting Research Areas:

Selected Publications:


SESSION V: THERAPEUTIC STRATEGIES II

TARGETING RIBOSOME BIOGENESIS IN CANCER

Wound healing requires cell growth. Cell growth results from the accumulation of protein and requires an increased amount of ribosomes. The rate-limiting step in ribosome biogenesis is rDNA transcription by RNA polymerase I (Pol I). There are several molecular components of the transcription apparatus that are targets for regulating rDNA transcription, including a transcription factor referred to as UBF and even the assembly of the polymerase itself. For example, we have found that the fraction of RNA polymerase I that contains a protein required for transcription initiation is subject to regulation.

The activity of the rDNA transcription factor UBF (Upstream Binding Factor) is regulated when rDNA transcription is adjusted in response to numerous stimuli. The levels of UBF activity, endogenous or ectopic, correlate with the level of rDNA transcription in both immortal cell lines and differentiated cells. Interestingly, UBF activity can be regulated in different ways in the same cell type depending upon the stimulus. We have shown that agonists that cause cardiac hypertrophy can either regulate the amount of UBF mRNA in hypertrophic cardiomyocytes or increase UBF activity by modulating its phosphorylation state. Moreover, UBF activity can be modulated by its association with the anti-oncogene Rb.

Studies from our laboratory have demonstrated that the assembly of various polymerase associated proteins with the core polymerase regulate steps such as initiation and elongation. One of these proteins is Rrn3. The assembly of Rrn3 with core Pol I is required for the formation of a polymerase complex that is capable of specific transcription initiation. The rpa43 subunit of Pol I is essential for the recruitment of Rrn3. The detailed molecular study of the interaction between Rrn3 and rpa43, has led to the discovery of a twenty-two amino acid long peptide that can inhibit cell proliferation and, in the case of many cancer cells, cause cell death. In some cancer cell lines we have observed 90% cell death within 8-24 hr. These observations are consistent with reports from other laboratories that have demonstrated the death of tumor cells in response to an inadequate rate
of ribosome biogenesis, e.g., J Cell Sci. 124:3017 (2011). Interestingly, the resulting cell death is p53 independent and not necessarily through apoptosis. The 22mer is a small molecule inhibitor of rDNA transcription that is based on our understanding of the mechanism of rDNA transcription and appears to be specific for the rDNA transcription apparatus. As such, we hypothesize that it represents a novel way to interfere with cell growth, and we believe that it demonstrates a potentially novel pharmaceutical target for the treatment of cancer cells.
BRIEF CURRICULUM VITAE

Education:
B.S. Union College, Schenectady, NY, US
Ph.D. Drexel University College of Medicine

Representative Careers:
Adjunct Professor University of Oklahoma, Norman, OK, US
Professor and Chair University of Oklahoma, Oklahoma City, OK, US
Adjunct Professor Penn State University, Hershey, PA, US
Senior Scientist Sigfried and Janet Weis Center for Research,
Geisinger Clinic, Danville, PA, US

Interesting Research Areas:
provide the basis for understanding its regulation; provide a mechanism
for its inhibition under conditions where it is dysregulated or pathological

Selected Publications:
Cavanaugh, A.H., Hirschler-Laszkiewicz, I., Hu, Q., Dundr, M., Smink, T.,
Misteli, T., Rothblum, L.I. Rrn3 phosphorylation is a regulatory checkpoint
for ribosome biogenesis. J. Biol. Chem. 277: 27423-27432, 2002. PMID:
12015311

Hirschler-Laszkiewicz, I., Cavanaugh, A., Mirza, A., Lun, M., Hu, Q., Smink, T.,
Rothblum, L.I. Rrn3 becomes inactivated in the process of ribosomal DNA

Cavanaugh, A. H., Evans, A. Rothblum, L.I. Mammalian Rrn3 Is Required for
the formation of a Transcription Competent Preinitiation Complex Conta-
aining RNA Polymerase I. Gene Expression 14:131-147, 2008. PMID:
18590050 PMCID: PMC2526047

Stepanchick, A. Zhi, H-J., Cavanaugh, A., Rothblum, K., Schneider, D.A.,
Rothblum, L.I. DNA-binding by the ribosomal DNA transcription factor
Rrn3 is essential for ribosomal DNA Transcription. J Biol Chem.;288:9135-
44, 2013 PMID: 23391315 PMCID: PMC3610986

Rothblum, K., Hu, Q., Penrod, Y., Rothblum L.I. Selective Inhibition of rDNA
Transcription by a Small-Molecule Peptide that Targets the Interface Be-
PMID: 25033839 PMCID: PMC4233170
SESSION V: THERAPEUTIC STRATEGIES II

BIOLOGY AND THERAPEUTIC TARGETING OF PAKS IN CANCER

Reorganization of cytoskeleton and formation of motile structures are part of distinct phenotypic responses in cancer cells exposed to extracellular signals. At the cellular level, these changes are regulated by the p21-activated kinases (PAKs) and its downstream effectors and targets. Biochemically, PAKs are enzymes with kinase and scaffolding activities. In addition, PAK functions as a key signaling node due to its ability to cross-talk with signaling network, and phosphorylate downstream effector molecules. The spectrum of PAK’s functions ranges from cell growth, invasion, gene expression and chromatin remodeling to DNA damage response and modifying therapeutic responsiveness of cancer cells. PAK family members are widely overexpressed in human cancers and closely associated with the growth and invasive phenotypes. In addition, PAKs dysregulation also contributes to the development of therapeutic resistance to anti-cancer therapies. Because PAKs are at the center of signaling cascades with distinct nuclear functions, the PAK-regulated cellular processes are involved in a number of human diseases including cancer. Over the last decade, there has been substantial progress in developing approaches to target PAKs by a wide-variety of promising therapeutic agents with alone or in-combination with pathway-centered inhibitors, and the field might be moving towards combinational target therapeutics. The lecture will discuss the impact of our broader understanding of the PAK biology in cancer cells has helped to targeting PAKs in cancer, the progress made during the last decade, the nature of limitations faced by the field to develop effect PAK-directed molecules, and the next step to develop effective PAK-directed molecules for cancer.
BRIEF CURRICULUM VITAE

Education:
Ph.D. All India Institute of Medical Sciences, Delhi, IN

Representative Careers:
Deputy Chairman MD Anderson Cancer Center, Houston, TX, US
Professor George Washington University, Washington DC, US
Chairman George Washington University, Washington DC, US
Chair Catherine Birch Williams and McCormick, George Washington University, Washington DC, US
Visiting Dist. Professor Rajiv Gandhi Centre Biotechnology, Government of India

Interesting Research Areas:
Phenotypic Signaling, Cytoskeleton and Chromatin Remodeling, Transcriptomics

Selected Publications:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Kumar+R+Pak1
http://www.ncbi.nlm.nih.gov/pubmed/?term=Kumar+R+MTA1

Representative Awards:
East Shanghai Cancer Forum Award, 2013
Lifetime Achievement Award, American Association of Indian Scientists in Cancer Research, 2013
Elaine H. Snyder Cancer Research Award, 2011
Ranbaxy Research Award – India, 2008
Outstanding Achievement Award, Society of American Asian Scientists in Cancer Research, 2008
MD Anderson Cancer Center Faculty Achievement Award in Basic Science, 2004
SESSION V: THERAPEUTIC STRATEGIES II

TARGETED NANO-THERAPEUTICS FOR DRUG RESISTANT TUMORS

Development of tumor multidrug resistance (MDR) is a major challenge in clinical cancer medicine, where there are limited options for refractory patients often leading to fatal consequences. With support from the National Cancer Institute’s Alliance for Nanotechnology in Cancer over the past twelve years, we have focused on the use of multimodal strategies that aim at improving drug delivery and residence to tumor mass as well as altering the resistant cell phenotype (e.g., tumor stem cells) in order to improve clinical outcomes.

Based on our central hypothesis that tumor MDR develops due to the micro-environmental selection pressures induced by hypoxia, aerobic glycolysis, and the production of lactate that elevates cell-kill threshold, our approach relies on the use of combination therapeutic strategies with passive- and active-targeted nanoparticle-encapsulated agents. Specifically, we have investigated the role of genes that regulate ATP dependent efflux pumps, cellular apoptosis, glucose metabolism, and cell-cycle check point and evaluate RNA interference therapy for combination siRNA/small molecule drug delivered using combinatorial-designed nanoparticle formulations.

In each of the example, our focus is to understand the medical challenge and then develop an effective solution for tumor MDR. Special emphasis is placed on the use safe materials and scalable methods of nanoparticle fabrication in order to facilitate the clinical translation and improve patient outcomes.
BRIEF CURRICULUM VITAE

Education:
B.S. Pharmacy, Northeastern University, Boston, MA, US
Ph.D. Pharmaceutical Sciences, Purdue University, West Lafayette, IN, US

Representative Careers:
Senior Research Scientist Columbia Research Laboratories, Madison, WI, US
Assistant Professor Northeastern University, Boston, MA, US
Associate Professor Northeastern University, Boston, MA, US
Professor Northeastern University, Boston, MA, US
Bouve College Dist. Prof. Northeastern University, Boston, MA, US
University Dist. Professor Northeastern University, Boston, MA, US

Interesting Research Areas:
development of biocompatible materials from natural and synthetic polymers, target-specific drug and gene delivery systems for cancer and infectious diseases, and nanotechnology applications for medical diagnosis, imaging, and therapy

Selected Publications:
six books, over 45 book chapters, and over 200 peer-reviewed articles. Specific peer-reviewed publications can be found at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Amiji.

Representative Awards:
Nano Science and Technology Institute’s Award for Outstanding Contributions towards the Advancement of Nanotechnology, Microtechnology, and Biotechnology – American Association of Pharmaceutical Scientists
Meritorious Manuscript Award
Nagai Award – Controlled Release Society
American Association of Pharmaceutical Scientists Fellowship
Controlled Release Society Fellowship
SESSION VI: TUMOR MICROENVIRONMENT: BIOLOGY AND THERAPEUTIC TARGETS
SESSION CHAIRS: Min Li, PhD
Xin Zhang, MD, PhD

Notch4 as an Oncogenic Signal in Pancreatic Tumorigenesis
Gloria Su, PhD

Targeting the TGF-b Signaling Pathway for Oncology
Rosemary Akhurst, PhD

Therapeutic Strategy TGF-b-Smad3 Signaling in Metastatic Cancers
Jinah Park, PhD

Ephrin-A Ligands Regulate Cutaneous Tumor Etiology and Metastasis through Cell Autonomous and Non-Autonomous Mechanisms
Bingcheng Wang, PhD

Astrocytes in the Microenvironment Influences Metastasis
Ramani Ramchandran, PhD
SESSION VI: TUMOR MICROENVIRONMENT: BIOLOGY AND THERAPEUITIC TARGETS

NOTCH4 ACTS AS AN ONCOGENIC SIGNAL IN PANCREATIC TUMORIGENESIS

The Notch signaling network is an evolutionarily conserved intercellular signaling pathway which regulates interactions between adjacent cells. The Notch family receptor and its signaling pathways are involved in the development of numerous tissues in multicellular organisms. Recent studies from our \textit{Acvr1b}^{\text{flox/flox}};\textit{LSL-Kras}^{G12D};\textit{Pdx1-Cre} mice suggest that Notch4 plays an oncogetic role in dictating cell fate and contributes to pancreatic tumorigenesis, particularly in the development of pancreatic intraductal papillary mucinous neoplasms (IPMNs). The perinuclear localization of the activated Notch4 (but not other Notch members) intracellular domain (ICD) in the apical cytoplasm of neoplastic cells appeared to be associated with the expansion of the IPMN lesions. The unique role of Notch4 signaling pathway in IPMN development was also confirmed by unbiased RNA-Seq analyses. The deletion of Notch4 in the \textit{p16}^{\text{flox/flox}};\textit{LSL-Kras}^{G12D};\textit{Pdx1-Cre} mice prolonged survival, further supporting its oncogenic role in pancreatic tumorigenesis.

The COSMIC database search indicates that NOTCH4 mutation is rare across all cancer types (~1.5%) with missense mutations presented as the most frequent alteration.

Significant mutations (missense, nonsense, insertion and deletion frameshifts) in the Notch family cause loss of function in proteins, which renders them inoperative. **Purpose:** The association of transforming growth factor-\(\beta\) (TGF-\(\beta\)) signaling pathway with human tumorigenesis, including pancreatic cancer, has been rigorously demonstrated. However, little is known about activin signaling, one of three major TGF-\(\beta\) family members, in pancreatic tumorigenesis. We have previously reported sporadic mutations of the Activin receptor type 1B (ACVR1B) gene in human pancreatic ductal adenocarcinoma (PDA); therefore we hypothesized that ACVR1B acts as a tumor-suppressor gene in pancreatic tumorigenesis.

**Methods:** To demonstrate the tumor suppressive role of \textit{Acvr1b} in pancreatic tumorigenesis in vivo, \textit{Acvr1b}^{\text{flox/flox}};\textit{Pdx1-Cre} and \textit{Acvr1b}^{\text{flox/flox}};\textit{LSL-Kras}^{G12D};\textit{Pdx1-Cre} mice were generated and examined.
Results: Acvr1b inactivation alone led to increased proliferation of pancreatic epithelial cells and induced focal inflammatory changes in the pancreases of Acvr1b\(^{\text{flox/flox}}\)Pdx1-Cre mice beyond eight months of age. In combination with oncogenic Kras\(^{G12D}\) expression, loss of Acvr1b preferentially accelerated the growth of pancreatic intraductal papillary mucinous neoplasms (IPMNs), but not pancreatic intraepithelial neoplasias (PanINs). The perinuclear localization of the activated Notch4 (but not other Notch members) intracellular domain (ICD) in the apical cytoplasm of neoplastic cells appeared to be associated with the expansion of the IPMN lesions; the unique role of Notch4 signaling pathway in IPMN development was confirmed by unbiased RNA-Seq analyses. Additional loss of the p16 gene was required for the progression of IPMNs to invasive carcinoma in our model and in human PDA.

Conclusion: Our data supports the hypothesis that Acvr1b acts as a tumor-suppressor gene in vivo and that the disruption of activin signaling preferentially promotes the development of pancreatic IPMNs.

Significance: This is the first study that demonstrates the specific involvements of activin and Notch4 signaling in the development of IPMNs. Furthermore, we have also shown that Notch4 signaling regulates differential gene expressions from the canonical Notch signaling pathway.
BRIEF CURRICULUM VITAE

Education:
B.A. Northwestern University, Evanston, IL, US
Ph.D. University of Chicago, Chicago, IL, US

Representative Careers:
Assistant Professor The Johns Hopkins University, Baltimore, MD, US
Assistant Professor Columbia University Medical Center, New York, NY, US
Associate Professor Columbia University Medical Center, New York, NY, US

Interesting Research Areas:
Novel mouse models for pancreatic diseases; Potential role of wild-type KRAS in pancreatic tumorigenesis; The PTEN-PI3K axis in IPMN/PDA and head and neck cancer; Activin signaling in tumorigenesis

Selected Publications:


Representative Awards:
Permanent Reviewer, NIH Tumor Progression and Metastasis (TPM) Study Section, 2013-2019

Ruth Leff Siegel Award for Excellence in Pancreatic Cancer Research, 2014

Distinguished Achievement Award from Shanghai Tongji University East Hospital for “Exceptional Contribution to Pancreatic Cancer Research and Clinical Management, 2015
SESSION VI: TUMOR MICROENVIRONMENT: BIOLOGY AND THERAPEUTIC TARGETS

TARGETING THE TGF-β SIGNALING PATHWAY FOR ONCOLOGY

Over the last two decades, it has become clear that TGFβ signaling is a driver in several common human diseases, including cancer, fibrosis, vascular disease and inflammation. TGF-β signaling is often elevated in the pathological state and exacerbates that state. The Akhurst lab made several seminal contributions to an understanding of the in vivo functions of the TGFβ signaling pathway in tumorigenesis, including demonstration of the dichotomous function of this signaling pathway in tumor suppression versus tumor promotion and its function in epithelial mesenchymal transition (EMT). The importance of TGF-β in promoting tumor progression and metastasis is now widely recognized, and pharmaceutical companies have developed a panel of TGF-β inhibitory drugs for cancer treatment, some of which are in clinical trial. Despite these developments, the response of each tumor to such drugs will vary due to somatic genetic differences intrinsic to that tumor and because of germline genetic variants that affect the tumor microenvironment. We have demonstrated this effect in mouse models of cancer and we have identified variant genetic modifiers that influence TGFβ signaling. Our lab uses an integrated molecular and biological approach utilizing mouse models of cancer and cancer therapeutics, developmental biology, mouse and human genetics, together with bioinformatics and in vitro cell and molecular biology, in order to study these mechanisms of TGF-β action during in vivo angiogenesis and tumorigenesis, and to investigate how genetic variants influence pathology. We also study rare diseases caused by mutations in genes encoding components of the TGFβ/BMP signaling pathway, such as the vascular disorder, Hereditary Hemorrhagic Telangiectasia, in order to understand how interacting genetic variants influence the severity of this human disease and to gain insight into mechanisms of maintenance of normal in vivo angiogenesis and vascular stability in human.

In the cancer field we currently investigate genetic modifiers of metastasis and collaborate with drug companies to investigate efficacy and preclinical mechanisms of novel TGFβ blockade drugs. We are studying the potential of TGFβ ligand blockade to enhance cancer immunotherapy, and it is this topic that will be covered in the presentation.
BRIEF CURRICULUM VITAE

Education:
B.Sc. Hons Imperial College, London, England, UK
Ph.D. Beaton Institute for Cancer Research, Glasgow, UK

Representative Careers:
EMBO Fellow California Institute of Technology, Pasadena, CA, US
University Lecturer St. Mary’s Medical School, Imperial College, London, England, UK
University Reader University of Glasgow, UK
Senior Scientist Onyx Pharmaceuticals
Professor University of California San Francisco Hellen Diller Family Comprehensive Cancer Center, San Francisco, CA, US

Interesting Research Areas:
Role of TGF beta signaling in development, tumorigenesis and vascular biology; Tumor Microenvironment and Therapeutic Resistance

Selected Publications:


Representative Awards:
Ewart Sticking’s Award for Excellence in Biochemistry Imperial College, 1978
EMBO Fellowship, 1981
New Blood Lectureship London University, 1984
SESSION VI: TUMOR MICROENVIRONMENT: BIOLOGY AND THERAPEUTIC TARGETS

THERAPEUTIC STRATEGY TARGETING TGF-β-SMAD3 SIGNALING IN METASTATIC CANCERS

Transforming growth factor β (TGF-β) affects growth, survival and differentiation of most cell types. Following ligand-induced hetero-tetramerization of type I and type II serine/threonine kinase receptors, Smad2 and 2 are phosphorylated and then they form complexes with Smad4, which are translocated to the nucleus where they regulate the transcription of certain genes. Smad signaling leads to growth arrest as well as epithelial-to-mesenchymal transition (EMT) of epithelial tumor cells. Smad3 functions as both a positive and negative regulator in carcinogenesis. In response to TGF-β, the TGF-β receptor phosphorylates serine residues at the Smad3 C-tail. Cancer cells often contain high levels of MAPK and CDK activities, which can lead to the Smad3 linker region becoming highly phosphorylated at the basal state. In vitro/in vivo study revealed that the mutation of the Smad3 linker phosphorylation sites greatly intensifies the TGF-β-induced EMT with an increased invasive activity, growth arrest and apoptosis together with reduction in the size of putative cancer stem cell subpopulation, suggesting that the linker phosphorylation negatively regulates the canonical TGF-β signaling. In this talk, I will present our recent studies about role of TGF-β signaling in metastasis and cancer stemness, which provide a basis for future clinical studies.
BRIEF CURRICULUM VITAE

Education:
Ph.D. Tsukuba, JP

Representative Careers:
Director CHA, Cancer Research Institute, KR
Distinguished Professor CHA University of Medicine and Science, KR
Adjunct Professor Ireland Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA
Visiting Professor Tsukuba University, JP
Director Nano-Bio Medicine Research Center, Advanced Institutes of Convergence Technology of Seoul National University, Seoul, KR

Selected Publications:
Park, Y. et al. Cytoplasmic DRAK1 overexpressed in head and neck cancers inhibits TGF-β1 tumor suppressor activity by binding to Smad3 to interrupt its complex formation with Smad4. Oncogene, 34, 5037-5045, 2015
Kang, J. M. et al. KIAA1324 Suppresses Gastric Cancer Progression by Inhibiting the Oncoprotein GRP78. Cancer Res. 75, 3087-3097, 2015
SESSION VI: TUMOR MICROENVIRONMENT: BIOLOGY AND THERAPEUUTIC TARGETS

EPHRIN-A LIGANDS REGULATE CUTANEOUS TUMOR ETIOLOGY AND METASTASIS THROUGH CELL AUTONOMOUS AND NON-AUTONOMOUS MECHANISMS

Glycophosphatidylinositol-anchored ephrin-A ligands target EphA receptor tyrosine kinases (RTKs) to promote keratinocyte differentiation. Accordingly, genetic ablation of the major epidermal EphA subtype, EphA2, increases susceptibility to DMBA/TPA-induced cutaneous chemical carcinogenesis. Defining the corresponding role of ligands for EphA2 in skin cancer has been more cumbersome as the three ephrin-A genes (Efnα1, Efnα3, Efnα4) are all prominently expressed in skin. We met this challenge by engineering a triple Efnα1/3/4 knockout (TKO) mice that reflects the pattern of reduced Efnα gene expression found in mouse and human cutaneous SCCs. Skin tumors developed earlier and grew faster in mice lacking EphA2 or these three ephrin-A ligands. Interestingly TKO mice displayed accelerated malignant progression toward invasive SCC that metastasized to the lymph nodes and lungs by 25 weeks following DMBA-TPA treatment. Using keratinocyte culture models, we found that ephrin-A ligands act within the epidermis to limit keratinocyte migration in a manner that depends on their targeting of EphA2. We also illustrated a key role for ephrin-A ligands in the surrounding tumor microenvironment by re-introducing isogenic SCC cell lines into the skin of wild-type or TKO mice on congenic FVB background; tumor growth and metastasis was facilitated in mice lacking ephrin-A ligands. Importantly, the invasive phenotype of TKO mouse tumor cell lines was normalized by genetic reintroduction of either Efnα1 or Efnα3. Integrating our findings from human tumors, mouse models, primary cell cultures, and allograft models provides strong support for the notion that ephrins operate within tumor cells and also in the microenvironment to suppress skin tumor initiation and metastasis.
BRIEF CURRICULUM VITAE

Education:
B.S. Nanjing University, China
PhD University of Wisconsin-Madison, Madison, WI, US

Representative Careers:
Professor Case Western Reserve University School of Medicine, Cleveland, OH, US
Chief Division of Cancer Biology, Case Western Reserve University School of Medicine
Co-Leader Genitourinary Malignancy Program
Co-Leader NCI-Des. Case Comprehensive Cancer Center
Co-Leader Molecular Oncology Program
Co-Leader NCI-Des. Case Comprehensive Cancer Center

Interesting Research Areas:
Tumor cell-intrinsic and extrinsic signaling in tumor initiation and progression; Mouse models of tumorigenesis; Mechanism-based cancer drug discovery

Selected Publications:


Representative Awards:
John A. and Josephine B. Wootton Endowed Chair in Cancer Research, 2012
Prayer from Maria Foundation Award, 2010
FAMRI Investigator Award, 2008
SESSION VI: TUMOR MICROENVIRONMENT: BIOLOGY AND THERAPEUTIC TARGETS

ASTROCYTES IN THE MICROENVIRONMENT INFLUENCE BREAST CANCER CELL METASTASIS

Microenvironment plays a critical role in the metastasis and progression of tumor cells. Our laboratory has recently identified that cells in the brain microenvironment namely the astrocytes, play a critical role in breast cancer cell metastasis in vivo and in vitro. Previous data from our lab provide evidence that the both adult and neonatal rat astrocyte secretome influences the local matrix, thereby facilitating extravasation of cancer cells into brain parenchyma and other distant sites. In that study, we injected astrocyte-conditioned breast cancer cells (ABCs) via the intra-cardiac route. Now, we have injected the ABCs into the mammary fat pad and intravenousous route, and find that irrespective of the route, these cells are highly metastatic in vivo with a few cells reaching the brain as well. ABCs also showed marked change in phenotype when cultured and passaged in the astrocyte culture media, and became increasingly invasive, a phenotype that intriguingly was reversed when the ABCs were cultured in normal tumor media (NBCs) over subsequent passages. Based on this data, we hypothesized that solid tumors with propensity for brain metastasis respond to molecules secreted by astrocytes that induce genomic changes in cancer cells that creates a transitional state in these cells to facilitate metastasis. To investigate this hypothesis, the purpose of this study was to determine the genomic changes in ABCs, and in turn the underlying mechanisms governing ABCs metastasis. We performed microarray analysis on ABCs and NBCs and identified significant up regulation of metastasis regulators in ABCs with a concomitant down regulation of the same genes in NBCs thereby providing excellent correlation between genotype and phenotype. On a phenotypic level, we identified two different cellular morphologies in ABCs, one a small spindle like and a second large irregular cell, and FACS sorting of these two cell populations revealed that the invasive phenotype is associated with the larger irregular cell type. We also have evidence now that human astrocytes differentiated from induced pluripotent stem cells also induce breast cancer cell invasion in vitro, and the ABCs invasion and metastasis phenomenon is
broadly observed in other cancers including lung cancer albeit the genomic changes are not conserved suggesting a level of specificity to these changes. Collectively, these findings suggest a metastasis plan induced by astrocytes on solid tumors with a propensity to make these cells highly tumorigenic and metastatic thus providing novel avenues for intervention.
BRIEF CURRICULUM VITAE

Education:
B.S. University of Bombay, Bombay, IN
M.S. University of Bombay, Bombay, IN
Ph.D. Augusta University, Augusta, GA, US

Representative Careers:
Associate Professor Medical College of Wisconsin, Milwaukee, WI, US
Professor Medical College of Wisconsin, Milwaukee, WI, US
Vice Chair for Research Department of Obstetrics and Gynecology, Medical College of Wisconsin, Milwaukee, WI, US

Interesting Research Areas:
Developmental Vascular Biology: Vasculogenesis and Angiogenesis Mechanisms in Zebrafish and Mice, Vessel and Axon Guidance, Zebrafish Chemical Biology, Translational Models of Disease, Tumor Metastasis

Selected Publications:


Representative Awards:
Clinical & Translational Science Institute, 2012
Distinguished Alumnus Award, Augusta University, 2013
SESSION VII: CANCER TARGET DISCOVERY AND PATHWAY ANALYSIS
SESSION CHAIRS: Junho Chung, MD, PhD
Resham Bhattacharya, PhD

Mechanism Based Repurposing of Neurodegenerative Disease Drugs for Breast Cancer Treatment
Ajay Rana, PhD

Novel Anti-Glioma Therapies Assessed in Pre-Clinical Models
Rheal Towner, PhD

Histone Demethylase JMJD2A in Prostate Cancer
Ralf Janknecht, PhD

Roles and Mechanisms of JAK1/JAK2 Genetic Deficiencies in Cancer
Jie Wu, PhD

A Systems Biology Application in Cancer: Pathome-Web
Taesung Park, PhD
SESSION VII: CANCER TARGET DISCOVERY AND PATHWAY ANALYSIS

MECHANISM BASED REPURPOSING OF NEURODEGENERATIVE DISEASE DRUGS FOR BREAST CANCER TREATMENT

Breast cancer account for the second most cause of cancer related mortality in women. The detailed underlying molecular mechanisms of breast cancer pathogenesis of all the sub-types are not fully understood, however the roles of Estrogen Receptor (ER), Progesterone Receptor (PR), and Epidermal Growth Factor Receptor 2 (HER2) in promoting growth, survival, invasion and acquired resistance to therapies have begun to unravel. The prognosis of ER+ breast cancer that accounts for 60-70% of breast cancers is favorable, however it is dismal for the remaining Triple Negative (TNBC) and HER2+ breast cancer. Quite unexpectedly, we landed onto identifying a pathway that seems to be important for TNBC breast cancer cell survival. While dissecting the MLK3-mediated signaling pathway, we observed a robust interaction between MLK3 and p21-activated kinase 1 (Pak1). Subsequent detail studies showed that Pak1 was phosphorylated and activated by MLK3 in breast cancer cells. Furthermore, the MLK3, Pak1 and NF-κB activities were significantly higher in ER+ primary human breast tumor. These results are intriguing because there is little doubt that level and activity of Pak1 are frequently increased in various cancers, including breast cancer. Our results clearly showed that the small molecule inhibitor of MLKs that went for clinical trial for Parkinson’s Disease can specifically induce cell death in TNBC, suggesting that this pathway could serve as a viable target for TNBC breast cancer.
BRIEF CURRICULUM VITAE

Education:
B.S. Calcutta University, Calcutta, IN
M.S. Calcutta University, Calcutta, IN
Ph.D. Indian Institute of Chemical, Calcutta, IN

Representative Careers:
Research Health Scientist Hines VA Medical Center, Chicago, IL, US
Endowed Professor Kubinski/Das Gupta, University of Illinois at
Chicago, Chicago, IL, US
Director of Research University of Illinois at Chicago, Chicago, IL, US
Research Health Scientist Jesse Brown VA Medical Center, Chicago, IL, US

Interesting Research Areas:
defining the physiological function of a novel group of kinases, called
Mixed Lineage Kinases (MLKs)

Selected Publications:
Sondarva G, Kundu CN, Mehrotra S, Mishra R, Rangasamy V,
Sathyanarayana P, Ray RS, Rana B and Rana A. TRAF2-MLK3 interaction is
PMID: 19918265; PMCID: PMC2801772.

Rangasamy V, Mishra R, Sondarva G, Das S, Lee TH, Bakowska JC, Tzivion G,
Malter JS, Rana B, Lu KP, Kanthasamy A, Rana A. Mixed-lineage kinase 3
phosphorylates prolyl-isomerase Pin1 to regulate its nuclear translocation
2012, May 7]. PMID 22566623; PMCID: PMC3361382.

Rana A, Rana B, Mishra R, Sondarva G, Rangasamy V, Das S, Viswakarma N
and Kanthasamy A. Mixed Lineage Kinase-c-Jun N-Terminal Kinase Axis: A
Potential Therapeutic Target in Cancer. Genes & Cancer
1947601913485415, first published on April 24, 2013.

Representative Awards:
Susan Komen Breast Cancer Foundation Independent Award, 2005-2007
VA Vision 17 award for presentation, 2006
Outstanding achievement award, Soc. of American Asian Scientists in Can-
cer Research (SAASCR), 2011
Rheal A. Towner, PhD
Associate Member and Director of the Advanced
Magnetic Resonance Center
Oklahoma Medical Research Foundation
Oklahoma City, Oklahoma, United States

SESSION VII: CANCER TARGET DISCOVERY AND PATHWAY ANALYSIS

NOVEL ANTI-GLIOMA THERAPIES ASSESSED IN PRE-CLINICAL MODELS

Novel drug therapies against gliomas, including OKN-007 (Oklahoma Nitrone 007), anti-ELTD1 antibody therapy, and AG119, will be discussed. OKN-007 is a nitrone-based compound that is currently an investigational drug for recurrent adult glioblastomas (GBM). ELTD1 is a G-coupled protein receptor. AG119 is a combined tyrosine kinase inhibitor with antimicrotubule cytotoxicity. All of these agents were assessed in either orthotopic mouse (GL261)/rat (F98) glioma models and/or human xenografts in nude mice/rats. Magnetic resonance imaging (MRI) techniques were used to assess tumor growth and morphology and/or tumor vascularity, which provides invaluable information on the effect of therapeutic strategies on the tumor microenvironment. OKN-007 was found to be effective in both adult (rat F98 and human U87 xenograft in nude rats) and pediatric (patient-derived 3752GBM xenografts) GBM models, and both anti-ELTD1 antibody therapy and AG119 were found effective in adult GBM (mouse GL261 for both, and human G55 xenografts in nude mice) models. OKN-007 primarily affects the transforming growth factor (TGFβ1) pathway by modulating the extracellular matrix. Anti-ELTD1 antibody therapy mainly induces an anti-angiogenic effect on both tumor micro- and macro-vascularty. AG119 possess both anti-angiogenic and anti-microtubule cytotoxicity. In all cases, tumor growths were significantly decreased and animal survivals were significantly increased. Tumor vascularity was also significantly decreased for all therapeutic agents. In addition, OKN-007 was able to significantly decrease cell proliferation and increase apoptosis, as well as significantly decrease necrosis. In some cases, the novel therapeutic agents were compared to current or other anti-cancer therapies. These novel therapies can provide additional support to standard-of-care treatment for GBMs, as well as be considered in combination therapies.
BRIEF CURRICULUM VITAE

Education:
B.Sc. University of Guelph, Guelph, Ontario, CA
M.Sc. University of Guelph, Guelph, Ontario, CA
Ph.D. University of Guelph, Guelph, Ontario, CA

Representative Careers:
MRI Facility Manager University of Guelph, Guelph, Ontario, CA
Post-Doc Fellow University of Queensland, Brisbane, AT
Senior Lecturer James Cook University, Townsville, AT
Assoc. Member/Director Advanced Magnetic Resonance Center,
Oklahoma Medical Research Foundation,
Oklahoma City, OK, US
Associate Member Stephenson Cancer Center, Oklahoma City, OK, US

Interesting Research Areas:
Use of MRI techniques to assess pre-clinical models for various cancers;
Anti-cancer agents for gliomas; Development and characterization of mo-
lecular-targeted MRI probes for assessing tumor growth and therapeutic
efficacy

Selected Publications:
Ziegler J, Pody R, Coutinho de Souza P, Evans B, Saunders D, Smith N, Mal-
lory S, Njoku C, Dong Y, Chen H, Dong J, Lerner M, Mian O, Tummala S,
Battiste J, Fung K-M, Wren JD, Towner RA. ELTD1, an effective anti-
angiogenic target for gliomas: preclinical assessment in mouse GL261 and

Coutinho de Souza P, Mallory S, Smith N, Saunders D, Li X-N, McNall-Knapp
RY, Fung K-M, Towner RA. Inhibition of pediatric glioblastoma tumor
growth by the anti-cancer agent OKN-007 in orthotopic mouse xenografts.

Towner RA, Ihnat M, Saunders D, Bastian A, Smith N, Pavana RK, Gangjee. A
new anti-glioma therapy, AG119: Pre-clinical assessment in a mouse

Representative Awards:
Distinguished Scientist, Indian Society for Radiation Biology, 2015

93
Ralf Janknecht, PhD
Professor, Cell Biology, University of Oklahoma
Health Sciences Center
Oklahoma City, Oklahoma, United States

SESSION VII: CANCER TARGET DISCOVERY AND PATHWAY ANALYSIS

HISTONE DEMETHYLASE JMJD2A IN PROSTATE CANCER

Histone demethylase upregulation has been observed in human cancers, yet it is unknown if this is a bystander event or drives tumorigenesis. We discovered that the histone demethylase JMJD2A (also called KDM4A) is overexpressed in human prostate tumors that positively correlated with Gleason score and metastasis. Transgenic mice in which we mimicked this overexpression developed prostatic intraepithelial neoplasia, establishing JMJD2A as a novel initiator of prostate cancer development. Moreover, joint overexpression of JMJD2A and the ETS transcription factor ETV1, a newly identified JMJD2A binding protein, resulted into prostate carcinoma formation in mice haplodeficent for the Pten tumor suppressor gene, emphasizing the oncogenic nature of the JMJD2A-ETV1 complex. In addition, JMJD2A cooperated with ETV1 to increase expression of YAP1, a Hippo pathway component that itself was associated with prostate tumor aggressiveness. ETV1 facilitated the recruitment of JMJD2A to the YAP1 promoter leading to changes in histone lysine methylation. Further, YAP1 expression largely rescued the growth inhibitory effects of JMJD2A depletion in prostate cancer cells, indicating that YAP1 is a seminal downstream effector of JMJD2A. Taken together, these data reveal a previously unrecognized JMJD2A-ETV1-YAP1 axis whose inhibition may represent a novel treatment strategy for prostate and possibly other cancers.
BRIEF CURRICULUM VITAE

Education:
Ph.D. University of Bochum, Germany
Habilitation Hannover Medical School, Germany

Representative Careers:
Faculty Mayo Clinic, Rochester, MN, US
Faculty University of Oklahoma Health Sciences Center, Oklahoma City, OK, US

Interesting Research Areas:
Cancer Biology, Gene Transcription, Epigenetics

Selected Publications:


SESSION VII: CANCER TARGET DISCOVERY AND PATHWAY

ROLES AND MECHANISMS OF JAK1/JAK2 GENETIC DEFICIENCIES IN CANCER

Recognition of MHC class I neoantigens on tumor cells by cytolytic T lymphocytes (CTLs) is mandatory for the CTLs to kill tumor cells, which is involved in cancer immune surveillance and is required for immune checkpoint blockade therapy. JAK1/JAK2 mediate interferon (IFN)-γ-regulated MHC class I antigen presentation on tumor cells. By analyzing mutation data of >3,000 cases of human cancer, we previously found loss-of-function (LOF) JAK1 mutations in ~9% of endometrial cancer. The major mechanism of JAK1 LOF mutations in endometrial cancer is frameshift mutations in homopolymer regions of JAK1 gene. IFN-γ-induced antigen processing machinery (APM) protein expression and MHC class I antigen presentation in cancer cells that expressed wildtype JAK1 but not in cancer cells that had LOF JAK1 mutations. Moreover, IFN-γ inhibited proliferation of gynecologic cancer cells that had wildtype JAK1 but it had no effect in JAK1 mutated cells. IRF1 is a transcription factor downstream of JAK1/JAK2 in the IFN-γ-regulated antigen presentation pathway. Analysis of The Cancer Genome Atlas (TCGA) data showed that IRF1 expression correlated with the levels of granzyme A (GZMA) and perforin (PRF1) that are secreted by CTLs to destroy tumor cells. Furthermore, high IRF1 level is associated with better overall survival of endometrial cancer.

In comparison, genetic defects in the IFN-γ-IRF1 signaling axis genes occurred prevalently in the JAK2 gene (3.2%) and often through homozygous deletions among 1,016 cases of non-small cell lung cancer (NSCLC) in TCGA. Interestingly, JAK2 gene is co-localized with PD-L1 (CD274) and PD-L2 (PDCD1LG2) genes at chromosome 9p24.1. CD274 and PDD1LG2 copy number alterations (CNA) were always accompanied by JAK2 CNA, possibly as a mechanism to prevent tumor killing in the absence of the immune checkpoint inhibitors. Chromosome 9p21, 9p23, and 9p24 were found previously by others as frequently deleted regions in the NSCLC cancer genomes. Tumor suppressor genes CDKN2A/CDKN2B and PTPRD are located at chromosome 9p21.3 and 9p23-9p24.1, respectively, and were often used
to explain the frequent 9p deletion. JAK2 deletion in NSCLC may be due in part to deletions of PTPRD or CDKN2A/CDKN2B locus that accidently extended beyond these tumor suppressor genes. However, JAK2, PTPRD, and CDKN2A/CDKN2B deletions did not always occur in a contiguous manner. JAK2 deletion in some cases occurred without PTPRD or CDKN2A/CDKN2B deletion. These suggest that JAK2 deletion by itself offers an advantage to the tumor cells. Our findings suggest that JAK2 is a previously unrecognized tumor suppressor gene located at chromosome 9p24.1 and that JAK2 deficiency impairs MHC class I antigen presentation and allows tumors to evade CTL-mediated immune surveillance.
BRIEF CURRICULUM VITAE

Education:
B.S. Xiamen University, China
Graduate Student Shanghai Institute of Cell Biology, Chinese Academy of Sciences
Ph.D. University of Kansas Medical Center

Representative Careers:
Research Asst. Professor University of Virginia, Charlottesville, VA, US
Assistant Professor H. Lee Moffitt Cancer Center, Tampa, FL, US
Associate Professor H. Lee Moffitt Cancer Center, Tampa, FL, US
Sr. Member and Prof. H. Lee Moffitt Cancer Center, Tampa, FL, US
Professor Stephenson Cancer Center, Oklahoma City, OK, US

Interesting Research Areas:
Protein kinases and phosphatases in oncogenesis, oncogenes and tumor suppressor genes, cancer genomics, drug sensitivity and resistance mechanisms, discovery and development anticancer drugs, animal models

Selected Publications:


Representative Awards:
Elkin Lecture, Emory University, 2009

Oklahoma TSET Research Scholar, 2015
SESSION VII: CANCER TARGET DISCOVERY AND PATHWAY ANALYSIS

A SYSTEMS BIOLOGY APPLICATION IN CANCER: PATHOME-WEB

To analyze publically available mega-datasets, web-interfaced network analysis tools, with reasonable computation times, remain limited. Here, we implemented our established network biology algorithm to a web server, “PATHOME-web”, to provide simple, statistically relevant subnetwork extraction from highly complex Regarding performance, PATHOME-web aligned comparatively close with a “gold standard” cancer signaling reference set and exceeded other gene set analysis tools. Utility and caveat of our tool enable users to statistically identify enriched biological entities (within the subnetworks) which can be effectively targeted. We show PATHOME-web’s unique chemoinformatics feature successfully identified an oncoprotein, EPHA3, as a target for the anti-cancer drug imatinib. Through experiment of a drug/target interaction by surface plasmon resonance (including the low dissociation constant), we validated EPHA3-imatinib binding. The uniqueness of our PATHOME-web (http://statgene.snu.ac.kr/software/pathome) i) provides a web-based, simple and accurate tool for delineating highly complex biological networks, ii) provides a valuable asset for users’ own data sets as well as publicly available data sets to identify target-binding therapeutics, and iii) provides a solution of simple visual output of complex biological subnetworks. In conclusion, we provide much needed web-based system for biological researchers.
BRIEF CURRICULUM VITAE

Education:
B.S. Seoul National University, Seoul, KR
M.S. Seoul National University, Seoul, KR
Ph.D. University of Michigan, MI, USA

Representative Careers:
Professor, Chair Seoul National University, Seoul, KR
Director National Creative Research Laboratory of
Bioinformatics and Biostatistics, Seoul National
University, Seoul, KR
Visiting Professor University of Washington, USA
Head Interdisciplinary Program in Bioinformatics,
Seoul National University, Seoul, KR

Interesting Research Areas:
Statistical Genetics, Bioinformatics, Microarray Data Analysis, NGS data
analysis

Selected Publications:
Wang LH, Kim SH, Lee JH, Choi YL, Kim YC, Park TS, HongYC, Wu CF and,
Shin YK (2007) Inactivation of SMAD4 Tumor Suppressor Gene During Gas-
tric Carcinoma Progression. Clin Cancer Res, 13(1), 102-110

Lee JH, Kim SH, Wang LH, Choi YL, Kim YC, Kim JH, Park TS, Hong YC and,
Shin YK (2007) Clinical significance of CD99 downregulation in gastric ade-
nocarcinoma, Clin Cancer Res, 13(9), 2584-91

Cho YS, Go MJ, Kim YJ, Park T et al. (2009 ) A large-scale genome-wide asso-
ciation study of Asian populations uncovers genetic factors influencing
eight quantitative traits, Nature Genetics, 41(5);, 527-34.

Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki
M, Park T et al. (2010) Biological, clinical and population relevance of 95

Kim YJ, Go MJ, Hu C, Hong CB, Kim YK, Park T et al. (2011) Large-scale ge-
nome-wide association studies in East Asians identify new genetic loci
influencing metabolic traits. Nature Genetics, 43, 990-5
Characterization of a Natural Product that Effectively Suppresses Myeloproliferative Neoplasm Phenotypes in Mice
Joe Zhao, PhD

Role of HDAC-7 in RD3-Loss Dependent Evolution of MYCN-Non-Amplified Neuroblastoma
Natarajan Aravindan, PhD

Targeting Tumor Stem Cell Marker Doublecortin-Like Kinase in Cancers
Naushad Ali, PhD
SESSION VIII: TARGET DISCOVERY AND VALIDATION

CHARACTERIZATION OF A NATURAL PRODUCT THAT EFFECTIVELY SUPPRESSES MYELOPROLIFERATIVE NEOPLASM PHENOTYPES IN MICE

Myeloproliferative neoplasms (MPNs) represent a group of hematological diseases characterized by elevated levels red blood cells, platelets, and/or white blood cells. A major molecular defect in MPNs is JAK2V617F, a gain-of-function mutant form of tyrosine kinase JAK2 that is found in the majority of MPN patients. In earlier studies, we generated transgenic mice by expressing JAK2V617F in hematopoietic cells. These mice develop MPN-like phenotypes in a transgene dose-dependent manner. In this study, we employed this animal MPN model to test the efficacy of homoharringtonine (HHT), a natural plant alkaloid. Treatment of JAK2V617F transgenic mice with a daily dose of 1 mg/kg HHT markedly reduced blood cell counts and the spleen size. HHT causes a preferential reduction of myeloid cells in JAK2V617F transgenic mice. HHT also effectively prevented development of myelofibrosis. With a JAK2V617F bone marrow transplant mouse model, HHT showed a similar effect. Although it did not increase the ratio of JAK2V617F-negative cells to JAK2V617F-positive, it stopped further expansion of JAK2V617F-containing malignant cells in JAK2V617F bone marrow recipient mice. In vitro experiments with cultured primary hematopoietic cells and cell lines demonstrated that HHT potently inhibited formation of erythroid and myeloid colonies with an IC_{50} value of 1-3 nM. Although it does not show a preferential inhibition of JAK2V617F-containing cells, some cells are much more susceptible to HHT than others. The underlying mechanism is to be investigated further. Taken together, HHT is a promising candidate for development of therapeutic drugs to treat MPNs and perhaps other hematological malignancies.
SESSION VIII: TARGET DISCOVERY AND VALIDATION

ROLE OF HDAC-7 IN RD3-LOSS DEPENDENT EVOLUTION OF MYCN-NON-AMPLIFIED NEUROBLASTOMA

Outcomes for high-risk neuroblastoma (NB) patients remains poor, with <10% overall survival. Recently, we showed that the Retinal Degeneration Protein 3 (RD3) is lost in MYCN non-amplified progressive NB-CSCs that exhibited extreme plasticity, adaptive stemness and heightened metastatic state. However, RD3 re-expression affects the stemness maintenance and metastatic potential. Accordingly, this study recognized the contribution of HDACs in the evolution of progressive NB, and that targeting HDAC-7 with second generation HDAC inhibitor, JNJ-26481585 restores RD3 in NB-CSCs and promotes cell differentiation and death. The results identified a robust transcription and translation of HDAC-7 (of all class I-V HDACs) in CD133+CD34+ MYCN non-amplified NB-CSCs. JNJ-26481585 concentration-dependent HDAC inhibition experiments defined the selective HDAC-7 inhibition associated regulation of cell viability, cell death, clonal expansion, tumorosphere formation capacity and stemness maintenance. Selective HDAC-7 inhibition with JNJ-26481585 demonstrated a complete transcriptional/translational restoration of RD3. These results provide insight into upstream regulator of RD3 in MYCN non-amplified progressive NB. Further, this study identified that JNJ-26481585 could effectively restore RD3 (by targeting HDAC-7) and impede CSCs’ stemness maintenance and survival and, could thus serve as a potential deliverable in the treatment and cure of high-risk MYCN non-amplified NB.
BRIEF CURRICULUM VITAE

Education:
M.S.
M.Phil.
Ph.D.
C.C.A.

Representative Careers:
Associate Professor University of Oklahoma Health Sciences Center
Oklahoma City, OK, US

Interesting Research Areas:
Radiation Biology, Radiation Oncology, Cancer Biology, Experimental
Therapeutics, Oxidative Stress, Inflammation, Tumor progression and me-
tastasis, Space Radiation, Neuroblastoma, Pancreatic Cancer, bystander
effects

Selected Publications:
Ramraj S, Aravindan S, Somasundaram DB, Herman TS, Natarajan M and
Aravindan N. 2016. Serum-circulating miRNAs predict neuroblastoma pro-
gression in mouse model of high-risk metastatic disease Oncotarget. 2016
Feb 23. doi: 10.18632/oncotarget.7615. PMID: 26921195

Aravindan S, Ramraj S, Natarajan M, Herman TS, Somasundaram ST and
Aravindan N. 2015. Polyphenols from marine brown algae target radio-
therapy-coordinated EMT and stemness-maintenance in residual pancre-
-0173-3. PMID: 26395574.

Khan FH, Pandian V, Ramraj S, Azadi S, Aravindan S, Natarajan M, Herman
TS and Aravindan N. 2015. RD3 loss dictates high-risk aggressive neuro-
PMID: 26375249.

neuroblastoma cancer stem cells exhibit flexible plasticity and adaptive
s13287-015-0002-8. PMID: 25888913.

Aravindan S, Natarajan M, Ramraj SK, Pandian V, Khan FH, Herman TS, Ara-
vindan N. 2014. Abscopal effect of low-LET γ-radiation mediated through
Rel protein signal transduction in a mouse model of non-targeted radia-
SESSION VIII: TARGET DISCOVERY AND VALIDATION

TARGETING TUMOR STEM CELL MARKER DOUBLE-CORTIN-LIKE KINASE IN CANCERS

Introduction: Hepatocellular Carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide. Chronic viral hepatitis, non-alcoholic steatohepatitis (NASH), cirrhosis, and metabolic diseases such as obesity and diabetes are considered to be major risk factors for the development of HCC. Currently recommended sorafenib, a non-specific multi-kinase inhibitor, increases patient’s survival rate only by ~3 months. It has been speculated that HCC resistance to chemotherapeutic agents is mediated, in part, through tumor/cancer initiating stem-like cells (CSCs) that exhibit unlimited self-renewal and differentiation capacity. In addition to aberrant signaling pathways, multiple oncogenic and stem cell-related proteins have been proposed to control CSC proliferation and survival. Our recent studies suggest that a CSC marker, doublecortin-like kinase (DCLK1) is a promising target for the treatment of gastro-intestinal cancers including HCC.

Methods: Genome-wide mRNAs and miRNAs were analyzed by RNA-Seq method. The gain and loss of DCLK1 functions in hepatoma cells and primary human hepatocytes were investigated using DCLK1 overexpression vectors and specific anti-DCLK1 siRNAs/shRNAs respectively. The hepatoma xenograft tumor model and diethylnitrosamine (DEN)/carbon tetrachloride (CCL₄)-induced hepatic injury in immunocompetent C57BL/6 mice were used to evaluate the impacts of DCLK1 targeting on neoplastic development.

Results: HCC Patients (n= 369) overexpressing DCLK1 in liver showed approximately 3 times reduction in 5-year survival rate. Specific siRNA against DCLK1 inhibited hepatoma cell line-derived tumor growth. DEN/CCL₄-led hepatic injury extensively induced DCLK1 expression in the liver of C57BL/6 mice. Z-TMS exhibited hepatoprotective effects against DEN/CCL₄-induced injury by reducing DCLK1 expression and improving histological outcomes. Anti-tumor activities of Z-TMS (1 μM) appear to be due to its ability to induce G2/M cell cycle arrest, inhibit Akt phosphorylation,
and upregulate p21<sup>Cip1/Waf1</sup> in hepatoma cells. Z-TMS also inhibited proliferation of erlotinib-resistant lung adenocarcinoma cells (H1975) bearing the T790M EGFR mutation by promoting microtubule bundling, autophagy and nuclear fragmentation.

Conclusions: Z-TMS interferes with DCLK1 functions and putative DCLK1<sup>+</sup> CSC population in liver. It may also be effective against cancers of breast, pancreas, colon, and intestine where DCLK1 is involved in tumorigenesis.
BRIEF CURRICULUM VITAE

Education:
Ph.D.
M.Phil.

Representative Careers:
Senior Research Officer
Senior Scientist
Assistant Research Professor

Interesting Research Areas:
Liver cancer and treatment, tumor/cancer stem cells, hepatitis viruses, translation mechanism in normal and cancer cells, gastro-intestinal cancers

Selected Publications:


Representative Awards:
Post Graduate Merit Scholarship, AMU, 1984-1986
SRO Fellowship, Department of Biotechnology, Ministry of Science and Technology, Government of India, 1992-1994
First Prize, Best Presentation, Indian Association for Study of the Liver (INASL), Jaipur, India, 1993
American Liver Foundation Scholar Award, 1999-2002
POSTER SESSION

A Novel Extra-Nuclear Role of BMI1 in Regulating Mitochondrial Bioenergetics
Soumyajit Banerjee Mustafi, PhD

The Role of Short-Form Ron Kinase in Ovarian Cancer
Magdalena Bieniasz, PhD

Cystathionine Beta Synthase Regulates Lipid Metabolism in Ovarian Cancer
Prabir K. Chakraborty, PhD

Augmented Autophagy Induction Results in a Programmed Necrotic Cell Death in Ovarian Cancer
Anindya Dey, PhD

Apelin/APJ Pathway Promotes Ovarian Tumor Microenvironment and Cancer Progression
Samrita Dogra, PhD

miR-15a and miR-16 for Chemo-resistant Ovarian Cancer Therapy
Shailendra Kumar Dhar Dwivedi, PhD

Effects of Ovarian-Cancer Chemotherapy on the Cognitive Processing of Treatment-Relevant Verbal Directives
Blas Espinoza-Varas, PhD

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Xunhao Xiong, PhD

ELTD1 as a Novel Therapy Against Gliomas
Jadith Ziegler, PhD
A NOVEL EXTRA-NUCLEAR ROLE OF BMI1 IN REGULATING MITOCHONDRIAL BIOENERGETICS

Ink4a/Arf-dependent pathways. Recently many Ink/Arf-independent functions of BMI1 have also been described including a role in regulating mitochondrial function and ROS production. However, the mechanistic link by which BMI1, a predominantly nuclear protein can directly regulate mitochondrial functions remains elusive. We identified that a moderate but significant fraction of the total cellular BMI1 was localized in the mitochondrial inner membrane. Nuclear localization-defective BMI1 mutant also localized in the mitochondria and was able to completely rescue the impaired mitochondrial respiration and rate of ATP synthesis in BMI1 knockdown cells. This provides a direct proof that BMI1 can function independently of its nuclear role. Mechanistically we identified that within the mitochondria; BMI1 interacted with PNPass, a mitochondrial ribonuclease and prevented mitochondrial mRNA degradation. This finding of a novel extra-nuclear function of BMI1 will help us to reassess the role this proto-oncogene in stem cell differentiation, neuronal aging, and cancer.
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POSTER SESSION

THE ROLE OF SHORT-FORM RON KINASE IN OVARIAN CANCER

Background: Although 70–80% of women respond to standard platinum-based chemotherapy, a majority of patients will develop recurrent platinum-resistant disease. Novel treatment approaches directed against key oncogenic drivers and/or the use of novel drug combinations to prevent/overcome platinum resistance are promising opportunities to combat this disease. sfRon is an understudied, alternative isoform of the full-length Ron receptor tyrosine kinase, the latter of which has been investigated in cancer for several years. Unlike full-length Ron, the sfRon protein lacks the extracellular ligand-binding domain, but organizes into a constitutively active transmembrane protein. Our in vitro and in vivo studies indicate that sfRon expression is associated with the acquisition of aggressive and invasive ovarian tumor phenotype.

Results: Our studies using mice with a specific genetic deletion of sfRon (sfron) revealed the striking and unexpected discovery that lack of sfRon completely protected the mice from carcinogen-induced ovarian cancer. The frequency of ovarian tumors was 25% in wild-type mice vs. 0% in sfron mice (p<0.0011). Our further studies using ovarian tumors from patients revealed that sfRon is robustly expressed in several different subtypes of ovarian cancer, with no expression in healthy ovarian tissue. The in vitro experiments revealed that introduction of sfRon into OVCAR3 cells leads to activation of the PI3K pathway and PDK1 signaling cascade, which is associated with the acquisition of aggressive and invasive tumor phenotype through the induction of EMT, increased proliferation and migration of cells and decreased cell adhesion. The in vivo studies demonstrated the profound effect of sfRon expression on ovarian cancer growth and spreading to abdominal cavity. Moreover, our studies using a large cohort of high-grade serous ovarian cancer (HG-SOC) patients showed that Ron and/or sfRon are expressed in 86/126 (68%) of all cases. Statistical analysis revealed that significantly more patients in the cisplatin resistant group express high levels of Ron receptors, compared to patients in the cisplatin sensitive group, which suggest, that high levels of Ron and/or sfRon could contribute to cisplatin resistance.
Conclusion: Our data implicate sFRon in ovarian cancer pathogenesis, and indicate that Ron kinase inhibitors targeting both Ron and sFRon may not only suppress ovarian tumor progression, but also have potential to overcome resistance to chemotherapy. These data could have significant impact on future clinical trials for both Ron kinase inhibitors and platinum compounds, which has high potential to impact patients in the short-term.
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POSTER SESSION

CYSTATHIONINE BETA SYNTHASE REGULATES LIPID METABOLISM IN OVARIAN CANCER

Deregulated lipid metabolism is implicated in poor survival in various cancers including ovarian cancer (OC); however, current strategies targeted towards lipid metabolism in cancer cells lack specificity. Here, we establish an unique role of cystathionine beta-synthase (CBS), a sulphur amino acid metabolizing enzyme in driving deregulated lipid metabolism in OC. We examined the role of CBS in regulation of triglycerides, cholesterol and lipogenic enzymes via the lipogenic transcription factors SREBP1 and SREBP2. CBS silencing diminished the expression of number of key enzymes involved in lipid synthesis. Additionally, CBS abrogates lipid uptake in OC cells. Gene silencing of CBS or SREBPs negated cellular migration and invasion in OC, while ectopic expression of SREBPs can rescue phenotypic effects of CBS silencing by restoring cell migration and invasion. Mechanistically, CBS represses SREBP1 and SREBP2 at the transcription levels by modulating the transcription factor Sp1. We further established the roles of both CBS and SREBPs in regulating ovarian tumor growth in vivo. In orthotopic tumor models, CBS or SREBP silencing resulted in reduced tumor cells proliferation. Hence, cancer-selective disruption of the lipid metabolism pathway is possible by targeting CBS and, at least for OC, promises a profound benefit.
AUGMENTED AUTOPHAGY INDUCTION RESULTS IN A PROGRAMMED NECROTIC CELL DEATH IN OVARIAN CANCER

BMI1 (BMI1 proto-oncogene, polycomb ring finger), a member of the polycomb repressor Complex 1 (PRC1) that mediates gene silencing by regulating chromatin structure, is preferentially expressed in stem cells where it supports self-renewal and clonal growth. BMI1 is frequently upregulated and its expression correlates with poor prognosis in all major types of cancer including ovarian cancer. We report here that, genetic or pharmacologic inhibition of BMI1 significantly impacts clonal growth and induces autophagy in ovarian cancer (OvCa) cells through ATP depletion. While autophagy can promote survival or induce cell death, targeting BMI1 engages the PINK1/PARK2 dependent mitochondrial pathway and induces a novel mode of non-apoptotic, necroptosis mediated cell death. In OvCa, necroptosis is potentiated by activation of the RIPK1-RIPK3 complex that phosphorylates its downstream substrate, MLKL. Thus, we have discovered a novel molecular link between BMI1, clonal growth, autophagy and necroptosis (programmed necrosis) in ovarian cancer. Thus, in chemoresistant ovarian cancer where other major cell death pathways (eg. apoptotic) are frequently impaired, necroptotic cell death modalities provide an important alternate strategy that leverage overexpression of BMI1.
POSTER SESSION

APELIN/APJ PATHWAY PROMOTES OVARIAN TUMOR MICROENVIRONMENT AND CANCER PROGRESSION

Purpose: Ovarian cancer is associated with a unique biology presenting as a tumor consisting of histologically and molecularly diverse subtypes and metastasis confined mainly to the peritoneal surface and omentum, an organ primarily composed of adipocytes. The activation of angiogenesis and tumor cells’ ability to invade and metastasize are two hallmark of ovarian cancer progression and dependent on tumor microenvironment (TME). Thus, TME modulation by targeting new pathways could possibly lead to development of promising alternative therapeutics. Apelin and its receptor APJ are adipokines involved in glucose/energy metabolism and angiogenesis. The objective of this study is to assess the functional role of apelin/APJ pathway in ovarian cancer progression and associated benefits from antagonizing strategies as a novel TME-targeting therapy.

Methods: The effects of apelin/APJ signaling were studied on tumor cell proliferation and migration using human ovarian cancer cell lines (SKOV3, OVCAR-4, and TYKNU) and on angiogenic potential by tube formation using endothelial cells (HUVEC). Effects of overexpression and knockdown (via siRNA) of apelin or APJ on tumor cell proliferation and migration were evaluated. To study apelin/APJ downstream signaling a phosphoproteome array was performed. In vivo homing assay was performed to evaluate the role of apelin/APJ in attracting ovarian cancer cells to the omentum. Soluble apelin levels in ascites from ovarian cancer patients were measured using ELISA and APJ expression was measured in human tissue microarray of high grade serous ovarian tumors (n=126) using immunohistochemistry.

Results: Apelin (10-100 ng/mL) promoted mitogenesis (by 50-70%) and chemotaxis (by 150-200%) in both human ovarian cancer cells and endothelial cells. Apelin-induced proliferative and migratory effects were inhibited by a pharmacological APJ inhibitor (ML-221) in a dose dependent manner. APJ overexpression promoted angiogenic activity in HUVEC. It also increased ‘homing-in’ of the ovarian cancer cells to the omentum up to 4 folds as compared to control cells. APJ knockdown by siRNA reduced
tumor cell proliferation and migration. Apelin/APJ signaling induced phosphorylation of AKT, STAT, CREB, and AMPKα2 in SKOV-3 cells. Soluble apelin levels in ascites ranged from 6.3-4000 pg/ml. Immunohistochemistry of human ovarian tumor samples revealed APJ expression mainly in tumors and high APJ expression was significantly associated with reduced overall survival by 13 months.

**Conclusions:** Our results indicate that apelin/APJ pathway promotes ovarian cancer progression by stimulating angiogenesis, cell proliferation, migration, and metastatic potential and reveals the potential for development of a novel anti-TME therapy in ovarian cancer.
POSTER SESSION

miR-15a & miR-16 FOR CHEMO-RESISTANT OVARIAN CANCER THERAPY

Treatment of chemo-resistant ovarian cancer (OvCa) remains clinically challenging and there is a pressing need to identify novel therapeutic strategies. Recent reports have underscored the importance of microRNA (miR) regulatory networks in the pathogenesis of OvCa; regulating epithelial to mesenchymal transition (EMT) and chemo-resistance. Importantly the miR-15a/16–1 locus has been reported to be lost in 23.9% of ovarian and 24.7% of breast cancers. In addition, accumulating evidences implicate BMI1 as a clinically relevant therapeutic target based on its role in drug resistance and stem cell biology. We previously reported that miR-15a and miR-16 directly target BMI1; here we evaluated effects of miR-15a and miR-16 ectopic overexpression on OvCa progression and chemo-resistance.

Here we report that multiple mechanisms that promote OvCa progression and chemo-resistance could be inhibited by ectopic expression of miR-15a and miR-16. Significant correlations between low expression of miR-16, high expression of BMI1 and shortened overall survival (OS) were noted in high grade serous (HGS) OvCa patients upon analysis of The Cancer Genome Atlas (TCGA). Targeting BMI1, in vitro with either microRNA reduced clonal growth of OvCa cells. Additionally, epithelial to mesenchymal transition (EMT) as well as expression of the cisplatin transporter ATP7B were inhibited by miR-15a and miR-16 resulting in decreased degradation of the extra-cellular matrix and enhanced sensitization of OvCa cells to cisplatin. Nanoliposomal delivery of the miR-15a and miR-16 combination, in a pre-clinical chemo-resistant orthotopic mouse model of OvCa, demonstrated striking reduction in tumor burden compared to cisplatin alone. Thus, with the advent of miR replacement therapy some of which are in Phase 2 clinical trials, miR-15a and miR-16 represent novel ammunition in the anti-OvCa arsenal.
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United States

POSTER SESSION

EFFECTS OF OVARIAN-CANCER CHEMOTHERAPY ON THE COGNITIVE PROCESSING OF TREATMENT-RELEVANT VERBAL DIRECTIVES

Rationale. Adherence to cancer treatment plans has a major impact on outcomes and depends heavily on fluid communication between patients and health-care professionals. An important component of treatment adherence entails complying with verbal directives (e.g., “quit smoking!” or “go on a diet!”) issued by nurses and physicians to impede or instigate treatment-relevant behaviors; the directives emotional voice tone (VT), lenient or stern, signifies optional or mandatory adherence. Adherence could increase if the patient has keen sensitivity to the emotional VT; however, information or response conflict could decrease the sensitivity pre or post adjuvant, ovarian-cancer chemotherapy (CHT), and decrease adherence. The ability to identify the directives VT in information- or response-conflict conditions that place demands on executive functions (EF) could serve as in index of how compliant is a patient with verbal directives.

Method. Between surgery and CHT cycle 1, and between cycles 3 and 4 of ovarian-cancer patients (n=14), we assessed the effects of three EF demands on VT identification for impeding and instigating verbal directives. 1) Inhibitory control trials presented the cue word “left” or “right” followed by impeding directives in lenient or stern tone, mapped onto a left or right response; the cue and ear side could be congruent or in conflict with the correct response side. Trials presenting instigating directives (“go!”) mapped lenient or stern onto a right or left response. 2) Response-mapping switching conditions interleaved impeding and instigating directives within the same trial block, and required switching the mapping rule depending on the directive, impeding or instigating. 3) Working-memory conditions asked whether the directive presented on the most-recent trial was equal to or different from the one presented two trials prior to the most recent one.

Results. Compared to that of healthy young adults, the patients’ VT identification accuracy was significantly lower, both prior to and after
three CHT cycles. With impeding and instigating directives, the patients’ VT identification errors were small in conditions free of EF demands, but increased significantly when EF demands were imposed, being largest in condition 2. Relative to conditions without EF demands, identification latencies increased significantly only in condition 2. CHT effects did not reach significance, but individual differences were large.

Conclusions. Even prior to undergoing CHT, the ability to identify the VT of verbal directives is significantly diminished in cancer patients; as a result, they could have difficulty discerning between a mandatory and an optional verbal directive. This difficulty could decrease treatment adherence and lead to poor outcomes.
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POSTER SESSION

DIFFERENTIAL REQUIREMENT OF AMINO ACIDS ON CELL SURVIVAL OF OVARIAN CANCER CELL

Amino acids (AAs) were traditionally classified as nutritionally essential AAs (EAAs) or nonessential AAs (NEAAs) for animals and humans. Recent evidences have been demonstrated that each of specific AAs, such as glutamine, prolin, serine, leucine, or asparate, has an important role as a metabolic source for energy in cancer cells. However, it has not been clarified yet on differential requirement of each of AAs in cell survival of human cancer.

We examined the requirement of extracellular AA on cell survival by cultivation with media depleted individual AA in ovarian cancer (OVC) cell lines. OVC cells examined could be divided into two groups, EAA-required cells or -non-required cells. Interestingly, EAA-required cells also showed dependency on the requirement of at least one AA among 4 NEAAs, arginine, cystine, glutamine, and tyrosine, on cell survival. While NEAAs are endogenously synthesized by each synthetase enzyme, the expression level of glutamine synthetase (GS) was significantly down-regulated in OVC cells with the sensitivity to depletion of extracellular glutamine. These results suggest that GS-down-regulated OVC cells showed dependency on only extracellular glutamine, but not endogenous production of glutamine, on cell survival. Thus, our findings suggest that the requirement of AAs on cell survival may be cell-type dependent manner and provide information on the potential of AA requirement-based cancer therapy.
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POSTER SESSION

DIFFERENTIAL REQUIREMENT OF AMINO ACIDS ON CELL SURVIVAL OF OVARIAN CANCER CELL

Objectives: Hypoxia-inducible factor-1α (HIF-1α) is a well-known biomarker affecting tumor angiogenesis under decreased oxygen tension by chronic hypoxia. Moreover, apelin is also a factor stimulating angiogenesis in cardiac disease and some types of malignancies. However, there is no evidence of the role of apelin, especially compared with HIF-1α, in cervical cancer. Thus, we investigated their expressions affecting cervical carcinogenesis and prognosis.

Methods: We collected paraffin-embedded blocks including cervical tissues of 178 patients who received loop electrosurgical excision procedure or hysterectomy between 2006 and 2010. All tissues consisted of three groups: group 1 (normal, n=24; cervical intraepithelial neoplasia [CIN] 1, n=16; CIN 2, n=32); group 2 (CIN 3, n=20; cervical carcinoma in situ, n=16); group 3 (invasive squamous cell carcinoma, n=70). We made tissue microarray using them, and performed immunohistochemistry using mouse monoclonal antibody for HIF-1α (1:30) and rabbit polyclonal antibody (1:100) for apelin.

Results: higher expression of HIF-1α was observed more commonly in groups 2 (75%) and 3 (65.7%) than group 1 (37.5%), whereas higher expression of apelin was shown more frequently in groups 1 (20.8%) and 2 (22.2%) than group 3 (15.7%) (p<0.05). Moreover, patients with higher expression of HIF-1α showed poor progression-free survival than those with lower expression of HIF-1α (mean, 84.2 and 94.3 months; p<0.05). However, higher expression of apelin was related with improved PFS (mean, 92.3 and 79.4 months, p<0.05).

Conclusions: Although both HIF-1α and apelin were related with tumor angiogenesis, we found that they showed paradoxical expressions affecting cervical carcinogenesis and progression-free survival in patients with invasive squamous cell carcinoma.
POSTER SESSION

EXOSOME-MEDIATED TRANSFER OF METASTASIS-ASSOCIATED PROTEIN 1 (MTA1) IN BREAST CANCER

Background and Objective: Exosomes are small vesicles that mediate cell-to-cell communication and contribute to tumor metastasis by modifying the tumor microenvironment. Metastasis-associated protein 1 (MTA1) is a master co-regulatory molecule that is over-expressed in many cancers and correlates with tumor metastasis and progression. Our objective was to determine the role of MTA1 in exosome-mediated signaling in the tumor microenvironment of breast cancer.

Methods: An antibody array was used to identify MTA1 in exosomes. Exosome-MTA1 expression was confirmed by western blot. MTA1-tdTomato expression and transfer were monitored by fluorescent microscopy and flow cytometry. Luciferase reporter constructs were used to monitor expression regulation by exosome-MTA1 transfer. The CRISPR/Cas9 technique was used to knockout MTA1 in breast cancer cells. Endothelial cell tube-formation assays were performed to ascertain the role of exosome-MTA1 in angiogenesis.

Results: MTA1 protein expression was detected in exosomes derived from breast cancer cells, ductal fluids, and patient plasma samples. MTA1-tdTomato expression and exosome-mediated transfer of MTA1 was observed by fluorescent microscopy and flow cytometry. Importantly, we found that exosome-MTA1 regulates hypoxia signaling via exosome-transfer between breast cancer and endothelial cells. Furthermore, exosome-MTA1 modified the tube formation by endothelial cells.

Discussion and Conclusions: This is the first report showing that breast cancer exosomes contain MTA1 and that exosome-MTA1 alters signaling events in the tumor microenvironment. These observations suggest that exosome-mediated transfer of MTA1 contributes to breast cancer progression.
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POSTER SESSION

CD82 REGULATES MEMBRANE DOMAIN ORGANIZATION THROUGH LIPID ASSOCIATION AND GALECTIN CLUSTERING

Membrane protein CD82 inhibits metastasis formation in a variety of cancers, and expression of CD82 is frequently down regulated or lost in aggressive or late stage cancers. Though it has been shown that CD82 inhibits cell movement in vitro, the mechanism how CD82 inhibits cell movement is not clear.

Our study revealed that CD82 regulates cell membrane domains organization: CD82 promotes tetraspanin enriched microdomains (TEM) components such as tetraspanins, integrins and growth factor receptors localization to lipid raft in a cholesterol binding dependent manner. And this enhanced localization to lipid raft is corrected with increased endocytosis of proteins in the TEM. By site directed mutagenesis of the cholesterol binding motif, we made a cholesterol binding deficient mutant that can no longer enhance lipid raft localization of TEM proteins, and this mutant failed to inhibit cell movement in vitro, also this mutant does not promote endocytosis of TEM proteins. Though a variety of TEM proteins are down-regulated on the cell surface of CD82 over-expressing cells, it remains a question whether CD82 inhibits TEM components such as integrin and growth factor receptor activity on the cell surface in a cholesterol binding dependent manner. We will determine the activity of integrins and growth factor receptors on the cell surface later.

Conclusion: CD82 regulates cell membrane domain organization in a cholesterol binding dependent manner, and proper membrane domain organization is required for CD82 promoted endocytosis of TEM proteins.
POSTER SESSION


Objective: There is little information on the natural change in the prevalence and type distribution of HPV infection over time which could affect the efficacy of the current HPV vaccines. The aim of this study was to assess the temporal change in the prevalence of HPV infection in unvaccinated women with cervical intraepithelial neoplasia (CIN) between 1994–1998 and 2006–2010 in Korea.

Methods: HPV genotyping was performed on formalin-fixed paraffin-embedded cervical tissues diagnosed with CIN from the years 1994–1998 (204 cases) and 2006–2010 (257 cases) using the Goodgene HPV Genotyping Chip. Distribution of HPV types were compared between the two periods according to the severity of CIN.

Results: HPV was detected in 99.5% (203/204) and 97.7% (251/257) of the cases from 1994–1998 and 2006–2010, respectively (p = 0.140). The prevalence of specific HPV types was similar in CIN1 between the two periods, whereas the prevalence of HPV59, 53, 11, 40, and 70 in CIN2/3 was higher in 2006–2010 than in 1994–1998 (p < 0.05). The proportion of cases with HPV16 and/or HPV18 in CIN2/3, either alone or as coinfection with other types, was 52.9% in 1994–1998 and 52.8% in 2006–2010 (p = 0.993).

Conclusions: Although the prevalence of some HPV types (HPV59, 53, 11, 40, and 70) in CIN2/3 has increased in recent years, the prevalence of most of the HR HPV types in CIN has been stable in our study period. Our data suggest that the efficacy of current HPV vaccines might not change over time.
POSTER SESSION

ALDEHYDE DEHYDROGENASE INHIBITORS AS POTENTIAL ANTI-CHEMORESISTANCE DRUG FOR OVARIAN CANCERS

Aldehyde dehydrogenase is well known to play an important role including cancer chemoresistance. We tested the compound that selectively inhibit ALDH activity could restore chemosensitivity in cancer cells that express this isoenzyme.

ALDH activity was higher in platinum-resistant ovarian cancer cell lines (SKOV3-carbo R and CP70) than platinum sensitive ovarian cancer cells (SKOV3, A2780). In western blot analysis, the expression of ALDH3A1 and ALDH2 are significantly increased in platinum resistant cell lines than platinum sensitive cell lines. Then, we performed cell viability analysis to investigate the effect of ALDH inhibitor (ALDI-6) on platinum sensitivity in platinum resistant cells that showed highly expressed ALDH. Cell proliferation was determined by MTT assay. Treatment of SKOV3-carbo resistant cells and CP70 with carboplatin in the presence of different doses of ALDI-6 showed marked increase in carboplatin sensitivity. This study suggested that ALDH inhibitors can increase the platinum sensitivity in ovarian cancer.
POSTER SESSION

CARCINOSARCOMA OF THE OVARY: ANALYSIS OF A CASE SERIES

Objective: The ovarian carcinosarcoma is a very rare malignancy. The aim of this study was to determine the response rate, recurrence-free survival, and overall survival of patient with ovarian carcinosarcoma who were treated with various combination of chemotherapy.

Methods: Between 2000 and 2015, 15 patients with histologically confirmed ovarian carcinosarcoma were identified for analysis at Cheil general hospital. Data were extracted from medical records and pathology records.

Results: Patient age ranged from 29 to 73 years (mean: 51.4). Stage of each patient was as follows: 3, 2, 7, and 3 patients showed stage I, II, III, and IV, respectively. All patients underwent surgical resection and 11 were cytoreduced to less than 1cm. All patients received chemotherapy after surgery. Nine patients (60%) received carboplatin and paclitaxel, 2 (13%) received cisplatin and ifosfamide, 2 (13%) received cyclophosphamide, adriamycin and cisplatin, 1 (6%) received cisplatin and paclitaxel, 1 (6%) received paclitaxel, carboplatin and ifosfamide. The median disease-free survival was 28 months, median overall survival was 21.5 months. The one year overall survival rate was 40% and five year overall survival rate was 20%, respectively. Disease-free survival was better in optimal cytoreductive group (36.1 months vs. 14.3 months).

Conclusion: Ovarian carcinosarcoma is a poor prognostic disease. Optimal debulking surgery appears to be of prognostic significance.
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POSTER SESSION

PHENETHYL ISOTHIOCYANATE ACTIVATES ROS-MEDIATED CYTOPROTECTIVE AUTOPHagy AND APOPTOSIS IN HUMAN OVARIAN CANCER CELLS THROUGH ERK

Ovarian cancer is the deadliest malignancies in women due to the frequent acquisition of chemoresistance and higher recurrent rate. Developing novel effective therapeutic regiments is highly desired. In our study, Phenethyl Isothiocyanate (PEITC) displayed strong cytotoxicity and induced apoptosis on human ovarian cancer cells. Autophagy has bidirectional effects during anticancer treatments, cell survival or death, according to different cell type and chemoagent. We found that PEITC could induce autophagy in ovarian cancer cells characterized by the conversion of LC3B-I to LC3B-II and the formation of acidic vesicular organelles (AVOs), and pharmacological inhibition of autophagy, 3-methyladenine(3-MA) and chloroquine(CQ), led to obviously reduced cell proliferation, implying a protective role of autophagy. Interestingly, inhibition of autophagy have no significant effect on apoptosis. Further, increased intracellular ROS level can be produced by PEITC, we also found that application of ROS scavenger (NAC) could decrease cell death, inhibited autophagy and apoptosis simultaneously. In our study, we now show that PEITC treatment triggers protective autophagy and apoptosis via ROS-dependent manner in human ovarian cancer cells. Thus, combination of PEITC and pharmacological autophagy inhibitor may impose greater anti-cancer effect on human ovarian cancer cells.
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POSTER SESSION

ROLE OF DNPH1 IN BREAST TUMORIGENESIS

DNPH1 is an enzyme that cleaves the N-glycosidic bond of dNMP yielding deoxyribose 5’-monophosphate and a free base. Conceivably, free bases may increase dNTP levels through a salvage pathway and thereby stimulate cell proliferation, while deoxyribose 5’-monophosphate could stimulate angiogenesis. However, these predictions have remained untested and the physiological roles of DNPH1 unexplored. Here we found that DNPH1 is overexpressed in human breast cancer and it positively correlates with reduced survival and increased metastasis. To investigate DNPH1’s role in vivo, we generated DNPH1-knockout mice and crossed them with MMTV-HER2/Neu transgenic mice, a mouse model for breast cancer. Mice lacking DNPH1 showed delayed HER2/Neu-induced mammary gland tumor onset, reduced tumor multiplicity and less metastasis, highlighting the oncogenic character of DNPH1. Moreover, utilizing metabolomics, we identified potential mechanisms by which DNPH1 affects tumor cells. We conclude that DNPH1 is a valid new drug target in the treatment of breast cancer patients.
POSTER SESSION

STRUCTURE ACTIVITY RELATIONSHIP OF ANALOGS OF A CANCER-SELECTIVE SMALL MOLECULE, OK-1

OK-1 is a small molecule flexible heteroarotinoid (heterocycle and benzene ring connected by a flexible linker) that has shown promise in cancer treatment and prevention. Tissue culture studies revealed that OK-1 selectively causes apoptosis in cancer cells, while its effect on normal cells is limited to G1 cell cycle arrest. Preclinical studies determined that OK-1 has a large therapeutic index, with a toxic dose being 33 to 200 fold higher than the effective doses in vivo. Formulation of OK-1 capsules for clinical trials is hindered by the high hydrophobicity and poor bioavailability of this compound. Our objective is to develop improved analogs of OK-1 that have increased bioavailability and greater affinity for the OK-1 target protein mortalin (HSPA9). Mortalin is overexpressed in cancer cells and may be the key to understanding OK-1’s selectivity for cancer cells. Our hypothesis is that if we increase the affinity for mortalin, we will increase the selective apoptosis activity.

A series of structurally-related OK-1 analogs were designed, synthesized and tested for cytotoxicity against the A2780 ovarian cancer cell line and hFTSECs in order to identify important structural components responsible for the selective cytotoxicity. The results of these structure activity relationship (SAR) studies revealed that the two gem-dimethyls attached to the heterocycle and the nitro group on the benzene ring are important for OK-1’s cytotoxicity to ovarian cancer cells. The linker can be changed to a urea to improve solubility, however in some structures it was necessary to also change the sulfur in the heterocyclic to oxygen in order to maintain potency. Active analogs also had no-to-low toxicity to hFTSECs. Using SeeSAR (BioSolveIT GmbH) molecular modelling software, combined with our SAR results, we are designing analogs of OK-1 predicted to bind to mortalin with greater affinities and have lower IC_{50}'s for selective apoptosis. GastroPlus with ADMET Predictor Software (Simulations Plus, Inc) is being used by collaborators to predict absorption, distribution, metabolism, and excretion of the proposed compounds in order to select those with optimal pharmaceutical properties for synthesis and study. Binding and activity of the compounds will be determined biochemically and with tissue culture studies, respectively. As the research progresses, two other
OK-1-binding proteins, Hsc70 (HSPA8), which appears to mediate G1 cell cycle arrest, and BiP (HSPA5), which appears to mediate cell survival responses that counteract the apoptosis, will be incorporated into the modeling.

This strategy to develop a pipeline of OK-1 analogs is a critical component of our overall drug development program. As results from molecular, tissue culture, animal model and clinical studies of OK-1 reveal more about the mechanism and pharmaceutical properties, we will be able to draw upon this pipeline for compounds predicted to have improved properties for clinical application.
IDENTIFICATION AND CHARACTERIZATION OF DRUG RESISTANT KIF5B-RET MUTATIONS

Oncogenic fusions of RET protein tyrosine kinase (PTK) are associated with non-small cell lung cancer and parathyroid cancer and are being targeted for precision treatment. Previous clinical experience in PTK-targeted therapies showed that oncogenic PTKs usually acquired resistance to the PTK inhibitors (TKIs) after the initial responses. A major mechanism of TKI resistance is secondary mutations in the PTK domain that interfere with drug binding. Moreover, secondary drugs can be developed to prolong the therapeutic responses. We performed preclinical investigation to identify the spectrum and prevalence of KIF5B-RET mutations resistant to RET TKIs and to find secondary drugs to inhibit these KIF5B-RET mutants. Using random mutagenesis followed by drug-resistant selection in KIF5B-RET dependent cells, we identified 56 mutations of KIF5B-RET affecting 9 different RET amino acid residues in 87 cell lines that were resistant to cabozantinib, vandetanib, or lenvatinib. TKI resistance of these mutations were confirmed by re-expression of these KIF5B-RET mutants into BaF/3 cells. We then profiled these drug-resistant cell lines to identify secondary drugs that could effectively inhibit these mutants. Thus, we have identified a panel of novel drug-resistant RET mutations and found some of secondary drugs to inhibit these RET mutants.
POSTER SESSION

EARLY IN VIVO DETECTION OF BLADDER TUMOR IN MICE USING MOLECULAR MRI

Introduction: Early detection of bladder tumors would assist in initiating treatment options that could help with the treatment of bladder carcinoma. We used a bladder tumor-binding peptide (BTBP)\(^{1}\) coupled to a Gd-DOTA MRI contrast agent (BTBP-probe) to visualize early detection of bladder cancer in an orthotopic mouse model, and verified the detection of BTBP coupled to a Cy5 florescence probe.

Methods: Mice (8-10 weeks old; female; n=12; n=7 BTBP-probe and n=5 control) were anesthetized with isoflurane (2-3%) for bladder cancer cell (MB49-TR) injection into the bladder via an intravesical catheter, and for MRI scans. A contrast agent, BTBP (CSNRDARRC)-Gd-DOTA was used. A non-specific scrambled peptide (CASRRNRDC) was used as a control contrast agent. MRI experiments were done on a Bruker Biospec 7.0 Tesla/30 cm horizontal-bore imaging system. Multiple bladder region \(^1\)H\(_{\text{MR}}\) image slices were taken using a RARE multislice (repetition time (TR) 1.3 s, echo time (TE) 9 ms, 256x256 matrix, 4 steps per acquisition, 3x3 cm\(^2\) field of view, 0.75 mm slice thickness). Mouse bladders were imaged at 0 (pre-contrast) and at 3-4 hours post-contrast agent injection. Mice were injected intravenously with the BTBP-Gd-DOTA contrast agent (100µl/mouse; 50µmol/L). T\(_1\)-weighted images were obtained using a variable TR (repetition time) spin-echo sequence (TR, 200-1600 ms; TE, 15 ms; NA, 2). Pixel-by-pixel relaxation maps were reconstructed from a series of T\(_1\)-weighted images using a nonlinear two-parameter fitting procedure. The T\(_1\) value of a specified region-of-interest (ROI) was computed from all the pixels in the identified ROIs.

Results: MRI was used to detect the presence of the BTBP-probe via a substantial decrease in T\(_1\) relaxation, measured as T\(_1\) relaxation difference, within bladder tumor regions of mice administered the BTBP-probe (p<0.05) compared to the controls.

Discussion: We used mMRI to show for the first time non-invasive in vivo early detection of bladder tumors in a mouse model for bladder carcinoma. Using mMRI with a bladder tumor-binding peptide targeted probe
provides the advantage of \textit{in vivo} image resolution and spatial differentiation of regional events in early tumor detection.
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POSTER SESSION

PGC1α INDUCED BY REACTIVE OXYGEN SPECIES IN TUMOR SPHERES AND PATIENT-DERIVED ASCITES CELLS CONFERS CHEMORESISTANCE TO OVARIAN CANCER

Due to altered metabolism, malignant cells suffer from oxidative stress by a high level of reactive oxygen species (ROS). To relieve the stress, they activate antioxidant mechanisms, resulting in resistance to chemotherapeutic agents. Here, we found that PGC1α, a key molecule facilitating mitochondrial biogenesis and activating antioxidant enzymes, enhances chemoresistance in response to ROS generated under the sphere-forming culture condition of ovarian cancer cells. Spheres exhibited stem cell-like phenotypes, such as a high activity of aldehyde dehydrogenase (ALDH) and expression of stemness-related genes with the drug-resistant phenotype. Intriguingly, scavenging ROS using N-acetyl-cysteine diminished ALDH-positive population and inhibited proliferation of spheres. Production of ROS triggered expression of PGC1α, which in turn resulted in enriched mitochondrial biogenesis and reduced mitochondrial activity in spheres. The drug-resistant phenotype was observed in both spheres and PGC1α-overexpressed cells but not in parent cells. Knocking down of PGC1α by siRNA, however, sensitized spheres to cisplatin. Similarly, patient-derived malignant cells floating in ascites had ALDH-positive population and displayed the tendency of a positive correlation between chemoresistance and PGC1α. This is the first article suggesting that PGC1α induced by ROS mediates drug resistance, and provides a potential as a new therapeutic target to overcome chemoresistance in ovarian cancer.
POSTER SESSION

EFFECTS OF ANGIOGENIC FACTORS ON TRANSCRIPTION FACTOR E2F8 mRNA ABUNDANCE IN OVARIAN THECA CELLS

E2F transcription factor 8 (E2F8) is considered an atypical member of the E2F transcription factor family that is closely associated with the function of retinoblastoma family of tumor suppressors. However, recent studies indicated that E2F8 expression was upregulated in ovarian cancer and was shown to be a tumor promoter in hepatocellular carcinomas. The present study was conducted to determine if angiogenic factors affect E2F8 gene expression in normal ovarian tissue. Bovine ovaries were collected from non-pregnant heifers from a local slaughterhouse and theca cells were isolated from large (> 8 mm) follicles via blunt dissection and enzyme digestion after follicular fluid was aspirated and follicles bisected with a scalpel. Cells were plated in 24-well Falcon multiwell plates with 1 mL of serum-free medium per well and cultured in 10% fetal calf serum (FCS) for 48 h to 96 h. Medium was changed every 24 h. Cells were washed twice with serum-free medium, treatments were applied for 0 to 24 h (depending on experiment), and cells were collected for RNA extraction. In Experiment 1, treatments were: Control, 100 ng/mL of either fibroblast growth factor 2 (FGF2), FGF9, and/or vascular endothelial growth factor A (VEGFA) applied for 24 h. When compared to controls, FGF2, FGF9 and VEGFA alone increased (P < 0.05) E2F8 mRNA abundance by 2.2-, 2.6- and 4.4-fold, respectively. A combined treatment of VEGFA with FGF9 showed a further significant increase in E2F8 expression above either treatment alone. In Experiment 2, cells were cultured as in Experiment 1 except that after the first 48 h in 10% FCS, cells were serum starved for 24 h before treatments were applied. Cells were treated with 0 or 30 ng/mL of FGF9 and cellular RNA was collected at 0, 2, 4, 6, 12 and 24 h. A significant time by treatment effect was observed such that E2F8 mRNA abundance increased (P < 0.05) after 12 h and 24 h of FGF9 treatment, whereas E2F8 mRNA abundance did not change (P > 0.05) over time in Controls. E2F8 expression was greater (P < 0.05) at 12 h than at 24 h in FGF9-treated theca cells. At 0, 2, 4, and 6 h, Control and FGF9 treatments did not differ (P > 0.05). These results indicate that the angiogenic factors FGF9 and VEGFA induce theca cell E2F8 mRNA and that their effects are addi-
tive, implicating E2F8 in the induction of angiogenesis within ovarian follicles. Further research will be required to elucidate the various intra-cellular signaling pathways involved in these processes.
POSTER SESSION

TUMOR TARGETED ENZYME-PRODRUG THERAPY FOR METASTATIC OVARIAN CANCER

Ovarian cancer accounts for most deaths associated with gynaecological cancers and nearly 80% is detected after the tumor has spread to the peritoneal cavity. Once metastasis has occurred the cure rate using standard surgery followed by platinum- and taxane-based chemotherapy decreases significantly. Due to the lack of effectiveness of current therapies novel approaches need to be investigated and implemented. One such approach is an enzyme-prodrug treatment which utilizes a mutant cythathionine-γ-lyase (mCGL) fused with annexin V (AV) for tumor targeting. The mCGL enzyme converts selenomethionine prodrug into 200-1000X more toxic methylselenol that generates reactive oxygen species leading to apoptosis. There is also a strong bystander effect associated with the diffusion of the methylselenol to associated cancer cells for deeper tumor penetration. The AV binds to phosphatidylserine (PS) which has been shown to be normally internalized on healthy cells but externalized on tumor cells and vasculature. The proposed approach ensures tumor specific delivery of a highly cytotoxic agent with minimum side effects to the surrounding healthy tissue.

Mouse ovarian cancer cells (ID8) have been tested in vitro to validate this therapy. Initially, a binding study was conducted, which found the dissociation constant to be 18.53 ± 6.1 nM, indicating strong affinity binding. Fluorescence microscopy confirmed the binding the mCGL-AV fusion protein to the tumor cell. Previous studies have shown that mCGL-AV also binds non-confluent endothelial (HAEE-1) cells, which mimic endothelial cells in the tumor vasculature. This therapy can therefore cut off the blood supply to the tumor leading to minimized tumor growth as well diffuse through the leaky vasculature and directly attack the tumor cells for regression. In addition, the fusion protein injected into the peritoneum where the ovarian cancer has spread will bind directly to the tumor cells. A cytotoxicity study was conducted to confirm complete tumor cell death after only 2 days of enzyme-prodrug treatment. Similar results were seen with tumor vasculature representing cells. These results shed a promising light on the potential for this therapy in animal studies and beyond.
To demonstrate the effectiveness of this therapy for treating peritoneum metastatic ovarian cancer, tests in immune-competent mice are planned to determine the optimum dosage cycle which maximizes effectiveness while minimizing drug required. Currently, clinical therapies often utilize combinatorial approaches to attack the tumor from multiple pathways which will be implemented here to achieve the final objective of tumor erratication. The enzyme prodrug therapy will be combined with pairs of immunostimulants (selected from anti-PD-1, anti-CD73, and anti-OX40), along with carboplatin (alkylating agent to sustain the DNA damage caused and lead to apoptosis) and/or rapamycin (prevent hypoxic response survival).
POSTER SESSION

CD82/KAI1 INHIBITS COLLECTIVE CELL MIGRATION OF PROSTATE CANCER CELL THROUGH DOWN-REGULATED THE CELL SURFACE LEVEL OF INTEGRIN aVb3

Tetraspanin CD82/KAI1 is a tumor metastasis suppressor and traffics between plasma membrane and endosomes/lysosomes. CD82 contains a YXXF motif in its C-terminal cytoplasmic domain. We found that this motif is not required for CD82 endocytosis and trafficking to late endosomes, but it can prevent CD82 lysosomal targeting. Mutation of CD82 YXXF motif results in the loss of CD82-mediated inhibition of solitary and collective cell migration of prostate cancer cells. Mechanistically, our results demonstrated that CD82 can down-regulate the cell surface levels of integrins aVb3 and aVb5 and reduced the distribution of integrins aVb3 and aVb5 at the microprotrusion, but CD82 mutation has lost these functions. Moreover, low dose of integrin inhibitor cilengtide (specifically largely inhibit integrin aVb3) can inhibit collective cell migration, but not solitary cell migration. Meanwhile, high dose of cilengtide, which can specifically inhibit integrin aVb3 and aVb5 together, cannot further increase the inhibition level of collective cell migration. In conclusion, CD82 can inhibit collective cell migration of prostate cancer cell, and this inhibitory function maybe fulfill partially through down-regulates the cell surface level of integrin aVb3, but not integrin aVb5.
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POSTER SESSION

GOLD NANOPARTICLES DISRUPT THE COMMUNICATIONS BETWEEN TUMOR-ASSOCIATED FIBROBLASTS AND OVARIAN CANCER CELLS

Epithelial ovarian cancer (EOC) is one of the deadliest gynecological malignancies of women in the western world. Although the ovarian cancer cells are sensitive to primary chemotherapies, most patients ultimately recur and develop chemo-resistance leading to 5-year survival less than 30%. More and more evidence pointed the association between chemo-resistance and the tumor microenvironment (stroma) which is made up of endothelial cells, Tumor-associated fibroblasts (TAFs), adipocytes, mesenchymal cells, mesenchymal stem cells (MSCs), and cells from the immune and inflammatory systems. Here, we isolated and characterized several lines of TAFs from ovarian cancer patients and found that self-therapeutic gold nanoparticles (GNPs) treatment inhibited the fibroblast activity of the TAFs and down regulated the expression of several growth factors and stem cell marker genes. To understand the interactions among stromal, epithelial and endothelial, we set up co-culture systems and showed that GNPs inhibited proliferation, migration and invasion of ovarian cancer cells, and tubular formation of endothelial cells by altering the secretion of TAFs. Thus, gold nanoparticles could potentially be utilized as a tool to effectively explore communications in the tumor microenvironment, re-program it and inhibit ovarian tumor growth by its therapeutic function.
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POSTER SESSION

ELTD1 AS A NOVEL THERAPY AGAINST GLIOMAS

Gliomas consist of up to 80% of malignant brain tumors that are invasive and typically resistant to radiotherapy and chemotherapy. Finding biomarkers to high-grade gliomas can enable better diagnosis and therapeutic intervention for this disease. ELTD1 has been identified as a biomarker for high-grade human gliomas. Here, we report our findings in vivo using anti-ELTD1 (at two different concentrations), Bevacizumab, and IgG antibodies on human G55 xenograft glioma models. Using MRI, we investigate tumor growth, perfusion, tumor blood flow, and microvessel density changes in mice. Using molecular magnetic resonance imaging (mMRI), we measured differing levels of vascular endothelial growth factor receptor 2 (VEGFR2), which is an important angiogenic marker that is overexpressed in gliomas. The different VEGFR2 levels were assessed by the intravenous administration of an anti-VEGFR2 probe (anti-VEGFR2-albumin-Gd (gadolinium)-DTPA (diethylene triamine penta acetic acid)-biotin) into nude glioma-bearing mice and visualized with mMRI.

Mice were implanted with human G55 xenograft glioma cells, and when tumors reached 10-15 mm³, they were either left untreated, or administered anti-ELTD1 antibody (2 mg/kg every 2-3 days), Bevacizumab (2 mg/kg every 2-3 days), or IgG (1 mg/kg every 2-3 days). MRI experiments were performed to assess tumor growth and calculate tumor volumes. In order to assess angiogenesis, representative histology slides were obtained and stained for blood vessels using CD34 antibody and microvessel density (MVD) was then calculated. In addition, relative cerebral blood flow (rCBF) rates from MR perfusion imaging were obtained, as well as MR angiography to determine tumor blood volume from mice in each group. In vivo VEGFR2 levels were obtained using mMRI with a variable repetition time sequence to calculate T1 relaxation values and MR signal intensities.

Our results show a significant decrease in tumor volumes and increase in percent survival for mice treated with 2 mg/kg of ELTD1 antibody compared to untreated mice and IgG treated mice. Mice also had an increase in perfusion, decrease in tumor blood volume and decrease in MVD. Additionally, lower levels of VEGFR2, measured from minimal change in T1 val-
ues, for the anti-ELTD1 treated mice when administered with the anti-VEGFR2 probe, was detected (see Fig. 1). Anti-ELTD1 antibody therapy reduced tumor volumes, prolonged life, and overall decreased angiogenesis in our mouse model. Anti-ELTD1 therapy may be an ideal anti-angiogenic treatment for high-grade gliomas.