## Mitochondrial Regulation of Inflammasome Activation in Chronic Obstructive Pulmonary Disease

Min-Jong Kang, MD, PhD (1991)
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Chronic obstructive pulmonary disorder (COPD) is characterized by enhanced chronic airway and lung inflammatory responses to noxious particles or gases. It is a major unmet medical need worldwide and, in western society, it is strongly associated with cigarette smoke (CS) exposure. CS-induced inflammation is believed to be a key immune driver in the pathogenesis of COPD. Since the concept of inflammasome was first introduced nearly a decade ago, the inflammasome has been increasingly recognized as a central player in innate immune and inflammatory responses. However, the functional roles of inflammasome and the underlying mechanisms of the inflammasome activation in the context of COPD pathogenesis have not yet been adequately elucidated.

In this presentation, with the recent understanding of mitochondrial molecules involved in inflammasome activation, a previously unidentified novel pathway of NLRX1/MAVS-mediated inflammasomes signaling is discussed in the context of COPD pathogenesis. We believe that these evolving concepts offer new framework with which to better understand the pathogenesis of COPD. We hope that the discussion presented here will stimulate further research to explore the roles as well as the underlying mechanisms of mitochondria and their molecules in the COPD pathogenesis.

## Zika virus disease quick review

## Jeong Youn Hong MD, PhD (1991)

Zika virus disease (Zika) is a disease caused by Zika virus infection that is spread to people primarily through the bite of an infected Aedes species mosquito. Also Zika virus can be passed from a pregnant woman to her fetus during pregnancy and delivery and via sexual contacts (men to their partners).

The most common symptoms of Zika are fever, rash, joint pain, and conjunctivitis (red eyes). The illness is usually mild with symptoms lasting for several days to a week after being bitten by an infected mosquito. People usually don't get sick enough to go to the hospital, and they very rarely die of Zika. For this reason, many people might not realize they have been infected. Once a person has been infected, he or she is likely to be protected from future infections.

In 1952, the first human cases of Zika were detected and since then, outbreaks of Zika have been reported in tropical Africa, Southeast Asia, and the Pacific Islands. Zika outbreaks have probably occurred in many locations. Local transmission has been reported in many other countries and territories.

Brazil has experienced a significant outbreak of Zika virus since May 2015. In recent months, Brazilian officials reported an increase in the number of babies born with microcephaly. Although still not firmly confirmed, there is increasing evidence for the link between Zika and microcephaly as shown in the presence of Zika virus in the brains of babies born with microcephaly. In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed Zika virus infection in Brazil and on Feb 1, 2016, the World Health Organization (WHO) declared Zika virus a public health emergency of international concern (PHEIC).

Zika virus will likely continue to spread to new areas. The latest travel notices are Cape Verde, Caribbean (Aruba; Barbados; Bonaire; Curaao; Dominican Republic; Guadeloupe; Haiti; Jamaica; Martinique; the Commonwealth of Puerto Rico, a U.S. territory; Saint Martin; Saint Vincent and the Grenadines; Sint Maarten; Trinidad and Tobago; U.S. Virgin Islands), Mexico, Pacific Island (American Samoa, Marshall Islands, Samoa, Tonga), and South America (Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Suriname, Venezuela). No local mosquitoborne Zika virus disease cases have been reported in US, but there have been travel-associated cases.

## Development of personalized targeted strategies for lung squamous cell carcinoma

Youngtae Jeong, MD (2001)
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In contrast to lung adenocarcinoma (LUAD) for which several targeted therapies have been developed, personalized targeted therapies for lung squamous cell carcinoma (LSCC) have not been reported yet. We previously established genetically engineered mouse models for LSCC and LUAD by inactivating Trp53 and/or Keap1. Utilizing these mouse models, we demonstrated that activating mutations of the Keap1-Nrf2 antioxidant pathway contributes to the radioresistance of LSCC and are highly predictive of the local failure and cancer recurrence of the non-small cell lung cancer patients treated with radiation therapy. Thus, inhibition of this pathway could radiosensitize LSCCs with KEAP1/NRF2 mutations. I will discuss our ongoing efforts to develop personalized strategies to target LSCC.

## **Recent Advancements in Radiation Oncology**

### Seung Shin Hahn, MD

Professor of Radiation Oncology, Upstate Medical University

Within few years after the discovery of X-ray by Wilhelm Roentgen (1895) and Radioactive Isotope (Radium) by Marie Curie (1898), radiation was used for the treatment of various neoplasms. Soon, it was noted that the applications of radiation to the tumor bed often control the growth of neoplasms and occasionally eradicate them completely. However, the application of radiation was limited to the superficial malignancies only, skin cancers, due to limited penetrability of low energy X-rays produced in early 1900s. The only curative treatment achieved in deep seated malignancy was cervix cancer with the 1st cure by Radium insertion reported in 1913. As the energy of X-ray generated by more powerful X-ray tube increased, reports of cure for lymphomas as well as skin cancers and cervix cancers have increased. It was not until 1950s (synthetic radioactive source Cobalt 60 was readily available in the clinics) when the deep seated malignancies such as lung cancers, esophageal cancers and prostate cancers were frequently treated by radiotherapy. With the development of Linear Accelerators in 1960s, delivery of radiation to deep seated tumor became easier avoiding radiation skin reactions for most of malignancies inside of body.

Since late 1980s, the technology in Radiation Oncology has experienced a rapid progress owing to the improvement of imaging technology including availability of CT / MRI and more recently PET/CT as well as advancement of computer technology. With improvement of imaging and computer technology, more conformal radiotherapy was developed through 1990s and early 2000s such as 3 D conformal therapy and IMRT (Intensity Modulated Radiotherapy). Since 2000s, IGRT (Image Guided Radiotherapy) and SBRT (Stereotactic Body Radiotherapy) have been introduced to the clinic allowing precise delivery of high dose radiation to the target (tumor) avoiding any significant dose of radiation to nearby organs at risk. These techniques are now available at most of academic centers and some community cancer centers. Currently, 4 D radiotherapy is actively investigated to precisely deliver radiation to the target accounting for the organ movement during the delivery of daily radiotherapy; tumor tracking.

Finally, particle therapy including proton therapy which allows almost complete radiation dose drop behind the target is becoming more available as once prohibitively high cost (more than 100 million dollars) of facility comes down gradually. Currently, 12 facilities are in operation and another 12 facilities are under construction in the United States.

## Test-Retest Reproducibility of The Metabotropic Glutamate Receptor 5 Ligand [18F]FPEB with Bolus Plus Constant Infusion in Humans

## Eunkyung Park, MD, PhD

Former Associate Research Scientist Yale University PET Center

## Purpose

[18F]FPEB is a promising PET radioligand for the metabotropic glutamate receptor 5 (mGluR5), a potential target for the treatment of neuropsychiatric diseases. The purpose of this study was to evaluate the test-retest reproducibility of [18F]FPEB in the human brain.

#### Methods

Seven healthy male subjects were scanned twice, 3 - 11 weeks apart. Dynamic data were acquired using bolus plus infusion of  $162 \pm 32 \text{MBq}$  [18F]FPEB. Four methods were used to estimate volume of distribution (VT): equilibrium analysis (EQ) using arterial (EQA) or venous input data (EQV), multilinear analysis 1 (MA1), and a two-tissue compartment model (2T). Binding potential (BPND) was also estimated using cerebellar white matter (CWM) or gray matter (CGM) as the reference region using EQ, 2T and MA1. Absolute test-retest variability (aTRV) of VT and BPND was calculated for each method. Venous blood measurements (CV) were compared with arterial input (CA) to examine their usability in EQ analysis.

#### Results

Regional VT estimated by the four methods displayed a high degree of agreement (r2 ranging from 0.83 to 0.99 among the methods), although EQA and EQV overestimated VT by a mean of 9% and 7%, respectively, compared to 2T. Mean values of aTRV of VT were 11% by EQA, 12% by EQV, 14% by MA1 and 14% by 2T. Regional BPND also agreed well among the methods and mean aTRV of BPND was 8 - 12% (CWM) and 7 - 9% (CGM). Venous and arterial blood concentrations of [18F]FPEB were well matched during equilibrium (CV = 1.01 · CA, r2 = 0.95).

#### Conclusion

[18F]FPEB binding shows good TRV with minor differences among analysis methods. Venous blood can be used as an alternative for input function measurement instead of arterial blood in EQ analysis. Thus, [18F]FPEB is an excellent PET imaging tracer for mGluR5 in humans.

## 3d Printing: New Horizonsin Medical Imaging and Intervention

James Shin MD, MSc

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Since the expiration of key patents held by several of the biggest companies in the industry less than a decade ago, 3D printing technology has penetrated multiple economic sectors and quickly led to transforming ideas and attitudes towards rapid prototyping and small batch manufacturing. When combined with recent advances in medical imaging, these technologies work synergistically to provide new opportunities for anatomic modeling, education and training, preoperative planning, device customization, and therapeutic intervention. Publications in the medical literature containing the keyword "3D printing" have nearly doubled every year since 2012, illustrating the rapidity with which this manufacturing revolution has gained a foothold within the field of medicine.

Following a brief history of selected milestones in the recent history of 3D printing, this review will provide an overview of current clinical applications of this technology, examine safety, quality, regulatory, and financial issues governing their use in everyday practice; and identify key personnel and expertise necessary to drive development of this clinical service even further. Example cases both from the published literature and the author's unpublished clinical experience will be provided to illustrate these concepts and their potential to enhance individual patient care both in the present day and as imagined in the very near future, as innovations within manufacturing and medical imaging continue to advance their respective horizons.

## Golfing and Sports Medicine: Update

## Dai O. Moon, MD

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Although it may appear to be a low stress activity, golfing as a lifetime sports can cause a variety of injuries. These are often aggravated because golfers routinely play despite pain not only from golf injuries but also from their preexisting musculoskeletal problems.

The unique aspect of golfing is that the activity continues throughout golfer's lifetimes. In fact, players' interest often increase as they age and thus the frequency and intensity of golfing are quite high even among elderly.

Golf swing is a complex neuromuscular process that involves a highly coordinated effort between the upper and lower extremities.

Here we will discuss how to modify the basic components of golf swing for specific injuries and preexisting musculoskeletal problems. A wide range of conditions will be covered, including injuries to the lower back and upper and lower extremities. As for therapeutic measures, we will discuss non-operative as well as operative treatment strategies including arthroscopy. These measures together can help players for specific components of their games.

### **Poster Review for Clinical Studies**

## Seung Shin Hahn, MD

Professor of Radiation Oncology, Upstate Medical University

Four clinical posters will be reviewed. The titles and the authors of those studies are

- 1) The long term results of intracranial AVM treated by Proton Stereotactic Radiosurgery by Daniel Kim, MD
- 2) Curative Surgical Resection of Adrenocortical Carcinoma: Determining Long-Term Outcome Based on Conditional Disease-Free Probability by Yuhree Kim, MD
- 3) Pre-transplant HbA1c Predicts Post-transplant Diabetes Mellitus among Kidney Transplant Recipients by Jung-Im Shin, MD
- 4) Quality measures that focus on patient and family engagement in oncology by Kyungmin Song, MD

AVM is a congenital vascular malformation, usually asymptomatic, but carries a high mortality rate when ruptures. The options of treatment include surgical resection, embolization, radiosurgery or a combination of the above. If the AVM is located in an eloquent area, surgery is too risky. Thus, radiosurgery, embolization or a combination of the two becomes standard treatment. Dr. Daniel Kim reviewed 248 cases of AVM treated by Proton Radiosurgery showing 10 year obliteration rate of 91 % and post-treatment 5 year hemorrhage rate of 7%. These are excellent treatment results for AVMs achieving high obliteration rate with minimal morbidity. It will be interesting to compare these results with those of Photon Stereotactic Radiosurgery such as Gamma Knife Radiosurgery.

The evaluation of the efficacy in cancer treatments often requires analysis of Overall Survival (OS) or Disease Free Survival (DFR). However, the traditional DFS does not reflect changes in prognosis over time. Conditional DFS (CDFS) accounts for elapsed time since achieving remission and may provide more relevant prognostic information for patients and clinicians. CDFS is commonly used to predict the prognosis of ovarian cancer patients who achieved few years of DFS after initial treatment. Adrenocortical carcinoma (ACC) is a rare malignancy causing Cushing's syndrome and/or virilization (functional tumor) or mass effect in the abdomen (nonfunctional). The only known curative treatment is surgical resection and the role of adjuvant treatment is not well established. Dr. Yuhree Kim analyzed 192 patients with the diagnosis of ACC who underwent surgery with curative intent. She analyzed DFS and CDFS. She found that DFS estimates for patients with ACC improved dramatically over time, in particular among patients with initial assessment of worse prognoses. CDFS estimates appear to provide clinically more relevant information about changing likelihood of DFS over time in ACC.

It is well known that the risk of developing diabetes for the group of patients who undergo Kidney transplantation is high, up to one third according to various studies. This impacts on mean survival post transplantation (8.1 year for new onset diabetes after transplant Vs. 11 years for non-diabetic patients). Dr. Kyung-Im Shin analyzed 1,499 non-diabetic primary kidney transplant recipients with available HbA1c values in the United States Renal Data System (USRDS) from 2005 - 2011. Out of

1,499, a total of 395 recipients developed post-transplant diabetes mellitus (PTDM) over a median follow-up of 1.8 years. She found pre-transplant HbA1c below 5.4% was not significantly associated with risk of PTDM, whereas a 1% higher HbA1c above 5.4% was associated with an adjusted hazard ratio of 1.85. This study indicates that the increased risk for PTDM starts at significantly lower HbA1c levels than current thresholds for prediabetes (5.7 - 6.4 according to American Diabetes Association Criteria). This information should be useful for clinicians who take care of patients who are potential kidney transplantation candidates.

Quality measures have not attracted attention from either physicians or hospitals until 1990s. As the U.S. Government and American Society as a whole begin to raise questions whether Americans receive high quality of care they deserve considering the high cost of health care, alternative pay models emphasizing "paying for the performance" away from traditional model of "paying for the procedures" are being actively considered. At the same time, it became easier to collect health care data as more hospitals incorporate electronic medical record system. Hence, Affordable Care Act of 2010 included a provision to develop the Hospital Value-Based Purchasing program. Under this program, the payments that are used to pay hospitals are reduced by a specified percentage (1.5 % in 2015) and these funds are used to fund the additional incentive payments, which are based on a combination of clinical process (70%) and patient experience (30%) measures. These measurements include mortality outcome in acute myocardial infarction, pneumonia and heart failure. In the field of oncology, more emphasis has been placed on improving quality of life rather than improving cure rates alone. Thus, measuring quality of life in cancer survivors has become very important. So far, the majority of studies in oncology have reported quality of life measurements evaluated by physicians or patients. Dr. Song has evaluated quality measures which are expected to be influenced by family engagement such as patient education, care preference and care planning. She found none of these measures were related to specific cancers. She found that there is lack of measures that reflect patient and family engagement in oncology. Opportunities exist to improve care through measurement and evaluation of patient and family engagement in oncology.

#### Poster Review for Basic Science Studies

## Chang-Gyu Hahn, MD, PhD (1981)

Department of Psychiatry, University of Pennsylvania

A number of posters that are to be presented this year reflect a current trend that cuts across virtually all disciplines in medicine; namely leveraging molecular or mechanistic insights to enhance pathophysiologic understanding of the illness or guiding therapeutic strategy. Dr. Young Jae Nam's work reflects a remarkable new direction that could mark a new era in treatment of cardiac illnesses. A fundamental limitation that the field of cardiology faces is that injured cardiomyocytes cannot regenerate. This indeed has shaped most of conventional strategies of interventional as well as pharmacological treatment. Accumulated knowledge from the stem cell biology and recent successes in regenerative medicine no longer acknowledges post-mitotic cells as a static entity. Predicated on this, Dr. Nam and his colleagues have pioneered a strategy to generate cardiomyocytes from skin fibroblasts from patients by expressing cardiogenic transcriptional factors.

One of the most exciting recent developments of recent in oncology is the unprecedented successes that the immunotherapy has witnessed. An important strategy is to trigger immune responses in an autologous and antigen specific manner, which Dr. Jong Chul Park's research is based upon. Sipuleucel-T is an autologous cellular immunotherapy that triggers immune responses specific to antigens of metastatic prostate cancers. Dr. Park hypothesizes that therapeutic efficacy could be further augmented if antigenecity is further exposed by additional measures, such as radio chemicals. Dr. Park thus proposes a randomized phase 2 trial for a combined use of sipuleucel-T with or without radium-223, in which patients will be followed for clinical improvement as well as for biological parameters that may serve as markers for immune responses.

Therapeutic strategies constructed to modify disease processes often affect target tissues as well as other organs, in which the molecular strategies employed for therapeutic efficacy could precipitate side effects. Sunitinib and sorafenib are vascular endothelial growth factor receptor tyrosine kinase inhibitors approved for treatment of renal cell carcinoma. These agents inhibit trophic effects for vascular endothelium, thus it was not unexpected that they may cause cardiovascular side effects. Dr. Sekwon Jang has recently completed a study in which he examined the incidence of side effects, cardiovascular in particular, and reports that sunitinib or sorafenib use was indeed associated with an increased risk of stroke (HR = 3.36,95% CI 1.45-7.66).

Congenital adrenal hyperplasia (CAH) is one of the ten most common recessive diseases that can be screened by the 10 deleterious CYP21A2 variants with 95% detection sensitivity. Noting that the need for including these in diagnostic panel, Dr. Hyunseok Kang has developed a NGS based carrier screen, which will now permit a highly accurate screening platform.

Molecular and cell biological signatures can also be found in complex trait disorders such as depression. Dr. Chang-Gyu Hahn and his group have examined olfactory neuroepithelial cells, the only neural cells obtainable from living subjects without genomic reprogramming, derived from patients with depression and healthy subjects and found that glucocorticoid receptor translocation is strikingly altered in those cells of patients with depression. Such alterations in stress signaling are expected to impact ultrastructure and function of excitatory synapses. Indeed, Dr. Hahn's group found striking changes in glutamatergic and trophic signaling in synapses accompanied by proteomic dysregulations in postsyanptic microdomains that are critical for synaptic plasticity.

### **Personalized Preventive Care for Cancer**

## Daehee Kang, MD, PhD

Dean and Professor,
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Seoul, Korea

Extended life expectancy in this post-genomic era is inseparably linked with aging as well as chronic diseases. Among the many noncommunicable diseases, cancer is one of the leading causes of morbidity and mortality worldwide, and its incidence is expected to rise by about 70% over the next twenty years. Thus, in order to promote a healthier life, we need to unravel the problem at its causal origin by stressing the importance of preventive care. Preventing diseases before their occurrence will aid in minimizing public health consequences that are wide-ranging, from medical costs to health disparities.

In the area of personalized prevention, past and ongoing efforts range from preventive trials and risk prediction based on biomarkers and genes. For example, a Korean risk assessment model for breast cancer risk prediction has been recently developed using data from the Seoul Breast Cancer Study (SeBCS), proving to be an effective tool specific to Korean women. Furthermore, a mathematical model has been developed using Seoul Gastric Cancer Study (SeGCS) data to help predict the occurrence of gastric cancer at a personal level, enabling early detection and prevention of the disease.

The path to personalized preventive care is still a long way to go, with a need for more concrete, objective results to support this movement. Various cohort studies provide the foundation for new hypotheses and epidemiological validity for conducting preventive trials. As accumulation and facilitation of knowledge and data are occurring at a fast rate, individual cohorts need to come together to form a collaborative force to strengthen potential associations. The importance of collaboration is key to the successful implementation of personalized preventive care. These efforts will allow researchers to continue their pursuit of viable outcomes such as the development of national guidelines for prevention of various cancers in the near future.

## **Progress in Treatment and Prevention of Alzheimer's Disease**

### James Lah, MD, PhD

Associate Professor of Neurology, Emory University, School of Medicine.

Alzheimer's disease (AD) presents a global challenge that erodes the quality of life for tens of millions of people and threatens to bankrupt healthcare systems worldwide. Part of the strategy for dealing with this threat in the US is the National Alzheimer's Project Act (NAPA), which was signed into law in 2011. The overarching goal of the national plan calls for us to "prevent and effectively treat Alzheimer's disease by 2025". Is this goal achievable?

Alzheimer's has been studied for over a century, and we have attained a fairly good understanding of the underlying pathology and disease mechanisms. However, current treatments are of limited clinical benefit and fail to alter the underlying disease process. Progress in the development of AD biomarkers has improved diagnostic accuracy and provides opportunities for earlier disease detection. Work in this area has also fundamentally changed our view of AD, and has convincingly demonstrated that clinical symptoms of dementia represent the end result of 20-30 years of disease progression. Therapeutic strategies targeting key underlying pathogenic mechanisms, such as amyloid-beta peptide, are in late stages of clinical development and will likely emerge as the first class of drugs able to slow disease progression or delay onset. Continuing research is identifying additional disease mechanisms that can be targeted for novel therapeutics. With continued research investment and development of innovative treatment strategies, there is reason for optimism that subsequent generations will be spared the rayages of this frightening illness.

## **Treatment of Orthostatic Hypotesion**

## Dongin Sinn, MD

Fellow in Neurology, Beth Israel Deaconess Medical Center, Boston, MA

Orthostatic hypotension (OH) is defined as sustained pathological fall in blood pressure within 3 minutes after orthostatic stress such as tilt-table test or active standing. Neurogenic OH can be seen in  $\alpha$ -synucleinopathies in various stages and is associated with increased risk of morbidity and mortality. The non-pharmacologic therapies including avoiding offending drugs, adequate water/salt intake, physical coutermaneuvers, support garments, regular exercise and a rapid drinking of a bolus of free water should be tried as a first measure prior to pharmacologic treatments. Pharmacological agents commonly used to manage orthostatic hypotension include fludrocortisone, midodrine, pyridostigmine, and droxidopa. Only midodrine and droxidopa have received FDA approval for the treatment of orthostatic hypotension.

## **New Horizons in Medicine?- Personalized Medicine for Type 2 Diabetes**

## Young Min Cho, MD, PhD

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Department of Internal Medicine,
Seoul National University College of Medicine

Common chronic metabolic diseases such as type 2 diabetes mellitus, obesity, and dyslipidemia are the major health threat for people living in developed countries, which increases the risk of atherosclerotic cardiovascular disease. There are considerable differences in clinical manifestations of such diseases and treatment responses individually and ethnically. For example, incretin effect (amounts of insulin secretion in response to oral glucose relative to intravenous glucose) is universally decreased in Caucasian patients with type 2 diabetes compared to normal control but it is comparable in their Asian counterparts. Intriguingly, glucose lowering efficacy of incretin-based therapy is superior in Asians than in non-Asians. The major pathophysiologic defect in type 2 diabetes is insulin resistance for Caucasians and impaired pancreatic beta-cell function in Asians (especially in East Asians). Postprandial glucose excursions vary interpersonally according to the genetic background and gut microbiome. Therefore, there is no such "one-size-fits-all" dietary guideline to optimize post-meal glucose levels. In this lecture, I will discuss compelling needs for personalized medicine for metabolic disorders with a special emphasis on type 2 diabetes.

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## GLUT1-Dependent Glycolysis Regulates Age-Related Lung Fibrogenesis

## Soo Jung Cho, MD

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Aging is associated with metabolic diseases such as type 2 diabetes mellitus, cardiovascular disease, cancer and neurodegeneration (Ford et al., 2002). Aging contributes to common processes including metabolic dysfunction, DNA damage and reactive oxygen species (ROS) generation. While dysregulated glycolysis has been linked to cell growth and proliferation, the mechanisms by which aging and glycolysis contribute to fibrogenesis remain unclear. Here, we demonstrate that glucose transport 1 (GLUT1)-induced glycolysis provides an essential mechanism for age-dependent fibrogenesis of the lung. Moreover, we demonstrate that up-regulation of GLUT1 protein expression causes enhanced glycolysis leading to augmented fibrosis in lungs of aged mice when compared to younger animals. Downregulation of glycolysis by inhibition of GLUT1 attenuated the expression of  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), a key cytoskeletal component of activated fibroblasts. These results suggest that GLUT1-dependent glycolysis regulates age-related susceptibility to lung fibrogenesis.

## Crosstalk between EGFR and Notch Signaling Pathways in Menetrier's Disease

## Won Jae Huh, MD, PhD (2002)

Clinical Fellow in Gastrointestinal and Hepatic Pathology Vanderbilt University Medical Center, Nashville, TN, USA

Menetrier's disease, protein-losing hypertrophic gastropathy, is a rare acquired premalignant disorder characterized by giant gastric rugal folds, often restricted to the body and fundus of the stomach, decreased acid secretion, increased gastric mucus production, and hypoalbuminemia due to protein loss in the gastric mucosa. It affects middle-aged men more frequently than women. Clinical symptoms include nausea, vomiting, diarrhea, abdominal pain, weight loss, malnutrition, and peripheral edema secondary to hypoalbuminemia. The onset is insidious and the symptoms are progressive. Microscopically, it is characterized by massive foveolar hyperplasia, oxyntic gland atrophy, and repatterning of cell specification. No effective medical treatment has been available until recently so that patients with intractable disease and/or with a high risk of gastric cancer development undergo gastrectomy. Based on the observation that overexpression of the EGF receptor (EGFR) ligand TGF-α in the mouse stomach phenocopies Menetrier's disease and that TGF is overexpressed in the stomach of Menetrier's disease patients, we have proposed that Menetrier's disease is caused by EGFR activation secondary to TGF- $\alpha$  overexpression, inducing stem cells to be pushed down pit cell lineage at the expense of parietal and chief cell lineages. In a clinical trial with the EGFR inhibiting antibody cetuximab, we have shown that it is the first effective medical therapy for Menetrier's disease. All nine patients in the trial showed objective and subjective clinical improvement. Although one patient has had a long term remission, eight patients subsequently required gastrectomy, indicating that more effective medical treatments are needed for this debilitating disorder. We performed proteomics analysis from the stomach tissue of Menetrier's disease patients before and after cetuximab treatment and identified an EGFR inhibition signature consisting of nine proteins. One was the Notch ligand, Jagged 1. We tested whether Notch is activated in the stomach of TGF-α transgenic mice and found that Notch was indeed upregulated in the pit, isthmus, and neck compartments of the stomach of TGF- $\alpha$  transgenic mice compared to wild-type mice. Our hypothesis is that the phenotypes of Menetrier's disease caused by EGFR activation are mediated through Notch signaling.

## The Interplay between Mobility, Cognition, and Emotion in Aging

## Mooyeon Oh-Park, MD

Professor, Rutgers New Jersey Medical School,
Dept of Physical Medicine & Rehabilitation,
Director of Geriatric Rehabilitation,
Kessler Institute for Rehabilitation, West Orange, New Jersey

Mobility disability (also known as "difficulty in moving around") in older individuals have become major public health issues with the rapid aging population worldwide. In US, approximately 40% of community dwelling older individuals over age 65 have gait impairment which is the main risk factor for falls. In the past, the emphasis of intervention for mobility disability is heavily on the physical domain. However, recent studies have shown a close association between cognitive, emotional, and physical functions that may increase risk of disability and falls in older patients. Therefore, it is essential for the healthcare providers to understand this relationship and accurately assess the mobility in various clinical settings to plan and guide interventions.

We and others found that gait velocity is a highly reliable measure predicting functional decline, falls, hospitalization, and death in older individuals. We reported that gait velocity of  $\geq 1 \text{m/sec}$  serves as a valid cutoff for preserved mobility in community dwelling older adults. Performance of gait is affected not only by muscle power or joint function, but also by emotional distress (e.g. fear of falling, social isolation) and simultaneous performance of cognitive tasking. The taxing effect of cognitive tasks on mobility also predicts falls indicating a significant cognitive contribution in mobility. This presentation intends to discuss the epidemiology of mobility disability in US, practical assessments of mobility (e.g. gait speed) in older individuals to identify high risk patients, elucidating the relationship among physical, emotional, and cognitive domains of mobility, and evidence-based interventions for mobility.

## Dysregulation of Stress Signaling and Synaptic Proteome in depression

## Chang-Gyu Hahn, MD, PhD

Department of Psychiatry, University of Pennsylvania

Central to the pathophysiology of major depressive disorder (MDD) is stress-mediated modulation of neurobiological substrates for the illness, namely cortico-limbic circuit abnormalities. Glucocorticoid receptor (GR) chaperone interactions pivot the impact of stress mediated neurobiological changes. However, it is presently unknown how these molecular events are altered in neural cells of individuals with MDD. We examined GR chaperone interactions in olfactory neuroepithelial (olfactory NE) cells, the only neural cells obtainable from living individuals without genomic reprogramming. In 15 matched pairs of MDD subjects and healthy controls, nuclear translocation of GR (GR translocation), a key step for GR signaling, was strikingly reduced in the MDD group compared to the control. In addition, we found that protein interactions of GRs with FKBP51, which decreases GR translocation and thus serves as a negative regulator of GC signaling. were increased in the MDD group. Our results therefore provide the first direct evidence for dysregulated GR translocation in neural cells of MDD subjects and point to altered protein interactions between FKBP-51 and GR complexes as an underlying mechanism. Such alterations in GC signaling may dysregulate ultrastructural and functional integrity of synapses, which may in turn precipitate cortico-limbic abnormalities. The postsynaptic density (PSD) is the hub of synaptic transmission, wherein hundreds of proteins and multitudes of signaling pathways reside and interact. To test the integrity of the PSD signaling in depression, we chose to examine a female cynomolgus macaque model that strikingly recapitulates behavioral, metabolic and brain morphometric phenotypes of depression. We assessed ligand induced postsynaptic signaling of BDNF-TrkB and NMDAR pathways and delineated protein composition of the PSD by liquid chromatography-selected reaction monitoring mass spectrometry (LC-SRM/MS). Behaviorally depressed monkeys exhibited decreased postsynaptic NMDAR signaling, which may contribute to spine deficits in depression. Post-receptor TrkB activity, however, was increased, suggesting a possible compensatory mechanism for decreased BDNF signaling as widely postulated in depression. LC-SRM/MS revealed microdomain-specific alterations in individual proteins in behaviorally depressed monkeys, including those critical for synaptic adhesion, glutamatergic signaling and vesicular transport. Our results together implicate alterations in postsynaptic NMDA and TrkB receptor functions, and subtle but coordinated dysregulation of vesicular transport and signaling proteins in the PSD as the molecular underpinnings for synaptic dysregulations associated with behavioral and volumetric phenotypes of female depression.

## The long term results of intracranial AVM treated by Proton Stereotactic Radiosurgery

## **Daniel Kim, MD, MBA**Advisor to the Mayor of Boston

## Purpose

The objective of this study was to evaluate the obliteration rate and adverse effects of single fraction proton beam stereotactic radiosurgery (PSRS) in patients with cerebral arteriovenous malformations (AVMs)

#### Methods and Materials

From 1991-2010, 248 consecutive patients with 254 cerebral AVMs received single fraction PSRS at Massachusetts General Hospital. Median AVM nidus volume was 3.5 cc (range, 0.1-28.1 cc), 23% of AVMs were in deep/critical locations (basal ganglia, thalamus, or brainstem), and the most common prescription dose was 15 Gray (relative biological effectiveness) (Gy(RBE)). Univariable and multivariable analyses were performed to assess factors associated with obliteration and hemorrhage.

#### Results

At a median follow-up of 35 months (range, 6-198 months), 64.6% of AVMs were obliterated. Median time to total obliteration was 31 months (range, 6-127 months) and the 5- and 10-year cumulative incidence of total obliteration was 70% and 91%, respectively. On univariate analysis, smaller target volume (hazard ratio [HR] 0.78, 95% CI 0.86-0.93, p<0.0001), smaller treatment volume (HR 0.93, 95% CI 0.90-0.96, p<0.0001), higher prescription dose (HR 1.16, 95% CI 1.07-1.26, p=0.001), and higher maximum dose (HR 1.14, 95% CI 1.05-1.23, p=0.002) were associated with total obliteration. Deep/critical location was also associated with decreased likelihood of obliteration (HR 0.68, 95% CI 0.47-0.98, p=0.04). On MVA, critical location (adjusted HR [AHR] 0.42, 95% CI 0.27-0.65, p<0.001) and smaller target volume (AHR 0.81, 95% CI 0.68-0.97, p=0.02) remained associated with total obliteration. Post-treatment hemorrhage occurred in 13 cases (5-year cumulative incidence of 7%), all among patients with less than total obliteration, and 3 of these events were fatal. The most common complication was seizure, controlled with medications, both acutely (8%) and long-term (9.1%).

#### Conclusions

This study represents the largest modern series of PSRS for cerebral AVMs. PSRS can achieve a high obliteration rate with minimal morbidity. Post-treatment hemorrhage remains a potentially fatal risk among patients who have not yet responded to treatment.

## Reprogramming Specific Cardiac Cell Fates: New Paradigm for Heart Repair

## Young-Jae Nam MD, PhD (1994)

Assistant Professor
Division of Cardiovascular Medicine, Department of Medicine,
Department of Cell and Developmental Biology, Vanderbilt Center for Stem Cell Biology,
Vanderbilt University School of Medicine

Heart disease leading to myocardial infarction, heart failure and arrhythmia is the number one cause of morbidity and mortality worldwide. Despite remarkable advances in cardiovascular medicine, a fundamental but unsolved problem is the myocardium's inability to repair itself by regeneration of cardiomyocytes. Once the heart loses cardiomyocytes upon injury or aging, this loss is irreversible and replaced by fibrotic scar. This leads to loss of pump function and provides a substrate for lifethreatening arrhythmias which are a common mode of death in heart failure. Thus, the ability to make new cardiomyocytes has been an imperative scientific focus. Toward this goal, an exciting progress has been made in recent years toward stem cell based cell therapy and transplantation of embryonic stem cell derived cardiomyocytes. As an alternative approach, we and others showed that forced expression of core cardiac transcription factors in non-myocytes after heart injury induces cardiomyocyte-like cells in vivo. Although all these innovative approaches hold great potential, realistic application of these strategies to treat diverse cardiovascular diseases must overcome the issue of multiple cardiomyocyte subtypes (i.e. atrial, ventricular, and nodal) that play mutually exclusive roles in cardiovascular physiology to coordinate cardiac contraction and effective blood circulation. Inability to direct subtype specification of newly generated cardiomyocytes has been a major barrier to clinical application. Based on the mechanistic insights we have learned from our preliminary studies, we propose to develop an entirely new heart repair strategy which can specifically target an affected cardiac cell type. These experimental approaches will provide important new insights into the mechanisms of cardiac cell fate specifications and a unique opportunity to develop entirely new treatment paradigms for a wide spectrum of cardiovascular diseases. The scientific and clinical impact of our discoveries will extend beyond cardiovascular biology and medicine. The knowledge we obtain from this project, in principle, can be applied to repair other tissues by the conversion of the most abundant cell type to a clinically useful cell type and to even more specific subset if the rapeutically necessary.

# A Randomized Phase 2 Study of Sipuleucel-t with or without Radium-223 in Men with Asymptomatic or Minimally Symptomatic Bone-metastatic Castrate-resistant Prostate Cancer

## Jong Chul Park, MD (1999)

A. Oliver Sartor, Rana Sullivan, Serina King, Emmanuel S. Antonarakis

## Background:

Sipuleucel-T is an autologous cellular immunotherapy indicated for men with asymptomatic/minimally symptomatic metastatic castrate-resistant prostate cancer (mCRPC). Recent analysis of immune responses in men treated with sipuleucel-T showed that antigen-specific immune responses to sipuleucel-T may be associated with survival, confirming the immune-based mechanism of action and suggesting the possibility that producing a stronger immune response may translate into the better clinical outcomes. Radiopharmaceutical agents have been shown to enhance immune modulation through a variety of mechanisms including enhanced display of tumor-associated antigens. Based on the immunomodulatory effects of radiopharmaceutical drugs, we hypothesized that combined use of radium-223 and sipuleucel-T may enhance the sipuleucel-T-induced immune response, translating into better clinical outcomes.

#### Methods:

This is a randomized phase-2 study comparing antigen-specific immune responses to sipuleucel-T versus sipuleucel-T plus radium-223 in mCRPC patients with bone metastases and no visceral disease. Patients will be randomly assigned (1:1) to receive sipuleucel-T plus radium-223 (Arm 1) or sipuleucel-T alone (Arm 2); men in Arm 2 will receive 3 infusions of sipuleucel-T alone, while men in Arm 1 will receive 6 infusions of radium-223 plus 3 infusions of sipuleucel-T starting after the second dose of radium-223. The primary objective is to determine whether addition of radium-223 to sipuleucel-T enhances immune response to sipuleucel-T, as measured by peripheral PA2024-specific T-cell proliferation (stimulation index: SI) using a tritiated thymidine incorporation assay at 6 wks after the first sipuleucel-T infusion in each arm. With 15 men per arm, there is 80% power to detect a 3.6-fold increase in mean SI between the two treatment arms. PSA responses and radiographic responses (in men with measurable disease) will also be assessed. Incidence and severity of adverse events will be graded according to CTCAE v4.0. Various immune parameters, both humoral and T-cell antigen-specific responses will be analyzed at multiple time points during the treatment period, and an exploratory assessment of antigen spread will also be performed.

## An NGS-based carrier screen for Congenital Adrenal Hyperplasia with 95% detection rate

Hyunseok Kang, MD (2000) Medical Director, Counsyl, Inc

Two lines of arguments support including congenital adrenal hyperplasia (CAH) on expanded carrier screen (ECS) panels: (1) with a carrier rate of 1 in 60, it is one of the ten most common recessive diseases, and (2) screening only ten variants in CYP21A2 can yield a 95% detection rate. However, CAH is absent from most ECS panels or at best detected at a rate <20% because 99% homology between the coding sequences of CYP21A2 and its pseudogene CYP21A1P complicates variant identification. Indeed, eight of the ten common variants are pseudogene-derived; thus, expensive, low-throughput assays (e.g., long-range PCR + Sanger sequencing) are typically used to assess CAH carrier status. Here we report the development of an NGS-based carrier screen for CAH that detects all ten common deleterious variants in CYP21A2. The screen has a detection rate of 95% and has been so far applied to more than 100,000 patient samples.

## Cardiovascular toxicity following anti-angiogenic therapy in persons over age 65 with advanced renal cell carcinoma

Sekwon Jang1, Chaoyi Zheng2, Huei-Ting Tsai2, Alex Z Fu2, Ana Barac3, Michael B Atkins2, Andrew N Freedman4, Lori Minasian4, Arnold L Potosky2

Inova Comprehensive Cancer and Research Institute, Fairfax, VA
 Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC
 MedStar Washington Hospital Center, Washington, DC
 National Cancer Institute, Bethesda, MD

### Backgrounds

Sunitinib and sorafenib are oral vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) approved for treatment of renal cell carcinoma (RCC) in 2005-6. Cardiovascular adverse events have been reported, although the overall risk on elderly patients treated in general practice remains unclear.

#### Methods

Using the US surveillance, epidemiology, and end results (SEER)-Medicare database, we conducted an observational cohort study on the cardiovascular effects of sunitinib or sorafenib in RCC patients diagnosed from 2000-2009 who were 66 years and older and were followed through 2010. Use of sunitinib and sorafenib was identified from Part D claims using National Drug Codes (NDC). We examined cardiovascular adverse events including congestive heart failure and cardiomyopathy (CHF/CM), acute myocardial infarction (AMI), stroke, and cardiovascular-related deaths. We performed Cox-proportional hazard model to estimate the risk of cardiovascular events associated with sunitinib or sorafenib.

#### Results

A total of 171 out of 670 patients who received either sunitinib or sorafenib had cardiovascular events. The incidence rates for CHF/CM, AMI, stroke, and cardiovascular death in those who received one of the two drugs were 0.87, 0.14, 0.14, and 0.05 per 1000 person-days, respectively. After adjustment for age, sex, comorbidity, and use of other systemic therapy, sunitinib or sorafenib use was associated with an increased risk of stroke (HR = 3.36, 95% CI 1.45 -7.66) compared with 788 patients diagnosed with advanced RCC from 2007-2009 who had no Part D claims for either sunitinib or sorafenib. There was no statistically significant increase risk of CHF/CM, AMI, or cardiovascular-related deaths.

#### Conclusion

VEGFR TKIs are significantly associated with an increased risk of stroke although the absolute risk is very low. Clinicians should be aware of this adverse effect to provide early intervention and balance therapeutic benefit with adverse events.

## Pre-transplant HbA1c Predicts Post-transplant Diabetes Mellitus among Kidney Transplant Recipients

## Jung-Im Shin, MD, MPH

University of Wisconsin School of Medicine and Public Health

### Background

Post-transplant diabetes mellitus (PTDM) is a common complication among kidney transplant recipients and is associated with a higher risk of cardiovascular events and poorer graft and patient survival. Identifying recipients at greatest risk of PTDM may help guide monitoring and treatment strategies to prevent or delay the onset of PTDM. In this study, we examined whether pre-transplant HbA1c can predict the risk for PTDM in a retrospective study.

#### Methods

We analyzed data from 1,499 non-diabetic primary kidney transplant recipients with HbA1c values in the United States Renal Data System (USRDS) from 2005-2011. We assessed the association of pre-transplant HbA1c with PTDM using Cox proportional hazards models.

#### Results

A total of 395 recipients out of 1,499 developed PTDM over a median follow-up of 1.8 years. Prediabetes (HbA1c≥5.7%) prior to transplantation was associated with an adjusted hazard ratio (HR) of 1.32 (95% confidence interval (CI): 1.07, 1.62) for PTDM. Pre-transplant HbA1c below 5.4% was not significantly associated with risk of PTDM, whereas a 1% higher HbA1c above 5.4% was associated with an adjusted hazard ratio of 1.85 (95% CI: 1.28, 2.67).

#### Conclusions

Higher pre-transplant HbA1c is independently associated with greater risk of PTDM among kidney transplant recipients. A continuous relationship between pre-transplant HbA1c and a risk of PTDM suggests that increased risk is conferred at HbA1c levels well below current thresholds for prediabetes.

## Quality measures that focus on patient and family engagement in oncology

**Kyung Min Song, MD, MPH, MBA**Senior Manager,
Evidence Translation & Implementation, Avalere Health

### Background

National Quality Strategy set forth by the Department of Health and Human Services emphasizes that each person and family are engaged as partners in their care. Appropriate usage of quality measures can serve as a means to achieve this. Studies have shown that patient engagement can lead to improved healthcare outcomes, lower resource utilization, and reduced costs. As such, Avalere has sought to identify oncology-related quality measures that address patient and family engagement, and determine ways to advance engagement in oncology through the use of quality measures.

#### Methods

Avalere assessed publicly available information to identify person and family engagement measures related to oncology, including measures related to patient education, care preferences, and care planning. Avalere also assessed the current use of these measures in CMS' quality programs.

#### Results

Avalere identified six oncology-specific measures related to person and family engagement. One of the measures is included in CMS' Physician Quality Reporting System and the Electronic Health Record Incentive Programs. Three measures identified are related to documenting patients' preferences during the end of life care, two are related to care planning for pain and depression, respectively, and one is related to patient education on treatment. None of the measures are related to specific cancers.

#### Conclusions

Avalere found lack of measures related to patient and family engagement in oncology. Given the importance of patient and family engagement during the course of disease management, opportunity exists to improve the quality of patient care through measurement and evaluation of engagement. The quality of patient care in oncology can be improved through data support, stakeholder buy-in, standardized methodology for measuring engagement, evidence linking engagement and outcomes, and implementation measures in incentive programs.

## Curative Surgical Resection of Adrenocortical Carcinoma: Determining Long-Term Outcome Based on Conditional Disease-Free Probability

Yuhree Kim, MD (2011)

## Objective

To evaluate the conditional disease-free survival (CDFS) for patients who underwent curative intent surgery for adrenocortical carcinoma (ACC).

### Background

ACC is a rare but aggressive tumor. Survival estimates are usually reported as survival from the time of surgery. CDFS estimates can be clinically more relevant by accounting for changing likelihood of disease-free survival (DFS) according to time elapsed following surgery.

#### Methods

CDFS was assessed using a multi-institutional cohort of patients. Cox proportional hazards models were used to evaluate factors associated with DFS. 3-year CDFS estimates at "x" year after surgery were calculated as follows: CDFS3 = DFS(x+3)/DFS(x).

#### Results

192 patients were included in the study cohort: median patient age was 52 years. At presentation, 36% of patients had a functional tumor and median size was 11.5 cm. Most patients underwent R0 resection (75%) and 9% had N1 disease. Overall 1-, 3-, and 5-year DFS was 59%, 34%, and 22%, respectively. Using CDFS estimates, the probability of remaining disease-free for an additional 3 years when the patient had survived without disease at 1-, 3-, and 5-years, was 43%, 53% and 70%, respectively. Patients with less favorable prognosis at the baseline demonstrated greater increase in CDFS3 over time (e.g. capsular invasion: 28% to 88%,  $\Delta$  60% vs. no capsular invasion: 51% to 87%,  $\Delta$  36%).

#### Conclusions

DFS estimates for patients with ACC improved dramatically over time, in particular among patients with initial assessment of worse prognoses. CDFS estimates may provide clinically more relevant information about changing likelihood of disease-free survival over time.

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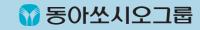
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