

**National Institutes of Health  
National Institute of Diabetes and Digestive and Kidney Diseases**

**Network of Minority Health Research Investigators  
16th Annual Workshop**

**DoubleTree Hotel Bethesda  
Bethesda, Maryland  
April 12–13, 2018**

**Meeting Summary**

**Thursday, April 12, 2018**

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**INTRODUCTIONS**

*Jose Romero, Ph.D., Associate Physiologist, Brigham and Women's Hospital, Harvard Medical School  
Lawrence Agodoa, M.D., Director, Office of Minority Health Research Coordination (OMHRC),  
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)*

Dr. Jose Romero, chair of the Network of Minority Health Researchers (NMRI) Planning Committee, welcomed participants to the NMRI 16th Annual Workshop, which represents the beginning of the next stage of the Network. He remarked on the full agenda and the networking sessions included. Dr. Romero expressed appreciation to NMRI leadership for their continuous support.

Dr. Lawrence Agodoa, Director, OMHRC, also welcomed participants and noted that the NMRI was established in 2002 by the OMHRC at the NIDDK to encourage new investigators and foster mentoring relationships. This model has worked well to propel its members to higher levels of achievement in academia. The OMHRC's current role in relation to the NMRI, a member-led network, is to provide the necessary resources for members to succeed. Dr. Agodoa invited meeting participants to introduce themselves and describe their recent awards or accomplishments. Participants ranged from premedical and predoctoral students to tenured professors. Research areas of study included diabetes, epidemiology, endocrinology, health disparities, hematology, nephrology, nutrition, and obesity. Recent accomplishments included accepted manuscripts, new grants and research funding, speaker invitations, promotions, and new collaborations. Some participants were first-time attendees of a national NMRI workshop.

**KEYNOTE SPEAKER**

**Development of Novel Therapies for Sickle Cell Disease**

*Betty S. Pace, M.D., Professor, Department of Pediatrics, Augusta University*

Dr. Betty Pace, an established National Heart, Lung, and Blood Institute (NHLBI) investigator, thanked the organizers for the invitation to speak and noted that this was her first time attending a NMRI workshop. She reported on the development of novel therapies for sickle cell disease (SCD) and the work of the Pace research laboratory, and she shared her story. Dr. Pace remarked on how the influences of

family and friends, education and training, and an academic career have helped shape her journey. Her family's humble beginning, hard work ethic, and values shaped her early life. She first encountered SCD at the age of 13 while in middle school, when her good friend was diagnosed and later died at a young age. This experience had an effect on her decision to study SCD several years later. Her college education and training included critical decisions and mentorship at each phase, starting as a computer programmer after graduating Marquette University. She continued her education at the Medical College of Wisconsin, where she later became director of the Sickle Cell Program and then moved to train at the University of Colorado after receiving a hematology/oncology fellowship. Her advanced training and enhanced skills included a Robert Wood Johnson Minority Medical Faculty Development Program Award (since renamed in honor of Dr. Harold Amos) to study at the University of Washington. Strong mentorship and advanced laboratory skills allowed her to become an independent investigator and led to her recruitment to a faculty position at the University of South Alabama in 1994. She continued her academic career at the University of Texas at Dallas (UTD) in 2002 and received funding from the NHLBI Summer Institute Program to Increase Diversity in Health-Related Research (SIPID) training program. Dr. Pace currently is a faculty member at Augusta University, where she serves as program director of the NHLBI Programs to Increase Diversity Among Individuals Engaged in Health-Related Research (PRIDE) training program. Dr. Pace next detailed her research and training experience, including work as academic faculty, funding from the NHLBI and the NIH, and participation in additional research and training programs.

SCD accounts for more than 350,000 deaths worldwide each year, is more prevalent in the African countries, and has been shown to be present in regions with high incidences of malaria. A single point mutation in the beta-globin ( $\beta$ -globin) gene—a subunit of hemoglobin (Hb)—leads to the clinical manifestation of SCD: abnormal red blood cells (hemoglobin S) commonly referred to as sickle red blood cells (sickle cells). These sickle cells block blood flow, causing vaso-occlusive crisis (VOC) events that result in ischemia, and also are susceptible to chronic hemolysis, which leads to severe anemia and organ damage. Although effective therapies for SCD are limited, the first drug discovered to treat SCD—Droxia<sup>®</sup> (generic name hydroxyurea)—was approved by the U.S. Food and Drug (FDA) in 1998 for use in adults and in 2017 for use in children. Droxia, a deoxyribonucleotide reductase inhibitor, is a nitric oxide donor and a cyclic guanosine monophosphate (cGMP) activator of fetal hemoglobin ( $\alpha_2\gamma_2$ -globin or HbF) induction. In 2017, a second drug, Endari<sup>™</sup>, an over-the-counter L-glutamine supplement, was FDA-approved for treatment of SCD in those 5 years of age and older. Endari acts to improve the nicotinamide adenine dinucleotide (NAD) redox potential of sickle cells by increasing the reduced glutathione levels and reducing oxidative damage, resulting in a reduction in VOC. Developing new therapies and affordable and easy-to-use treatments for patients in African countries remains the focus of the SCD research community.

Dr. Pace remarked that research has shown the benefits of HbF. In fact, the NHLBI Cooperative Study of SCD, a natural history study conducted from 1978 to 1998 that followed approximately 4,000 individuals with SCD, showed that long-term survival correlated to HbF levels and that HbF levels greater than 8.6 percent improved survival. Hydroxyurea has been effective in achieving this HbF level but often is not accepted as a treatment by families because of its dual indication as a chemotherapeutic agent and its high level of cytotoxicity. The clinical and translational efforts of the Pace laboratory have focused on developing improved treatments for SCD. Dr. Pace was the site principal investigator for the Penicillin Prophylaxis in SCD (PROPS) study and the Evaluation of Purified Poloxamer 188 in Vaso-Occlusive Crisis of SCD (EPIC) multicenter trial testing the efficacy of MST-188. Her laboratory was able to show that n-acetyl cysteine improves glutathione levels, and the laboratory performed high-throughput screening (HTS) of 10,000 FDA-approved or European Medicines Agency–approved drugs to identify novel HbF-inducing drugs.

In 2015, the Pace laboratory reported that novel inducers of HbF identified through HTS were active *in vivo* in anemic baboons (the large-animal model) and  $\beta$ -yeast artificial chromosome (YAC) transgenic

mice ( $\beta$ -YAC mouse model). The laboratory investigated two promising candidates—benserazide, a dihydroxyphenylalanine decarboxylase inhibitor approved in Canada and the United Kingdom for treatment of Parkinson's disease, and dimethylfumarate (DMF or Tecfidera<sup>®</sup>), an anti-inflammatory drug that was FDA-approved in 2013 for the treatment of multiple sclerosis. Results showed that benserazide induces HbF and stimulates red blood cells in the large-animal model and induced sustained HbF levels in the  $\beta$ -YAC mouse model. Preclinical safety and efficacy studies are being conducted in collaboration with Leidos Biomedical Research Inc., (Leidos Biomed) and an FDA investigational new drug application is in progress. To determine whether DMF would be effective in SCD, the Pace laboratory developed a primary erythroid culture system using human peripheral blood cells from normal donors. Results showed that DMF induced HbF in human sickle erythroid cells, that DMF plus hydroxyurea (HU) produced a higher induction of HbF compared to DMF or HU alone, and that DMF reduced red blood cell sickling under hypoxic conditions. Dr. Pace hypothesized that DMF induces HbF, which produces a hybrid of hemoglobin S and HbF cells, leading to a reduction of sickling under hypoxic conditions.

Prior studies have shown that DMF exhibits its effects (e.g., HbF induction) via activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant pathway. Oxidative stress has been shown to play a role in the effects of SCD. The Pace laboratory demonstrated *in vivo* that DMF activated the Nrf2 pathway to induce  $\gamma$ -globin and mediated Nrf2 translocation to the nucleus, which was confirmed by its association with macrophage-activating factor (MAF) proteins. The laboratory also showed that DMF increases HbF in a sickle cell mouse model and that the loss of Nrf2 decreased  $\gamma$ -globin gene expression in a sickle cell/Nrf2 knockout mouse model they generated. These data clearly show that Nrf2 is critical for the HbF production in normal development and that Nrf2 activation is beneficial in SCD to improve symptoms and decrease complications. Studies are ongoing in the Pace laboratory to further develop DMF for clinical trials and as a treatment for SCD.

Throughout her career, Dr. Pace has been conscious of diversity and sought to make a personal contribution as a minority investigator. Understanding the meaning and importance of diversity in the workforce, in general, is key. Dr. Pace embraced this diversity of thought in her laboratory and appreciates how it fuels creativity in training new biomedical researchers. Dr. Pace has personally trained more than 80 individuals who have spanned the educational and career spectrum from middle and high school students to postdoctoral fellows. UTD was one of three institutions to receive funding in 2006 to support an NHLBI-sponsored SIPID program, which Dr. Pace led. Since 2010, Augusta University has been one of six institutions funded in the PRIDE program, of which Dr. Pace is the program director. The SIPID program ended in 2010, and the new initiative, PRIDE, began. The SIPID/PRIDE program involves mentoring and research training built specifically for junior faculty from underrepresented groups or disabled persons who are conducting blood disorders research at U.S. academic institutions. The Pace group has trained and mentored 76 underrepresented faculty members from 40 U.S. institutions in the SIPID/PRIDE program. Of these, the majority were African American, Hispanic, or American Indian; 70 percent were women; 42 percent received mentored career development awards (K01, K08, K12, or K23) or Research Program Grants (R01, R03, or R23); and, collectively, they have published more than 500 peer-reviewed papers. The Pace SIPID/PRIDE Group also established an effective peer mentoring program.

Dr. Pace shared final thoughts on diversity and paying forward the help received. She encouraged participants to adopt a mindset of diversity by learning more about it and practicing it daily, understanding that teams of diverse people support creativity, and making a personal commitment to promote diversity.

## *Discussion*

A meeting participant noted the odds of having to resubmit before receiving a first K award and asked about ways to encourage and motivate new clinical investigators, given the challenge current researchers face in securing NIH funding. Dr. Pace acknowledged that resubmitting the application is the likely scenario for most K awards. To increase the odds of success, applicants should set aside 6 months to prepare before applying and continue to refine the application or grant proposal after it has been submitted. Regarding a first R01, a 2011 report indicated that underrepresented minorities had a much lower probability of receiving funding and were less likely to resubmit an application. The NIH is actively working to address these issues. Funding mechanisms have been implemented to support early stage investigators (ESIs) so that they are not competing with established investigators early in their careers. Dr. Pace pointed out some of the opportunities available to clinicians desiring to receive research experience, including health disparities research and implementation science. As a longtime mentor, she finds that a career path should be tailored to the individual, not broadly based on models.

When asked about the effects of overexpressing Nrf2 in the SCD model and other targets, Dr. Pace replied that Nrf2 overexpression experiments have not been done and would be a challenge in the existing mouse models. Work is ongoing with the potential drugs dimethyl fumarate and its control of the transcription factors Nrf2 and MAF that regulate gamma globin gene expression and fetal hemoglobin levels as a treatment for sickle cell disease. A Nrf2/sickle cell disease mouse model has been established to expand these efforts in Dr. Pace's lab.

## **WRITING WORKSHOP—SESSION I: ABCS OF PUBLISHING A NARRATIVE REVIEW**

*Patricia Heyn, Ph.D., Associate Professor, University of Colorado Denver, Anschutz Medical Campus*  
*Lillian Hoffecker, Ph.D., Research Librarian, University of Colorado Denver, Anschutz Medical Campus*

Dr. Patricia Heyn and Dr. Lillian Hoffecker presented a writing workshop that addressed the growing amount of scientific evidence and knowledge available in the biomedical field and how that affects an investigator's future research. Dr. Heyn noted that Session I would be an overview of the fundamentals of publishing a narrative review and the review synthesis methodology, and Session II would be an interactive session on how to conduct a systematic review (SR) and its practical application. She emphasized that conducting a literature review, the main component of an SR, is an art and a journey, as well as a process. An SR is defined by the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. Similar to a research report, the steps of conducting an SR include formulating answerable questions, gathering the evidence, synthesizing and appraising the evidence, reporting the evidence, and evaluating and making recommendations. The SR is in demand today because judgment is heavily influenced by opinion and bias, conclusions that are drawn without the benefit of evidence may be erroneous, and the health sciences rely on scientific discovery to advance public health.

The synthesis methodology involves rigorous quality research that requires the systematic application of the scientific method, the fundamental feature of which is the testable hypothesis. Dr. Heyn remarked that the SR is a critical analysis highlighting the strengths and weaknesses of existing research in the field of interest. It requires critical understanding of the field; provides opportunities to reflect on the similarities, patterns, trends, and differences of existing research; and defines gaps in the literature that would justify future research. Key features of an SR that make it desirable to researchers are its structure and orientation, as well as descriptive and well-organized data tables. The appraisal—the interpretation and discussion of the strength of the evidence, potential biases of the review, generalizability of the results, weighted benefit to risk, and implications—is critical to the SR. Dr. Heyn reiterated that synthesis of an SR is similar to a process of discovery that begins with the identification of a problem or issue to study. The next steps are to review the literature, specify the purpose of the study (design), formulate a research

plan (methods), gather data in a systematic manner, and perform the appraisal; this process culminates in a published report that is evaluated and used by the scientific community.

Dr. Hoffecker detailed the comprehensive search process, core databases and other sources used to conduct a literature search, and ways to manage the data. The literature search is specific, and citations are screened based on the study inclusion and exclusion criteria. Three core databases—PubMed or Ovid Medline, Embase, and Cochrane Library—are used in the SR. Embase, often referred to as the Western PubMed, is a large biomedical database that includes conference abstracts and citations and is becoming popular for SRs, especially at academic institutions. Other resources include bibliographies of reviews, subject-specific databases (e.g., Web of Science), literature published in non-mainstream platforms (e.g., dissertations or conference abstracts), and communication with previous authors. Prior to beginning a search, a table or search matrix is developed consisting of the databases used and search criteria or concepts to address the question being asked. For example, using the PICO (patient/problem, intervention, comparator, outcome) model for such clinical questions as “is digoxin effective in reducing readmission in congestive heart failure patients?” the primary searchable concepts in PubMed using a basic Boolean operator—AND/OR—would be “digoxin,” “readmission,” and “congestive heart failure.” The challenge lies in arriving at a single clinical question for the SR. The manuscript must include descriptions of the search methods, including names of resources (e.g., databases) and years covered; the date and time the author spent searching; the search concepts; the citation management software; and the search limits applied. All edits or updates to the search record should be tracked and retained. Dr. Hoffecker led participants in interactive search exercises using the PubMed and Embase databases.

## **WELCOME REMARKS**

*Griffin P. Rodgers, M.D., Director, NIDDK, NIH*

Dr. Griffin Rodgers welcomed participants to the 16th workshop of the NMRI and noted that many organizations try to emulate the main work of this research network. The NIDDK evaluates its successful programs and initiatives, such as NMRI, to better understand what makes them successful. Dr. Rodgers stated that the mission of the NIH is to seek fundamental knowledge about the nature and behavior of living systems and apply that knowledge to enhance health, lengthen life, and reduce illness and disability. The research mission of the NIDDK—one of 27 NIH Institutes and Centers—supports research on diabetes and other endocrine disorders and metabolic disorders; digestive diseases, nutritional disorders and obesity; kidney diseases, urologic, and hematological diseases. These comprise the most common, costly, and consequential diseases affecting many people in the United States and abroad. The NIDDK biomedical research programs include basic and applied research for knowledge acquisition, clinical investigations and clinical trials for knowledge validation, and dissemination and education research for knowledge transfer.

Dr. Rodgers remarked that knowledge acquisition is an ecosystem of research discovery extending from basic or fundamental research conducted at the molecular and cellular levels and in animal models to translational research, clinical studies, and clinical trials. He emphasized that research is dynamic and circular, from bench to bedside, rather than a linear trajectory. Discoveries advance and inform clinical application; therefore, it is critical to support a broad range of research in a multidisciplinary approach in which researchers collectively advance this research ecosystem. One example of translation from discoveries to a new class of diabetes drugs in the NIDDK is the recent FDA-approved sodium-glucose co-transporter-2 (SGLT2) inhibitor to lower glucose in people with type 2 diabetes. In a timeline that extends from 1980 to 2014, NIH investments enabled key basic research discoveries and advances that led to new treatment. In the 1980s and 1990s, researchers identified the genes for sodium-glucose co-transporters (SGLTs) and gained insights into the role of SGLT2 in glucose reabsorption in the kidney. Researchers also were able to reverse hyperglycemia in the diabetic rat model using phlorizin, a natural

compound that had been studied decades earlier but was toxic to humans and needed further investigation. Building on prior NIH-funded research, further studies revealed that SGLT2 genetic variants caused glucose loss in the urine in familial renal glucosuria. Researchers from industry and academic and medical institutions developed a phlorizin derivative that lowers blood glucose by inhibiting SGLTs in a small-animal model. In subsequent research, largely funded by industry, researchers developed improved SGLT inhibitors, which were tested in clinical trials, leading to the first FDA-approved medication in this new class of diabetes drugs in 2013 and others in 2014.

The Artificial Pancreas (AP) technology, a closed-loop system that would replace a non-functioning pancreas in type 1 diabetes patients, is an example of how the research ecosystem advances basic discovery to technology development to treatments. Technological advances supported by NIDDK-sponsored research and NIDDK's small business programs that have informed the development of the AP technology include the insulin pump (1970–current), self-monitoring of blood glucose (1970s–1980s), and interstitial glucose monitoring (1980s–current). Clinical studies that helped moved these devices into clinical practice led to the proven benefits of glucose control and reduced the risk of diabetes-related complications (e.g., diabetic retinopathy). In 2006, the FDA approved electrode-based continuous glucose monitors. Wireless technologies, microprocessors, and cell and smart phones also have helped to advance the AP technology. Finally, these advances led to the launch of four pivotal NIDDK-supported multicenter trials in 2017–2018: the International Diabetes Closed Loop Trial; a full-year trial of AP in youth ages 6–18; a CER trial of Medtronic hybrid AP to next-generation AP; and a 6-month trial in adults of bihormonal AP.

Dr. Rodgers called attention to efforts within the NIDDK to offset the perception that a career in biomedical research is a mountain of staggering obstacles. The NIDDK supports research training and career development programs for the next generation of biomedical researchers by building a ladder to transverse the obstacles. He highlighted NIDDK programs and activities that support critical moves between career levels, including the Loan Repayment Program (LRP) and workshops focused on life after a K award and new principal investigators. The LRP repays up to \$35,000 annually (up to \$50,000 under the 21st Century Cures Act) of a researcher's qualified educational debt in return for a commitment to engage in NIH mission-relevant research. The NIDDK also provides benefits to ESIs by setting more generous paylines for ESIs compared to established investigators. Participants were encouraged to visit the NIDDK website, which has been extensively updated and serves at the central point of contact for the Institute.

### *Discussion*

A participant who is a registered dietician and 4th year Ph.D. student in nutrition research, wondered about the timeline and eligibility for the LRP and asked for advice on applying for a postdoctoral fellowship. Dr. Rodgers explained that NIDDK's Division of Digestive Diseases and Nutrition might be the best fit for nutrition research, but recommended contacting Dr. Tracy Rankin, Deputy Director, Division of Kidney, Urologic, and Hematologic Diseases, for details on applying for F32 fellowships.

## **ROUNDTABLE DISCUSSIONS—SESSION I**

Participants attended one of five roundtable discussions focused on various career-oriented topics and emerging research related to NIDDK's mission. Meeting participants attended the session of their choice. Moderators facilitated each roundtable discussion.

### **Table 1: Community-Based Participatory Research**

*A. Celeste Farr, Ph.D., Assistant Professor, Oakland University William Beaumont School of Medicine*

**Table 2: Epigenetics Mechanisms in Diabetes Complications**

*Marpadga Reddy, Ph.D., Assistant Research Professor, Beckman Research Institute of City of Hope*

**Table 3: NIH Intramural Research**

*Roland Owens, Ph.D., Assistant Director, Office of Intramural Research, NIH*

**Table 4: Research Supplements to Promote Diversity and the NIH Funding Mechanism**

*Robert Rivers, Ph.D., Program Director, NIDDK, NIH*

**Table 5: Successful Approaches for Grant Funding**

*Francisco Villarreal, Ph.D., Professor, University of California, San Diego*

**ROUNDTABLE DISCUSSIONS—SESSION II**

Session II provided participants the opportunity to switch discussion tables.

**PARALLEL SESSION I**

Session I provided the opportunity for participants to attend mock study sessions for different types of NIH awards—R01 Basic/Clinical, K01 Basic/Clinical, and R21 Basic/Clinical. During these sessions, session leaders were given sample grant applications to review and critique. Meeting participants attended the session of their choice.

**Mock Study Section 1: R01**

*Francesco Villarreal, M.D., Ph.D., Professor, University of California, San Diego*

*Ann Jerkins, Ph.D., Scientific Review Officer, NIDDK, NIH*

**Mock Study Section 2: K01 Awards**

*Mark Lawson, Ph.D., Professor, University of California, San Diego*

*Karn Wijarnprecha, M.D., Chief, Training and Mentored Research Section, NIDDK, NIH*

**Mock Study Section 3: R21**

*Jose Romero, Ph.D., Associate Physiologist, Brigham and Women's Hospital, Harvard Medical School*

*Ryan Morris, Scientific Review Officer, NIDDK, NIH*

**CHARTING YOUR COURSE FOR SUCCESS**

*Ricardo Azziz, M.D., M.P.H., M.B.A., Chief Officer, Academic Health and Hospital Affairs, State University of New York*

Dr. Ricardo Azziz pointed out that minority researchers have a dual role as effective investigators and as role models and leaders. For perspective, he relayed to participants that their educational attainment placed them in the top 5 percent of the U.S. population and top 1 percent of the world's population. Additionally, underrepresented minorities (URMs) comprise less than 1 percent of individuals with doctorate degrees in the United States. Per the 2016 U.S. Census report, 0.77 percent of African Americans had earned a professional degree, and 0.91 percent had earned a doctoral degree. Furthermore, 0.65 percent of Hispanics had earned a professional degree, and 0.69 had earned a doctoral degree. He emphasized to the participants that solely by being in attendance at the workshop they had beaten those odds, and they have a responsibility as minority researchers to lead. Charting a course for success involves hard work, perseverance, and leadership.

Dr. Azziz pointed out that leadership is a learned skill and a trained art, and he noted the differences between administration, management, and leadership. Leaders serve as external agents for the company or organization, manage change, and interpret the environment; they also provide a vision, empower and create teams, engage communities, and model good behavior. Dr. Azziz elaborated on basic lessons for being an executive leader, such as understanding politics with a small ‘p’ and learning the necessary leadership skills and competencies; developing a network and finding good mentors; understanding expectations, spoken or unspoken; and learning how to “manage up” by enhancing your manager’s work. Executive leaders also understand their roles, responsibilities, and career path; expand their skill sets and experience; quantify their skills and experience; and are involved.

Dr. Azziz discussed some of the unique challenges that minority faculty may encounter as they develop as leaders. U.S. medical schools and universities have fewer faculty from URM groups than from majority groups, and more URM faculty are assistant professors than associate and full professors. Therefore, the pool of role URM models in the biomedical sciences is limited. Issues of racial inequality, stereotyping, and discrimination remain challenges, and further work is required in the areas of cultural competency, emotional intelligence, and language and communication. In addition, URMs often face the so-called “minority tax”—the minority faculty disparity of additional duties and responsibilities to promote diversity. Furthermore, considering the higher levels of leadership in academia, only 13 percent of the nation’s university presidents are URMs. Dr. Azziz encouraged participants to make investments to develop their own leadership competencies and skills, leverage their strengths and compensate for weaknesses, and proactively document their achievements.

## **PARALLEL SESSION II**

Session II provided the opportunity for participants to learn the aspects of a mentoring training program for clinical and translational researchers, engage in case studies activities, and work in teams to address guiding questions. Moderators facilitated each activity. The session was intended to allow informal, interactive discussions among participants.

### **Mentoring Training Program—Session I: Aligning Expectations**

*Mark Dewhirst, D.V.M., Ph.D., Gustavo S. Professor of Radiation Oncology, Associate Dean of Faculty Mentoring, Duke University Medical Center*

### **Mentoring Training Program—Session II: Assessing Understanding**

*Leonor Corsino, M.D., Associate Professor of Medicine, Duke University School of Medicine*

### **Mentoring Training Program—Session III: Fostering Independence**

*Stephanie Freel, Ph.D., Director, Clinical Research Education and Research, Duke University School of Medicine*

## **MARCO CABRERA POSTER AND NETWORKING SESSION**

All meeting participants were invited to view the posters submitted to the NMRI 16th Annual Workshop and to converse with their presenters. Judges examined the posters and discussed the described research with each poster’s presenters. Winners were selected for each of three categories—Basic Science, Translational Science, and Clinical Science—and awards were presented to the winning recipients in the final session of the workshop.



## **DR. LAWRENCE Y. AGODOA HONORARY LECTURE OF THE NETWORK OF MINORITY HEALTH RESEARCH INVESTIGATORS**

Dr. Romero welcome participants to the Dr. Lawrence Y. Agodoa Honorary Lecture. Each year, the Planning and Oversight Committees honors exemplary achievers, leaders, and mentors; Dr. Agodoa is this year's honoree. His dedication, hard work, contributions, and leadership of the NMRI have been outstanding and unmatched. Dr. Agodoa is a trained nephrologist, director of the OMHRC, and program director at the NIH who established the annual workshop that has continued for 16 years and, through his conceptualization and vision, has led this network to the success it is today.

Dr. Agodoa was humbled to be honored at this workshop. He reflected on the 16 years of NMRI and the beginning of the OMHRC at NIDDK. Observing that minority investigators were not well represented in his portfolio as program director, he saw the opportunity to prompt change and broadly address health disparities for the NIDDK. The OMHRC staff at the time included Dr. Agodoa, Ms. Winnie Martinez, and a third staff member who has since left the office; the staff now comprises six members. In 2000, Dr. Agodoa and the OMHRC led the efforts to develop NIDDK's Strategic Plan on Minority Health Disparities. The goal was to build the research pipeline by developing special initiatives and diversity programs that span the stages of a career. Current programs include summer internships for high school students, the NIDDK Diversity Summer Research Training Program (DSRTP) for Undergraduate Students, Short-Term Research Experience for Underrepresented Persons (STEP-UP), and the NMRI. Early on, the OHMRC recognized that the NMRI, which was established in 2002, should not be regulated on an institutional level; its members could better regulate and implement its mission. The NMRI has a mentoring program that is unique to the NIDDK. Dr. Agodoa remarked on the interesting journey of the NMRI and expressed gratitude to the members for their participation in making the NMRI a success and addressing disparities research.

### **Racial and Ethnic Disparities in Diabetes Care**

*Guillermo Umpierrez, M.D., Professor of Medicine, Emory University School of Medicine*

Dr. Guillermo Umpierrez, director of diabetes and endocrinology at Grady Health System, presented an overview of diabetes mellitus (DM) in minority populations. The percentage of minority populations in the United States has increased steadily since 1960; the Hispanic population has seen the largest increase, followed by Asian and African Americans. The prevalence of DM in U.S. adults ages 20 to 79 also increased from 1980 to 2012. The estimated age-adjusted prevalence of DM was higher in U.S. adults 18 years and older in minority populations than in non-Hispanic whites from 2013 to 2015 and was higher among women in the minority populations than among men. The overall prevalence of DM in the United States is 7.2 percent and is higher in the eastern United States. The American Diabetes Association (ADA) reports that 30 percent of people with DM in the United States are not being diagnosed.

Genetic, medical, and lifestyle factors may play a role in the increased prevalence of DM in minority populations. A genetic basis for DM was first proposed in 1962 by geneticist Dr. James V. Neel in his thrifty gene hypothesis, which suggests that genes associated with fat storage in the body during periods of famine would, in times of caloric excess, predispose the body to obesity and diabetes. Genome-wide association studies and whole-exome sequencing studies have revealed more than 100 genetic variants associated with the modified risk for type 2 diabetes, including population-specific variants in African Americans, Hispanics, and American Indians. Yet genetic factors account for a small percentage of the estimated heritability of diabetes. Minority populations show increased prevalence of DM after relocating to the United States. Furthermore, a 1994 study comparing the lifestyle of Pima Indians living in Arizona to their counterparts in Mexico revealed similar genetic markers in both groups, but Arizona Pima Indians

had higher body mass indexes (BMIs) and spent fewer hours doing hard work each week than Mexican Pima Indians.

Such lifestyle factors as obesity, dietary change, physical inactivity, and insulin resistance are known to play a role in the increased incidence of DM. The Centers for Disease Control and Prevention (CDC) reported a correlation of age-adjusted prevalence of obesity and diagnosed DM in U.S. adults in 2014. Findings from National Health and Nutrition Examination Survey (NHANES) data from 1988 to 1994 and 1999 to 2002 and from the Racial and Ethnic Approaches to Community Health (REACH) study investigating the prevalence of obesity (BMI greater than 30 kg/m<sup>2</sup>) and overweight (BMI of 25 to 30 kg/m<sup>2</sup>) in the diabetic population showed similar results, linking obesity to diabetes. Dr. Umpierrez emphasized the need to address the industrialized and urbanized diet to define the underlying cause of the diabetes epidemic in minority populations. Given that long-term dieting in adults often leads to decreased metabolic rates, increased appetite, and a tendency to regain the weight, adopting early prevention strategies is critical. Starting places include decreasing consumption of high sugar content soft drinks and increasing physical activity in youth.

Dr. Umpierrez remarked that diabetes—obesity-related diabetes—is the driver of the DM epidemic in the United States. BMI is linked to the relative risk of DM, and the prevalence of type 2 diabetes significantly increases in African Americans and Hispanics with BMIs greater than 25 kg/m<sup>2</sup> and in Asian Americans with BMIs greater than of 23 kg/m<sup>2</sup>. Reports show that obesity leads to inflammation and insulin resistance, resulting in epigenetic changes in adipose tissue macrophages. Fifty percent of obese persons with intra-abdominal subcutaneous fat accumulations (i.e., apple-shaped) and a compromised pancreas (abnormal levels of adipocytokines and/or fatty acids) will more than likely develop diabetes during their lifetime. Additionally, insulin resistance is more prevalent in minority populations. Dr. Umpierrez speculated that epigenetic changes predispose insulin-resistant minority populations to physical inactivity and weight gain, leading to an increase in complications from DM, such as retinopathy, end-stage renal disease, and lower-extremity amputation. African Americans have higher incidences of diabetes-related complications than other minority groups due to other risk factors (e.g., hypertension). The relative risk of lower-extremity amputations is highest in Native Americans and lowest in Asian Americans. The CDC reports that diabetes-related mortality rates were higher in minority populations and that diabetes-related conditions are the sixth leading cause of death in these groups.

Dr. Umpierrez pointed out that the health disparities in DM in minority populations have been known for more than 20 years; the NIH has been actively addressing this issue. Potential sources of care disparities are seen on the patient, provider, and health care system levels. For example, ethnic minorities tend to have worse glycemic control and age-adjusted Hb A1c levels greater than 9 percent, but these trends have been improving for all minority groups except Mexican Americans. Adherence to extensive insulin therapy and glucose self-monitoring is less in ethnic minorities than non-Hispanic whites. Racial disparities were observed in the Medicare managed care system, such that routine eye exams and glucose and cholesterol screenings were less frequent in African Americans, as reported in 1999 and 2003. From 2009 to 2014, ethnic minorities had worse hypertension and DM control when treated in community health centers.

Dr. Umpierrez described intervention strategies to address racial and ethnic disparities in the United States, including the efforts in the Diabetes Management Program within the Grady Health System. Intensified glucose control was an effective intervention to reduce A1c levels in African Americans and Hispanic patients, but Hispanic patients tend to drop from the system on follow-up. A shortage of community-based physicians to care for DM patients likely plays a role in the access to DM care. Evidence showed no difference in diabetic patient health outcomes between patients treated by doctors and those treated by appropriately trained nurses (e.g., certified diabetes educators). In the Hispanic population, low English proficiency and overall low literacy are factors. Intervention and programs

should be tailored to the community, and health care workers improve DM care in the community, especially in the Hispanic population. DM care in ethnic groups also is affected by care disparities; removing access to care barriers would help reduce the disparity in diabetes-related complication rates.

Dr. Umpierrez emphasized the importance of developing programs to prevent and improve DM care in minority populations, educating the health care workforce, and improving access to care. DM care in minority populations requires a unique approach due to heterogeneity within populations regarding socioeconomic status, language, diet, and religion. Randomized controlled clinical trials must include Asian Americans of similar demographics and genetics. All studies should consider cultural and social factors more broadly, and clinical practice guidelines must account for the diversity of these factors. Additionally, the low clinical trial participation rates for minority population must be addressed to better understand responses to treatment.

### *Discussion*

Dr. Francisco Villarreal asked about the low incidences of diabetes in Cuban populations. Dr. Umpierrez pointed out that the Caribbean populations in general have high incidences of obesity, which could be related to diet or genetics. He was aware of those details on diabetes in Cuban populations.

A participant in the surgical field pointed out that glucose levels precipitously drop to a nondiabetic level 1 week after bariatric surgery and asked whether any mechanisms for this rapid change are known. Dr. Umpierrez observed that age-adjusted BMIs and body weight do not correlate equally to complications from fatty acid disease across racial groups. Prior to bariatric surgery, patients are required to adhere to a strict diet, which decreases glucose levels. Hormones that monitor insulin and glucagon secretion (e.g., integrin) then increase in the gastrointestinal tract and contribute to this effect that occurs before surgery. Patients likely are exhibiting a remission from DM rather than a cure; weight gain will reverse the effect.

When asked about community-based intervention in diabetes control, Dr. Umpierrez noted the various community efforts that are occurring in cities and states such as engaging the local farmer's market, adopting exercise and fitness initiatives, and providing nutritional meals.

**Friday, April 13, 2018**

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## **MENTOR/MENTEE SESSION**

Junior investigators who had signed up for this session had the opportunity to meet with one of several senior NMRI investigators who offered to serve as mentors. During the session, each mentor hosted a roundtable discussion with his or her mentees, answering questions and providing advice.

## **ROLE OF SCIENTIFIC SOCIETIES AND PROFESSIONAL ORGANIZATIONS**

Dr. Agodoa thanked the societies and organizations for their continued support and acknowledged the 16th Annual NMRI Workshop travel award winners.

### **American Society of Nephrology (ASN)**

*Mark D. Okusa, M.D., President, ASN*

Dr. Mark Okusa described the ASN, which has 18,300 members from 125 different countries, and its mission to prevent, treat, and cure kidney diseases throughout the world by educating health professionals and scientists, advancing innovation, communicating knowledge, and advocating for patients. He noted

that the ASN is committed to diversity and inclusion, career development, and mentorship within the Society. To frame the nephrologists' perspective, Dr. Okusa first reviewed kidney disease statistics. More than 850 million people worldwide are estimated to have kidney diseases; of the 850 million, 843 million have chronic kidney disease (CKD) stages 1–5; 13.3 million have acute kidney injury (AKI); 7 million have end-stage renal disease (ESRD); 3.9 million are treated with renal replacement therapy; and more women than men have CKD. The ASN enterprise includes the Foundation for Kidney Research, the Kidney Health Initiative (KHI), and the Nephrologists Transforming Dialysis Safety (NTDS) initiative. Recognizing the need to continuously fund kidney research, the ASN established the Foundation for Kidney Research in 2012. The KHI, a collaboration between the FDA and the broader nephrology community, was started in 2012 to optimize kidney health and evaluate the safety of drugs, devices, biologics, and food products. More than 25 organizations from academia, private industry, and the pharmaceutical industry are members of the KHI. In 2016, ASN partnered with the CDC to form the NTDS to actively pursue eliminating preventable infections in dialysis facilities.

Dr. Okusa discussed the ASN's diversity and inclusion efforts. He pointed out that the guiding principles of the ASN's values statement on diversity and inclusion—inclusiveness, mentorship, health equity, patient advocacy, and engagement—have not changed. A Diversity and Inclusion Work Group established in 2013 was renamed the Diversity and Inclusion Committee in 2017. Dr. Okusa acknowledged Committee chair and NMRI member Dr. Diedra Crews and noted the diverse background of the members, and he highlighted the Committee's activities and accomplishments. The Committee has provided travel awards to 72 NMRI workshop participants from 2015 to 2018, recommended strategies for improving the diversity of ASN speakers and presenters, and nominated Committee member Dr. Jason Cobb to represent the ASN on the National Collaborative for Improving the Clinical Learning Environment Health Care Disparities Work Group. The Committee's 2018 priorities include expanding the ASN member demographic metric collection; funding a second ASN-Harold Amos Medical Faculty Development Program (AMFDP) Award; presenting an abstract at the American Association of Medical Colleges' Health Workforce Research Conference; establishing an LGBTQI (Lesbian, Gay, Bisexual, Transgender, Queer/Questioning, and Intersex) and ally member networking event during Kidney Week; and engaging in outreach related to NIH's *All of Us* Research Program.

ASN's commitment to career development for kidney professionals is threefold. Its first goal is to improve opportunities for sponsorship and mentorship by connecting early and mid-career professionals with influential leaders in the field. A new online mentor-mentee curriculum tool tailored specifically for this purpose will be linked to the new ASN Career Advancement Community for interactive dialogue. The ASN Career Advancement, Diversity and Inclusion, and Workforce and Training Committees have been engaged to develop animated presentations, case studies, and informational guides related to this goal. The second goal is to develop, support, and disseminate career development and leadership training resources and best practices for all career levels. The ASN Career Advancement Committee, charged with identifying gaps in advancing careers for kidney professionals, was established in 2017 and has made significant accomplishments in the first year. The third goal is to develop tools for broader information exchange between professionals. To date, the ASN Career Advancement Community has had 1,121 contributors, 15 communities, and 3,868 international logins.

Dr. Okusa detailed the ASN funding opportunities for students, trainees, and early career professionals. Research fellowships for M.D.'s, D.O.'s, and Ph.D.'s include the Ben J. Lipps Research Fellowship Program Award and the William E. Mitch International Scholars Program Travel Award. The new ASN Predoctoral Fellowship Award Program is available to Ph.D. students. The Kidney Students and Residents at Kidney Week Travel Award supports students, residents, and Ph.D. candidates. Medical and

graduate students are supported by the Student Scholar Grants Program and the Kidney Tutored Research and Education for Kidney Scholars (TREKS) Award. Two TREKS program sites are available: Mount Desert Island Biological Laboratory in Bar Harbor, Maine, and the University of Chicago in Chicago, Illinois. The ASN supports early career professionals through career development grants, the William and Sandra Bennett Clinical Scholars Program, and the AMFDP Award.

### **American Association for the Study of Liver Disease (AASLD)**

*Charles Howell, M.D., Professor, Howard University*

Dr. Charles Howell described the activities intended to foster diversity and inclusion in the AASLD and provided an overview of the AASLD Foundation and Research Program. The AASLD was founded in 1950 and has become the leading organization of scientists and health care professionals committed to preventing and curing liver diseases. The mission of the AASLD is to advance and disseminate the science and practice of hepatology and to promote liver health and quality patient care. Dr. Howell emphasized that the AASLD is committed to diversity and inclusion; the AASLD Diversity Committee, which he currently chairs, was established in 2016. The Diversity Committee is tasked with defining the demographic composition of the AASLD membership and proposing strategies to promote recruitment and increase engagement of diverse groups that are underrepresented in the medical profession. The Diversity Committee also will promote health disparities education and research within the AASLD, improve health outcomes, and reduce disparities. The Diversity Committee will sponsor a workshop on ethnic and racial disparities in liver disease at the 2018 Annual Liver Meeting on November 12, 2018, in San Francisco, California, as part of its health disparities education and research-first initiative. In addition, the Diversity Committee will continue to host the Annual Liver Meeting Diversity Reception, which has been ongoing since 2016. Dr. Howell acknowledged the Diversity Committee members, many of whom also are NMRI members.

Dr. Howell informed participants that the AASLD Foundation is the largest private supporter of hepatology research and training in North America, with goals to invest in innovative hepatology research and the people who study and treat liver disease. The Foundation's Research and Career Development Awards Program supports basic, clinical, and translational and outcomes research; travel awards; and career awards that extend from the advanced practice provider to the mid-career researcher. From 2000 to 2017, the AASLD invested \$42.9 million in hepatology research and supported 1,133 total awards. In 2017 alone, more than \$3.5 million was made available for research to support 114 awards. Among all the research awardees funded from 2008 to 2015, 48 percent later received federal funding as independent investigators. This success speaks to the positive outlook and bright future for hepatology researchers. Additional information on grants and funding can be accessed at the AASLD website.

### **American Society for Bone and Mineral Research (ASBMR)**

*Alexandra Aguilar-Perez, Ph.D., Postdoctoral Fellow, Indiana University (Travel Award Winner)*

Dr. Alexandra Aguilar-Perez described the ASBMR, its mission, and its activities. The ASBMR has served the bone, mineral, and musculoskeletal scientific community for more than 40 years and has a diverse membership of approximately 4,000 members worldwide; 52 percent are in the United States and 48 percent are international; 54 percent are Ph.D.'s; 46 percent are M.D.'s; and 18 percent are early stage investigators (ESIs). The Society's programs and education are driven by its mission to advance excellence in bone, mineral, and musculoskeletal science worldwide and promote translation of basic and clinical research to improve human health. The ASBMR Annual Meeting is the world's largest and most diverse meeting in the bone, mineral, and musculoskeletal research field, attracting more than 3,000 attendees from more than 70 countries. In 2017, 1,100 posters and more than 100 educational sessions were presented. More than 100 travel grants and awards are available to U.S. and international members

at every stage of their career. The 2018 Annual Meeting will be held in Montreal, Quebec, Canada, from September 28, 2018, to October 1, 2018.

Dr. Aguilar-Perez highlighted the ASBMR Annual Meeting travel grants, including the Young Investigator Diversity Travel Grant, which provides \$500 for the top-scoring abstract submitted by a young investigator from a URM group. The Mid-Career Faculty Travel Grant, the Research Team Travel Grant, and the Young Investigator Emerging Country Travel Grant were introduced in 2017 and are continuing. Other awards presented at the Annual Meeting include the President's Award, the Phoebe Leboy Professional Development Award, and the Fund for Research and Education Research Grant Award. The Society's newest award is the Federation of American Societies for Experimental Biology (FASEB) Mentored Poster/Platform Presenter Travel Award to attend the 2018 Annual Meeting, which is available to students from URM groups and postdoctoral/clinical trainee fellows.

The ASBMR publishes the *Journal of Bone and Mineral Research (JBMR)*, *JBMR Plus*, and *The Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. Members receive online access to all publications free of charge, are afforded significant discounts on article submissions, and have free access to the online Education Resource Center. In addition, members receive more than \$350 in savings on Annual Meeting registrations, engage with a global network of scientific researchers and clinician scientists to foster future collaborations, and are provided the opportunity to apply for research funding and travel grants exclusive to ASBMR members.

Dr. Aguilar-Perez remarked that the ASBMR continues to increase its activities and visibility of underrepresented members throughout the Society. The Diversity in Bone and Mineral Research Committee has advocated for increased travel grant funding for URM in the United States and globally, has secured funding in perpetuity to ensure that the NMRI Travel Grant is offered annually, and has secured funding for the new FASEB Mentored Poster/Platform Presenter Travel Awards. The Diversity Committee also is working to continue its annual programming and networking activities at the 2018 Annual Meeting—including a Networking Reception, a Networking Lounge in the Discovery Hall, and a Poster Competition—as well as working to increase the visibility and representation of diverse members in the program's speakers and moderators. Dr. Aguilar-Perez encouraged participants to join the ASBMR and to visit the website for additional information.

### **American Diabetes Association (ADA)**

*Allison McElvaine, Ph.D., Director, Research Communications, ADA*

Dr. Allison McElvaine described ADA's research programs and noted the increasing trend in DM across the United States from 1994 to 2017. In fact, DM affects 1 in 11 Americans; increases the risk of serious health complications; disproportionately affects individuals from racial and ethnic minority groups; and accounts for rising health care costs of more than \$327 billion annually. Dr. McElvaine emphasized that to address its mission to prevent and cure DM and improve the lives of all people affected by DM, the ADA recognizes that the only way to ultimately end the burden of DM is through research. Advances in research have resulted in 12 classes of medications to treat DM; the ADA's Standards of Care for DM; and reduced complications from the disease. To date, the ADA has invested more than \$807 million in DM research, including \$37.4 million in 2017. The return on investment shows that within 5 years of completing an ADA project, nine out of 10 ADA-funded researchers successfully received funding from other sources to expand their work.

Dr. McElvaine informed participants that the Association's research activities consist of three distinct programs: the Core Research Program, the Collaborative Targeted Research Program, and the Pathway to Stop DM Program. The objective of the Core Research Program is to support innovative early stage

research and ESIs. Funding opportunities support topics relevant to all types of DM, DM risk, and complications and are available at all career stages. Specific funding mechanisms are available to support minority undergraduate students and postdoctoral fellows. The Core Research Program has been successful in retaining scientists dedicated to DM research (99 percent), leveraging investments (\$7.36 gained for each \$1 invested), and advancing the science (six publications per grant).

The Collaborative Targeted Research Program supports research on specific high-need, emerging, or promising topic areas not represented in the core research portfolio. Dr. McElvaine emphasized that grants are made available only when a sponsor or donor provides funding. Recent projects include the GlaxoSmithKline-supported initiative to explore the emerging connections between the microbiome, nutrition, and metabolism and the Pfizer Inc.-supported initiative that funds postdoctoral fellows in cardiometabolic research at institutions in the New England region.

Dr. McElvaine noted that the ADA Core and Targeted Research Programs are achieving their goals, yet challenges remain. Few scientists are choosing DM research careers, and many experts in the field are retiring; the innovation process can take time to advance; and the prevalence of DM and diabetes-related complications continues to grow. Furthermore, DM research is underfunded at the federal level in terms of prevalence and research dollars allotted compared to other diseases, including cancer and HIV/AIDS. To address these challenges, the ADA launched the Pathway to Stop DM Program in 2013 to attract brilliant minds at the peak of their creativity, invest in people rather than projects, and provide freedom, autonomy, and resources to researchers. Three Pathway to Stop DM funding mechanisms are available: the Initiator Award available to postdoctoral fellows, the Accelerator Award for ESIs, and the Visionary Award, which is open to scientists established in other disciplines who are interested in applying novel approaches to DM research. From 2012 to 2017, 29 researchers were selected from more than 540 nominations; six Pathway Initiator awardees have secured faculty positions; and Pathway awardees have collectively published 60 papers and filed seven patents.

Dr. McElvaine encouraged participants to apply for grants, share data at the ADA's annual Scientific Sessions and in peer-reviewed journals, volunteer to review grants or serve on committees, and support the ADA in its mission.

### **Endocrine Society**

*Rocio Pereira, M.D., Assistant Professor, Joslin Diabetes Center*

Dr. Rocio Pereira informed participants that the Endocrine Society is an international community consisting of clinical practitioners and basic and clinical researchers representing 122 countries. The Society has more than 18,000 members, 60 percent in the United States and 40 percent international. Peer-reviewed publications include *Endocrine Reviews*, *Endocrinology*, and the *Journal of the Endocrine Society*. The Endocrine Society has incorporated health disparities into many of its activities, including the publication of feature articles. The Society convenes an annual meeting (commonly called ENDO), and features an online career center (Endocareers), which provides a mentor exchange program, in-training and early career resources, as well as board certification training for clinical endocrinologists.

The Endocrine Society awards program spans all career levels and includes ENDO travel awards, scientific achievement awards, summer research fellowships, and student and early career awards. In addition, one of the Society's diversity initiatives is the NIDDK-sponsored Future Leaders Advancing Research in Endocrinology (FLARE) program to support training in endocrine research for URM. Components of the FLARE program include workshops, internship paths, mentorship paths, and ENDO travel awards.

## **WRITING WORKSHOP—SESSION II: LET’S START WITH THE SYSTEMATIC REVIEW**

*Patricia Heyn, Ph.D., Associate Professor, University of Colorado Denver, Anschutz Medical Campus*  
*Lillian Hoffecker, Ph.D., Research Librarian, University of Colorado Denver, Anschutz Medical Campus*

Drs. Heyn and Hoffecker led participants in an exercise to perform the steps for conducting a SR using the synthesis methodology discussed in Session I. Participants were introduced to SR software and tools and reviewed examples of search data tables, checklists, and published SRs. Participants selected one of four protocol topics and worked in teams to develop an SR question.

## **POSTER SESSION AWARDS**

The workshop’s four scientific presenters, who were selected from the pool of submitted abstracts, were presented with plaques commemorating their achievements. All the meeting participants who presented posters at this year’s workshop were thanked for their time and willingness to share their research with the NMRI community. The four winners of the poster session awards were then announced and congratulated:

### **Basic Science Poster Award**

*Yaritza Inostroza-Nieves, Ph.D., Assistant Professor, University of California, San Diego*  
“Endothelin-1 Regulates Molecules of the Major Histocompatibility Complex: Role in Sickle Cell Disease”

### **Translational Science Poster Awards**

*Wairimu Magua, Ph.D., Postdoctoral Fellow, Emory University*  
“A System-Level Multiple Component Intervention to Increase Awareness of the Impact of the New Kidney Allocation System on Patient Care in Dialysis Facilities”

*Elimelda Moige Onger, Ph.D., Associate Professor, North Carolina A&T University*  
“Undiagnosed Kidney Injury in Uninsured and Underinsured Diabetic African American Men and Putative Role of Meprin Metalloproteases in Renal Pathology”

### **Clinical Science Poster Award**

*Melawhy Garcia, Ph.D., Postdoctoral Research Fellow, University of California, San Diego*  
“Correlates of Low-Adherence to Oral Hypoglycemic Medications Among Hispanic/Latinos with Type 2 Diabetes”

## **BUSINESS MEETING AND COMMITTEE REPORTS**

### **Oversight Committee Report**

*Rocio Pereira, M.D., Assistant Professor, Joslin Diabetes Center*

Dr. Pereira explained that the Oversight Committee helps to guide the NMRI and relies heavily on the feedback of its members. The Oversight Committee advocates for funding, recruits new members, and coordinates with professional societies and organizations to facilitate informal gatherings at scientific conferences, such as the NMRI Annual Workshop. Dr. Pereira reminded members to complete the evaluation survey, increase awareness of the Network among their peers and home institutions, and share news of accomplishments and personal anecdotes to be included in the 2019 NMRI Newsletter.



## **Planning Committee Report**

*Jose Romero, Ph.D., Associate Physiologist, Brigham and Women's Hospital, Harvard Medical School*

Dr. Romero encouraged members to forward comments and suggestions for future NMRI meetings to the Planning Committee, and he provided an update on the 2017 activities. The Planning Committee convened by conference call once each month to share and discuss ideas and make decisions related to the broad mandate of the Committee. He introduced the incoming chair, Dr. Francisco Villarreal, who noted that the 2019 Annual Workshop is being planned and is scheduled to be held in Bethesda, Maryland; the dates are to be determined. The theme of the 2019 workshop will focus on NIDDK women investigators. Members are welcome to provide input on the theme and topical sessions.

Dr. Agodoa, accompanied by Ms. Martinez, presented NMRI Committee chairs with certificates in appreciation of their service.

## **SCIENTIFIC PRESENTATIONS**

### **Aspirin and Other NSAIDs Reduce the Risk of Biliary Tract Cancers: A Swedish Population-Based Cohort Study**

*Lorena Marcano-Bonilla, Predoctoral Fellow, Mayo Clinic*

Ms. Lorena Marcano-Bonilla presented her research on the population-based study of the risk and protective factors of biliary tract cancers (BTCs). Originating in the bile duct epithelium, bile duct cancer or cholangiocarcinoma (CCA) is classified into two categories: intrahepatic CCA (iCCA) or extrahepatic CCA (eCCA). The eCCA type is further divided into perihilar CCA (pCCA) and distal CCA (dCCA). BTCs are comprised of gall bladder cancers (GBCs) and CCAs. Previous case control studies have shown that the use of aspirin significantly decreased the risk of CCA and its subtypes. Case control studies, although informative, may overestimate the treatment effects.

The aim of this study was to determine whether the use of low-dose aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) affects the risk of BTC and its subtypes in a nationwide population-based cohort of Swedish adults. The hypothesis is that the use of low-dose aspirin and NSAIDs decreases the risk of BTC. The Mayo Clinic (Dr. Lewis R. Roberts) collaborated with the Karolinska Institutet (Dr. Nele Brusselaers) to conduct this study, which compared cohorts of adult patients exposed to maintenance therapy with low-dose aspirin, other NSAIDs, or statins to unexposed adult patients. Exposure was determined by the Anatomical Therapeutic Classification codes recorded in the Swedish Prescribed Drug Registry. Outcomes were evaluated using the International Classification of Diseases (ICD) codes recorded in the Swedish Cancer Registry. Information on the covariates was obtained from the Swedish National Patient Registry. The cohort consisted of 5.76 million unique individuals. Patients younger than 18 years of age and those having a preexisting cancer, other than non-melanoma skin cancer, were excluded from the study. Statistical analysis was performed using a time-dependent Cox proportional hazard model to determine hazard ratios (HR).

Ms. Marcano-Bonilla discussed the study results. The baseline characteristics of low-dose aspirin users revealed that 18 percent of the cohort used low-dose aspirin, whereas 82 percent did not. Data were graphically illustrated in a forest plot in which a hazard ratio (HR) of 1 indicates no effect, a HR of less than 1 indicates decreased risk, and a HR greater than 1 indicates increased risk. The HRs were adjusted for BTC and associated diseases, cirrhosis and viral hepatitis, autoimmune diseases, cardiovascular and metabolic diseases, and lifestyle habits. Users of low-dose aspirin were 19 percent less likely to develop BTCs. Similar results were observed for CCA, GBC, and eCCA, but not for iCCA. The baseline characteristics of users of other NSAIDs showed that 42 percent of the study cohort used other NSAIDs

and 58 percent did not. Use of other NSAIDs appears to increase the risk of BTC, and the effects hold for all subtypes. This effect could be due to an indication bias rather than the drugs themselves.

In summary, Ms. Marcano-Bonilla presented a population-based cohort study that investigated the risk and protective factors for BTC and its subtypes. The cohort of 5.7 million adults represents with virtually complete enumeration the use of low-dose aspirin and other NSAIDs in the Swedish population. This study provides strong epidemiological evidence in favor of the chemopreventive role of low-dose aspirin and has important translational implications. Ms. Marcano-Bonilla acknowledged her mentor, Dr. Roberts, Mayo Clinic; study collaborator, Dr. Brusselaers, Karolinska Institutet; and the Mayo Clinic statistical team.

### *Discussion*

Dr. Crews pointed out that this epidemiological study assessed the association of aspirin use on the risk of developing BTCs, an observation that differs from inferring protection from the use of aspirin. She also asked about the number of study participants that developed BTCs who did not use aspirin. Ms. Marcano-Bonilla commented that additional studies are needed to further clarify the protective role of aspirin. Animal studies would be essential to elucidate the mechanism of action. If further preclinical evidence supporting aspirin as a chemopreventive agent is generated, clinical trials would be the next steps. These, however, would be challenging because this is a rare form of cancer that would require a large number of participants to be followed for a prolonged period of time. A viable option would be conducting trials on patients with primary sclerosing cholangitis, who are known to be at high risk for developing BTCs.

A participant asked whether other antiplatelet therapies were considered for this study. Ms. Marcano-Bonilla explain that only aspirin and other non-aspirin NSAIDs were used in the study. Assessing other antiplatelet therapies could be considered for the future.

### **Impact of Education and Protocol-Based Management of Community-Acquired Acute Kidney Injury: Preliminary Results from the Oby25 Pilot Feasibility Project**

*Etienne Vasconcellos DeMacedo, M.D., Ph.D., Assistant Adjunct Professor, University of California, San Diego*

Dr. Etienne Vasconcellos DeMacedo presented preliminary results of the International Society of Nephrology's AKI Zero Preventable Deaths by 2025 (Oby25) pilot project, which aims to assess the feasibility of implementing interventions to optimize care of AKI in low-resource settings. Preventable deaths are those involving missed identification or delayed recognition of a diagnosis of AKI. Most of the studies assessing AKI have focused on critical care patients in hospital intensive care units; very few have addressed community-acquired AKI, in which the patient had developed AKI prior to hospitalization. Community-acquired AKI often is undiagnosed, associated with worse outcomes, and more prevalent in low-resource settings.

The first part of the feasibility study was conducted at three sites—Dharan, Nepal; Blantyre, Malawi; and Cochabamba, Bolivia—and was implemented in three phases: observation, education/training, and intervention. Patients receiving care in community health care centers were screened and assigned a risk score for AKI based on their symptoms. Patients with moderate to high risk were consented and enrolled in the study. Serum creatinine levels were tested using two methods: StatSensor® Point-of-Care Creatinine Analyzer and the conventional urine dipstick test. Patients were monitored and outcomes measured. During the intervention phase, health care providers also contacted a physician in the supporting hospital for guidance on patient management.

Patients were assigned to one of two disease categories—CKD or acute kidney disease (AKD)—based on history and point-of-care test results. Repeat creatinine testing was used to identify development of AKI by 7 days. Patient course outcomes, renal outcomes, and overall outcomes were determined at 1, 3, and 6 months.

A total of 3,577 patients were screened, 1,929 in the observation phase and 1,630 in the intervention phase. Of these patients, 91 percent were adults and 9 percent were children. At enrollment, more than two-thirds of the patients had evidence of renal dysfunction, 9.4 percent had a history of CKD, and 66.3 percent were considered to have AKD. More patients with AKI were identified in the intervention phase (35 percent) than in the observation phase (25 percent). Patients with AKD at enrollment and at 7 days were more likely to be admitted in community health centers or hospitals. Fluid therapy was more frequent in the intervention phase, and the volume of oral and intravenous fluid therapy was higher in the intervention phase than in the observation phase. The mortality rate in patients with moderate or stage 2 AKI was significantly lower in the intervention phase than in the observation phase.

Dr. DeMacedo noted that the Oby25 pilot feasibility project successfully demonstrated the utility of a symptom-based health assessment risk score, coupled with a point-of-care serum creatinine test and a urine dipstick test, to detect kidney disease in patients presenting to health care centers in low resource settings. Recognition and management of patients was facilitated and improved with the combination of staff education and training about AKI, the point-of-care test, and guidance through teleconsultation. Dr. DeMacedo thanked the study participants, study collaborators, and health care providers for supporting this work.

### *Discussion*

A participant observed that creatinine is a late marker for AKI asked whether patients in this setting would likely be diagnosed properly based on creatinine levels. Dr. DeMacedo explained that most patients would not be diagnosis in this setting due to a lack of resources and barriers to care.

### **Outcomes of Donor and Recipient Obesity in Kidney Transplantation**

*Jacantha Buggs, M.D., Procurement Surgeon and Research Physician, Tampa General Hospital*

Dr. Jacantha Buggs described a study to evaluate kidney transplant outcomes relative to donor and recipient obesity. The increasing trend in obesity has been linked to increases in type 2 diabetes, ESRD, and kidney failure, therefore increasing the odds of a patient's needing a transplant. Prior studies on transplant outcomes and obesity have focused on obese recipients, rather than obese donors. This study investigated the outcomes of donor and recipient obesity in kidney transplantation and tested the hypothesis that the outcomes differ based on the combination of obesity in the donor and recipient. The objective was to evaluate kidney transplant patient and graft survival based on different combinations of donor and recipient obesity.

A retrospective cohort study of all consecutive kidney transplants performed at Tampa General Hospital (TGH) from January 1, 2012, to December 31, 2016, was conducted. Patients were stratified into four categories: (1) obese donor and obese recipient (ODR), (2) non-obese donor and non-obese donor recipient (NODR), (3) obese donor and non-obese recipient (OD/NOR), and (4) non-obese donor and obese recipient (NOD/OR). Variables used included delayed graft function, graft survival, and patient survival. The TGH study reviewed 1,131 kidney transplants: 96 ODR (8.5 percent); 608 NODR (53.8 percent); 208 OD/NOR (18.4 percent); and 219 NOD/OR (19.4 percent). The BMIs ranged from 13 to 63 kg/m<sup>2</sup>. The kidney donor profile index (KDPI) is a measure of donor quality. Lower KDPI values indicate better quality. In this study, KDPIs were significantly lower when both donor and recipient were not obese and higher when both donor and recipient were obese, suggesting that poor donor quality is

related to donor/recipient obesity. The delayed graft function was significant for ODR (25 percent) compared to NODR (10.4 percent) and for ODR (25 percent) compared to OD/NOR (11.5 percent). There were no differences in overall graft survival. Overall patient survival was significant for OD/NOR (98.1 percent) compared to ODR (94.8 percent), NODR (94.7 percent), and NOD/OR (90.9 percent).

Dr. Buggs noted that the national transplant population profile evaluated during the same study period and stratified accordingly was similar to the TGH study population. The next step was to conduct a retrospective cohort study of the national population from the same study period, this time investigating one donor/two recipient kidney transplants, stratified into the four categories described earlier. Living, pediatric, multi-organ, bilateral, and *en bloc* kidneys were excluded. The single-donor national population consisted of 18,104 kidney transplants—3,291 ODR (18.2 percent); 5,761 NODR (31.8 percent); 3,291 OD/NOR (18.2 percent); and 5,761 NOD/OR (31.8 percent)—and confirmed the prior findings.

Dr. Buggs concluded that outcomes with obesity in kidney transplantation vary based upon the combination of obesity in both the donor and the recipient. Delayed graft function was significantly worse with obesity in both the donor and recipient (local [i.e., TGH], national, and single donor). Graft survival outcomes were significantly worse when both donor and recipient were obese in the national and single-donor studies. Patient survival outcomes were significantly worse when both the donor and recipient were obese in the local and national cohorts.

Dr. Buggs thanked the study team, LifeLink of Florida Legacy Fund, and the University of South Florida for supporting this work.

### **Loss of Endothelin B Receptor Function Activates NOD-Like Receptor and Inflammasome Pathways in Renal Outer Medulla During Type 1 Diabetes Through an ER Stress-Independent Mechanism**

*Carmen De Miguel, Ph.D., Instructor, The University of Alabama, Birmingham (UAB)*

Dr. Carmen De Miguel described the results of a study on the loss of endothelin B (ET<sub>B</sub>) receptor function and activation of the nucleotide-binding oligomerization domain-like (NOD-like) receptor and inflammasome pathways in type 1 diabetes. Endothelin-1 (ET-1) has been shown to be involved in diabetes-related inflammation, has proinflammatory properties in renal tissue, and mediates its actions via two receptors, the endothelin A (ET<sub>A</sub>) receptor and the ET<sub>B</sub> receptor. The objective of this study was to determine the role of the endothelin system in the activation of the inflammasome pathways in the kidney during type 1 diabetes. In the experimental design, ET<sub>B</sub>-deficient rats and transgenic (TG) control rats were used, and baseline urine samples were collected prior to the study. Total lack of the ET<sub>B</sub> receptor is lethal, so this rat strain was rescued years ago by the reintroduction of the ET<sub>B</sub> receptor exclusively in the neuronal tissue. These rats have elevated levels of circulating ET-1, and have overactivation of the ET<sub>A</sub> receptor. Animals (four to six per group) were dosed intravenously with 65 mg/kg of streptozotocin to induce type 1 diabetes. Insulin pellets were implanted 1 day after injections, and animals were monitored for 10 weeks. Ten weeks after diabetes was induced, kidneys and urine were collected and analyzed.

Results showed that diabetic ET<sub>B</sub>-deficient rats developed exaggerated renal damage that was not observed in diabetic TG control rats. This effect was persistent in the cortex and renal outer medulla regions of the kidney. Markers of kidney damage, albumin and protein excretion, and Kidney Injury Molecule-1 (KIM-1) were significantly higher in ET<sub>B</sub>-deficient rats than in the diabetic TG control rats. The expression of inflammasome genes was assessed in the kidney renal outer medulla, because this area of the kidney also presented elevated cell death. DM led to statistically significant upregulation of the NOD-like receptor family pyrin domain containing 5 (NLRP5) and interleukin-1 beta (IL-1β). Endoplasmic reticulum (ER) stress has been identified as an inducer of inflammasome activation. In this

study, there were no differences in ER stress markers between diabetic ET<sub>B</sub>-deficient rats and TG control rats.

Dr. De Miguel noted that loss of ET<sub>B</sub> receptor function leads to overactivation of the renal inflammasome and worsening of diabetic kidney disease. Activation of the inflammasome pathway is not mediated by ER stress in this diabetic animal model. She proposed a working hypothesis that ET-1 is upregulated in type 1 diabetes, leading to activation of the ET-1 receptors. When the ET<sub>B</sub> receptors are dysfunctional, as in many diabetic patients, ET<sub>A</sub> receptors are overactivated and subsequent inflammasome activation occurs, resulting in kidney injury. Dr. De Miguel thanked her mentors, Drs. Jennifer S. and David M. Pollock, UAB, for their support and the UAB Division of Nephrology.

## **NEXT STEPS AND ADJOURNMENT**

*Jose Romero, Ph.D., Associate Physiologist, Brigham and Women's Hospital, Harvard Medical School*

Dr. Romero thanked participants for attending the 16th Annual NMRI Workshop and Meeting.

Ms. Martinez thanked everyone for attending and noted that the NMRI South Regional meeting is scheduled for November 2018. Members wishing to participate in planning that meeting were encouraged to use the signup sheet in the foyer. Ms. Martinez reminded members to update their NMRI profiles to keep the Network current and accurate.

Dr. Agodoa remarked that the NMRI, which started as an experiment 16 years ago, is a success today because of the members. He thanked participants for supporting the meeting and expressed appreciation to Ms. Martinez for her continued support. Members are welcome to send any comments or suggestions to the NIDDK.