

Volume 7 Issue 1

# Forefront

LEADING THE WAY TO A CURE FOR DIABETES

## INSIDE:

- Searching for new therapeutics through type 2 genetics
- Studying the role of cellular stress in type 1 diabetes
- Connecting obesity and the immune response
- Discovering new connections between diabetes and Vitamin D
- Improving beta cell survival
- Helping to stop diabetic cardiac complications

## Research Grant Review Committee Chair Letter Laurence Kennedy, MD, FRCP



Welcome to the latest edition of *Forefront*. With each passing week, day, and hour, millions of people continue to struggle with diabetes. Therefore, the American Diabetes Association will continue to honor its commitment to people with diabetes by investing in scientifically sound and clinically relevant research. Continuing financial support of Association-funded researchers, especially our young investigators, is key to achieving these objectives. On their behalf, I want to thank you for your continuing support in these financially challenging times.

Our latest issue has some exciting changes in format. We have expanded the number of Association-funded investigator profiles and are now presenting these based on geographical regions. We are giving greater prominence to featured donor profiles and have added informational pages to provide the latest updates from our Research Foundation. We also hope you enjoy the *Hot Topics*, which features timely information about cancer and diabetes.

My term as Chair of the RGRC is ending – it has been a pleasure and privilege to serve the Association and the wider diabetes community in this capacity. I wish my successor, Dr. David Bleich, well and I know that under his guidance the ADA will continue to fund the most innovative diabetes research.

Sincerely,

A handwritten signature in black ink, appearing to read "Laurence Kennedy".

Laurence Kennedy, MD, FRCP



## Research Foundation Chair Letter Ralph Yates, DO

Dear Friends,

During the February 2009 Research Foundation Board meeting, the question was asked, “When will we find a cure?” There was complete silence around the table. When finally conversation ensued, we all recognized that this was the wrong question. The seminal issue is *how*. How will we find a cure?

The majority of scientific funding comes annually from the National Institutes of Health (NIH), and in 1980, a first-time NIH grant recipient was age 37; now they are 42. At this rate, by 2020, there will be more researchers older than 68 than in their 20s and 30s, according to Elias Zerhouni, past Director of the NIH. Some within the diabetes research community say we have lost an entire generation of researchers.

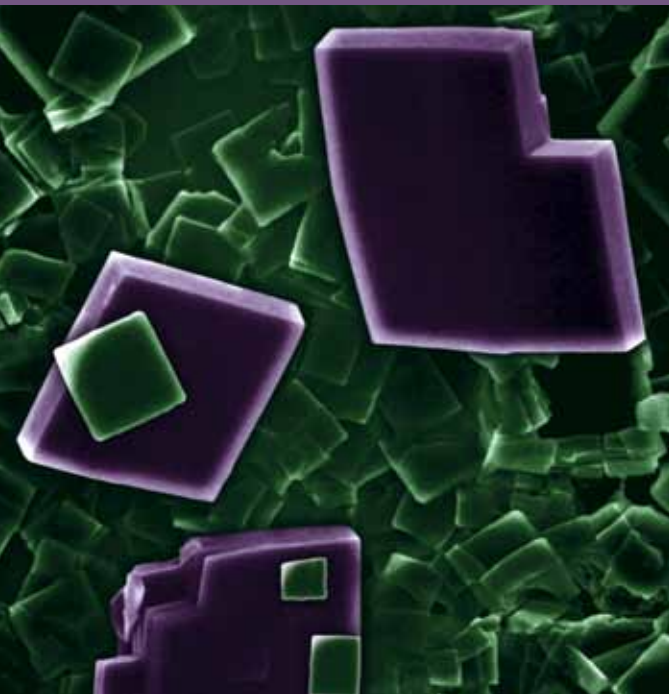
As destructive as this is to our pipeline of new scientists, this exposes a far larger problem. The most creative years for scientists are generally in the first ten years of their careers. Frederick Banting and Charles Best were 30 and 22, respectively, when they discovered insulin. All too often, promising individuals must choose a scientific field based on where consistent funding is available.

This brings us back to the question “how will we find a cure?” In our quest to find the next Banting and Best, we need to provide researchers with seed money—enough money to encourage a lifetime of study. We are working on a plan to correct this. Stay tuned.

Thank you and all my best,

A handwritten signature in black ink, appearing to read "Ralph Yates".

Ralph Yates, DO



A scanning electron micrograph was made of glargine (lantus) insulin crystals. The magnification is 1000x.

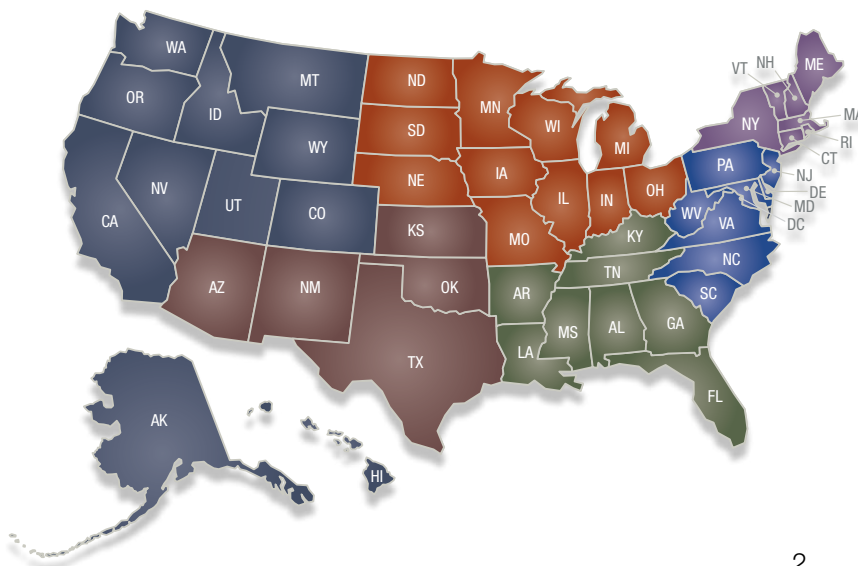
Submitted by: David S. Schade, MD Professor of Medicine and Chief, Division of Endocrinology University of New Mexico School of Medicine

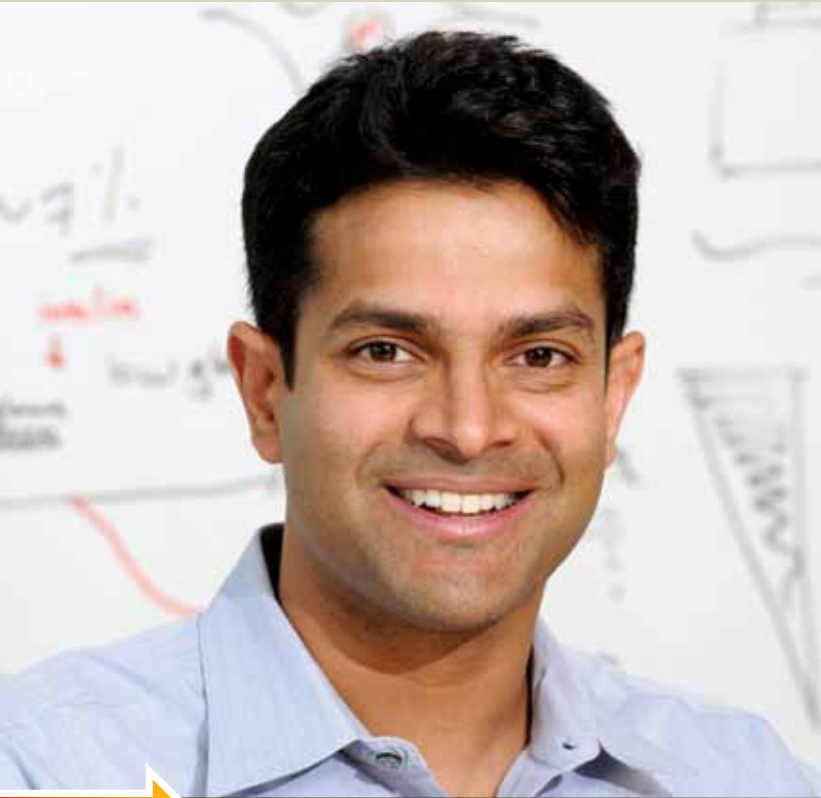
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## Table of Contents

<b>Research Grant Review Committee Chair Letter</b>	
<b>Research Foundation Chair Letter</b>	<b>1</b>
<b>NorthEast</b>	
Vamsi Mootha	<b>3</b>
Mary Elizabeth Patti	<b>5</b>
<b>MidAtlantic</b>	
Jon Piganelli	<b>6</b>
H. Henry Dong	<b>8</b>
<b>SouthEast</b>	
Alyssa Hasty	<b>9</b>
Deborah Young-Hyman	<b>11</b>
<b>MidWest</b>	
Carlos Bernal-Mizrachi	<b>12</b>
Kurt Fisher	<b>14</b>
<b>Research Updates-Announcements, In the News</b>	<b>15,16</b>
<b>Donor Profiles</b>	
Richard A. and Susan F. Smith	<b>19</b>
Joe C. and Judith E. Cook and Family	<b>20</b>
<b>SouthWest</b>	
Philipp Scherer	<b>21</b>
Melanie Cobb	<b>23</b>
<b>Mountain/West</b>	
Evan Dale Abel	<b>24</b>
John David Symons	<b>26</b>
<b>Hot Topics</b>	<b>27</b>
<b>Research Updates-Noteworthy Advances</b>	<b>33</b>
<b>Research Foundation News</b>	<b>37</b>
<b>Research Foundation Breakthrough Highlights</b>	<b>38</b>
<b>Viewpoint</b>	<b>back cover</b>





© Mootha lab

**Occupation:** Associate Professor of Systems Biology and Medicine, Massachusetts General Hospital, Harvard Medical School; Senior Associate Member, Broad Institute, Boston, Massachusetts

**Professional Focus:** Mitochondrial biology, genomics, metabolism

**Outside Interests:** Tennis, squash, watercolor painting

**Research Funding:** American Diabetes Association  
Smith Family Foundation Pinnacle Program  
Project III  
*“Cellular models of human type 2 diabetes genes”*

**Amount Awarded:** \$993,818

*Funded by the Richard and Susan Smith Family Foundation, Chestnut Hill, Massachusetts*

## Vamsi Mootha, MD

**F**or the past five years, I have been a grantee of two “Pinnacle Program Project Awards.” These awards were created in 2003 to stimulate collaborative projects with a focus on type 2 diabetes. Through the American Diabetes Association Research Foundation and the Smith Family Foundation, I have been funded since 2005 with the “ADA-Richard and Susan Smith Family Foundation Pinnacle Program Project Awards,” which have funded my joint projects in genetics of diabetes.

At the onset of the first Smith Family Pinnacle Award in 2003, I was a postdoctoral fellow with Eric Lander, PhD, at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts. There, I had the privilege of collaborating closely with

Drs. David Altshuler, Todd Golub, Joel Hirschhorn, and Gary Ruvkun, then the co-investigators on the inaugural Smith Family Pinnacle Program Project Award.

The group’s goal was to use human and worm genetics to dissect the pathways that are operative in type 2 diabetes and obesity. I collaborated closely with Dr. Altshuler’s team to help discover a metabolic program that was consistently altered in type 2 diabetic muscle in humans.

Thanks to the success of that first generation project, David Altshuler and Joel Hirschhorn were awarded a Pinnacle Project renewal in 2005. This time, the collection of investigators also included three newly-minted Assistant Professors—Kaveh Ashrafi,

Mark Daly, and myself. We continued to successfully dissect the genetics of diabetes and obesity. However, I then launched a new effort in chemical screening aimed at discovering drug-like compounds. The compounds targeted the cellular pathway we previously showed to be altered in type 2 diabetes.

In 2008, the award was renewed once again for a third iteration, and this time, it included myself, as well as Evan Rosen, MD, PhD, from the Beth Israel Deaconess Medical Center in Boston. Today, my current project funded by a Smith Family Pinnacle Award is entitled *“Cellular models of human type 2 diabetes genes.”*

Thanks to advances in human genetics, including those from the first two Smith

Family Pinnacle Awards, we now know many primary genes underlying human diabetes. Prior to these genetic discoveries, only a few genes were known to be involved in increasing the risk for type 2 diabetes. Now that more type 2 diabetes genes have been identified, scientists have more information to help understand and fight the disease. Genetics, along with lifestyle behaviors and environment, provide the most accurate picture of one's diabetes risk.

Now, my laboratory's goal is to develop chemical screening strategies to discover lead compounds that target the pathways identified through human genetics/genomics. My collaborator, Dr. Rosen, is an expert mouse biologist and is engineering "humanized" mouse models of diabetes that may more accurately resemble human diabetes. We hope to test some of the compounds emerging from our drug screens in these mouse models. It is notable that the strategy we are developing is generic and, in principle, could be applied to virtually any disease whose genetic basis is discovered.

We are very fortunate to be funded by the Association and the Smith Family, as our proposed research remains highly ambitious (and perhaps too uncertain) for more conservative funding agencies. It is notable that the Smith Family Pinnacle Award has aided current and past Smith Family Pinnacle Award investigators generate the key (more "certain") preliminary data required to land longer-term funding from either the NIH or from industry.

Hence, the Pinnacle Awards have been extremely catalytic in allowing us to pursue very ambitious, but potentially very high-impact, science. Foundation support is valuable for more than just this reason, as it allows us to be more flexible in our scientific trajectory. Science moves rapidly, and the Association allows us to change our direction at the drop of a dime when necessary.

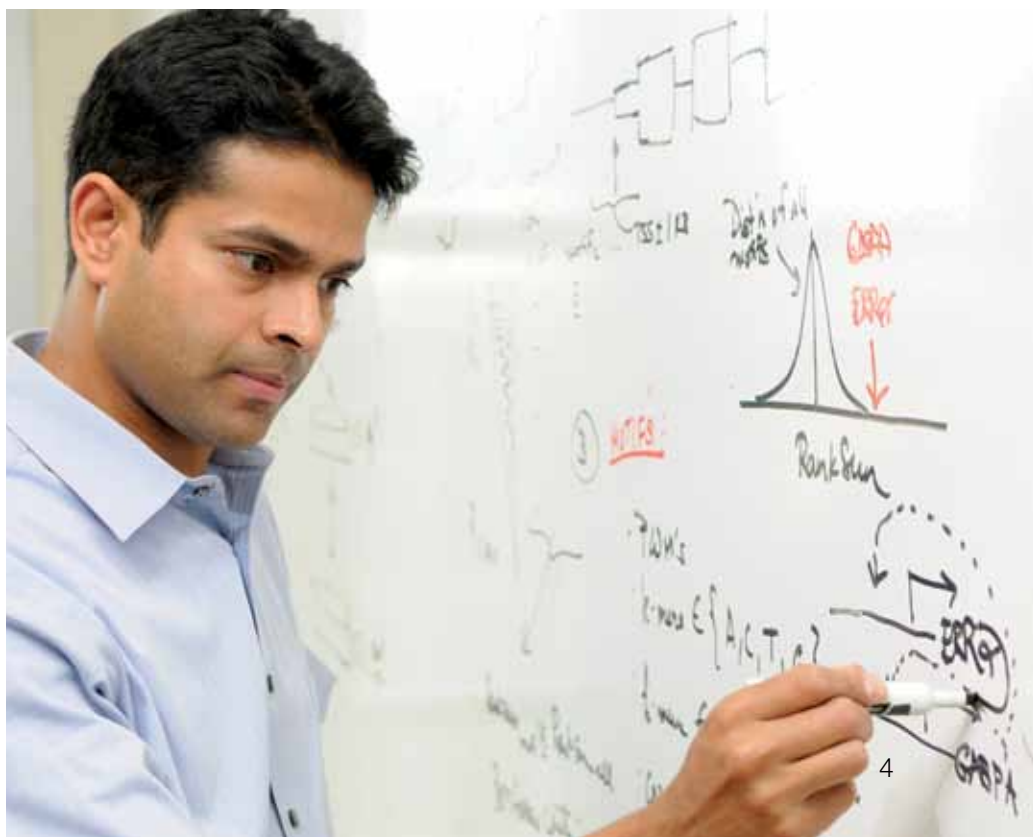
**“ We are very fortunate to be funded by the Association and the Smith Family, as our proposed research remains highly ambitious... ”**

Another very special feature of the Pinnacle Program Project Awards is that it allows scientific teams to coalesce or turn over, when appropriate, based on the scientific opportunities and emergence of new technologies. For example, the first Smith Family Pinnacle Program Project Award used genetics and genomics to identify pathways

contributing to diabetes and obesity in human patients and included Drs. Altshuler, Golub, Hirschhorn, and Ruvkun.

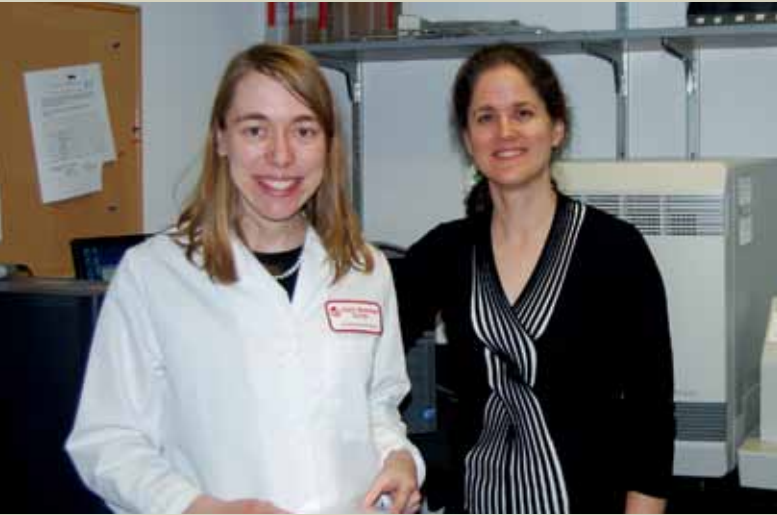
The second Smith Family Pinnacle Program Project Award focused on additional genetics, as well as chemical screening, and included Drs. Altshuler, Ashrafi, Daly, Hirschhorn, and myself. The latest phase further integrates drug screening and genetics, and now includes mouse biology. Accordingly, it now supports Dr. Rosen and myself.

The road to drug discovery is a long and challenging one for pharmaceutical companies and virtually unheard of in academia. But the Pinnacle Program Project Award is allowing us to develop potentially new strategies that could be useful for diabetes and other human diseases. I am incredibly indebted to this unique funding mechanism for allowing us to assemble research teams that can take on such grand challenges in biomedicine. ■



### Mary Elizabeth Patti, MD

#### Assessing the early risks of obesity and type 2 diabetes



Elvira Isganaitis, MD and Mary Patti, MD

Diabetes researcher Mary Patti, MD and her postdoctoral fellow, Elvira Isganaitis, MD of the Joslin Diabetes Center in Boston, Massachusetts are directing their efforts toward understanding the molecular mechanisms of insulin resistance with a focus on how key factors (i.e. family history, adverse intrauterine environment, and obesity), impact gene expression and metabolism in both humans and mice. Specifically, they are examining low birth weight (LBW) infants that undergo a period of rapid growth in the early postnatal period. They are at risk for obesity and developing type 2 diabetes in adulthood.

Dr. Patti's Mentor-Based Postdoctoral Award is entitled, "*Molecular mechanisms of diabetes risk.*" The award supports the training of Dr. Isganaitis, a pediatric endocrinology fellow, who is committed to understanding developmental mechanisms underlying diabetes risk. Dr. Patti comments, "This award will allow me to continue to train postdoctoral fellows in diabetes-related research and hopefully inspire them to commit to prevention and cure of diabetes as well."

Drs. Patti and Isganaitis have created a mouse model that identifies the mechanisms contributing to excessive adipose fat tissue growth following prenatal under nutrition

and prenatal exposure to maternal insulin resistance. They evaluated the effects of dietary interventions in LBW animals including the effects of high fat diets on inflammation and metabolic phenotypes (observable characteristics). They also evaluated the low glycemic index (how fast a carbohydrate-containing food raises the blood glucose levels) to potentially prevent glucose intolerance and obesity.

The creation of LBW mice models was accomplished by restricting food during the last week of pregnancy. This reduced the birth weight by 20%. The LBW offspring "catch-up" or gain weight by three weeks of age; however, they develop obesity and glucose intolerance by six months. The model has been modified to investigate the effects of growth on disease risk by restricting food during the lactation period, limiting postnatal growth. Manipulating the diet of the mice demonstrated that the mice with restricted growth and LBW did not develop the glucose intolerance compared to the LBW mice that had "catch up" growth. This suggests that the early postnatal period may be a critical window during which a therapeutic intervention could improve adult disease outcomes.

Other parallel studies have included investigation of whether postnatal treatment of LBW mice with a low glycemic index diet protects against obesity and glucose intolerance. Researchers noted significant increases in weight gain and glucose intolerance in mice compared to the controls. However, adjusting the maternal glycemic index did not affect weight gain or glucose intolerance in LBW mice compared to controls. Other therapies are being considered.

These results highlight the importance of very early critical time periods and diet in the development of obesity and type 2 diabetes. Dr. Patti states, "It is our hope that we will identify mechanisms responsible for changes in the prenatal and postnatal environments in order to tailor the nutritional environment to high-risk infants, offering hope that prevention strategies will become more effective when targeting early life." ■

**Occupation:** Associate Professor, Department of Pediatrics, Children’s Hospital of Pittsburgh, University of Pittsburgh Medical College, Pittsburgh, Pennsylvania

**Professional Focus:** T-Cell mediated beta cell destruction

**Outside Interests:** Family, tennis, guitar, cooking

**Research Funding:** Career Development Award “*Environmental triggers, ER-stress and type 1 diabetes*”

**Amount Awarded:** \$888,350

Funded in part by Alan and Vicky Peters, Portland, Oregon



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## Jon Piganelli, PhD



I began my career in this field because I thought I could help to find a cure for diabetes, having watched my own mother succumb to the complications associated with the disease. Studying type 1 diabetes leaves me with a strong sense of urgency to further understand this illness in order to help the children it hurts. Helping the families I see every day at the Children’s Hospital of Pittsburgh (CHP) is our lab’s objective.

Our lab at CHP works to find the triggers of type 1 diabetes, hopefully bringing us closer to a cure. It is a sobering site to see the parents of a child with newly diagnosed type 1 diabetes; they are mystified and want to find someone or something to blame. However, there is nobody to blame, and our best

approach to improving these children’s lives is through research.

Our current Career Development Award study, now in its third year, is entitled “*Environmental triggers, ER-stress and type 1 diabetes*”. The study focuses on how we may better understand the environmental factors that instigate diabetes and the series of events that make the immune system attack normal tissue.

Currently, the scientific world does not know exactly what activates the onset of type 1 diabetes. Previous research, however, has shown that certain environmental triggers, like viral infections, target the pancreas and may lead the beta cells to undergo a program that

helps to protect the islets from the infection, termed ER-stress (endoplasmic reticulum stress).

This program helps the islets to “weather the storm,” so to speak. In mouse models with type 1 diabetes, this induction of ER-stress occurs in beta cells during normal function as well; however in mice that are autoimmune prone, the immune system reacts against this normal protective event and attacks the islets instead.

Under ER-stress, the beta-cell antigens (beta cell protein markers) are mistakenly recognized by the individual’s immune system as foreign, and this leads to specific T-cells attacking and promoting beta-cell death,

# “Diabetes doesn’t take a holiday, because it affects people every day.”

ultimately leading to diabetes. Our laboratory believes that this T-cell recognition of beta-cells is in response to the attempt of the islets to activate the anti-stress signals in an effort to protect themselves. These anti-stress signals are possibly not tolerated well by people who are prone to autoimmunity, which could lead to diseases such as diabetes.

Our hypothesis is that, in autoimmune-prone individuals, the normal production of ER-stress leads to the development of detrimental T-cells and beta-cell death. To test this, we are focusing on T-lymphocytes (a.k.a. T-cell, a type of white blood cell), that recognize beta-cell antigen. We are observing the window of time where the T-lymphocytes are stimulated and correlating this to ER-stress-induced cell death.

To date, we have studied our hypothesis in a mouse model using a T-cell system with ER stress induced by chemical treatments. Now, we are employing a viral infection to determine if it can also induce the same stress as the chemical method and achieve the same response in beta cells. In an effort to control the ER-stress early in mice with a predisposition to autoimmunity, our goal is to determine what environmental triggers lead to the induction of stress and reactivity in the immune system.

Our work may help us better understand how stress affects the machinery that controls protein production in cells, helping us link environmental triggers that initiate diabetes

and tell us why the autoimmune-prone immune system mistakenly attacks normal tissue. If we can better understand how these triggers activate the immune system, perhaps we may develop prevention therapies to suppress this negative response.

Once we establish our understanding of these processes, we will have embarked upon a major milestone toward developing early intervention techniques for type 1 diabetes. I believe that, in the future, if we can comprehend abnormal immune function and learn how to control it, we will be able to not only predict those who may get diabetes, but learn ultimately how to prevent it.

Although we have a long road ahead before we unveil new prevention strategies, I always tell my staff in the lab, “Diabetes doesn’t take a holiday, because it affects people every day.” We work hard every day to reach our goals. Those of us who are searching for a cure for type 1 diabetes are in a unique professional situation; we are working to put ourselves out of work by finding a cure. The sooner we no longer have a job, the better. Only the truly passionate would be motivated by that prospect.

I would like prospective donors to know that, when you decide to study a chronic disease like type 1 diabetes, you

must dedicate your life to it, as I have. Please know that this career path takes on something more than “just a job.” I never leave my work at work.

The American Diabetes Association Research Foundation echoes my passion for diabetes and has been a major supporter of my career over the last decade. I encourage others donors to support research at a Pinnacle Society level to support other laboratories like ours. ■

*From left to right: Gina Coudriet, Grad Student, Jen Profozich, Technician, JT Coneybeer, Technician, Meghan Delmastro, Grad Student*



## H. Henry Dong, PhD



## A potential alternative to insulin injections could be found using the liver

H. Henry Dong, PhD is conducting research at the Children's Hospital of Pittsburgh. His Association-funded research entitled, "*Insulin gene therapy for type 1 diabetes*", focuses on the development of a novel gene therapy strategy to replace the need for insulin injections. Insulin injections have been the primary treatment for type 1 diabetes by replacing the lack of insulin production by the pancreas. Dr. Dong and his research team aim to determine whether restoration of insulin production using gene therapy can be a potential option in the management of type 1 diabetes. Specifically, his project works on restoring insulin production by introducing insulin genes into the liver, such that the insulin will be produced endogenously (from within the liver itself), and released into the circulation for blood sugar reduction.

Upon receiving his Career Development Award Dr. Dong stated, "This award affords me a great opportunity to execute these plans in animal models and make potential breakthroughs to overcome the critical hurdles in the development of gene therapy. I have devoted a number of years to insulin gene therapy research and appreciate deeply the number of critical limitations (technical and conceptual) that must be overcome prior to the development of effective insulin gene therapy."

Developing insulin gene therapy has not been without its hurdles and limitations. Insulin-producing beta cells in the pancreas can control the timing and amount of insulin released, whereas the liver cannot perform this function. Dr. Dong has proposed overcoming this limitation by using the natural genetic elements that the liver has evolved to turn on and switch off gene expression under fasting or fed conditions.

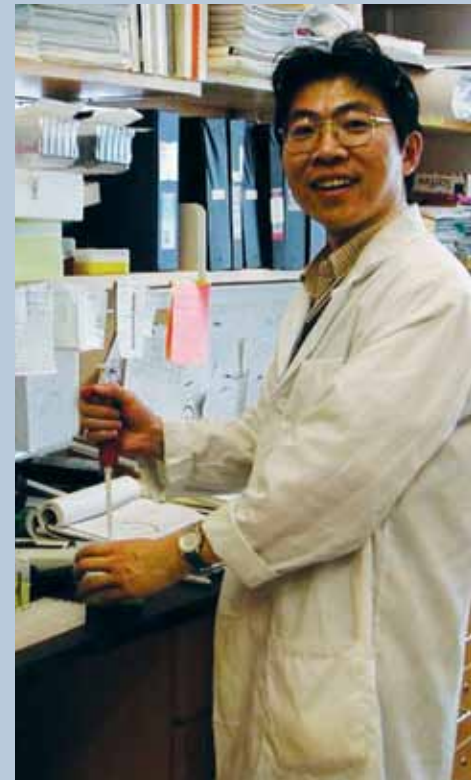
Although challenging, if Dr. Dong can develop a safe and effective insulin gene therapy strategy, the rewards may be great. It may be possible to restore near physiological control of blood sugar, perhaps eliminating the need for daily glucose monitoring and daily insulin injections. This strategy may also provide long-term physiological control

of blood sugar, thereby delaying the onset of complications. Insulin genes introduced into non-beta cells would likely not be subjected to autoimmune attack. Thus, immunosuppressive agents may not be required, as is the case with beta cell replacement in islet transplantation.

Dr. Dong has made significant strides in the third year of his Career Development Award. He has developed a potentially new production and release system for insulin in the liver and shown that this does control blood sugar in mice. The cloning and characterization of two essential genetic elements in the liver have been promising as well. One stimulates insulin production at higher blood sugar levels, whereas the other acts as an inhibitor to prevent too much insulin from being produced. This system has been validated in cultured liver cells and in mice that exhibit type 1 diabetes.

There is much work to be done to develop an insulin gene therapy protocol for humans. Safety and efficacy of the protocol must be proven. Dr. Dong's therapeutic concept holds promise, and he is committed to accomplishing his research goals.

*Dr. Dong received a 2004 "Islet cell replacement in type 1 diabetes" Award, funded by Edsel and Cynthia Ford. ■*



H. Henry Dong, PhD



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**Occupation:** Associate Professor of Molecular Physiology & Biophysics and Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

**Professional Focus:** Obesity-related increases in adipose tissue macrophages leading to inflammation and insulin resistance

**Outside Interests:** Running, family, reading, my two dachshunds

**Research Funding:** Career Development Award  
*"Hyperlipidemia-induced macrophage infiltration into white adipose tissue: contribution of macrophage inflammatory protein-1alpha"*

**Amount Awarded:** \$900,425

*Funded in part by Joe and Judy Cook  
Nashville, Tennessee*

## Alyssa Hasty, PhD

Soon after I obtained my position as Associate Professor of Molecular Physiology and Biophysics and Medicine here at Vanderbilt University, I received a Junior Faculty Award from the American Diabetes Association in 2004. This award early in my career allowed me to hire a competitive staff of graduate students and postdoctoral fellows for my lab.

Due to this award and those from similar organizations, I was able to start publishing my work at the onset of my career and show evidence that I could receive independent research support for my projects. These aspects were critical to demonstrating to other, larger funding sources like the NIH that I had the grant writing capabilities and a

productive laboratory that could compete with larger, more established scientific programs.

It takes several years for a young investigator to become competitive with other labs, especially with reduced funding in today's economy, which is why this award from the American Diabetes Association and its Research Foundation was so important. As a result of this initial boost from the Association, I was able to obtain two grants from the NIH and my current Career Development Award.

Now in my third year of this five-year, mid-career grant, I can say without a doubt that the American Diabetes Association helped make it possible for me to continue my diabetes research. The Association and its

Research Foundation gave me the time and money I needed to cultivate my grant writing skills, the background knowledge I needed in my area of science, and resources to develop a strong staff and get organized. Most importantly, over the course of my five years of funding from the Association, I have been able to train 28 young people in diabetes-related science. The exponential nature of the Association's support is priceless.

I am immeasurably grateful in particular to the Cooks for funding this particular grant through the Association's Research Foundation. Their passion for diabetes research and their generosity to the organization is extraordinary. The Association, the Cooks and fellow donors may be

reassured that I believe my current research studying the role of obesity in metabolic diseases is what I was truly meant to do.

Our lab's Association-funded study "*Hyperlipidemia-induced macrophage infiltration into white adipose tissue: contribution of macrophage inflammatory protein-1alpha*" focuses on diabetic factors like immunity, insulin resistance and obesity. With this combination of elements, I feel our lab is fully committed to one of the American Diabetes Association's major objectives: to support obesity-related research and to better understand diabetes.

Meanwhile, our laboratory's long-term goal is to determine mechanisms by which obesity increases risk for insulin resistance, diabetes and cardiovascular disease. As adipose tissue (body fat) expands and becomes inflamed during obesity, the body begins to respond improperly to insulin. The body releases lipids into the body's circulation in an uncontrolled manner, causing insulin sensitivity problems in the liver, muscle and pancreas, thus leading to diabetes. Scientists have recently shown that, during obesity, immune cells enter adipose tissue and are responsible for the inflammation.

I would like to find out through my study what attracts these immune cells to the adipose tissue, leading to all of these health problems, including diabetes. Our Association-funded project focuses on a protein called macrophage inflammatory protein-1 alpha (MIP-1 $\alpha$ ), which is commonly secreted from fat. MIP-1 $\alpha$  attracts macrophages (white blood cells in tissues) to places in the body where it is present in high concentrations. We have hypothesized that MIP-1 $\alpha$  helps to guide immune cells to adipose tissue, thus leading to obesity-related health issues.

So far, we have seen that obese mice have elevated amounts of MIP-1 $\alpha$  in their adipose tissue. Meanwhile, mice without MIP-1 $\alpha$  in their macrophages have reduced plasma cholesterol and triglycerides, reduced body weight and improved insulin sensitivity. Working with genetically altered mice without the MIP-1 $\alpha$  protein, we have enough data that suggests that blocking the effects of MIP-1 $\alpha$  or other similar proteins could be beneficial in humans with metabolic diseases.

Although I am extremely passionate about my work and feel that this research is a worthy cause, it would be easy for reluctant donors to say that people should eat healthier and exercise more, rather than devoting dollars to science. The American Diabetes Association contributes immensely to prevention techniques and diabetes awareness, but it is clearly not enough.

It is imperative that we learn how all components of the body react to over-nutrition and altered insulin

“ I feel our lab is fully committed to one of the American Diabetes Association's major objectives: to support obesity-related research and to better understand diabetes. ”

sensitivity. We can design better treatment therapies and improved prevention techniques for all types of individuals so that the numbers of persons developing diabetes decreases. We must do more. I was once a young investigator and know the positive impact the Association's Research Foundation makes. The next generation of young researchers can accomplish even more with your donor support. ■



### Deborah Young-Hyman, PhD

#### The importance of understanding the relationship between disordered eating behavior and type 1 diabetes



Deborah Young-Hyman, PhD

Maintaining a healthy weight and good glycemic control can prove to be a daunting task. This is especially true for adolescents who are concerned about fitting in with peers and meeting the expectations of healthcare providers and/or family members. To prevent weight gain, an adolescent may develop disordered eating behaviors (DEB). Weight gain is often an unintended consequence of good control of type 1 diabetes.

For Deborah Young-Hyman, PhD, from the Medical College of Georgia, this weight gain is the focus of concern. She is studying adolescents to examine whether following the recommended type 1 diabetes treatment guidelines contributes to the development of DEB. Dr. Young-Hyman comments, "This will be the first study of the development of disordered eating behavior in children and adolescents with type 1 diabetes in the context of their treatment, their family, and in the cultural context within which they live, beginning at the time of diagnosis or when they transition to insulin pump use."

Typically, type 1 diabetes is characterized by several factors including non-physiologic insulin dosing, hypoglycemia, food preoccupation, and a loss of satiety and feelings of fullness. Still, other factors include cultural, health and family pressure to remain thin after diagnosis. Self-management recommendations which unintentionally result in loss of control over eating patterns, such as carbohydrate counting and restriction, could amplify the potential for extreme eating behaviors and thus develop into DEB. Along with a potential poor self-image, adjusting to living with diabetes and other typical psychological stresses of adolescence could also be contributing factors, as teenagers focus on reaching an "ideal" self and body image.

With funding from her Clinical Translational Research Award, Dr. Young-Hyman has examined 52 patients with type 1 diabetes. The 10 to 17 year olds are either in the beginning stages of their type 1 diagnosis regimen or transitioning to an insulin pump. They answered questions regarding their behavior and attitudes about weight, eating and hunger, their psychological well-being and control over their illness, and match these attitudes and behaviors against their diabetes care regimen.

Ideally, vulnerable adolescents will be recognized, will have clinicians provide early identification, and treatment will be modified to help them avoid the potentially negative consequence of weight gain associated with achievement of good glycemic control. In addition, their parents have completed questionnaires assessing the contribution of parental attitudes about their own weight and eating habits as well as that of their children.

In her second year of research, Dr. Young-Hyman has preliminary data to be presented at the Society for Behavioral Medicine meeting. The initiation of treatment in newly diagnosed teens is associated with depressive symptoms and weight concerns. After diagnosis, teens and their parents' depressive symptoms remain elevated if the teen's weight increases and decreases in association with lower weight gain. Both weight gain and depression are known to be risk factors for the development of DEB. There are also e-published results in the November 11, 2009 issue of *Pediatric Diabetes* showing that depressive symptoms are associated with low insulin sensitivity among healthy adolescents who are overweight.

With the continued support of Association funding, study results could be reproduced in a larger population to strengthen our understanding of the factors which can lead to DEB. Understanding mechanisms behind what appears to be maladaptive behavior, but may not be in the control of the patient, will offer alternative solutions for care and could lead to better patient-provider communication and outcomes. ■

**Occupation:** Assistant Professor, Internal Medicine, Molecular Cell Biology Program Washington University, St. Louis, Missouri

**Professional Focus:** Vitamin D deficiency and tissue glucocorticoid excess

**Outside Interests:** Family, soccer, traveling

**Research Funding:** Clinical/Translational Research Award  
*“Vitamin D deficiency, insulin resistance, and cardiovascular disease”*

**Amount Awarded:** \$564,000



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## Carlos Bernal-Mizrachi, MD

I was born into a family of physicians, including both my parents. My mother, who is a practicing endocrinologist in Cali, Columbia, instilled in me and my three brothers a passion for medical research and a compassion for people with diabetes. She has dedicated the last two decades to creating a foundation that provides underserved populations with therapies and prevention techniques for diabetes.

The driving force of my medical research is to learn how to control the suffering related to chronic medical conditions like diabetes and cardiovascular disease. Through my research at the Washington University at St. Louis, I am working to find novel therapies to control these diseases.

The Clinical and Translational Research Award from the American Diabetes Association’s Research Foundation funds the next stage of our previous research on the positive effects that vitamin D has on cardiovascular disease. Of the greater than 20 million people in the United States struggling with type 2 diabetes, most have elevated blood pressure and/or an increased risk of cardiovascular disease. These elements combined are the most common cause of morbidity in Western populations.

My goal is to decrease the burden of these complications. People with type 2 diabetes also have higher rates of vitamin D deficiency than the general population. However, it is still not clear whether vitamin D replacement decreases blood pressure.

In our Association-funded study *“Vitamin D deficiency, insulin resistance, and cardiovascular disease”*, we will examine 90 patients with diabetes and low levels of vitamin D who have a recent diagnosis of high blood pressure and have not taken blood pressure medications. Patients will receive either a placebo or vitamin D for 16 weeks. At the beginning and end of the study, we will assess blood pressure, blood flow, and blood levels of the hormones that control vascular inflammation.

In the interim, participants will receive non-pharmacologic dietary advice and supplements to control their hypertension and diabetes. Our lab will be able to determine if there are any changes in these risk factors and markers of cardiovascular disease after the participants

## MidWest

receive the placebo or vitamin D. This type of knowledge will provide us with a better understanding of hypertension and heart disease in people with diabetes and whether vitamin D is a therapeutic target to reduce these related illnesses.

The Association has shown great enthusiasm and support for this trial, recognizing the importance of the relationship between diabetes, cardiovascular disease and hypertension. Clinical trials are necessary to make a scientific impact and change health care practice for the better. Although my laboratory and the laboratories of others have done extensive work with animals on the benefits of vitamin D on diabetes and cardiovascular disease, the progression toward the development of larger, randomized, controlled clinical trials like this one has not been simple.

Clinical trials are expensive and take a long time to complete. Although recruiting and testing 90 study participants over the course of a few years sounds manageable, each participant must go through extensive screening and tests before they are deemed eligible to participate. Even before we begin our actual tests applicable to our study, the prescreening lab work costs nearly \$3,000 per person. When we factor in the recruitment efforts, patient interventions, participant compensation and staff salaries, it adds up to about \$8,000 per participant.

Now in our second year of the study, we already know that this research is valuable. My laboratory has published in *The American Journal of Obstetrics and Gynecology* and in *Endocrinology, Metabolism, and Lipid Research* as a result of our current and previous Association funding for our work in vitamin D. We have successfully reported that vitamin D deficiency has major implications in pregnancy.

“ **The Association has shown great enthusiasm and support for this trial, recognizing the importance of the relationship between diabetes, cardiovascular disease and hypertension.** ”

Additionally, we published an interesting paper in *Circulation* in the summer of 2009 which concluded that vitamin D deficiency is a potential reason for increased foam cell formation in patients with diabetes. Foam cells are the first cells found at the site of atherosclerosis. The accumulation of these macrophages, named for their foamy appearance as they fill with cholesterol, is one of the early signs of the development of cardiovascular disease.

Considering how far we have come, it would be a shame to let such promising research lose momentum. Problematically, we may not be able to complete our study and work with all 90 patients if the necessary funds are not available to the American Diabetes Association. Although we have budgeted for all 90 participants to be treated, research and laboratory fees are becoming more expensive. The Association has had to make tough choices

on whom they can continue to fund through this difficult economy.

The application of our clinical trial findings to the diabetic population has the potential to have great public health impact. We have already seen the positive effects of implementing vitamin D supplements into patient care, and this intervention is practical and simple. Clinical research is imperative to reach the next stage of improving patient care. However, it is expensive. To run a clinical study, there are many requirements: multidisciplinary personnel, laboratory and interventional tests, and patient recruitment.

With your help as donors, we can continue our good work at the American Diabetes Association. Many thanks for your help and support. Your generous donations will generate better treatments and prevention strategies for people with diabetes. ■

*Dr. Bernal-Mizrachi and Amy Riek, MD*



## Kurt Fisher



## Clinical Scientist Training in obesity and insulin resistance

Just like Dr. Bernal-Mizrachi, diabetes has always been a part of the life of Clinical Scientist Training Award recipient Kurt William Fisher. Having both parents in the medical field, there were regular dinner table conversations about diabetes. He grew up the son of a registered dietician and



Kurt Fisher

a PhD diabetes educator who taught patients specifically how to manage their diabetes. Diabetes further impacted Mr. Fisher's life when in high school his grandmother began to suffer from the effects of diabetes. Naturally, this inspired the young investigator to follow in his parents footsteps, honor his grandmother, and pursue a medical degree.

A MD/PhD candidate, Kurt Fisher is studying obesity and insulin resistance in type 2 diabetes. He is working with mice that have genetically been altered to exhibit obesity attributes. His American Diabetes Association research project is entitled, "*Novel mechanisms regulating obesity and insulin resistance.*" "This grant has allowed me for the first time to become intimately involved in researching the development of insulin resistance and diabetes," Fisher states. Mr. Fisher conducts his research at the University of Nebraska Medical Center.

The mice Mr. Fisher uses are born at a normal weight, but subsequently become obese and insulin resistant. These particular mice don't overeat, which is common to most other mouse models of obesity. Rather, these mice have a defect in nutrient sensing, the cell's ability to recognize and respond to fuel substrates such as glucose.

In his first year of Association-funding, Mr. Fisher is studying two related proteins that help direct metabolic pathways. In the absence of this specific protein KSR2, cells have a deficiency in glucose uptake that is related to the development of diabetes. Researchers will now use a depletion strategy to analyze cells at a faster rate in a high-speed genome screening facility. They are depleting every protein in a cell one-by-one to assess the impact of the loss of specific protein function.

Utilizing this technology will allow Mr. Fisher's lab to examine a greater number of genes with similarities to KSR2 action. This could lead to new therapeutic targets for diabetes and insulin resistance. Fisher states, "We hope that learning about these new metabolic pathways will teach us more about the development of diabetes so that we may be able to prevent and potentially cure diabetes."

The training of a clinical scientist not only ensures that the future of diabetes research moves forward, but also benefits his future patients as well. Mr. Fisher comments, "Physicians with training in both medicine and research can provide a vital link to help direct research toward clinically-relevant goals that will directly benefit patients with diabetes. And, as a team, we work better at reaching those goals." ■

## ADA-APMA cooperatively fund a diabetes fellowship award

The American Diabetes Association and the American Podiatric Medical Association are co-funding a unique opportunity for a podiatrist to receive postdoctoral training in a diabetes research environment. The July 2009 award recipient, Kristy Osgood, DPM, was selected from a competitive field of candidates as the postdoctoral fellow collaborating with Dr. Clifton Bogardus at the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, in Phoenix, Arizona.

Dr. Bogardus is working to determine the causes of obesity and type 2 diabetes in the Pima Indian population of Southwestern Arizona. Working in collaboration with the Pimas for the past 40 years, it is clear that lifestyle, environment and genetic factors play a role in the high prevalence of this disease. Focusing on the genetic factors of the disease will greatly improve both treatment and preventative measures.

The fellowship research opportunity is located at The Obesity and Diabetes Clinical Research Section (ODCRS) in the Phoenix Epidemiology Clinical Research Branch in Phoenix, Arizona. Dr. Osgood is working on a diabetes research project, *"Etiology and Treatment of Obesity and Type 2 Diabetes Mellitus"*, where she will gain experience in multiple aspects of clinical trial management. Dr. Osgood will also have access to extensive previously collected data where she will learn statistical programming and use of epidemiologic techniques. She will use this collected data to investigate risk factors for changes in weight and energy expenditure.

Congratulations to both Dr. Bogardus and Dr. Osgood on their unique endeavor. ■

*Kristy Osgood, DPM and  
Dr. Clifton Bogardus*



## Current body mass index measurements could overestimate obesity for African-Americans

Results of a study indicate that the current methods used to estimate obesity, body mass index (BMI) and waistline circumference, may overestimate the incidence of obesity in African-Americans. Samuel Dagogo-Jack, MD, the recipient of a Mentor Based Postdoctoral Fellowship Award from the American Diabetes Association, was highlighted in the June 22, 2009 issue of *ScienceDaily*. Dr. Dagogo-Jack and his postdoctoral fellow, Nicoleta Ionica, MD, compared the indirect measure of body fat by BMI to body fat directly measured in the same patients using Dual Energy X-ray Absorptiometry (DEXA). They compared the correlation of these two measurements in both Caucasians and African-Americans. The correlation between DEXA-measured total fat and BMI was higher in whites than in blacks.

While BMI is an indirect method of estimating body fat, waist circumference identifies abdominal obesity. BMI ranges identify a person who is underweight (less than  $18.5 \text{ kg/m}^2$ ), normal weight ( $18.5$  to  $24.9 \text{ kg/m}^2$ ), overweight ( $25$  to  $29.9 \text{ kg/m}^2$ ) or obese (more than  $30 \text{ kg/m}^2$ ). Waist measurements of greater than 40 inches in men and 35 inches in women are defined as obese. Increased waist circumference can indicate an increased risk for complications such as heart disease and diabetes. More specialized methods, such as DEXA or computer tomography (CT), can directly measure the total body fat in a given region; however these techniques are more time consuming and expensive.

In this study, comparison measurements were also made for directly measured abdominal fat and waist size demonstrating again that Caucasians have a higher correlation than African-Americans. This is a significant finding given that national data reports that African-Americans have higher rates of obesity and type 2 diabetes



*Samuel Dagogo-Jack, MD and Nicoleta Ionica, MD*

than Caucasians. Dr. Dagogo-Jack explains that African-Americans may have a higher muscle mass and this could explain the dissociation of BMI compared to body fat in the study data. Confirming research results in a larger study population is needed and could indicate the need to develop ethnic specific values for obesity measures.

**Results were presented June 16, 2009 at the Endocrine Society's 91st Annual Meeting in Washington, D.C. ■**

## Ethnicity plays role in development of gestational diabetes, especially for Chinese-American and Korean-American women

Teresa Hillier, MD, MS, has co-authored a study highlighted in the December 14, 2009 issue of *Medical News Today*. The American Diabetes Association-funded study found that more than 10% of women of Chinese and Korean heritage may be at risk for developing diabetes during pregnancy. The study also found that Korean-American and Chinese-American women have a one-third higher than average risk of developing gestational diabetes, which is more than double the risk for Caucasian and African-American women. Pacific Islander, Filipino, Puerto Rican, and Samoan women are also at a higher than average risk for gestational diabetes, while Caucasian, Native American, and African-American women have a lower than average risk. Dr. Hillier states, "Many previous studies have lumped all Asians and Pacific Islanders together; now we know that the risk for developing gestational diabetes mellitus (GDM) varies greatly depending on your specific ethnic background."

groups. Dr. Hillier's evidence supports the existence of some differences among the Asian groups when they are divided into five ethnic sub-groups. Korean and Chinese women have the greatest risk of developing GDM, followed by Filipinos, but Japanese and Vietnamese women have the same risk as the rest of the population. If Pacific Islanders are subcategorized into three groups, Samoans and other Pacific Islanders (including women from Fiji and Tahiti) have a higher than average risk, while Native Hawaiians are at an average risk.

As another co-author explains, "This study has important implications for the diagnosis and treatment of gestational diabetes. All pregnant women and their caregivers need to be educated about gestational diabetes, but it is especially important for women in these ethnic groups at higher risk."

(Pedula, K, Hillier, TA, Schmidt, M, Mullen, J, Charles, M-A, Pettitt, D. Korean-American & Chinese-American Women at Highest Risk for Developing Diabetes During Pregnancy. *Ethnicity and Disease*. 2009 Autumn; 19(4): 414-9. <http://www.kpchr.org/research/public/News.aspx?NewsID=44>) ■



Teresa Hillier, MD, MS

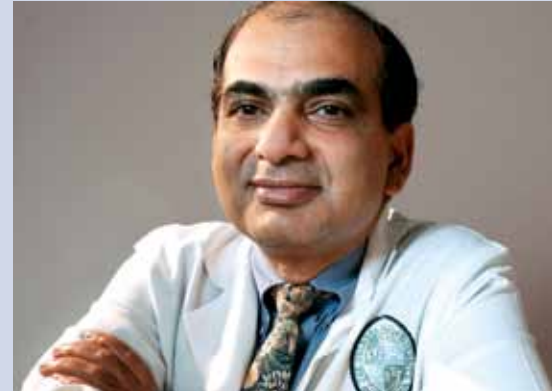
With funding from her Clinical Translational Research Award, Dr. Hillier examined 16,000 women in Hawaii because it is one of the most ethnically diverse populations in the world. Previous studies have shown that GDM is more prevalent among Asians and Pacific Islanders and this is the first study to sub-categorize the ethnic

## Hurricane Katrina significantly impacted persons with diabetes

A September 16, 2009 *Reuters Health* article featured Clinical/Translational Award recipient Vivian Fonseca, MD at Tulane University School of Medicine in New Orleans, Louisiana for his study on the devastating impact of Hurricane Katrina on persons with diabetes. He compared the medical records from patients at a Veterans Administration (VA) Hospital, The Medical Center at Louisiana (the city's charity care system) and those with private health insurance at a local University Hospital. The medical records contained A1C (average blood glucose for the past 2-3 months) data measurements on file before and after the hurricane. Of the 1,795 medical records, those in the charity health care system had worse long-term blood sugar control up to twenty-two months after Katrina. Although the VA and private health insurance carriers did not have a significant change in their blood glucose control, they did have an increase in their levels of LDL (low-density lipoprotein) or bad cholesterol. All groups experienced an across the board increase in blood pressure. Dr. Fonseca conducted his research entitled, "*Impact of Hurricane Katrina on Diabetes and its Co-Morbidities*", with funding from the American Diabetes Association.

Continued testing many months after the natural disaster demonstrated a breakdown in the overall healthcare system in that region. Based on their data, researchers ascertained that estimated life expectancy was reduced by about four months for charity system patients, about three months for the VA patients, and less than one month for those with private insurance. Despite the reduced life expectancy, the healthcare costs of the patients still had a substantial economic impact due to the large size of the population affected by Hurricane Katrina. Lifetime healthcare costs were calculated based on a projection of future costs using a well established model called the CORE model. It estimates future costs in a population based on changes in health such as glucose, blood pressure or cholesterol. Assuming that the adult prevalence of diabetes in the

area was 9.2%, the lifetime healthcare costs increased across all compared groups with a cumulative total of \$504 million. The study did not account for factors such as those who died after the hurricane or those who relocated permanently from the city. Not accounting for these results may actually cause an underestimation of the effects.



Vivian Fonseca, MD

"The real lesson here is that if a major disaster strikes, we should not only think about the short term and acute care, but also plan for taking care of people who have chronic diseases so that their long-term care is not affected", states Dr. Fonseca. Dr. Fonseca adds that persons with diabetes should keep emergency phone numbers, and waterproof kits of syringes, medications, insulin, testing strips and even prepackaged snacks. Dr. Fonseca's research demonstrates that not only were people with diabetes negatively affected by the hurricane in the short term, but these effects and health disparities are still present four years later.

For details about the American Diabetes Association task force statement on disaster preparedness, refer to the September 2007 issue of *Diabetes Care*.

(Fonseca VA, Smith H, Kuhadiya N, Leger SM, Yau CL, Reynolds K, Shi L, McDuffie RH, Thethi T, John-Kalarickal J., *Impact of a natural disaster on diabetes: exacerbation of disparities and long-term consequences.*, *Diabetes Care*. 2009 Sep;32(9):1632-8. Epub 2009 Jun 19.) ■

## Richard A. and Susan F. Smith Family Foundation

Forty years ago, business entrepreneur, Richard “Dick” Smith and his wife, Susan Smith, began a family foundation that would ultimately impact the lives of millions of people who struggle with illness, poverty and poor education.

Still changing lives for the better, today the Richard A. and Susan F. Smith Family Foundation has embraced the American Diabetes Association’s Research Foundation as one of its preferred partners.

Remarkably, the Smith Family Foundation has generously donated \$4.1 million to the Association, making the Smiths one of the Research Foundation’s most philanthropic families.

“One of the missions of the Smith Family Foundation is to support the community by combating specific diseases,” says Mr. Smith, a native of Chestnut Hill, Massachusetts. “We specifically reached out to the Association, because diabetes affects so many people. It is one of the biggest health care problems this country has ever seen.”

Mr. Smith has type 2 diabetes and passionately believes in the importance of funding research that will improve the lives of the other 24 million individuals who have this illness. “We believe that diabetes is a genetic disease, therefore, we feel collaborative research has the best chance of discovering what is needed to develop therapeutic targets,” asserts Mr. Smith.

Therefore, the Smith Family Foundation partnered with the Research Foundation seven years ago to create the first ever “Pinnacle Program Project Award,” which was designed to facilitate collaborations amongst research investigators in a particular area of research.

Due to the success of the first Smith Family Foundation Pinnacle Program Project Award,



*Richard and Susan Smith*

which focused on the connections between type 2 diabetes and obesity, the Association and the Smith Foundation approved a second and third iteration of this unique project. Consequently, the Smith Foundation currently funds the breakthrough work of Vamsi Mootha, MD, of the Broad Institute, and Evan Rosen, MD, PhD, of Beth Israel Deaconess Medical Center, both of whom are in the Boston area and part of the Harvard system (see page 3-4).

Drs. Mootha and Rosen are leading projects meant to develop new type 2 therapies that target recently-identified diabetes-related genes. “Dr. Mootha’s thrust of his study, in particular,” says Mr. Smith, “is to isolate a few of the important genes associated with diabetes and establish targets for therapeutics.”

Although diabetes is a controllable disease, the Smith Family Foundation stresses that research is crucial to mitigate the harmful effects of diabetes. The best way to achieve long-term scientific results, they believe, is through well funded collaborative projects like the Pinnacle Program Projects and the involvement of talented researchers, like Rosen and Mootha.

As the Smith Family Foundation continues to support high-impact science through joint projects, Mr. Smith supports the principle that the Research Foundation should begin focusing on funding new to the field of diabetes research investigators.

“We must motivate individuals who are in the field of diabetes research to stay and encourage those outside the field to enter,” says Mr. Smith. “Much of science is serendipitous—young investigators in the field must collaborate with each other in order to make great things happen,” he continues.

“Our mutual goal at the Smith Foundation and the Research Foundation will be to support and encourage these new investigators,” Smith says. “Diabetes is a problem that is not going away soon.” ■

## Joe C. and Judith E. Cook and Family

“To whom much is given, much is expected.”

These are the words by which Joe Cook, Jr., and his wife, Judy, live. This Nashville couple’s dedication to the American Diabetes Association Research Foundation is just one of many testaments of their belief to give back.

Once a group vice president of Eli Lilly and Company, Mr. Cook made a conscious decision to give back to the health world in the tradition of Eli Lilly, a past president and the grandson (and namesake) of the company’s founder.

“Mr. Lilly believed that we should take care of patients first,” says Mr. Cook, who retired from Lilly in 1993. After Lilly, Mr. Cook began working with Amylin Pharmaceuticals and, in 1998, became Chairman and CEO. While at Amylin, he was able to transfer this “patient-first” focus to the young company.

“The culture of serving rather than being served is based on sound business and moral principles,” says Mr. Cook. “As a faith-based family, we also believe that this is a calling for managing the resources with which we have been entrusted.” The Cooks have been among a growing family of generous individual supporters of the Association.

Because of his long-time professional familiarity with diabetes at Lilly and Amylin, Mr. Cook felt “closely connected” with the Association’s mission to help people with diabetes. “A logical relationship” evolved between the Cooks and the Association and its Research Foundation. Ultimately, Mr. Cook became a Research Foundation Board member and helped raise funds for the organization. Today, Mr. Cook is on the Association’s National Board.

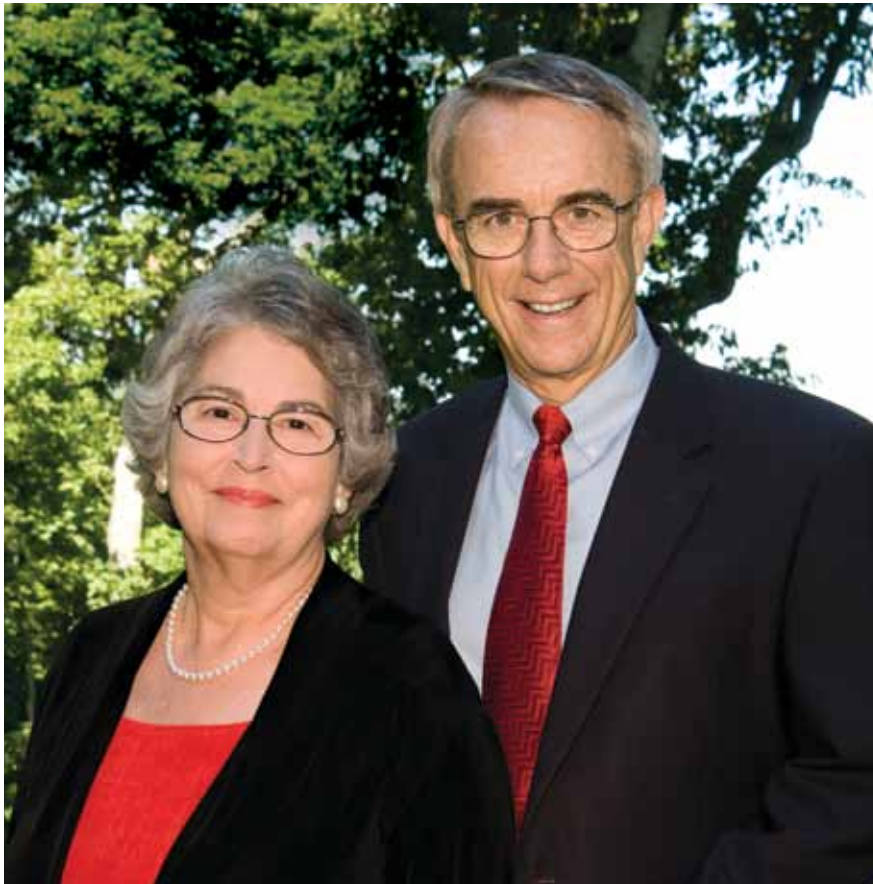
Always ready to discuss the Research Foundation with potential donors, the Cooks closely identify with several of the aspects that make the Research Foundation special. “We find it reassuring that all the Association-funded scientific projects are vetted through the peer review process,” they said.

“More than ever, donors are concerned about the efficiency of their dollars,” they continued. “100% of the money donated to the Research Foundation stays with research.”

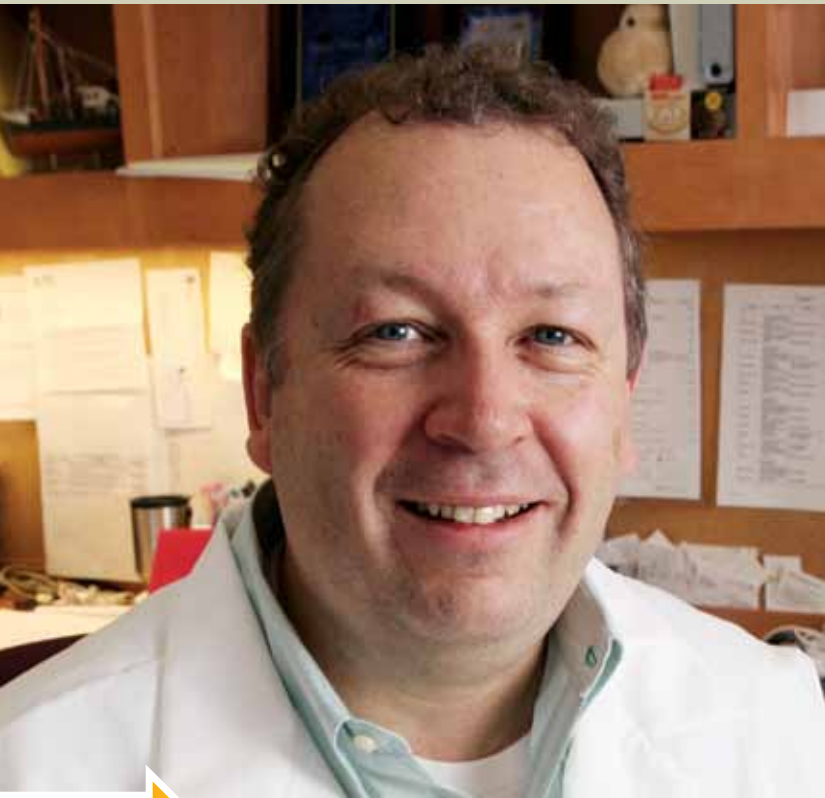
The Cooks also appreciate what they call the Association’s “open spirit of accountability.” They believe the transparent nature of the peer review process and the “full disclosure” of study results—whether planned or unplanned—are advantageous to the diabetes community as a whole.

The family wisely decided to use their dollars to fund a Research Foundation project headed by research investigator, Alyssa Hasty, PhD, of nearby Vanderbilt University (see page 9-10). Dr. Hasty, whose Career Development Award focuses on insulin resistance and obesity, says of the Cooks, “Their passion for diabetes research and their generosity to the organization on my behalf is extraordinary.”

Fortunately for the Association and organizations like it, philanthropy is a family affair for the Cooks. They encourage their children and their families to support causes that are important to them, encouraging them to give from the heart—willingly and cheerfully. ■



*Joe and Judy Cook*



© University of Texas Southwestern

**Occupation:** Director, Touchstone Diabetes Center, University of Texas Southwestern, Dallas, Texas

**Professional Focus:** Islet biology / Metabolic regulation

**Outside Interests:** Skiing, traveling

**Research Funding:** Mentor-based Postdoctoral Fellowship Award

*“Inducible activation of the XBP-1 unfolded protein response pathway: Implications for beta cell survival”*

**Amount Awarded:** \$171,900

## Philipp Scherer, PhD

For twelve years, I have had the privilege of receiving research grants from the American Diabetes Association and its Research Foundation. My initial funding from the Association over a decade ago was instrumental to my laboratory’s past and current successes in the study of adiponectin, the adipocyte-derived protein that controls glucose regulation.

The seed funding we received in 1998 from the Association for a study on vesicular trafficking in adipocytes was integral for my then-team at Albert Einstein College of Medicine to obtain subsequent NIH funding. This primary grant from the Association represented one of the first efforts funded in this particular area of diabetes research,

leading to nearly 5,000 papers published from laboratories all over the world.

The Association saw something promising in this area of diabetes science and gave us a chance. They were the first funding agency to recognize the potential adiponectin research had to unveil. Now that the scientific world knows the importance of adiponectin’s role in the suppression of metabolic problems, it is apparent that the Association displayed remarkable foresight in funding this work at the early stages.

Now, as a more seasoned investigator and Director of the Touchstone Diabetes Center at the University of Texas Southwestern in Dallas, I have been charged by the Association to usher my postdoctoral fellow, Yingfeng

Deng, PhD, into the next stage of her diabetes research career.

With funds from the American Diabetes Association’s Research Foundation, I am able to impart my background and knowledge of metabolic regulation to Dr. Deng, helping to support the next generation of diabetes scientists. In addition to supporting solid science, the Postdoctoral Fellowship Award provides the time and funds for Dr. Deng to develop a complete research effort in a specific diabetes research area plan and long-term experimental strategies.

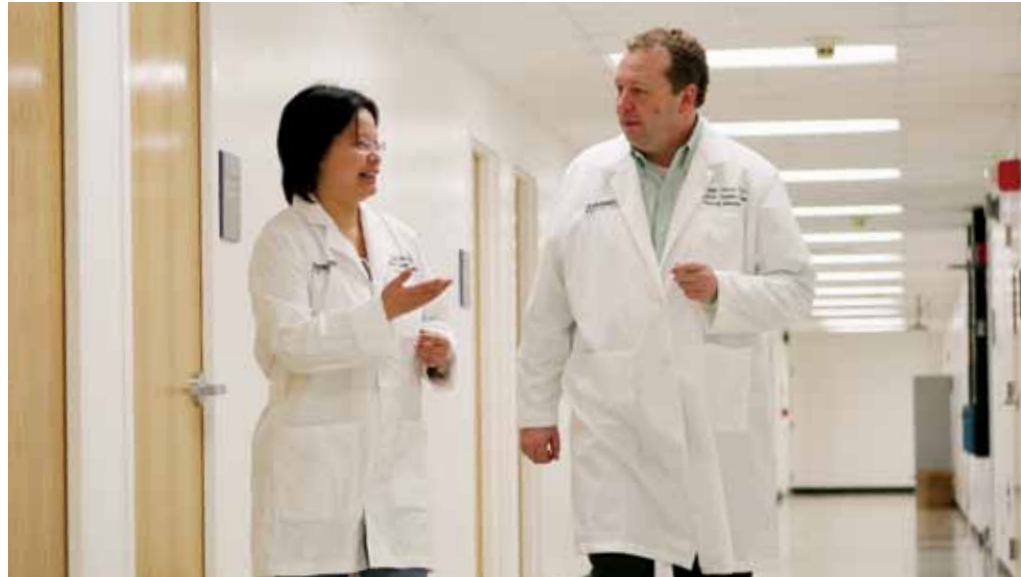
My Mentor-based Postdoctoral Fellowship Award funds the study *“Inducible activation of the XBP-1 unfolded protein response pathway: Implications for beta cell*

*survival*", which focuses on a particular pathway that involves a protein called XBP-1. Certain pathways can protect beta cells from damage, and our ultimate goal is to stop beta cell death (apoptosis). Pancreatic beta cell malfunction and apoptosis result in poor production and/or secretion of insulin, which is the defining trait of diabetes.

If Dr. Deng and I learn to better understand the involvement of XBP-1 through our study, we could identify potential pharmacological interventions that may encourage beta cell survival for people with diabetes. A novel mouse model developed in my laboratory allows Dr. Deng to activate XBP-1 on command in beta cells, permitting for the first time a look at the protective attributes of this protein. In this particular Association-funded project, Dr. Deng and I are working to illuminate the ability pancreatic beta cells have to cope with beta cell stress originating in the secretory pathway.

One of the core scientific missions of the American Diabetes Association is to research the process of beta cell survival. When submitting this proposal to the Association, we felt that this project was an ideal fit for the organization. Fortunately for us, the Association felt the same way.

**“ Many research projects in the diabetes scientific arena are on the cusp of reaching discoveries that may produce viable pharmaceutical interventions... ”**



*Fellow Yingfeng Deng, PhD and Dr. Scherer*

As everyone else who works in science, Dr. Deng and I experience the daily frustration of laboratory disappointments. Research requires persistence that results often in only small successes. However, our determination is maintained throughout our daily struggles, because we know that, at diabetes' most basic level, we must learn how to effectively protect beta cells from death and increase the number of new beta cells for people with type 1 and type 2 diabetes. Incrementally, we are getting closer to our goal.

That is why investing in research is so important. Many research projects in the diabetes scientific arena are on the cusp of reaching discoveries that may produce viable pharmaceutical interventions, potentially improving the lives of millions of people with diabetes.

Today, the United States is only investing a relatively small amount of research dollars on a disease that is, comparatively, rapidly expanding to affect so many people. Meanwhile, diabetes costs the United States billions of dollars each year in healthcare dollars. Research is a small price to pay to save our healthcare system and, more importantly, lives.

During these times of reduced NIH funding, the American Diabetes Association fulfills an important role, sponsoring niche research that would not have otherwise been funded by a more conservative funding agency. During my tenure on the Association's Grant Review Committee, I have witnessed the dramatic increase of applications and the frustrating regret when a peer who has a feasible study cannot be funded due to limited resources.

However, to those individuals and groups who have supported our work thus far, thank you. Your gifts have made strides already, like in my work over the last decade. Thanks to your donations, the Association and its Research Foundation have paid for this unique scientific area of metabolic regulation that is not covered by any other organization at this stage. In addition, you have invested in the career of young investigators, like Dr. Deng who will follow up on the work I have started.

The future of diabetes science is bright, but we must keep investing to find the edge over a disease that is overwhelming our health care system and the daily lives of friends and family. Imagine what knowledge would have been lost if the Association was unable to support my initial grant, ten years and 5,000 publications ago. ■

### Melanie Cobb, PhD

#### Mentoring young investigators in pancreatic beta cell research

Funding research efforts in pancreatic beta cell biology not only brings us steps closer to uncovering answers for a cure, but also creates a great training opportunity for young investigative scientists. Such is the case in the research laboratory of Melanie Cobb, PhD, recipient of a Mentor Based Postdoctoral Fellowship Award. Dr. Cobb conducts her research at the University of Texas Southwestern Medical Center in Dallas, Texas.

Providing a strong mentor environment for postdoctoral fellow Eric Wauson, PhD, Dr. Cobb has obtained three separate Mentor Awards from the Association over the past ten years. Dr. Cobb's project entitled, "*MAP kinases in beta cell function*", will allow Dr. Wauson to focus his investigative efforts on the molecular steps that allow glucose to control the rate of production of insulin in pancreatic beta cells. In the process of completing his research, Dr. Wauson will receive training in analysis of protein phosphorylation, transcriptional regulation and MAPK signaling, both in intact islets and in cell culture. Dr. Cobb states, "This training will help to prepare him for a career as an independent scientist, able to apply any methods to develop research projects of relevance to the treatment of diabetes." Establishing career goals is just as much of a priority as completing research project tasks for postdoctoral fellows.

The long-term goal of Drs. Cobb and Wauson's current study is to define the functions of the MAPK (mitogen-activated protein kinase) family in pancreatic beta cells. The MAPKs ERK1/2 respond to and also integrate signals from nutrients and hormones to maintain the insulin demand needed for gene transcription and other beta cell functions. ERK1/2 are activated and inhibited with varying increases and decreases in concentrations of glucose and hormones.

Facts revealed about ERK1/2 and its signaling pathways have allowed the laboratory to develop a different focus. In the most current year of their work, Drs. Cobb and Wauson began to study the actions of amino acids on beta cell signaling and insulin secretion. Previously, researchers have

confirmed findings that amino acids, the building blocks of proteins, were thought to cause insulin secretion by being metabolized in pancreatic beta cells. Currently, the work of Drs. Cobb and Wauson suggests that amino acids actually cause changes in intracellular proteins that lead to enhanced insulin secretion. This is accomplished by acting on the receptor protein on the surface of beta cells, which could be coupled with proteins that send chemical signals



*Eric Wauson, PhD and Dr. Cobb*

outside of the cell and cause changes inside the cell.

In the upcoming year of study, they will take a closer look at physiological studies which demonstrate that amino acids affect essential functions of pancreatic beta cells including insulin secretion and gene transcription. These mechanisms are still not completely understood.

An important goal in diabetes research is to identify novel points of therapeutic intervention to treat the disease. With funding from the American Diabetes Research Foundation, training the next generation of investigators goes hand in hand with identifying new treatment possibilities. This exciting work had led to a potential target for drug treatment. As Dr. Cobb states, "we are optimistic that the receptors mediating this action of amino acids will provide new drug targets that were not previously recognized on beta cells." ■

**Occupation:** Chief, Division of Endocrinology and Metabolism, University of Utah School of Medicine, Salt Lake City, Utah

**Professional Focus:** Cardiac dysfunction in diabetes, Regulation of myocardial growth and metabolism by insulin signaling

**Outside Interests:** Family, church, travel, photography

**Research Funding:** ADA-Takeda Cardiovascular Postdoctoral Fellowship  
*“Molecular Pathogenesis of Diabetic Cardiomyopathy”*

**Amount Awarded:** \$90,000

*Funded by Takeda Pharmaceuticals North America Inc.*



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## Evan Dale Abel, MD, DPhil

**W**hat does the face of diabetes look like? Diabetes touches everyone, either directly or indirectly.

Therefore, the face of diabetes is simply the human face—regardless of age, gender, ethnicity or background.

There are many misconceptions about diabetes, including what types of people are diagnosed, particularly with type 2. Increasing the dissemination of information about risk factors for diabetes might serve to reduce the number of new cases. Meanwhile, for those individuals who already have this illness, encouraging them to be mindful of potential complications of diabetes will help their quality of life and the healthcare system in general.

As the American Diabetes Association works to promote awareness, one of my jobs as Chief of

the Endocrinology and Metabolism Division at the University of Utah is to focus my research on the risk factors and complications that make diabetes one of the deadliest diseases in our society.

Until about ten years ago, many research funding opportunities focused on the development of the disease (pathogenesis) and the classic types of diabetic complications, such as neuropathy, nephropathy and retinopathy. These still remain serious and deadly consequences of diabetes. However, until recently, another set of complications remained relatively unaddressed: cardiovascular events, like heart attacks, strokes and heart failure. Cardiovascular complications represent the major causes of death in individuals with diabetes.

This growing revelation encouraged groups like the American Diabetes Association and its Research Foundation to dedicate funding opportunities to address this critical area of diabetes science. In 2006, the Association and Takeda Pharmaceuticals, Inc. decided to fund the education of upcoming diabetes researchers who specialize in this area of diabetes science. Through the “ADA-Takeda Cardiovascular Complications in Diabetes Postdoctoral Fellowship Program,” the Association hopes to foster research and clinical initiatives that will improve diabetes care in general and specifically cardiovascular disease.

I have had the privilege of being funded by an ADA-Takeda Cardiovascular Postdoctoral Fellowship Award for the last year and a half.

## Mountain/West

**“ Every dollar spent on diabetes research is an immense investment in our future—in healthcare dollars and, most importantly, in lives. ”**

This competitive grant supports the education of my post-doctoral fellow, Sandra Sena, PhD, who is one of five fellows in our laboratory. Dr. Sena is an excellent example of the available talent in this upcoming generation of researchers, which must not be lost. With the diabetes landscape changing so quickly, it is especially important to train this group of researchers in my lab, as they will continue to discover better ways to prevent and treat heart disease in people with diabetes. The goal of the ADA-Takeda award is to provide Dr. Sena with a strong environment to receive the training necessary to become a leading contributor to this goal.

Our project entitled “*Molecular Pathogenesis of Diabetic Cardiomyopathy*” increases our understanding of the ways in which diabetes leads to heart muscle damage. Dr. Sena is conducting experiments to further understand how diabetes results in malfunctioning mitochondria in the heart. Mitochondria are the cellular organelles responsible for the production of cellular energy.

Through our experiments, Dr. Sena and other members of the laboratory are focusing on: 1) understanding the role that insulin resistance plays in the regulation of mitochondrial function in the heart, particularly in the context

of cardiac hypertrophy and cardiac ischemia; 2) identifying novel roles for insulin signaling in the heart that may contribute to cardiac muscle injury in diabetes; and 3) understanding how increased dietary lipid might lead to cardiac dysfunction in diabetes.

Ultimately, we hope these discoveries might lead to new treatments aimed at preventing heart failure in people who have diabetes or are obese and/or insulin-resistant. I am pleased to report that, so far in the last 18 months, we have found that decreased insulin signaling in the heart, as occurs in diabetes, impairs the function of mitochondria. Therefore, treatments designed to increase the heart’s sensitivity to insulin might improve mitochondrial and heart function, thereby lessening the impact of diabetes on the heart.

We also found that as little as two weeks of a high-fat and high sucrose diet caused the heart to significantly increase the amount of fatty acid that it metabolizes and reduces the amount of glucose that is metabolized. This pattern is associated with a reduced ability of the heart to efficiently utilize oxygen to make energy for heart muscle contraction. This suggests that short-term changes in diet can have a profound effect on heart function. Our laboratory research efforts clearly show that rigorous research programs hold the promise of not only discovering causes of diabetic complications, but also for developing new insights into treatments for diabetes and its complications.

Diabetes complication research has dramatically increased in scope over the past few decades. Our lab has been actively

engaged at the forefront of the effort to better understand cardiovascular complications. At the same time, as we advance our knowledge of mechanisms of cardiovascular complications associated with diabetes, we are also training the next generation of researchers. Research solves problems, informs the direction in which new therapeutic developments should occur and provides the human capital to continue new discoveries in the future.

Every dollar spent on diabetes research is an immense investment in our future—in healthcare dollars and, most importantly, in lives. Although there are groups of individuals who are genetically predisposed to have diabetes, all classes, age groups and genders can be affected and die from its complications. Diabetes can strike anyone. As the number of people with diabetes increases, the world will incur a great burden of disease and its devastating cardiovascular complications. We believe our efforts will help to lessen, or perhaps eliminate, this burden. ■

*Dr. Abel and postdoctoral fellow Sandra Sena, PhD*



## John David Symons, PhD



### The role of fat in obesity-related cardiovascular complications

It is well known that obesity predisposes individuals to insulin resistance, type 2 diabetes, and cardiovascular complications. The specific causes of obesity-related cardiovascular complications are unclear. However, with funding from the American Diabetes Association, we are getting closer to uncovering the answers we desire.

J. David Symons, PhD, of the University of Utah is examining cardiovascular complications such as hypertension (high blood pressure) and arterial dysfunction (inability of blood

vessels to function appropriately) in mice. He is the recipient of a Basic Science Award. In his research entitled *"The role of ceramide in obesity-related vascular dysfunction"* Dr. Symons explains that persons with diabetes are predisposed to cardiovascular complications such as high blood pressure

and poor vessel function. Obtaining information about these complications is key in the fight against diabetes.

Dr. Symons is specifically focusing on the contribution of the breakdown of fat during metabolism and how it relates to high blood pressure and blood vessel dysfunction. Using mice that consume a high fat diet, pharmacological and genetic methods are being used to eliminate the contribution from one product of fat metabolism called ceramide. As Dr. Symons explains, "This could be directed toward development of an intervention that might have similar effects in humans."

Dr. Symons is testing the hypothesis that increased accumulation of ceramide in response to over nutrition (e.g., high-fat feeding) might contribute to cardiovascular complications by reducing the available amount of a

chemical compound called nitric oxide. Nitric oxide is a vasodilator (widens and relaxes the blood vessels) and it is also produced by cells that line the inner surface of the blood vessels. There is a delicate balance between the production of nitric oxide and the destruction of this compound. If the destruction of nitric oxide (e.g., by ceramide) outweighs the production of this compound, the balance might be tipped toward developing cardiovascular complications.

Preliminary results have supported his hypothesis. For example, mice that consume a high fat diet and become obese develop cardiovascular complications. Interestingly, when mice consume a high fat diet and are treated with blockers of ceramide production, the cardiovascular complications do not develop. Similar results have been obtained when individual blood vessels are incubated directly with the saturated fatty acid palmitate (a fatty acid that is commonly consumed by humans). In these studies palmitate causes blood vessel dysfunction. Again, these effects can be markedly improved when the accumulation of ceramide is prevented.

Dr. Symons research now is focusing on exactly how ceramide might reduce nitric oxide bioavailability and promote cardiovascular complications. Dr. Symons comments, "An urgent need exists to define the factors that contribute to cardiovascular complications so that new therapeutic targets and interventions can be designed. I would not be able to continue this research without the generous funding from the American Diabetes Association. I am grateful to the Association for finding the research worthy and the donors for providing the financial support." ■

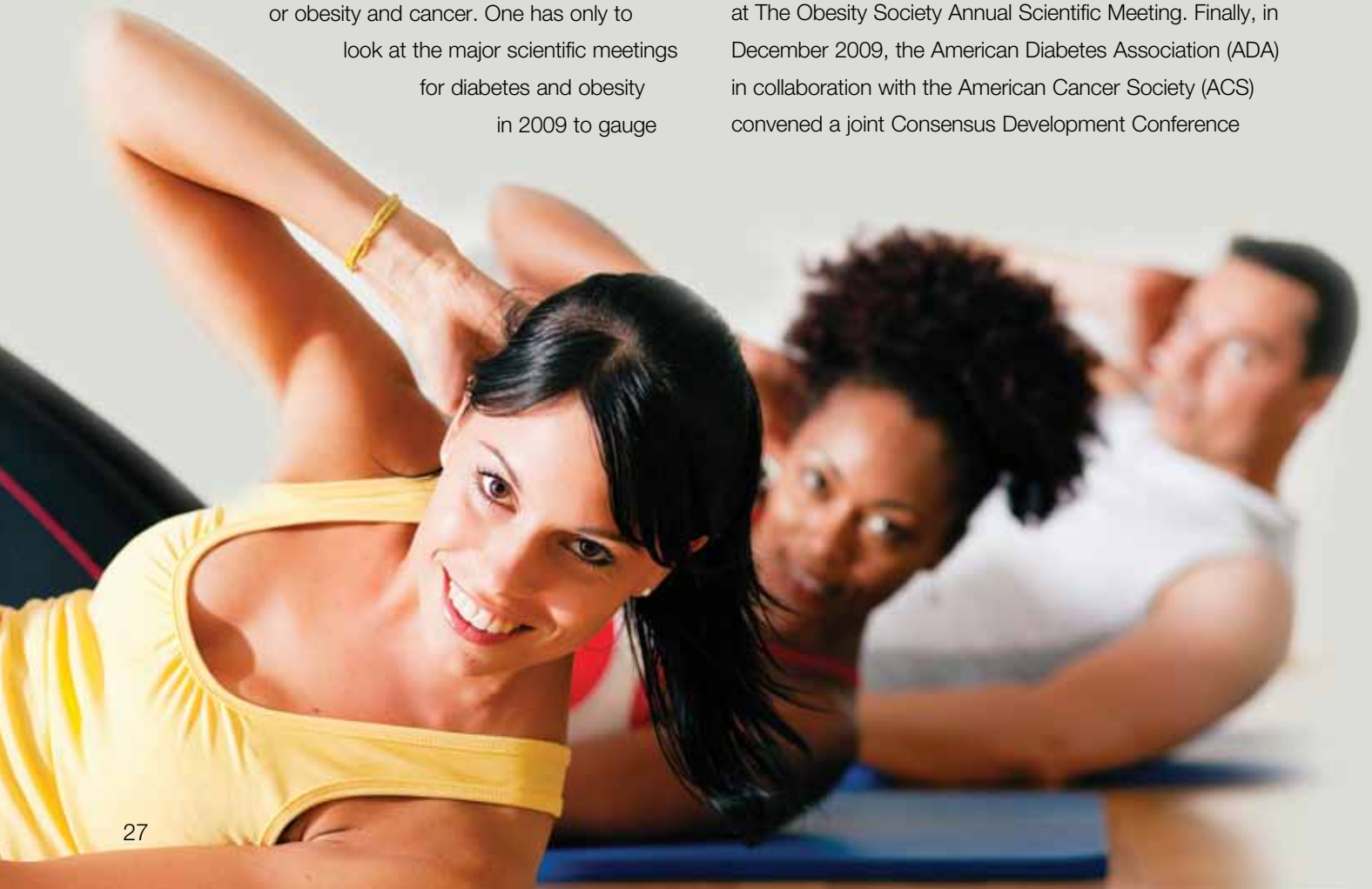


J. David Symons, PhD

# “True, True... and Related?”

**D**iabetes, in particular type 2 diabetes, as well as obesity, which increases the risk of developing type 2 diabetes in many people, rarely exist in isolation. Other pathophysiological processes often co-exist (referred to as co-morbidities) to complicate the picture like high blood pressure, high cholesterol, insulin resistance, etc. Relatively recently, more and more data have pointed to a possible link/relationship between diabetes and/or obesity and cancer. One has only to look at the major scientific meetings for diabetes and obesity in 2009 to gauge

the interest in this important topic. Major symposia on the topic of diabetes/obesity and cancer, or treatment of diabetes and cancer risk, were presented in June at the American Diabetes Association Scientific Sessions in New Orleans, in early October at the European Association for the Study of Diabetes Annual Meeting in Vienna, in mid-October at the International Diabetes Federation World Diabetes Congress in Montreal, and in Washington, D.C. at The Obesity Society Annual Scientific Meeting. Finally, in December 2009, the American Diabetes Association (ADA) in collaboration with the American Cancer Society (ACS) convened a joint Consensus Development Conference



on Cancer and Diabetes. Research experts in both the diabetes and cancer fields were brought together to review the evidence to date supporting the link between diabetes and cancer. Furthermore, they discussed what still needed to be done to provide more definitive data to convincingly establish the relationship. A Consensus Report from this effort will be jointly published mid-year 2010 in the ADA journal *"Diabetes Care"* and the ACS journal *"CA: A Cancer Journal for Clinicians"*. In an effort to provide a more general overview of this hot topic, some recently published data will be provided that supports the link between obesity/diabetes and cancer.

### **Obesity and Cancer**

Simply put, most data to date indicates that the more weight a person carries on their body, the greater the odds of developing cancer. A recent report issued by the American Institute of Cancer Research and the UK-based World Cancer Research Fund, and supported by data presented at the most recent Obesity Society Scientific Meeting, indicates that obesity is associated with an increased risk for some types of cancer, but not all types of cancer. Strong evidence exists for an increased risk for the following types of cancer in obese individuals: colorectal (primarily colon) 2-2.5 fold; kidney (primarily clear-cell renal cell cancer) 2-3 fold; breast (postmenopausal) 50% increase; pancreatic 20-30% increase; liver 40-50% increase; and ovarian 20-25% increase. Although risk appears to still be increased, less convincing evidence exists for an association between obesity and prostate, cervical, stomach, bladder, gall bladder, blood (lymphoma, multiple myeloma, leukemia), testicular, melanoma and thyroid cancers.

Within any one type of cancer, the increased risk of cancer related to obesity may vary with gender, ethnic background, or other confounding variables. For example,

the association between obesity and colon cancer is much stronger in men than in women. In the Asia-Pacific population, a stronger association exists between BMI (body mass index, a general measure of overweight/obesity and whole body adiposity) and both premenopausal and postmenopausal breast cancer compared to some other ethnicities. It appears that obesity might actually protect from premenopausal breast cancer in most women, while postmenopausal risk is increased modestly/moderately as previously indicated. In a recent study published in the *"Journal of the American Medical Association"* (JAMA), individuals who were overweight (BMI 25-29.9) from ages 14-39 years or obese (BMI > 30) from ages 20-49 years had an associated increased risk of pancreatic cancer, independent of diabetes status. The association was stronger in men than in women, and in individuals who had ever smoked compared to those that never smoked. Those who were overweight or obese from ages 20-49 years also had an earlier onset of pancreatic cancer compared to those of normal weight. The pattern of fat distribution in the body may also have an effect. A recent prospective Swedish study indicated that waist-hip ratio, a measure of central adiposity (abdominal body fat), was positively associated with increased risk of prostate cancer before age 65. However in the same study, general adiposity measured by BMI or body fat percentage was not associated with prostate cancer risk. While the specifics may vary, it has been generally stated however that 20% of all cancers can be attributed to obesity.



Perhaps just as troubling is the fact that the presence of overweight/obesity at the diagnosis of cancer may significantly impact one's chances of survival. In the previously mentioned JAMA study in pancreatic cancer, individuals who were overweight or obese from ages 30-79 years had a reduced overall survival of pancreatic cancer compared to normal weight individuals regardless of disease stage or tumor resection status. A recent study published in *"The Lancet Oncology"* examined information on more than 2,500 men who had been followed for 24 years as part of the Physician's Health Study. Overweight

men had a 47 percent higher risk of dying from prostate cancer, while obese men were greater than 2.5 times more likely to die from prostate cancer, compared with men of healthy weight (BMI under 25). Men with the highest C-peptide concentrations (a measure of insulin levels in the blood) also had greater than double the risk of dying from their cancer compared with men with the lowest insulin levels. Finally, men who had a BMI greater than 25 and high C-peptide levels had four times the risk of dying from prostate cancer compared to men with lower BMIs and lower C-peptide levels. The potential role of insulin in the link between obesity/diabetes and cancer will be explored further below.

### **Diabetes and Cancer**

As is the case with obesity, current epidemiological evidence indicates that there is a link between diabetes and cancer. Most of the existing data points primarily to type 2 diabetes increasing cancer risk and mortality from cancer. The connection between type 1 diabetes and cancer is far more tenuous, if existent at all. Recent reports have indicated a significantly increased risk for pancreatic, liver, and colon cancer in patients with type 2 diabetes, with slightly less increased risk seen for breast, urinary tract (bladder) and female reproductive organ (primarily endometrial) cancer. Interestingly, diabetes has been reportedly associated with a decreased risk of prostate cancer. However, if a diabetic man does develop prostate cancer, his risk of dying from the cancer increases approximately 1.8 fold compared to men with prostate cancer and no diabetes.

Similar to the case for obesity, the increased risk of cancer related to diabetes may vary with gender, ethnic background or other variables. The association between colon cancer and diabetes is much more evident in males compared to females and in males the risk continues to increase as the duration of diabetes increases. Ethnic



differences may also exist for colorectal cancer. A recent study from the University of North Carolina confirmed that the risk for both colon and rectal cancer was increased by approximately 40% in Caucasians with diabetes compared to those without diabetes. Diabetes however was not associated with colon or rectal cancer among African Americans. A recent review of published data to date that evaluated the effect of pre-existing diabetes on cancer outcome concluded that having diabetes when given a cancer diagnosis increases the risk of death by 41%. Diabetes was significantly associated with increased long-term, all-cause mortality for endometrial, breast and colorectal cancer. Non-significant increases in mortality risk were seen with diabetes and prostate, gastric, liver, lung and pancreatic cancer. Possible explanations for the findings include the possibility that diabetes may make cancer more aggressive, that people with diabetes may get different cancer treatment than those with normal glucose levels (or have a poorer response to identical treatment), or perhaps patients with diabetes are diagnosed later in the cancer course.

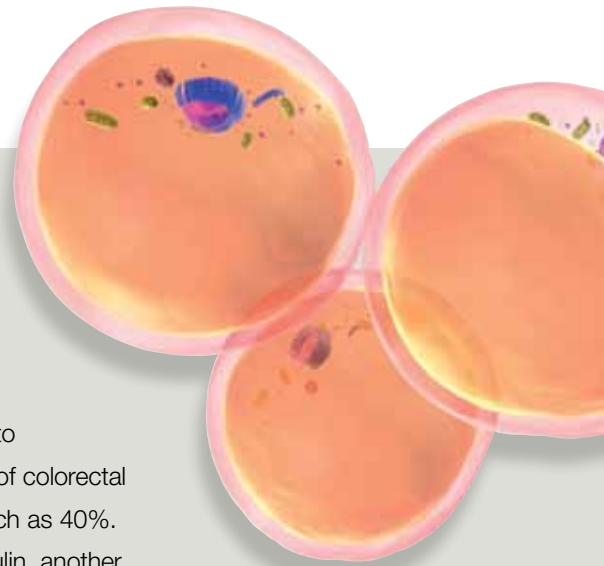
### **Potential Mechanisms Linking Obesity/Diabetes and Cancer**

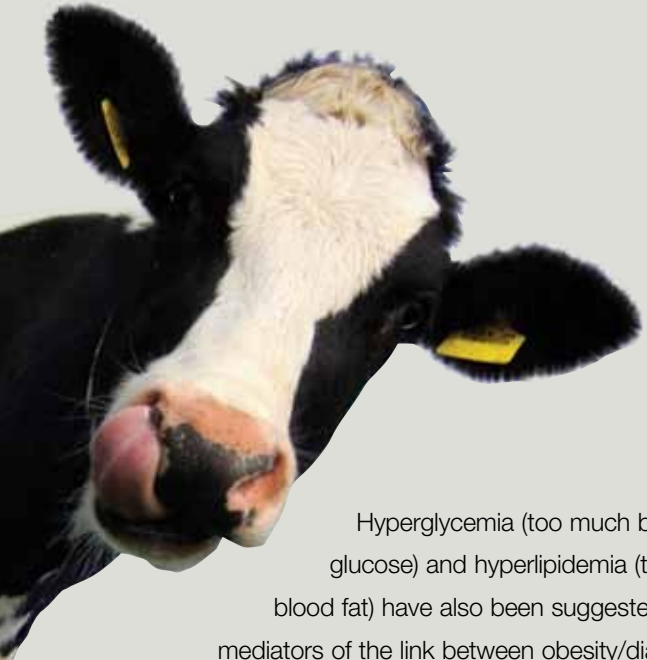
The mechanism(s) by which diabetes may be linked to cancer is not definitively known. The most popular hypothesis involves insulin. In addition to insulin being an important hormone regulating the body's metabolism, acting through a different insulin receptor than that mediating the metabolic effects, insulin can also promote cell growth. Due to the presence of insulin resistance in obesity and type 2 diabetes most individuals are hyperinsulinemic (produce more insulin than normal). The increased circulating insulin levels are needed to overcome the decreased response to insulin (resistance) present. Too much circulating insulin may predispose more toward the cell growth side of the equation than toward the normal predominance of metabolic effects. For example, insulin has been shown to increase breast cancer cell growth in

*in vitro* (in cell culture).

Increased insulin has also been suggested to increase the risk of colorectal cancer by as much as 40%. In addition to insulin, another compound called insulin-like growth factor (IGF) can act through its receptor and/or specific insulin receptors to promote cell growth. Increased IGF-1 levels has been reported to be associated with an increased risk for some cancers.

Other molecules that are altered in obesity and diabetes might also be involved in the association between obesity/diabetes and cancer. In association with increased oxidative stress, inflammatory mediators are increased in obesity/diabetes. For example, interleukin 6 (IL-6) and C-reactive protein (CRP, a systemic marker of inflammation) are increased and have been found positively correlated to obesity/type 2 diabetes and increased risk of breast cancer. Higher CRP levels have also been shown to be associated with higher risk for colorectal cancer. Molecules produced by fat cells (adipocytokines) are also altered in obesity/type 2 diabetes. For example, the adipocytokine leptin is increased and it has been linked to increased risk for endometrial, breast, prostate and colon cancer. A beneficial adipocytokine called adiponectin is decreased in obesity/type 2 diabetes. Adiponectin has been shown to be protective against breast and endometrial cancer. A recent report suggests a potential unifying factor for the obesity/diabetes and cancer link. Many of the aforementioned molecules increase the activity of a pathway called the PI3K/Akt signaling pathway. This pathway in turn can activate signals for cell survival, cell growth and cell cycle potentially leading to carcinogenesis. Much more work remains to better determine the role of this pathway and perhaps others not yet identified.





Hyperglycemia (too much blood glucose) and hyperlipidemia (too much blood fat) have also been suggested as mediators of the link between obesity/diabetes and cancer. Increased glucose levels have been associated with a 20% increase in the risk of colorectal cancer. A recent study from the National Cancer Institute at the NIH showed an increased pancreatic cancer risk related to increased intake of total fat, saturated fat, and monounsaturated fat, but not of polyunsaturated fat. Increased intakes of red meat and dairy products were both significantly associated with increased pancreatic cancer risk. An association has also been found between increased red meat consumption and the risk for colon cancer. A recent *“International Journal of Cancer”* report states that smoking, diabetes, obesity and high meat intake were each associated with a significant 20% increased risk for colorectal cancer compared with individuals in the lowest categories for each variable.

#### **Does Treatment for Obesity, Diabetes or Cancer Influence Risk?**

A recent set of observational studies published in *“Diabetologia”* reported a potential link between insulin treatment and cancer. More specifically, it was suggested that treatment with insulin, in particular the long-acting

insulin analog insulin glargine (Lantus), increased the incidence rate for some cancers including breast, and perhaps colorectal and pancreatic, cancer. However, inconsistencies among the studies has led experts to doubt whether there truly is an association between Lantus use and cancer. These provocative reports have led the FDA and some insulin manufacturers to more closely examine completed clinical trials involving insulin treatment to better determine whether such an increased risk exists.

Other diabetes therapies have also been examined to determine if a potential cause and effect relationship exists between the treatment and incidence of cancer. There is some indication that sulfonylureas may increase the risk for some cancers. The data is by no means definitive. Synthetic PPAR-gamma agonists like thiazolidinediones (TZDs, e.g. Actos or Avandia) appear at worst neutral. TZDs are known to down-regulate the IGF system and to lower insulin levels. There is some evidence that TZDs may in fact decrease the incidence of lung cancer by 60% in African Americans and by 30% in white males. There appears to be no effect on risk for breast, colon, or prostate cancer with TZDs. Perhaps the most prescribed drug for people with diabetes, metformin, actually appears to lower the risk for some cancers. For example, a recent report indicated that diabetics who took metformin had a 62% lower risk of pancreatic cancer. In Caucasian men, a 44% reduction in risk for prostate cancer was seen with metformin treatment.

It is also possible that non-therapeutic treatment may also affect the link between obesity/diabetes and cancer. Physical activity may have beneficial effects on risk for some cancers. Positive effects have been reported for increased physical activity and decreased risk for colorectal, postmenopausal breast and endometrial cancer. Physical activity may also benefit to some extent prostate and ovarian cancer as well. Swedish researchers have recently reported that bariatric surgery may reduce the risk for

developing cancer in women, but there appears to be no such benefit for men. A very recent study from the University of Utah School of Medicine reported a 24 year follow-up in gastric bypass patients. Total cancer incidence was significantly decreased by 24% in surgical patients versus severely obese controls, and cancer mortality was 46% lower in the surgery group compared to controls.

Finally, treatment for cancer may be affected by the presence of diabetes, or may affect the risk of developing diabetes. A recent report from the M.D. Anderson Cancer Center indicated that patients who have breast cancer and diabetes are at increased risk of chemotherapy-related toxicities, compared with non-diabetic patients who are receiving chemotherapy, and have higher all-cause mortality. Another recent study indicated that childhood cancer survivors may be at elevated risk for developing diabetes, especially those who received whole-body or abdominal radiation. Diabetes was nearly twice as common among long-term cancer survivors compared to their siblings, and up to 12.6 fold more likely for those who received total body irradiation in childhood.

### **Breaking the Link**

A recent report from Mt. Sinai School of Medicine concludes that obesity and type 2 diabetes are independently associated with an increased risk of developing cancer and increased mortality. Although the specific etiology is yet undetermined, insulin resistance and hyperinsulinemia are thought to be important factors. Hyperglycemia, hyperlipidemia and inflammatory cytokines are also potentially involved in the process. It appears that the old adage, "An ounce of prevention is worth a pound of cure" still resonates today. Data from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study confirms that a healthy lifestyle can reduce risk of chronic disease. Four factors are key: never smoking,

having a BMI lower than 30, performing at least 3.5 hours of physical activity per week and following a healthy diet. Those who follow all four lifestyle factors have a 93% lower risk of diabetes, 81% lower risk of heart attack, 50% lower risk of stroke and a 36% lower risk of cancer. In association with World Cancer Day on February 4, 2010 the International Union Against Cancer recommends that people stop smoking, limit their alcohol consumption, avoid too much sun and maintain a healthy body weight through diet and exercise in order to prevent as much as 40% of all cancers. Certainly words to live by in order to break the links between obesity, diabetes and cancer. ■



## Glucose intolerance reversed with carnitine supplementation in obese animals

Deborah Muoio, PhD, the recipient of a Career Development Award from the American Diabetes Association, has recently published study results in the August 21, 2009 issue of the *Journal of Biological Chemistry*. She has found that providing obese rats with carnitine supplements helps them to clear the extra sugar they have trouble removing from their blood. Dr. Muoio, who is also the past recipient of a Junior Faculty Award, is conducting her research at the Duke University Medical Center. Dr. Muoio's current Association project is entitled, "Mitochondrial Stress and Insulin resistance in skeletal muscle."



Deborah Muoio, PhD

Carnitine is made in the liver and recycled by the kidneys. In its dietary form, it can be obtained from red meat. Carnitine also plays a role in the cellular energy process, transporting long-chain fatty acids across the cell membrane to enter the mitochondria where they are "burned" for energy. It also

helps move excess fuel from the cells into the circulating blood, which then redistributes this energy source to needier organs or to the kidneys for removal from the body.

Observing the skeletal muscle of obese rats, Dr. Muoio's research team determined that there was an imbalance in the cells' burning of both fat and glucose fuel. As Dr. Muoio explains, "It appeared that carnitine could no longer do its jobs when chronic metabolic disruptions were stressing the system. That's when we designed an experiment to add extra carnitine to rats' diet."

Dr. Muoio's research design involved obese rats whose cells' fuel burning ability was genetically reduced and was shut down by a lack of natural carnitine. After eight weeks of supplementation with carnitine, the fuel burning ability was restored. An added outcome was the improvement in glucose tolerance and a lower risk of diabetes.

The results offer new hope for those with glucose intolerance and type 2 diabetes. In a related study with human muscle cells, Dr. Muoio has also determined that carnitine supplementation might help older people with glucose metabolism disorders such as pre-diabetes and diabetes. Dr. Muoio's next research focus is to begin a small clinical trial of carnitine supplementation in people with glucose intolerance.

(Noland RC, Koves TR, Seiler SE, Lum H, Lust RM, Ilkayeva O, Stevens RD, Hegardt FG, Muoio DM. Carnitine insufficiency caused by aging and overnutrition compromises mitochondrial performance and metabolic control. *Journal of Biological Chemistry*. 2009 Aug 21;284(34):22840-52. Epub 2009 Jun 24.) ■

## Development of metabolic syndrome could be associated with bearing children

Erica Gunderson, PhD is the first author on a study conducted at the University of Alabama at Birmingham and published in the August 2009 issue of the *American Journal of Obstetrics and Gynecology*. She is the past recipient of a Research Award entitled, “*Prospective studies of childbearing and correlates of insulin resistance in non-diabetic women*”. Her study provides evidence that for most pregnant women, a healthy pregnancy modestly contributes to the development of metabolic syndrome even after accounting for excess weight gain and lower physical activity. Metabolic syndrome is defined as abdominal obesity, high triglycerides, insulin resistance and other cardiovascular risk factors.

Data was collected from the CARDIA (Coronary Artery Risk Development in Young Adults) study. Preconception data established a comparison baseline to the changes brought on by pregnancy which has not been available in previous studies. The study analysis included 1,451 women, with 706 women having no births and 745 women having at least one birth in the past twenty years.



Erica Gunderson, PhD

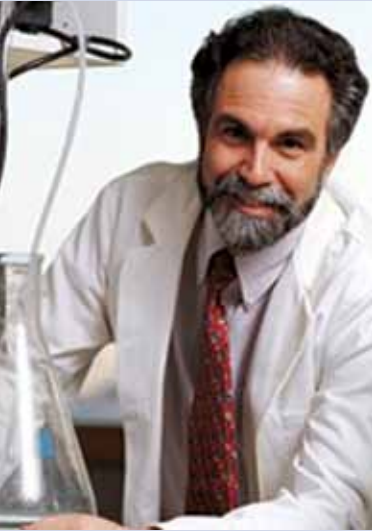
Researchers controlled for preconception measurements such as body mass index, metabolic syndrome components and physical activity. Results revealed that women who had children and maintained normal blood sugars were more likely to develop metabolic syndrome later in life and their risk increased with their number of children (33% for one birth, 62% for two or more births).

However, those same women were not more likely to develop type 2 diabetes compared to non-child bearing women. For women who have had gestational diabetes, the risk is even greater. The risk of developing metabolic syndrome was 2.4 times more likely than non-child bearing women and they were also four times more likely to develop diabetes later in life.

Pregnancy can affect a woman's risk of developing metabolic syndrome. Other risks factors could include an increase in belly fat or an increase in cholesterol levels. In the future,

studies could focus on postpartum prevention of metabolic syndrome in areas such as reductions of weight retention, cholesterol and triglycerides. Postpartum screening for cardio-metabolic risks, especially for women who developed gestational diabetes, may also serve as an opportunity for disease prevention. ■

## Saving limbs using combination of gene and cell therapy



Gregg Semenza, MD, PhD

In the December 1, 2009 issue of *Proceedings of the National Academy of Sciences USA*, Dr. Gregg Semenza, MD, PhD, published findings that could improve a common condition of diabetes called peripheral arterial disease (PAD). PAD results in blood vessel blockage, which, in turn, leads to low blood flow. As a result, tissues in the affected leg may not receive enough oxygen to survive, leading to gangrene and the need for amputation. “People with diabetes have a 40 times higher risk of losing a limb to amputation,”

explained Dr. Semenza. “We also know that the risk of this happening increases with age.”

With his American Diabetes Association Research Award, Dr. Semenza developed a mouse model of PAD and showed that gene therapy that increases the levels of HIF-1, which is an important regulator of blood vessel formation, can increase blood flow, improve movement, and decrease tissue death, thus eliminating the need for amputation. Dr. Semenza’s research project entitled, “*Interaction of diabetes, aging, and HIF-1 deficiency in peripheral vascular disease*,” was conducted at Johns Hopkins University School of Medicine in Baltimore, Maryland.

Previously, researchers on Dr. Semenza’s team showed that HIF-1 turns on genes that are necessary for building new blood vessels. The blood flow was partially restored in the animals that were treated with HIF-1 gene therapy. Researchers then tested whether the same treatment could improve blood flow in animals with diabetes. The team tested mice with and without diabetes that had reduced

blood flow in one leg. Twenty-one days after treatment, both groups of treated mice exhibited greatly improved recovery of blood flow compared with the mice who did not receive the gene therapy.

In the current study, a new question was posed. Could the same gene therapy be used to help improve blood flow in mice with advancing age? Mice usually live two to three years. The researchers compared 13-month-old mice with three-month-old mice. When the researchers cut off the blood supply to the leg, all of the younger mice could recover without tissue damage, but none of the old mice were able to recover without tissue destruction. It was known that one of the cell types that helps stimulate new vessel growth were cells that come from the bone marrow. Returning to the lab, the researchers treated the mice with the HIF-1 gene therapy and injected bone marrow cells and found that older mice receiving the combination therapy were less likely to lose their legs than their untreated counterparts.

Dr. Semenza stated, “Our results are promising because they have demonstrated that a combination of gene and cell therapy can improve the outcome in the case of critical limb ischemia associated with aging. And that’s critical for bringing such treatment to the clinic.”

**(Rey S, Lee K, Wang CJ, Gupta K, Chen S, McMillan A, Bhise N, Levchenko A, Semenza GL. Synergistic effect of HIF-1alpha gene therapy and HIF-1-activated bone marrow-derived angiogenic cells in a mouse model of limb ischemia. *Proc Natl Acad Sci USA*. 2009 Dec 1;106(48):20399-404. Epub 2009 Nov 30.) ■**

## Deaf1 gene has possible link to the development of type 1 diabetes

C. Garrison Fathman, MD, the recipient of a Mentor-Based Postdoctoral Fellowship Award from the American Diabetes Association, has published research results identifying a gene and its potential role in the development of type 1 diabetes. Dr. Fathman, and his postdoctoral fellow Linda Yip, PhD, both of Stanford University, focused their research efforts on the deformed epidermal autoregulatory factor 1 (Deaf1) gene.

Drs. Fathman and Yip identified two forms of the Deaf1 gene within the pancreatic lymph nodes of mice that may be related to the development of the type 1 diabetes. The full-length, functional form of Deaf1 controls the production of molecules needed to eliminate immune cells that can destroy insulin-producing cells. The Deaf1 variant or shorter non-functional form prevents the full-length form from functioning normally.

Drs. Fathman and Yip then turned their focus to patients with type 1 diabetes. Levels of the shorter form of the gene were much higher in people with type 1 diabetes than that seen in similar tissues from healthy controls. In addition, levels of the inhibitory short form of the gene behaved in the same way as they did in mice, blocking the action of the beneficial full-length form.

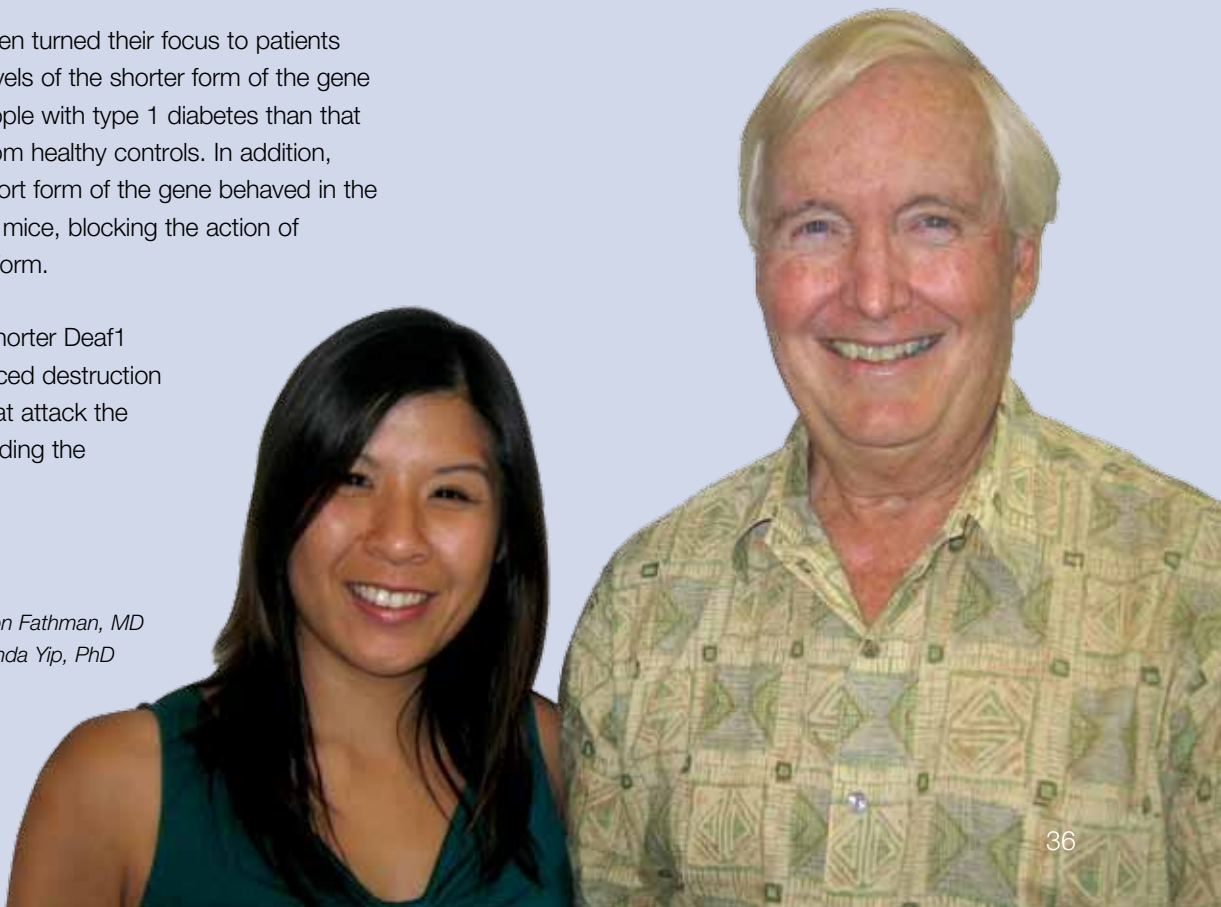
Increased levels of the shorter Deaf1 variant may lead to reduced destruction of the immune T cells that attack the body's own tissues including the

insulin producing cells of the pancreas. This could be a link to the development of type 1 diabetes. The results of this study potentially identify a novel risk factor for type 1 diabetes and a new therapeutic target for the disease.

Study results were published in the September 2009 issue of *Nature Immunology*.

(Yip L, Su L, Sheng D, Chang P, Atkinson M, Czesak M, Albert PR, Collier AR, Turley SJ, Fathman CG, Creusot RJ. Deaf1 isoforms control the expression of genes encoding peripheral tissue antigens in the pancreatic lymph nodes during type 1 diabetes. *Nature Immunology* 2009 Sep;10(9):1026-33. Epub 2009 Aug 9.) ■

C. Garrison Fathman, MD  
and Linda Yip, PhD



## Pinnacle Society and Summit Circle

Those who have made major gifts to the Research Foundation are members of our Pinnacle Society. As the Association's most prominent giving society, the Pinnacle Society is comprised of venture philanthropists who make generous gifts to the Association and its Research Foundation of \$10,000 or more.

Forward-thinking individuals who have left the Research Foundation as a beneficiary in their estate plans are members of the Summit Circle, the Association's planned giving honor society. These generous donors have chosen to "leave a legacy" to support advancement in diabetes research.

We thank these individuals and their families for dedicating the necessary funds to help others live their lives to the fullest now and in the future.

The American Diabetes Association Research Foundation welcomes over 50 new members to the Pinnacle Society and Summit Circle!\*

### **Pinnacle Society**

AIS, Inc. – Terry Phillely, President

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Mr. Jerry Donnelly

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Mr. James E. Kemp & Mrs. Geneva A. Kemp

Katheryn Korczyk

Cynthia Levy

David G. & Kay Marrero

Ms. Melba N. McKeen

Mr. David Hollander

Mrs. Marianne B. Patterson

Mr. Gary R. Pieper

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Ms. Susan J. Tompos

Diabetes research takes time and money to perform excellent work. If you would like to support ongoing studies of diabetes and its complications, please consider joining these remarkable donors by becoming a Pinnacle Society or Summit Circle member at the American Diabetes Association.

\*As of December 31, 2009

# Research Foundation Breakthrough **Highlights** 2009

## **Vivian Fonseca, MD**

Tulane University School of Medicine

*Clinical Research Award: \$597,922*

Natural disasters have recently been prevalent in the news and the impact of these events goes far beyond the acute devastation, particularly for those with chronic diseases.

Dr. Fonseca found a worsening of long-term blood sugar control, as well as higher blood pressure and cholesterol levels, in adult patients with diabetes up to 2 years after Hurricane Katrina in New Orleans, with patients in the city's charity health care system most negatively affected. Better disaster planning is needed to address the needs of those with chronic health conditions like diabetes in order to avoid negative effects on long term care, exacerbation of existing health care disparities and resultant increases in lifetime healthcare costs.

## **Christian Bjorbaek, PhD**

Beth Israel Deaconess Medical Center, Harvard University

*The Richard and Susan Smith Family Foundation Pinnacle Program Project: \$2,999,998*

Funded by Richard and Susan Smith Family Foundation

While communication between fat cells and the brain are known to be important for metabolic control in obese individuals with type 2 diabetes, the pathways holding the most promise for future treatments for obesity/type 2 diabetes related to these pathways remain to be identified. Dr. Bjorbaek has found that receptors for the fat cell hormone leptin in a specific set of neurons in the brain (POMC neurons) are essential in the regulation of blood glucose and stimulation of physical activity. This information may lead to the development of novel anti-diabetes drugs targeted at obese patients suffering from type 2 diabetes.

## **Laura McCabe, PhD**

Michigan State University

*Basic Science Award: \$300,000*

Type 1 diabetes is a known risk factor for osteoporosis, but the specific mechanisms contributing to diabetic bone loss are still unclear. Dr. McCabe has demonstrated that type 1 diabetes increases bone marrow fat and

decreases osteoblast (the cells that make bone) number, in part mediated by inflammation, in bone. Future work will determine if bone marrow adiposity (fat) might serve to identify patients at risk for bone loss and these findings also identify novel therapeutic targets to treat type 1 diabetes-induced osteoporosis.

## **Jeffrey Bluestone, PhD**

University of California, San Francisco

*Mentor-Based Postdoctoral Fellowship Award: \$173,700*

A subgroup of white blood cells called T regulatory (Treg) cells are essential to maintaining normal immune status and are thought to be a relatively stable population. Dr. Bluestone has found a higher than expected instability in this important T cell population and that the unstable cells can actually convert to cells that promote, rather than block, autoimmunity contributing to type 1 diabetes. Considering that the generation of unstable cells is accelerated in the progression to autoimmune type 1 diabetes, a better understanding of signals that maintain or destabilize Tregs may have important therapeutic implications for not only type 1 diabetes and other autoimmune diseases, but also cancer and infectious diseases.

## **Michael Boehnke, PhD**

University of Michigan

*Mentor-Based Postdoctoral Fellowship Award: \$173,700*

To date only two loci (gene locations) called FTO and MC4R have been identified as reproducibly associated with body mass index (BMI) in humans. Dr. Boehnke, and his ADA-funded fellow Cristen Willer, using genome-wide association studies (GWAS) have identified 6 new loci linked to BMI. Several of these causal genes are highly expressed or act in the central nervous system (CNS), indicating a role of the CNS in predisposition to obesity and may contribute to risk for type 2 diabetes.



# Viewpoint ▶

*Scott Campbell, PhD, Vice President of the ADA Research Program, answers questions about the granting process and philosophy at the American Diabetes Association.*

**Q:** Can you please describe the process the ADA uses to pick who gets research grant funding?

**A:** The ADA uses a “Peer Review” process to determine who receives grant funding similar to that used by the National Institutes of Health (NIH). Twice a year, a volunteer Research Grant Review Committee (RGRC) comprised of approximately 150 diabetes research scientists, the applicant’s “peers”, are responsible for reviewing and scoring research grant applications submitted to the ADA. Each application is assigned to 3 different reviewers with expertise in the research subject of the application. After reading the application, an initial score (the average of the 3 reviewer’s scores) and comments relevant to the application are given. On average, the top scoring one-third of applications received move on to a face-to-face meeting of the RGRC. The bottom two-thirds are triaged (eliminated from further consideration) and given an opportunity to revise and resubmit the application one time, taking into account the critiques given by the reviewers. Each of the top one-third of applications is presented to a larger group of RGRC members for further discussion and rescore. Applications are ranked from best score to worst score and the number of grants funded is based on funding available for that application cycle. All grant applications submitted to the ADA for consideration for funding must undergo peer review.

**Q:** Is the ADA looking to raise the number of clinical research grants any time soon?

**A:** The ADA has always funded both basic science and clinical research grants. However, it is true that up until a few years ago, the number of basic science grants funded far exceeded the number of clinical research grants. As part of its 2008-2011 Strategic Plan, the ADA decided to fund more clinical/translational grants. Taking into account that clinical research grants are on average more expensive to perform, the ADA decided to double the dollar amount of these grants compared to basic science grants. The dollar amount of our clinical grants are not at the level to fund an entire clinical trial, but is sufficient to perform preliminary “proof of concept” trials, as well as small patient interventions, psychosocial behavioral studies, as well as epidemiological investigations. Health care delivery, outcomes and disparity are also subjects of interest for ADA funding with clinical research grants. We are now funding approximately the same number of new basic science and clinical research grants. Of course, clinically relevant grants are also funded amongst our training and career development awards as well. It is important to fund the full spectrum of research grants, from bench to bedside, but we are now funding more patient-oriented investigations to get closer to a cure and in the meantime improve the lives of all people affected by diabetes.

*If you have questions related to the articles in this issue or diabetes research in general, please email them to:*

**ResearchFoundation@diabetes.org.**