

2007 ANNUAL REPORT
OF THE PROGRESSIVE OSSEOUS HETEROPLASIA (POH)
COLLABORATIVE RESEARCH PROJECT

June 2007

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The POH Collaborative Research Group is an international team of physicians and scientists who have contributed to clinical and basic research on progressive osseous heteroplasia (POH). Research efforts dedicated to finding the cause and to establishing a cure for POH are continuing at the University of Pennsylvania School of Medicine with the support of the Progressive Osseous Heteroplasia Association (POHA). In 1996, the first POHA grant was awarded to study the molecular basis of POH. Since then, the POH research program has also been supported through grants from the National Institutes of Health (NIH) and a Focused Giving Award from Johnson & Johnson. In September 2004, the NIH research grant was reviewed and approved for continuation for an additional five-year period.

In this report of the POH Collaborative Research Project, we present an overview of some of the key research findings by the collaborative research group and include the progress of our program over the past year.

PROGRESSIVE OSSEOUS HETEROPLASIA (POH)

POH is a genetic disorder of heterotopic ossification (extra-skeletal bone formation) that is characterized by bone formation within the skin followed by progressive heterotopic ossification of skin, subcutaneous fat, deep connective tissues, and skeletal muscle at sporadic locations throughout the body. The first signs of POH bone formation commonly occur during childhood. POH is a very rare human condition, with approximately 60 people identified worldwide. Our studies that identified mutations in the GNAS gene in many POH patients have indicated that classic features of POH form the extreme end of a spectrum of genetically related conditions.

POH RESEARCH

Identification and Characterization of POH

POH was recognized and described as a unique developmental disorder in 1994. The distinguishing clinical characteristic of POH is the formation of bone in skin (dermis) and subcutaneous tissues followed by progressive and extensive bone formation in deeper soft tissues such as skeletal muscle, tendons, ligaments, and fascia. However, it is likely that many patients who have POH are misdiagnosed. As information is disseminated about POH through scientific journals, meetings, the Progressive Osseous Heteroplasia Association (POHA), the National Organization for Rare Diseases (NORD), and the National Institutes of Health (NIH), more patients who have POH will be accurately diagnosed.

Defining the diagnostic criteria by which additional individuals who have POH can be identified continues to be an important aspect of our research. Only by learning as much as possible about the condition, including the types and severity of associated symptoms, can we fully understand the effects that POH has on patients. The diagnosis of patients who have POH is important not only for advising and counseling those affected individuals and families, but also to help learn more about the condition so that the most productive research can be undertaken in order to develop the most effective treatments.

Heterotopic ossification is the most obvious clinical characteristic of POH, however other more subtle features may also be associated. Over the last two years, we have been evaluating clinical information in patients with POH and POH-like conditions and their families. We have identified clear clinical features that can serve as minimal diagnostic criteria to define and distinguish POH from related conditions. This study was presented at the Annual Meeting of the American Society for Bone and Mineral Research in September 2006 and a manuscript describing these findings has been submitted for publication in a medical journal. This analysis has been conducted by post-doctoral fellow Nichelle Abegbite MD with supervision from Robert J. Pignolo MD PhD, an Assistant Professor in the Department of Medicine at the University of Pennsylvania. Dr. Pignolo has been an associated member of our research program in POH and FOP since 2002. Additional support for this study was provided by Rita Bhagat, R.N., clinical coordinator of the Center for Research in FOP and Related Disorders, and by Meiqi Xu, a senior Research Specialist.

Identification of the Altered Gene in POH

In 1998, the POH collaborative research group began the experimental analyses that led to the identification of the damaged gene responsible for POH. The gene that we identified is called *GNAS* and is located on the long arm of human chromosome 20. (Note: A change in gene nomenclature has replaced the previously used gene name “*GNAS1*” with “*GNAS*”.)

As far back as 1995, we had recognized the similarities between POH and a condition known as Albright hereditary osteodystrophy (AHO). Patients with AHO are generally identified by characteristic skeletal morphology (such as the shape of the face and hands) and they frequently show a decreased response to various hormone signals. (When hormone resistance is noted, such patients are often described as having pseudohypoparathyroidism type Ia or PHPIa.) Some patients with AHO have mild ossification of the skin, although their bone formation typically does not progress to affect the deeper tissues such as muscle - as occurs in people who have POH. People with POH have generally normal skeletal features and have normal response to hormones. Since bone formation in the skin is rare, however, we hypothesized that the *GNAS*

gene, which was altered in many patients who had AHO/PHPIa (and had been determined to be the genetic cause of these conditions), might also be the cause of POH.

Our hypothesis that the *GNAS* gene is involved in POH was strengthened by the identification of two patients who had clinical features of both AHO/PHPIa and POH and who showed reduced activity of the *GNAS* protein. Furthermore, a mutation in the *GNAS* gene was identified in one of these patients. These findings were not conclusive that alterations in the *GNAS* gene and/or activity of the *GNAS* protein (known as Gs-alpha) caused the extensive bone formation that occurred in these patients, since it was possible that changes in the *GNAS* gene caused the AHO/PHPIa characteristics while a second independent gene alteration caused ectopic bone formation. However, concurrent with these investigations, we were also studying a child with unique POH-like heterotopic ossification (clinically described as plate-like osteoma cutis or POC). The discovery of a mutation in the *GNAS* gene of this child's DNA was the first example of a *GNAS* gene alteration that was associated with extensive heterotopic ossification independently of AHO/PHPIa features.

Our next studies examined DNA samples from all available people with POH, and we discovered disease-causing alterations in the *GNAS* gene in a high percentage of POH patients. Results of ongoing studies suggested that the inheritance patterns of mutations in the *GNAS* gene determined whether a *GNAS* mutation results in POH or AHO/PHPIa in a given individual. In each case for which we can follow the inheritance of a *GNAS* mutation in a family with more than one member with POH, the inheritance of the condition is from a father to his children.

***GNAS*: Mothers and Fathers Make a Difference**

Since we know only a small number of families that show inheritance of POH from parent to child, the possibility that the observed paternal inheritance pattern is just an “interesting coincidence” could not be excluded. In a recent series of complex studies, we investigated whether identified *GNAS* mutations in “spontaneous” cases (i.e. patients who are the only person with POH in their family) always occur on the chromosome inherited from their father. In these patients, the *GNAS* mutation was not inherited; instead, the DNA change that caused the *GNAS* mutation occurred in that person, likely at a very early stage of embryonic development. Since

half of the chromosome set of each cell is inherited from a person's father and half from a person's mother, we investigated whether the "spontaneous" *GNAS* mutation that caused POH occurs randomly on the *GNAS*-containing chromosome from either parent or specifically on a chromosome of a particular parental origin. Consistent with our observations in inherited POH, we determined that the *GNAS* mutation occurred on the chromosome inherited from the father in every case of spontaneous POH that was examined.

Families with AHO/PHPIa typically show the reciprocal pattern, with inheritance of the *GNAS* mutation from a mother to her children. This genetic phenomenon, in which the parental origin of a gene affects its expression in cells, has been recognized for several other genes and is known as genetic imprinting.

Our conclusive demonstration that POH is dependent on *GNAS* mutations that occur on the paternally-inherited chromosome was a very exciting finding. It tells us that there is a special function for the *GNAS* gene copy when it is inherited from fathers. We are using this important information to continue our investigation of the expression and regulation of the *GNAS* gene and how this expression and function leads to bone formation in POH.

The *GNAS* Gene

Our studies continue to examine the *GNAS* gene in all known patients with POH in order to develop a comprehensive understanding of the range of alterations in this gene that can cause POH. We also examine the *GNAS* gene in family members of POH patients in order to more fully understand the inheritance pattern of the *GNAS* gene - necessary information for comprehending the expression and regulation of the *GNAS* gene. Understanding the effects that reduced *GNAS* gene activity has on the functions of cells is critical to determining why mutations in this gene lead to the extensive bone that forms in POH patients and to determining how we can correct the effects of altered functioning of this gene. We are very interested in studying the *GNAS* gene in as many people with POH as possible in order to continue to learn about the genetic changes that can cause POH.

The structure and regulation of the *GNAS* gene are extraordinarily complex. *GNAS* encodes a protein called Gs-alpha located on the inside of the cell membrane in nearly every cell in the

body. The protein is extremely versatile and appears to have different functions in different cells. Generally, Gs-alpha functions as a relay switch in a multi-protein complex that monitors the environment of the cell and sends signals to the nucleus (the site of the chromosomes), providing instructions to direct cell “behavior”.

An enormous amount of additional research is necessary to understand exactly how mutations in the *GNAS* gene and the corresponding abnormalities in the Gs-alpha protein trigger ectopic bone formation. One likely possibility is that the Gs-alpha protein may normally act as an inhibitor of bone formation in soft connective tissue (skin, fat, and skeletal muscle) by suppressing the activity of other genes involved in bone formation. When the switch is broken, the inhibition ceases, and the cell becomes a bone cell by default. In children who have POH, bone formation occurs in the skin and fat tissue underneath the skin and then progresses into deeper tissue such as muscle, tendon, and ligament.

Experiments conducted by laboratory Research Specialist Meiqi Xu are investigating the gene expression and activity of the *GNAS* gene in POH. In cells from POH patients, the mRNA that encodes the Gs-alpha protein occurs at 20-60% of the average levels for non-POH individuals. This is consistent with our findings that in most POH patients we only detect the mRNA that is synthesized from the non-mutated *GNAS* gene copy. The mRNA from the mutated *GNAS* gene copy is either not synthesized or is rapidly degraded. Likewise, we found that the Gs-alpha protein is synthesized at reduced levels and we have confirmed that the function of the Gs-alpha protein is also reduced.

Although Gs-alpha is its main gene product, the *GNAS* gene also produces other mRNAs and proteins. The synthesis of these additional *GNAS* gene products is regulated by a special type of mechanism known as “genomic imprinting”. Genes that are “imprinted” synthesize mRNAs only from one of the two gene copies in the cell. A *GNAS* mRNA known as Nesp55 is synthesized only from the gene copy that was inherited from the mother, while the XL-alpha-s and 1A mRNAs are synthesized only from the gene copy that was inherited from the father.

We are currently investigating whether this parental mRNA expression pattern can be correlated with the inheritance of POH from fathers. Our experiments have shown that POH cells have reduced amounts of XL-alpha-s and 1A mRNAs, suggesting that the clinical expression of

GNAS inactivating mutation in POH patients may not be solely dependent on the level of Gs-alpha expression, but may also be influenced by the levels of other *GNAS* gene products. To investigate this question, our research studies include a “DNA methylation analysis” of *GNAS* in people who have POH in order to determine whether altered DNA methylation may be the mechanism regulating changed *GNAS* expression in POH. Methylation is a modification of DNA that is associated with gene expression. We are nearing the end of this set of experiments and the data support some subtle differences in the DNA methylation pattern, however additional work is needed to confirm these results and determine a correlation with functional consequences.

The Role of *GNAS* in Bone Cell Differentiation

With the identification of *GNAS* as the mutated gene that causes POH, we now have the opportunity to investigate the role of this gene in directing the fate of cells to become bone. Understanding the cellular and molecular pathways in bone formation that are controlled by *GNAS* gene products will help us develop treatments for patients with POH and also for many more common diseases of bone formation.

Dr. Robert Pignolo M.D., Ph.D. has developed cellular systems that will help us address the role of *GNAS* in bone cell differentiation (osteogenesis). Because of the close association of POH bone formation with the dermal subcutaneous fat layer and with the fat tissue that occurs within skeletal muscle, we have hypothesized that the cells that differentiate into heterotopic osteoblasts (bone cells) may normally be directed toward an adipocyte (fat cell) fate. Using the mouse (which has a *GNAS* gene that is 99% identical to the human gene) as a model system, Dr. Pignolo has successfully developed the methodology to isolate “stem cells” from peripheral adipose tissue. This tissue is analogous to the dermal layer in which bone forms at early stages of POH. We are using assays to induce and evaluate adipocyte and osteoblast differentiation and find that the peripheral fat “stem cells” (but not stem cells from at least some other tissues) have an enhanced osteogenic potential when the expression of the *GNAS* gene is reduced. This fascinating finding is very consistent with the development of heterotopic bone in the dermal fat of POH patients but not, for example, in the bone marrow cavity which is a rich source of osteogenic precursor cells.

[Due to the difficulty in breeding mice with the *GNAS* mutation, these experiments have progressed slowly. However, improvements in our approaches have been successful and we are now making substantial progress with this approach.]

Research to investigate the effects of *GNAS* gene inactivation in bone cell development is supported by our National Institutes of Health grant. In addition to Dr. Pignolo, two post-doctoral fellows who joined the lab in 2007, Shengliang Zhang, Ph.D. and Josef Kaplan, Ph.D., along with Research Specialist Deyu Zhang are working on this important area of investigation. In a new series of studies, Dr. J. Kaplan is using RNAi approaches to investigate the cell signaling pathways that are changed in response to inactivation of the *GNAS* gene. Identification and characterization of these pathways will be vital for developing treatment strategies for POH.

Families and the Inheritance of POH

With the identification of the gene alteration that causes POH, families of affected individuals will have many questions regarding the inheritance of the condition. Since we are still learning about the inheritance patterns of POH (and are very grateful to the families who have and will help us understand these patterns), we do not yet have all of the answers.

However, we feel that it is very important for families to note that gene alterations are a very common occurrence in human biology - in fact, it is thought that all of us harbor a handful of genetic alterations. The effects of some of these changes are readily detected (like POH), some may be expressed in later life (such as heart disease), and some will never have any substantial impact on us. These genetic changes are thought to occur randomly and at a low frequency in our DNA. Most of the people who have POH likely have spontaneous mutations in the *GNAS* gene. This means that the altered *GNAS* gene first occurred in that individual and was not inherited from either parent.

However, once an individual has a mutation that causes POH (or AHO/PHPIa), this person has a 50% chance of passing that mutation to his or her child. If no mutation is inherited by the child, he/she will have neither POH nor AHO/PHPIa. If a mutation is inherited by the child, the gender of the parent who transmits the mutated gene may determine whether the child develops

POH or AHO/PHPIa. However, we have also uncovered two cases in which a mutation appears to be completely "silent" and these individuals are free of either POH or AHO/PHPIa symptoms.

Our studies on the variable expression and the inheritance patterns of *GNAS* mutations are still continuing and more remains to be learned. As we learn more about the altered gene in POH and its inheritance patterns, we will be better able to trace the inheritance within a family. While this information may be uncomfortable for some families to know (and we will not reveal details to any family who does not wish to know this information), these family inheritance studies are critical to providing a foundation for development of the best possible treatments for POH.

POH and FOP

When POH bone formation is extensive in its distribution, POH can be as disabling as its sister disease, fibrodysplasia ossificans progressiva (FOP). Although the gene mutations that cause the two conditions are different, we suspect that part of the bone-inducing pathway that is mis-activated in POH is also involved in FOP bone formation.

In May 2006, we reported the identification of the gene that is mutated in FOP. This gene, known as *ACVRI*, encodes a bone morphogenetic protein (BMP) type I receptor. BMP and *GNAS* are parts of distinct cell signaling pathways, however experimental evidence indicates that these two pathways interact to regulate bone and cartilage cell differentiation. Such possibilities will be investigated as part of our cell signaling studies.

It is also interesting and important to note that the *GNAS* gene that is damaged in POH is the same gene that causes several other severe bone diseases including fibrous dysplasia (or McCune-Albright syndrome and its variants), Albright Hereditary Osteodystrophy (AHO), pseudohypoparathyroidism (PHP), and plate-like osteoma cutis (POC). By understanding more about these disorders, a clearer understanding of POH will also be gained.

SUMMARY: WHAT WE HAVE LEARNED ABOUT POH

Since the initiation of the POH research program, the working group on POH has made several advancements toward understanding POH both on clinical and cellular/molecular levels.

?? ? Clinical observations and studies led to the discovery, naming, and identification of POH as a distinct developmental disorder of heterotopic ossification in humans, and provided a detailed clinical description of the disease phenotype, including the histopathology (microscopic tissue characteristics) of heterotopic ossification in POH. POH has been clearly distinguished from fibrodysplasia ossificans progressiva (FOP), another autosomal dominant disorder of heterotopic ossification in children. We have also now clearly defined similarities and differences between POH and Albright Hereditary Osteodystrophy (AHO), an autosomal dominant disorder that can exhibit cutaneous and subcutaneous heterotopic ossification.

?? ? Approximately 60 patients with POH and POH-like conditions have been identified and/or examined, and risk profiles for heterotopic ossification have been established. Some patients with atypical presentations (a child with unilateral hemimelic POH; four children with features of both AHO/PHP and POH) have also been examined and may provide additional insight into POH. A small number of multigenerational families with POH are known.

?? ? A connection between the molecular genetics of AHO/PHPIa and POH was recognized and we established *GNAS* as the leading candidate gene for POH. Heterozygous *GNAS* mutations have now been discovered in several families with classic expression of POH, as well as a heterozygous 4-bp deletion in *GNAS* in a patient with severe plate-like osteoma cutis (POC), a variant of POH.

?? ? Our molecular studies have demonstrated that, at least in some cells from POH patients, there is reduced expression of *GNAS* mRNA and Gs-alpha protein, and that the functional activity of the Gs-alpha protein, as determined by cAMP activity, is reduced as well.

?? ? We recently determined that POH is dependent on mutations in the paternally-inherited *GNAS* allele in both familial and spontaneous cases of POH, further supporting an important role of imprinting in POH. The *GNAS* gene products that are specifically expressed from the

paternally-inherited *GNAS* allele (XL-alpha-s and 1A) show little expression in cells from POH patients, suggesting that their function may be important in POH.

?? ? We are conducting studies on the role of *GNAS* expression in the regulation of bone cell formation and differentiation using newly-developed cellular systems to investigate the role of *GNAS* in regulating bone and fat cell differentiation in stem cells derived from various tissues. Investigations of the signaling pathways that are changed in response to inactivation of the *GNAS* gene (potential targets for POH treatments) are also ongoing.

?? ? With the support and contributions of the POHA, we wrote and published “*What is POH? A Guidebook for Families.*” The first edition, published in 1997, was updated and revised in 2003. The **First International Workshop on POH** was held as part of the Second International Symposium on FOP (October 1995) and was attended by sixty physicians and scientists and by three POH families. This Workshop provided the scientific basis for establishing our international POH collaborative working group. The **Second International Workshop on POH** was held as part of the Third International Symposium on FOP (November 2-5, 2000). This meeting was attended by approximately two hundred physicians and scientists and by nine POH families.

THE GOALS OF POH RESEARCH

Having established that heterozygous inactivating mutations of the *GNAS* gene are the cause of progressive osseous heteroplasia (POH), and that these mutations occur on the *GNAS* gene copy that is inherited from fathers, our goal is to understand how these *GNAS* gene changes alter cellular signaling pathways that direct the formation of bone cells.

We will continue to screen genomic DNA for mutations in the *GNAS* gene in POH patients and will develop a more complete picture of the clinical changes that are associated with these DNA sequence changes. Comparisons of both *GNAS* DNA sequences and clinical characteristics for patients with POH and AHO/PHPIa will be made in order to further understand the differences and similarities between these two conditions.

The mRNA and protein products of the *GNAS* gene determine the function of the gene. Investigations of the relative expression levels of the multiple *GNAS* products will proceed along with studies to investigate the gene regulatory mechanisms that may be altered in POH. The specific regulation of the *GNAS* gene copy that is inherited from fathers is of particular interest.

A growing focus is to investigate the effects of *GNAS* inactivation on the cell signaling pathways that result in bone formation and to define the role of *GNAS* during the formation of bone cells. These studies will facilitate our ability to develop and test treatments to impede heterotopic ossification.

THE IMPORTANCE OF POH RESEARCH

At present, there are no effective treatments or prevention for POH. Analysis of the molecular genetics of POH will increase the understanding of the cellular and molecular pathways that initiate skeletogenesis and osteogenesis in POH and will lead to development of a more rational diagnostic and therapeutic approach to treating POH.

The importance of POH research for affected children and their families is unquestionable. However, the significance of POH research for the general medical community is far greater than its rarity might indicate. By unraveling the complex pathogenesis of POH, there is great hope that more common disorders of bone formation will become understandable and treatable.

Knowledge gained from this work has the likelihood of uncovering not only the basic molecular mechanisms of POH, but also the basic molecular mechanisms involved in disorders as diverse as congenital limb anomalies, bone cancer, osteoarthritic bone spurs, osteoporosis, and abnormal fracture repair. Research in POH, therefore, has the possibility of elucidating the pathophysiology of common disorders such as cancer, aging, and valvular heart disease.

During the past several years, great progress has been made in understanding not only the cellular and molecular mechanisms involved in normal bone formation, but also in understanding the complex mysteries of POH. The work undertaken by the collaborative research group is focused on understanding the underlying molecular causes of POH, and using that knowledge to design medications and treatments that will be genuinely useful to the children and adults who have POH.

REPORTS ON POH RESEARCH

Presentation of our research on POH - through national and international conferences, university seminars and journal publications – provides opportunities to educate the medical and scientific community about POH. Dissemination of such information stimulates new ideas and approaches for understanding POH and encourages others to investigate relevant research questions.

1. The results of some of our research findings on POH have been presented at scientific meetings and reported in scientific/medical journals (2006-2007):

Pignolo, R.J., N.S. Adegbite, M. Xu, F.S. Kaplan, and E.M. Shore. Clinical Features and Diagnostic Criteria for Progressive Osseous Heteroplasia (POH) and POH-like Syndromes. *J. Bone Min. Res.* 21 (Suppl 1), S431. (Presented at the American Society for Bone and Mineral Research Annual Meeting; Philadelphia, PA; September 2006.)

Kanaan, R., B. Saucy, F.S. Kaplan, and E.M. Shore. Myoblasts Are not the Likely Targets of Gs-alpha Inactivating Mutations in Progressive Osseous Heteroplasia. *J. Bone Min. Res.* 21 (Suppl 1), S311. (Presented at the American Society for Bone and Mineral Research Annual Meeting; Philadelphia, PA; September 2006.)

Kaplan, F.S., Glaser, G. L. and E.M. Shore (2006). Fibrodysplasia (myositis) ossificans progressiva. In: *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, Sixth Edition. M.J. Favus, Editor. ASBMR, Washington, DC. Chapter 80; pp. 450-453. (Includes section on POH.)

Gelfand, I., R.S. Hub, E.M. Shore, F.S. Kaplan, L.A. DiMeglio (2007). Progressive osseous heteroplasia-like heterotopic ossification in a male infant with pseudohypoparathyroidism type Ia: A case report. *Bone* 40, 1425-1428

Yeon, H., F.S. Kaplan, E.M. Shore, A.E. Rosenberg, J. Jupiter (2007). Focal nodular heterotopic ossification: a new syndrome. *J. Bone Joint Surg (Am)*. 89(6): 1329-1336

2. During the past several years, Dr. Shore and Dr. Kaplan have presented work on POH at scientific conferences and universities. Presentations for 2005-2007 are listed:

“POH: A New Perspective on Osteogenesis.” Northeastern Ohio Universities College of Medicine (NEOUCOM), Rootstown, OH; March 10, 2005.

“Progressive Osseous Heteroplasia (POH), a Human Disorder of Ectopic Ossification, is Caused by Mutations in the Paternally Inherited Allele of GNAS.” International Meeting on Genomic Imprinting, Development and Disease; Oxford, UK; April 12, 2005.

“Extra-skeletal ossification in inherited human disease.” University of Medicine and Dentistry of New Jersey (UMDNJ), New Jersey Medical School, Department of Biochemistry and Molecular Biology, Newark, NJ; June 22, 2006.

“FOP and POH – Human Genetic Disorders of Extra-Skeletal Bone Formation.” Endocrine Division Conference, Children’s Hospital of Boston, Boston, MA; April 25, 2007

ACKNOWLEDGEMENTS

The POH Collaborative Research project arose out of a desire to identify the cause of POH and to develop treatments and a cure for this disabling condition. We are enormously grateful for many colleagues and collaborators at medical offices, clinics, hospitals, research laboratories, centers, and universities around the world without whose help our work would be more difficult – if not impossible. We are appreciative and acknowledge the generous support of our sponsors over the past several years in helping us to achieve our long-term goals:

- 1) The Progressive Osseous Heteroplasia Association (POHA)
- 2) The Italian Progressive Osseous Heteroplasia Association (IPOHA)
- 3) The International Fibrodysplasia Ossificans Progressiva Association (IFOPA)
- 4) The Center for Research in FOP and Related Disorders, University of Pennsylvania
- 5) The New Jersey Association of Student Councils (NJASC)
- 6) The Four Schools (University of Pennsylvania, Johns Hopkins University, Duke University, Washington University) Medical Student Fellowship Program
- 7) National Institutes of Health (NIH); National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
- 8) Johnson & Johnson Focused Giving Program
- 9) The Hartford/American Federation for Aging Research Academic Fellowship Program