NIAMS
IRPartners
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A newsletter for patients of the Intramural Research Program (IRP), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

Spotlight on Pompe Disease

For the past two decades, NIAMS researchers – Dr. Paul Plotz, Chief of the NIAMS Arthritis and Rheumatism Branch (left), and a group of scientists in his lab led by Dr. Nina Raben (right) – have made significant strides toward our understanding of Pompe disease.

For the past two decades, NIAMS intramural researchers have made significant strides in the understanding of Pompe disease. This issue of *IRPartners* provides an overview of Pompe disease and describes the Institute's contribution to the field.

What Is Pompe Disease?

Pompe (POM-pay) disease, also known as glycogen storage disease type II or acid maltase deficiency, is a rare genetic disorder that results in profound muscle weakness. The disease is caused by mutations in the gene that instructs the body to make an enzyme called acid alpha-glucosidase (GAA). Normally, the body uses this enzyme to break down glycogen (stored sugar) into glucose (sugar). But in Pompe disease, GAA is absent or significantly reduced, causing excessive amounts of glycogen to accumulate in the body's tissues, which results in major damage. The heart and skeletal muscles are most affected.

Pompe disease is an autosomal recessive condition – meaning that each parent of an affected individual must pass on a copy of the mutated gene. This is part of the reason that the disease is relatively rare, affecting one in 40,000 people.

SPOTLIGHT ON POMPE DISEASE, *continued on page 5*

From the Scientific and Clinical Directors

We are pleased to bring you the Spring/Summer 2010 issue of *IRPartners*. In this issue, we focus on a rare genetic muscle disorder, Pompe disease, and describe how NIAMS intramural scientists have advanced our understanding of the disease. You'll also get an inside look at how funds from the American Recovery and Reinvestment Act (ARRA) have benefitted NIAMS intramural research activities.

We welcome new staff members to NIAMS and celebrate the accomplishments of others. In addition, we provide a synopsis of recent intramural research highlights and introduce you to two new NIAMS health information products – a bilingual booklet on joint replacement and an online fact sheet on autoinflammatory disorders.

We hope you enjoy this issue, and we look forward to sharing future highlights and advances with you.

John O'Shea, M.D.
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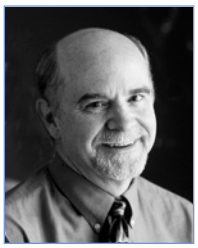

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NIAMS Welcomes New Staff Members

Gerda Gallop-Goodman

Gerda Gallop-Goodman recently joined NIAMS as a writer-editor in the Office of Communications and Public Liaison. Gallop-Goodman has been a writer and editor for the American Association for Cancer Research and MEE Productions, Inc., a communications, research, and marketing firm, as well as several media outlets, including *Child* magazine, KidsHealth.org, *Black Enterprise* magazine, *HealthQuest* magazine, and the *Battle Creek Enquirer*. She has freelanced for various publications such as *Essence* and *Heart & Soul* magazines and the *Philadelphia Tribune* newspaper. She has community outreach experience in cancer education and support for minority populations in the greater Philadelphia area. Gallop-Goodman also was a research assistant at the University of Pennsylvania for studies on racial and ethnic disparities in health related to cancer and cardiovascular disease. She obtained her bachelor's degree in journalism from the University of North Carolina at Chapel Hill and will complete her master's degree in public health from the George Washington University in May. In addition to writing and editing articles, Web site content, and publications, Gallop-Goodman will assist with activities related to the National Multicultural Outreach Initiative. ▲

Alice Fike, M.S., C.R.N.P.

Alice Fike, M.S., C.R.N.P., recently joined NIAMS as a family nurse practitioner for the NIAMS Cardozo Community Health Center. She was raised in Atlanta, Georgia. After earning a B.S. in nursing from Syracuse University, Fike spent 2 years working as a Peace Corps volunteer at a rural community health clinic in the West African country of Burkina Faso. Because of a lack of physicians in Burkina Faso, registered nurses performed duties that nurse practitioners do in the United States. This experience sparked her interest in becoming a nurse practitioner. Fike received her M.S. in nursing from the University of California, San Francisco.

Being a nurse has exposed Fike to a variety of professional experiences, both domestically and abroad. She has worked in sub-Saharan Africa, juvenile and adult detention centers, and urban teaching hospitals. She also has experience in tuberculosis care and health disparities research. Although Fike's career has taken her numerous places, the common thread is her work with underserved populations. ▲

NIAMS IRP and the American Recovery and Reinvestment Act

NIAMS is grateful for the opportunity afforded by the American Recovery and Reinvestment Act (ARRA) to further our mission to invest in vital biomedical research related to diseases affecting the bones, joints, muscles and skin.

ARRA-Funded Genetic Analyzer Boosts NIAMS Sequencing Efficiency

It's roughly the size of a small copy machine. But in the minds of scientists in the NIAMS Intramural Research Program (IRP), it stands a lot taller.

The Institute recently acquired a genome analyzer, an instrument that examines genes and investigates the genetic makeup (genome) of different organisms. Purchased with funds from the American Recovery and Reinvestment Act of 2009 (ARRA), this genetic analyzer saves NIAMS researchers time and costs by performing large-scale DNA processing that results in billions of bases of high-quality gene sequences. The easy-to-use technology minimizes handling errors and concerns about contamination.

With it, scientists can measure epigenetic changes: changes to the DNA machinery (called chromatin) that regulates gene expression. As a practical example, John O'Shea, M.D., IRP scientific director and chief of the NIAMS Molecular Immunology and Inflammation Branch, and his colleagues recently discovered a new explanation for the flexibility of responses of one type of immune system cell (T lymphocytes) by using the new technology to survey the cells' epigenomes – the collection of epigenetic elements within the cells. Their work has generated the largest blueprint of its kind for studying the biology of these cells and provides new clues about the epigenetic regulation of key immune genes – clues that one day could be used to treat diseases, particularly autoimmune and infectious diseases.

To Dr. O'Shea, the new instrument is a way to help explore an evolving view of the molecular mechanisms that govern the body's normal functions as well as those involved in disease. The analyzer, he says, "will help us better understand the genetic code, allowing us to identify disease markers and perhaps develop potential gene therapies to combat them."

The completion of the human genome a few years ago was the starting point of research that will benefit from the instrument's capabilities, says Dr. O'Shea. "The bottom line is that the analyzer allows us to put the information gleaned from the genome to work."

New Tool Expands Microscope Capabilities

Purchased with ARRA funds, a new confocal microscope attachment – called FLIM (fluorescence lifetime imaging microscopy) – will allow NIAMS intramural scientists to probe biomedical images with increased precision.

Confocal microscopes, like the one used by Institute researchers, narrow the depth of field of an image so that an area of interest, even deep in a piece of tissue, can be in focus. The resulting three-dimensional pictures and measurements give a detailed view inside cells, at the limit of resolution. FLIM allows the confocal microscope to detect additional information about individual molecules, allowing scientists to learn more from each image.

"FLIM gives us a glimpse into the intrinsic properties of a fluorescent molecule, which are affected by its environment," says Evelyn Ralston, Ph.D., chief of the IRP's Light Imaging Section. "Most often, the instrument is used to investigate fluorescent molecules attached to a protein, and it's a most useful way to find out when the protein is on its own and when it forms a pair with another protein. From such measurements, we can, for example, obtain information about the energy state of skeletal muscle and discover differences between healthy and diseased muscle."

NIAMS IRP AND ARRA, *continued on page 4*

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Images produced by confocal microscopy usually rely on viewing fluorescent markers specifically bound to the samples under investigation. Biological features are often distinguished by different marker colors, and data are obtained using parameters such as location, shape, and color intensity. However, FLIM adds another dimension of analysis by tracking the decay time of the fluorescent signal, rather than its intensity. Signal decay times are specific to particular fluorophores (components of a molecule that cause it to fluoresce).

"Imaging has always been a critical component of our clinical and basic research efforts," says John O'Shea, M.D., IRP scientific director and chief of the Institute's Molecular Immunology and Inflammation Branch. "Our acquisition of FLIM technology will help propel us to a new level of knowledge about the molecular landscape."▲

NIAMS Releases Autoinflammatory Disorders Fact Sheet

Autoinflammatory diseases are a relatively new category of diseases that are different from autoimmune diseases. However, autoimmune and autoinflammatory diseases share common characteristics in that both groups of disorders result from the immune system attacking the body's own tissues and result in increased inflammation. NIAMS recently released a new online fact sheet, "Understanding Autoinflammatory Diseases." This overview contains general information on the immune system and provides brief descriptions of some of the more common autoinflammatory diseases. The fact sheet can be accessed from the alphabetized Health Information section of the NIAMS Web site at www.niams.nih.gov. Just click on "Autoinflammatory Diseases." ▲

Autoinflammatory diseases are a relatively new category of diseases that are different from autoimmune diseases.

NIAMS' O'Shea Receives Arthritis Foundation Award

John O'Shea (right) receiving the Howley Prize, presented by Steven Goldring, chief scientific officer at the Hospital for Special Surgery.

The Arthritis Foundation awarded the 2009 Lee C. Howley, Sr., Prize to NIAMS Scientific Director Dr. John O'Shea for his continued research contributions in the treatment and control of rheumatic diseases. The Howley Prize is given each year in recognition of researchers whose contributions during the previous 5 years have represented a significant advance in the understanding, treatment, or prevention of arthritis and rheumatic diseases. The Arthritis Foundation recognized O'Shea for his work on cytokine signal transduction and the elucidation of the roles of Janus kinases (Jaks) and STAT family transcription factors in immune cell development and differentiation.

The research of O'Shea and his colleagues led to a patent held by NIH pertaining to targeting Jaks as a new class of immunosuppressive drugs. O'Shea developed a cooperative research and development agreement with the pharmaceutical company Pfizer, which generated one such compound that is now in Phase III studies in rheumatoid arthritis. The Pfizer Jak inhibitor is also being tested in kidney transplantation, psoriasis and inflammatory bowel disease. A number of other pharmaceutical firms have preclinical programs testing other Jak inhibitors. ▲

How Does the Disease Progress?

Two forms of Pompe disease have been identified: a severe "infantile" form, and a milder "late-onset" form. The infantile form of the disease usually occurs within the first months of life and progresses rapidly, with severe muscle weakness, heart failure, and often death before the age of one or two. The late-onset form of the disease (also referred to as the juvenile/adult form) presents after infancy and progresses more slowly. Muscle weakness is the primary symptom, and the heart is typically spared. Life expectancy is usually shortened due to weakness of the respiratory (breathing) muscles in people with this form of the disease.

How Is the Disease Diagnosed?

Pompe disease is diagnosed by screening for the common mutations in the GAA gene, by measuring the level of the GAA enzyme in a blood sample, or by a muscle biopsy. Once a diagnosis is obtained, consultation with a geneticist and screening of other family members is recommended.

Is There Any Treatment?

The U.S. Food and Drug Administration has approved alglucosidase alfa (Myozyme) for use in patients with Pompe disease. A type of enzyme replacement therapy, Myozyme is a form of GAA – the enzyme that is absent or reduced in the disorder. The drug is usually administered via intravenous infusion every other week. Myozyme has been remarkably successful in reversing cardiac muscle damage and in enhancing life expectancy in those with the infantile form of the disease. The therapy, however, is less effective in skeletal muscle.

People with Pompe disease need highly specialized care from a variety of specialists, especially as the disease progresses.

What Are Some Key Areas of Pompe Research at NIAMS?

For the past two decades, researchers from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) – Dr. Paul Plotz, Chief of the NIAMS Arthritis and Rheumatism Branch, and a group of scientists in his lab led by Dr. Nina Raben – have made significant strides toward our understanding of Pompe disease. While it was originally hoped that enzyme replacement therapy could cure Pompe disease, the NIAMS group discovered that skeletal muscle is resistant to the treatment. This finding was made in mouse models of the disease that were generated in the lab; these models are now used throughout the world by scientists involved in the research and development of Pompe therapies.

The group is focusing its current efforts on using the new information to improve treatment of the resistant muscle fibers. These studies are partially funded by a cooperative research and development agreement (CRADA) with Genzyme, the company that produces Myozyme.

The NIAMS group recently uncovered new clues related to the cellular defects in Pompe disease. They identified structures in many skeletal muscle cells in Pompe patients and mice that appeared to be large collections of cellular debris that should have been delivered to, and processed in, the lysosomes, the "recycling centers" of the cell. This debris would normally have been digested in the lysosomes into the building blocks that the cell uses to keep itself in shape – amino acids to build proteins, sugars like glucose to provide energy, and fatty acids to build membranes and to provide energy. So, not only were the lysosomes filled with glycogen which could not be digested, but other materials were building up outside – unable to reach the recycling place. This buildup looked like the kind of material that is normally carried to the lysosomes by a remarkable system, called "autophagy" – literally meaning self-eating. This system picks up worn out cell parts for delivery to the lysosomes for recycling. Dr. Raben recognized that this pick-up and recycling system does not function properly in Pompe skeletal muscle, and the stressed recycling centers appear to be overwhelmed. The NIAMS group is currently testing new strategies to intervene in Pompe disease by exploring ways to modulate the autophagic machinery. ▲

NIAMS IRP Research in the News

A Clinical Perspective of Autoinflammatory Diseases

The science of autoinflammatory diseases has progressed rapidly since the term was first coined in the late 1990s to distinguish this group of illnesses from the more well-defined autoimmune diseases, such as rheumatoid arthritis and lupus. Advances in genetic technologies have expanded the understanding of the molecular and cellular basis of autoinflammatory diseases and have broadened the field to include disorders that no longer fit within the original classification. In a recent issue of *Cell*, Daniel Kastner, M.D., Ph.D., NIAMS Clinical Director and Director of Translational Research, and his colleagues Ivona Aksentijevich, M.D., and Raphaela Goldbach-Mansky, M.D., M.H.S., argue that the definition of autoinflammatory diseases needs updating. In an effort to converge the clinical concept of these diseases with advances in the basic science of immunity, they suggest a revised classification that focuses on abnormally increased inflammation mediated predominately by the innate immune system, with a significant host predisposition. The host predisposition could result from genetic factors or could be triggered by gene-environment interactions.

Kastner DL, Aksentijevich I, Goldbach-Mansky R. Autoinflammatory disease reloaded: a clinical perspective. Cell. 2010 Mar 19;140:784-90.

NIAMS Researchers Discover a New Mechanism for Stem Cell Development

Researchers in the NIAMS Laboratory of Muscle Cells and Gene Regulation, led by Vittorio Sartorelli, M.D., along with colleagues at the Whitehead Institute for Biomedical Research and the Massachusetts Institute of Technology, have discovered a new mechanism for cell differentiation in mouse embryonic and skeletal muscle stem cells. The team looked at mouse skeletal muscle and embryonic stem cells during the short window of time when the cells just started to differentiate. They found high levels of microRNA 214 (miR-214) in these cells. MicroRNAs are small strands of ribonucleic acid that work with proteins to carefully modulate gene expression. The researchers also found that they were able to induce the differentiation process in uncommitted cells by increasing levels of miR-214. Their results showed that miR-214 blocks Ezh2, thereby leading to the production of molecules that favor cell differentiation. These findings, reported in *Molecular Cell*, may have future applications for the use of human embryonic stem cells in research.

Juan AH, Kumar RM, Marx JG, Young RA, Sartorelli V. Mir-214-dependent regulation of the polycomb protein Ezh2 in skeletal muscle and embryonic stem cells. Molecular Cell. 2009 Oct 9;36:61-74.

Protein and Muscle Cell Structures Linked in Muscular Dystrophy Muscle Loss

In collaboration with researchers from the University of Minnesota, Evelyn Ralston, Ph.D. and her colleagues from the NIAMS Light Imaging Section have found that dystrophin, the large protein absent from people with Duchenne muscular dystrophy, plays a direct role in properly aligning microtubules, cell components that provide structure and organization to essential cellular functions. Without dystrophin, microtubules are disorganized and essential proteins may be mislocalized, contributing to the cell destruction during contraction that characterizes the disease. This new information, say researchers, could provide additional benchmarks in the development of gene and other molecular therapies to restore the function of dystrophin, and reverse the pathology of the disease. The work was reported in the *Journal of Cell Biology*.

Prins, KW, Humston JL, Mehta A, Tate V, Ralston E, Ervasti JM. Dystrophin is a microtubule-associated protein. J Cell Biol. 2009 Aug 3;186(3):363-69.

IRP RESEARCH IN THE NEWS, *continued on page 7*

IRP RESEARCH IN THE NEWS, *continued from page 6*

B Cell Mutator Enzyme Promotes Resistance to Gleevec in Chronic Myeloid Leukemia

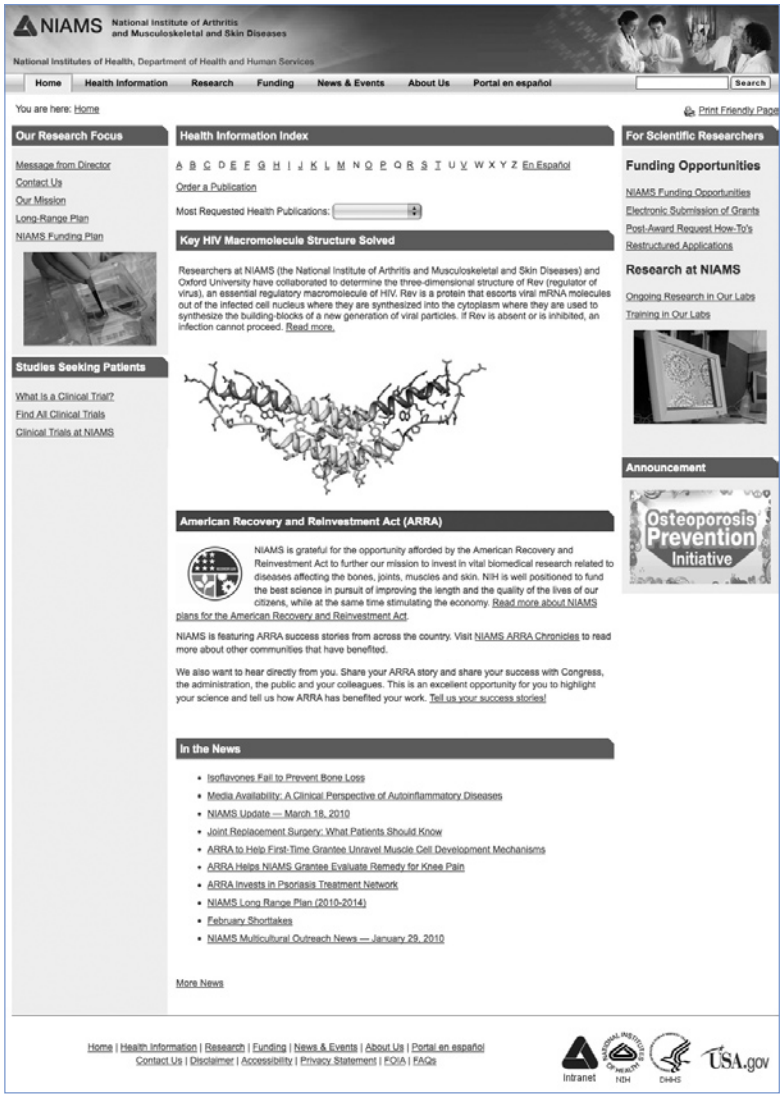
Rafael Casellas, Ph.D., with his colleagues from the NIAMS Genomics and Immunity Section and an international team of investigators, have discovered that a protein that normally mutates antibody genes in B cells triggers resistance to the drug Gleevec in patients with chronic myeloid leukemia (CML). The scientists found that the protein, activation-induced cytidine deaminase (AID), exists in high concentrations in CML cells that develop resistance to the drug, in comparison to CML cells that are effectively treated with the drug. This finding may lead to the development of therapies to improve survival in CML patients who develop drug resistance. The study appeared in the journal *Cancer Cell*.

Klemm L, Duy C, Iacobucci I, Kuchen S, von Levetzow G, Feldhahn N, Henke N, Li Z, Hoffmann TK, Kim Y, Hofmann W, Jumaa H, Groffen J, Heisterkamp N, Martinelli G, Lieber MR, Casellas R, Müschen M. The B cell mutator AID promotes B lymphoid blast crisis and drug resistance in chronic myeloid leukemia. Cancer Cell. 2009 Sept 8;16:232-45. ▲

NIAMS Web Site Highly Rated by ACSI

The NIAMS Web site recently surpassed the threshold for excellence in the American Customer Satisfaction Index (ACSI) E-Government Satisfaction Index. The study, a quarterly look at citizen reactions to more than 100 government Web sites, allows federal sites to be benchmarked to private sector Web offerings. NIAMS' score of 82 was among the highest compared with other government sites and higher than most retail sites measured via ACSI.

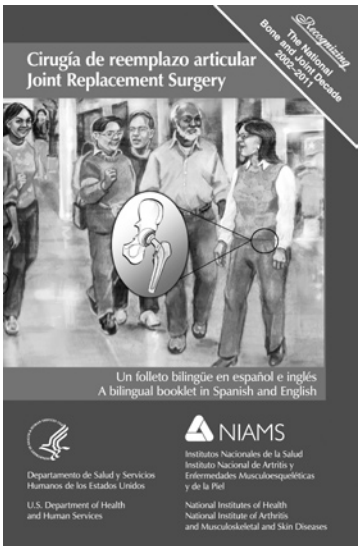
The NIAMS Web site can be found at www.niams.nih.gov. ▲



Questions To Consider Before Joining a Study

- What is the purpose of the study?
- What is required of me?
- Will the study benefit me or others?
- Are there risks? If so, what are they and what are the chances that they will occur?
- What discomforts are involved?
- How long will the study last?
- What will happen if I decide to leave the study?

NIAMS Introduces Bilingual Joint Replacement Booklet



Joint replacement surgery, which is becoming increasingly common across the United States, can help restore a person's mobility and quality of life. In fact, it is estimated that, each year, more than three-quarters of a million Americans have joint replacement surgery for hips, knees, shoulders, fingers, ankles and elbows.

Of course, not every person with joint pain needs joint replacement surgery, and only a doctor can tell if an operation is needed. But those considering surgery can find answers to many of their questions in a new booklet from NIAMS called "Joint Replacement Surgery: Information for Multicultural Communities," available at no charge in English only or bilingual Spanish/English. NIAMS is involved in supporting research into the causes, treatment, and prevention of diseases of bones, joints, muscles, and skin. NIAMS-funded research contributed to the information in the booklet. The easy-to-read guide explains what to expect with joint replacement surgery, including some of the possible risks and side effects of the procedure.

Here's a closer look at some of the facts and answers:

What Is Joint Replacement Surgery?

Joint replacement surgery is removing a damaged joint (where two or more bones come together, like the knee, hip and shoulder) and putting in a new one, which can be made of plastic, metal or both. It may be cemented into place or not cemented, so that your bone will grow into it. The surgery is usually done by an orthopaedic surgeon.

Do I Need To Have My Joint Replaced?

Joints can be damaged by arthritis and other diseases, injuries, or other causes, or simply wear away. This can cause pain, stiffness, and swelling. Joint replacement is often the answer if you have constant pain and can't move the joint well. Replacing a joint can relieve pain and help you move and feel better.

What Happens After Surgery?

Joint replacement surgery is usually successful for 90 percent of patients who have it. With knee or hip surgery, you may be able to go home in 3 to 5 days. But for the elderly or those with additional disabilities, you may need to spend several weeks in an intermediate-care facility before going home. Physical therapy can begin the day after surgery to help strengthen the muscles around the new joint and help you regain motion in the joint.

Learning More

You can order or view the NIAMS booklet about joint replacement surgery online and find out more information about diseases of bones, joints, muscles, and skin at www.niams.nih.gov. Or you can order the free booklet by emailing NIAMSinfo@mail.nih.gov or calling 877–22–NIAMS (877–226–4267). ▲

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