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INSIDE

UNCLE SAM'S BOOST TO BIOMEDICAL RESEARCH

Or, *"How I Spent My Stimulus Funding"*

BY NELLY EDMONDSON GUPTA

In the years since the implementation of the 2009 American Recovery and Reinvestment Act (ARRA), highways and bridges have been built, clean drinking water projects have been initiated, school districts have restored cut programs—and NYMC researchers received grants totaling approximately $4 million. Here we revisit those investigators to find out what progress they've made—and their hopes for the future.

1// PRAVEEN BALLABH, M.D., PROFESSOR OF PEDIATRICS

Research challenge: To figure out how to prevent cerebral palsy in infants with *Germinal-Matrix intra-ventricular hemorrhage* (GM-IVH) by trying to understand the mechanisms involved in *hypomyelination* (a dearth of insulation around the brain's internal wiring) and employing mechanism-based strategies in preterm rabbit models of IVH for the restoration of myelin.

Why it's important: GM-IVH occurs in about 12,000 premature infants every year in the U.S. Babies who experience this "bleeding in the brain" are at high risk of developing cerebral palsy and cognitive problems. Currently, there is no good way to prevent this bleeding, or to treat the resulting brain damage.

How ARRA funding helped: It enabled Dr. Ballabh to hire additional, temporary staff to help carry out key animal experiments. These experiments showed that intervening with specific drugs—including inhibitors of COX-2, tumor necrosis factor-alpha, or morphogenetic protein—immediately after a brain bleed could "significantly protect" the brain, by promoting development of the myelin sheath around the brain's wiring.

What's next? Dr. Ballabh hopes to eventually develop ways to prevent cerebral palsy in surviving premature infants with IVH.

2// DEBRA BESSEN, PH.D., PROFESSOR OF MICROBIOLOGY AND IMMUNOLOGY

Research challenge: To determine exactly how *Group A streptococci* (GAS) cause pharyngitis and impetigo, in the hope of developing a better understanding of more severe GAS diseases, like toxic shock syndrome and rheumatic heart disease.

Why it's important: No vaccine against GAS currently exists. While most GAS infections cause relatively mild illnesses, they can occasionally cause severe and life-threatening diseases.

How ARRA funding helped: The money enabled Dr. Bessen to reorganize her lab to make the best use of her staff. Her team conducted animal studies showing that the strains of strep that cause pharyngitis differ genetically from those that cause impetigo. "These genes encode proteins that have numerous functions," she says. "By understanding those functions we can better see how some strains adapt to the throat and others adapt to the skin. And if we can break the chain of transmission by respiratory or skin contact, those more severe infections will never come to be."

What's next? Dr. Bessen hopes that her work, along with that of other investigators, will contribute to the development of a successful GAS vaccine.

3// FELIPE CABELLO, M.D., PROFESSOR OF MICROBIOLOGY AND IMMUNOLOGY

Research challenge: To understand the functions of some genes of *Borrelia burgdorferi* in the pathogenesis of Lyme disease.

Why it's important: "We know much about the clinical presentation and treatment of Lyme disease," says Dr. Cabello, "But we don't know how *B. burgdorferi* survives in animals and humans—nor all the mechanisms by which it produces disease."

How ARRA funding helped: Dr. Cabello hired doctoral fellows and purchased reagents and other materials that his team used to study an *in vitro* tissue model of *B. burgdorferi* infection. This model illustrated how the organism interacts with collagen in connective tissue.

What's next? Gaining a better understanding of how *B. burgdorferi* interacts with collagen and survives in animal—and human—connective tissue will help scientists have an improved understanding of the pathogenic mechanisms underlying Lyme disease, and may provide new avenues to treatment.

4// ZBIGNIEW DARZYNKIEWICZ, M.D., PH.D., PROFESSOR OF PATHOLOGY, MEDICINE, MICROBIOLOGY AND IMMUNOLOGY

Research challenge: To assess the DNA damage caused by anti-cancer drugs.

Why it's important: The efficacy of anti-cancer drugs depends on our knowledge of the DNA damage they cause.

How ARRA funding helped: The money, in the form of a shared instrument grant, enabled NYMC to buy a $500,000 high-speed cell sorter that can swiftly separate and purify cells.

Among other things, the cell sorter helped Dr. Darzynkiewicz's team to study premature aging in ovary cells during chemotherapy. The team also published an article about the properties of seven DNA-protecting, anti-cancer and anti-aging substances, including aspirin and vitamin D3.

What's next? The researcher plans to continue using the new technology and instrumentation to develop new and more effective cancer treatments. Other researchers at NYMC and at neighboring biotech firms continue to keep the high-tech instrument busy.

5// LEONARD EISENBERG, PH.D., PROFESSOR OF PHYSIOLOGY AND MEDICINE

Research challenge: To determine how cardiac muscle regenerates in the adult heart.

Why it's important: Scientists have long sought to understand how this crucial organ maintains itself throughout a person's life, and how it heals from "insults" such as a high-fat diet.

How ARRA funding helped: The money enabled Dr. Eisenberg and his team to conduct animal experiments showing how cardiac muscle responds to stress at the cellular level. They found that following injury, some myocytes (heart muscle cells) start to exhibit an "embryonic program," indicating that the mechanisms that regulate the development of the human heart *in utero* might also promote regeneration of the heart in adults.

What's next? Dr. Eisenberg hopes that identifying what happens to the heart at the cellular level during the disease process could eventually help scientists develop strategies to intervene before irrevocable damage occurs.

6// MARIETTA LEE, PH.D., PROFESSOR OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

Research challenge: To better understand how DNA—the nucleic acid that carries genetic information in cells—replicates and repairs itself.

Why it's important: The maintenance of "genomic integrity" is essential for the avoidance of mutations and chromosome alterations that lead to the development of cancer.

How ARRA funding helped: Dr. Lee says the funding "provided a major boost to our research" when it was used to purchase high-tech equipment that could speed the production of proteins involved in synthesizing DNA needed for conducting key experiments.

What's next? Dr. Lee hopes her research will help investigators understand precisely how mutations and defects in the DNA system contribute to the development of human cancers. The research also could lead to the discovery of novel compounds that may help prevent and treat cancer.

7// CHRISTOPHER LEONARD, PH.D., PROFESSOR OF PHYSIOLOGY

Research challenge: To figure out how defective signaling by the neuropeptide orexin (also known as hypocretin) results in narcolepsy, a chronic sleep disorder characterized by overwhelming daytime drowsiness, disturbed sleep, sudden sleep attacks and cataplexy—the abrupt loss of muscle tone often triggered by strong emotions.

Why it's important: Narcolepsy affects approximately 1 in 2,000 people and is likely underdiagnosed. It is a debilitating disorder that puts victims at increased risk for accidents, obesity and depression, and hinders the ability to succeed at school, work and relationships.

How ARRA funding helped: Past research has shown that mice and dogs lacking the orexin peptide exhibit symptoms resembling human narcolepsy. Dr. Leonard believes that the loss of orexin results in changes in brain circuits regulating waking and sleep. Funding enabled his team to buy high-tech telemetry equipment which they use to study sleep in narcoleptic mice in order to understand which circuits change.

What's next? Dr. Leonard believes his work will aid in identifying brain circuits altered in narcolepsy and their role in normal waking and sleep. This could hasten our understanding of how the brain controls sleep and waking, as well as the development of new medications to treat narcolepsy and other sleep disorders.

8// DANA MORDUE, PH.D., ASSISTANT PROFESSOR OF MICROBIOLOGY AND IMMUNOLOGY

Research challenge: To figure out how to prevent infection and disease reactivation by *Toxoplasma gondii,* a single-cell pathogen that can cause severe disease in people with compromised immune systems, such as the elderly, patients undergoing organ transplants and people with AIDS.

Why it's important: There is currently no therapeutic agent that can eliminate the chronic stage of *T. gondii* infection. Consequently, the infection can reactivate years later, and this can trigger the parasite to activate in the brain, causing encephalitis, blindness, pneumonia and lethal septicemia.

How ARRA funding helped: The money enabled Dr. Mordue to support a research technician and two high school interns to help conduct animal experiments to find ways to "interrupt" the establishment of chronic *T. gondii* infection.

What's next? Dr. Mordue hopes to learn how to make *T. gondii* susceptible to destruction by the human immune system to eliminate chronic infection. To do this, she is collaborating with scientists at Weill Cornell Medical Center.

9// MICHAL SCHWARTZMAN, PH.D., PROFESSOR AND CHAIR OF THE DEPARTMENT OF PHARMACOLOGY

Research challenge: To study a newly discovered anti-inflammatory and cytoprotective circuit in the cornea.

Why it's important: Since the cornea must repair itself by using non-blood cells, greater understanding of the genetic and molecular factors that underlie this process could lead to new treatments for human corneal disorders.

How ARRA funding helped: Funding allowed Dr. Schwartzman to "accelerate the tempo" of her animal research by employing three postdoctoral fellows and five research assistants during the two-year funding period. It also covered the cost of equipment, including a fluorescent plate reader and an infrared imaging system that can measure the presence in the eye of inflammatory protein and lipid mediators.

What's next? Dr. Schwartzman hopes that this research will help to hasten the discovery of new treatments for corneal ulcers, infections and injuries.

10// PATRIC K. STANTON, PH.D., PROFESSOR OF CELL BIOLOGY AND ANATOMY AND NEUROLOGY

Research challenge: To study how changes in the brain's electrical activity affect the way memories are stored.

Why it's important: Understanding how changes in neurotransmitter release relate to memory storage could enhance our understanding of diseases like Alzheimer's, epilepsy and depression.

How ARRA funding helped: Among other things, the funding helped Dr. Stanton and his team make "huge progress" in understanding the development of long-term memory problems in mice with Alzheimer's disease, and in protecting the brains of mice exposed to lab-created blasts that simulate what happens to soldiers exposed to real-life explosive blasts.

What's next? Dr. Stanton says this research could lead to the development of groundbreaking drugs, including an anti-depressant currently in phase-2 clinical trials that works by "normalizing" the plasticity of the brain.

11// RAJ TIWARI, PH.D., PROFESSOR OF MICROBIOLOGY AND IMMUNOLOGY

Research challenge: To find ways to reduce unnecessary surgery in "thyroid proliferative diseases" (TPDs) like goiter and thyroid cancer.

Why it's important: TPDs affect 200 million people worldwide, making these disorders a significant health threat.

How ARRA funding helped: Dr. Tiwari was able to retain two postdoctoral fellows and one assistant professor for two years; the additional staff helped conduct experiments that involved cultivating *in vitro* thyroid cell lines and treating them with estrogen and/or Diindolylmethane (DIM) an anti-estrogenic compound derived from cruciferous vegetables like broccoli and cabbage. The research showed that dietary anti-estrogens could modulate the action of TPDs.

What's next? Dr. Tiwari hopes that this work will lead to the development of a dietary supplement that will reduce the risk of developing, and prevent the progression of, TPDs.

12// ZHONGTAO ZHANG, PH.D., ASSISTANT PROFESSOR OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

Research challenge: To investigate pharmacologic interventions using an enzyme, Quinone reductase 2 (QR2), to treat Parkinson's disease.

Why it's important: Parkinson's disease affects 1.5 million people in the United States, and there is currently no cure for this progressive nervous system disorder.

How ARRA funding helped: Dr. Zhang was able to hire two summer interns to assist in his lab. They did *in vitro* experiments, which showed that QR2, which exists in neurons—along with an electron donor, a product of metabolism—can reduce oxidation and help prevent neurons from dying.

What's next? Dr. Zhang hopes to secure funding to carry out animal studies using mice. Investigators would bring on Parkinson-like symptoms in mouse brains and then treat the animals by manipulating QR2 activity, followed by monitoring the brains to see if the enzyme activity alterations slowed the disease process. Eventually, Dr. Zhang hopes this research could lead to the development of more effective treatments for Parkinson's disease and other forms of neurologic degeneration. ■

These projects also received support from stimulus grants:

- **Mairead A. Carroll, Ph.D.,** *Professor of Pharmacology*
  "Adenosine and Epoxyeicosatrienoic Acids"
- **John G. Edwards, Ph.D.,** *Associate Professor of Physiology*
  "Doxorubicin-induced Cardiac Progenitor Cell Death Is Antecedent to Heart Failure"
- **Michael Goligorsky, M.D., Ph.D.,** *Professor of Medicine and Pharmacology*
  "Endothelial Dysfunction, Nitric Oxide and Renal Failure"
  "Prevention of Vasculopathy and Nephropathy in Metabolic Syndrome"
- **Matthew D. Plotkin, M.D.,** *Assistant Professor of Medicine*
  "Vaculogenesis and Renal Mesodermal Progenitor Cells"
- **Ira Schwartz, Ph.D.,** *Professor and Chairman of Microbiology and Immunology*
  "B. Burgdorferi Hematogenous Dissemination"
  "Genotypic Variation and B. Burgdorferi Pathogenesis"
- **Yuk-Chin Tse-Dinh, Ph.D.,** *Professor of Biochemistry and Molecular Biology*
  "Bacterial Cell Killing by Topoisomerase I Mediated DNA Lesion"