

PHILADELPHIA INTERNATIONAL MEDICINE® NEWS BUREAU

Contact: Leonard N. Karp
215/575-3720; lkarp@philadelphiamedicine.com
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For immediate release:

Editors note: Research, new techniques and improved facilities by Philadelphia International Medicine hospitals and physicians may lead to new ways to treat some of our most challenging diseases. Below are just some examples from our hospitals.

In this month's edition

1. **Neurology Journal Devotes Special Issue to Penn Research**
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3. **Blocking Growth Protein Kills Prostate Cancer Cells, Inhibits Tumor Growth, Jefferson Scientists Find**

Neurology Journal Devotes Special Issue to Penn Research

Philadelphia – The entire January issue of NeuroSignals is devoted to describing neurodegenerative disease research at the University of Pennsylvania School of Medicine and Health System (See www.karger.com/nsg for a Table of Contents and Abstracts).

“Neurodegenerative diseases are a public health problem and we are doing the basic and translational science to improve how we care for people with these diseases,” says John Trojanowski, MD, PhD, Director of the PENN Institute on Aging, who wrote the introductory paper, entitled, “PENN Neurodegenerative Disease Research - In The Spirit of Benjamin Franklin” for the issue.

The United States and nations across the globe are experiencing a seismic demographic shift due to the rapidly growing segment of the population 65 and older. These demographic changes reflect astonishing increases in life expectancy in the last millennium. For example, life expectancy has increased by about 27 years from 1900 to 1990, while a similar increase has occurred over the prior 5 millennia extending from the Bronze Age to 1900.

“The good news about this longevity revolution is that Americans are not only living longer, but their disabilities continue to decline,” says Trojanowski. “However, if action is not taken immediately to plan for

this demographic ‘sea change’, aging-related disorders like Alzheimer’s disease will have ominous consequences. Significantly, the costs to Medicare for treating Alzheimer’s and related dementias were \$62 billion in 2000 but will increase to \$1 trillion by 2050 if no effective treatments are developed.

“Although demography is the history of the future as written today, it is still possible to change the future now. For example, the burden of Alzheimer’s and its costs could be reduced by half in the coming years

if interventions can be developed that delay the onset of the disease by five years. This realization motivated Penn scientists to pursue research to enhance healthy brain aging and reduce the burden of Alzheimer's and other aging-related neurodegenerative diseases globally as well as nationally in our lifetime.”

This special issue of NeuroSignals provides an overview of these research programs at Penn:

- John Q. Trojanowski -- “PENN Neurodegenerative Disease Research - In The Spirit of Ben Franklin”
- Christopher M. Clark, Christos Davatzikos, Ari Bortakur, Andrew Newberg, Susan Leight, Virginia M.-Y. Lee and John Q. Trojanowski -- “Biomarkers for the Early Detection of Alzheimer's Disease Pathology” Applications of biomarkers in the real world--Use of biomarkers to make diagnoses for clinical trials.
- Leslie Shaw -- “Penn Biomarker Core of the Alzheimer Disease Neuroimaging Initiative” Validation of chemical biomarkers and blood tests for Alzheimer's
- Rachel Goldmann Gross, Andrew Siderowf and Howard Hurtig -- “Cognitive Impairment in Parkinson's Disease and Dementia with Lewy Bodies: A Spectrum of Disease” Penn Udall Center is the only such center to look at cognitive impairment and Parkinson's disease
- Sarah M. Kranick and John E. Duda -- “Olfactory Dysfunction in Parkinson's Disease” Early detection of Parkinson's disease using a smell test
- Benoit I. Giasson and Vivianna M. van Deerlin -- “Mutations in LRRK2 as a Cause of Parkinson's Disease” Genetics of Parkinson's disease; LRRK2 is one of the most frequent mutations in this disease
- Linda Kwong, Kunihiko Uryu, John Q. Trojanowski and Virginia M.-Y. Lee -- “TDP-43 Proteinopathies: Neurodegenerative Protein Misfolding Diseases Without Amyloidosis” Update on TDP-43 dementias in ALS and FTD
- Aaron Gitler -- “Beer and Bread to Brains and Beyond: Can Yeast Cells Teach us About Neurodegenerative Diseases?” Using yeast models to study neuron diseases
- James Shorter -- “Hsp104, A Potential Weapon to Combat Diverse Neurodegenerative Disorders” Heat shock proteins' role in neuron diseases
- Brett A. McCray and J. Paul Taylor -- “The Role of Autophagy in Age-Related Neurodegeneration” New pathways towards neurodegeneration
- Lauren Elman, Leo McCluskey and Murray Grossman -- “ Motor Neuron Disease and Frontotemporal Dementia: A Tale of Two Disorders Linked To TDP-43” TDP-43 protein's role in Lou Gehrig's Disease
- Jason Karlawish -- “Measuring Decision Making Capacity in Cognitively Impaired Individuals” Understanding how patients with neuron diseases can make informed decisions

CHOP Researcher Named Howard Hughes Medical Institute Investigator

Dr. Vivian Cheung, genetics researcher at The Children's Hospital of Philadelphia, was selected as a Howard Hughes Medical Institute Investigator on the basis of patient-oriented research.

Like all those chosen, Dr. Cheung focuses on translating research discoveries into improved medical treatments. "We are extremely pleased and proud of the fact that one of our pediatricians was honored by one of the world's leading biomedical research institutions," said Philip R. Johnson, MD, chief scientific officer and senior vice president of Children's Hospital. "This appointment recognizes Dr. Cheung's accomplishments in advancing genetic discovery."

Dr. Cheung investigates how the sequence of DNA units in a person's chromosomes affects that person's susceptibility to disease. She uses microarray technology to rapidly measure how strongly genes are expressed within cells. By determining how gene expression changes in response to drugs and other treatments, she discovers how each patient's DNA variations are associated with the effectiveness of their disease treatments.

Her goal is to help physicians predict how a patient will respond to a given drug or treatment, based on the patient's particular genetic profile. Ultimately, providing refined genetic tools may remove some of the guesswork in making treatment decisions and in providing the best preventive and therapeutic care. Trained in neurology, Dr. Cheung has a specific interest in a neurogenetic disease called ataxia telangiectasia, which affects movement, muscle control, the immune system and susceptibility to cancer.

Because different children may react very differently to their treatments, her research aims to customize treatment to a patient's genetic profile, thus minimizing side effects and providing maximum benefits. Dr. Cheung's studies could be applied to a broad range of common and uncommon diseases, in using genetic tools to eventually routinely guide physicians and patients to better treatments.

As a pediatrician at Children's Hospital, Dr. Cheung is continuing to work at the Hospital and has become an employee of HHMI, which provides a research budget and funding for laboratory space. Dr. Cheung remains an associate professor of Pediatrics and Genetics at the University of Pennsylvania School of Medicine.

After earning her MD degree from Tufts University School of Medicine, Dr. Cheung completed her residency at the UCLA Medical Center, before coming to The Children's Hospital of Philadelphia in 1996. She holds the William Wikoff Smith Endowed Chair in Pediatric Genomic Research at Children's Hospital, where she leads an NIH-funded laboratory.

About the Howard Hughes Medical Institute: HHMI is one of the world's largest philanthropies, with laboratories across the United States and grants programs throughout the world. The Institute is a nonprofit medical research organization that employs hundreds of leading biomedical scientists working at the

forefront of their fields. In addition, through its grants program and other activities, HHMI is helping to enhance science education at all levels and maintain the vigor of biomedical science worldwide. HHMI's endowment at the end of the 2006 fiscal year was approximately \$16.3 billion.

Blocking Growth Protein Kills Prostate Cancer Cells, Inhibits Tumor Growth, Jefferson Scientists Find

Researchers at Jefferson's Kimmel Cancer Center have shown that they can effectively kill prostate cancer cells in both the laboratory and in experimental animal models by blocking a signaling protein that is key to the cancer's growth. The work proves that the protein, Stat5, is both vital to prostate cancer cell maintenance and that it is a viable target for drug therapy.

The scientists, led by Marja Nevalainen, MD, PhD, associate professor of Cancer Biology at Jefferson Medical College of Thomas Jefferson University, wanted to prove that Stat5 was indeed necessary for prostate cancer cells to be viable. They blocked the protein's expression and function in several ways, including siRNA inhibition, antisense inhibition and adenoviral gene delivery of an inhibitory form of Stat5. All of these techniques killed the prostate cancer cells in cell culture. The researchers also showed when they transplanted such cancerous tissue into mice and blocked Stat5 expression, prostate tumors failed to grow.

"This provides the proof of principle that Stat5 is a therapeutic target protein for prostate cancer, and may be specifically useful for advanced prostate cancer, where there are no effective therapies," Dr. Nevalainen says. "These results are very reproducible."

She and her team report their findings March 1, 2008 in the journal *Clinical Cancer Research*.

Hormone resistant prostate cancer is especially dangerous. Men with primary prostate cancer usually have either surgery or radiation, whereas subsequent disease is frequently treated by hormone therapy. But if the cancer recurs again, years later, it can be more aggressive and typically fails to respond to hormone treatment, often leaving few treatment options.

The findings, Dr. Nevalainen notes, are particularly relevant because her team worked with urologists to get human prostate cancer tissue specimens from surgeries, putting them into cell tissue cultures. That way, she says, the hypothesis could be tested in real human prostate cancer tissue specimens.

While she and her team continue to work on establishing Stat5 as a therapeutic target for hormone-resistant prostate cancer, they are also testing whether or not blocking Stat5 can make prostate cancer cells more sensitive to other treatments, such as radiation and chemotherapy. Another next step in the work, Dr. Nevalainen says, is to find pharmacological agents that inhibit the protein.

In work reported recently in *Cancer Research*, Dr. Nevalainen and her co-workers showed that Stat5 is turned on in nearly all recurrent prostate cancers that are resistant to hormone therapy. In addition, the researchers also showed that the convergence of Stat5 and androgen receptor could be responsible for making such prostate cancers especially dangerous.

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