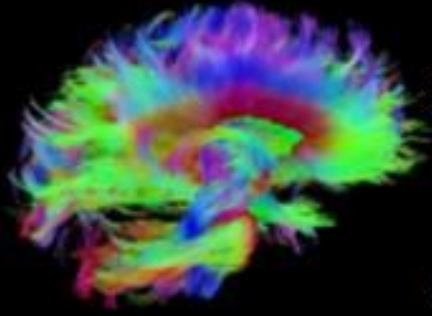Herbert & Jacqueline Krieger Klein
Symposium on Alzheimer's Disease and
Neurodegeneration
April 12, 2019
Organized by the Rutgers Brain Health Institute

## Rutgers-New Jersey Medical School, MSB, B-610, 185 S. Orange Ave., Newark, NJ

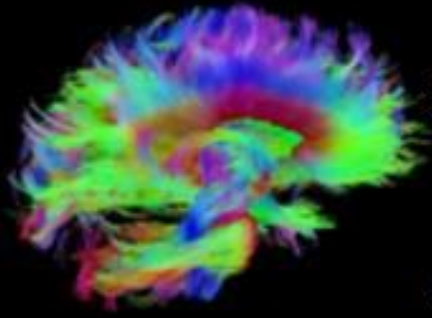| | | |
|---|---|---|
| 8.30-9.00 AM | Check-in/Breakfast | Gellene Room, MSB |
| 9.00 – 9.15 AM | **Gary Aston-Jones, PhD** <br> *Director, Rutgers Brain Health Institute* <br> *Strongwater Endowed Chair in Neuroscience and Brain Health* <br> **Chancellor Brian Strom, MD, MPH** <br> *Rutgers Biomedical and Health Sciences* | Gellene Room, MSB |
| 9.15 - 9.30 AM | **Hon. Herbert C. Klein, Esq.** <br> *Rutgers alum, emeritus member of the Rutgers Foundation Board of Overseers, Represented NJ in US Congress, served in NJ General Assembly* | Gellene Room, MSB |
| 9.30 - 10.10 AM | **Ottavio Arancio, MD, PhD** <br> *Professor of Pathology & Cell Biology, The Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, NY.* <br><br> *Amyloid-Beta and Tau Proteins in Alzheimer's Disease: Is the Amyloid Hypothesis Correct?* | B-610, MSB |
| 10.15 -10.40 AM | **Mark Gluck, PhD** <br> *Professor of Neuroscience and Public Health, Director, Aging and Brain Health Alliance, Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, NJ.* <br><br> *Interactions Between Physical Fitness and ABC7 Gene Variations on Alzheimer's Disease Biomarkers in Older African Americans* | B-610, MSB |
| 10.45 -10.55 AM | Coffee break | Gellene Room, MSB |
| 11.00 -11.25 AM | **Daniel P. Schneider, MD** <br> *Associate Professor of Neurology and Psychiatry,* <br> *Rutgers- Robert Wood Johnson Medical School, New Brunswick, NJ.* <br><br> *Challenges of a Dementia Clinic in 21st Century America* | B-610, MSB |

## Herbert & Jacqueline Krieger Klein Symposium on Alzheimer's Disease and Neurodegeneration
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|---|---|---|
| 11.30 -12.10 PM | **Riqiang Yan, PhD**<br>*Professor and Chair, Neuroscience, William Beecher Scoville Professor in Neuroscience, University of Connecticut School of Medicine, Farmington, CT.*<br><br>*Enhancing Neurogenesis to Reverse Neuronal Loss in AD Mouse Models by CX3CL1 Back Signals* | B-610, MSB |
| 12.15 – 1.25 PM | Lunch | Gellene Room, MSB |
| 1.30 - 2.10 PM | **Domenico Pratico, MD, FCPP**<br>*Professor of Pharmacology and Microbiology and Immunology, Scott Richards North Star Charitable Foundation Chair for Alzheimer's Research, Professor and Director, Alzheimer's Center at Temple University Lewis Katz School of Medicine, Philadelphia, PA.*<br><br>*The Vacuolar Protein Sorting System and Alzheimer's Disease Pathogenesis* | B-610, MSB |
| 2.15 -2.40 PM | **Monica Driscoll, PhD**<br>*Distinguished Professor of Molecular Biology and Biochemistry, Rutgers University, New Brunswick, NJ.*<br><br>*Neurons Put Out the Trash: A Novel Facet of Proteostasis and Mitochondrial Quality Control* | B-610, MSB |
| 2.45 – 3.10 PM | **Christopher Rongo, PhD**<br>*Professor and Vice-Chair of Genetics, Undergraduate Director of Genetics, Waksman Institute of Microbiology, Rutgers University, New Brunswick, NJ.*<br><br>*Impaired Mitochondrial Transport in a C. elegans Tauopathy Model* | B-610, MSB |
| 3.15 -3.25 PM | Coffee break | Gellene Room, MSB |

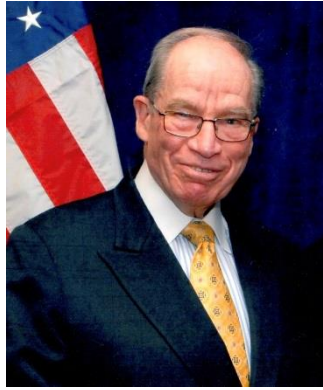# Herbert & Jacqueline Krieger Klein Symposium on Alzheimer's Disease and Neurodegeneration
## April 12, 2019
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**Rutgers-New Jersey Medical School, MSB, B-610, 185 S. Orange Ave., Newark, NJ**

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|---|---|---|
| 3.30 – 3.55 PM | **Federico Sesti, PhD**<br>*Professor of Neuroscience and Cell Biology, Rutgers- Robert Wood Johnson Medical School, New Brunswick, NJ.*<br><br>*Oxidation of Potassium Channels in Alzheimer's Disease* | B-610, MSB |
| 4.00 – 4.25PM | **Hyung Jin Ahn, PhD**<br>*Assistant Professor of Pharmacology, Physiology and Neuroscience, Rutgers Brain Health Institute, Rutgers- New Jersey Medical School, Newark, NJ.*<br><br>*Hereditary Cerebral Amyloid Angiopathy-linked Mutations Enhance Cerebral Deposits of Plasma Protein Fibrinogen* | B-610, MSB |
| 4.30 – 5.00PM | **Luciano D'Adamio, MD, PhD**<br>*Herbert C. and Jacqueline Krieger Klein Endowed Chair in Alzheimer's Disease and Neurodegeneration Research, Professor of Pharmacology, Physiology & Neuroscience, and Neurology, Associate Director, Rutgers Brain Health Institute, Director, Herbert C. and Jacqueline Krieger Klein Center in Alzheimer's Disease and Neurodegeneration Research, Rutgers-New Jersey Medical School, Newark, NJ.*<br><br>*APP Processing in Dementia Knock-In Rats* | B-610, MSB |

# Hon. Herbert C. Klein and Jacqueline Krieger Klein



The symposium is being held to honor the establishment of the Herbert C. and Jaqueline Krieger Klein Endowed Chair in Alzheimer's disease and Neurodegeneration at Rutgers Brain Health Institute. The Endowed Chair was established by Hon. Hebert Klein and, his late wife, Jacqueline Krieger Klein.

Mr. Klein obtained a BA in Political Science from Rutgers College in 1951 and went on to obtain his JD and LLM degrees from Harvard and New York University, respectively. Mr. Klein was a member of the New Jersey General Assembly from 1972 to 1976, where he was chair of the majority caucus. He wrote the law that created the New Jersey Economic Development Authority and was co-counsel on bond issue for New Jersey Sports and Exposition Authority. In 1993, Mr. Klein was elected to the 103rd Congress. During his tenure in the United States House of Representatives, Mr. Klein was a leader on the House Banking Committee, where he was responsible for several major legislative initiatives. He co-authored the bills that authorized interstate branch banking and was the architect of the provision which sparked passage of the legislation that ended the problems in the savings and loan industry. Mr. Klein also served on the House Science Committee, where he co-authored the National Competitiveness Act which helped American industry regain global control in manufacturing. He was a member of Governor James Florio's transition team, and a Trustee of the Democratic National Committee. He joined Genova Burns in September 2015 as Of Counsel and member of the Commercial Real Estate & Redevelopment Law Practice Group. Prior to joining Genova Burns, he was a Partner with the firm Nowell Amoroso Klein Bierman. In addition to his law practice, Mr. Klein serves as a Trustee at First Real Estate Investment Trust of New Jersey, an equity real estate investment trust.

Mr. Klein is an Emeritus member of the BOO and former member of the BOT. He served on the Class of 1951's 65th Reunion Campaign Committee and previously served as the Campaign Co-chair for his class' 60th reunion. As a Rutgers student, he was editor-in-chief of the Targum, a member of the Crown and Scroll and Cap and Skull honor societies, as well as a brother of Tau Delta Phi. He is a Loyal Son of Rutgers. Mr. Klein and his late wife Jacqueline have been generous donors to Rutgers. He is a member of the Society of Queen's College, which recognizes donors whose lifetime giving to Rutgers has exceeded $1 million.

Mrs. Jacqueline Krieger Klein, who passed away in April 2017, was a graduate of Wellesley College, where she established the Jacqueline Krieger Klein '53 Fellowship. Jacqueline was a member of the Democratic National Committee, a member of the Board of Trustees of the New Jersey Y Camps, a member of the Board of Trustees and former Secretary of the Boys & Girls Club of Clifton as well as a member of the Board of Trustees of the Jewish Federation of Passaic & Clifton. Mr. and Mrs. Klein were married for 64 years.

# Rutgers Alzheimer's Disease Research Center (RUADRC)

Alzheimer's disease (AD) and related dementias are a major cause of disability and death in the elderly. Approximately 6 million people have been diagnosed with AD and related dementias and the aging of America's population suggests that the number of Alzheimer's patients in the U.S. will, by 2050, increase to nearly 14 million people. Worldwide, approximately 40 million people have AD and related dementias. This number could also climb to nearly 120 million by 2050. With Americans spending $226 billion annually to treat the symptoms of AD, and other dementias, rather than the cause of this disease itself, this disease alone could cost Americans $1.1 trillion by 2050. As 5% of AD cases are familial and ~95% are sporadic, disease-modifying drugs that treat both sporadic and familial AD are desirable. Despite recent advances in our understanding of basic biological mechanisms underlying AD and related dementias, we do not yet know how to prevent AD and related dementias, nor do we have an approved disease-modifying intervention. A major reason that these problems persist is that current animal models of AD and related dementias have not been able to predict the effectiveness of proposed therapies, so that many that have moved into clinical trials fail, which greatly slows the development of new therapies and increases their cost. Thus, there is a great need to develop the next generation of animal models (NexGeMo) of AD and related dementias to provide greater predictive power of potential therapies and thus accelerate the drug testing/clinical trial pipeline.

## Vision

The ultimate goals of the proposed RUADRC are:

➢ To develop therapies to cure AD and related dementias or, at the very least, effectively slow down the course of disease progression.

➢ To discover novel diagnostic and prognostic biomarkers that can forewarn the initiation of pathogenic processes before symptoms occur and also be used to monitor disease progression and treatment efficacy.

To achieve the above goals, research at RUADRC will focus on identifying disease mechanisms using genetic, cellular, organismal and behavioral approaches in animal and human model systems. Understanding of disease mechanisms will help uncover pathways that need to be targeted by drugs to achieve therapeutic efficacy. Development of relevant *in vitro* and *in vivo* models will be important for pre-clinical evaluation of novel drugs. A dementia clinic for patient recruitment, assessment and treatment will also be needed for translating research to clinic.

To fulfill the vision, RUADRC will have three components:

*Component 1*: Include cores for: development of novel animal models; histopathology; small animal imaging; electrophysiology; and, behavioral testing.

*Component 2*: Include cores for: developing novel human cell model systems, such as isogenic hIPSC lines carrying AD genetic variants; high-throughput drug-screening; and immunohistochemistry.

*Component 3*- Include a Dementia clinic and cores for: development of novel neurocognitive psychological test and novel neuro-cognitive rehabilitation approaches; human pathology assessment, human imaging; and collecting human samples (brain tissue, cerebrospinal fluids, blood/serum samples etc.).

Mr. Klein, has recently donated, generously, additional funds to support the recruitment of a junior faculty, Dr. Hyung Jin Ahn, to help fulfill the above vision of growing RUADRC into a premier AD research Center.

# SPEAKER ABSTRACTS

# Ottavio Arancio, MD, PhD

*Professor of Pathology & Cell Biology, The Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, NY.*

## Amyloid-Beta and Tau Proteins in Alzheimer's Disease: Is the Amyloid Hypothesis Correct?

The "Amyloid Cascade Hypothesis" has dominated studies on Alzheimer's disease (AD) in the last 30 years. It postulates that an increase of amyloid-beta levels triggers tau pathology leading to neuronal death. However, therapies decreasing amyloid-beta levels have so far failed, and tau-based clinical trials have not yet been successful. This asks for a re-evaluation of the hypothesis. Dr. Arancio will present data showing that the two proteins can act concurrently to produce synaptic dysfunction and memory loss. Most importantly, he will show that suppression of tau expression does not protect against damage of long-term synaptic plasticity and memory, indicating that amyloid-beta and tau do not act in series. He will also discuss novel findings showing binding of both amyloid-beta and tau oligomers to amyloid-beta precursor protein (APP), which is required for both amyloid-beta and tau to enter neurons and induce abnormal synaptic plasticity and memory, supporting the need for further studies on APP to better understand the pathogenesis of the disease. In light of these findings, he will propose a novel view of AD pathogenesis in which extracellular oligomers of amyloid-beta and tau act in parallel at the upstream level of APP. Such a view calls for a reconsideration of therapeutic approaches aimed at amyloid-beta or tau, highlighting the relevance of therapies acting towards APP, or at the downstream level of APP.

# Mark Gluck, PhD

*Professor of Neuroscience and Public Health, Director, Aging and Brain Health Alliance, Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, NJ.*

## Interactions Between Physical Fitness and ABC7 Gene Variations on Alzheimer's Disease Biomarkers in Older African Americans

Although the association of ABCA7 risk variants with Alzheimer's disease (AD) has been confirmed worldwide, its effect size on the relative odds of being diagnosed with AD is significantly higher in African Americans. Two common ABCA7 loci (rs115550680 and rs3764650) have been confirmed to increase the risk of AD; however, little is known about the neural correlates of cognitive function in African Americans and how they relate to AD risk conferred by ABCA7. Two studies were performed to elucidate the relationship between ABCA7 genotype and AD risk in healthy older African Americans. First, in a case-control fMRI study, we observed ABCA7 related impairments in behavioral generalization that was mediated by dissociation in entorhinal cortex (EC) resting state functional connectivity. Specifically, ABCA7 rs115550680 was associated with EC-hippocampus hypersynchronization and EC-mPFC hypo-synchronization. Carriers of the risk genotype also had a significantly smaller anterolateral EC (alEC), despite no group differences on standardized neuropsychological tests. Second, in a case-control sample we observed that ABCA7 rs3764650 genotype modulates the association between aerobic fitness and behavioral generalization following rule learning. For carriers of the non-risk genotype, higher levels of aerobic fitness were significantly associated with fewer generalization errors, while carriers of the risk genotype did not show any relationship between aerobic fitness and generalization. Taken together, these results suggest that carriers of ABCA7 risk genotypes can develop prodromal or preclinical impairments in behavioral generalization, brain structure, and functional connectivity, and they may not benefit from the neuroprotective effects of aerobic fitness.

## Daniel P. Schneider, MD

*Associate Professor of Neurology and Psychiatry, Rutgers- Robert Wood Johnson Medical School, New Brunswick, NJ.*

### *Challenges of a Dementia Clinic in 21st Century America*

Dr. Schneider will review the challenges of designing and running an effective dementia clinic given the economic and society realities of 21st century America. We will look at such issues as the increasing fragmentation and specialization within medicine, limitations in payment opportunities for physicians, and, most importantly, financial hardships for patients, and increasingly complex bureaucratic systems becoming obstacles for care for many patients.

## Riqiang Yan, PhD

*Professor and Chair, Neuroscience, William Beecher Scoville Professor in Neuroscience, University of Connecticut School of Medicine, Farmington, CT.*

### *Enhancing Neurogenesis to Reverse Neuronal Loss in AD Mouse Models by CX3CL1 Back Signals*

Previous studies have revealed the cellular functions of CX3CL1 via interaction with its receptor CX3CR1.  In this study, we report a unique role of CX3CL1 that is independent from this mechanism. We show that the intracellular CX3CL1 fragment, which is released after γ-secretase cleavage, translocates into the cell nucleus and induces transcriptional regulation of genes important for cell growth and proliferation.  Mice overexpressing either full-length CX3CL1 (Tg-CX3CL1) or its C-terminal fragment (Tg-CX3CL1ct) exhibit enhanced adult neurogenesis via activation of TGFβ2/3 and Smad2.  Enhanced adult neurogenesis was suppressed when Smad2 expression was deleted in neurons, supporting a role for the CX3CL1ct-TGFβ-Smad pathway in adult neurogenesis.  When Tg-CX3CL1 mice were crossed with an Alzheimer's mouse model, which overexpresses mutant tauP301S and develops neurodegeneration with a shorter lifespan, we noted reversal of neurodegeneration, significantly increased survival time, and enhanced learning and memory.  Hence, CX3CL1ct has a back-signaling function by reversing neuronal loss.

# Domenico Pratico, MD, FCPP

*Professor of Pharmacology and Microbiology and Immunology, Scott Richards North Star Charitable Foundation Chair for Alzheimer's Research, Professor and Director, Alzheimer's Center at Temple University Lewis Katz School of Medicine, Philadelphia, PA.*

## *The Vacuolar Protein Sorting System and Alzheimer's Disease Pathogenesis*

The vacuolar protein sorting system, aka retromer, is a highly conserved multimeric complex present in all eukaryotic cells whose activity is essential for regulating the recycling and retrieval of numerous protein cargos from the endosome to trans-Golgi network or the cell surface. In recent years, molecular and genomic studies have provided evidence that aberrant regulation of this complex could be implicated in the pathogenesis of several neurodegenerative diseases. Thus, deficiency or mutations in one or more protein components of the retromer leads to increased accumulation of protein aggregates as well as enhanced cellular neurotoxicity. In this paper, we will discuss the neurobiology and the functional role that the retromer complex plays in the context of Alzheimer's disease (AD) and related tauopathies. We will present data showing how its genetic manipulation (gain of function and silencing) directly modulates cellular and molecular events of functional importance in the development of the AD-like phenotype in vivo and in vitro. Lastly, we will discuss the viability of targeting the retromer complex to enhance or restore its function as a novel and unifying disease-modifying strategy against these diseases.

# Monica Driscoll, PhD

*Distinguished Professor of Molecular Biology and Biochemistry, Rutgers University, New Brunswick, NJ.*

## *Neurons Put Out the Trash: A Novel Facet of Proteostasis and Mitochondrial Quality Control*

Aging is an inescapable component of human biology. Age-associated decline in functionality and the striking rise in risk for diseases such as diabetes, cancer and Alzheimer's disease that accompanies age, couple to create one of the most pressing medical, social and economic challenges of our time. Toxicity of misfolded proteins and mitochondrial dysfunction are pivotal factors that promote age-associated functional neuronal decline and neurodegenerative disease across species. Although these neurotoxic challenges have long been considered to be cell-intrinsic, evidence now supports that misfolded human disease proteins originating in one neuron can appear in neighboring cells, a phenomenon proposed to promote pathology spread in human neurodegenerative disease. Likewise, mammalian mitochondria can be sent out of the cell that made them for transcellular degradation. We discovered a previously unknown capacity of C. elegans adult neurons to extrude large (~5μM) membrane-surrounded vesicles that can include aggregated proteins (including human neurodegenerative disease proteins), and damaged mitochondria. We suggest that "throwing out the trash" may be a conserved mechanism that constitutes a fundamental, but formerly unrecognized, branch of neuronal proteostasis and mitochondrial quality control, which, when imbalanced, might actively contribute to neurodegenerative disease.

# Christopher Rongo, PhD

*Professor and Vice-Chair of Genetics, Undergraduate Director of Genetics, Waksman Institute of Microbiology, Rutgers University, New Brunswick, NJ.*

## *Impaired Mitochondrial Transport in a C. elegans Tauopathy Model*

The microtubule-associated protein Tau is implicated in Alzheimer's Disease and various tauopathies, forming hyperphosphorylated aggregates and fibrillary tangles, yet the mechanism by which Tau impairs neuron function remains controversial.  One well-characterized tauopathy is Frontotemporal Dementia with Parkinsonism-Chromosome 17 (FTDP-17), patients with which have Tau mutations, including the amino acid substitution V337M. Here, we use the genetic model organism C. elegans to model tauopathy *in vivo*.  We find that expressing human Tau with the V337M mutation in C. elegans neurons results in Tau aggregation, impaired mitochondrial transport, and uncoordinated locomotive behavior. The introduction of a Kinesin-Tom7 chimeric protein, which directly couples mitochondria to microtubules without the need of motor adaptors, improves mitochondria distribution in mutant Tau animals, suggesting that mutant Tau acts by impairing mitochondrial association with kinesin motors. Activation of the hexosamine metabolite pathway, either genetically or through metabolite supplementation, reverses Tau protein aggregation, improves locomotion and increases neuronal mitochondrial number compared to untreated control. Our study suggests that the aggregation properties of Tau impair mitochondrial transport, and that the promotion of protein homeostasis through activation of the hexosamine pathway could be a potential therapeutic strategy to treat tauopathy.

# Federico Sesti, PhD

*Professor of Neuroscience and Cell Biology, Rutgers- Robert Wood Johnson Medical School, New Brunswick, NJ.*

## *Oxidation of Potassium Channels in Alzheimer's Disease*

A pathological condition common to a number of neurodegenerative diseases including Alzheimer's disease (AD) is the imbalance between the production of reactive oxygen species (ROS)--which can damage major cellular components, and the ability of the cells to detoxify them. One protein known to undergo oxidation is the voltage-gated K+ channel subfamily B member 1 (KCNB1, Kv2.1) which carries a major somatodendritic current in cortex and hippocampus. This implies that oxidized KCNB1 channels may be present in the Alzheimer's brain and contribute to its pathology. To address this question we examined post mortem hippocampal tissue of AD donors and age-matched controls and further sought to determine the effects of KCNB1 oxidation in mouse model of AD (3xTg-AD mouse). The results of our studies indicate that KCNB1 channels undergo extensive oxidation in the human AD brain. Furthermore, two key components of a toxic pathway activated in response to oxidation of the channel, Focal Adhesion Kinase (FAK) and Src tyrosine kinases, are also more active in AD compared to control brains. In the 3xTg-AD rodent brain, KCNB1 oxidation is associated with inflammation and oxidative stress which act in concert to increase intra-neuronal $\beta$ amyloid. These cellular injures correlate with behavioral deficit, suggesting that oxidation of KCNB1 channels may contribute to human AD pathology.

# Hyung Jin Ahn, PhD

*Assistant Professor of Pharmacology, Physiology and Neuroscience, Rutgers Brain Health Institute, Rutgers- New Jersey Medical School, Newark, NJ.*

## *Hereditary Cerebral Amyloid Angiopathy-linked Mutations Enhance Cerebral Deposits of Plasma Protein Fibrinogen*

Increasing evidence suggests that cerebrovascular dysfunction is one of the pathological hallmarks of Alzheimer's disease (AD). Cerebral amyloid angiopathy (CAA), where Aβ deposits around cerebral blood vessels, is a major contributor of vascular dysfunction in AD and is observed in more than 80% of AD patients. Hereditary cerebral amyloid angiopathy (HCAA) is a rare familiar form of CAA. HCAA patients display exaggerated CAA pathology, and suffer from severe neurological disorders in mid-adulthood, including stroke and dementia. While most amyloid precursor protein mutations increase total β-amyloid (Aβ) production or promote formation of the more toxic Aβ42, a subset of mutations related to HCAA causes an increase in vascular deposits of Aβ. However, it is unclear how these HCAA mutations increase CAA and lead to severe cerebrovascular pathology. Our previous studies suggest that the direct interaction between Aβ and fibrinogen leads to increased CAA, abnormal fibrin clot formation, inflammation, and cerebrovascular damage. Based on these findings, we tested whether HCAA mutations increase Aβ's binding affinity for fibrinogen and subsequently induces more severely altered fibrin clotting and exacerbates cerebrovascular damage. We found that HCAA-type mutant Aβs increase the Aβ-fibrinogen interaction up to 50-fold compared to wildtype Aβ. In addition, HCAA-type mutations induced more severely altered fibrin clot and a greater delay in fibrinolysis. Furthermore, Immunofluorescence analysis of human HCAA occipital cortex tissue showed extensive increase of fibrinogen/Aβ co-deposition around sites of CAA compared to that of early-onset AD patients and non-demented control individuals. Our results suggest the stronger interaction between fibrinogen and HCAA-type mutant Aβs may dramatically contribute to CAA-related cerebrovascular pathology observed in HCAA patients.

# Luciano D'Adamio, MD, PhD

*Herbert C. and Jacqueline Krieger Klein Endowed Chair in Alzheimer's Disease and Neurodegeneration Research, Professor of Pharmacology, Physiology & Neuroscience, and Neurology, Associate Director, Rutgers Brain Health Institute, Director, Herbert C. and Jacqueline Krieger Klein Center in Alzheimer's Disease and Neurodegeneration Research, Rutgers-New Jersey Medical School, Newark, NJ.*

## *APP Processing in Dementia Knock-In rats*

Mutations in APP and PSEN1 cause Familial dementia. In contrast, an APP variant protects humans from dementia. To understand the role of APP processing in dementia's pathogenesis we built rats carrying some of the pathogenic mutations in APP and PSEN1 as well as the protective APP variant. A preliminary biochemical analysis of these rats suggest several pathways by which alteration in APP metabolism may cause dementia.

Transformations in Translational Neuroscience

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