Prusiner-Abramsky Research Awards

Previous Winners 2016

DR. AVI PRIEL
Institute for Drug Research
School of Pharmacy
Faculty of Medicine
Inflammatory Pain: Elucidating the Cellular and Molecular Basis

DR. YUVAL TABACH
Department of Developmental Biology and Cancer Research
Institute for Medical Research Israel-Canada
Hebrew University-Hadassah Medical School
Combined Computational and Experimental Methods Suggest a
Unified Theory to Explain 40 Neurodegenerative Disorders

DR. SHAHAR ARZY
Department of Neurology
Hebrew University-Hadassah Medical School
The Human Self in Space, Time, and Person: Physiology and Pathology

DR. NETTA LEVIN
Department of Neurology
Hebrew University-Hadassah Medical School
Cortical and White Matter Mapping in Understanding Visual System
Pathologies

Previous Winners 2015

DR. EHUD COHEN
Department of Biochemistry and Molecular Biology
Institute for Medical Research Israel-Canada
Hebrew University-Hadassah Medical School
Dissecting the Mechanistic Roles of Aging
in the Emergence of Neurodegenerative Disorders

DR. YORAM BEN-SHAUL
Department of Medical Neurobiology
Institute for Medical Research – Israel-Canada
Hebrew University-Hadassah Medical School
Neuronal Circuits Underlying Social Behavior

DR. DAVID ARKADIR
Department of Neurology
Hebrew University-Hadassah Medical School
DYT1 Dystonia Links Corticostriatal Synaptic Plasticity and Learning
Behavior in Humans

DR. MARC GOTKINE
Department of Neurology
Hebrew University-Hadassah Medical School
Identification of Serological, Cytological and Genetic Factors
Associated with the Development and Progression of ALS in Israel

Previous Winners 2014

PROF. ALBERT TARABOULOS
Department of Microbiology and Molecular Genetics
Institute for Medical Research – Israel-Canada
Hebrew University-Hadassah Medical School
Prion Neurotoxicity: From Protein Misfolding to Lipid Disease

PROF. HAGAI BERGMAN
Department of Medical Neurobiology
Institute for Medical Research – Israel-Canada
Hebrew University-Hadassah Medical School
Computational Physiology and Pathophysiology of the Basal Ganglia
and their Disorder – From Understanding to Closed Loop Deep
Brain Stimulation Treatments

DR. DANA EKSTEIN
Department of Neurology
Hebrew University-Hadassah Medical School
Development of Tools for Patient-Specific Individualized Diagnosis
and Treatment of Epilepsy

DR. ADI VAKNIN-DEMBINSK
Department of Neurology
Hebrew University-Hadassah Medical School
Personalized Medicine in Multiple Sclerosis and
Neuromyelitis Optica: Predicting Disease Outcome and
Treatment Responsiveness

Previous Winners 2013

PROF. ALEXANDER LOSSOS
Department of Neurology
Hebrew University-Hadassah Medical School
Diagnosis and Treatment of Adult Polyglucosan Body Disease

DR. HANNA ROSENMANN
Department of Neurology
Hebrew University-Hadassah Medical School
Alzheimer's Disease and Tauopathies - Improved Animal Models,
Pathogenesis, and Therapeutic Approaches

DR. SARA EYAL
Institute for Drug Research
School of Pharmacy
Imaging CNS Function in Health and Disease

DR. ADI INBAL
Department of Medical Neurobiology
Institute for Medical Research – Israel-Canada
Hebrew University-Hadassah Medical School
Molecular Mechanisms of Forebrain and Eye Development

Previous Winners 2012

DR. RONIT SHARON
Institute for Medical Research Israel-Canada
Hebrew University-Hadassah Medical School

PROF. RONEN LECKER
Department of Neurology
Hebrew University-Hadassah Medical School

DR. ALEXANDER M. BINSHTOK
Institute for Medical Research Israel-Canada
Hebrew University-Hadassah Medical School

PROF. HAIM OVADIA
Department of Neurology
Hebrew University-Hadassah Medical School

The Authority for Research and Development
The Hebrew University of Jerusalem

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THE PRUSINER-ABRAMSKY
RESEARCH AWARDS

IN CLINICAL AND BASIC NEUROSCIENCE

AT THE HEBREW UNIVERSITY OF JERUSALEM
BY THE ORION FOUNDATION

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תשע"ז   2017

THE HEBREW
UNIVERSITY
OF JERUSALEM

PRUSINER-ABRAMSKY

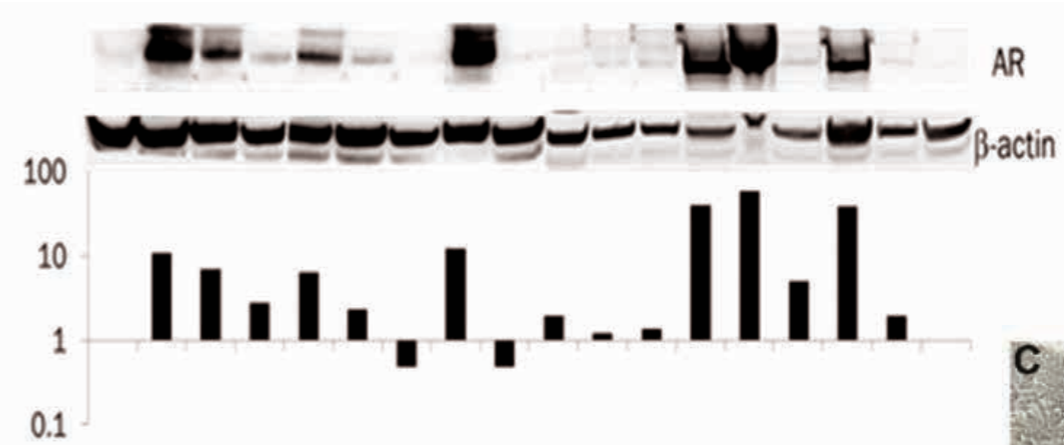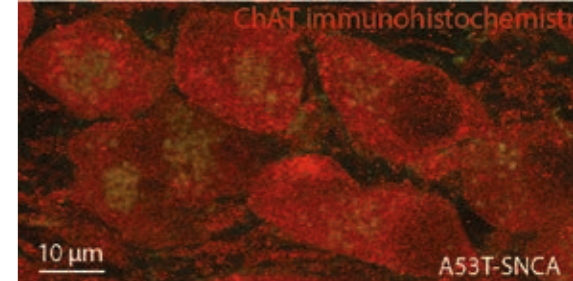## Research Awards - 2017

### Prof. Stanley B. Prusiner, M.D.

Stanley B. Prusiner, M.D., is Director of the Institute for Neurodegenerative Diseases and Professor of Neurology at the University of California, San Francisco (UCSF), where he has worked since 1972. Born in Des Moines, Iowa, in 1942, he spent his childhood there and in Cincinnati, Ohio. He received his undergraduate degree and medical training at the University of Pennsylvania and his postgraduate clinical training at UCSF. From 1969-72, he served in the U.S. Public Health Service at the National Institutes of Health. He is the author of over 500 research articles and the book Madness and Memory.

Prof. Prusiner is a member of the U.S. National Academy of Sciences, the Institute of Medicine, the American Academy of Arts and Sciences, the American Philosophical Society, and a foreign member of the Royal Society of London. He is the recipient of numerous prizes, including the Potamkin Prize for Alzheimer's Disease Research of the American Academy of Neurology (1991); the Richard Lounsbery Award for Extraordinary Scientific Research in Biology and Medicine from the National Academy of Sciences (1993); the Gairdner Foundation International Award (1993); the Albert Lasker Award for Basic Medical Research (1994); the Paul Ehrlich Prize from the Federal Republic of Germany (1995); the Wolf Prize in Medicine from the State of Israel (1996); the Keio International Award for Medical Science (1996); the Louisa Gross Horwitz Prize from Columbia University (1997); the Nobel Prize in Physiology or Medicine (1997); and the U.S. National Medal of Science (2009).

Prof. Prusiner's groundbreaking research on prion diseases, beginning in the late 1970s, led him to propose an explanation for the cause of bovine spongiform encephalopathy ("mad cow" disease) and its human equivalent, Creutzfeldt-Jakob disease, for which he was awarded the Nobel Prize. In this work, he coined the term prion (derived from "proteinaceous" and "infectious") to refer to a previously undescribed form of infection caused by the self-propagation of alternatively folded proteins.

His research has elucidated a fundamental understanding of the proteins underlying such illnesses as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) and PrP prion diseases. These advances in understanding the molecular, genetic and cellular basis of neurodegenerative diseases have fueled progress toward the development of targeted drug therapies.
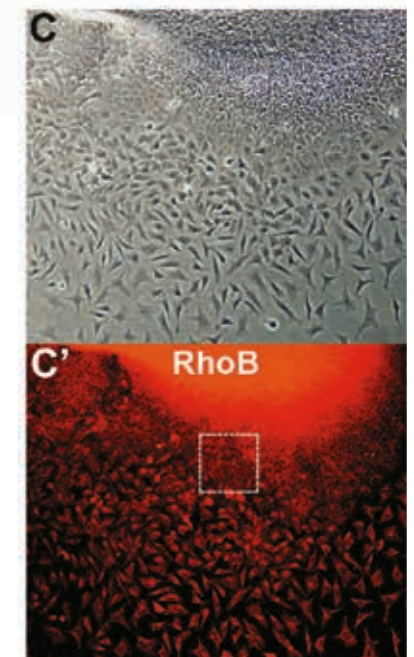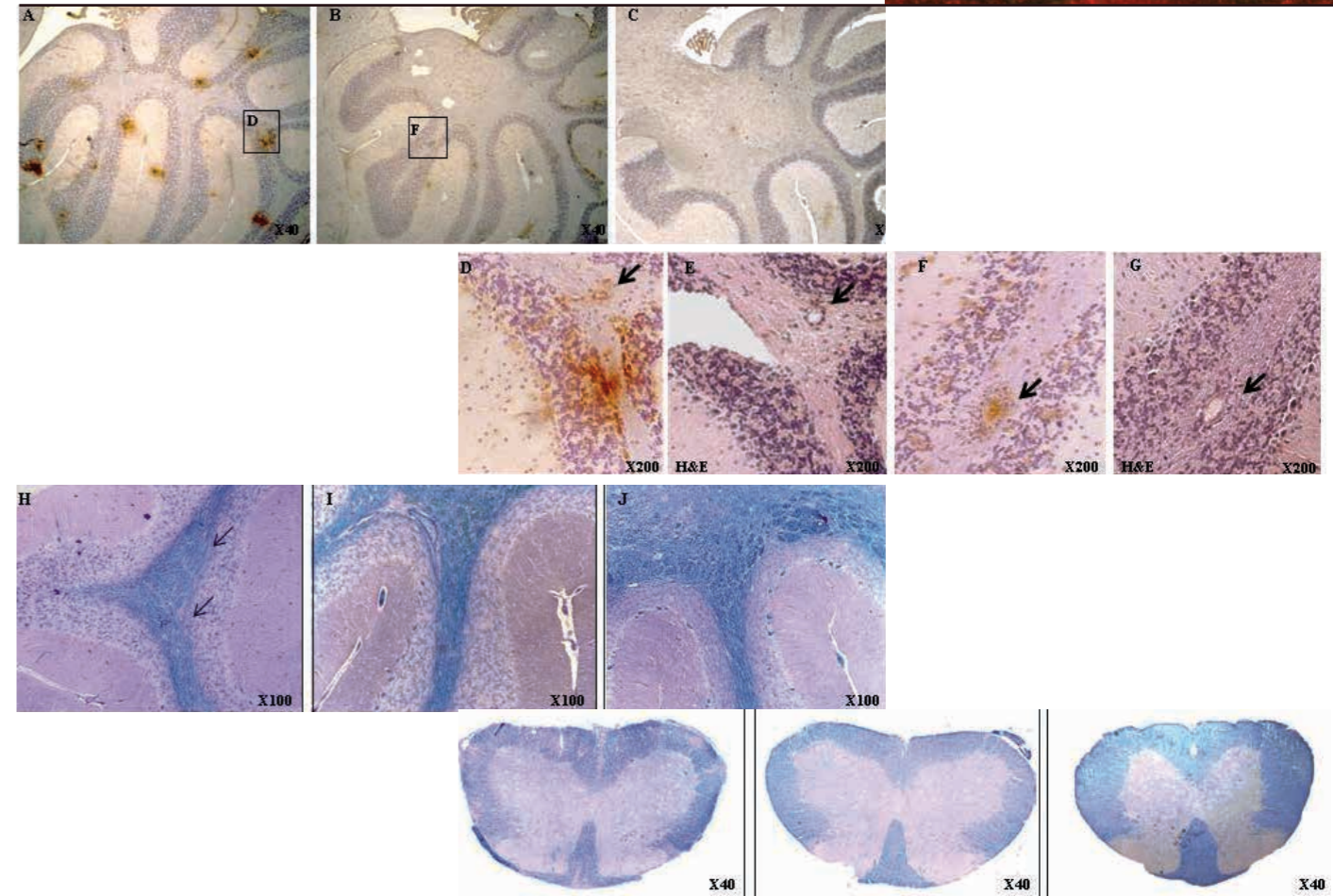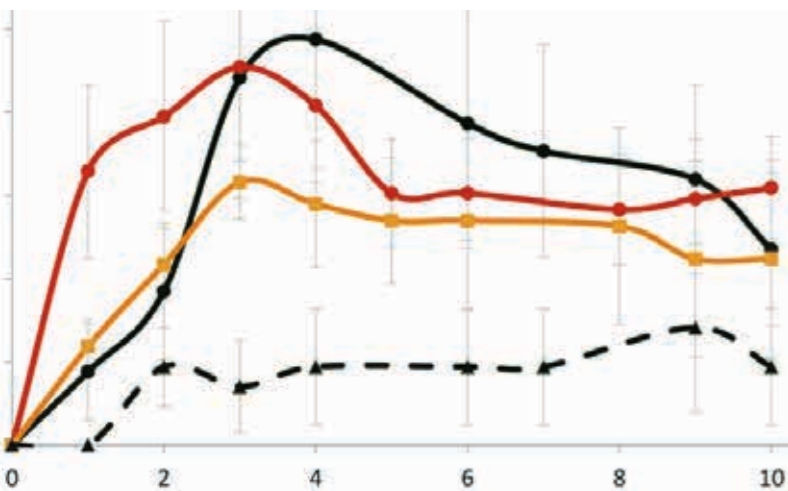
PRUSINER-ABRAMSKY

## Prof. Oded Abramsky, M.D., Ph.D.

Oded Abramsky was born in Jerusalem and received his M.D. and Ph.D. degrees from The Hebrew University of Jerusalem. He completed his residency in neurology at Hadassah University Hospital, where he was later appointed Head of the Neuroimmunology Unit (1982) and Chairman of the Neurology Department (1988-2005). He was appointed Professor of Neurology at Hebrew University-Hadassah Medical School in 1982, holding the Israel S. Wechsler Chair in Neurology. He served as Dean of the Faculty of Medicine of The Hebrew University (1992-96) and subsequently was appointed Chairman of the Agnes Ginges Center for Human Neurogenetics at Hadassah University Medical Center.

Prof. Abramsky has been actively involved in many aspects of medical research and holds prominent positions in numerous professional organizations concerned with both clinical practice and medical research. He was Chief Scientist of the Israel Ministry of Health (1987-1992), Chairman of the National Medical Research Organization, and served as Chairman of the Israel National Council for Research and Development. He is an Honorary President of the Israel Society of Neuroimmunology; Honorary Member of the American Neurological Association; Member of the Institute of Medicine, National Academy of Sciences (USA); Fellow by Distinction of the Royal College of Physicians (FRCP); and Member of the Israel Academy of Sciences and Humanities, among many other affiliations. In 2008, the Oded Abramsky Chair in Neuroimmunology was established in his honor by Biogen USA at the Hadassah University Medical Center.

Prof. Abramsky's clinical and scientific research focuses on autoimmune neurological diseases. He was a pioneer in the field of neuroimmunology and demonstrated immune pathogenesis in various neurological diseases of the central and peripheral nervous systems and muscle. Indeed, he proved that myasthenia gravis (MG) is an autoimmune disease, and showed the beneficial effect of corticosteroids and chemotherapy on induced experimental MG. His research served as a guideline to successful immunotherapy of MG and many other autoimmune diseases.
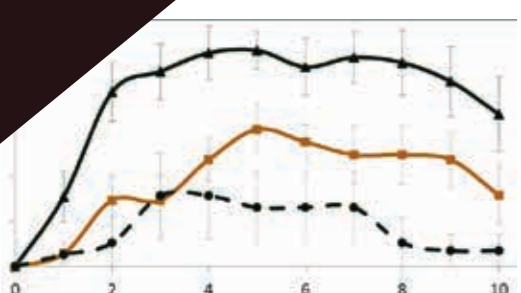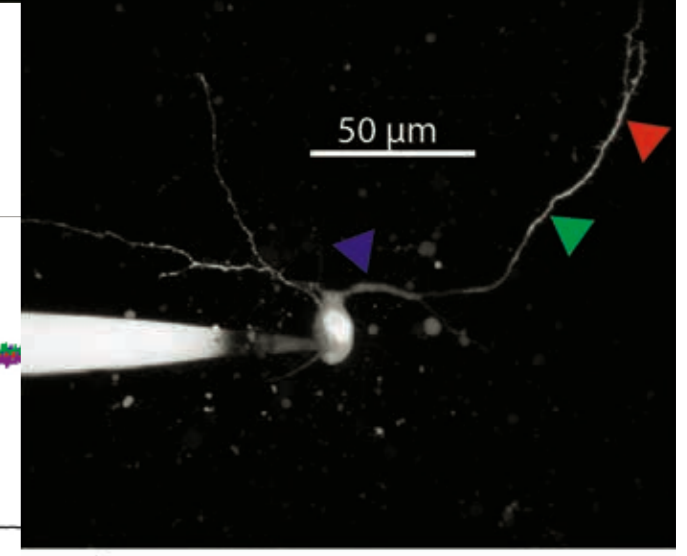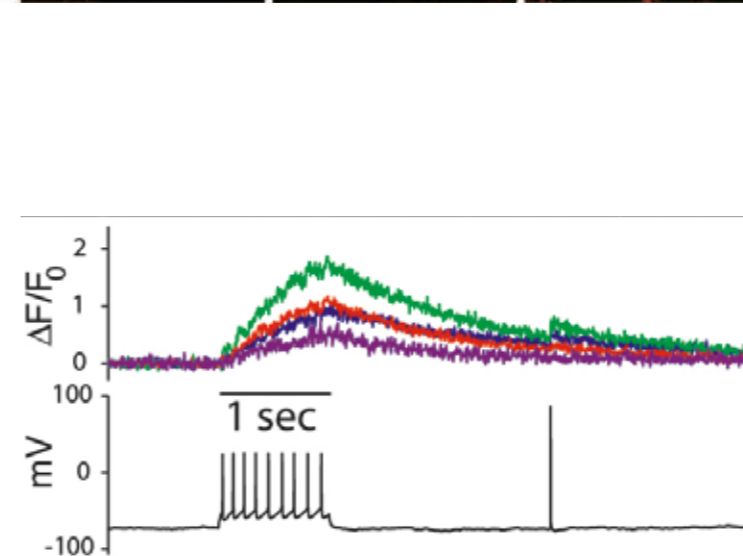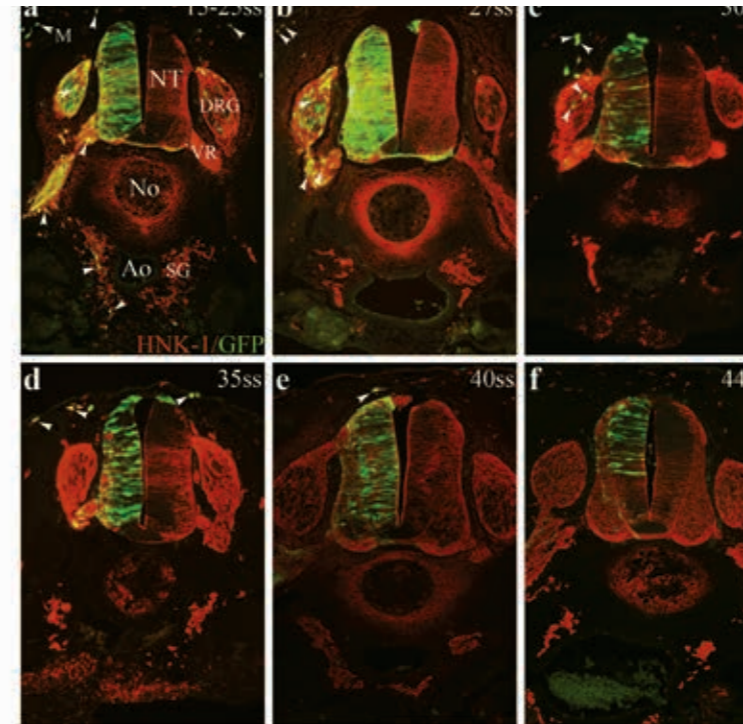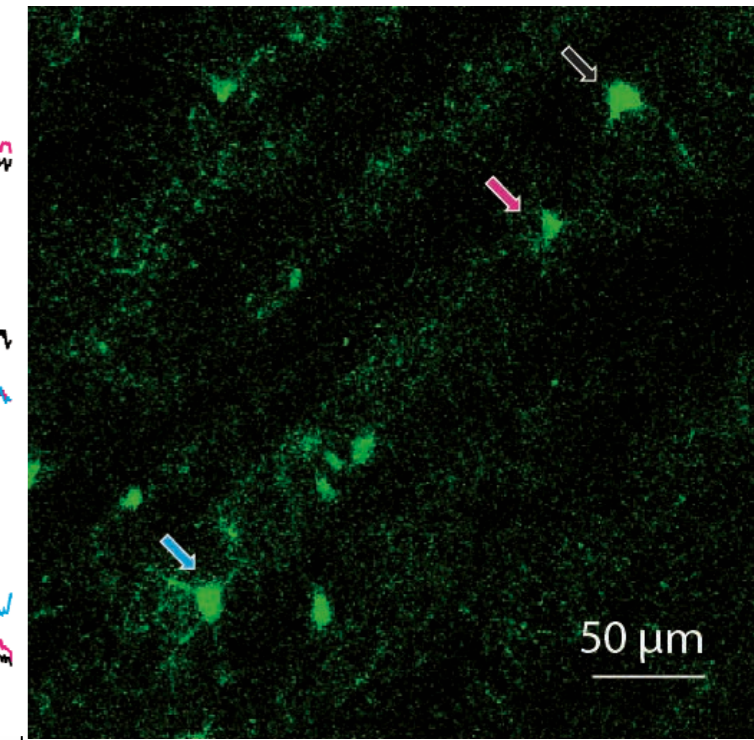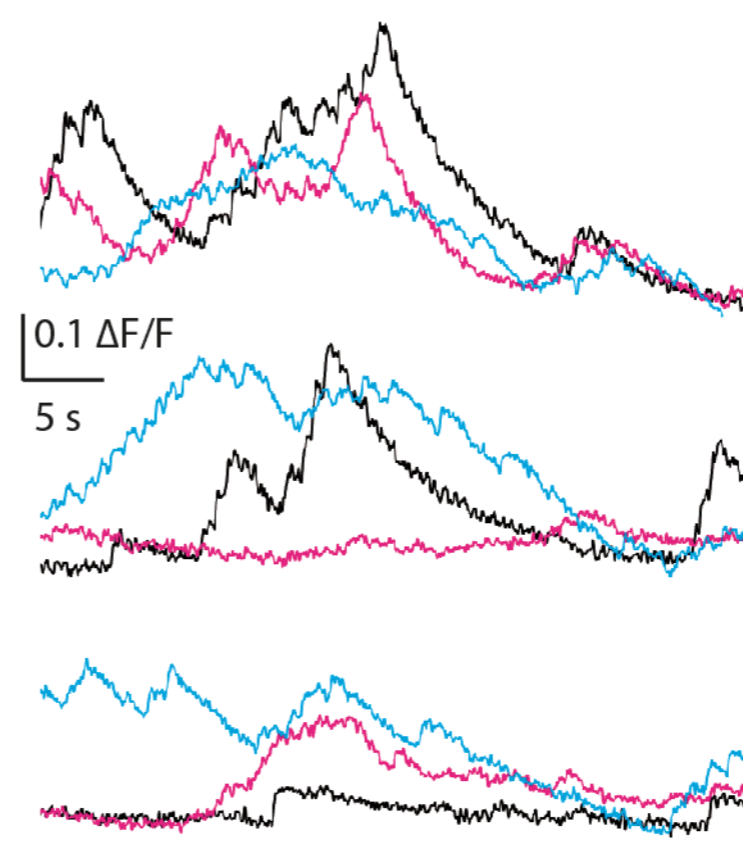
PRUSINER-ABRAMSKY

Research Awards - 2017

The prestigious **Prusiner-Abramsky Research Awards in Clinical and Basic Neuroscience by The Orion Foundation** honor Professors Stanley Prusiner and Oded Abramsky. Prof. Prusiner of the University of California at San Francisco is a Nobel Prize Laureate in Medicine (1997) and an Honorary Doctor of the Hebrew University of Jerusalem.

Prof. Abramsky is the former Chairman of the Neurology Department and a former Dean of the Faculty of Medicine at Hebrew University.

The awards are intended for outstanding researchers from all fields of basic clinical neurosciences at the Hebrew University and the Hadassah University Medical Center.
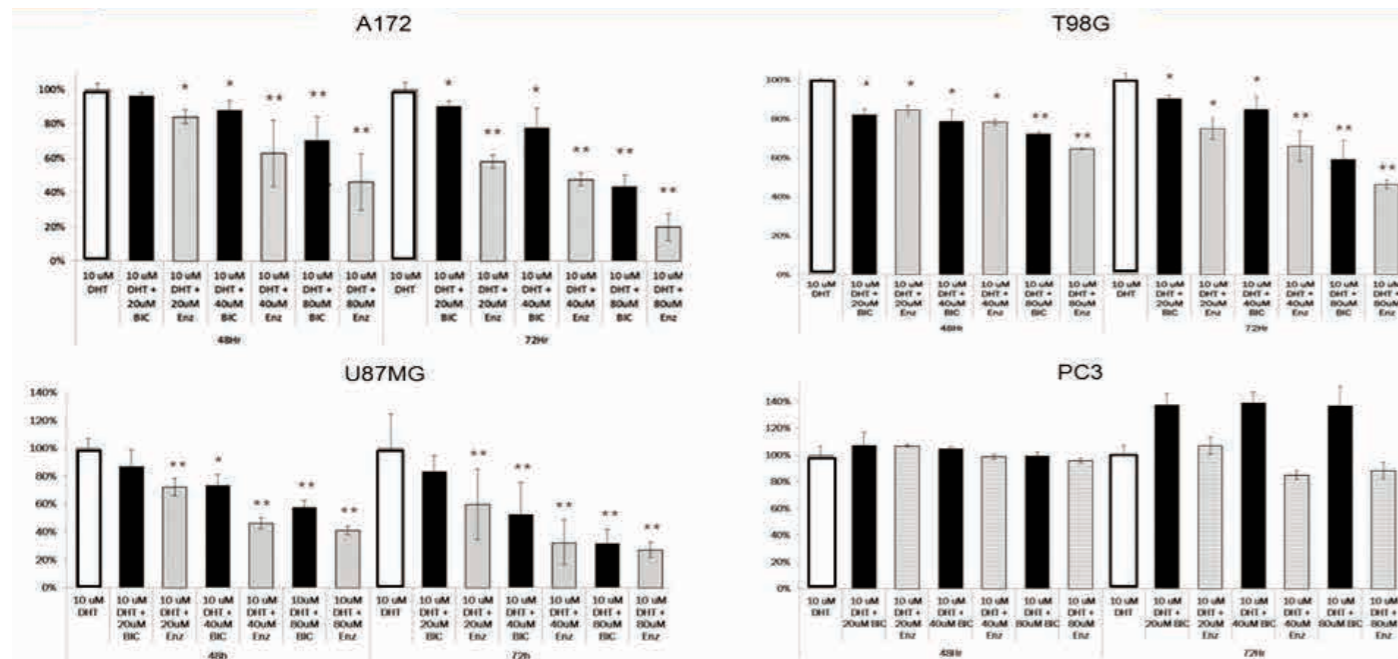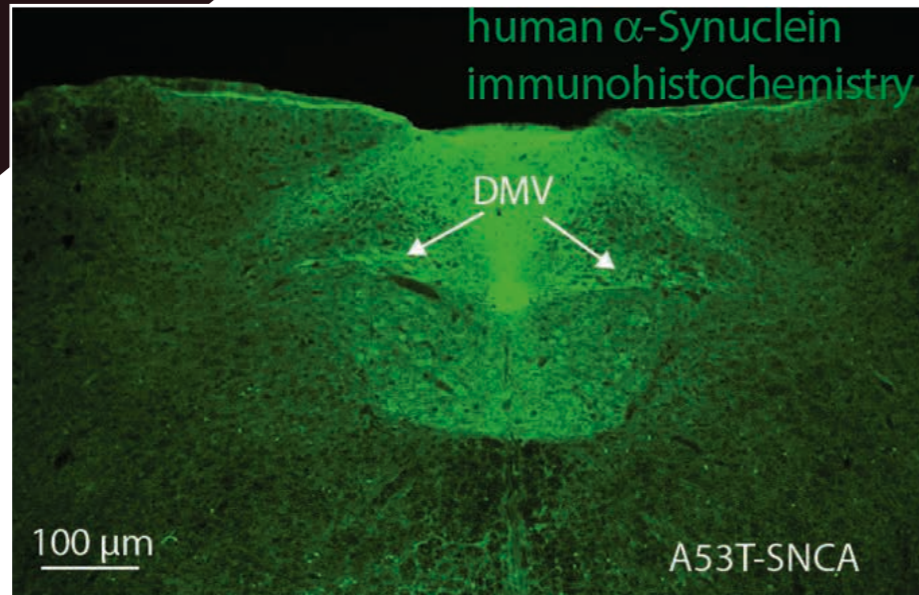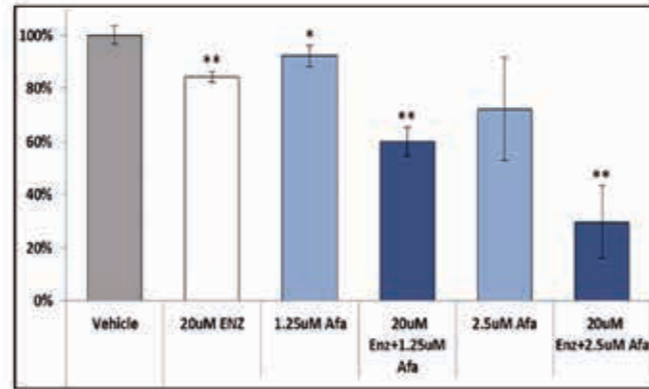
human α-Synuclein immunohistochemistry

DMV

100 μm

A53T-SNCA

A172

T98G

U87MG

PC3

PROF. CHAYA KALCHEIM

Department of Medical Neurobiology
Institute for Medical Research Israel-Canada
Hebrew University-Hadassah Medical School

Embryonic Development of the Nervous System: The Transition between Peripheral and Central Branches

DR. JOSHUA GOLDBERG

Department of Medical Neurobiology
Institute for Medical Research Israel-Canada
Hebrew University-Hadassah Medical School

Physiological Underpinnings of Neurodegeneration and Neuronal Adaptations in Movement Disorders

DR. PANAYIOTA PETROU

Department of Neurology
Hebrew University-Hadassah Medical School

Testing the Effect of Pomegranate Seed Oil (Grana Gard) on the Clinical Symptoms and the Quality of Life in Patients with Multiple Sclerosis and Alzheimer's Disease

DR. IRIS LAVON BEN MOSHE

Department of Neurology
Hebrew University-Hadassah Medical School

Clarifying Molecular Mechanisms that could Aid in the Development of New Treatment and Diagnostic Strategies in Brain Tumors and Neurodegenerative Diseases

RESEARCHERS

PROF. CHAYA KALCHEIM

Department of Medical Neurobiology
Institute for Medical Research Israel-Canada
Hebrew University-Hadassah Medical School

Prof. Kalcheim earned her Ph.D. at the Weizmann Institute studying the formation of the neuromuscular synapse. In 1984, she began her post-doctoral training in developmental neurobiology in the Institut d'Embryologie Cellulaire et Moleculaire of the French National Center for Scientific Research (CNRS). She joined The Hebrew University's Faculty of Medicine in 1987 and has been a full professor since 2001. Her goal is to understand the logic that underlies the embryonic development of the nervous and muscular systems and the interactions between them. Prof. Kalcheim has published over 100 papers including "The Neural Crest", a book written with Prof. Le Douarin that became a classic in the field. She has been awarded numerous prizes including the Bernard Katz Prize from the University of Heidelberg.

Embryonic Development of the Nervous System: The Transition between Peripheral and Central Branches
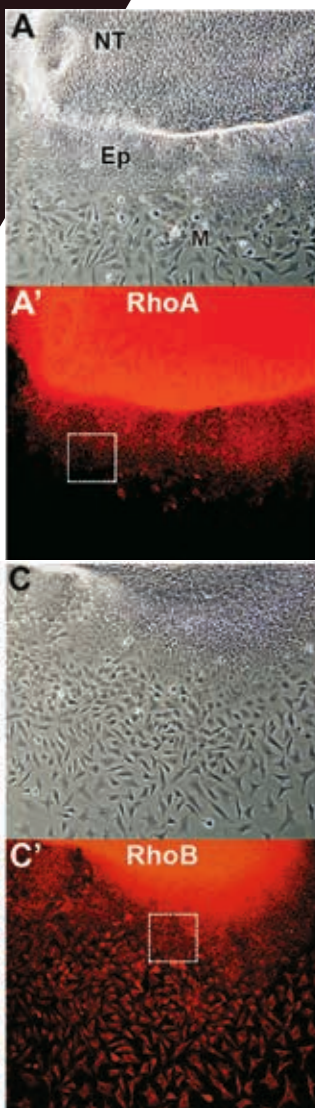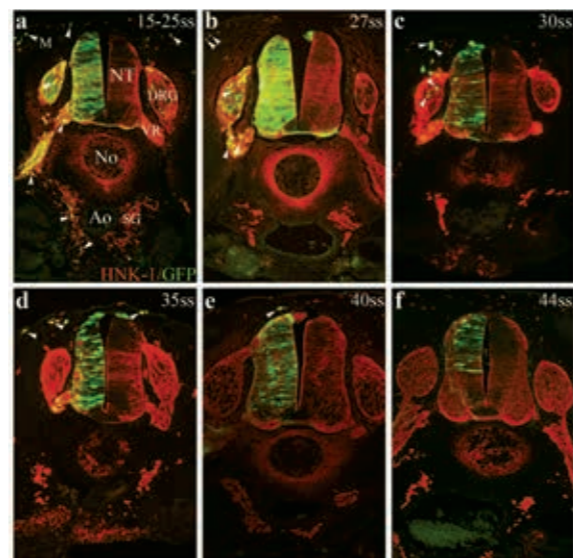
The adult nervous system arises during embryonic development from a sheet of epithelial cells and then closes to form a tube. This tube generates the brain, spinal cord and neural crest cells, progenitors of the peripheral nervous system. The latter leave the neural tube to localize throughout the body and provide, among other derivatives, all components of sensory and autonomic ganglia (sympathetic, parasympathetic and enteric). Researching this unique embryonic population has revealed important insights into basic biological and developmental principles that govern the emergence of complexity in one of the most amazing body systems. These principles are likely to assist in clarifying the etiology and in finding strategies for the treatment of neural crest diseases, collectively termed neurocristopathies.

The Kalcheim laboratory aims at elucidating basic processes that take place during development of neural crest and neural tube progenitors. Additionally, since neural and skeletal cells closely interact to correctly pattern the body plan, understanding the molecular nature of skeletal muscle development and the cross talk with neural components is a central tenet.

Over the years, the Kalcheim team has significantly contributed to several aspects of neuro-mesodermal development that include:

1. The establishment of a molecular network responsible for the generation of cellular migrations of neural crest cells, which is required for their proper homing at peripheral sites and is thus a hallmark of their behavior.

2. The mechanisms underlying the formation of a segmentally organized peripheral nervous system.

3. Neurotrophin-dependent mechanisms of differentiation of sensory neurons.

4. Lineage analysis and molecular requirement for the development of the neural crest-derived sympathoadrenal lineage.

5. Defining the emergence of cell restrictions during neural crest development and attaining initial insights into the molecular mechanisms.

6. The mechanism leading to the end of neural crest production and the transition into the definitive roof plate of the spinal cord.

7. Cellular and molecular networks of early myogenesis comprising the mode of progenitor cell migration, regional derivation of diverse cell types (skeletal versus smooth muscle, endothelium, dermis) and how they segregate from a common founder cell.

8. How skeletal (muscle) and neural (motoneuron) components coordinately develop via shared signaling of the morphogen sonic hedgehog.

DR. JOSHUA GOLDBERG

Department of Medical Neurobiology
Institute for Medical Research Israel-Canada
Hebrew University-Hadassah Medical School

Dr. Goldberg received his B.Sc. in physics and his Ph.D. in computational and systems neuroscience from the Hebrew University of Jerusalem. He did his postdoctoral training in cellular neurophysiology at The University of Texas at San Antonio. He was a research assistant professor at Northwestern University before joining the faculty of The Hebrew University in 2013. Prior to his appointment, Dr. Goldberg held research positions in the Israeli medical device industry. Dr. Goldberg works on mouse models of Parkinson's disease and other movement disorders. His work focuses on the physiological mechanisms underlying neurodegeneration; and the ensuing pathophysiological brain adaptations that occur in these disorders.

# Physiological Underpinnings of Neurodegeneration and Neuronal Adaptations in Movement Disorders

Our research focuses on two central questions pertaining to the pathophysiology of movement disorders:

a) What physiological processes predispose particular neurons to degenerate in various movement disorder such as Parkinson's disease (PD) and Huntington's disease (HD);

b) What adaptations (or maladaptations) occur in neuronal networks—particularly in the basal ganglia—in response to neurodegeneration in these diseases.

We have recently discovered that certain brainstem neurons launch a successful adaptive response to a key PD stressor (alpha-synuclein), widely believed to hasten the demise of midbrain dopamine cells, and thereby causing the symptoms of PD. This finding may explain why these brainstem neurons outlive dopamine cells despite contracting the stressor earlier in life, and may give rise to future therapies aimed at emulating the brainstem's adaptive response.

In other laboratory projects, we study the cholinergic neurons that are implicated in the famous "dopamine-acetylcholine imbalance" of PD and HD. Using a combination of cutting-edge techniques including: i) slice physiology in conjunction with optogenetics and two-photon laser scanning microscopy; and ii) endoscopic brain imaging with miniaturized microscopes of the activity of neuronal assemblies in freely moving mice, we are discovering that these neurons (both individually and in concert) adapt their biophysical properties and wiring to compensate for the network degradation that both these diseases cause. I believe our work re-establishes these neurons as important therapeutic targets —alongside dopamine cells—in battling these debilitating disorders.
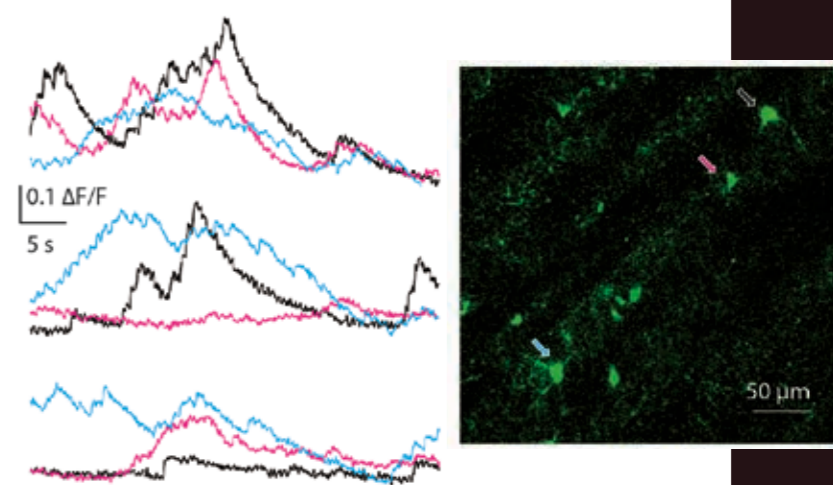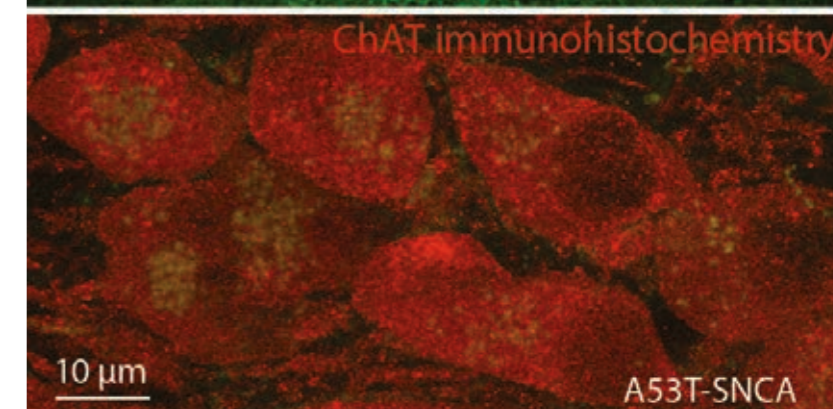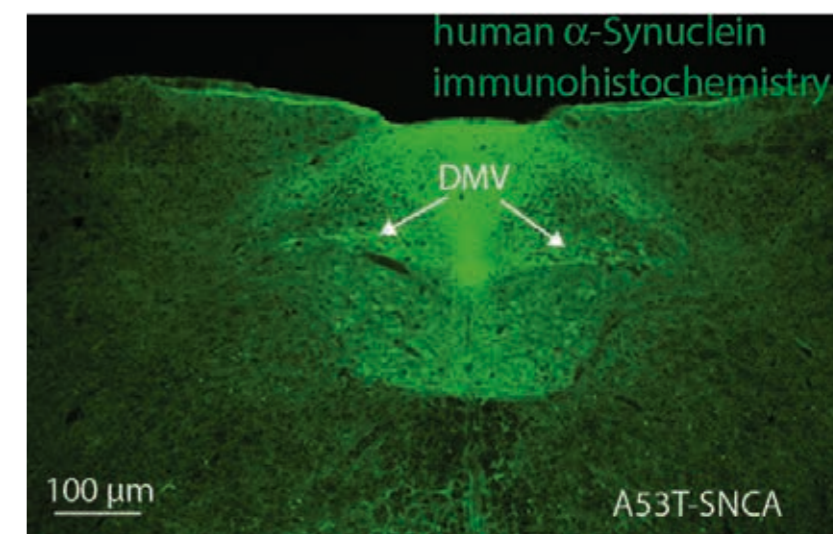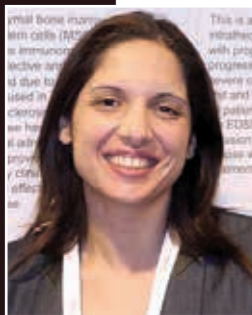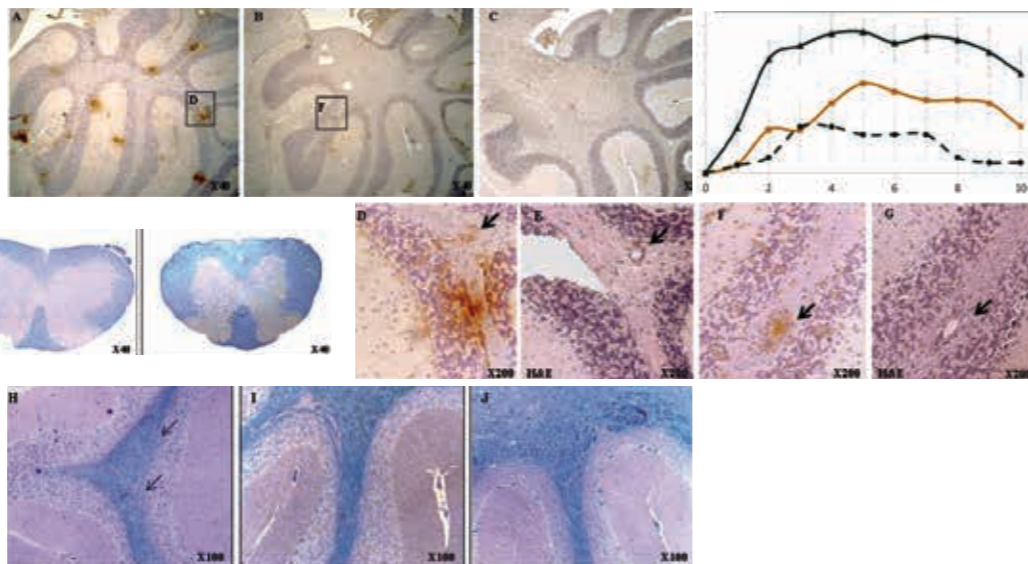
DR. PANAYIOTA PETROU

Department of Neurology
Hebrew University-Hadassah Medical School

Dr Petrou Panayiota was born in Cyprus in 1978. She graduated from medical school of Aristotelion University of Thessaloniki in 2002. Dr Petrou moved to Jerusalem in 2007. She completed her neurology specialization at Hadassah Medical School in 2011. Since then she has been working at Hadassah's Multiple Sclerosis Center as a senior neurologist. Currently, she is coordinating the clinical trials with stem cells in MS and ALS where she has gained unique expertise in stem cell therapies and neuroimmunology.


Testing the Effect of Pomegranate Seed Oil (Grana Gard) on the Clinical Symptoms and the Quality of Life in Patients with Multiple Sclerosis and Alzheimer's Disease

Background:
Injury due to oxidative stress is a common pathological feature in neurological degenerative diseases like Alzheimer's disease (AD). Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system associated with inflammation and neuro-degeneration that exhibits also significant oxidative damage.

Pomegranate seed oil (PSO) comprises Punicic Acid (PA), a poly-saturated fatty acid, which is considered one of the strongest antioxidants in nature. To increase its bioavailability and activity, PSO was prepared in oil-in-water nano-emulsions. This approach allows the distribution to organs and especially reaches and passes the blood brain barrier.

In previous studies, PSO was administered to mice afflicted with the animal model of MS. The treatment reduced demyelination and oxidation of lipids in the brains of the animals and improved their clinical disease course.

Rationale of the study:
Multiple sclerosis treatments successfully reduce the systemic inflammatory component but fail to affect the degenerative component of the disease. Likewise, there is no treatment that can effectively slow down the progression of Alzheimer's disease. The aim of our study is to examine the effect of PSO in MS patients and the effects on the clinical course of AD patients.

Design of the study:
MS group: Thirty patients with confirmed diagnosis of progressive MS will be included and will examine the effect of PSO on the clinical course of the disease. Follow up with quality-of-life scores, 25-feet walk, and cognitive functions.

AD group: Thirty patients with mild cognitive impairment (MCI) will be included. In this case we will examine the effect of PSO on the time to progression into clinical definite AD. Patients will be separated into two subgroups. The first group will receive the treatment upon recruitment into the study and the second group will start the treatment six months later, allowing us to determine whether PSO may delay the progression of disease from MCI to AD. All patients will be followed up with quality-of-life scores and mini-mental tests.

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DR. IRIS LAVON BEN MOSHE

Department of Neurology
Hebrew University-Hadassah Medical School

Dr. Iris Lavon Ben Moshe completed her doctoral studies in cancer immunology and molecular biology at The Hebrew University in the laboratory of Prof. Yinon Ben-Neriah. Currently, she is head of the Molecular Neuro-Oncology Laboratory in the Department of Neurology at Hebrew University-Hadassah Medical Center. Her main research interest is individualizing therapy for patients with brain tumors and neurodegenerative diseases by clarification of molecular mechanisms that could aid in the development of effective treatments and diagnostic strategies. Some of the laboratory discoveries have been patented and were shown to have clinical application in the development of new diagnostic and therapeutic approaches for the management of patients with brain tumors and neurodegenerative diseases.
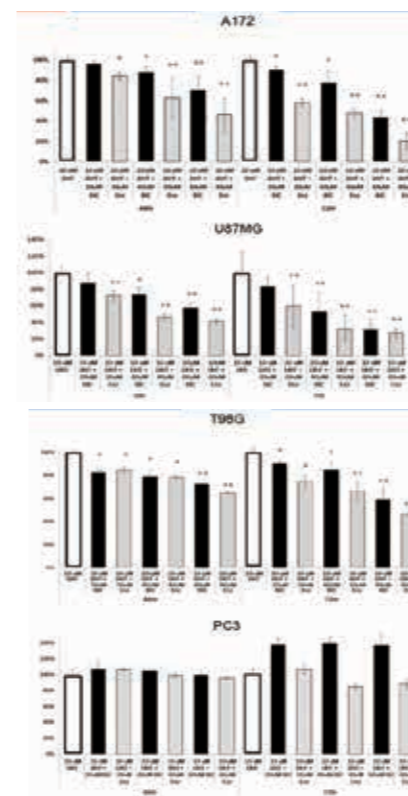
Clarifying Molecular Mechanisms that could Aid in the Development of New Treatment and Diagnostic Strategies in Brain Tumors and Neurodegenerative Diseases

Glioblastoma multiforme (GBM) is an extremely aggressive brain tumor. Despite extensive efforts made so far, the median survival time is still very poor (14.6 months), in part due to a lack of good therapeutic options. Although under the microscope all glioblastomas look similar and are currently treated—at least at the initial treatment stage—with the same treatment regimen, the genetic characteristic of these tumors can vary considerably. Thus, the identification of new molecular therapeutic targets remains an unmet need.

To address this need we performed a genome-wide array on DNA extracted from GBM samples obtained from five women and found that androgen receptors (AR) were amplified in four of the five samples. Further analysis on more samples from patients of both sexes revealed that the majority of GBMs exhibit relatively high levels of AR RNA and protein. This finding was very surprising, since AR is a nuclear receptor activated by binding to the androgenic hormones and primarily responsible for the development of male sexual characteristics.

However, based on its involvement in prostate cancer amenable to treatment with AR antagonists, such as enzalutamide and bicalutamide, we tested three glioma cell lines with these agents in vitro. This treatment yielded dose-dependent cell cytotoxicity in all cell lines, with enzalutamide demonstrating a better efficacy than bicalutamide.

Furthermore, we found that 30% of GBM samples express an AR variant that does not respond to its normal ligand and is involved in induction of AR via other signal transduction, such as the epithelial growth factor receptor (EGFR) pathway. Combination therapy with anti-AR agent carrying an EGFR inhibitor in cell lines bearing such an AR splice variant yielded better efficacy than an AR-antagonist alone.

With the objective of transferring these promising in vitro results into the clinic, we propose testing the efficacy of the AR antagonist enzalutamide and of a combination therapy with an EGFR inhibitor afatinib in a xenograft mouse model of human glioblastoma. Together with our ongoing laboratory efforts, we hope that this study will lead to a new approach for the treatment of human GBM.