BIOGRAPHICAL SKETCH

NAME Itzhak MANO	POSITION TITLE Assistant Medical Professor
eRA COMMONS USER NAME: ITZHAKMANO	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as*

INSTITUTION AND LOCATION (Mentor/Project Supervisor)	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Hebrew Univ. Jerusalem, Israel (R. Sperling)	B. Sc.	1984-1987	Molecular Biology
Weizmann Inst Sci, Rehovot, Israel (V Teichberg)	M.Sc.	1988-1991	Molecular Neurobiology
Weizmann Inst Sci, Rehovot, Israel (V Teichberg)	Ph.D.	1991-1996	Molecular Neurobiology
Mol Bio & Biochem, Rutgers U, NJ (M. Driscoll)	(Post Doc)	1997-1999	Genetics, Neuroscience

A. Personal Statement

I study signaling physiology and the molecular events that lead to neurodegeneration in Excitotoxicity, a neurodegenerative condition seen in many diseases and in brain ischemia/stroke. Stroke is a leading cause of death in the US and minority populations are especially at high risk. Glutamate, the main excitatory neuro-transmitter in the brain, causes neuronal damage in brain ischemia because it accumulates to excessive levels in the synapses and over excites neurons. We combine the powerful research tools of *C. elegans* genetics and state-of-the-art approaches in neuronal imaging and molecular genomics to study normal glutamate physiology and processes of cell death, both being signaling cascades that are highly conserved in evolution.

As an undergrad in the Hebrew university in Jerusalem I specialized in transcriptional regulation in HIV and in splicing mechanisms. I did my MSc & PhD at the Weizmann Institute in molecular neuroscience with Dr. Vivian I Teichberg (deceased). I cloned the cDNA encoding one of the first members of the glutamate receptor/channel family (chKBP), and used site-directed mutagenesis and electrophysiology in *Xenopus* oocytes to study structure-function relations in mammalian AMPA receptors. I studied the relationship between ligand binding and receptor activation and desensitization, and was the first to find that GluRs are tetramers. I brought my interest in glutamate signaling to my postdoctoral training with Dr. Monica Driscoll at Rutgers University, a lab that leads the field in using *C. elegans* to study neuronal necrosis. In the Driscoll lab I characterized the glutamate transporters in *C. elegans*, created a model for nematode excitotoxicity, and studied the initial steps in neurodegeneration. I collaborated with Dr. R. Kalb from UPenn and found that cellular aging increases the susceptibility of neurons to excitotoxicity in both nematodes and mammals.

After considerable logistical difficulties, my lab in CCNY is now fully productive (we had no lab space for two years, and fragmented partial spaces for 2.5 years. We got our renovated lab in Apr 2013, and moved to a state of the art facility with a neuro-cluster open space floor in Apr 2015). We use the nematode model to follow two lines of research on the normal and pathological roles of glutamate transporters. One line of research addresses normal physiology of glutamate clearance and focuses on the ability of glutamate transporters outside the immediate vicinity of the synapse to control synaptic function, prevent spillover and excitotoxicity. We use the ability to image neuronal activity in intact animals to study how diverse properties and location of different transporters come together to keep circuitry precision and prevent toxicity. The other line of research addresses the biochemical pathways that lead from synaptic accumulation of excess glutamate to cell death of the postsynaptic neuron by excitotoxicity. We study candidate processes and molecular switches (e.g. DAPK) that determine the choice of neurodegenerative process. We study how CREB/CRH-1 and Foxo3a/DAF-16 control transcriptional neuroprotective programs. Finally we perform an unbiased genetic screen to search for new regulators of excitotoxicity. Together, we rely on the special tools of *C. elegans* studies to help us identify key processes in normal physiology and cell death cascades that are conserved in higher animals. We therefore hope that new insights gained in this system might help us focus attention on similar processes in in higher animals.

We promote CCNY's values of inclusion & promotion of under-represented and disadvantaged communities. In addition to other undergrads, URM undergrads lab alumni now attend superb medical schools (Yale, NYU, Mount Sinai), Biology PhD programs (Cornell, Rutgers), and MA program (U Buffalo).

B. Positions and Honors

Positions

1997-1999 Post Doctoral fellow, laboratory of Dr. Monica Driscoll, Mol Bio & Biochem, Rutgers U.
2000-2008 Research Associate, Dept. Molecular Biology & Biochemistry, Rutgers University, NJ
2007-2008 Adjunct Assistant Professor, Dept. of Biology, Rider University, NJ.
2008-present Assistant Medical Professor, Sophie Davis Biomed. School, City College, CUNY, NY.

Honors & Awards

1985-1987 Full tuition merit award & Dean's list, Hebrew University, Jerusalem, Israel.
1991-1996 The Erwin and Claire Weiner Scholarship for Ph.D. studies, Rehovot, Israel.
1997-1999 Human Frontier Science Program Fellow, France.
2010-2013 Sinsheimer Scholar, The Alexandrine and Alexander L. Sinsheimer Fund.

2009 Chair, Cell Death & Neurodegeneration, the 17th International *C. elegans* Meeting, UCLA, Los Angeles, CA.
2012-present Co-Chair, The New York regional Worm Meeting (PA to CT), now hosting @CCNY.

Other Experience

Professional Memberships

2008-present Society for Neuroscience
2008-present American Physiological Society
2008-present Genetic Society of America
2010-present New York Academy of Science

Journal Editorial Board

2016-present Frontiers Neuroscience

Grant Review Panels

2015 Israel Science Foundation
2014 The German - Israeli Foundation for Scientific Research and Development
2013 NSF BIO IOS - Neuronal System Cluster grants, Ad Hoc reviewer
2013 The Mack Lipkin Broader Horizons Fellowship Program
2012 NSF BIO IOS - Processes Structure and Integrity Cluster grants, Ad Hoc reviewer.
2011 NSF BIO IOS - Neuronal System Cluster grants, Ad Hoc reviewer
2011-2012 CCNY white paper competition for NIH SCORE submission
2010 CCNY President's Collaborative Grants
2000 Israel Science Foundation Long-Term Grants

University Internal Appointments

2015-present CUNY Medical School new curriculum – Pharmacology coordinator.
2013-2014 CCNY new neuroscience PhD program setup committee, new MolBiol PhD program.
2012-present Sophie Davis Medical Curriculum Reform/ Clinical Skills Curriculum subcommittee.
2012 CCNY Dept of Biology: Faculty Search Committee (Molecular Neuroscientist opening)
2011-2012 Sophie Davis Biomed School Strategic Planning Team – Student Experience.
2011-2012 Member, The Graduate Council (the governing body of The CUNY Graduate School).
2010-2012 Executive committee, PhD program in Neurobiology, CUNY Graduate Center.
2010-2012 Medical School Admission Committee, Sophie Davis Biomed School, CCNY, CUNY.
2010-2012 Graduate Students Coordinator, Physio Pharm & Neuro, Sophie Davis Biomed School.

C. Contribution to Science

Full PubMed/NCBI Bibliography List: www.ncbi.nlm.nih.gov/myncbi/browse/collection/47403013

***I*) Cloning and Structure-Function Analysis of Glutamate Receptors (GluRs):** In the lab of V. Teichberg (Weizmann) I was fortunate enough to clone and sequence one of the first members of the ionotropic GluR family, ChKBP. I then provided one of the first examples of structural communication between the GluR ligand binding site and channel to desensitization. I was then the first to determine that contrary to the then-held dogma, GluRs are tetramers, and are therefore very different from nAChR-like channels.

1) Gregor, P., Mano, I., Maoz, I., McKeown, M. & Teichberg, V.I.(1989). Molecular structure of the chick cerebellar kainate-binding subunit of a putative glutamate receptor. *Nature* 342, 689-692. http://www.nature.com/nature/journal/v342/n6250/abs/342689a0.html PMID: 2480525
2) Gregor, P., Yang, X., Mano, I., Takemura, M., Teichberg, V. I. and Uhl, G. R. (1992). Organization and expression of the gene encoding chick kainate binding protein, a member of the glutamate receptor family. *Mol. Brain Res.* 16, 179-186. PMID: 1337927
3) Mano, I., Lamed, Y. and Teichberg, V.I., (1996). A Venus flytrap mechanism for activation and desensitization of AMPA receptors. *J. Biol. Chem.* 271: 15299-15302. http://www.jbc.org/cgi/content/full/271/26/15299 PMID: 8663365
4) Mano, I. and Teichberg, V.I., (1998). A tetrameric subunit stoichiometry for a glutamate receptor/channel complex. *NeuroReport* 9: 327-331 . PMID: 9507977 http://www.ncbi.nlm.nih.gov/pubmed/?term=9507977

***II*) Structure-Function Analysis of Mechanosensory Channels in *C. elegans*:** Joining the Driscoll lab (Rutgers) I first collaborated on the analysis of structure-function relations in MEC-4, a mechanosensory channel.

1) Mano, I. and Driscoll, M. (1999). The DEG/ENaC Channels: A touchy superfamily that watches its salt. BioEssays 21 (7): 568-578. http://www3.interscience.wiley.com/journal/62004632/abstract PMID: 10472184
2) Thieringer, H., Sahota, S., Mano, I. and Driscoll, M. (1999). *C. elegans* degenerin channels: form and function. Curr. Top. Membr. 47: 297-314 .
3) Hong, K. Mano, I. and Driscoll, M. (2000). In-vivo structure/function analysis of *C. elegans* candidate mechanotransducing ion channel subunit MEC-4. *J. Neurosci.* 20: 2575-2588. http://www.jneurosci.org/cgi/content/full/20/7/2575 PMID: 10729338

***III*) Identification of Glutamate Transporters and Novel Clearance Strategies in *C. elegans*.** Turning to my independent project in the Driscoll lab, I was the first to provide a complete picture of Glutamate Transporters (GluTs) in the nematode. Surprisingly I found that some of the most important GluTs in the nematode are expressed away from the major synapses they regulate. Now in my own lab at CCNY we are expanding on this theme, and use optogenetics and microfluidics to describe novel strategies in Glu clearance and circuit isolation in the absence of synaptic separation (Manuscript under review in *Frontiers Neural Circuits*).

1) Mano, I., Straud, S., and Driscoll, M. (2007). *C. elegans* glutamate transporters influence synaptic function and behavior at sites distant from the synapse. *J Biol Chem* 282: 34412-34419. http://www.jbc.org/cgi/content/full/282/47/34412 PMID: 17681948

***IV*) Establishment of a Model of Excitotoxicity in *C. elegans* and Characterization of Cell Death Mechanisms.** While in the Driscoll lab I established the first (and so far only) model of excitotoxic necrosis in an invertebrate genetic model system. By combining a sensitive background and GluT KO I was able to trigger neuronal necrosis that depends on iGluRs. In my own lab at CCNY we were then able to show that excitotoxicity is mediated by an evolutionary conserved mechanism where DAPK has a central role. Sifting among many proposed downstream effects, we found that a popular suggested mechanism of DAPK's action is not conserved, while another mechanism, which depends on Pin1, is important in excitotoxicity in both nematodes and mammals.

1) Mano, I., and Driscoll, M., (2009) *C. elegans* Glutamate Transporter Deletion Induces AMPA-Receptor/Adenylyl Cyclase 9-Dependent Excitotoxicity. *J. Neurochem.* 108:1373-1384. http://www3.interscience.wiley.com/journal/121541103/abstractUUTT PMID: 19054279
2) Del Rosario, J., Feldman, K.G., Ahmed, T., Amjad, U., An, JH, Mahmud, T., & **Mano, I**. (2015). Death Associated Protein Kinase (DAPk) –Mediated Cell Death Mechanisms in Nematode Excitotoxicity. *BMC Neuroscience* 16(25) . http://www.biomedcentral.com/1471-2202/16/25 PMID: 25899010

***V*) Identification of Neuroprotective Signaling Cascades in Nematode Excitotoxicity.** Initiated as collaboration between the Driscoll & Kalb lab (UPenn), we found that the transcription factor FoxO/*daf-16* (known as a regulator of aging and stress resistance) is an important player in neuroprotection from excitotoxicity in mammals and nematodes. We continue this project in my own lab at CCNY and we identified a protein complex that serves as an upstream regulator of this neuroprotective transcriptional program. We are now testing how this and another neuroprotective transcriptional program (regulated by CREB) might work in concert to provide a measure of neuroprotection during excitotoxicity (in preparation).

1) Mojsilovic-Petrovic, J., Nedelsky, N., Mano, I., Georgiades, S.N., Zhou, W., Liu, Y., Neve, R.L., J.P., Driscoll, M., Merry, D., and Kalb, R.G.,(2009). FOXO3a is broadly neuroprotective *in vitro* and *in vivo* against insults implicated in motor neuron diseases. *J. Neurosci.,* 29: 8236-8247. http://www.jneurosci.org/cgi/content/full/29/25/8236 MCID: PMC2748231

2) Tehrani, N., Del Rosario, J., Dominguez, M., Kalb, R, and Mano, I., (2014). The Insulin/IGF Signaling Regulators Cytohesin/GRP-1 and PIP5K/PPK-1 Modulate Susceptibility to Excitotoxicity in *C. elegans*. *PLoS One* 9(11):e113060 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0113060 PMID: 25422944

D. Research Support

Current Support

2015-2016 PSC-CUNY Award: "Triggering CREB-Mediated Neuroprotection in a Nematode Model of Excitotoxicity" (PI, $5999).

Previous Support

2010-2013 (No cost extension to July 2015) National Science Foundation (Integrative Organismal Systems, Neural Systems) (award# IOS-1022281): "A System Perspective on Uptake of the Neurotransmitter Glutamate in *C. elegans*" (PI, $305,808 direct). The goal of this study is to understand the overall strategy of glutamate clearance in *C. elegans* by comparing the structure & function of transporters located proximally vs. distally from glutamatergic synapses, using electrophysiology, imaging & behavior. (Manuscript: Lee et al., 2015, in re-review).

2010-2013 (No cost extension to June 2014) The Alexandrine and Alexander L. Sinsheimer Fund: "Cell Death Signaling in a Nematode Model of Excitotoxic Neurodegeneration" (PI, $ 130,434 direct). The goal of this study is to study the mechanism of excitotoxic neurodegeneration in *C. elegans*, focusing on conserved signaling cascades like cell stress and autophagy. (Manuscripts: Tehrani et al., 2014 ; Del Rosario et al., 2015, Feldmann et al., *in prep* ; Chowdhury et al., *in prep.*).

2006-2011 Scientist Development Grant, American Heart Association, National Center (award #0635367N): "Glutamate Transporters & Excitotoxicity in *C. elegans*: Searching for Ways to Block Neurodegeneration in Brain Ischemia" ($260,000 including indirect).
The goal of this study has been to establish a model of stroke-like neurodegeneration in *C. elegans* and to reveal the initial steps in the cell death process. (Manuscripts: Mano et al., 2007, Mano & Driscoll, 2009, Mojsilovic-Petrovic et al., 2009)

Pending applications

NIH R21 (submitted October 2015): "Novel strategies for glutamate clearance in a glia- deprived synaptic hub: Lessons from *C. elegans"*. (March 2016 score: 4th percentile)

NIH R21 & Am Heart Assoc. (submitted January & March 2016): "Activation of Transcriptional Neuroprotective Programs in Nematode Excitotoxicity". (Score on previous round: 21st & 16th percentile).