BIOGRAPHICAL SKETCH

NAME: Mirjana Maletic-Savatic

eRA COMMONS USER NAME (credential, e.g., agency login): MIRJANA

POSITION TITLE: Assistant Professor of Pediatrics and Neuroscience

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Belgrade, Serbia	M.D., Ph.D. *cum laude*	1996	Medicine, Biophysics, Neurobiology
Cold Spring Harbor Laboratory, New York	Postdoc	1998	Neuroscience
Stony Brook University, New York	Residency	2002	Child Neurology

A. PERSONAL STATEMENT

I am interested in the longevity of cognition. It might be possible to maintain our capacity to learn and remember, regardless of age, if we could harness neurogenesis, the process by which the mammalian hippocampus continues to form new neurons throughout life. Thus, I focus on understanding the mechanisms of adult neurogenesis with the ultimate goal to develop regenerative therapies, i.e., to learn how to stimulate birth and survival of new neurons in a targeted and controlled manner to enable safe treatment of a variety of disorders that affect learning and memory.

I use molecular biology, neuroimaging, metabolomics, computational and systems biology tools, to gain insight into adult neurogenesis from cells to mice to people. I have been strategically acquiring the expertise to carry out this research since my postdoctoral training in learning and memory under the mentorship of Drs. Roberto Malinow and Karel Svoboda at Cold Spring Harbor Laboratories. I then completed my Child Neurology residency at Stony Brook University while studying neurogenesis at Cold Spring Harbor Laboratories under the mentorship of Dr. Grigori Enikolopov. My first independent paper, published in *Science* (2007), reported the discovery of a novel metabolomic biomarker enriched in neural stem cells, which enabled us to detect these cells in the human brain *in vivo*. Having been recruited by Dr. Huda Zoghbi to Baylor College of Medicine and the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, I can capitalize on the unique environment of these institutions and their substantial strengths in stem cell research, neuroscience, and translational bioinformatics to perform the studies I am interested in.

I firmly believe that an interdisciplinary approach to our questions has the best chance to produce meaningful data for the benefit of our patients. Thus, I have deliberately structured my lab to be able to translate research seamlessly between the laboratory and the clinic, and back: we have expertise in different fields of science such as mathematics, statistics, neuroinformatics, chemistry, molecular and cell biology, imaging and neurophysiology. I have successfully mentored numerous students and postdoctoral fellows, who have continued with the academic career. At the graduate school, I direct the course Topics in Developmental Biology and teach From Bench to Bedside (Translational Medicine Program) and Computational Mathematics (SCBMB Program). Two of my MSTP students have been fortunate to receive the National Library of Medicine/ Keck fellowships, and two postdoctoral fellows received foundation grants. I am a New Investigator with a long-standing interest in science and demonstrated research productivity. I believe that my knowledge and track record in successful collaborations and mentoring qualify me to successfully conduct the proposed research.

B. POSITIONS AND HONORS

Positions and Employment

2001-2002 *Chief Resident*, Dept. Neurology, Stony Brook University, Stony Brook, New York
2001-2004 *Visiting Scientist*, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York
2002-2006 *Instructor*, Dept. of Neurology, Stony Brook University, Stony Brook, New York
2004-2008 *Director for Biological Research*, Cody Center for Autism, Stony Brook University, New York

2005-2008 *Adjunct Assistant Professor*, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York
2006-2008 *Assistant Professor*, Departments of Neurology and Neuroscience, Stony Brook University, Stony Brook, New York (I have maintained adjunct status since 2008)
2009- *Assistant Professor*, Departments of Pediatrics, Neurology, and Neuroscience; Program in Developmental Biology; Structural and Computational Biology and Molecular Biophysics Program, Baylor College of Medicine, Houston, Texas
Assistant Professor, Division of Child Neurology, Texas Children's Hospital, Houston, Texas
Cynthia and Anthony G. Petrello Endowed Scholar

Other Experience and Professional Memberships

2003-2008 *Chair, Scientific Advisory Board*, Committee on Research Planning, Cody Center for Autism and Developmental Disabilities, Stony Brook University
2003-2008 *Reviewer*, Curriculum and Clerkship, School of Medicine, Stony Brook University
2004 *Board Certified in Neurology with Special Competence in Child Neurology*
2005-2008 *Advisory Committee,* MRI in Translational Research, Brookhaven National Laboratory, NY
Departmental Liaison, Women in Medicine, School of Medicine, Stony Brook University
2006-2008 *Dean's Leadership Advisory Committee*, School of Medicine, Stony Brook University
Stem Cell Initiative Committee, School of Medicine, Stony Brook University
Steering Committee, Center for Biomedical Imaging, Stony Brook University
Search Committee, Institute for Computational Biology, School of Medicine, Stony Brook Univ.
2009- *Director*, Topics in Developmental Biology course, Program in Developmental Biology, BCM
Executive Committee, Small Animal Imaging Facility, BCM
2015 *Board Maintenance of Certification in Neurology with Special Competence in Child Neurology*

Journal Reviewer: *Molecular Psychiatry, Nature Communications, Scientific Reports, eLife, J. Neuroscience, J. Cell Biology, Neuroimage, J. Neurophysiology, Psychiatry Research, Hippocampus, PlosOne, Neuron Glia Biology, Metabolome*, *Behavioral Brain Research*

Editorial Board: *Scientific Reports*, Nature Press; *Frontiers in Biology*

Grant Reviewer: NIH Metabolomics Roadmap, Autism Speaks, Dunn Foundation, Hercules Foundation (Belgium), Alpha Omega Alpha Honor Medical Society, Targeted Research Opportunity Grants (Stony Brook University), Multiple Sclerosis Society (United Kingdom)

Meetings Organized

09/2015 *Co-organizer*, 3rd International workshop on adult neurogenesis, France (http://rng.org.au/provence2015/), Guest Editor for *Frontiers in Biology* special issue

09/2016 *Co-organizer*, Metabolomics in Clinical Practice, International Symposium, Houston, Texas
10/2016 *Organizing Committee*, 3rd Pan-Slavic and 1st Mediterranean Congress of Child Neurology, Croatia(http://en.childneuro2016.eu/child-neurology-congress/)

Professional Membership

2004- Society for Neuroscience
2000- Child Neurology Society
2007- New York Academy of Sciences
2009- Texas Neurological Society

Teaching – graduate school:

Spring	2002-2008	Neuropharmacology BHS 433 (2 seminars)
Fall	2004-2008	Neuroscience core course, 2nd year medical students (4 seminars)
	2004-2008	Child Neurology for medical students (12 seminars, one monthly)
Spring	2006-2008	Pharmacology core course, 2nd year medical students (2 seminars)
Spring	2009-on	Director, Topics in Developmental Biology
Spring	2010	Neural Development (Neuroscience core course, 1 seminar)
Fall	2014	From Bench to Bed Side (1 seminar)
Fall	2015-on	Computational Mathematics (2 2h-seminars)

Honors and Awards

1999 *Science* journal Breakthrough Publication of the Year runner-up
2002 *Outstanding Junior Member*, Child Neurology Society
Career Development Award, National Institutes of Health
2004 *Physician Scientist Training Award*, United States Army

2007 *Finalist*, New Innovator Award, National Institutes of Health
Phillip R. Dodge Young Investigator Award, Child Neurology Society
Top 5% Scientific Achievement, Society for Neuroscience
Top 5% Scientific Achievement, American Academy of Neurology
2007-2010 *Best Doctors in America* (Castle Connolly)
2008 *Neuroscience of Brain Disorders Award,* McKnight Foundation
Brain Neuroimmunology Imaging Award, Dana Foundation
2010 *Virginia and L.E.Simmons Collaborative Research Award*
2013 *Nancy Chang Award for Research Excellence*
2014 *Women in Medicine Award*, Harris Medical Society and Health Museum Houston

Patents/Disclosures
BLG 15-050 Automated identification and quantification of metabolites from NMR data
US20090247860 Detection of Neural Stem Cells from Magnetic Resonance Spectroscopy Measurements

C. SCIENTIFIC CONTRIBUTIONS

1. Activity-dependent subcellular plasticity: spine morphogenesis and synaptic plasticity. During my postdoctoral fellowship at Cold Spring Harbor Laboratory, I made a breakthrough discovery that neuronal dendrites exhibit a form of regulated exocytosis and that the molecular mechanisms underlying it are NMDA-dependent. At that time, these results met great resistance (after a 30-month review process, a similar discovery was published by another lab (Lledo et al., Science, 1998). Today, activity-dependent exocytosis of postsynaptic receptors is a widely accepted underlying mechanism of synaptic plasticity and memory formation in the mammalian brain. I then continued to challenge the dominant concept of activity-dependent neuronal plasticity, namely that synapses, once formed, can only be pruned and that no new ones are formed. In collaboration with Karel Svoboda, I combined several methodologies new at the time (transfection of neurons with the GFP and two-photon laser microscopy). I clearly remember the thrill of seeing in real time the new filopodia forming upon local electrical stimulation: clear evidence that plasticity-inducing stimuli produce morphological changes in living adult neurons. These studies have completely changed our views of synaptic plasticity and the capacity of the adult neurons to adapt their structure based on different experiences.

Maletic-Savatic, M., and Malinow, R. (1998) Calcium-evoked dendritic exocytosis in cultured hippocampal neurons. Part I: Trans-Golgi network-derived organelles undergo regulated exocytosis. *J. Neurosci.* 18: 6803-6813

Maletic-Savatic, M., Koothan, T., and Malinow, R. (1998) Calcium-evoked dendritic exocytosis in cultured hippocampal neurons. Part II: Mediation by calcium/calmodulin-dependent protein kinase II. *J. Neurosci.* 18: 6814-6821

Maletic-Savatic, M., Malinow, R., and Svoboda, K. (1999) Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. *Science*, 283: 1923-1927

Selected as a runner-up for Best Publication of the year in *Science*, was reported in *Scientific American* and numerous other journals.

2. Activity-dependent cellular plasticity: adult hippocampal neurogenesis. The intrinsic ability of the hippocampus to generate new neurons holds potential to develop therapies for many pathologies, from epilepsy to Alzheimer's disease and psychiatric disorders. While most of research in the field concentrates on the biology of immature neurons, I focus on the mechanisms that influence and govern the primary neural stem cells (NSCs), which produce new neurons. We have made several key discoveries: (i) a major critical period of newborn cell survival that happens within the first three days its life; (ii) the role of microglia for proper function of the neurogenic niche; (iii) the profound change in biology of NSCs when exposed to conditions of extreme neuronal network activity, such as seen in epilepsy, when they directly transform into reactive astrocytes, contributing to gliosis and ensuing pathology. Our most recent studies, currently in review, report discoveries of new computational tools, gene-metabolome networks and cell-cell communication pathways common for most quiescent stem cells in any organ. Our body of work has been widely recognized for challenging accepted dogma and demonstrating the need to reframe our approaches if we are to use adult hippocampal neurogenesis for therapy.

Sierra A, Encinas JM, Deudero JJ, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, Tsirka SE, **Maletic-Savatic M.** (2010) Microglia shape adult hippocampal neurogenesis through apoptosis-phagocytosis coupling, *Cell Stem Cell* 7(4):483-95. PMID: 20887954

Cited by Faculty 1000 Prime and was subject to an Editorial in *Cell Stem Cell* (Mattocks and Tropepe, 7(4): 421-2).

Sierra A, Martín-Suárez S, Valcárcel-Martín R, Pascual-Brazo J, Aelvoet S-A, Abiega O, Deudero JJP, Brewster AL, Bernales A, Anderson AE, Baekelandt V, **Maletić-Savatić M**[*], Encinas JM* (2015) Neuronal Hyperactivity Accelerates Depletion of Neural Stem Cells and Impairs Hippocampal Neurogenesis. *Cell Stem Cell*, 16 (5) 488-503. PMID: 25957904 * Co-senior authors

Editorial in *Cell Stem Cell* (Ibrayeva and Bonaguidi, 16 (5):451-2).

3. Metabolomics: new algorithms for analysis of cells and biofluids *in vitro* (bottom-up approach for biomarker discovery). In 2005, the field of metabolomics, a systems biology approach to studying small molecules and metabolites, was just starting to develop. Attracted by the possibility of using metabolomics to translate the data directly from *in vitro* studies to living organisms *in vivo*, I became interested in nuclear magnetic resonance spectroscopy (NMR, traditionally used for structural biology studies) and its correlate, magnetic resonance spectroscopy (MRS, used in clinical medicine). I realized that the major roadblock for application of NMR metabolomics in clinical practice stems from analysis of these data, because it is cumbersome, operator-biased and time consuming. In collaboration with several computational scientists and chemists, we have started to develop different approaches for NMR metabolomics data analysis, identification of cell-specific fingerprints, metabolite content and quantification. Ultimately, my goal is to develop and validate a Push-Button-NMR analytical software that will enable high-throughput screening of a multitude of diagnostic metabolites in daily clinical practice as well as discovery of novel compounds in biological samples, aiding both biomedical and pharmacological research.

Allen GI, **Maletic-Savatic M**. (2011). Sparse Non-Negative Generalized PCA with applications to metabolomics.*Bioinformatics*; 27 (21):3029-35. PMID: 21930672

Allen GI, Peterson C, Vannucci M, **Maletic-Savatic M**. (2013). Regularized partial least squares with an application to NMR spectroscopy. *Stat Anal Data Min*, 6: 302-314. PMID: 24511361

Peterson C, Vannucci M, Karakas C, Choi W, Ma L, **Maletic-Savatic M**. (2013). Inferring metabolic networks using the Bayesian adaptive graphical lasso with informative priors. *Stat Interface*, 6: 547-558. PIMD: 24533172

4. Metabolomics - new algorithms for analysis of human brain *in vivo* (top-down approach for biomarker discovery). To begin to explore the molecular composition of the brain tissue to a greater detail, I have sought to develop methods to apply metabolomics to human brain MRS. We have made two important contributions: (i) To detect neural stem cells (NSCs) *in vivo*, we designed an unorthodox method to extract, amplify, and quantify a very low signal originating from NSCs in the noisy *in vivo* MRS data. This approach, based on singular value decomposition, enabled us to measure adult hippocampal neurogenesis in the living human brain for the first time. (ii) To mine the rich MRS data of the human brain, we applied systems biology approach to MRS spectrum as a whole, in contrast to traditional analysis which focuses only on 6-8 known metabolites. For the first time, we showed that advanced statistical learning can be used for discovery of molecular signatures of specific clinical aspects of disease, in our case, multiple sclerosis. Since our approach does not use *a priori* information about the metabolites in the sample, more features can be extracted and correlated to an aspect of disease. Our pioneering studies allow us now to explore the role of NSCs not only during normal human brain development and aging, but also in a variety of diseases that affect hippocampus. Moreover, the new concepts and analytical algorithms we developed may be extended to other neurological diseases, ultimately leading to improved diagnosis, prognosis, and individualized treatment.

Manganas, L., Zhang, S., Li, Y., Hazel, R., Smith, D., Wagshul, M., Henn, F., Enikolopov, G., Benveniste, H., Djuric, P., **Maletic-Savatic, M.** (2007) Magnetic Resonance Spectroscopy identifies neural progenitor cells in the live human brain. *Science*, 318 (5852): 980-5. PMID: 17991865

Cited by Faculty 1000; subject of Editorials in *Science, Nature Neuroscience* and other journals; numerous press throughout the world.

Djuric, P., Wagshul, M., Henn, F., Beneniste, H., Enikolopov, G., **Maletic-Savatic, M.** (2008) Singular Value Decomposition algorithm for detection of neural progenitor cells in the live human brain. Technical Report, *Science*, 321 (5889):640-2. PMID: 26380846 (Response to comments on Manganas et al., 2007)

Vingara LK, Yu HJ, Wagshul ME, Serafin D, Christodoulou C, Pelczer I, Krupp LB, **Maletic-Savatic M**. (2013). Metabolomic approach to human brain spectroscopy identifies associations between clinical features and the frontal lobe metabolome in multiple sclerosis. *Neuroimage*, 82: 586-94. PMID: 23751863

Link to full list of my published work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1n7el5VhHgrAd/bibliography/47937077/public/?sort=date&direction=descending