BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Krichevsky, Anna M., Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): AMK123

POSITION TITLE: Associate Professor of Neurology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Second Moscow Medical School, Russia	B.S.	1990	Medical & Biological Studies
Hebrew University of Jerusalem, Israel	M.Sc.	1994	Microbiology
Hebrew University of Jerusalem, Israel	Ph.D.	1999	Molecular Biology

A. Personal Statement

My background is in molecular biology, neurobiology, and cancer biology, and my overall goal is to develop basic microRNA research toward a cure for human CNS disorders. I believe that my knowledge, experience and leadership can be applied to reaching the goals of the current project. As a postdoctoral fellow, I was involved in the work that led to the recognition of miRNA functions in brain physiology and pathology. Specifically, I performed the first successful RNA interference in mammalian neurons (Krichevsky et al., PNAS 2002); contributed to identification of first miRNAs in mammalian brain (Kim et al., PNAS 2004); developed first high-throughput arrays for miRNA expression profiling (Krichevsky et al., RNA 2003); and identified the first oncogenic miRNA, miR-21, in gliomas (Chan et al., Cancer Res 2005). Over the last years, my laboratory has developed tools for identification and studying miRNA regulators involved in human brain tumors and neurodegenerative disorders (Gabriely et al., Cancer Res 2011; Wong et al., Hum Mol Genetics 2013; Absalon et al., J Neuroscience 2013; Teplyuk et al., EMBO Mol Med 2016). We identified a miRNA and its targets that promote microglia quiescence and suppresses EAE, a mouse model of human multiple sclerosis (Ponomarev et al., Nature Medicine 2011). We also focused on extracellular miRNAs as biomarkers and potential mediators of intercellular communication in the brain (Skog et al., Nature Cell Biol 2008; Teplyuk et al., Neuro-Oncology 2012). All our recent projects were based on successful collaborations that involved building very diverse teams. My most relevant experience on GBM-related projects is summarized in the following manuscripts:

a. Skog J, Wurdinger T, Meijer D, Sena-Esteves M, Carter RS, **Krichevsky AM**, Breakefield XO. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. ***Nature Cell Biology***, 10(12): 1470-1476 (2008).

b. Teplyuk NM, Mollenhauer B, Gabriely G, Giese A, Kim E, Smolsky M, Kim RY, Saria MG, Pastorino S, Kesari S, **Krichevsky AM**. MicroRNAs in cerebrospinal fluid identify glioblastoma and metastatic brain cancers and reflect disease activity. ***Neuro-Oncology***. 2012 PMCID: PMC3367845.

c. Godlewski J, **Krichevsky AM**, Johnson MD, Chiocca EA, Bronisz A. Belonging to a network--microRNAs, extracellular vesicles, and the glioblastoma microenvironment. ***Neuro-Oncology***. 2015 May;17(5):652-62. PMID: 25301812.

d. Teplyuk NT, Uhlmann UE, Gabriely G, Volfovsky N, Wong Y, Teng J, Karmali P, Marcusson E, Peter M, Mohan A, Kraytsberg Y, Cialic R, Chiocca EA, Godlewski J, Tannous B, **Krichevsky AM**. 2016. Therapeutic potential of targeting microRNA-10b in established intracranial glioblastoma: first steps toward the clinic. ***EMBO Mol Medicine***, 2016 Feb 9. PMCID: PMC4772951.

B. Positions and Honors

1991-1993 Teaching Assistant in the course "Basic Techniques in Cell Culture"
Institute of Microbiology, Hebrew University of Jerusalem, Israel
1994-1999 Teaching Assistant in the graduate course "Genetic Engineering: Advance Chapters", Institute of Microbiology, Hebrew University of Jerusalem, Israel
1999-2003 Research Fellow, Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital, Boston, MA
1999-2003 Research Fellow in Neurology, Harvard Medical School, Boston, MA
2003-2006 Research Associate, Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital, Boston, MA
2003-2006 Instructor in Neurology, Harvard Medical School
2006-2012 Associate Scientist, Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital, Boston, MA
2006-2012 Assistant Professor in Neurology, Harvard Medical School, Boston, MA
2012 - Scientist, Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital, Boston, MA
2012 - Associate Professor of Neurology, Harvard Medical School, Boston, MA
2016- Associate Professor and Faculty Member at the Institute of RNA Medicine, Harvard Medical School, Boston, MA

Ad hoc reviewer for: Nature, Nature Genetics, Neuron, Cancer Cell, Proceedings of the National Academy of Science USA, Journal of Neuroscience, Cancer Research, Oncogene, Acta Neuropathologica, Human Molecular Genetics, Neuro-Oncology, Molecular and Cellular Biology, Journal of Biological Chemistry, Journal of Cellular and Molecular Medicine, FEBS Letters, RNA, International Journal of Cancer, BMC Genomics, BMC Cancer and other journals. *Ad hoc* grant reviewer for: National Institutes of Health (NIH), Department of Defense, Alzheimer's Association, French National Centre for Research (CNRS), Swiss National Science Foundation, Italian Ministry of Health, and other governmental and private foundations.

Honors and Awards

1986-1990 Scholarship for Outstanding Students
Second Moscow Medical School, Russia
1991-1994 Scholarship of the Institute of Microbiology
Faculty of Medicine, Hebrew University of Jerusalem, Israel
1994 Research Faculty Award for an Excellent M.Sc. Thesis
1995 The Wolf Foundation Young Scientists Award, Israel
1998 Faculty Award for the Best Teaching Assistant (Hebrew University of Jerusalem)
2002 Included in America's Registry for Outstanding professionals
(for demonstrated leadership and dedication to the profession)
2005 Beverly Nesson Leadership Chair of Research, Brain Tumor Society
2006 Goodman-Gerson Leadership Chair of Research, Brain Tumor Society
2009 Sontag Foundation Distinguished Scientist Award
2011 Hamill Family Chair of Research, National Brain Tumor Society
2013-2015 Nominated for Excellence in Mentoring Award, Harvard Medical School

C. Contributions to Science

1. *Neuronal RNA granules: mRNA localization and translation in the neuron.* Although it was known that synaptic activation could induce local protein synthesis, how activation is coupled to translation of specific mRNAs was poorly understood. In my postdoctoral work, I attempted to link the translational regulation of dendritic mRNAs to synaptic activity. The delivery of new mRNAs to dendrites occurs in RNA granules, a widely observed but poorly characterized organelle. I have isolated and characterized the RNA granules as a macromolecular site where specific mRNAs involved in implementing long-lasting synaptic changes are held in translational arrest until stimulated. This work published in Neuron opened an entirely new view of how mRNAs

translocation to dendrites is coupled to the local protein synthesis, and was followed by numerous studies from other groups.

a. **Krichevsky AM** and Kosik KS. Neuronal RNA granules: a link between RNA localization and stimulation-dependent translation. ***Neuron,*** 32(4):683-96 (**2001**). *This paper has been cited in 390 publications.*

b. Kosik KS and **Krichevsky AM**. The Message and the Messenger: Delivering RNA in Neurons. ***Science's STKE*** (126): PE16, Review (**2002**).

2. *Development of RNA interference and microRNA (miRNA) profiling technologies.* My early work led to the recognition of microRNA (miRNA) functions and RNA interference mechanisms in brain physiology and pathology. The discovery of RNA interference (RNAi) about 15 years ago truly revolutionized the biology; however, a common misconception at that time was that mammalian neurons are resistant to RNAi, and RNAi mechanisms and tools do not operate in the CNS. I performed and reported the first successful RNAi experiments in primary mammalian neurons in 2002; today RNAi is one of the most widely applied techniques in various neural systems *in vitro* and *in vivo*. I also contributed to the identification of the first miRNAs in mammalian brain (Kim et al., PNAS 2004), and developed first high-throughput arrays for miRNA expression profiling (Krichevsky et al., RNA 2003). At that time, the common belief was that expression of tiny miRNA molecules cannot be profiled in a high-throughput fashion. Development and application of this technology generated multiple collaborations and led to diverse projects. Today various high-throughput miRNA profiling platforms are manufactured by numerous companies and serve basis for countless biomedical discoveries.

a. **Krichevsky AM**, Kosik KS. RNAi functions in cultured mammalian neurons. **Proc. Natl. Acad. Sci. U.S.A**., 99(18):11926-9 (2002). *This paper has been cited in 243 publications.*

b. Kim J, **Krichevsky A**, Grad Y, Hayes GD, Kosik KS, Church GM, Ruvkun G. Identification of many microRNAs that copurify with polyribosomes in mammalian neurons. **Proc. Natl. Acad. Sci. U.S.A**., 101(1):360-5 (2004). *This paper has been cited in 550 publications.*

c. **Krichevsky AM**, King KS, Donahue CP, Khrapko K, Kosik KS. A microRNA array reveals extensive regulation of microRNAs during brain development. ***RNA***. 9(10):1274-81 (2003). *This paper has been cited in 932 publications.*

d. **Krichevsky AM**, Sonntag KC, Isacson O, Kosik KS. Specific microRNAs modulate embryonic stem cell-derived neurogenesis. ***Stem Cells,*** 24(4): 857-64 (**2006**). *This paper has been cited in 606 publications.*

3. *miRNA functions in cancer and development of miRNA-based therapies for brain tumors.* A decade ago, miRNA functions in mammalian tissues generally, and in human health and disease specifically, were unknown. Our array analysis of miRNA expression in glioblastoma, human most common and malignant brain tumor, revealed a clear "signature" of miRNAs that were dysregulated. Strongly up-regulated miR-21 appeared as a common onco-miRNA elevated in GBM and a variety of other solid cancers as well. We, therefore, discovered the first oncogenic miRNA, miR-21, in gliomas (Chan et al., 2005), which is today the most studied and one of the most promising miRNA targets for various human diseases, including cancer. We have also studied miRNAs involved in glioma-associated angiogenesis and identified miR-296 as a potent "angio-mir". Further work led us to the identification of additional oncogenic and survival-associated miRNAs (miR-10b, miR-148a), with a current focus on 1) characterization of key miRNAs that may represent therapeutic targets for glioma treatments, and 2) developing strategies and delivery modalities for miRNA-based therapies for GBM and other malignant brain tumors. We are convinced that this work will lead to the miRNA-based human clinical trials for GBM in the near future.

a. Chan J*, **Krichevsky AM***‡, Kosik KS. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. ***Cancer Research***. 65(14):6029-33 (2005). *equal contribution, ‡corresponding author. *This paper has been cited in 2261 publications.*

b. Würdinger T, Tannous B, Saydam O, Skog S, Grau S, Weissleder R, Breakefield XO, **Krichevsky AM**. miR-296 regulates growth factor receptor overexpression in angiogenic endothelial cells. ***Cancer Cell*** (5):382-93 (2008). PMCID: PMC2597164. *This paper has been cited in 347 publications.*

c. Gabriely G, Yi Ming, Narayan RS, Niers JM, Wurdinger T, Imitola J, Ligon KL, Kesari S, Esau C, Stephens RM, Tannous BA, **Krichevsky AM**. Human Glioma Growth is Controlled by MicroRNA-10b. ***Cancer Research***. 2011 Apr 6. PMCID: PMC3096675. *This paper has been cited in 175 publications.*

d. Wong HK, Fatimy RE, Onodera C, Wei Z, Yi M, Mohan A, Gowrisankaran S, Karmali P, Marcusson E, Wakimoto H, Stephens R, Uhlmann EJ, Song JS, Tannous B, **Krichevsky AM**. The Cancer Genome Atlas Analysis Predicts MicroRNA for Targeting Cancer Growth and Vascularization in Glioblastoma. ***Molecular Therapy*** 2015 Jul;23(7):1234-47. PMID: 25903473 PMCID: PMC4817797.

4. *miRNA functions in human neurodegenerative disorders.* Several years ago the role of small non-coding RNA such as miRNA in human neurodegenerative diseases was completely unknown. Over the last years, we have identified and investigated some key miRNAs involved in human neurodegenerative disorders such as Alzheimer's disease (AD) and multiple sclerosis (MS). For example, we identified miR-124 as a key regulator of microglia quiescence in the central nervous system, and novel modulator of monocyte and macrophage activation, which administration suppresses experimental autoimmune encephalomyelitis, a model of MS. We have established miRNA expression profiles of human postmortem tissues and cells of subjects with Mild Cognitive Impairment and AD. Whereas there is little consensus among the studies of miRNA expression in AD, miR-132, the top miRNA we have discovered (Wong et al., 2013), now emerges as the most significantly dysregulated not only in AD but several other tauopathies as well. We demonstrated that miR-132 is a critical regulator of neuronal survival that controls several targets along the Akt signaling pathway. The goal of our ongoing projects is to validate the neuroprotective potential of key miRNAs *in vivo*.

a. Ponomarev ED, Veremeyko T, Barteneva N, **Krichevsky AM*****, Weiner HL*****. MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the CEBPa/PU.1 pathway. ***Nature Medicine*** 2011 Jan; 17(1): 64-70. *****equal contribution. PMCID: PMC3044940. *This paper has been cited in 312 publications.*

b. Wong HK, Veremeyko T, Patel N, Lemere CA, Walsh DM, Esau C, Vanderburg C, **Krichevsky AM**. De-repression of FOXO3a death axis by microRNA-132 and -212 causes neuronal apoptosis in Alzheimer's disease. ***Hum Mol Genet.*** 2013 Aug 1;22(15):3077-92. PMID: 23585551.

c. Absalon S, Kochanek DM, Raghavan V, **Krichevsky AM**. MiR-26b, upregulated in Alzheimer's disease, activates cell cycle entry, tau-phosphorylation, and apoptosis in postmitotic neurons. ***J Neurosci***. 2013 Sep 11;33(37):14645-59. PMCID: PMC3810537.

5. *Extracellular vesicles and exRNA in biology and diagnostics.* Together with Xandra Breakefiled laboratory, we discovered that glioblastoma cells release exosomes/microvesicles containing mRNA and miRNA (Skog et al., 2008). Coding and regulatory RNA (e.g. miRNA) in such tumor-derived vesicles can be taken up by recipient cells of the tumor microenvironment and provide a mean of intracellular communication, as well as diagnostic biomarkers. This discovery opened up the new field and led to numerous reports highlighting potential functions of exosomes released by various types of cells. We have further established that miRNA profiling of cell-free cerebrospinal fluid (CSF) enables highly sensitive and accurate detection of glioblastoma, discrimination between glioblastoma and metastatic brain tumors, and reflects disease activity. This study, published in 2012 and patented by BWH (with Dr. Krichevsky as a lead Inventor) suggested a new noninvasive, simple, and inexpensive way for diagnostics and monitoring of primary and metastatic brain tumors.

a. Skog J, Wurdinger T, Meijer D, Sena-Esteves M, Carter RS, **Krichevsky AM**, Breakefield XO. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. ***Nature Cell Biology***, 10(12): 1470-1476 (2008). *This paper has been cited in 1776 publications.*

b. Teplyuk NM, Mollenhauer B, Gabriely G, Giese A, Kim E, Smolsky M, Kim RY, Saria MG, Pastorino S, Kesari S, **Krichevsky AM**. MicroRNAs in cerebrospinal fluid identify glioblastoma and metastatic brain cancers and reflect disease activity. ***Neuro-Oncology.*** 2012 PMCID: PMC3367845. *This paper has been cited in 98 publications.*

c. Godlewski J, **Krichevsky AM**, Johnson MD, Chiocca EA, Bronisz A. Belonging to a network--microRNAs, extracellular vesicles, and the glioblastoma microenvironment. ***Neuro-Oncology***. 2015 May;17(5):652-62. PMID: 25301812.

d. Laurent LC, et al. Meeting report: discussions and preliminary findings on extracellular RNA measurement methods from laboratories in the NIH Extracellular RNA Communication Consortium. ***J Extracell Vesicles.*** 2015 Aug 28;4:26533. PMCID: PMC4553263.

Complete List of Published Work in PubMed:

http://www.ncbi.nlm.nih.gov/pubmed/?term=Krichevsky+am
Total citations 15,166; 11,043 since 2011