BIOGRAPHICAL SKETCH

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NAME: Rasin, Mladen-Roko

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

POSITION TITLE: Associate professor

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
University of Zagreb School of Medicine, Zagreb	MD	10/2002	Medicine
University of Zagreb School of Natural Sciences (thesis and trainings done at Yale University), Zagreb, Croatia	PHD	11/2006	Neurobiology
Yale University, New Haven, CT	OTH	09/2009	Predoctoral and postdoctoral training - Neurobiology

A. Personal Statement

My research is focused on understanding the roles of post-transcriptional events in normal and abnormal development of neocortical neurons and associated circuits. In particular, we are revealing the role of mRNA translation (protein synthesis) mechanisms that are at the developmental cross-road between the genome and proteome networks in developing neocortical stem cells and neurons. My previous expertise and achievements ensure that I will successfully carry out the proposed research project.

My lab draws on multi-discplinary backgrounds of my trainings, including biomedicine, neuroanatomy, genetics, behavior and molecular and cellular biology. During my M.D. trainings, I was extensively trained on human prenatal neocortical development and on morphological characteristics of distinct subpopulations of developing human neocortical neurons. During my Ph.D. and postdoctoral trainings done at Yale University, I was introduced and extensively trained to the tantalizing labyrinth of transcriptional and cellular mechanisms involved in neocortical stem cell and neuronal development. These diverse trainings gave me strong foundation for my current, independent research in my lab. My lab has been one of the frontrunners at connecting developmental neurobiology and RNA metabolism, particularly in understanding the role of mRNA translation steps in neocortical neuronal development. Furthermore, we develop and utilize new tools and methodologies (e.g. polysomics, RIP-seq, sn-RNAseq, Cryo-EM, *in utero* electroporation) to answer the most intriguing neuroscience questions.

I am also deeply committed to training the next-generation of scientists with an emphasis on promoting both female and diversity students. During my independent years, I have research trained 9 Ph.D. students, 6 postdocs, more than 50 undergraduate students, and 11 high school students. Training a new generation of female and under-represented minority (URM) scientists is at the core of my research and training program. In particular, I have mentored 6 are female and/or URMs high school students, 21 female and/or URM undergraduate, 5 female Ph.D. students, 1 female UMR M.D. student, and 1 female M.S. student, as well as 3 female postdoctoral fellows.

Recent work and publications are related to the proposal. My lab showed the role of RNA binding proteins and mRNA decapping associated proteins in neocortical migration, connectivity and identity acquisition. This

work together with my previous studies confirm the role of mRNA metabolism in early neocortical circuit formation, and that mRNA translation is one of the key crossroads in neuronal development. Since I became independent researcher, I was fortunate to publish as the senior corresponding coauthor in *Nature Communications, PNAS USA, J Neuroscience, Cerebral Cortex, Cells, RNA, Neuroscience, International Journal of Developmental Neuroscience, Methods in Molecular Biology, Frontiers in Neuroanatomy, Scientific Reports*. All of this recently published work is focused on the mRNA metabolism in developing neocortices.

B. Positions, Honors, and Employment

Positions and Employment

2016 - present	Associate Professor, Department of Neuroscience and Cell Biology, Rutgers University, RBHS-Robert Wood Johnson Medical School, Piscataway, NJ
2014 - 2016	Assistant Professor, Department of Neuroscience and Cell Biology, Rutgers University, RBHS-Robert Wood Johnson Medical School, Piscataway, NJ
2009 - 2014	Assistant Professor, Department of Neuroscience and Cell Biology, UMDNJ-Robert Wood Johnson Medical School, Piscataway, NJ
2007 - 2009	Postdoctoral fellow, Department of Neurobiology, Yale University, New Haven, CT
2003 - 2006	Graduate student/Postdoctoral associate, Department of Neurobiology, Yale University, New Haven, CT
1995 - 2002	Medical student/Research Assistant, Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Zagreb

Selected honors

2019-present	Ad-hoc study section member for R01/R21/R03 MNG, NCF and special emphasis panels
2019-present	Study section member, NIH F01A fellowships
2018-present	Study section member for NSG GRFP fellowships
2016	Excellence in Research award, New Jersey Health Foundation
2010-present	Committee member, RU-RWJMS/Princeton M.D./Ph.D. Graduate School admission committee
2010-2020	Committee member, RU-RWJMS Neuroscience Graduate School admissions committee
2010	Study section member, NIH/NINDS NST-2 K99/R00 and MD/PhD Study Section
2009	K99 NIH Pathway to independence (PI) award, NIH/NINDS
-	Member, Society for Neuroscience
-	Member, International Brain Research Organization
-	Member, Croatian Society for Neuroscience
	RNA society member

C. Contributions to Science

1. *When I started my independent research path, my main hypothesis was that precisely controlled gene expression in space and time is essential for the spatiotemporal development of complex biological systems like the neocortex, with its exceptional cellular diversity and intricate circuits. I was particularly focused on mechanisms generating rapid and targeted functional gene expression in neural stem cells and developing neurons, complementing previous work that had focused primarily on global transcriptional control during neuronal differentiation. Post-transcriptional regulation is a good candidate for this mechanism, which culminates in functional protein synthesis. We profiled the landscape of post-transcriptional regulation at key time points during prenatal neocortical neurogenesis and have found that temporal control of mRNA translation in the developing neocortex may be particularly dynamic. We then identified RBPs to be major regulators of mRNA translation that defines neocortical development.*

    a. DeBoer EM, Azevedo R, Vega TA, Brodkin J, Akamatsu W, Okano H, Wagner GC, Rasin MR. (2014) Prenatal deletion of the RNA-binding protein HuD disrupts postnatal cortical circuit maturation and behavior. J Neurosci 34, 3674-3686.

b. Kraushar ML, Thompson K, Wijeratne HR, Viljetic B, Sakers K, Marson JW, Kontoyiannis DL, Buyske S, Hart RP, Rasin MR. (2014) Temporally defined neocortical translation and polysome assembly are determined by the RNA-binding protein Hu antigen R. Proc Natl Acad Sci USA 111, E3815-24.
c. Popovitchenko T, Park Y, Page NF, Luo X, Krsnik Z, Liu Y, Salamon I, Stephenson JD, Kraushar ML, Volk NL, Patel SM, Wijeratne HRS, Li D, Suthar KS, Wach A, Sun M, Arnold SJ, Akamatsu W, Okano H, Paillard L, Zhang H, Buyske S, Kostovic I, De Rubeis S, Hart RP, Rasin MR. (2020) Translational derepression of Elavl4 isoforms at their alternative 5' UTRs determines neuronal development. Nat Commun 11, 1674.
d. Kraushar ML, Krupp F, Harnett D, Turko P, Ambrozkiewicz MC, Sprink T, Imami K, Günnigmann M, Zinnall U, Vieira-Vieira CH, Schaub T, Münster-Wandowski A, Bürger J, Borisova E, Yamamoto H, Rasin MR, Ohler U, Beule D, Mielke T, Tarabykin V, Landthaler M, Kramer G, Vida I, Selbach M, Spahn CMT. (2021) Protein Synthesis in the Developing Neocortex at Near-Atomic Resolution Reveals Ebp1-Mediated Neuronal Proteostasis at the 60S Tunnel Exit. Mol Cell 81, 304-322.

2. *Next, we profiled the protein components of the neocortical translation machinery across development by mass spectrometry. This analysis revealed that the polysomal enrichment of ribosomal protein subsets associated with the large (Rpl) and small (RPs) ribosomal subunits is temporally dynamic during neocrtical development. We termed the spatiotemporal combinatorial composition of R-proteins in neocortical ribosome complexes the "ribosome signature." Next, we reported that the morphogen Wingless-related MMTV integration site 3 (WNT3) is a timed thalamic signal secreted into the developing neocortex from arriving thalamic afferents to have strong impact on temporal neocortical ribosome diversity. We also found that this timed arrival of thalamic WNT3 affects neocortical mRNA translation driving neuronal development through a receptor Fzd-7. Taken together, these findings point to a complex mechanism with an interaction between ribosome biogenesis, mRNA translation, and neuronal subtype specification in the developing neocortex that is controlled by extracellular factors.*

a. Kraushar ML, Viljetic B, Wijeratne HR, Thompson K, Jiao X, Pike JW, Medvedeva V, Groszer M, Kiledjian M, Hart RP, Rasin MR. (2015) Thalamic WNT3 Secretion Spatiotemporally Regulates the Neocortical Ribosome Signature and mRNA Translation to Specify Neocortical Cell Subtypes. J Neurosci. 35, 10911-10926.
b. Kraushar ML, Popovitchenko T, Volk N, Rasin MR. (2016) The frontier of RNA metamorphosis and ribosome signature in neocortical development. Int J Dev Neuroscience 55, 131-139.
c. Park Y, Lofton M, Li D, Rasin MR. (2021) Extrinsic Regulators of mRNA Translation in Developing Brain: Story of WNTs. Cells 10, 253.

3. *We found that the distinct phosphorylation-states of HuR regulate mRNA translation of neocortical Forkhead box protein (Foxp) mRNAs that are associated with neurodevelopmental disorders, including autism. Using RBP-immunoprecipitation, we identified direct HuR targets during neocorticogenesis and their differential regulation through development, including Foxp1 and Foxp2 mRNAs associated with ASD. Additionally, we found a significant overlap of early-bound HuR mRNA targets and those bound by FMRP (51 genes, not shown) with some genes found in the SFARI autism database (12 genes overlap with early, 13 with common, and 2 with late neocortical HuR RIP; www.sfari.org, Simons Foundation). We showed that HuR-phsphorylation states dictate differential regulation of HuR bound mRNAs.*

a. Popovitchenko T, Thompson K, Viljetic B, Jiao X, Kontonyiannis DL, Kiledjian M, Hart RP, Rasin MR. (2016) The RNA binding protein HuR determines the differential translation of autism-associated FoxP subfamily members in the developing neocortex. Sci Rep 6, 28998.
b. Popovitchenko T, Rasin MR. (2017) Transcriptional and Post-Transcriptional Mechanisms of the Development of Neocortical Lamination. Front Neuroanat 11,102.

4. *We found further effects of mRNA translation in neocortical neuronal development and potential risk for translational dysregulation in comorbid neurodevelopmental disorders. In particular, using RNA-seq analysis of mouse neocortical polysomes, we reported translationally repressed and derepressed mRNA*

isoforms during neocortical neurogenesis whose orthologs include risk genes for neurodevelopmental disorders. We demonstrated that the translation of distinct mRNA isoforms of the RNA binding protein (RBP), Elavl4, in radial glia progenitors and early neurons depends on its alternative 5' UTRs. Furthermore, 5' UTR-driven Elavl4 isoform-specific translation depends on upstream control by another RBP, Celf1. Celf1 regulation of Elavl4 translation dictates development of glutamatergic neurons. Our findings reveal a dynamic interplay between distinct RBPs and alternative 5' UTRs in neuronal development and underscore the risk of post-transcriptional dysregulation in co-occurring neurodevelopmental disorders. Finally, we started to reveal expression sites of RBPs in developing human brains, such as CELF1 and ELAVL4.

a. DeBoer EM, Kraushar ML, Hart RP, Rasin MR. (2013) Post-transcriptional regulatory elements and spatiotemporal specification of neocortical stem cells and projection neurons. Neuroscience. 248, 499-528.
b. Popovitchenko T, Park Y, Page NF, Luo X, Krsnik Z, Liu Y, Salamon I, Stephenson JD, Kraushar ML, Volk NL, Patel SM, Wijeratne HRS, Li D, Suthar KS, Wach A, Sun M, Arnold SJ, Akamatsu W, Okano H, Paillard L, Zhang H, Buyske S, Kostovic I, De Rubeis S, Hart RP, Rasin MR. (2020) Translational derepression of Elavl4 isoforms at their alternative 5' UTRs determines neuronal development. Nat Commun. 11, 1674.
c. Park Y, Page N, Salamon I, Li D, Rasin MR. (2021) Making sense of mRNA landscapes: Translation control in neurodevelopment. Wiley Interdiscip Rev RNA. 17, e1674.
d. Salamon I, Rasin MR. (2022) Evolution of the Neocortex Through RNA-Binding Proteins and Post-transcriptional Regulation. Front Neurosci. 15, 803107.

5. *We were also first to report the role of mRNA decapping protein DcpS, in neocortical development. DcpS mutations are associated with Intellectual disability and we found that DcpS controls neocortical connectivity, migration and identity acquisition. In addition, we also contributed to better understanding on the roles of disrupting prenatal mRNA metabolism in postnatal behavior through collaborative efforts. Finally, we started to reveal discrete expression sites of TFs in developing cells of human brain, such as CUX2 and FEZF2.*

a. Salamon I, Palsule G, Luo X, Roque A, Tucai S, Khosla I, Volk N, Liu W, Cui H, Pozzo VD, Zalamea P, Jiao X, D'Arcangelo G, Hart RP, Rasin MR, Kiledjian M. (2022) mRNA-Decapping Associated DcpS Enzyme Controls Critical Steps of Neuronal Development. Cereb Cortex 32, 1494-1507.
b. Boitnott A, Garcia-Forn M, Ung DC, Niblo K, Mendonca D, Park Y, Flores M, Maxwell S, Ellegood J, Qiu LR, Grice DE, Lerch JP, Rasin MR, Buxbaum JD, Drapeau E, De Rubeis S. (2021) Developmental and Behavioral Phenotypes in a Mouse Model of DDX3X Syndrome. Biol Psychiatry 90, 742-755.
c. Miškić T, Kostović I, Rašin MR, Krsnik Ž. (2021) Adult Upper Cortical Layer Specific Transcription Factor CUX2 Is Expressed in Transient Subplate and Marginal Zone Neurons of the Developing Human Brain. Cells 10, 415.
d. Gu Z, Kalambogias J, Yoshioka S, Han W, Li Z, Kawasawa YI, Pochareddy S, Li Z, Liu F, Xu X, Wijeratne HRS, Ueno M, Blatz E, Salomone J, Kumanogoh A, Rasin MR, Gebelein B, Weirauch MT, Sestan N, Martin JH, Yoshida Y. Control of species-dependent cortico-motoneuronal connections underlying manual dexterity. Science. 2017 Jul 28;357(6349):400-404.