BIOGRAPHICAL SKETCH

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NAME: MUGE N. KUYUMCU-MARTINEZ

eRA COMMONS USER NAME (credential, e.g., agency login): MUGE11

POSITION TITLE: Professor (Tenured)

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
Middle East Technical University, Ankara, Turkey	B.S.	07/1997	Biological Sciences
Baylor College of Medicine, Houston, TX	Ph.D.	10/2003	Molecular Virology/RNA binding proteins
Baylor College of Medicine, Houston, TX	Post-Doc	12/2008	RNA biology/heart/muscle disease/development
Baylor College of Medicine, Houston, TX	Instructor	11/2010	RNA biology/heart/muscle disease and development

A. Personal Statement

Using state of the art RNA-sequencing technologies, molecular, and cellular biology methods with rodent models, my team investigates clinically relevant questions about gene regulatory RNA networks and their regulation by RNA-binding proteins in normal and diseased hearts. My leadership, expertise and commitment to the field are clearly demonstrated through successful publications in RNA biology of heart development and heart disease.

Over the years, we have made significant contributions to our understanding of RNA regulatory networks (splicing and polyadenylation) that impact gene expression and function in the heart and their contributions to pathogenesis of heart diseases. We identified signaling pathways and several different RNA binding proteins including PTBP1, RBFOX2 and CELF1 that contribute to aberrant gene expression in diabetic hearts or in hypoplastic left heart syndrome.

Our research is funded by several different grants. The list of ongoing grants that I would like to highlight:

Kuyumcu-Martinez (PI)
ACTIVE
HL157780-01 05/01/22 – 06/30/26
National Institutes of Health/NHLBI
“The role of RNA binding proteins in heart development and congenital heart defects”

Kuyumcu-Martinez (PI) 01/2022 – 12/2024
ACTIVE
Additional Ventures/ Single Ventricle Research Fund
“Defining Cell-Specific Roles of RBFOX2 in Cardiovascular Development and in HLHS”

Kuyumcu-Martinez (PI) 07/2022 – 06/2023
ACTIVE
Additional Ventures Expansion Award
“Defining Cell-Specific Roles of RBFOX2 in Cardiovascular Development and in HLHS”

Kuyumcu-Martinez (PI) 01/2021-12/31/2023
ACTIVE
20TPA35490206
American Heart Association Transformational Project Award
"RNA regulatory networks in normal and diseased hearts"

Kuyumcu-Martinez (co-I) 04/2022 – 03/2026
ACTIVE
Name of PD/PI: Zhang, Lilei
R01 HL150589
National Institutes of Health/NHLBI
"Deciphering the role of a circadian lncRNA in cardiac remodeling"

I have not published or created research products under a different name.

B. Positions, Scientific Appointments, and Honors

Positions

Feb 2023- present	Professor, Department of Molecular Physiology and Biological Physics, University of Virginia Medical School, Charlottesville, VA
July 2021- Feb 2023	Director, Biochemistry, Cellular and Molecular Biology Graduate Program
Sep 2018- Feb 2023	Associate Professor with Tenure, Department of Biochemistry and Molecular Biology, Department of Neuroscience and Cell Biology, Institute for Translational Sciences UTMB, Galveston, TX
Nov 2010- Aug 2018	Assistant Professor, Department of Biochemistry and Molecular Biology, Department of Neuroscience and Cell Biology, Institute for Translational Sciences UTMB, Galveston, TX
2008-2010	Instructor, Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX
2004-2007	Post-doctoral fellow, Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX (Thomas Cooper, supervisor)
1998-2003	Graduate student, Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX (Richard Lloyd, preceptor)
1997-1998	Teaching Assistant, Department of Biological Sciences, Middle East Technical University, Ankara, Turkey

Honors and Awards

2021-2023	Director, Biochemistry, Cellular and Molecular Biology Graduate Program, UTMB
2019	CPRIT High Risk High Impact Research Award
2018	Tramonte Endowment Graduate School Faculty Award, UTMB
2014	Scholar, Institute for Translational Sciences, UTMB
2012	Basil O'Connor Starter Scholar, March of Dimes Foundation
2007	Travel award, International Myotonic Dystrophy Meeting, Milan, Italy
2007	Young scientist accommodation award, International Myotonic Dystrophy Meeting, Milan, Italy
2007	Outstanding platform presentation, International Myotonic Dystrophy Meeting, Milan, Italy
2005	Travel award for International Myotonic Dystrophy Meeting, Quebec City, Canada
2005	National Institute of Health Ruth L. Kirschstein National Research Service Award
2001	Travel Award for American Society for Virology Meeting Madison, WI
2000	Poster award, Molecular Virology & Microbiology Retreat, Houston, TX
1998	PhD Scholarship from Higher Education Council

Referee for: Nature Communications, Cell Reports, EMBO Reports, Cardiovascular Research, RNA, Communications Biology, International Journal of Cardiology, Molecular and Cellular Biology, International Journal of Molecular and Cellular Cardiology, PLoS, Scientific Reports, MicroRNA, Journal of Molecular Endocrinology, Molecular and Cellular Endocrinology, Journal of Histology and Cytology, Experimental and Molecular Pathology

Editorial Board:

Frontiers in Cell and Developmental Biology, Cellular Biochemistry, Associate Editor
Frontiers in Molecular Biosciences, Cellular Biochemistry, Associate Editor

Grant reviewer: **Ad hoc reviewer for:**

International

- Natural Sciences and Engineering Research Council of Canada**,** Genes, Cells and Molecules Study Section (2021)
- Diabetes UK, United Kingdom (2020)

National

- National Institutes of Health, Cardiovascular Differentiation and Development (CDD) study section (2017, 2019, 2019, 2020, 2022, 2023)
- Department of Defense, Congressionally Directed Medical Research Programs (2018, 2019 and 2023)
- Graduate Women in Science National Fellowship Program (2019)
- American Heart Association (2017)
- National Sciences and Engineering Research Council of Canada (2020)
- Diabetes United Kingdom Research (2020)

Other experience and Professional Memberships:

2009- present Member, RNA Society
2009- present Member, American Heart Association

C. Contributions to Science

1. Discovered a novel mechanism by which positive-strand RNA viruses inhibit host mRNA translation.

My PhD work provided an exceptional foundation in RNA biology, in particular, the regulation of mRNA translation, RNA-binding proteins, and virology. I identified alternative mechanisms used by RNA viruses to manipulate cellular translation. Our findings were the first to demonstrate that the poly(A)-binding protein associated with ribosomes is preferentially targeted by viral proteases to block protein synthesis in the infected cell. I discovered a unique mechanism used by RNA viruses to modulate and disrupt host mRNA translation. This work was a paradigm change in the field.

1. **Kuyumcu-Martinez N.M.,** Belliot G., Sosnovtsev S.V., Chang K.O., Green K.Y., Lloyd R.E. Calicivirus 3C-like proteinase inhibits cellular translation by cleavage of poly(A)-binding protein. *Journal of Virology.* **2004** Aug;78(15):8172-82 (PMCID: PMC446144).

2. **Kuyumcu-Martinez M.N,** Van Eden M.E., Younan P., Lloyd R.E. Cleavage of poly(A)-binding protein by poliovirus 3C protease inhibits host cell translation: a novel mechanism for host translation shutoff. *Molecular and Cellular Biology.* **2004** Feb;24(4):1779-90 (PMCID: PMC344173).

3. Graham K.L., Gustin K.E., Rivera C., **Kuyumcu-Martinez N.M.**, Choe S.S., Lloyd R.E., Sarnow P, Utz PJ. Proteolytic cleavage of the catalytic subunit of DNA-dependent protein kinase during poliovirus infection. *Journal of Virology.* **2004** Jun;78(12):6313-21(PMCID: PMC416498).

4. **Kuyumcu-Martinez N.M.**, Joachims M., Lloyd R.E. Efficient cleavage of ribosome-associated poly(A)binding protein by enterovirus 3C protease. *Journal of Virology*. **2002** Mar;76(5):2062-74 (PMCID:PMC135927).

2. A critical role of Protein Kinase C signaling in Myotonic Dystrophy Cardiac Pathogenesis: Dysregulation of alternative splicing by modulating RNA-binding proteins.

My post-doctoral training with Dr. Thomas Cooper at Baylor College of Medicine focused on alternative splicing (AS) dysregulation by RNA-binding proteins in Myotonic Dystrophy. My published and funded work demonstrated that activation of protein kinase C signaling leads to dysregulation of the RNA binding proteins and aberrant AS in Myotonic Dystrophy patient hearts.

1. **Kuyumcu-Martinez, N.M.**, G.S. Wang, T.A. Cooper. Increased steady state levels of CUGBP1 in Myotonic Dystrophy 1 are due to PKC-mediated hyperphosphorylation. *Molecular Cell.* **2007** 28:68-78. (PMCID: PMC2083558)

2. **Kuyumcu-Martinez, N.M**. and T.A. Cooper. Misregulation of alternative splicing causes pathogenesis in Myotonic Dystrophy. *Progress in Molecular and Subcellular Biology.* **2006.** 2006;44:133-59 (PMID: 17076268).

3. Targeting PKC to ameliorate alternative splicing defects and cardiac manifestations of Myotonic Dystrophy.

Using pharmacological inhibitors of PKC activity, we were able to alleviate cardiac symptoms in the Myotonic Dystrophy mouse model by restoring RNA-binding protein function and AS defects.

1. Wang G.S.*, **Kuyumcu-Martinez M.N.*,** Sarma S., Mathur N., Wehrens X.H.T, Cooper T.A. PKC inhibition ameliorates the cardiac phenotype in a mouse model of myotonic dystrophy type 1. *Journal of Clinical Investigation.* **2009** Dec; 119(12):3797-806 (PMCID:PMC2786786) **(* Equal contribution)**

4. Mechanism of aberrant gene regulation by RNA binding proteins in diabetic heart disease.

Since we identified the RNA binding proteins CELF1 and RBFOX2 as targets of PKC and PKC is aberrantly activated in diabetic hearts, we hypothesized that RNA regulatory gene networks regulated by CELF1 and RBFOX2 are dysregulated in diabetic hearts. Indeed, we found genome wide alternative splicing changes in diabetic hearts and identified several RNA binding proteins including RBFOX2, CELF1 and PTBP1 that are altered in diabetic hearts, contributing to abnormal alternative splicing of genes. We demonstrated that RBFOX2 has a loss of function in diabetic hearts due to upregulation of a dominant negative isoform of RBFOX2. We showed that expression of dominant negative RBFOX2 adversely affects splicing and intracellular calcium transients in cardiomyocytes.

1. Nutter CA, **Kuyumcu-Martinez M.N**. Emerging roles of RNA binding proteins in diabetes and their therapeutic potential in diabetic complications. Wiley interdisciplinary reviews. RNA. **2018**; 9(2).

2. Nutter C.A., Jaworski E., Verma S.K., Perez-Carrasco Y., **Kuyumcu-Martinez M.N**. Developmentally regulated alternative splicing is perturbed in diabetic skeletal muscle. *Muscle and Nerve.* **2017** Oct;56(4):744-749.

3. Nutter C.A., Jaworski E., Verma S.K., Deshmukh V., Botvinnik O.B., Wang Q., Lozano M.J., Abass I. J., Iljaz T., Brasier A. R., Garg N.J., Wehrens X.H.T., Yeo G.W., **Kuyumcu-Martinez M.N**. Dysregulation of RBFOX2 is an early event in cardiac pathogenesis of diabetes. *Cell Reports.* **2016** Jun 7; 15(10):2200-13.

4. Verma S.K., Deshmukh V., Liu P., Nutter, C**.** A., R. Espejo, M-L. Hung, G-S Wang, Yeo G. W., **Kuyumcu-Martinez M.N**. Reactivation of fetal splicing programs in diabetic hearts is mediated by protein kinase C signaling. *Journal of Biological Chemistry.* **2013** Dec; 288(49): 35372-86 (PMCID:PMC3853285).

5. Post-transcriptional gene regulatory networks in developing heart and in congenital heart disease.

Human genetic studies showed that *RBFOX2* mutations are associated with hypoplastic left heart syndrome. We showed that RBFOX2 contributes to abnormal gene expression in patients with hypoplastic left heart syndrome. To determine the role of RBFOX2 in heart development, we ablated *RBFOX2* in cardiac progenitor cells and found that it is essential for heart development specifically for 4-chambered heart and OFT formation (*Nucleic Acids Research,* 2022). Our recent work identified a novel role for RBFOX2 in alternative polyadenylation that leads to changes in mRNA levels of mitochondrial and contractile genes (*Cell Reports, 2021*). By establishing a strong role for RBFOX2 in heart development and HLHS, we will decipher cell specific targets of RBFOX2 in the embryonic heart and reveal novel RBFOX2-regulated pathways necessary for cardiovascular development disrupted in HLHS.

1. Cao J., Verma, S.K., Jaworski E., Mohan S., Nagasawa C.K., Rayavara K., Sooter A., Miller S.N., Holcomb R.J., Powell M.J., Ji P., Elrod N., Yildirim E., Wagner E.J., Popov V., Garg N.J., Routh A.L., **Kuyumcu-Martinez M.N**. Rbfox2 is critical for maintaining alternative polyadenylation and mitochondrial health in myoblasts. *Cell Reports*. **2021 (doi:** https://doi.org/10.1101/2020.05.13.093013).

2. Verma, S.K., Deshmukh, V., Thatcher, K., Belanger, K., Rhyner, A.M., Meng, S., Holcomb, R.J., Bressan, M., Martin, J.F., Cooke, J.P., Wythe, J.D., Lincoln, J., **Kuyumcu-Martinez, M.N.** RBFOX2 is required for establishing RNA regulatory networks essential for heart development. *Nucleic Acids Research*. **2022***.* Feb 28;50(4):2270-2286. (doi: 10.1093/nar/gkac055)

Complete list of my published work can be found in NCBI using the link below:

http://www.ncbi.nlm.nih.gov/sites/myncbi/muge.kuyumcu-martinez.1/bibliography/40908336/public/?sort=date&direction=descending