BIOGRAPHICAL SKETCH

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NAME: Madireddy, Advaitha

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

POSITION TITLE: Assistant 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
SRM University, India	B.Tech	08/2008	Genetics
University of Pittsburgh, USA	Ph.D	07/2012	Human Genetics/DNA repair
Albert Einstein College of Medicine, USA		09/2018	Cell Biology/DNA Replication

A. Personal Statement

My research program is focused on understanding the molecular mechanisms in our cells that encounter and overcome the effects of endogenous and exogenous genotoxins. Built at the crossroads of DNA replication and DNA repair, our research identifies and examines genomic hotspots of instability, known as fragile sites, to understand the contribution of instability arising from these regions to different cancer-predisposition syndromes, virus-mediated disorders, and healthy human cells. Through our studies, we try to understand the process of age-associated mutagenesis and understand how deficiencies of specific genes and the associated processes can driving pathogenic outcomes. Importantly, since mechanisms driving age-associated mutagenesis are difficult to study given the human life span, our studies on cancer predisposition and premature aging disorders, give us accelerated insights into to the age-associated mutagenesis process. We are employing a specialized set of tools and interdisciplinary approaches to test our hypotheses.

Ongoing projects that I would like to highlight include:

- New Jersey Commission on Cancer Research (COCR22PRG002)
  Madireddy (PI)
  07/01/1/2022 – 06/30/2025
  Novel Molecular Mechanisms Dysregulated in the Absence of the PHF6 Tumor Suppressor in Pediatric T-ALL.
- Department of Defense (W81XWH-21-1-0935)
  Madireddy (PI)
  09/15/2021 – 09/14/2024
  Project Goals: Understanding the mechanisms driving Clonal Hematopoiesis-associated mutations
- National Institute of Health (U01OH012271)
  Verma (PI); Madireddy (Co-PI)
  07/01/1/2021 – 06/30/2024
  Project Goals: Early detection of clonal hematopoiesis and leukemia associated mutations in WTC exposed firefighters after the 9/11 attacks.

B. Positions, Scientific Appointments, and Honors

Positions
08/2012 - 10/2018: Postdoctoral Fellow, Albert Einstein College of Medicine, NY
08/2014 - 10/2017: Co-chair of the Einstein Postdoctoral Association, Albert Einstein College of Medicine, NY

Scientific Appointments
10/2018 - Present: Assistant Professor, Rutgers Cancer Institute of New jersey, NJ

Honors
03/2022 - Distinguished Alumni-Academic Excellence Award
04/2017 - K99/R00 Pathway to Independence award
06/2017 - Dennis Shields Award
09/2016 - Harry Eagle Scholar Award
08/2006 - Fellowship Award for Exceptional Undergraduate Research

C. Contributions to Science

1. Delineating the mechanisms driving somatic mutagenesis in humans due to environmental exposures. The terms civilization and urbanization have been redefined over the last century and have brought with it an unprecedented increase in environmental pollution. Human beings are constantly exposed to low levels of DNA damaging agents, either by respiration, physical contact, or dietary ingestion. Nearly 20% of pre-mature deaths have been attributed to environmental pollution. Over the years, while the immediate health outcomes resulting from specific exposures has been well studied, our understanding of the sustained long-term effects of these exposures is still evolving. Research from our lab has revealed that the long-term age-associated effects of acute or chronic exposures is likely far worse than the immediate health issues observed today. In this study, we evaluated the long-term impact of the toxic environmental exposure to highly toxic carcinogens on first responders to the world trade center disaster. The study revealed that exposure is associated with a high burden of Clonal Hematopoiesis in 9/11 first responders due to massive genomic instability stemming from DNA replication dysregulations at fragile sites. This emerging idea is further complicated by endogenous factors such as genetics that could play a critical role in accelerating the adverse health outcomes. In a second study, evaluating the importance of Translesion polymerase eta to fragile sites replication, we showed that regions of replication fork stalling identified in the absence of Pol eta were associated with increased genetic variations in human cells indicating that structural variations at these genomic locations are mediated by Pol eta.

- Jasra S+, Giricz O+, Zeig-Owens R+, Pradhan K+, Goldfarb DG+, Barreto-Galvez A+, Silver AJ+, Chen J, Sahu S, Gordon-Mitchell S, Choudhary G, Aluri S, Bhagat TD, Shastri A, Bejan CA, Stockton SS, Spaulding TP, Thiruthuvanathan V, Goto H, Gerhardt J, Haider HS, Veerappan A, Bartenstein M, Nwankwo G, Landgren O, Weiden MD, Lakostaj J, Bender R, Fletcher F, Greenberger L, Ebert B, Steidl U, Will B, Nolan A* **Madireddy A***, Savona MR*, Prezant DJ*, Verma A* (**2022**). *High burden of Clonal Hematopoiesis in Firefighters Exposed to the World Trade Center Disaster*. ***Nature Medicine*** Mar;28(3):468-471. doi: 10.1038/s41591-022-01708-3. Epub 2022 Mar 7. PMID: 35256801
  corresponding author
- Twayana S+, Bacolla A+, Barreto-Galvez A, De-Paula RB, Drosopoulos WC, Settapong T. Kosiyatrakul, Bouhassira E, Tainer JA, **Madireddy A*,** Schildkraut CL* (**2021**). *Translesion polymerase eta both facilitates DNA replication and promotes increased human genetic variation at common fragile sites.* ***Proceedings of the National Academy of Sciences*** pnas.2106477118; PMID: 34815340
  corresponding author

2. Replication Through Repetitive DNA Elements and Their Role in Human Diseases. Human cells contain various repetitive DNA sequences, which can be a challenge for the DNA replication machinery to travel through and replicate correctly. Repetitive DNA sequence can adopt non-B DNA structures, which could block the DNA replication. Prolonged stalling of the replication fork at the endogenous repeats in human cells can have severe consequences such as genome instability that includes repeat expansions, contractions, and chromosome fragility. Hundreds of genes and proteins, involved in essential cellular pathways, work together in a well-coordinated manner to regulate DNA replication. However, through our research, we have revealed that DNA replication at fragile sites requires additional proteins and signaling components for normal replication to ensure stability of these replication even during an unchallenged s-phase. Summarized here are some of the manuscripts that have contributed to this finding.

- Nanez, SA, da Silva Almeida, AC, Galvez, AB, Albero, R, Gunning, T, Aparicio, T, Wendorff, A, Piovan, E, van Vlierberghe, P, Gygi S, Gautier J, **Madireddy, A**, Ferrando, A (2022) The PHF6 tumor suppressor couples chromatin remodeling and replication dynamics for prevention of replicative stress-induced DNA damage in satellite DNA. ***Blood.*** *2022 Mar 25:blood.2021014103. doi: 10.1182/blood.2021014103. PMID: 35338774*
- Paniza, T, Deshpande, M, Wang, N, Edwards, MM, O'Neil, R, **Madireddy, A**, James, D, Ecker, J, Rosenwaks, Z, Egli, D and Gerhardt, J (2020) *PSC with low differentiation potential contain incompletely reprogrammed DNA replication.* ***The Journal of Cell Biology***. PMID: 32673399
- **Madireddy, A,** Gerhardt, J. (2017) Replication Through Repetitive DNA Elements and Their Role in Human Diseases. *Advances in Experimental Medicine and Biology, Springer* (Editors: Hisao Masai and Marco Foiani) PMID: 29357073
- Gerhardt J, Zaninovic N, Zhan Q, **Madireddy A**, Nolin SL, Ersalesi N., Yan, Z., Rosenwaks Z, Schildkraut CL. (2014). *Cis-acting DNA sequence at a replication origin promotes repeat expansion to fragile X full mutation*. ***The Journal of cell biology***.; 206:599-607 PMID: 25179629, PMCID: PMC4151148.

3. Determining the mechanistic involvement of the FA/BRCA tumor suppressor pathway in DNA replication. FA is a rare genetic disorder that results in the absence of any one of 23 currently known genes in the human body, which together are referred to as the FA pathway. FA is characterized by bone marrow failure, developmental defects, and a high incidence of malignancies[24]. While the hematological abnormalities are largely managed by bone marrow transplants, the high incidence of malignancies is a prevailing challenge to patients and clinicians. While the mechanisms driving cancer development is FA patients are not clearly understood, cancer is still believed to be the primary cause for patient mortality. For this reason, a prominent line of Fanconi anemia research over the years has been focused on understanding the role(s) of the FA pathway proteins in the human body. Over the years, our research has contributed significantly toward establishing a new role for some of the FA pathway proteins in DNA replication. We have shown that Fanconi anemia complementation group D2 protein not only facilitates DNA replication at fragile sites by the timely resolution of DNA: RNA hybrids formed as a consequence of transcription: replication conflicts. In addition, we have shown that depletion of FANCM or its obligatory binding partners induces pronounced replication stress at ALT telomeres. More recently, we have collaboratively described a new role for BRCA2 in suppressing PRIMPOL-mediated repriming and single-stranded gap formation after DNA damage. In addition, we have shown that error-prone repair is the predominant mechanism driving loss of heterozygosity in BRCA1 haploinsufficient cells.

- Madhura Deshpande; Theodore Paniza; Amnon Koren; Nikica Zaninovic; Qiansheng Zhan; **Advaitha Madireddy**; Gouri Nanjangud; Zev Rosenwaks; Jeannine Gerhardt (2022) Error-prone repair of stalled replication forks drives mutagenesis and loss of heterozygosity in haploinsufficient BRCA1 cells ***Molecular Cell***, Sep 7;S1097-2765(22)00806-1.doi: 10.1016/j.molcel.2022.08.017 PMID: 36099913
- Kang, Z, Alcivar, AL, Fu, P, Fu, H, Redon, C, Foo, TK, Zuo, Y, Ye, C, Baxley, R, **Madireddy, A**, Buisson, R, Bielinsky, A, Zou, L, Shen, Z, Aladjem, MI and Xia, B (2021) *BRCA2 associates with MCM10 to suppress PRIMPOL-mediated repriming and single-stranded gap formation after DNA damage*. ***Nature Communication*** **12,** 5966 (2021). https://doi.org/10.1038/s41467-021-26227-6 PMID: 34645815
- Pan, X, Drosopoulos, WC, Sethi, L, **Madireddy, A**, Schildkraut, CL, and Zhang, D. (2017). FANCM, BRCA1, and BLM cooperatively resolve the replication stress at the ALT. ***Proceedings of the National Academy of Sciences***. 114(29):E5940-E5949 PMID: 28673972
- **Madireddy A***, Kosiyatrakul ST, Boisvert RA, Herrera-Moyano E, García-Rubio ML, Gerhardt J, Vuono EA, Owen N, Yan Z, Olson S, Aguilera A, Howlett NG, Schildkraut CL* (2016) *FANCD2 Facilitates Replication through Common Fragile Sites.* ***Molecular Cell***. 64(2):388-404. PMID: 27768874 ***corresponding author**

4. Understanding cancer pre-disposition and premature aging in inherited disorders of DNA repair. During my PhD, my project focused on understanding the mechanistic involvement of the DNA repair proteins XPF/ERCC1 in disorders such as Xeroderma pigmentosum (XP) and Fanconi anemia (FA) that predispose an individual to cancer and aging. My research mainly aimed at predicting and manipulating a patient's response to a chemotherapeutic regime with major emphasis on overcoming chemotherapy resistance. Using site directed mutagenesis (in collaboration with the Schärer Lab), we determined that mutations in specific domains of XPF and ERCC1 uncouple the functions of the proteins between the NER and ICL-R pathways. Further, we studied the role of the four C-terminal DNA binding domains of XPF/ERCC1 in mediating NER activity. We found that mutations in the helix-hairpin-helix domain of ERCC1 and the nuclease domain of XPF abolished cleavage activity on model substrates. Interestingly, mutations in multiple DNA binding domains were needed to

significantly diminish NER activity in vitro and in vivo, suggesting that interactions with proteins in the NER incision complex can compensate for some defects in DNA binding. Mutations in DNA binding domains of XPF-ERCC1 render cells more sensitive to the crosslinking agent mitomycin C than to ultraviolet radiation, suggesting that the ICL repair function of ERCC1-XPF requires tighter substrate binding than NER. These studies enabled us to specifically inhibit the ICL-R function of the proteins while keeping the NER roles intact.

- Su, Y., Orelli, B., **Madireddy, A**., Niedernhofer, L.J., and O.D. Schärer (2012) *Multiple binding domains mediate the function of ERCC1-XPF in nucleotide excision repair. J* Biol Chem. PMID:22547097
- **Madireddy, A**., Niedernhofer, L.J (2012) *Linking the multiple functions of XPF-ERCC1 endonuclease in DNA repair to health outcomes: Cancer and aging* (Thesis)

5. Understanding the molecular mechanisms driving virus-mediated carcinogenesis. A major line of investigation in my lab has focused on identifying and characterizing virus-mediated carcinogenesis. Over the years, we have focused on three viruses, the Kaposi's sarcoma associated herpes virus (KSHV), Human Lymphotropic Virus Type1 (HTLV-1) and Hepatitis B virus (HBV). KSHV is a causative agent of multiple human malignancies and establishes a lifelong latency in infected individuals. During latency, the KSHV genome exists as an episome and is tethered to the host chromosome, and through this association, the virus replicates along with the cellular DNA and segregates into the newly divided tumor cells. Through our studies directly visualizing KSHV genome replication, we show that replication forks pause at the viral terminal repeats that can form secondary structures called G-quadruplexes (G4). This led to the identification if G4 stabilizers as therapeutic agents in blocking KSHV associated malignancies. Our current studies are focused on the HTLV-1 ad HBV viruses.

- Jian Cao; Haozhen Ren; Xun Chen; Jinglin Wang; Ying Chen; Shreya Gandhi; Alex Bueker; Liqun Tu; Qian Xiao; Shiwei Fu; Madireddy, A; Wei Vivian Li; Xiaolei Shi (2022) Temporal and structural patterns of hepatitis B virus integrations in hepatocellular carcinoma. ***Cell Reports Medicine (In Revision)***
- Galvez, AB, Ye, BH and **Madireddy, A** (2019). *Understanding the Mechanisms Driving Genomic Instability in Adult T-Cell Leukemia/Lymphoma**. Blood*** 134, 5042
- Ye, BH, Chung, E, Pradhan, K, Villaorduna, AA, Wang, Y, Shastri, A, **Madireddy, A**, Verma, A, Sica, AA, Janakiram, M (2019) *S-Phase Progression of North American ATLL Cells Is Critically Regulated By the Proto-Oncogene BCL6 and Targetable By PARP Inhibition. **Blood*** 134, 3779
- **Madireddy, A**, Purushothaman, P., Robertson, E., Verma, S., and Schildkraut, CL. (2016) *G-quadruplex-interacting compounds alter latent DNA replication of KSHV.* Nucleic Acids Research PMID: 26837574

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