BIOGRAPHICAL SKETCH

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NAME: Aleman, Maria M.

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

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
Humboldt State University, Arcata, CA	BS	05/2002	Zoology
Univ of North Carolina at Chapel Hill, Chapel Hill, NC	PhD	01/2014	Pathology
Univ of North Carolina at Chapel Hill, Chapel Hill, NC	Postdoc	01/2015	Immunology

A. Personal Statement

I am an Assistant Professor of Pharmacology and member of the RNA Discovery Center (RDC). I run an independent research lab focused on mechanisms of RNA regulation. We use a spectrum of techniques (biochemical, cell-based, and *in vivo*) to answer basic and clinically relevant questions in the pathophysiology of vascular and blood-related diseases with a particular focus on erythropoiesis and iron deficiency. We are studying how intracellular iron levels impact posttranscriptional control of the transcriptome through modulation of poly C binding protein (PCBP) RNA regulation. We currently have a manuscript, in collaboration with Daniel Dominguez's lab, on this topic in revision at *Nucleic Acids Research* and available on bioRxiv (Forbes, et al., *bioRxiv*, 2024).

For this proposal for the RDC Collaborative Award, I am Principal Investigator with Co-Investigator, Daniel Dominguez. Our goal for this project is to define cell- and tissue-specific responses to changing iron levels using a multi-layered investigation of RNA regulation. We will probe alternative splicing, mRNA stability, and translation in response to iron deficiency. My group has established diet-induced mouse models of iron deficiency and iron deficiency anemia that will be used to generate tissue samples for this study. We will also work to identify novel iron regulatory elements by combining predictions from a new tool the Dominguez Lab has developed with proteomics and unbiased crosslinking and immunoprecipitation approaches. We expect to uncover interesting biology and deep molecular insights into iron-sensitive RNA regulation. These aims fit well with the goals of the RDC. Support from this award will provide needed resources to enable subsequent R-level applications to extend our work.

<u>On-going projects:</u>
R01DK124773 (NIH/NIDDK), Aleman (PI)
07/01/2020-04/30/2025
Iron-sensitive RNA regulation during erythropoiesis

2023ESR0000097 (Sanofi Inc), Aleman (PI)
09/12/2024-08/31/2025
Fibrin Formation Assays to Test Procoagulant Activity

Relevant Citations:

1. Forbes K*, Goda GA*, Eramo GA, Breen C, Porter DF, Khavari PA, Dominguez D[§], **Aleman MM[§]**. "Iron-sensitive RNA regulation by poly C binding proteins." *bioRxiv* 2024. doi: https://doi.org/10.1101/2024.10.17.618301. [§]*Co-corresponding*
2. Harris SE, Alexis MS, Giri G, Cavazos FF, Murn J, **Aleman MM**, Burge CB, Dominguez D. "Understanding species-specific and conserved RNA-protein interactions in vivo and in vitro." *Nature Communications*, 2024, 15(article number 8400). PMCID: PMC11436793
3. Missios P, Lummertz da Rocha E, Pearson DS, Philipp J, **Aleman MM**, Pirouz M, Farache D, Franses JW, Kubaczka C, Tsanov K, Jha D, Pepe-Mooney B, Powers J, Gregory R, Lee ASY, Dominguez D, Ting DT, Daley GQ. LIN28B alters ribosomal dynamics to promote metastasis in MYCN-driven malignancy. *Journal of Clinical Investigation*. 2021 Nov 15;131(22):e145142. PMCID: PMC8592552
4. Porter DF, Miao W, Yang X, Goda GA, Ji AL, Donohue LKH, **Aleman MM**, Dominguez D, Khavari PA. easyCLIP Analysis of RNA-Protein Interactions Incorporating Absolute Quantification. *Nature Communications*. 2021 12(1):1569. PMCID: PMC7946914

B. Positions, Scientific Appointments, and Honors

Positions

2022-Present Interim Co-Chair of Diversity Liaisons, UNC Chapel Hill
2021-Present Assistant Professor, Dept of Pharmacology, UNC Chapel Hill
2019-Present Diversity & Inclusion Liaison, Dept of Pharmacology, UNC Chapel Hill
2018-2021 Research Assistant Professor, Dept of Pharmacology, UNC Chapel Hill
2017-2018 Scientist II, Protein Therapeutics, Bioverativ (Biogen spin-off), Waltham, MA
2015-2017 Scientist I, Hematology Research, Biogen, Cambridge, MA
2014-2015 Postdoctoral Research Associate, UNC Chapel Hill
2008-2014 Graduate Student Researcher, UNC Chapel Hill
2004-2008 Research Specialist and Lab Manager, Emory University, Atlanta, GA

Scientific Appointments & Other Experience

2020-Present Member, RNA Society
2020-Present Member, Editorial Board, *Research Practices in Thrombosis and Haemostasis (RPTH)*
2019-2020 Reviewer, Pre- and Postdoctoral Fellowships study section, American Hearth Association
2018 Discussion Leader, Gordon Research Conference on Hemostasis, Waterville Valley, NH
2017 Session Co-chair, Immune Aspects of Thrombosis, XXVI ISTH Congress, Berlin, Germany
2017-Present *Ad hoc* Reviewer: *Haemophilia*, *Research Practices in Thrombosis and Haemostasis*, *The Veterinary Journal*
2016-Present *Ad hoc* Reviewer: *Journal of Thrombosis and Haemostasis*, *Thrombosis Research*
2015-Present *Ad hoc* Reviewer: *Arteriosclerosis, Thrombosis, & Vascular Biology*
2013 Session Co-chair, Prothrombin, XXIV ISTH Congress, Amsterdam, Netherlands
2013-Present Member, American Society of Hematology

Honors

2023 Leadership in Academic Medcine Program, UNC at Chapel Hill
2021 Invited Speaker, Cell Biology of Metals GRC, Mount Snow, VT
2020 Simmons Scholar Program, UNC at Chapel Hill
2019 Junior Faculty Development Award, UNC at Chapel Hill
2019 Top Performing Reviewer, *Research Practices in Thrombosis and Haemostasis* Journal
2015 Dean's Distinguished Dissertation Award, UNC at Chapel Hill
2014 Graduate Education Advancement Board Impact Award, UNC at Chapel Hill
2013 ASH Abstract Achievement Award, 55th Annual ASH Meeting, New Orleans, LA
2013 Trainee Choice Presentation Award, Pathology Department, UNC at Chapel Hill
2013 Young Investigator Award, XXIV ISTH Congress with 59th Annual SSC Meeting
2013 Sabin Travel Award, McAllister Heart Institute, UNC at Chapel Hill
2012-2014 F31 Predoctoral Fellowship, NIH/NHLBI
2012 Predoctoral Fellowship, American Heart Association
2012 Outstanding Graduate Student Presentation, Pathology Department, UNC at Chapel Hill

2011 Travel Award, Proteases in Hemostasis and Vascular Biology, Minority Access to Research Career Program, FASEB
2011 Outstanding Poster Presentation Award, McAllister Heart Institute/Integrative Vascular Biology Research Symposium, UNC at Chapel Hill
2010 Travel Award, Carl Storm Underrepresented Minority Fellowship, Gordon Research Conference on Hemostasis

1. **C. Contributions to Science**

Red blood cell (RBC) retention in venous thrombi is mediated by factor XIII: Venous thrombi are largely composed of RBCs and fibrin. Using in vivo and ex vivo techniques, I discovered that the activity of coagulation factor XIII (FXIII, a transglutaminase that crosslinks and stabilizes fibrin) is required for maximal RBC incorporation into venous thrombi (a). When FXIII is inhibited in human blood or knocked out in mice, clots that form have reduced RBCs and are significantly smaller, thereby reducing thrombotic burden. FXIII circulates in the blood bound to fibrinogen. Through the use of a mouse model with a mutant fibrinogen (Fibγ390-396), I discovered these fibrinogen residues bind to FXIII and demonstrated that the loss of FXIII localization on fibrinogen is sufficient to reduce RBC retention in venous thrombi. My findings established a new role for FXIII in venous thrombosis and led to several further detailed studies by the Wolberg Lab refining the mechanism. Of note, prior studies focusing on fibrinogen's role in inflammation had relied on Fibγ390-396 mice since these same residues bind integrin αMβ2. My study revealed potential alternative interpretations of those prior studies and subsequent studies using these mice (*e.g.,* Kopec et al. *JCI* 2017 Aug 1;127(8):3152-3166. PMCID: PMC5531415), have now controlled for the dual function of these fibrinogen residues.

   a. **Aleman MM**, Byrnes, JR, Wang, J-G, Tran R, Lam WA, Di Paola J, Mackman N, Degen JL, Flick MJ, Wolberg AS. Factor XIII activity mediates red blood cell retention in venous thrombi. *Journal of Clinical Investigation* 2014; 124(8):3590-3600. PMCID: PMC4109540. *Cover article.*
   b. **Aleman MM**, Byrnes, JR, Wang, J-G, Mackman N, Degen JL, Flick MJ, Wolberg AS. Fibrin Cross-linking is Required for Retention of Red Blood Cells in Venous Thrombi. 2013 American Society of Hematology Annual Meeting, New Orleans, LA. Abstract # 64374. Oral presentation. *ASH Abstract Achievement Award Winner*. *Included as Best of ASH: Thrombosis & Hemostasis.*

2. **Prothrombotic mechanisms:** Virchow's triad postulates that thrombosis results from combined risk factors from at least two of three areas: plasma hypercoagulability, vascular wall dysfunction, and/or altered blood flow, however the molecular mechanisms by which these properties confer that risk is often not clear. Across several studies during graduate school, I led or collaborated on projects aimed at resolving these gaps.

   a. **Aleman MM**, Gardiner C, Harrison P, Wolberg AS. Differential Contributions of Monocyte- and Platelet-derived Microparticles towards Thrombin Generation and Fibrin Formation and Stability. *Journal of Thrombosis and Haemostasis* 2011; 9: 2251-2261. PMCID: PMC3206146.
   b. Wang J-G, Gambone J, **Aleman MM**, Cardenas JC, Chantrathammachart P, Williams JC, Kirchhofer D, Bogdanov VY, Bach RR, Church F, Wolberg AS, Pawlinski R, Key NS, Yeh J-J, Mackman N. Tumor-derived Tissue Factor Activates Coagulation and Enhances Thrombosis in a Mouse Xenograft Model of Human Pancreatic Cancer. *Blood* 2012; 119(23):5543-52. PMCID: PMC3369688.
   c. **Aleman MM**, Walton BL, Byrnes JR, Wang J-G, Heisler M, Machlus KR, Cooley BC, Wolberg AS. Elevated prothrombin promotes venous, but not arterial, thrombosis in mice. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2013; 33(8):1829-1836. PMCID: PMC3779620.
   d. Cardenas JC, **Aleman MM**, Wang J-G, Whinna HC, Wolberg AS, Church FC. Murine Models Do Not Recapitulate the Pathophysiology of Age-Related Venous Thrombosis in Humans. *Journal of Thrombosis and Haemostasis* 2013; 11:990-992.

3. **Antibody-based treatments for hemophilia A:** New treatments in development for hemophilia have moved away from traditional factor replacement therapy towards non-factor approaches such as bispecific antibodies and inhibitors of coagulation inhibitors. During my time in industry we discovered bispecific

antibodies that could mimic factor VIII (FVIII) function in clotting assays and performed biophysical and mechanistic studies to understand the basis for their activity. Finally, we evaluated these antibodies and others against FVIII in clinically relevant assays to show that these standard assays are insufficient when dealing with non-FVIII drugs and that new assays that can measure the overall procoagulant potential of patient blood is badly needed.

a. Peters RT, Leksa N, Pearse BR, Kulman J, **Aleman M**, Goodman A, inventors; Bioverativ, a Sanofi company, assignee. Mono- and Bispecific antibodies binding to coagulation factor IX and coagulation factor X. World patent application WO2018/098363. 2016 Nov 23.
b. Leksa N, Arndt J, Goodman A, Knockenhauer K, **Aleman M***, Salas J, Peters R. Allosteric activation of factor IXa by an antibody binding to the protease domain. World Federation of Hemophilia 2018 World Congress. Abstract # M-P-036. Poster presentation. **Presenter*
c. **Aleman MM**, Leksa NL, Peters R, Salas J. Assay Challenges (and Opportunities) with Non-Factor VIII Therapies for Hemophilia A. *Expert Review of Molecular Diagnostics.* 2019; 19(1):1-3.
d. Leksa NC*, **Aleman MM***, Goodman A, Rabinovich D, Peters R, Salas J. Intrinsic differences between FVIIIa mimetic bispecific antibodies and FVIII prevent assignment of FVIII-equivalence. *Journal of Thrombosis and Haemostasis* 2019 Jul;17(7):1044-1052. PMCID: PMC6850022. **Co-first authors*.

4. **Oxidative stress and asthma:** Asthma exacerbations can be caused by exposure to ozone in the environment. These attacks are coupled with increased sputum levels of IL-1β. As part of my work during my postdoc we tested the effect of IL-1β antagonists and, separately, the antioxidant sulforaphane on ozone-induced lung inflammation in humans. Our clinical studies provided rationale for anti-inflammatory, but not oral antioxidant, intervention in allergic asthmatics.

a. Hernandez ML, Mills K, Almond M, Todoric K, **Aleman MM**, Zhang H, Zhou H, Peden DB. Interleukin-1 receptor antagonist reduces endotoxin-induced airway inflammation in healthy volunteers. *Journal of Allergy and Clinical Immunology* 2015; 135(2):379-85. PMCID: PMC4323893.
b. **Aleman MM**, Kesic MJ, Mills KH, Peden DB, Hernandez ML. The IL-1 axis is associated with airway inflammation after O3 exposure in allergic asthmatic patients. *Journal of Allergy and Clinical Immunology* 2015; 136(4):1099-101. PMCID: PMC4600417.
c. Duran CG, Burbank AJ, Mills KH, Duckworth HR, **Aleman MM**, Kesic MJ, Peden DB, Pan Y, Zhou H, Hernandez ML. A proof-of-concept clinical study examining the NRF2 activator sulforaphane against neutrophilic airway inflammation. *Respiratory Research* 2016; 17(1):89. PMCID: PMC4957339.

Complete list of my published works at:
https://www.ncbi.nlm.nih.gov/myncbi/1IlR5ZLjkLk5I/bibliography/public/