BIOGRAPHICAL SKETCH

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NAME: Maria M. Aleman

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
University of North Carolina at Chapel Hill	PhD	01/2014	Pathology
University of North Carolina at Chapel Hill	Postdoc	01/2015	Immunology

A. Personal Statement

I am a blood researcher working to elucidate molecular mechanisms regulating erythropoiesis. I have worked in the cardiovascular and blood fields since 2004 where I have focused on using a broad spectrum of techniques (biochemical, cell-based, and *in vivo*) to answer basic and clinically relevant questions in the pathophysiology of blood-related diseases. As a graduate student I explored both plasma and cellular contributions to hemostasis and thrombosis. In three distinct first-authored papers during this time, I gained extensive experience handling human and mouse blood, isolating primary cells from blood, using flow cytometry, performing biochemical, biophysical and kinetic assays, and mouse models. During my postdoc I gained experience with human clinical studies and analysis of primary human samples. This experience gives me the capability to facilitate future translational studies. For 3 years as a Scientist at Biogen/Bioverativ, I co-led a large drug discovery team (15 people) to find and test an antibody- based therapy for hemophilia A. There I designed and directed large screening efforts and guided biophysical and mechanistic studies of our antibody candidates. Despite publishing not being a priority at my company, I published two co-first authored papers (1 primary research and 1 commentary) as well as one patent application. I have since transitioned back into academia as an assistant professor and am pursuing science that I think is interesting and important. I was recently awarded an R01 from NIDDK to study the crosstalk between iron homeostasis and RNA regulation during erythropoiesis. M y career goal is to transition to a tenure-track assistant professor within a high-caliber research department.

1. **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* 2015; 124(8):3590-3600. PMCID: PMC4109540. *Cover article.*
2. **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.
3. **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.
4. 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 (*In press*)

B. Positions and Honors

Positions

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

Other Experience and Professional Memberships

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

Honors

2010 Travel Award, Carl Storm Underrepresented Minority Fellowship, Gordon Research Conference on Hemostasis
2011 Outstanding Poster Presentation Award, McAllister Heart Institute/Integrative Vascular Biology Research Symposium, UNC at Chapel Hill
2011 Travel Award, Proteases in Hemostasis and Vascular Biology, Minority Access to Research Career Program, FASEB
2012 Outstanding Graduate Student Presentation**,** Pathology Department, UNC at Chapel Hill
2013 Sabin Travel Award, McAllister Heart Institute, UNC at Chapel Hill
2013 Young Investigator Award, XXIV ISTH Congress with 59th Annual SSC Meeting
2013 Trainee Choice Presentation Award, Pathology Department, UNC at Chapel Hill
2013 ASH Abstract Achievement Award, 55th Annual ASH Meeting, New Orleans, LA
2014 Graduate Education Advancement Board Impact Award, UNC at Chapel Hill
2015 Dean's Distinguished Dissertation Award, UNC at Chapel Hill
2019 Top Performing Reviewer, *Research Practices in Thrombosis and Haemostasis* Journal
2019 Junior Faculty Development Award, UNC at Chapel Hill
2020 Simmons Scholar Program, UNC at Chapel Hill

C. Contributions to Science

1. **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 was 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 refining the mechanism (b-c). 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, such as Kopec et al. below, 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* 2015; 124(8):3590-3600. PMCID: PMC4109540.
b. Byrnes JR, Duval C, Wang Y, Hansen CE, Ahn B, Mooberry MJ, Clark MA, Johnsen JM, Lord ST, Lam WA, Meijers JC, Ni H, Ariëns RA, Wolberg AS. Factor XIIIa-dependent retention of red blood cells in clots is mediated by fibrin α-chain crosslinking. *Blood*. 2015 Oct 15;126(16):1940-8. PMCID: PMC4608241
c. Byrnes JR, Wilson C, Boutelle AM, Brandner CB, Flick MJ, Philippou H, Wolberg AS. The interaction between fibrinogen and zymogen FXIII-A2B2 is mediated by fibrinogen residues γ390-396 and the FXIII-B subunits. *Blood*. 2016 Oct 13;128(15):1969-1978. PMCID: PMC5064719.
d. Kopec AK, Abrahams SR, Thornton S, Palumbo JS, Mullins ES, Divanovic S, Weiler H, Owens AP 3rd, Mackman N, Goss A, van Ryn J, Luyendyk JP, Flick MJ. Thrombin promotes diet-induced obesity through fibrin-driven inflammation. *Journal of Clinical Investigation* 2017 Aug 1;127(8):3152-3166. PMCID: PMC5531415.

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 (*In press*) **Co-first authors*.

4. **Ozone-induced inflammation 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 (21 total) at:
https://www.ncbi.nlm.nih.gov/myncbi/1IIR5ZLjkLk5I/bibliography/public/