



The University of Wisconsin - Madison

**CMP**

Cellular and Molecular Pathology

**Andrew W. DeVilbiss**

Program of the Thesis Defense Seminar for the  
**Degree of Doctor of Philosophy**  
in Cellular and Molecular Pathology

**"Epigenetic Mechanisms Governing  
Erythroid Maturation and Function"**

Thursday, November 5th, 2015  
3:00 p.m.

Wisconsin Institutes for Medical  
Research, Tower I, Room 7001A

Research conducted in the lab of  
Emery H. Bresnick  
Department of Cell and Regenerative Biology

# Epigenetic Mechanisms Governing Erythroid Maturation and Function

*Andrew W. DeVilbiss*  
*Under the supervision of*  
*Professor Emery H. Bresnick, PhD*  
*at the University of Wisconsin-Madison*



## Andrew W. DeVilbiss's Thesis Abstract

Complex developmental programs require orchestration of intrinsic and extrinsic signals to control cell proliferation, differentiation and survival. Master regulatory transcription factors are vital components of the machinery that transduce these stimuli into cellular responses. This is exemplified by the GATA family of transcription factors that establish cell type-specific genetic networks and control the development and homeostasis of systems including blood, vascular, adipose, and cardiac. Dysregulated GATA factor activity/expression underlies pathologies including anemia, immunodeficiency, myelodysplastic syndrome and leukemia. Parameters governing the capacity of a GATA factor expressed in multiple cell types to generate cell type-specific transcriptomes include selective coregulator usage and target gene-specific chromatin states. GATA-1 interacts with ubiquitous and lineage-restricted transcription factors, chromatin modifying/remodeling enzymes, and other coregulators to activate or repress transcription and to maintain pre-existing transcriptional states. While many GATA factor coregulators have been defined, how GATA factors negotiate complex coregulator ensembles to establish cell type-specific transcriptomes is unknown. Unresolved questions regarding mechanisms of GATA factor coregulator usage include: how does a GATA factor selectively utilize diverse coregulators; do distinct epigenetic landscapes at target genes dictate coregulator requirements; and do gene cohorts controlled by a common coregulator ensemble function in identical pathways.

We sought to identify new mediators of GATA-1 function, with a particular interest in chromatin remodeling and modifying enzymes. Using a GATA-1 genetic complementation assay in GATA-1-null cells, we discovered that the lysine methyltransferase, SetD8, which monomethylates histone H4 at lysine 20 (H4K20me1) is a context-dependent corepressor for GATA-1. GATA-1 utilizes different combinations of SetD8, Friend of GATA-1 (FOG-1), and the NuRD component Mi2 to repress genes in a locus-specific manner, suggesting a matrix model for GATA-1 coregulator usage where unique molecular parameters of each locus dictate coregulator requirements. SetD8 promotes the GATA-1-dependent biological processes of erythroid maturation and erythroid cell survival. Importantly, SetD8 represses *Gata2* in proerythroblasts, and GATA-2 overexpression results in a similar maturation blockade as SetD8 knockdown. SetD8 establishes H4K20me1 at the critical +9.5 cis-regulatory element at *Gata2* and restricts *Scl/TAL-1* occupancy at the +9.5, resulting in *Gata2* repression. Our results establish SetD8 as a critical mediator of GATA-1 function and erythroid maturation/survival.

## Publications

1. **DeVilbiss AW**, Tanimura N, McIver SC, Katsumura KR, Johnson KD, Bresnick EH. 2015. Navigating Transcriptional Coregulator Ensembles to Establish Genetic Networks: A GATA Factor Perspective. *Curr Top Dev Biol. In Press*.
2. **DeVilbiss AW**, Sanalkumar R, Hall BDR, Katsumura KR, Fraga de Andrade I, Bresnick EH. 2015. Epigenetic determinants of erythropoiesis: role of the histone methyltransferase SetD8 in promoting erythroid maturation and survival. *Mol Cell Biol.* **35**(12): 2073-2087.
3. McIver SC<sup>1</sup>, Kang YA<sup>1</sup>, **DeVilbiss AW<sup>1</sup>**, O'Driscoll CA, Ouelette JN, Pope NJ, Campercios G, Chang CJ, Yang D, Bouhassira EE, Ghaffari S, Bresnick EH. 2014. The Exosome Complex Establishes a Barricade to Erythroid Maturation. *Blood* **124**(14): 2285-2297
4. **DeVilbiss AW<sup>1</sup>**, Sanalkumar R1, Bresnick EH. 2014. Hematopoietic Transcriptional Mechanisms: From Locus-Specific to Genome-Wide Vantage Points. *Exp Hematol.* **42**(8): 618-629
5. **DeVilbiss AW**, Boyer ME, Bresnick EH. 2013. Establishing a Hematopoietic Genetic Network through Locus-Specific Integration of Chromatin Regulators. *Proc Natl Acad Sci U.S.A.* **110**(36): E3398-3407. PMID: 23959865. PMCID: PMC3767509.

## Honor & Awards

2009 Deans Distinguished Research Fellowship, College of Science and Health, University of Wisconsin, La Crosse

2009 American Society for Biochemistry and Molecular Biology Undergraduate Affiliation Network (UAN) Travel Award

2010 Roberta A. and William W. Allen Chemistry Graduate Study Incentive Scholarship, UWL Foundation, University of Wisconsin, La Crosse

2011 UW-Madison Cell and Molecular Pathology T32 predoctoral training grant

2013 American Heart Association Predoctoral Training Grant

2014 Herbert Tabor Young Investigator Award, Journal of Biological Chemistry

2014 UW-Madison Cancer Biology T32 predoctoral training grant

2015 UW-Madison Vilas Conference Presentation Award

## Presentations

**DeVilbiss, AW,**

“Negative Design Induced Inhibition of Template-Assisted Hemolysis”.  
Seven Rivers Undergraduate Research Symposium, Viterbo University, La  
Crosse, WI. November 2009

**DeVilbiss, AW,**

Poster presentation: “Establishing a Hematopoietic Genetic Network  
through Locus-Specific Integration of Chromatin Regulators”. Gordon  
Research Conference on Red Cells, Andover, NH, July 2013.

**DeVilbiss, AW,**

Poster Presentation: “Establishing a Hematopoietic Genetic Network through  
Locus-Specific Integration of Chromatin Regulators”. Wisconsin Stem Cell  
Symposium. Madison, WI. April 2014.

**DeVilbiss, AW,**

"Establishing the Erythroid Transcriptome: Coregulator Matrix Model of  
GATA Factor Function". Midwest Chromatin and Epigenetics Meeting.  
Madison, WI. May 2014.

**DeVilbiss, AW,**

"Epigenetic determinants of erythropoiesis: Role of SetD8 in promoting  
erythroid cell maturation and survival". 12th Annual Signal Transduction  
Research Training Symposium. Madison, WI. March 2015.

**DeVilbiss, AW,**

"Epigenetic Mechanisms Governing Erythroid Maturation and  
Function". 2015 Gordon Research Conference on Red Cells, Holderness,  
NH. July 2015

**DeVilbiss, AW,**

Poster Presentation: "Epigenetic Mechanisms Governing Erythroid  
Maturation and Function" 2015 Gordon Research Conference on Red Cells,  
Holderness, NH. July 2015.

**DeVilbiss, AW,**

"Epigenetic Mechanisms Governing Erythroid Development and Function".  
University of Wisconsin, Department of Pathology and Laboratory Medicine  
Seminar Series. Madison, WI. September 2015.



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