BIOGRAPHICAL SKETCH

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NAME: Russell (Chip) Norris

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

POSITION TITLE: Assistant Professor (Tenure Track)

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
University of Cincinnati	BS	05/1995	Biology
Medical University of South Carolina	PhD	12/2000	Bone Development
Medical University of South Carolina	Postdoc	2001-2004	Anatomy & Embryology
Medical University of South Carolina	Postdoc	2005-2007	Heart Development

A. Personal Statement

Research in my laboratory is focused on the developmental mechanisms that contribute to the pathogenesis of cardiac valve diseases. The discovery of genes that cause valve disease and the regulatory pathways they control may reveal pathogenic mechanisms that hold potential for future therapies. I started my career roughly 20 years ago as a graduate student studying transcription factors that regulate bone development. During the latter part of my graduate training I began collaboration with other members of our cell biology and anatomy department whose focus was on cardiac development. These collaborations yielded a seminal paper on the initial discovery of the second heart field and its contribution to outflow tract development. These studies were the impetus for my continued interest in cardiac development. After completing 2 postdoctoral fellowship I have developed my own projects and goals and have my own lab as well as a tenure track position, which speaks to the university commitment of my science. I have always believed that the best way to succeed in science is through collaborative interactions not only with clinicians and scientists at other institutions but with those in the environment in which you work. This is most easily visualized with our Leducq Network that has since ended in funding but continues to integrate collaborators from all over the world. We collectively write grants and publish together. We recently published papers in Nature Reviews Cardiology, Nature, and Nature Genetics, among others. I am co-senior and co-corresponding author on these latter two manuscripts speaking to my independence and ability to lead and integrate large research projects.

B. Positions and Honors

Positions and Employment

1995-2000 Graduate student, Medical University of South Carolina, Department of Cell Biology and Anatomy (Dr. Michael Kern)
2001-2007 Post-doctoral fellowships, Medical University of South Carolina, Department of Cell Biology and Anatomy, Cardiovascular Developmental Biology Center
2007- Assistant Professor- Tenure Track, Medical University of South Carolina

Honors and Presentations (last 3 years)

2012 Platform Presentation, Leducq Cardiovascular Meeting, Jerusalem, Israel
2012 Platform Presentation, Leducq Cardiovascular Meeting, Paris, France
2012 Platform Presentation, Symposium on Development of the Heart, Amsterdam, Netherlands
2012 Invited Talk at University of South Carolina

2013 Invited Talk at CVRC Massachusetts General Hospital/Harvard (April 9th, 2013)
2013 Platform Presentation, Cardiovascular Development, Differentiation, and Disease Symposium, Charleston, SC
2013 Platform Presentation, Weinstein Cardiovascular Conference, Tuscon, Arizona
2013 Invited Talk at Vanderbilt University
2013 Invited Talk at Nationwide Children's Hospital Research Institute, Columbus, Ohio
2014 Platform Presentation, Cardiovascular Development, Differentiation, and Disease Symposium, Charleston, SC
2014 Invited Talk, Department of Pediatrics, MUSC
2014 Platform Presentation, Weinstein Conference, Madrid Spain
2014 Invited Talk, Pediatric Grand Rounds, Yale University
2014 Invited Talk, Valve Conference, Columbus, Ohio
2014 Invited Talk at Virginia Tech, Carilion
2014 Invited Talks at Imperial College and National Heart and Lung Institute, London
2014 AHA, Chicago, Il.—best in cardiovascular sciences presentation
2015 Platform Presentation, Keystone Symposium, Copper Mountain, Colorado
2015 3 Platform Talks at the Heart Valve Society Meeting, Monaco
2015 Keynote Presentation at the Heart Valve Society Meeting, Monaco

Grant Review Panels

2013- AHA Study Section Member for Cardiovascular Development
2014- NIH-NHLBI Study Section Member for R15/AREA Awards
2014- DOD/VA Study Section Member for CDMRP-PRMRP Congenital Heart Disease Panel
2015- AHA SURP Study Section Member

Editorial Positions

2014- Guest-Editor for **"Journal of Cardiovascular Development and Disease"**

Membership in Professional/Scientific Societies:

- Member of the American Association of Anatomists
- Member of the American Heart Association
- Member of the American Society for Matrix Biology
- Member of the International Heart Valve Society

C. Contribution to Science

1) When I entered the field of cardiovascular developmental biology as a postdoc, very little was known about valve morphogenesis past the initial EMT stage. We reasoned that defects in EMT were mostly incompatible with life and that studying post-EMT morphogenesis would provide a window into how cardiac valve diseases occur. During my postdoc we discovered that the gene periostin was a critical regulator of collagen synthesis and matrix organization. Additionally, we discovered that genetic in vivo and in vitro manipulation of this gene would cause defects in matrix compaction that is required for conferring proper structure and ultimately function to the valve. The papers that we published from these studies have accelerated a field of post-EMT morphogenesis and have led to periostin being an important marker for diseases outside the valves (e.g. myocardial infarction, lung fibrosis, etc.). The references below form a selection of the papers that resulted from these studies.

1. **Norris RA**, Kern CB, Wessels A, Moralez EI, Markwald RR, Mjaatvedt CH.Identification and detection of the periostin gene in cardiac development. Anat Rec A Discov Mol Cell Evol Biol. 2004 Dec;281(2):1227-33.
2. Butcher JT, **Norris RA**, Hoffman S, Moreno R, Markwald R. Periostin enhances atrioventricular cushion mesenchyme invasion and matrix condensation mediated by integrin signaling and Rho kinase. Dev Biol.2006 Oct 4
3. **Norris RA**, Damon B, Mironov V, Kasyanov V, Ramamurthi A, Moreno-Rodriguez R, Trusk T, Potts JD, Goodwin RL, Davis J, Hoffman S, Wen X, Sugi Y, Kern CB, Mjaatvedt CH, Turner DK, Oka T, Conway SJ, Molkentin J, Forgacs G, Markwald RR. Periostin regulates collagen I fibrillogenesis and the biomechanical properties of connective tissues. J Cell Biochem 2007; Jun 1; 101(3): 695-711.

4. **Norris, R.A.,** Moreno-Rodriguez, R.A., Sugi, Y, Hoffman, S., Amos, J., Hart, M.H., Potts, J., Goodwin, R.L., Markwald, R.R. Periostin Regulates Atrioventricular Valve Maturation. Dev Biol. 2008 Apr 15;316(2):200-13. Epub 2008 Jan 17.
5. **Norris RA**, Potts JD, Yost MJ, Junor L, Brooks T, Tan H, Hoffman S, Hart MM, Kern MJ, Damon B, Markwald RR, Goodwin RL. Periostin promotes a fibroblastic lineage pathway in atrioventricular valve progenitor cells. Dev Dyn. 2009 May;238(5):1052-63. doi: 10.1002/dvdy.21933.20.

2) A couple years after beginning my faculty position our group was asked to join forces with clinicians and scientists from around the world to collectively study valvular heart disease in humans. Our role in the project was to understanding the genetic and developmental etiologies of valve diseases in humans. Our initial starting point was the Filamin-A gene, which our colleagues had recently discovered causes a pan myxomatous valvular dystrophy in humans. We made important discoveries showing that developmental defects during post-EMT valvulogenesis were likely the underlying cause for this disease in humans. We found that Filamin-A interactions with serotonin were critical for imparting cytoskeletal activities important for contracting the extracellular matrix. Importantly, these discoveries have led to new mechanisms of valve pathogenesis with potential for remedial therapeutic interventions.

1. **Norris RA**, Moreno-Rodriguez, R, Wessels, A, Merot, J, Hagege, A, Slaugenhaupt, S, Schott, JJ, Harris, BS, Williams, LK, Richards, A, Levine, RA, Markwald, RR. Expression Of The Familial Cardiac Valvular Dystrophy Gene, Filamin-A, During Heart Morphogenesis. Dev Dyn. 2010 Jul;239(7):2118-27
2. Sauls K, de Vlaming A, Harris BS, Williams K, Wessels A, Levine RA, Slaugenhaupt SA, Goodwin RL, Pavone LM, Merot J, Schott JJ, Le Tourneau T, Dix T, Jesinkey S, Feng Y, Walsh C, Zhou B, Baldwin S, Markwald RR, **Norris RA**. Developmental basis for filamin-A-associated myxomatous mitral valve disease. Cardiovasc Res. 2012 Oct 1;96(1):109-19
3. Valvular dystrophy associated filamin A mutations reveal a new role of its first repeats in small-GTPase regulation. Duval D, Lardeux A, Le Tourneau T, **Norris RA**, Markwald RR, Sauzeau V, Probst V, Le Marec H, Levine R, Schott JJ, Merot J. Biochim Biophys Acta. 2013 Nov 4;1843(2):234-244. doi: 10.1016/j.bbamcr.2013.10.022.
4. Sauls K, Toomer K, Williams K, Johnson AJ, Markwald RR, Hajdu Z, **Norris RA**. Increased infiltration of extra-cardiac cells in Myxomatous valve disease. *J. Cardiovasc. Dev. Dis.* **2015**, *2*(3), 200-213

3) Although the previous studies listed above have focused on how valve mesenchyme compacts extracellular matrix during development, we reasoned that this one event cannot explain the complex morphogenesis of the valves. Thus, we performed TEM studies years ago and observed that cells become aligned in the valves during fetal life. This indicated that these cells are polarized. Around the same time we made this discovery, we had, in collaboration with our Leducq colleagues, just discovered the first gene that causes non-syndromic MVP. This gene, serendipitously was *DCHS1*, a cell polarity gene. This was a seminal discovery and studying the mechanisms of *DCHS1* function during development have led to important observations that help explain various aspects of valve development as well as the etiology of some heart valve diseases. The importance of cell polarity is further supported by our other genetic discoveries showing that this class of genes plays a major role in not only valve development but valve disease pathogenesis. Below I list the manuscripts that pertain to these studies.

1. de Vlaming A, Sauls K, Hajdu Z, Visconti RP, Mehesz AN, Levine RA, Slaugenhaupt SA, Hagège A, Chester AH, Markwald RR, **Norris RA**. Atrioventricular valve development: new perspectives on an old theme. Differentiation. 2012 Jul;84(1):103-16.
2. Levine R, Hagege A, Judge D, Padala M, Dal-Bianco J, Aikawa E, Beaudoin J, Bischoff J, Bouatia-Naji N, Bruneval P, Butcher J, Carpentier A, Chaput M, Chester A, Clusel C, Nesta-Delling F, Dietz H, Dina C, Durst R, Fernandez L, Handschumacher M, Jensen M, Jeunemaitre X, Le Marec H, Le Tourneau T, Markwald R, Mérot J, Messas E, Milan D, Neri T, **Norris R**, Peal D, Perrocheau M, Probst V, Puceat M, Rosenthal N, Solis-Martin J, Schott J, Schwammenthal E, Slaugenhaupt S, Song J, and Yacoub M. Unifying Concepts of Mitral Valve Disease: From Morphology to Mechanisms and Beyond. In Press Nature Reviews Cardiology (2015)
3. Durst R, Sauls K, Peal DS, deVlaming A, Toomer K, Leyne M, Salani M, Talkowski ME, Brand H, Perrocheau M, Simpson C, Jett C, Stone MR, Charles F, Chiang C, Lynch SN, Bouatia-Naji N, Delling FN, Freed LA, Tribouilloy C, Le Tourneau T, LeMarec H, Fernandez-Friera L, Solis J, Trujillano D, Ossowski S, Estivill X, Dina C, Bruneval P, Chester A, Schott JJ, Irvine KD, Mao Y, Wessels A,

Motiwala T, Puceat M, Tsukasaki Y, Menick DR, Kasiganesan H, Nie X, Broome AM, Williams K, Johnson A, Markwald RR, Jeunemaitre X, Hagege A, Levine RA, Milan DJ, **Norris RA[$#]**, Slaugenhaupt SA[$#]. **[$]-Co Senior Authors, [#]-Co-Corresponding** authors *Nature*. 2015Aug 10. doi: 10.1038/nature14670

4. Dina C, Bouatia-Naji N, Tucker N, Delling FN, Toomer K, Durst R, Perrocheau M, Fernandez-Friera L, Solis J; PROMESA investigators, Le Tourneau T, Chen MH, Probst V, Bosse Y, Pibarot P, Zelenika D, Lathrop M, Hercberg S, Roussel R, Benjamin EJ, Bonnet F, Lo SH, Dolmatova E, Simonet F, Lecointe S, Kyndt F, Redon R, Le Marec H, Froguel P, Ellinor PT, Vasan RS, Bruneval P, Markwald RR, **Norris RA[$]**, Milan DJ[$], Slaugenhaupt SA[$], Levine RA[$], Schott JJ[$], Hagege AA[$], Mvp-France, Jeunemaitre X[$]; Leducq Transatlantic MITRAL Network. **[$]-Co-Senior Author.** Nat Genet. 2015 Aug 24. doi: 10.1038/ng.3383.

4) I have been in the field of cardiovascular developmental biology for 15 years. Through these years I have had the opportunity of working with great scientists both inside and outside the valve world. To these collaborations I bring a unique skill set and specific expertise in cardiac anatomy that has been beneficial for these other groups. These studies have garnered novel understandings on developmental mechanisms of cardiovascular diseases. Below I list some of these impactful studies.

1. Angiotensin II-dependent TGF-β signaling contributes to Loeys-Dietz syndrome vascular pathogenesis. Gallo EM, Loch DC, Habashi JP, Calderon JF, Chen Y, Bedja D, van Erp C, Gerber EE, Parker SJ, Sauls K, Judge DP, Cooke SK, Lindsay ME, Rouf R, Myers L, Ap Rhys CM, Kent KC, **Norris RA**, Huso DL, Dietz HC. J Clin Invest. 2013 Dec 20. pii: 69666. doi: 10.1172/JCI69666.
2. Doyle AJ, Doyle JJ, Bessling SL, Maragh S, Lindsay ME, Schepers D, Gillis E, Mortier G, Homfray T, Sauls K, **Norris RA**, Huso ND, Leahy D, Mohr DW, Caulfield MJ, Scott AF, Destrée A, Hennekam RC, Arn PH, Curry CC, Laer LV, McCallion AS, Loeys BL, Dietz HC. Mutations in the Prototypical TGF-β Repressor SKI Cause Shprintzen-Goldberg Syndrome with Aortic Aneurysm. Nature Genetics. 2012 Nov;44(11):1249-54
3. Teekakirikul P, Eminaga S, Toka O, Alcalai R, Wang L, Wakimoto H, Nayor M, Konno T, Gorham JM, Wolf CM, Kim JB, Schmitt JP, Molkentin JD, **Norris RA**, Tager AM, Hoffman SR, Markwald RR, Seidman CE, Seidman JG. Cardiac fibrosis, in hypertrophic cardiomyopathy, is mediated by non-myocyte proliferation and requires Tgfb. J. Clin Invest. 2010 Sep 1. pii: 42028. doi: 10.1172/JCI42028
4. Kolpa HJ, Peal DS, Lynch SN, Giokas AC, Ghatak S, Misra S, **Norris RA**, Macrae CA, Markwald RR, Ellinor P, Bischoff J, Milan DJ. miR-21 represses Pdcd4 during cardiac valvulogenesis. Development. 2013 May;140(10):2172-80. doi: 10.1242/dev.084475. Epub 2013 Apr 11
5. Alk3 mediated Bmp signaling controls the contribution of epicardially derived cells to the tissues of the atrioventricular junction. Lockhart MM, Boukens BJ, Phelps AL, Brown CL, Toomer KA, Burns TA, Mukherjee RD, **Norris RA**, Trusk TC, van den Hoff MJ, Wessels A. Dev Biol. 2014 Dec 1;396(1):8-18. doi: 10.1016/j.ydbio.2014.09.031. Epub 2014 Oct 6.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1vmvSIvPKI5ku/bibliography/48085453/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1R01HL122906 - 01A1 Wessels (Principal Investigator) 09/01/15-8/31/18
Title of Project: **Mechanisms of DMP development and atrioventricular septation**
Goal of project: To specifically test the overarching hypothesis that the Wnt/β-catenin and BMP signaling pathways in the pSHF are part of a complex molecular network orchestrating the development of the DMPand are located down-stream of the cilia-associated Shh pathway.
Role in Grant: **Co-I**

R56 HL122906-01 Wessels (Principal Investigator) 08/01/14-8/31/15
Title of Project: **Mechanisms of DMP development and atrioventricular septation**
Goal of project: To specifically test the overarching hypothesis that the Wnt/β-catenin and BMP signaling pathways in the pSHF are part of a complex molecular network orchestrating the development of the DMPand are located down-stream of the cilia-associated Shh pathway.

Role in Grant: **Co-I**

R01 HL033756 Markwald (Principle Investigator) **07/01/12-06/30/16**
Title of Project: **Mucopolysaccharide Metabolism in Cardiac Anomalies**
Goal of Project: The major goals of this project are to determine if the heart defect (htd) gene is a prototype candidate for an embryonic segmentation gene; to determine if the fate of the luminal "face" of cushion mesenchyme is to expand into the definitive precursor valve leaflets; and to determine if a primary fate of cushions is to interact with the myocardium to complete septal development.
Role in Grant: **Co-I**

P20 GM103444-07 Vyavahare (Principle Investigator) **07/01/14-6/30/18**
Sub-Project Title: Developmental And Biomechanical Mechanisms of Valve Tissue Formation
Goal of Project: The goals of this project are to determine developmental mechanisms that contribute to mitral valve prolapse. Additionally, we aim to integrate biomechanical studies with development using novel bioreactors and cells derived from patients with mitral valve prolapse to gain a clear understanding for how valve developmental defects give rise to mechanically inferior adult valve tissues.
Role in Grant: **PI of Sub Project**

1R01 HL127692-01 Milan (Principle Investigator) **04/01/15-03/31/20**
Title of Project: Genetics and Mechanisms of Mitral Valve Prolapse
Goal of Project: Mitral Valve Prolapse affects about 7 million Americans and increases the risk of endocarditis and congestive heart failure, but relatively little is known about the underlying mechanisms leading to this disease. The goal of our application is to study the genetics and mechanisms of this disease. Characterizing new pathways for mitral valve prolapse will provide new targets for drug discovery to prevent and treat this heart disease
Role in Grant: **Institutional PI (Sub award from MGH/Harvard)**

American Heart Association Norris (Principle Investigator) **07/01/15-06/30/17**
15GRNT25080052
Title of Project: Etiology and Treatment for Mitral Valve Prolapse
Goal of Project: The specific questions we are asking in this proposal is: 1) What is the etiology of MVP, when does the disease begin, and why; 2) Whether the perturbed molecular pathways that we have identified in our mouse models can be pharmacologically blunted to reduce disease severity. We will perform these studies by performing state of the art imaging in combination with drug treatment regimens. Our studies will initiate at developmental timepoints since this is when we observe disease inception.

Completed Research Support:

- **1R01HL086856-01A1** **08/01/07-07/31/12**
  Role: Co-Investigator
  NIH-NHLBI
  The Role of Fluid Flow in Valvulogenesis
- **07CVD04** **10/1/08-09/30/14**
  Role: Co-Investigator
  Leducq Foundation
  Mitral Valve Disease: From Genetic Mechanisms to Improved Repair
- **3 P20 RR016434-09S2** **09/01/09-08/31/11**
  Role: Co-Investigator
  NIH NHLBI
  SC COBRE For Developmentally Based Cardiovascular Diseases
- **11SDG5270006** **01/01/11-12/31/14**
  Role: PI
  AHA Scientist Development Grant
  Pathogenetic Mechanisms of Myxomatous Mitral Valve Dystrophy