

# Seeing the Endothelium



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The endothelium is widely distributed organ system that forms the inner cell lining of vertebrate blood vessels, most of which are invisible to the naked eye. Today, it is widely recognized that endothelial cells are involved in most human diseases, either as a primary determinant of pathophysiology or as a victim of collateral damage. However, there exists a profound bench-to-bedside gap in endothelial biomedicine. While there are over 100,000 peer-reviewed publications related to the endothelium, the collective knowledge in basic science has failed to translate into significant improvements in patient care, with the exception of coronary artery disease. If we are to narrow the gap, we must first understand its origins. One consideration in explaining the bench-to-bedside gap is our inability to see the endothelium for what it really is. Far from being a giant monopoly or collective of identical cells, the endothelium comprises an enormous consortium of different enterprises, each with its own identity. Since the discovery of the endothelium in 1860, a series of technological advances, including intravital microscopy, histology, electron microscopy, cell culture and immunohistology, have opened up exciting new windows into the endothelium. However, each new technology has important limitations and falls well short of representing the reality of the “endothelial system”. A newer and more promising approach for “seeing” the endothelium is through the lens of dynamical systems theory and landscape topology. Dynamical systems modeling provides both a metaphoric and a quantitative platform for describing system-level features of the endothelium in health and disease. Such an approach may help to link theory with practice and to illuminate the endothelium as a clinically relevant organ.

## BIO

Dr. Aird completed medical school and internal residency training in Toronto, Canada. After completing a fellowship in hematology at the Brigham and Women's Hospital, Harvard Medical School and a postdoctoral fellowship in the Department of Biology at Massachusetts Institute of Technology, Dr. Aird established an independent research program at the Beth Israel Deaconess Medical Center in 1996. His research focuses on understanding how endothelial cells are differentially regulated in space and time, and on linking different levels of organization (cell, blood vessel, organ, and whole organism). His overriding goal is to promote an awareness of the endothelium as a clinically relevant organ. Dr. Aird is currently Director of the Center for Vascular Biology Research and Chief, Division of Molecular and Vascular Medicine at BIDMC, and Professor of Medicine at Harvard Medical School.

## SHORT LIST OF THE MOST RELEVANT PUBLICATIONS

1. Hwa C, Aird WC. The History of the Capillary Wall: Doctors, Discoveries and Debates. *Am J Physiol.* 2007;293:H2667-2679.
2. Aird WC. Phenotypic heterogeneity of the endothelium. Part I *Circ Res.* 2007;100:158-173.
3. Aird WC. Phenotypic heterogeneity of the endothelium. Part II *Circ Res.* 2007;100;174-190.
4. Aird WC. Proximate and evolutionary causation of endothelial heterogeneity. *Semin Thromb Hemost.* 2010;36:276-85.
5. Regan ER, Aird WC. Dynamical systems approach to endothelial heterogeneity. *Circ Res.* 2012;111:110-30.

# Curriculum Vitae

## General Information

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## Education:

1985 M.D. The University of Western Ontario, London, Canada

## Internship and Residencies:

1985-1986 Straight Medical Intern, St. Michael's Hospital, University of Toronto, Toronto, Canada

1986-1987 Junior Medical Resident, St. Michael's Hospital, University of Toronto

1987-1988 Senior Medical Resident, Toronto General Hospital, University of Toronto

1988-1989 Chief Medical Resident, St. Michael's Hospital, University of Toronto

## Fellowships:

1989-1990 Clinical Fellow in Medicine, Brigham and Women's Hospital

1990-1993 Research/Clinical Fellow in Medicine, Brigham and Women's Hospital

1990-1996 Postdoctoral Fellow, Department of Biology, Massachusetts Institute of Technology

## Licensure and Certification:

1989 Massachusetts License Registration

1989 FRCP (Internal Medicine), Royal College of Physicians and Surgeons of Canada

1989 Diplomate, Internal Medicine, American Board of Internal Medicine

1992 Diplomate, Subspecialty of Hematology, American Board of Internal Medicine

1993 Diplomate, Subspecialty of Hematology, Royal College of Physicians and Surgeons of Canada

### **Academic Appointments:**

- 1993-1996 Instructor in Medicine, Harvard Medical School
- 1997-2001 Assistant Professor of Medicine, Harvard Medical School
- 2001- Associate Professor of Medicine, Harvard Medical School
- 2009- Professor of Medicine, Harvard Medical School

### **Hospital Appointments:**

- 1993-1995 Associate Physician, Brigham and Women's Hospital
- 1993-1996 Attending Physician, Beth Israel Hospital
- 1996- Attending Physician, Beth Israel Deaconess Medical Center

### **Other Positions and Major Visiting Appointments:**

- 1996-2000 Visiting Scientist, Massachusetts Institute of Technology

### **Hospital and Health Care Organization Service Responsibilities:**

- 1993-1995 Attending Physician, Brigham and Women's Hospital
- 1995-1996 Attending Physician, Department of Medicine and Hematology-Oncology Division, Beth Israel Hospital
- 1996- Attending Physician, Department of Medicine and Hematology-Oncology Division, Beth Israel Deaconess Medical Center

### **Major Administrative Responsibilities:**

- 1998-2003 Director, Hematology Clinical Conference (CME course)
- 2003- Chief, Division of Molecular and Vascular Medicine, Beth Israel Deaconess Medical Center
- 2004-2007 Associate Director, Center for Vascular Biology Research, Beth Israel Deaconess Medical Center
- 2008- Director, Center for Vascular Biology Research, Beth Israel Deaconess Medical Center

### **Awards and Honors:**

- 1979-1980 Admission Scholarship, University of Western Ontario
- 1981 Medical Research Council of Canada Summer Research Grant

1979-1981 Dean's Honor List, University of Western Ontario  
1983-1985 Dean's Honor List, University of Western Ontario  
1987-1988 The Sopman Humanitarian Award for "clinical and academic excellence coupled with outstanding human qualities", University of Toronto  
1990-1992 Fellowship, Medical Research Council of Canada  
1992-1996 Clinician Scientist Award, Medical Research Council of Canada  
1998-1999 Junior Investigator Award, Beth Israel Deaconess Medical Center  
1999-2001 American Society of Hematology Scholar Award  
2001-2002 Enterprise Award, Beth Israel Deaconess Medical Center  
2005-2010 Established Investigator, American Heart Association  
2005-2007 New Investigator Award, Mount Desert Island Biological Laboratory  
2011-2013 Team Scientist Award, Mount Desert Island Biological Laboratory

### **Original Articles (2009-2015):**

1. Shapiro NI, Yano K, Sorasaki M, Fischer C, Shih SC, **Aird WC**. Skin biopsies demonstrate site-specific endothelial activation in mouse models of sepsis. *J Vasc Res*. 2009;46:495-502.
2. Baek KH, Zaslavsky A, Lynch RC, Britt C, Okada Y, Siarey RJ, Lensch MW, Park IH, Yoon SS, Minami T, Korenberg JR, Folkman J, Daley GQ, **Aird WC**, Galdzicki Z, Ryeom S. Down's syndrome suppression of tumour growth and the role of calcineurin inhibitor DSCR1. *Nature* 2009;459:1126-30.
3. Liu J, Kanki Y, Okada Y, Jin E, Yano K, Shih SC, Minami T, **Aird WC**. A +220 GATA motif mediates basal but not endotoxin-repressible expression of the von Willebrand factor promoter in Hpvt-targeted transgenic mice. *J Thromb Haemost*. 2009;7:1384-92.
4. Minami M, Yano K, Miura M, Kobayashi M, Suehiro J, Reid PC, Hamakubo T, Ryeom S, **Aird WC**, Kodama T. The Down syndrome critical region gene 1 short variant promoter directs vascular bed-specific gene expression during inflammation in mice. *J Clin Invest*. 2009;119:2257-70 (WCA, co-corresponding and co-senior author).
5. Song H, Suehiro J, Kanki Y, Kawai Y, Inoue K, Daida H, Yano K, Ohhashi T, Oettgen P, **Aird WC**, Kodama T, Minami T. Critical role for GATA3 in mediating Tie2 expression and function in large vessel endothelial cells. *J Biol Chem*. 2009;284:29109-24.
6. Jin E, Liu J, Suehiro J, Yuan L, Okada Y, Nikolova-Krsteovski V, Yano K, Janes L, Beeler D, Spokes KC, Li D, Regan E, Shih SC, Oettgen P, Minami T, **Aird WC**. Differential roles for ETS, CREB and EGR binding sites in mediating VEGFR1 expression in vivo. *Blood*. 2009; 114:5557-66.
7. Yuan L, Nikolova-Krsteovski V, Zhan Y, Kondo M, Bhasin M, Varghese L, Yano K, Carman CV, **Aird WC**, Oettgen P. Antiinflammatory effects of the ETS factor ERG in endothelial cells are mediated through transcriptional repression of the interleukin-8 gene. *Circ Res*. 2009 May 8;104:1049-57.
8. Suehiro J, Hamakubo T, Kodama T, **Aird WC**, Minami T. Vascular endothelial growth factor activation of endothelial cells is mediated by early growth response- 3. *Blood*. 2009;115:2520-32.
9. Damrauer SM, Fisher MD, Wada H, Siracuse JJ, da Silva CG, Moon K, Csizmadia E, Maccariello ER, Patel VI, Studer P, Essayagh S, **Aird WC**, Daniel S, Ferran C. Macrophage trafficking and decreasing adventitial neovascularization. *Atherosclerosis*. 2010;211:404-8.

10. Nassiri M, Liu J, Kulak S, Uwiera RR, Aird WC, Ballermann BJ, Jahroudi N. Repressors NFI and NFY participate in organ-specific regulation of von Willebrand factor promoter activity in transgenic mice. *Arterioscler Thromb Vasc Biol.* 2010;30:1423-9.
11. Fischer CM, Yano K, Aird WC, Shapiro NI. Abnormal coagulation tests obtained in the emergency department are associated with mortality in patients with suspected infection. *J Emerg Med.* 2012;42:127-32.
12. Lee M, Spokes KC, Aird WC, Abid MR. Intracellular Ca<sup>2+</sup> can compensate for the lack of NADPH oxidase-derived ROS in endothelial cells. *FEBS Lett.* 2010;584:3131-6.
13. Shapiro NI, Schuetz P, Yano K, Sorasaki M, Parikh SM, Jones AE, Trzeciak S, Ngo L, Aird WC. The association of endothelial cell signaling, severity of illness, and organ dysfunction in sepsis. *Crit Care.* 2010;14:R182.
14. Wada Y, Li D, Merley A, Zukauskas A, Aird WC, Dvorak HF, Shih SC. A multi-gene transcriptional profiling approach to the discovery of cell signature markers. *Cytotechnology.* 2010;63:25-33.
15. Liu J, Yuan L, Molema G, Regan E, Janes L, Beeler D, Spokes KC, Okada Y, Minami T, Oettgen P, Aird WC. Vascular bed-specific regulation of the von Willebrand factor promoter in the heart and skeletal muscle. *Blood.* 2010;117:342-51.
16. Schuetz P, Yano K, Sorasaki M, Ngo L, St Hilaire M, Lucas JM, Aird W, Shapiro NI. Influence of diabetes on endothelial cell response during sepsis. *Diabetologia.* 2011;54(5):996-1003.
17. Tozawa H, Kanki Y, Suehiro JI, Tsutsumi S, Kohro T, Wada Y, Aburatani H, Aird WC, Kodama T, Minami T. Genome-wide approaches reveal functional IL-4 inducible STAT6 binding to the vascular cell adhesion molecule-1 promoter. *Mol Cell Biol.* 2011;31:2196-209.
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20. Schuetz P, Jones AE, Aird WC, Shapiro NI. Endothelial cell activation in emergency department patients with sepsis-related and non-sepsis-related hypotension. *Shock.* 2011;36:104-8.
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22. Yuan L, Le Bras A, Sacharidou A, Itagaki K, Zhan Y, Kondo M, Carman CV, Davis GE, Aird WC, Oettgen P. ETS-related gene (ERG) controls endothelial cell permeability via transcriptional regulation of the claudin 5 (CLDN5) gene. *J Biol Chem.* 2012;287:6582-91.

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25. Herzig SJ, **Aird WC**, Shah BJ, McKernan M, Zeidel ML. From hagfish to humans: teaching comparative physiology to internal medicine residents. *Acad Med*. 2012;87:372-7.
26. Schuetz P, Kennedy M, Lucas JM, Howell MD, **Aird WC**, Yealy DM, Shapiro NI. Initial management of septic patients with hyperglycemia in the noncritical care inpatient setting. *Am J Med*. 2012;125:670-8.
27. Vijayaraj P, Le Bras A, Mitchell N, Kondo M, Juliao S, Wasserman M, Beeler D, Spokes K, **Aird WC**, Baldwin HS, Oettgen P. Erg is a crucial regulator of endocardial-mesenchymal transformation during cardiac valve morphogenesis. *Development*. 2012;139:3973-85.
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29. Yoshikawa M, Mukai Y, Okada Y, Tsumori Y, Tsunoda S, Tsutsumi Y, **Aird WC**, Yoshioka Y, Okada N, Doi T, Nakagawa S. Robo4 is an effective tumor endothelial marker for antibody-drug conjugates based on the rapid isolation of the anti-Robo4 cell-internalizing antibody. *Blood*. 2013;121:2804-13.
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39. Okada Y, Funahashi N, Tanaka T, Nishiyama Y, Yuan L, Shirakura K, Turjman AS, Kano Y, Naruse H, Suzuki A, Sakai M, Zhixia J, Kitajima K, Ishimoto K, Hino N, Kondoh M, Mukai Y, Nakagawa S, García-Cardena G, **Aird WC**, Doi T. Endothelial cell-specific expression of roundabout 4 is regulated by differential DNA methylation of the proximal promoter. *Arterioscler Thromb Vasc Biol*. 2014;34:1531-8.
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41. Rowe GC, Raghuram S, Jang C, Nagy JA, Patten IS, Goyal A, Chan MC, Liu LX, Jiang A, Spokes KC, Beeler D, Dvorak H, **Aird WC**, Arany Z. GC-1 $\alpha$  Induces SPP1 to Activate Macrophages and Orchestrate Functional Angiogenesis in Skeletal Muscle. *Circ Res*. 2014;115:504-17.

### **Books, Monographs and Textbooks**

1. **Aird WC**. Endothelium in Health and Disease. W.C. Aird, ed. Taylor and Francis, New York, 2005.
2. **Aird WC**. Endothelial Biomedicine. W.C. Aird, ed. Cambridge University Press, Cambridge, 2007.
3. **Aird WC**. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. V. Marder, WC Aird, J Bennett, S Schulman, G White, Eds. Lippincott Williams & Wilkins; Sixth edition, In Press.