

# Circulation Research

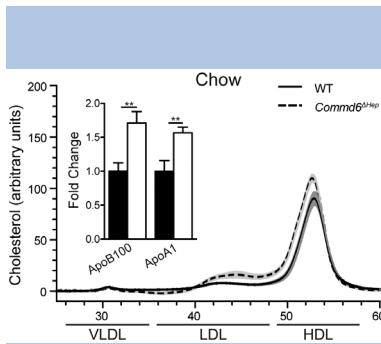
Volume 122 Number 12 June 8, 2018

★ **Featured Article**

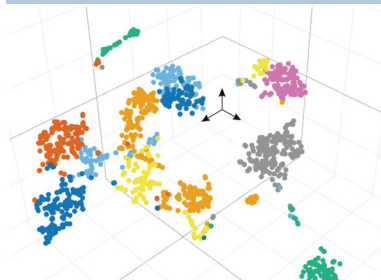
📄 Online supplementary information

🎬 Online movie files

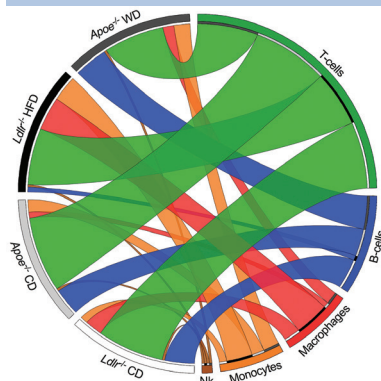
Available at <http://circres.ahajournals.org>



**COMMD Proteins Regulate Plasma Lipid Levels**  
*Fedoseienko et al.* page 1648



**scRNA-Seq of Aortic Macrophages in Atherosclerosis**  
*Cochain et al.* page 1661



**Leukocyte Heterogeneity in Atherosclerosis**  
*Winkels et al.* page 1675

**In This Issue** ..... 1625

**Meet the First Authors** ..... 1626

## Editorials

**The CCC Complex COMMANDs Control of LDL Cholesterol Levels**  
*Michael F. Keating, Anna C. Calkin* ..... 1629

**First Giant Steps Toward a Cell Atlas of Atherosclerosis**  
*Hanrui Zhang, Nancy R. Zhang, Mingyao Li, Muredach P. Reilly* ..... 1632

**Immunity Comes to Play in the “Sex Paradox” of Pulmonary Arterial Hypertension**  
*Mohammed S. Osman, Evangelos D. Michelakis* ..... 1635

## Leaders in Cardiovascular Science

**Alan R. Tall: The Downs and (Mostly) Ups of a Life in Science**  
*Susan Ince* ..... 1638

## Viewpoints

**Obesity Paradox and Smoking Gun: A Mystery of Statistical Confounding?**  
*Xi-Yong Yu, Ping Song, Ming-Hui Zou* ..... 1642

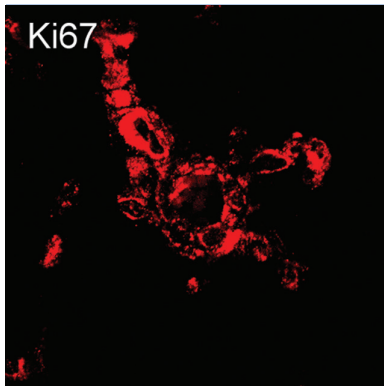
**Cardiovascular Disease and Fine Particulate Matter: Lessons and Limitations of an Integrated Exposure–Response Approach**  
*C. Arden Pope III, Aaron J. Cohen, Richard T. Burnett* ..... 1645

## Molecular Medicine

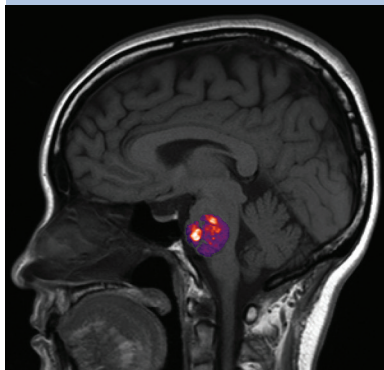
★ **The COMMD Family Regulates Plasma LDL Levels and Attenuates Atherosclerosis Through Stabilizing the CCC Complex in Endosomal LDLR Trafficking**

*Alina Fedoseienko, Melinde Wijers, Justina C. Wolters, Daphne Dekker, Marieke Smit, Nicolette Huijkman, Niels Kloosterhuis, Helene Klug, Aloys Schepers, Ko Willems van Dijk, Johannes H.M. Levels, Daniel D. Billadeau, Marten H. Hofker, Jan van Deursen, Marit Westerterp, Ezra Burstein, Jan Albert Kuivenhoven, Bart van de Sluis* ..... 1648 📄

*CIRCULATION RESEARCH* (ISSN 0009-7330 print / 1524-4571 online) is published semimonthly for 24 total issues a year by Wolters Kluwer Health, Inc. at 14700 Citicorp Drive, Bldg 3, Hagerstown, MD 21742. Business offices are located at Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103. Production offices are located at 351 West Camden Street, Baltimore, MD 21201-2436. Individuals may subscribe for their personal use at the following rates for print subscriptions: \$225 for AHA/ASA Domestic and International Members (excluding General Membership level), or \$833 for domestic non-members and \$989 for international non-members. AHA membership information can be found online at [professional.heart.org](http://professional.heart.org). Periodicals postage paid at Hagerstown, MD, and additional mailing offices. POSTMASTER: Send address changes to *Circulation Research*, American Heart Association, Wolters Kluwer Health, Inc., PO Box 1610, Hagerstown, MD 21740.



**Dominant Treg Effects  
in Females**  
Tamosiuniene *et al.* page 1689



**Plasma Predictors in Human  
CCM Disease**  
Girard *et al.* page 1716

**★ Single-Cell RNA-Seq Reveals the Transcriptional Landscape and Heterogeneity of Aortic Macrophages in Murine Atherosclerosis**

*Clément Cochain, Ehsan Vafadarnejad, Panagiota Arampatzi, Jaroslav Pelisek, Holger Winkels, Klaus Ley, Dennis Wolf, Antoine-Emmanuel Saliba, Alma Zernecke* ..... 1661

**★ Atlas of the Immune Cell Repertoire in Mouse Atherosclerosis Defined by Single-Cell RNA-Sequencing and Mass Cytometry**

*Holger Winkels, Erik Ehinger, Melanie Vassallo, Konrad Buscher, Huy Q. Dinh, Kouji Kobiyama, Anouk A.J. Hamers, Clément Cochain, Ehsan Vafadarnejad, Antoine-Emmanuel Saliba, Alma Zernecke, Akula Bala Pramod, Amlan K. Ghosh, Nathaly Anto Michel, Natalie Hoppe, Ingo Hilgendorf, Andreas Zirlik, Catherine C. Hedrick, Klaus Ley, Dennis Wolf* ..... 1675

**Cellular Biology**

**★ Dominant Role for Regulatory T Cells in Protecting Females Against Pulmonary Hypertension**

*Rasa Tamosiuniene, Olga Manouvakhova, Paul Mesange, Toshie Saito, Jin Qian, Mrinmoy Sanyal, Yu-Chun Lin, Linh P. Nguyen, Amir Luria, Allen B. Tu, Joshua M. Sante, Marlene Rabinovitch, Desmond J. Fitzgerald, Brian B. Graham, Aida Habtezion, Norbert F. Voelkel, Laure Aurelian, Mark R. Nicolls* ..... 1689

**Clinical Track**

**Rationale and Design of the CONCERT-HF Trial (Combination of Mesenchymal and c-kit<sup>+</sup> Cardiac Stem Cells As Regenerative Therapy for Heart Failure)**

*Roberto Bolli, Joshua M. Hare, Keith L. March, Carl J. Pepine, James T. Willerson, Emerson C. Perin, Phillip C. Yang, Timothy D. Henry, Jay H. Traverse, Raul D. Mitrani, Aisha Khan, Ivonne Hernandez-Schulman, Doris A. Taylor, Darcy L. DiFede, João A.C. Lima, Atul Chugh, John Loughran, Rachel W. Vojvodic, Shelly L. Sayre, Judy Bettencourt, Michelle Cohen, Lem Moyé, Ray F. Ebert, Robert D. Simari; for the Cardiovascular Cell Therapy Research Network (CCTRN)* ..... 1703

**Plasma Biomarkers of Inflammation and Angiogenesis Predict Cerebral Cavernous Malformation Symptomatic Hemorrhage or Lesional Growth**

*Romuald Girard, Hussein A. Zeineddine, Janne Koskimäki, Maged D. Fam, Ying Cao, Changbin Shi, Thomas Moore, Rhonda Lightle, Agnieszka Stadnik, Kiranj Chaudagar, Sean Polster, Robert Shenkar, Ryan Duggan, David Leclerc, Kevin J. Whitehead, Dean Y. Li, Issam A. Awad* **Short Communication** ..... 1716

**Reviews**

**NLRP3 Inflammasome and the IL-1 Pathway in Atherosclerosis**

*Alena Grebe, Florian Hoss, Eicke Latz* ..... 1722

**Sleep Apnea and Cardiovascular Disease: An Enigmatic Risk Factor**

*John S. Floras* ..... 1741

## Letter to the Editor

---

### Letter by Rupp and Jux Regarding Article, “Mechanisms of Cardiac Repair and Regeneration”

*Stefan Rupp, Christian Jux* **Online Only** ..... e90

## “In This Issue” Anthology

---

### *Circulation Research* “In This Issue” Anthology

*Ruth Williams, The Editors* **Online Only** ..... e92

---

**In April 2018, the average time from submission to first decision for all original research papers submitted to *Circulation Research* was 13.4 days.**

**On the Cover:** The cover image illustrates murine aortic leukocyte heterogeneity in 20-week-old *ApoE*<sup>-/-</sup> mice. Using a 35-marker pan-leukocyte mass cytometry (CyTOF) antibody panel, and a tSNE-based cluster detection algorithm, 23 leukocyte clusters were identified above a detection threshold. Most of these leukocyte populations, including T cells, B cells, and myeloid cells, show dynamic regulation between mice fed chow diet or a Western diet. The article within shows the unexpected complexity of the immune cell landscape in atherosclerosis using multiple omics approaches, demonstrates the association of individual murine aortic leukocyte population gene signatures with risk of developing secondary ischemic event in patients, and describes the existence of several novel leukocyte subsets as a launching point for future research. See related article, page 1675.

# Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION



122 (12)

*Circ Res.* 2018;122:e90-1764

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Copyright © 2018 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the  
World Wide Web at:

<http://circres.ahajournals.org/content/122/12>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Circulation Research* is online at:  
<http://circres.ahajournals.org/subscriptions/>