

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MURRAY & POOLE ENTERPRISES LTD.,
Petitioner,

v.

INSTITUT DE CARDIOLOGIE DE MONTREAL,
Patent Owner.

Case IPR2023-01064
Patent 11,400,063

DECLARATION OF JAMES L. MULLINS, Ph.D.

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I, James L. Mullins, am above the age of majority and hereby declare under penalty of perjury:

I. INTRODUCTION

1. I have been retained by Petitioner Murray & Poole Enterprises Ltd. (“Murray & Poole”) to provide expert opinions in connection with the *inter partes* review (IPR) of U.S. Patent No. 11,400,063.

2. I am being paid my usual hourly fee of \$275/hour. My compensation in no way depends on the content of my testimony or the outcome of the proceedings.

3. In this declaration, I address criticisms made by the Patent Owner in Paper No. 21 (Response) against the declaration of Mr. Raymond Cruitt (Ex. 1038) and his conclusion regarding Exhibit 1006, referred to in this case as COLCOT. Mr. Cruitt concluded in his declaration that COLCOT “would have been publicly available online by March 8, 2017 (its online posting date) and accessed publicly no later than October 20, 2017 (its Wayback archiving date).” Ex. 1038 ¶ 25. The Patent Owner criticized Mr. Cruitt’s conclusion in the Response at 20, asserting that Exhibit 1006 was not publicly available until July 16, 2020 and saying that Mr. Cruitt “is not an objective witness” and is “biased” because he is an employee of the law firm representing the Petitioner when the Petition was filed. I do not know Mr. Cruitt and cannot comment on his mindset when he undertook the analysis presented in his

declaration. I have therefore endeavored to independently analyze the same issue addressed by Mr. Cruitt to determine whether I objectively agree with his conclusions. Thus, I opine on the authenticity of “COLCOT” and explain when and how that document was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, could have located the document.

II. QUALIFICATIONS

4. I am the Founder and Owner of the firm Prior Art Documentation Librarian Services, LLC at 205 St Cuthbert, Williamsburg, VA 23188. Attached as Appendix A is a true and correct copy of my Curriculum Vitae describing my background and experience. Further information about my firm, Prior Art Documentation Librarian Services, LLC (PADLS), is available at www.priorartdoclib.com.

5. I am currently Dean Emeritus of Libraries and Esther Ellis Norton Professor Emeritus at Purdue University, 2018 – present. I was previously employed as follows:

- a. Dean of Libraries and Professor and Esther Ellis Norton Professor, Purdue University, West Lafayette, IN, 2004 – 2017;
- b. Assistant/Associate Director for Administration, Massachusetts Institute of Technology (MIT) Libraries, Cambridge, MA 2000 – 2004;

- c. University Librarian and Director, Falvey Memorial Library, Villanova University, Villanova, PA, 1996 – 2000;
 - d. Director of Library Services, Indiana University South Bend, South Bend, IN, 1978 – 1996;
 - e. Part-time Associate Professor, School of Library and Information Science, Indiana University, Bloomington, IN, 1979 – 1996;
 - f. Associate Law Librarian, and associated titles, Indiana University School of Law, Bloomington, IN, 1974 –1978;
 - g. Catalog Librarian, Assistant Professor, Georgia Southern College (now University), Statesboro, GA, 1973 – 1974.
6. During my more than forty-four years as an academic librarian and library science scholar, I have gained extensive experience with techniques and systems for cataloging and indexing printed materials in the library setting, including catalog records and online library management systems (“LMS”) built using Machine-Readable Cataloging (“MARC”) standards.
7. Additionally, throughout my career, I have been an active researcher and writer. I am an author of numerous publications in the field of library science and have given presentations in library sciences at national and international conferences. I am a member of the American Library Association (“ALA”), where

I served as the chair of the Research Committee of the Association of College and Research Libraries (“ACRL”). My service to ALA included service on the editorial board of the most prominent library journal, *College and Research Libraries*. I also served on the Standards Committee, College Section of the Association of College and Research Libraries, where I was instrumental in developing a re-issue of the *Standards for College Libraries* in 2000.

8. As an academic library administrator, I ensured that students were educated to identify, locate, assess, and integrate information garnered from research library resources. I have also facilitated the research of faculty colleagues either directly or through the provision of and access to the requisite print and/or digital materials and services at the universities where I worked.

9. For the purpose of this declaration, I have reviewed the documents and appendices referenced herein. These materials are records created in the ordinary course of business by publishers, libraries, indexing services, and others in my field. From my years of experience, I am familiar with the process for creating many of these records, and I know that these records are created by people with knowledge of the information contained within the record. Further, these records are created with the expectation that researchers and other members of the public will use and rely on them. All materials cited in this declaration and its appendices are of a type

that experts in my field would reasonably rely upon and refer to in forming their opinions.

III. LEGAL STANDARDS

10. *Authentication.* I am informed by counsel and understand that an item is considered authentic if there is sufficient evidence to support a finding that the item is what it is claimed to be by the proponent of the item. I am also informed that authenticity can be established based on the properties of the item itself, such as the appearance, content, substance, internal patterns, or other distinctive characteristics of the item.

11. *Public Accessibility.* I am informed by counsel and understand that a given reference qualifies as “publicly accessible” if it were disseminated or otherwise made available such that persons interested in and ordinarily skilled in the relevant subject matter could locate it through the exercise of ordinary diligence. I understand that one way that public accessibility can be shown is if a publication is cataloged and indexed by a library such that a person interested in the relevant subject matter could locate it. I also understand that there are other ways that a given reference may be deemed publicly accessible, including where that reference is cited by others in the field.

12. *The Critical Date.* I have been informed by counsel that for the purpose of this declaration I should consider evidence of public accessibility prior to November 15, 2019. As described further below, I have concluded that the reference discussed herein was publicly accessible, including to a person of ordinary skill in the art (“POSA”), prior to November 15, 2019.

13. *The Person of Ordinary Skill in the Art.* I have been informed by counsel that a POSA is a hypothetical person who is presumed to be familiar with the relevant field and its literature at the time of the inventions. This hypothetical person is also a person of ordinary creativity, capable of understanding the scientific principles applicable to the pertinent field.

14. In addition, I have been informed by counsel that as relevant to these proceedings, the POSA at the time of invention would have:

- An M.D. degree and be board-certified with a subspecialty in the treatment of cardiovascular disease.
- At least 3-5 years of experience, following board certification, in cardiology and cardiovascular disease treatment and sufficient clinical experience to understand standard good medical practice in patient management.
- Been familiar with acute coronary syndromes, stable coronary diseases, cardiovascular diseases, and their standard treatments, including the

acute management and long-term secondary preventions of myocardial infarction.

- Been aware of research relating to cardiovascular disease progression, including the role of inflammatory pathways in secondary cardiovascular events.

15. In my opinion, in November 2019, such a person would have had access to a vast array of online resources, as well as to a diminishing number of print resources.

IV. **BACKGROUND**

16. *Internet Archive/Wayback Machine.* The Internet Archive is a digital archive/library that began in 1996 to ‘scrape’ publicly accessible webpages. The Internet Archive created a service called the Wayback Machine that enables public access to surf more than 835 billion web pages (as of June, 2024) stored in the Internet Archive. Searches on the Wayback Machine can be undertaken by URL or name of entity. If an archive record for a URL is available, it will be shown. Through the Wayback Machine it is possible to view a specific webpage at a URL and see that page on that date as it then appeared. It is more or less a ‘snapshot’ of the website on that date, further information is available at this URL: <https://archive.org/about/>

V. EXHIBIT 1006

17. COLCOT is cited in the Petitioner's exhibit list filed with the Petition as follows:

1006	WayBack Machine archive of Clinical Trials.gov identifier NCT02551094, <i>Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLCOT)</i> , https://web.archive.org/web/20171020004013/https://clinicaltrials.gov/ct2/show/NCT02551094 (accessed Apr. 11, 2023)
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18. I have assessed authenticity and public access of COLCOT: (1) by assessing Exhibit 1006 provided by counsel; (2) by searching and retrieving the document from the *Wayback Machine*, Internet Archive; and (3) by retrieving citations to COLCOT published prior to November 15, 2019.

A. Authentication and Public Accessibility

19. I reviewed and assessed Exhibit 1006 provided by counsel. There does not appear to be text missing, each paragraph and page proceeds in a consistent manner with no apparent interruption in sentence structure or paragraphs caused by deletion. Exhibit 1006 will be compared with scans of that I retrieved of COLCOT to verify authenticity and public accessibility. To verify authenticity of and public access to COLCOT it is necessary to retrieve evidence from the *Wayback Machine*, Internet Archive.

20. As described above, the *Wayback Machine* was inaugurated by the Internet Archive to be a permanent repository of web pages available on a specific day. Not every day was archived, but downloads were made on a schedule that was determined by the Internet Archive or were downloaded into the Internet Archive by the owner of the website.

21. Attachment A-1 is a screen capture I created from the Wayback Machine when I accessed it on June 24, 2024. I compared the screen capture I obtained from the Wayback Machine, the webpage archived on October 20, 2017, which is Attachment A-1, with Exhibit 1006, and the content is an exact match.

22. To verify authenticity and public access, a citation to a publication is evidence that the publication (article, report, thesis, etc.) is considered authoritative and was publicly accessible as of the date of the published citation.

23. Attachment A-2 is an article by Peter Libby with the title "Interleukin-1 Beta as a Target for Atherosclerosis Therapy: Biological Basis of CANTOS and Beyond" published in the *Journal of the American College of Cardiology*, in volume 70, number 18, dated October 31, 2017, on pages 2278-2289. ("Libby-1")

24. I retrieved Libby-1 on June 26, 2024 through Purdue University Libraries at URL: <https://sso.purdue.edu/idp/profile/SAML2/Redirect/SSO?execution=e1s2>

Libby-1 is available through this open access URL:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5687846/>

On page 2289, in the References section, citation number 87 reads as shown below:

87. Tardif J-C, L'Allier P. Colchicine Cardiovascular Outcomes Trial (COLCOT). 2017. Available at: <https://www.clinicaltrials.gov/ct2/show/NCT02551094?term=colcot&rank=1>. Accessed October 10, 2017.

25. Therefore, as of the publication date of the *Journal of the American College of Cardiology*, volume 70, number 18, on October 31, 2017, pages 2278-2289, COLCOT was known and publicly accessible through the website at the URL: <https://www.clinicaltrials.gov/ct2/show/NCT02551094?term=colcot&rank=1>.

26. Attachment A-3 is an article by Peter Libby, Joseph Loscalzo, Paul M. Ridker, Michael E. Farkouh, Priscilla Y. Hsue, Valentin Fuster, Ahmed A. Hasan, and Salomon Amar with the title, "Inflammation, Immunity, and Infection in Atherothrombosis: JACC Review Topic of the Week" published in the *Journal of the American College of Cardiology*, volume 72, number 17, October 23, 2018, on pages 2071-2081. (Libby-2)

27. I retrieved Libby-2 on June 26, 2024 through Purdue University Libraries at URL: <https://www.sciencedirect.com/science/article/pii/S0735109718369572>

Libby-2 is available through an open access URL:

<https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC6196735&blobtype=pdf>

28. On page 2081, in the References section, citation number 102 reads as shown below:

102 Tardif J-C, L'Allier P. Colchicine Cardiovascular Outcomes Trial (COLCOT). 2017. Available at: <https://clinicaltrials.gov/ct2/show/NCT02551094> ↗. Accessed August 30, 2018.

29. Please note there is a discrepancy between the Reference numbering in the published version of Libby-2 and that accessible through the Open Access URL. In the published version, the citation to COLCOT is “Number 102” and in the Open Access full text version, the Libby-2 citation to COLCOT is “Number 103.” However, there is no substantive difference between the two references.

B. Conclusion Regarding COLCOT

31. Therefore, I opine that COLCOT, Exhibit 1006, is an authentic document, and was publicly accessible and documented by the evidence in Attachment A-1, Wayback Machine, October 20, 2017, and by the two citations as shown in Attachments A-2 and A-3, on October 31, 2017 and October 23, 2018. With the evidence articulated above, it is my opinion that COLCOT was authentic and publicly accessible as of at least October 20, 2017, well prior to November 15, 2019.

32. I therefore also conclude that the Patent Owner's criticisms of Mr. Cruitt's analysis and motives are not well founded. In other words, I believe that Mr. Cruitt reached the correct conclusion that COLCOT is an authentic document that was publicly accessible as of at least October 20, 2017.

VI. RIGHT TO SUPPLEMENT

33. I reserve the right to supplement my opinions in the future to respond to any arguments that the Patent Owner raises and to take into account new information as it becomes available to me.

VII. CERTIFICATION

34. In signing this declaration, I recognize that this declaration will be filed in support of the Petitioner in case number IPR2023-01064 at the U.S. Patent and Trademark Office.

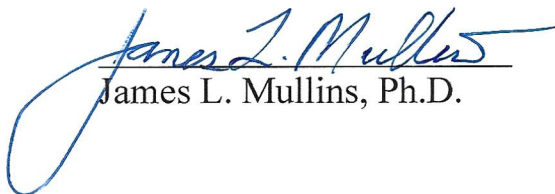
35. I acknowledge that, as part of this IPR, I may be subject to cross-examination in the United States regarding the content of this declaration. If cross-examination is required of me, I will make myself reasonably available for cross-examination within the United States during the time allotted for cross-examination.

36. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and, further, that these statements were made with the knowledge that willful false statements and

the like are punishable by fine, imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: June 28, 2024

Respectfully submitted,


James L. Mullins, Ph.D.

Appendix A

JAMES L. MULLINS, PhD

Prior Art Documentation Librarian Services, LLC

205 Saint Cuthbert, Williamsburg, VA 23188

jlmullins@priorartdoclib.com

ph. 765 479 4956

Prior Art Documentation Librarian Services, LLC. (PADLS). Founded January 2018. As of May 2024, 1 have completed 149 declarations for 43 law firms; seven depositions were scheduled, three cancelled a few days prior. One was held in February 2019, a second in June 2023, and a third in March 2024.

Library Experience:

2018-present Dean Emeritus, Libraries & Norton Professor Emeritus, Purdue University
2011 - 2017 Dean of Libraries & Esther Ellis Norton Professor, Purdue University
2004 - 2011 Dean of Libraries & Professor, Purdue University, West Lafayette, IN
2000-2004 Assistant/Associate Director for Administration, MIT Libraries, Massachusetts Institute of Technology, Cambridge, MA.
1996-2000 University Librarian & Director, Falvey Memorial Library. Villanova University, Villanova, PA.
1978-1996 Director of Library Services, Indiana University South Bend.
1974-1978 Associate Librarian, Indiana University Bloomington, School of Law.
1973-1974 Instructor/Catalog Librarian. Georgia Southern College (now University).

Teaching Experience:

1977-1996 Associate Professor (part-time), School of Library and Information Science, Indiana University. Subjects taught: Cataloging, Management, and Academic Librarianship.

Education:

1972 - University of Iowa. Honors Bachelor of Arts, History, Religion & Political Science.
1973 - University of Iowa. Master of Arts in Library Science.
1984 - Indiana University. Doctor of Philosophy. Concentration: Academic Library Administration. Emphasis: Law Librarianship.

Awards and Recognition:

2017 Wilmeth Active Learning Center/Library of Engineering and Science, Grand Reading Room, was announced by President Mitch Daniels, Purdue University, that it would be re-named the James L. Mullins Reading Room to honor his leadership and reputation in the academic library profession.

September 2017. Portrait unveiled December 2017.

2017 Distinguished Alumnus Award by the School of Informatics and Computing, Indiana University, Bloomington. Given June 25, 2017.

2016 Hugh C. Atkinson Memorial Award, jointly sponsored by the four divisions of the American Library Association (ALA), June 27, 2016.

2015 ACRL Excellence in University Libraries Award, April 23, 2015.

Named Esther Ellis Norton Professor of Library Science by Purdue Trustees, December 11, 2011.

International Review Panel to evaluate the University of Pretoria Library, February 20 – 24, 2011. Pretoria, South Africa.

Publications: (selected)

Designing the Academic Library, Chapter Contributor. Association of College and Research Libraries, American Library Association, 2022.

A Purdue Icon: Creation, Life, and Legacy, edited by James L. Mullins, Founder's Series, Purdue University Press, 138pp., August 2017.

"The policy and institutional framework." In *Research Data Management, Practical Strategies for Information Professionals*, edited by Ray, J M. Purdue University Press, pp.25-44, 2014.

"DataCite: linking research to data sets and content." In Benson, P and Silver, S. *What Editors Want: An Author's Guide to Scientific Journal Publishing*. University of Chicago Press, pp. 21-23, December 2012.

"Library Publishing Services: Strategies for Success," with R. Crow, O. Ivins, A. Mower, C. Murray-Rust, J. Ogburn, D Nesdill, M. Newton, J. Speer, C. Watkinson. *Scholarly Publishing and Academic Resources Coalition (SPARC)*, version 2.0, March 2012.

"The Changing Definition and Role of Collections and Services in the University Research Library." *Indiana Libraries*, Vol 31, Number 1 (2012), pp.18-24.

"Are MLS Graduates Being Prepared for the Changing and Emerging Roles that Librarians must now assume within Research Libraries?" *Journal of Library Administration*. Volume 52, Issue 1, 2012, p. 124-132

Baykoucheva, Svetla. What Do Libraries Have to Do with e-Science?: An Interview with James L. Mullins, Dean of Purdue University Libraries. *Chem. Inf. Bull.* [Online] 2011, 63 (1), 45-49. <http://www.acscinf.org/publications/bulletin/63-1/mullins.php> (accessed Mar 16, 2011).

“The Challenges of e-Science Data-set Management and Scholarly Communication for Domain Sciences and Technology: a Role for Academic Libraries and Librarians,” chapter in, *The Digital Deluge: Can Libraries Cope with e-Science?*” Deanna B. Marcum and Gerald George, editors, Libraries Unlimited/Teacher Ideas Press, 2009. (a monograph publication of the combined proceedings of the KIT/CLIR proceedings).

“Bringing Librarianship to e-Science,” *College and Research Libraries*. vol. 70, no. 3, May 2009, editorial.

“The Librarian’s Role in e-Science” *Joho Kanri (Journal on Information Processing and Management)*, Japan Science and Technology Agency (formerly Japan Information Center of Science and Technology), Tokyo, Japan. Translated into Japanese by Taeko Kato. March 2008.

The Challenge of e-Science Data-set Management to Domain Sciences and Engineering: a Role for Academic Libraries and Librarians,” KIT (Kanazawa Institute of Technology)/CLIR (Council of Library and Information Resources) International Roundtable for Library and Information Science, July 5-6, 2007. Developments in e-science status quo and the challenge, The Japan Foundation, 2007.

“An Administrative Perspective,” Chapter 14, *Proven Strategies for Building an Information Literacy Program*, Susan Curzon and Lynn Lampert, editors, Neal-Schuman Publishers, Inc., New York, 2007. pp. 229-237.

Library Management and Marketing in a Multicultural World, proceedings of the IFLA Management and Marketing (M&M) Section, Shanghai, China, August 16-17, 2006, edited. K.G. Saur, Munchen, Germany, June 2007. 390 pp.

Top Ten Assumptions for the Future of Academic Libraries and Librarians: a report from the ACRL Research Committee, with Frank R. Allen and Jon R. Hufford. *College & Research Libraries*, April 2007, vol.68, no.4. pp.240-241, 246.

To Stand the Test of Time: Long-term Stewardship of Digital Data Sets in Science and Engineering. A report to the National Science Foundation from the ARL Workshop on New Collaborative Relationships: the Role of Academic Libraries in the Digital Data Universe. September 26-27, 2006, Arlington, VA. p.141. <http://www.arl.org/bm~doc/digdatarpt.pdf>

“Enabling Interaction and Quality in a Distributed Data DRIS,” *Enabling Interaction and Quality: Beyond the Hanseatic League*. 8th International Conference on Current Research Information Systems, with D. Scott Brandt and Michael Witt. Promoted by euro CRIS. Leuven University Press, 2006. pp.55-62. Editors: Anne Garns Steine Asserson and Eduard J. Simons.

"Standards for College Libraries, the final version approved January 2000," prepared by the ACRL College Libraries Standards Committee (member), *C&RL News*, March 2000, p.175-182.

"Standards for College Libraries: a draft," prepared by the ACRL College Libraries Section, Standards Committee (member), *C&RL News*, May 1999, p. 375-381.

"Statistical Measures of Usage of Web-based Resources," *The Serials Librarian*, vol. 36, no. 1-2 (1999) p. 207-10.

"An Opportunity: Cooperation between the Library and Computer Services," in *Building Partnerships: Computing and Library Professionals*. Edited by Anne G. Lipow and Sheila D. Creth. Berkeley and San Carlos, CA, Library Solutions Press, 1995. p. 69-70.

"Faculty Status of Librarians: A Comparative Study of Two Universities in the United Kingdom and How They Compare to the Association of College and Research Libraries Standards," in *Academic Librarianship, Past, Present, and Future: a Festschrift in Honor of David Kaser*. Englewood, Colorado; Libraries Unlimited, 1989. p. 67-78. Review in: *College & Research Libraries*, vol. 51, no. 6. November 1990, p. 573-574.

Presentations: (Representative)

“How Long the Odyssey? Transitioning the Library and Librarians to Meet the Needs and Expectations of the 21st Century University,” David Kaser Lecture, School of Informatics & Computing, Indiana University, Bloomington, IN, November 16, 2015.

Presentation at University of Cape Town, Cape Town, South Africa, August 20, 2015.

“The Challenge of Discovering Science and Technology Information,” Moderator, International Federation of Library Associations (IFLA) Science and Technological Libraries Section Program, Cape Town, South Africa, August 18, 2015.

“An Odyssey in Data Management: Purdue University,” International Federation of Library Associations (IFLA) Research Data Management: Finding Our Role – A program of the Research Data Alliance, Cape Town, South Africa, August 17, 2015.

Presentation at University of Pretoria, Pretoria, South Africa, August 11, 2015.

Co-Convener with Sarah Thomas, Harvard University, at the Harvard Purdue Symposium on Data Management, Harvard University, Cambridge, MA, June 15-18, 2015.

“Strategic Communication,” panel discussion on the Director's role and perspective on library communications at Committee on Institutional Cooperation (CIC) Center for Library Initiatives (CLI) Annual Conference, University of Illinois Urbana-Champaign, May 20, 2015.

“Issues in Data Management,” panel discussion moderated by Catherine Woteki, United States Undersecretary for Research, Education & Economics at 20th Agriculture Network Information Collaborative (AgNIC) Annual Meeting in the National Agricultural Library, Beltsville, MD, May 6, 2015.

“Active learning/IMPACT & the Active Learning Center at Purdue University,” Florida Institute of Technology, Melbourne, FL, February 11, 2015.

“Science+art=creativity: libraries and the new collaborative thinking,” panel moderator, International Federation of Library Associations (IFLA) 80th General Conference and Assembly, Lyon, France, August 19, 2014.

“Purdue University The Active Learning Center—A new concept for a library,” Association of University Architects 59th Annual National Conference, University of Notre Dame, South Bend, IN, June 23, 2014.

“Big Data & Implications for Academic Libraries,” keynote speaker, Greater Western Library Alliance (GWLA) Cyber-infrastructure Conference, Kansas City, MO, May 28, 2014.

“Research Infrastructure,” panel moderator, Association of Research Libraries (ARL) 164th Membership Meeting, Ohio State University, Columbus, OH, May 7, 2014.

“An Eight Year Odyssey in Data Management: Purdue University,” International Association of Scientific and Technological University Libraries (IATUL) 2013 Workshop Research Data Management: Finding Our Role, University of Oxford, UK, December 2013.

“Purdue University Libraries & Press: from collaboration to integration,” Ithaka Sustainable Scholarship, The Evolving Digital Landscape: New Roles and Responsibilities in Higher Education, libraries as publishers, New York, New York, October 2013.

“Tsinghua and Purdue: Research Libraries for the 21st Century,” Tsinghua University, Tsinghua, China, August 2013.

“Purdue Publishing Experience in the Libraries Publishing Coalition,” Association of American University Presses Annual Meeting, Press-Library Coalition Panel, Boston, Massachusetts, June 21, 2013.

“Indiana University Librarians Day: Purdue University Libraries Ready for the 21st Century,” Indiana University Purdue University Indianapolis (IUPUI), June 7, 2013.

“Purdue University Libraries and Open Access; CNI Project Update,” Coalition for Networked Information, San Antonio, TX, April 5, 2013.

Memorial Resolution, honoring Joseph Brannon, to the Board of the Association of College & Research Libraries, Seattle, WA, January 2013.

“An overview of sustaining e-Science collaboration in an Academic Research Library—the Purdue experience,” Duraspace e-Science Institute webcast, October 17, 2012.

“The Role of Libraries in Data Curation, Access, and Preservation: an International Perspective,” Panel Moderator, 78th General Conference and Assembly, International Federation of Library Associations, Helsinki, Finland, August 15, 2012.

“21st Century Libraries,” moderator of First Plenary Session, International Association of Technological University Libraries 33rd Annual Conference, Singapore, June 4, 2012.

“Planning for New Buildings on Campus,” panel presenter, University of Calgary Building Symposium on Designing Libraries for the 21st Century, Calgary, Alberta, Canada, May 17, 2012.

“Data Management and e-Science, the Purdue Response.” Wiley-Blackwell Executive Seminar-2012, Washington, DC, March 23, 2012.

“An overview of Sustaining e-Science Collaboration in Academic Research Libraries and the Purdue Experience.” Leadership & Career Development Program Institute, Association of Research Libraries (ARL). Houston, TX, March 21, 2012.

“An overview of Data Activities at Purdue University in response to Data Management Requirements.” Coalition for Academic Scientific Computation (CASC). Arlington, VA, September 8, 2011.

“Getting on Track with Tenure,” Association of College and Research Libraries (ACRL) Research Program Committee. Washington, DC, June 26, 2011.

“Integration of the Press and Libraries Collaboration to Promote Scholarly Communication,” Association of Library Collections & Technical Services (ALCTS) Scholarly Communication Interest Group – American Library Association, New Orleans, Louisiana, June 25, 2011.

“Cooperation for improving access to scholarly communication,” with N. Lossau (Germany), C. Mazurek (Poland), J. Stokker (Australia), panel moderator and presenter, Second Plenary Session, International Association of Scientific and Technological University Libraries (IATUL) 32nd Conference 2011, Warsaw, Poland. May 29-June 2, 2011.

“Riding the Wave of Data,” STM Annual Spring Conference 2011. Trailblazing & transforming scholarly publishing 2011. Washington, D.C., April 28, 2011.

“Confronting old assumptions to assume new roles: physical and operational integration of the Press and Libraries at Purdue University,” keynote speaker, 2011 BioOne Publishers & Partners Meeting. Washington, D. C., April 22, 2011.

“Are MLS Graduates Being Prepared for the Changing and Emerging Roles that Librarians must now assume within Research Libraries?” University of Oklahoma Libraries Seminar, March 4, 2011, Oklahoma City, Oklahoma.

“The Future Role of University Librarians,” the University of Cape Town, South Africa, February 25, 2011.

“New Roles for Librarians: the Application of Library Science to Scientific/Technical Research – Purdue University – a case study. International Council for Science and Technology (ICSTI); Ottawa, Canada. June 9, 2009.

“Reinventing Science Librarianship: Models for the Future,” Association of Research Libraries / Coalition for Networked Information. October 16-17th, 2008, Arlington, VA. Moderator and convener of Data Curation: Issues and Challenges.

“Practical Implementation and Opportunities Created at Purdue University,” African Digital Curation Conference, Pretoria, South Africa, (live video transmission), February 12, 2008.

Keynote speaker. “*Scholarly Communication & Academe: The Winter of Our Discontent*,” XXVII Charleston Conference on Issues in Book and Serial Acquisition, Charleston, South Carolina. November 8, 2007.

Keynote speaker. “*Enabling Access to Scientific & Technical Data-sets in e-Science: a role for Library and Archival Sciences*,” Greater Western Library Alliance (GWLA), Tucson, Arizona. September 17, 2007. A meeting of library directors and vice presidents for research of member institutions.

“*The Challenge of e-Science Data-set Management to Domain Sciences and Engineering: a Role for Academic Libraries and Librarians*,” KIT (Kanazawa Institute of Technology)/CLIR (Council of

Library and Information Resources) International Roundtable for Library and Information Science, July 5-6, 2007. Invited to participate by the Deputy Librarian of Congress.

International Association of Technological University Libraries (IATUL), Stockholm, Sweden. June 8, 2007. Invited paper, *Enabling International Access to Scientific Data-sets: creation of the Distributed Data Curation Center (D2C2)*.

“A New Collaboration for Librarians: The Principles of Library and Archival Sciences Applied to the Curation of Datasets,” Symposium of the Libraries and the College of Engineering, University of Louisville, April 6, 2007.

“Purdue University Libraries: Through Pre-eminent Innovation and Creativity, Meeting the Challenges of the Information Age,” Board of Trustees, Purdue University, February 15, 2007.

ARL Workshop on New Collaborative Relationships: The Role of Academic Libraries in the Digital Data Universe, September 26-27, 2006, Arlington, VA. Invited participant.

NARA and SDSC: A partnership. A panel before the National Science Foundation, June 27, 2006. Arlington, VA. Invited participant.

“Kaleidoscope of Scientific Literacy: fusing new connections,” with Diane Rein, American Library Association, Association of College and Research Libraries, Science & Technology Section, Annual Conference, New Orleans, June 26th, 2006.

“Leadership for Learning: Building a Culture of Teaching in Academic Libraries – an administrative perspective,” American Library Association, Association of College and Research Libraries, Instruction Section, Annual Conference, New Orleans, June 25th, 2006.

“Building an interdisciplinary research program in an academic library: how the Libraries’ associate dean for research makes a difference at Purdue University,” International Association of Technological University Libraries (IATUL), Porto, Portugal, May 23rd, 2006.

“Enabling Interaction and Quality in a Distributed Data DRIS,” *Enabling Interaction and Quality: Beyond the Hanseatic League*. 8th International Conference on Current Research Information Systems, with D. Scott Brandt and Michael Witt. Promoted by euro CRIS, Bergen, Norway, May 12th, 2006, Brandt, and Witt presented in person

“Interdisciplinary Research,” with D. Scott Brandt, Coalition for Networked Information (CNI) Spring Meeting: Project Briefing, Washington, D.C., April 3rd, 2006.

“An Interview with Purdue’s James Mullins,” a podcast submitted by Matt Pasiewicz, on *Educause Connect*, http://connect.educause.edu/James_L_Mullins_Interview_CNI_2005

"Managing Long-Lived Digital Data-sets and their Curation: Interdisciplinary Policy Issues," Managing Digital Assets Forum, Association of Research Libraries (ARL), Washington, D.C., October 28th, 2005.

"The Odyssey of a Librarian." Indiana Library Federation (ILF), District 2 Meeting, South Bend, Indiana. October 4th, 2005.

"New College Library Standards," Standards Committee Presentation, ALA, Chicago, July 7, 2000. SUNY Library Directors, Lake George, New York. "*The College Library Standards: a Tool for Assessment.*" April 5, 2000.

Tri-State College Library Association, *Finding You Have Talents You Never Knew You Had*, Penn State Great Valley, March 25, 2000.

Using Web Statistics, American Library Association, New Orleans, June 24, 1999.

Keynote speaker at the JSTOR Workshop, January 29, 30, 1999. University of Pennsylvania, Philadelphia, PA.

"The New Standards for Electronic Resources Statistics," Society of Scholarly Publishers, Washington, D.C., September 17, 1998.

"Evaluating Online Resources: Now that you've got them what do you do?," joint presenter with Chuck Hamaker, LSU, at the NASIG Conference, Boulder, Colorado. June 1998.

"What Employers Are Looking for in New Librarians?" Pennsylvania Library Association, Philadelphia. September 26, 1997.

"The Theory of Matrix Management" panel presentation of the Comparative Library Organization Committee of the Library Organization and Management Section of the Library Administration and Management Association, a division of the American Library Association, Annual Meeting, Chicago, June 24, 1990.

Professional Involvement: (summary of recent emphasis)

The focus for my professional involvement and research has moved recently toward managing massive data-sets. This has resulted in working with faculty in the sciences and technology to determine how librarians can collaborate in managing, curating, and preserving data-sets for future access and documentation. This has included various speaking opportunities as well as participation in planning with the National Science Foundation (NSF) on ways in which librarians can be integrated more completely into the funded research process. Participation in the Kanazawa Institute of Technology/Council of Library Resources Roundtable was particularly rewarding and provided new opportunities to share with international colleagues the issues surrounding data-set management. I was

the champion for the creation of the Distributed Data Curation Center (D2C2) at Purdue University (<http://d2c2.lib.purdue.edu/>)

Throughout my career, beginning with my dissertation, I have been actively involved with assessing and evaluating libraries. In the fall of 1999, I contacted twenty-two academic library directors to determine whether the need was also felt by others. The response was overwhelmingly affirmative. This resulted in a meeting at ALA Midwinter, January 2000. A formal meeting followed at Villanova University in April 2000. As convener, I helped to form the University Libraries Group (ULG), modeled after the Oberlin Group for college libraries. The ULG is made up of university libraries that support diverse wide-ranging programs through doctoral level and have a level of support that places them in the top tier of academic institutions. A few of the member libraries, along with Villanova, are William and Mary, Wake Forest, Lehigh, Carnegie-Mellon, Tufts, Marquette, Miami of Ohio, and Southern Methodist. In 1994 appointed to the Standards Committee, College Section, Association of College and Research Libraries. During the next six years, the Committee concentrated on changing the focus of the standards from quantitative analysis of input and output factors to emphasis on assessment of the outcome. Culmination of the work was a re-issue of the *Standards for College Libraries* in 2000. The knowledge gained through my work experience enabled me to formulate the changes needed in the standards. This work allowed for close collaboration with accrediting agencies, both professional and regional. During this same time another focus emerged, the impact of digital resources. Through my work on the JSTOR Statistics Task Force, standards were developed on the collection of use of electronic databases. This Standard was later adopted in 1998 by the International Consortium of Library Consortia (ICOLC). In 2002, the American Library Association appointed me to serve as the liaison to the Marketing and Management Section of the International Federation of Library Associations (IFLA).

Professional Service: (representative list)

Nominations Committee, Association of Research Libraries (ARL), 2016.

Steering Committee, Scholarly Publishing and Academic Resources Coalition (SPARC), 2016 – 2017.
“Excellence in Library Services,” Chair, Review Team, University of Hong Kong, Hong Kong, August 24-27, 2015.

Chair, Management Advisory Board, 2015-2017; Member, Scientific Advisory Board, arXiv, Cornell University, 1/1/2013 – present.

Advisory Board for the Wayne State University School of Library and Information Science, July 2012 – present.

Advisory Board for Microsoft Academic Search, 2012 – 2015. Redmond, WA.

Transforming Research Libraries, a Strategic Direction Steering Committee of the Association of Research Libraries (ARL), 2012-2015.

Science and Technology section, representing ARL, International Federation of Library Associations (IFLA), Chair, 2013 – 2017; Member, 2011 to present.

Member of University of Pretoria, South Africa, Library Review Committee. August 2013.

Co-chair, Local Arrangements Planning Committee for 2013 Conference, Association of College and Research Libraries (ACRL), a division of the American Library Association (ALA).

Association of Research Libraries Leadership & Career Development Program Mentor, 2011-2017.

e-Science Task Force, Association of Research Libraries. July 2006 – present. Chair, October 2011 – October 2012.

Board of Directors, International Association of Technological University Libraries (IATUL). January 2008 – December 2014.

Midwest Collaborative for Library Services (MCLS); Board Member, October 2010 – December 2012.

Chair, Library Directors, Committee on Institutional Cooperation (CIC), July 2010 – June 2012.

Board of Directors, Association of Research Libraries (ARL); October 2008 – October 2011.

Scholarly Communication Steering Committee, Association of Research Libraries (ARL) 2008-2011.

Editorial Board, *College and Research Libraries*, Association of College and Research Libraries, American Library Association. January 2008 – December 2014.

Chair, Organizing Committee for IATUL Conference 2010, June 21-24, 2010, Purdue University, West Lafayette, Indiana/Chicago, Illinois.

Conference Planning Committee for National Conference of the Association of College and Research Libraries, 2009, Seattle, Washington.

Research Committee, Association of College and Research Libraries, ACRL, division of ALA. 2002-2007, chair, 2005-2007.

Association of Research Libraries, Search and Screen Committee, Executive Director. March – January 2008.

Center for Research Libraries, Board of Directors. April 2006 – April 2012.

Academic Libraries of Indiana, Board of Directors, 2004 – present. Vice-president, 2005-2007.

President, 2007- 2009.

ALA Representative to the International Federation of Library Associations (IFLA), Marketing and Management (M&M) Section, initial term 2003-2007, re-appointed for second term, 2007-2011.

Invited to represent Research Libraries at the ACRL/3M Wonewok Retreat to assess Marketing of Academic Libraries, October 2002.

Hugh A. Atkinson Award Committee, LAMA Representative, ALA, 2001-2005.

Program Committee, Library Administrators and Management Association (LAMA), a division of ALA. 1996-2001.

ACRL, Standards and Accreditation Committee, a division of ALA. Liaison to RBMS Section of ACRL. 1997-2002.

Elected to the Executive Committee of LAMA, LOMS, a division of the American Library Association, 1998-2000. Nominated as Chair/Elect for 2003 – 2005.

Columbia University Press Advisory Committee. 1996 - 2000.

LITA/LAMA Conference Evaluation Committee, Pittsburgh, Pennsylvania, October 1996.

"New Learning Communities," Coalition for Networked Information, Indianapolis. November 19-21, 1995. Facilitator for invitational, national conference committed to developing collaborative learning and teaching techniques, involving librarians.

Planning Committee-Evaluation. LITA/LAMA 1996 Conference, Pittsburgh. This first conference, to be held jointly between two divisions of ALA, will focus on new technologies within libraries.

Indiana Cooperative Library Services Authority (InCoLSA), elected to Executive Committee, April 1991, served as President in 1993-94. InCoLSA is a statewide network of academic, public, school, and special libraries that supports library cooperation for cataloging, interlibrary loan, collection development and application of new technologies.

Governor's Conference on Libraries and Information Services. Served on Planning Committee, Academic Libraries Representative, appointed by the Governor to represent academic libraries in Indiana, Chair, Finance Committee, April 1989-July 1991.

Indiana Library Endowment Foundation Board, 1984-92. Charter Member, 1984, President, 1988-1992. 2004-2005.

University Service: (Summary)

Served on search and screen committees for senior positions including chancellor, dean, and directors; most recently I have been asked to serve on the search committee for the provost of Purdue University. At MIT service included the Library Council & appointment to the Administrative Council by President

Vest, 2001-2003 & Member of the Faculty Committee on the Library System. At Purdue appointed by the President to the Search Committee for the Provost, October 2007 to May 2008; member of the Capital Projects Committee, and IT Operational Oversight Committee as senior academic dean, 2008-2014.

Global Council, Global Policy Institute, 2012 – 2016.

Academic Program Excellence and Rankings (APER) project team, 2014.

Representative of the Academic Deans on the Re-engineering Business Operations, Purdue University, 2016 –

Academic Deans Council chaired by Provost – 2004 – 2017.

University Promotion and Tenure Committee – 2006 – 2017.

"Outstanding Team Award, Electronic Reserve Project," served as Chair, recognition awarded by the President of Villanova University to one team who made an outstanding contribution to the operations of the University, selected by a committee of administrators, faculty, and staff. Awarded September 9, 1999.

Nominated for the IUSB Lundquist Award, 1995 & 1996. The Lundquist award is given to faculty who have "exhibited excellence in teaching, scholarly or artistic achievement, and diversified relevant service..."

Attachment A-1

INTERNET ARCHIVE

Wayback Machine

27 captures

20 Oct 2017 - 11 Apr 2024

https://clinicaltrials.gov/ct2/show/NCT02551094

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About t

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Study Record Detail

☐ Save this study

Saved Studies (

Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLCOT)

This study is currently recruiting participants.

See [▶ Contacts and Locations](#)

Verified March 2017 by Montreal Heart Institute

Sponsor:

Montreal Heart Institute

ClinicalTrials.gov Identifier:

NCT02551094

First Posted: September 16, 2015

Last Update Posted: March 8, 2017

⚠

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

Information provided by (Responsible Party):

Montreal Heart Institute

Full Text View

Tabular View

No Study Results Posted

Disclaimer

How to Read a Study Record

▶ Purpose

The study evaluates whether long-term treatment with colchicine reduces rates of cardiovascular events in patients after myocardial infarction. Patients who have suffered a documented acute myocardial infarction within the last 30 days, are treated according to the national guidelines and after having completed any planned percutaneous revascularization procedures associated with the initial infarction will receive either colchicine (0.5 mg per day) or matching placebo (1:1 allocation ratio) for an estimated 2 years period or until the target of 301 primary endpoints has been reached

Condition	Intervention	Phase
Coronary Artery Disease	Drug: colchicine	Phase 3
Myocardial Infarction	Drug: colchicine placebo	

Study Type: Interventional

Study Design: Allocation: Randomized

Intervention Model: Parallel Assignment

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Primary Purpose: Prevention

Official Title: Colchicine Cardiovascular Outcomes Trial (COLCOT)

Resource links provided by NLM:

[MedlinePlus](#) related topics: [Heart Attack](#)

[Drug Information](#) available for: [Colchicine](#)

[U.S. FDA Resources](#)

Further study details as provided by Montreal Heart Institute:

Primary Outcome Measures:

- Cardiovascular death [Time Frame: approximately 3 to 4 years]
number of days from randomization
- resuscitated cardiac arrest [Time Frame: approximately 3 to 4 years]
number of days from randomization
- acute myocardial infarction [Time Frame: approximately 3 to 4 years]
number of days from randomization
- stroke [Time Frame: approximately 3 to 4 years]
number of days from randomization
- hospitalization for angina requiring coronary revascularization [Time Frame: approximately 3 to 4 years]
number of days from randomization

Secondary Outcome Measures:

- total mortality [Time Frame: approximately 3 to 4 years]
number of days from composite of cardiovascular death
- total mortality [Time Frame: approximately 3 to 4 years]
number of days from composite of resuscitated cardiac arrest
- total mortality [Time Frame: approximately 3 to 4 years]
number of days from composite of acute myocardial infarction
- total mortality [Time Frame: approximately 3 to 4 years]
number of days from composite of stroke

Other Outcome Measures:

- deep venous thrombosis [Time Frame: approximately 3 to 4 years]
number of days from randomization
- pulmonary embolus [Time Frame: approximately 3 to 4 years]
number of days from randomization
- atrial fibrillation [Time Frame: approximately 3 to 4 years]
number of days from randomization
- heart failure hospitalization [Time Frame: approximately 3 to 4 years]
number of days from randomization
- coronary revascularization [Time Frame: approximately 3 to 4 years]
number of days from randomization

Estimated Enrollment: 4500
Study Start Date: September 2015
Estimated Study Completion Date: September 2019
Estimated Primary Completion Date: March 2019 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Active Comparator: colchicine 0.5 mg tablet of colchicine taken once a day	Drug: colchicine 0.5 mg tablet taken once a day Other Name: no other name
Placebo Comparator: colchicine placebo 0.5 mg tablet of placebo taken once a day	Drug: colchicine placebo sugar pill manufactured to mimic colchicine 0.5 mg tablet Other Name: no other name

Detailed Description:

Atherosclerosis is the most common cause of myocardial infarction, stroke and peripheral arterial disease. Research has clearly demonstrated that inflammation plays a key role in the initiation, progression and manifestations of atherosclerosis. Atherosclerotic lesions begin as an accumulation of lipid-laden cells (primarily macrophages) beneath the endothelium, and progress with the further accumulation of cells, connective-tissue elements, lipids and debris through immunological and inflammatory activation. Neutrophils and other inflammatory cells have been shown to invade culprit atherosclerotic lesions in acute coronary syndromes. It is likely that the inflammatory process is responsible for the high rate of cardiovascular events despite significant advances in the treatment of risk factors such as hypercholesterolemia and hypertension. It is vital to improve our understanding of the inflammatory nature of atherosclerotic disease and modify the inflammatory process with targeted therapies. Prospective cohort studies have consistently shown that high sensitivity C-reactive protein (hs-CRP) and several other biomarkers of inflammation are independently associated with increasing risk of future cardiovascular events in different populations. This together with animal models showing that reduced inflammation has anti-atherosclerotic effects, create the impetus to test the hypothesis that treatment of the underlying inflammatory process will contribute to improved cardiovascular clinical outcomes. Colchicine is an inexpensive, yet potent, anti-inflammatory drug approved for acute use in patients with gout and chronic use in patients with Familial Mediterranean Fever. The mechanism of action is through the inhibition of tubulin polymerization and potentially also through effects on cellular adhesion molecules and inflammatory chemokines. Colchicine may also have direct anti-inflammatory effects by inhibiting key inflammatory signaling networks known as the inflammasome and pro-inflammatory cytokines. Through the disruption of the cytoskeleton, colchicine is believed to suppress secretion of cytokines and chemokines as well as in vitro platelet aggregation. Considerable work has highlighted the potential of colchicine in the treatment of cardiovascular diseases mediated by pro-inflammatory processes. More recently colchicine has been evaluated for its effect on cardiovascular events in patients with coronary artery disease (CAD).

► Eligibility

Information from the National Library of Medicine



Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study.
To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, [Learn About Clinical Studies.](#)

Ages Eligible for Study: 18 Years and older (Adult, Senior)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Males and females of at least 18 years of age capable and willing to provide informed consent
- Patient must have suffered a documented acute myocardial infarction within the last 30 days
- Patient must be treated according to national guidelines (including anti-platelet therapy, statin, renin-angiotensin-aldosterone system inhibitor (preferably angiotensin-converting enzyme) and beta-blocker when indicated)
- Patient must have completed any planned percutaneous revascularization procedures associated with his or her qualifying myocardial infarction
- Female patient is either not of childbearing potential, defined as postmenopausal or is of childbearing potential and practicing at least one method of contraception and preferably two complementary forms of contraception
- Patient is judged to be in good general health as determined by the principal investigator
- Patient must be able and willing to comply with the requirements of this study protocol

Exclusion Criteria:

- Patient with a poorly controlled medical condition, such as New York Heart Association Class III-IV heart failure, a left ventricular ejection fraction of less than 35%, recent stroke (within the past 3 months), or any other condition which in the opinion of the investigator, would put the patient at risk if participating in this study
- Patient with a prior coronary artery bypass graft within the past 3 years, or planned
- Patient currently in cardiogenic shock or with hemodynamic instability
- Patient with a history of cancer or lymphoproliferative disease within the last 3 years other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and or localized carcinoma in situ of the cervix
- Patient with inflammatory bowel disease (Crohn's disease or ulcerative colitis) or patient with chronic diarrhea
- Patient with pre-existent progressive neuromuscular disease or patient with creatine phosphokinase level greater than 3 times the upper limit of normal (unless due to myocardial infarction which is allowed) as measured within the past 30 days and determined to be non-transient through repeat testing
- Patient with any of the following as measured within the past 30 days, and determined to be non-transient through repeat testing: hemoglobin less than 115 grams/L, white blood cell count less than $3.0 \times 10^9/L$, platelet count less than $110 \times 10^9/L$, alanine aminotransferase greater than 3 times the upper limit of normal, total bilirubin greater than 2 times the upper limit of normal (unless due to Gilbert syndrome, which is allowed), creatinine greater than 2 times the upper limit of normal
- Patient with a history of cirrhosis, chronic active hepatitis or severe hepatic disease
- Female patient who is pregnant, or breast-feeding or is considering becoming pregnant during the study or for 6 months after the last dose of study medication
- Patient with a history of clinically significant drug or alcohol abuse in the last year
- Patient is currently using or plan to begin chronic systemic steroid therapy (oral or intravenous) during the study (topical or inhaled steroids are allowed)
- Patient currently taking colchicine for other indications (mainly chronic indications represented by Familial Mediterranean Fever or gout); there is no wash-out period required for patients who have been treated with colchicine and stopped treatment prior to enrollment
- Patient with history of an allergic reaction or significant sensitivity to colchicine
- Patient who has used an investigational chemical agent less than 30 days or 5 half-lives prior to the screening visit (whichever is longer)
- Patient is considered by the investigator, for any reason, to be an unsuitable candidate for the study

► Contacts and Locations

Information from the National Library of Medicine



To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): **NCT02551094**

Contacts

Contact: Jean-Claude Tardif, MD 514 376-3330 ext 3612 jean-claude.tardif@icm-mhi.org

Contact: Mylène Provencher, MSc 514 461-1300 ext 2133 mylene.provencher@mhcc.org

Locations

Canada, Quebec

Montreal Heart Institute **Recruiting**

Montreal, Quebec, Canada, H1T1C8

Principal Investigator: Jean-Claude Tardif, MD

Sub-Investigator: Philippe L L'Allier, MD

Sponsors and Collaborators

Montreal Heart Institute

Investigators

Principal Investigator: Jean-Claude Tardif, MD Montreal Heart Institute

► More Information

Responsible Party: Montreal Heart Institute
ClinicalTrials.gov Identifier: [NCT02551094](#) [History of Changes](#)
Other Study ID Numbers: MHIPS-003
First Submitted: August 26, 2015
First Posted: September 16, 2015
Last Update Posted: March 8, 2017
Last Verified: March 2017

Additional relevant MeSH terms:

Infarction	Arterial Occlusive Diseases
Coronary Artery Disease	Vascular Diseases
Myocardial Ischemia	Colchicine
Coronary Disease	Gout Suppressants
Myocardial Infarction	Antirheumatic Agents
Ischemia	Tubulin Modulators
Pathologic Processes	Antimitotic Agents
Necrosis	Mitosis Modulators
Heart Diseases	Molecular Mechanisms of Pharmacological Action
Cardiovascular Diseases	Antineoplastic Agents
Arteriosclerosis	

Attachment A-2

THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Interleukin-1 Beta as a Target for Atherosclerosis Therapy

Biological Basis of CANTOS and Beyond

Peter Libby, MD



ABSTRACT

Inflammatory pathways drive atherogenesis and link conventional risk factors to atherosclerosis and its complications. One inflammatory mediator has come to the fore as a therapeutic target in cardiovascular disease. The experimental and clinical evidence reviewed here support interleukin-1 beta (IL-1 β) as both a local vascular and systemic contributor in this regard. Intrinsic vascular wall cells and lesional leukocytes alike can produce this cytokine. Local stimuli in the plaque favor the generation of active IL-1 β through the action of a molecular assembly known as the inflammasome. Clinically applicable interventions that interfere with IL-1 action can improve cardiovascular outcomes, ushering in a new era of anti-inflammatory therapies for atherosclerosis. The translational path described here illustrates how advances in basic vascular biology may transform therapy. Biomarker-directed application of anti-inflammatory interventions promises to help us achieve a more precise and personalized allocation of therapy for our cardiovascular patients. (J Am Coll Cardiol 2017;70:2278-89)

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INFLAMMATORY AND IMMUNE MECHANISMS PARTICIPATE IN ATHEROTHROMBOSIS

Multiple strands of experimental and clinical evidence implicate inflammation in atherogenesis and its complications (1-8). Inflammatory status, monitored by C-reactive protein (CRP) concentrations measured with a high-sensitivity CRP (hsCRP) assay can sharpen the prediction of first-ever and recurrent cardiovascular events beyond those predicted by conventional risk algorithms (9,10). Targeting therapies with anti-inflammatory actions based on inflammatory status can reduce cardiovascular

events (11). Reductions of events by statin therapy may result in part from muting inflammation both by reduction in LDL and by direct effects (12-14).

Despite these strong indications of the involvement of inflammation in atherosclerosis and the benefit of anti-inflammatory therapies, the use of agents such as statins, which alter both the causal risk factor, low-density lipoprotein (LDL), and inflammatory pathways, cannot demonstrate unequivocally that therapy that targets inflammation per se can reduce risk of atherosclerotic events. Moreover, high-dose statin treatment and other current standard measures only prevent a fraction of recurrent events



Listen to this manuscript's audio summary by JACC Editor-in-Chief Dr. Valentin Fuster.



From the Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Dr. Libby's laboratory has received research support from U.S. National Heart, Lung, and Blood Institute grant HL080472, the RRM Charitable Fund, and Novartis; is a member of the scientific advisory boards of Athera, Corvidia Therapeutics, DalCor Pharmaceuticals, Interleukin Genetics, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, and Novartis; and is an uncompensated consultant for AstraZeneca, Esperion Therapeutics, Ionis Pharmaceuticals, Kowa Pharmaceuticals, Merck & Co., Novartis, Pfizer, Sanofi-Regeneron, Takeda Pharmaceuticals, and XBiotech, Inc.

Manuscript received August 3, 2017; revised manuscript received September 7, 2017, accepted September 10, 2017.

in survivors of myocardial infarction (MI) (15-17). This residual burden of events presents a pressing unmet medical need.

CYTOKINES SERVE AS KEY MESSENGERS OF INFLAMMATORY SIGNALING

Inflammation does not necessarily primarily trigger atherogenesis but transduces the atherogenic effects of classic risk factors (8). Cytokines encompass a class of proteins that mediate inflammation and modulate immunity. One group of cytokines, the interleukins, bear that name because they were thought to mediate signaling between white blood cells (hence the name interleukin) (18). Cytokines contribute critically to atherosclerosis, among other inflammatory diseases (8,19,20).

IL-1: A PRIMORDIAL PROINFLAMMATORY CYTOKINE

As indicated by its name, interleukin (IL)-1 figures among the first cytokines recognized. Several pathways converged on the identification of the molecules we now denote as IL-1. The quest to identify the transferable sterile factor that induces fever (endogenous pyrogen activity) guided purification of the protein we now know as IL-1 (21,22). The cloning of IL-1 cDNAs identified 2 related but functionally distinct isoforms: IL-1 α and IL-1 β (18) (Table 1). This pair of mediators has many effects in host defenses and in the pathogenesis of a wide variety of diseases. Notable effects of IL-1 on many cell types include induction of prostaglandin production through the induction of cyclooxygenase-2; the elaboration of nitric oxide by elevation of levels of the inducible isoform of nitric oxide synthase; induction of the expression of many cytokines, including augmenting its own gene transcription; increased expression of leukocyte adhesion molecules and thrombogenic mediators; and activation of cells involved in innate immunity, prominently including the mononuclear phagocytes (23) (Figure 1).

IL-1 FAMILY AND ITS REGULATION

As is often the case in pluripotent biological mediators, multiple levels of regulation control IL-1 action. The IL-1 family includes the structurally related IL-1 receptor antagonist (IL-1ra) (Table 1) (18). The balance between the proinflammatory IL-1 α and IL-1 β isoforms and this endogenous inhibitor (IL-1ra) represents one important level of control. The IL-1 α and IL-1 β isoforms have distinct functional profiles. IL-1 α typically resides on the cell surface and signals at

short distances by direct contact. In contrast, IL-1 β can act at a distance.

Two receptors bind the principal members of the IL-1 family. IL-1 receptor I (IL-1RI) transduces IL-1 β signaling (Table 1). In contrast, IL-1 receptor II (IL-1RII) binds the ligands but does not signal, because it lacks a cytoplasmic domain. IL-1RII thus functions as a “decoy,” providing yet another level of negative regulation of IL-1 signaling. IL-1 can induce its own gene expression in many cell types, including those implicated in atherogenesis (Figure 2A) (24,25). In the case of IL-1 α or IL-1 β inducing themselves or each other, a positive feedback loop pertains (Figure 2B) (26). IL-1 α and IL-1 β can also increase the expression of IL-1ra, enabling negative feedback inhibition, a mechanism that resists untrammelled IL-1 signaling.

THE INFLAMMASOME ACTIVATES IL-1 β

In contrast to IL-1 α , the beta isoform requires processing to exert its biological actions. Several levels of control regulate the activation of IL-1 β . Pro-IL-1 β undergoes proteolytic cleavage to produce mature IL-1 β that possesses biological activity (Figure 3). The proteolytic enzyme responsible for producing the mature, secreted IL-1 β , first called IL-1 β -converting enzyme, now bears the name caspase-1. This enzyme cleaves the 33-kDa precursor of IL-1 to the active 17-kDa form, analogous to processing of angiotensin I to the active angiotensin II form by angiotensin-converting enzyme (Figure 2D). Macrophages in human atherosclerotic plaques contain caspase-1 (Figure 2E) (27).

Caspase-1 in turn undergoes activation by a supramolecular assembly known as the inflammasome (Figure 3) (28,29). The inflammasome transduces inflammatory signals, culminating in cleavage of procaspase-1 to its active form, which in turn activates IL-1 β . Certain rare genetic diseases demonstrate the importance of the inflammasome in control of the overwhelming proinflammatory potential of the active cytokine. Muckle-Wells syndrome and cryopyrin-associated periodic syndrome arise from gain-of-function mutations in the inflammasome (30). These mutations markedly augment IL-1 β maturation and produce debilitating inflammatory diseases in children, indubitably due to overproduction of active IL-1 β .

The inflammasome generally requires 2 signals to assemble and act (28). The coactivators or triggers of the inflammasome include components of infectious

ABBREVIATIONS AND ACRONYMS

ACS	= acute coronary syndromes
cDNA	= complementary DNA
hsCRP	= high-sensitivity C-reactive protein
ICAM	= intercellular adhesion molecule
IL	= interleukin
MI	= myocardial infarction
MMP	= matrix metalloproteinase
SMC	= smooth muscle cells
VCAM	= vascular cell adhesion molecule

TABLE 1 Interleukin-1 and Receptor Family Members		
		Comments
Cytokine		
Interleukin-1 alpha (IL-1 α)	IL-1 α generally remains associated with the cell surface or is released by dying cells and usually acts at short distances by juxtacrine or paracrine signaling	
Interleukin-1 beta (IL-1 β)	IL-1 β acts primarily extracellularly as a soluble mediator	
Interleukin-1 receptor antagonist (IL-1ra)	IL-1ra blocks the signaling receptor that binds either IL-1 α or β	
Receptors		
Interleukin-1 receptor 1 (IL-r1)	IL-1 receptor 1 binds both isoforms	
Interleukin-1 receptor 2 (IL-r2)	IL-1 receptor 2 does not signal and thus acts as an inhibitory decoy	

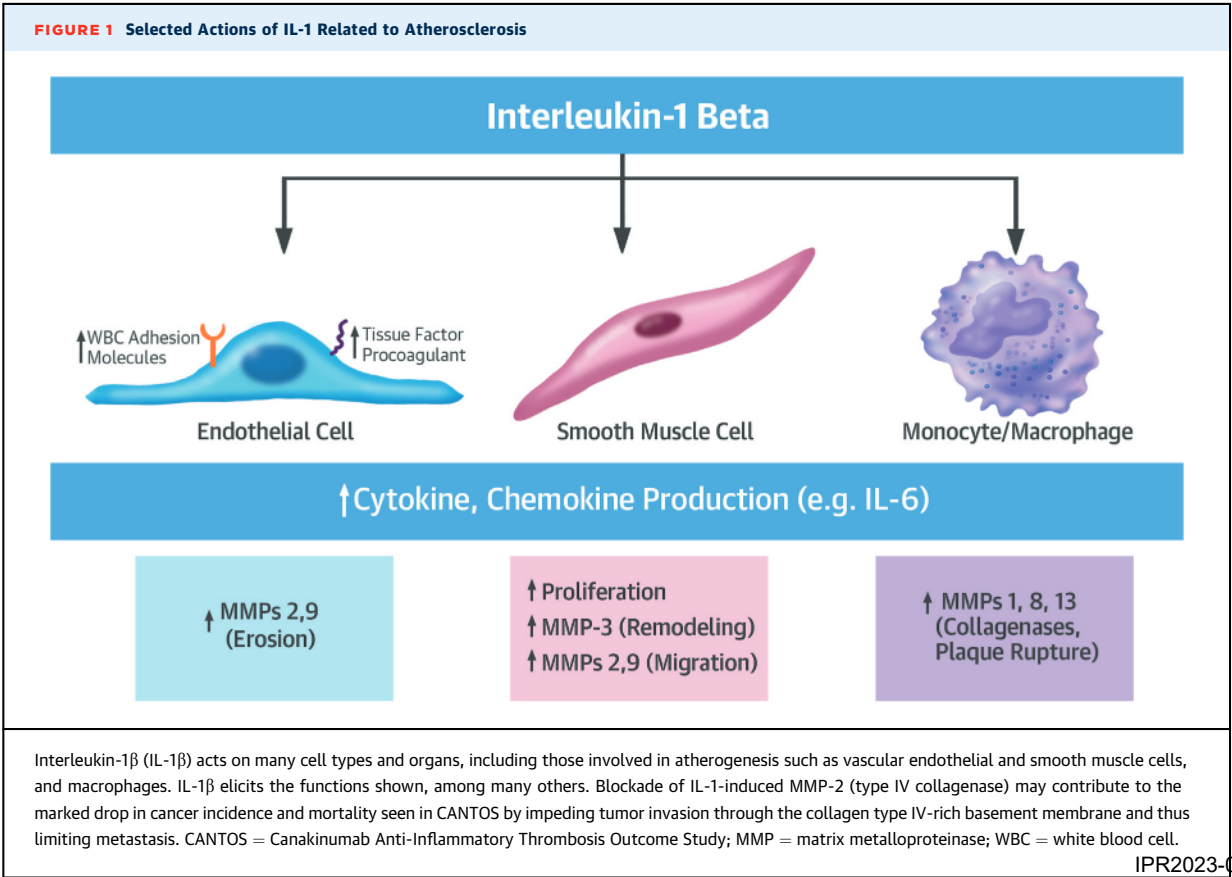
agents. Crystals can also costimulate the inflammasome. For example, urate crystals implicated in the pathogenesis of gout also act through the inflammasome to enhance production of mature IL-1 β (31). Cholesterol crystals also furnish a signal to the inflammasome (32,33). Human atheromata harbor activated inflammasomes (34). Other atherosclerosis-relevant stimuli that can augment inflammasome action include disturbed flow (such as prevails at sites of predilection to atheroma formation and

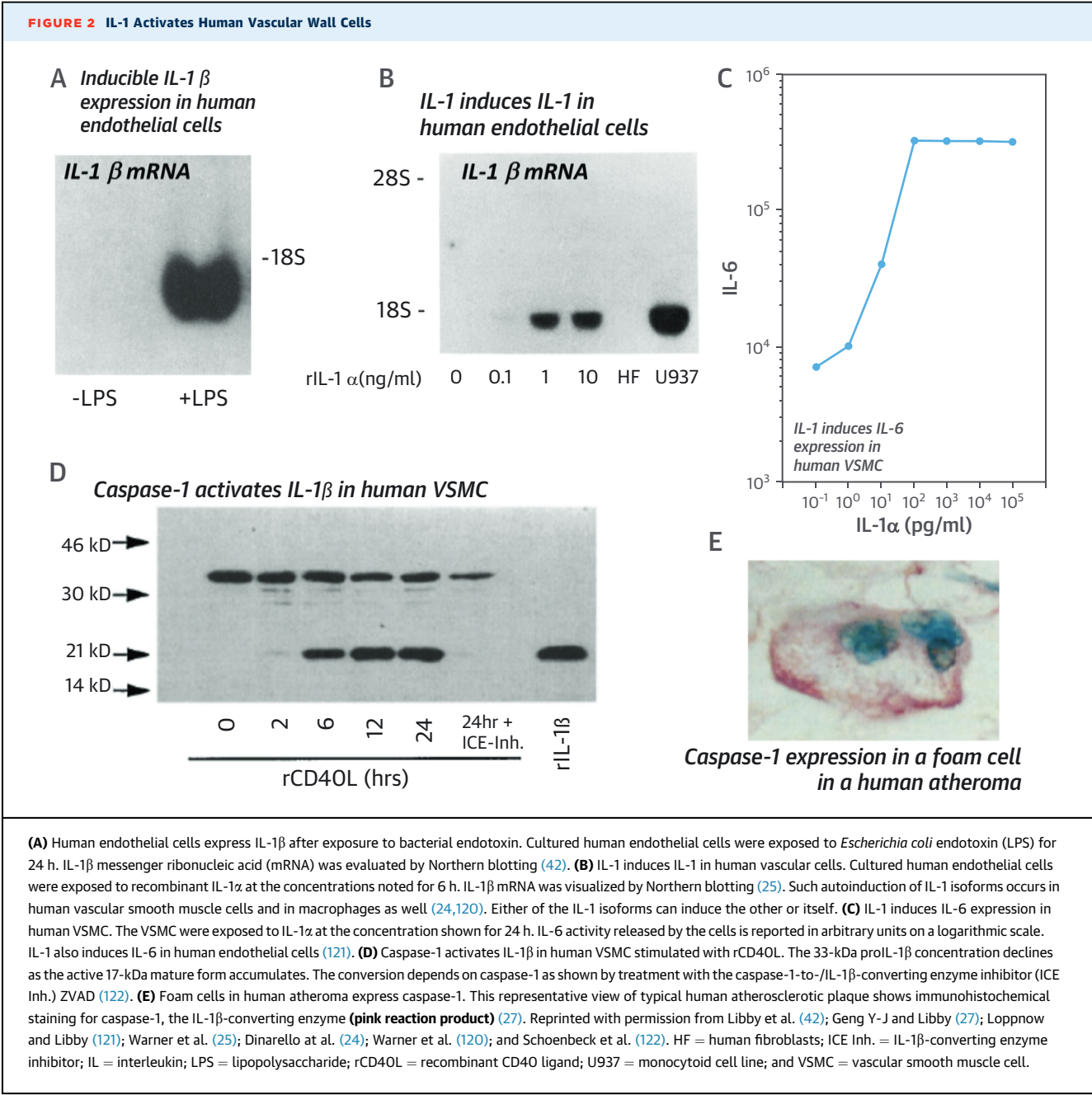
complication) (35,36), and moderate hypoxia and acidosis (common in the core of plaques) (Figure 3) (37,38).

IL-1 HAS MANIFOLD EFFECTS ON THE CARDIOVASCULAR SYSTEM

A wealth of data implicates IL-1 in a number of cardiovascular diseases (39,40). IL-1 induces inflammatory functions of human endothelial cells (Figure 1) (41). IL-1 stimulates adhesion molecules that recruit leukocytes including intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1. IL-1 also induces chemokines such as monocyte chemoattractant protein (MCP)-1 (C-C motif chemokine ligand [CCL]-2) a chemoattractant for mononuclear phagocytes strongly implicated in inflammatory cardiovascular diseases. Cells in the atheroma produce IL-1 when exposed to inflammatory stimuli (Figure 2) (42,43). These observations led to the explicit hypothesis in the mid-1980s that IL-1 participates in atherogenesis (42).

IL-1 has multiple effects on human vascular smooth muscle cells (SMCs), a cell type intimately involved in atherogenesis (Figure 1). IL-1 can induce autocrine





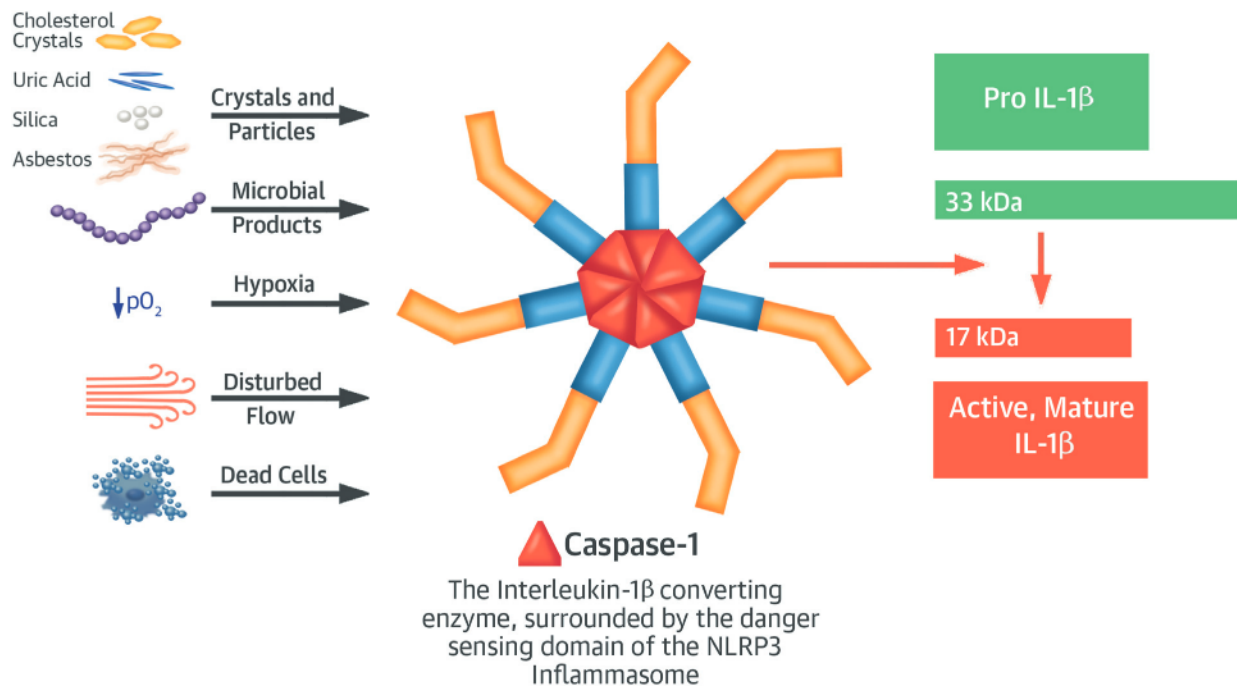
production of platelet-derived growth factor that can stimulate SMC proliferation (44). IL-1 induces its own gene expression in many cell types, including endothelial cells and SMCs, a powerful amplification loop denoted “autoinduction” (Figures 2B and 4) (24,25).

Treatment with IL-1 strongly induces SMCs and other cells to elaborate another cytokine, IL-6 (Figures 2C and 4) (45). IL-6 elicits the acute phase response: hepatocytes stimulated by IL-6 boost their synthesis of acute phase reactants, including fibrinogen and plasminogen activator inhibitor, molecules

intimately involved in promoting thrombosis (fibrinogen) or limiting fibrinolysis (plasminogen activator inhibitor [PAI-1]), as well as that of CRP, a marker of inflammatory status (Figure 4) (46,47).

IL-1 therefore mediates an amplification loop whereby a single molecule of IL-1 can beget many molecules of IL-6, which in turn drive the overexpression of atherothrombosis mediators, such as those listed above (Figure 2C). Human genetic studies support causality of IL-6 in coronary heart disease (48,49). Thus, IL-1 resides upstream in the pathway

FIGURE 3 Inflammasome Senses Danger Signals and Activates IL-1 β by Proteolytic Processing to the Mature Form by Caspase-1



Transcription of the IL-1 β gene produces proIL-1 β , a 33-kDa protein that lacks biological activity. This precursor undergoes cleavage by an enzyme known as ICE or caspase-1, to produce the active form of the cytokine with a molecular weight of 17 kDa. The activity of caspase-1 depends on the NLRP3 inflammasome that senses danger signals such as those shown. The inflammasome also activates pro-interleukin-18. Abbreviations as in [Figures 1 and 2](#).

that induces IL-6, a causal cytokine in atherothrombosis ([Figure 4](#)).

IL-1 alters functions of cardiac myocytes in addition to those of cells in the blood vessel wall. IL-1 impairs contractile function. This cytokine can aggravate ischemia-reperfusion injury and expansive cardiac remodeling after experimental MI ([50,51](#)). Experimental and small studies in humans suggest that antagonism of IL-1 can also benefit expansive remodeling after human MI and limit the release of CRP following acute coronary syndromes (ACS) ([52–54](#)).

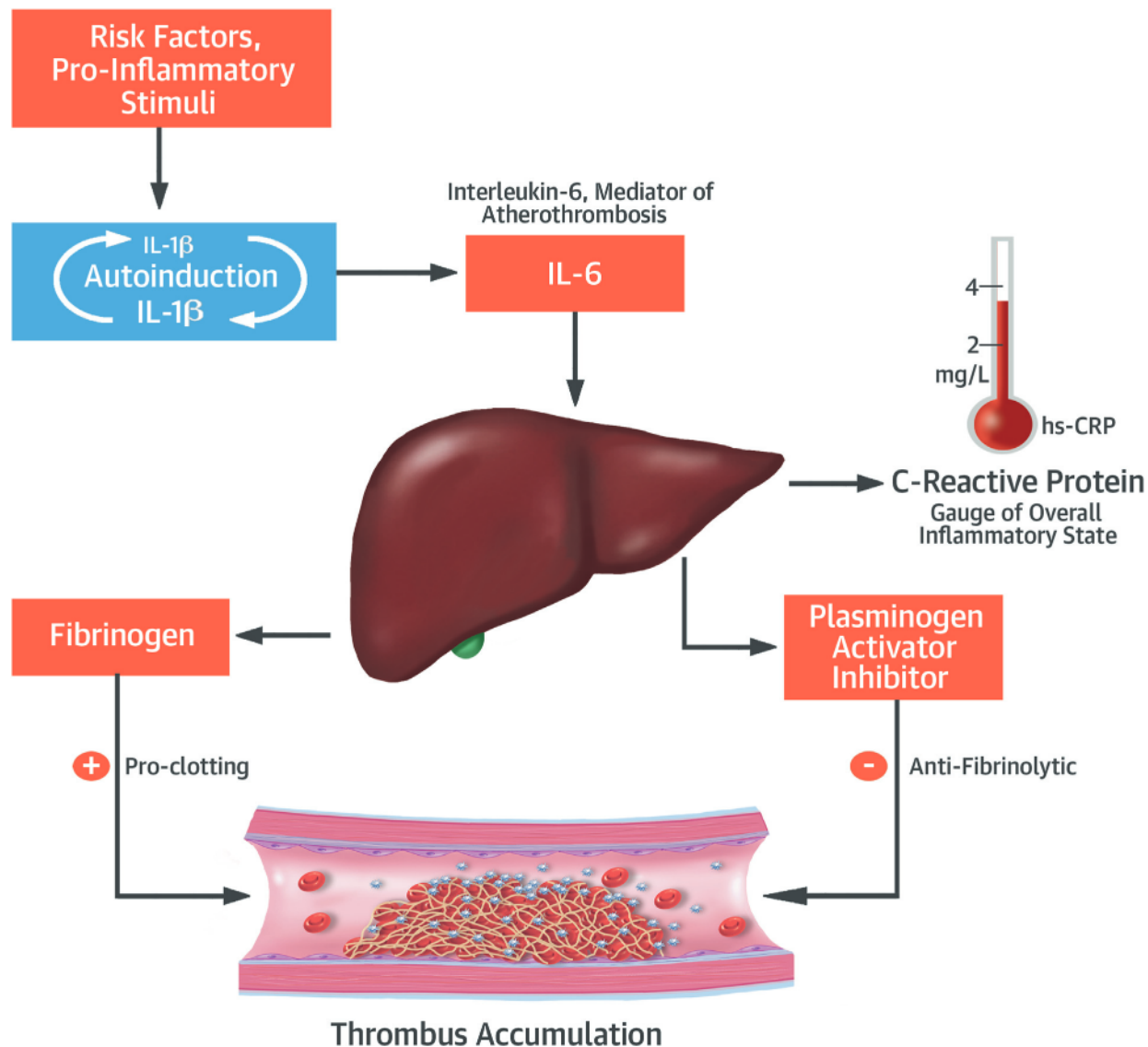
Numerous experiments involving genetically induced loss-of-function or gain-of-function of IL-1, manipulation of IL-1ra, and pharmacologic inhibition of IL-1 strongly implicate this cytokine in atherogenesis. Periadventitial application of IL-1 aggravates intimal thickening in pig arteries, implicating IL-1 in arterial hyperplasia, and IL-1 inhibition limits this response to injury ([55,56](#)). In hyperlipidemic mice, IL-1 generally promotes lesion formation, and interruption of IL-1 signaling limits atherogenesis ([57–60](#)). Deficiency of IL-1ra in mice augments arterial inflammation ([61](#)) and aneurysm formation ([62](#)), and hemizygous deficiency of IL-1ra

limits early atherosclerosis and reduces macrophage content in hyperlipidemic mice ([63](#)). IL-1 receptor 1-deficient hyperlipidemic mice have impaired expansive remodeling during lesion formation, attributable to reduced expression of the matrix metalloproteinase MMP-3 (stromelysin) ([Figure 1](#)) ([64](#)). Activated platelets can express IL-1 α and elaborate microparticles that bear functional IL-1 β , another link between this cytokine and atherothrombosis ([65,66](#)). The preponderance of data suggest a prominent contribution of IL-1 to the pathogenesis of multiple cardiovascular diseases ([67](#)).

THERAPEUTIC TARGETING OF IL-1 β

Given the wealth of findings that implicate inflammation in atherogenesis and the residual burden of recurrent cardiovascular events in survivors of acute coronary syndromes, even when they receive contemporary standard medical care that includes high-dose statins, potent anti-platelet combinations, and late generation stenting, the proposition that direct anti-inflammatory therapy could improve outcomes in such patients takes on considerable clinical

FIGURE 4 Amplification Cascades Boost IL-1 Actions Implicated in Atherothrombosis



Interleukin-1 can induce its own gene expression in many cell types, including those implicated in atherosclerosis. This property provides a positive feedback amplification loop for boosting IL-1 levels at sites of inflammation. IL-1 also strongly augments the production of IL-6 by various cell types. IL-6 mediates the acute phase response through which the liver produces proteins that participate in host defenses, but that also augments thrombosis and inhibits fibrinolysis as explained in the text. hs-CRP = high-sensitivity C-reactive protein; other abbreviations as in [Figure 1](#).

urgency, beyond its theoretical interest. Convincing links between IL-1 β and inflammatory diseases such as atherosclerosis highlighted this cytokine as a potential therapeutic target (68,69).

Several strategies can combat IL-1 action. Administration of the decoy receptor has not undergone substantive clinical development. The IL-1ra (anakinra) has conferred clinical benefit in some cases of rheumatoid arthritis, acute gouty arthritis, and

diabetes mellitus. Anakinra requires daily injections and blocks actions of both of the IL-1 isoforms, potentially impairing host defenses and hence susceptibility to infection to a greater extent than selective isoform inhibition. In contrast to the IL-1ra, canakinumab, a human monoclonal antibody, selectively neutralizes IL-1 β but not IL-1 α , whereas IL-1ra blocks both. An anti-IL-1 α antibody has also entered clinical evaluation (70). Canakinumab benefits

inflammatory diseases mediated by IL-1 β , including Muckle-Wells syndrome (71) and rarer forms of juvenile inflammatory arthritis (72) and common diseases such as acute gouty arthritis (73). Canakinumab has a prolonged biological half-life that permits subcutaneous doses administered every 3 months. Both anakinra and canakinumab seem to be well tolerated in most patients, although studies of IL-1ra have not evaluated infection risk with long-term exposure of large populations. Moreover, as atherosclerosis-related stimuli activate the inflammasome that generates mature IL-1 β but not IL-1 α , the β isoform emerged as the most disease-relevant target. In a phase II study of diabetic patients, canakinumab reduced plasma levels of fibrinogen, IL-6, and hsCRP in a dose-dependent manner (74).

CANTOS: AFFIRMATION OF THE ROLE OF INFLAMMATION IN ATHEROTHROMBOSIS

The strong biological basis for the hypothesis presented above provided the rationale for a large-scale clinical trial that tested the hypothesis that administration of canakinumab to neutralize IL-1 β activity could improve outcomes in individuals who have sustained a prior MI (75). The CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) enrolled over 10,000 individuals at least 1 month post-acute MI in almost 40 countries. The protocol mandated aggressive use of all standard secondary prevention therapies for MI, including treatment with high-dose statins and aspirin and other anti-platelet agents, beta-adrenergic blocking agents, and agents that interrupt renin-angiotensin signaling, according to prevailing guidelines. The patients enrolled had residual inflammation despite these guideline-mandated secondary prevention measures, as indicated by levels of hsCRP above 2.0 mg/l. Stable post-MI patients eligible for CANTOS randomly received placebo or 1 of 3 doses of canakinumab, administered subcutaneously 4 times per year. The primary endpoint included nonfatal MI, nonfatal stroke, or cardiovascular death. The trial ended when approximately 1,400 events accrued in early 2017.

Canakinumab, 150 mg subcutaneously every 3 months, met CANTOS' primary endpoint with a 15% reduction of non-fatal MI, nonfatal stroke, or cardiovascular death (76). The 150- and 300-mg doses had similar effects on this endpoint, yielding a p value of 0.007 when combined. A pre-specified expanded endpoint that included unstable angina requiring urgent revascularization showed a significant 17% reduction for the combined 150- and 300-mg groups. The 50-mg dose did not significantly lower events.

The anti-IL-1 β treatment did not alter LDL, but the 2 higher doses lowered hsCRP by approximately 60%.

These results affirm the clinical importance and therapeutic relevance of the biological aspects of IL-1 β reviewed herein. Moreover, as the first large-scale blinded and placebo-controlled, randomized clinical trial that targeted inflammation but not lipids, CANTOS affirmed the inflammatory hypothesis of atherosclerosis and set the stage for a new era of cardiovascular therapeutics. Furthermore, the CANTOS results highlight the utility of assessing both LDL and hsCRP post ACS, as targeting either of these biomarkers can reduce recurrent events.

Indeed, we have entered an exciting era of "precision medicine," which permits the allocation of therapies rationally based on readily measured biomarkers. Patients following ACS with LDL levels that remain above those desired despite statin therapy should receive consideration for addition of a cholesterol-absorption inhibitor (as validated in IMPROVE-IT [The Improved Reduction of Outcomes: Vytorin Efficacy International Trial] [77]) or a PCSK9 inhibitor (as validated in FOURIER [Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk] [78]). These patients represent residual LDL risk. Those who have persistently elevated inflammation despite a standard of care regimen, as gauged by an hsCRP >2 mg/l, could receive canakinumab. These patients could be categorized as having residual inflammatory risk (79,80). Of note, FOURIER and CANTOS achieved similar magnitudes of event reduction in addition to statin therapy by targeting distinct aspects of residual risk.

BEYOND CANTOS: OTHER TARGETS, OTHER INDICATIONS

IL-1 β represents only 1 of several potential avenues for targeting inflammation in atherosclerosis directly (Table 2). As inflammatory signaling pathways have considerable redundancy, targeting any 1 mediator (such as IL-1 β) may not block all inflammatory pathways implicated in atherogenesis. Following the success of CANTOS, a suite of studies should evaluate the roles of other measures that manipulate inflammation and immunity in clinical scenarios, beyond stable patients with prior myocardial infarction.

In this some confusion has prevailed regarding interventions that target inflammation per se versus those that target oxidative stress (81). The enzyme lipoprotein-associated phospholipase A₂ (LP-PLA₂) indeed arises primarily from inflammatory cells (e.g., macrophages) but acts to generate pro-oxidant lipid

TABLE 2 Selected Targets for Limiting Cardiovascular Inflammation Beyond IL-1 β
Inflammasomes
IL-1 α
IL-6
IL-18
IL-33
TNF
CD40/CD40L (CD164)
TRAF-6
Lipid mediators of resolution
CD = clusters of differentiation; IL = interleukin; TNF = tumor necrosis factor.

species. Two large clinical trials targeted LP-PLA₂ with a small molecule inhibitor (darapladib) but failed to reduce cardiovascular events (82,83). Thus, those trials did not vitiate the inflammatory hypothesis as they focused primarily on reducing oxidative stimuli rather than inflammation itself. An inhibitor of p38 MAP kinase (losmapimod) likewise failed to reduce cardiovascular events in secondary prevention. Oxidative stress also activates p38 MAP kinase, and its inhibition does not interfere selectively with the IL-6 pathway causally implicated in cardiovascular events (Figure 4) (84,85).

Clinical trials currently in progress target inflammation in ways that are less well defined. Colchicine, long used to mitigate certain inflammatory conditions, reduced cardiovascular events in an unblinded, relatively small clinical trial (LoDoCo [Low-Dose Colchicine]) (86). Two larger studies currently underway are following up this exciting and intriguing preliminary observation: the COLCOT (Colchicine Cardiovascular Outcomes Trial) and LoDoCo2 studies (87). The use of low-dose methotrexate has revolutionized the treatment of rheumatoid arthritis. The ongoing CIRT (Cardiovascular Inflammation Reduction Trial) is evaluating whether this anti-inflammatory agent can improve cardiovascular outcomes in an at-risk population (88).

A wealth of experimental work over the last several decades has identified a number of other inflammatory targets with well-characterized mechanisms of action that merit consideration for future clinical investigation. Although IL-1 α has distinct cell biological and biochemical characteristics from the β isoform, it shares many proinflammatory actions including induction of IL-6. Antibody reagents that neutralize IL-1 α have entered clinical trials and hold considerable interest for cardiovascular indications (70,89). Tocilizumab, an antibody that selectively neutralizes IL-6, can treat several inflammatory diseases but adversely perturbs the lipid profile. Other

strategies for neutralizing IL-6 that lack such unwanted actions definitely merit evaluation for cardiovascular indications. A small trial in patients with acute coronary syndromes showed that tocilizumab reduced the excursion of CRP post-primary coronary artery intervention (90).

IL-18, a member of the IL-1 family, depends, like IL-1 β , on the inflammasome for activation. Several lines of evidence suggest that IL-18 participates in atherogenesis (91-93). This cytokine also deserves consideration for therapeutic targeting in atherothrombosis. As the inflammasome pathway activates the immature precursors of both IL-1 β and IL-18, inhibition of the inflammasome NLRP3 could offer an approach to simultaneous limitation of the action of this pair of proinflammatory cytokines (94-96). However, given the potential risks of interfering with host defenses, such dual effects may have more liability than inhibition of a single isoform of a single cytokine.

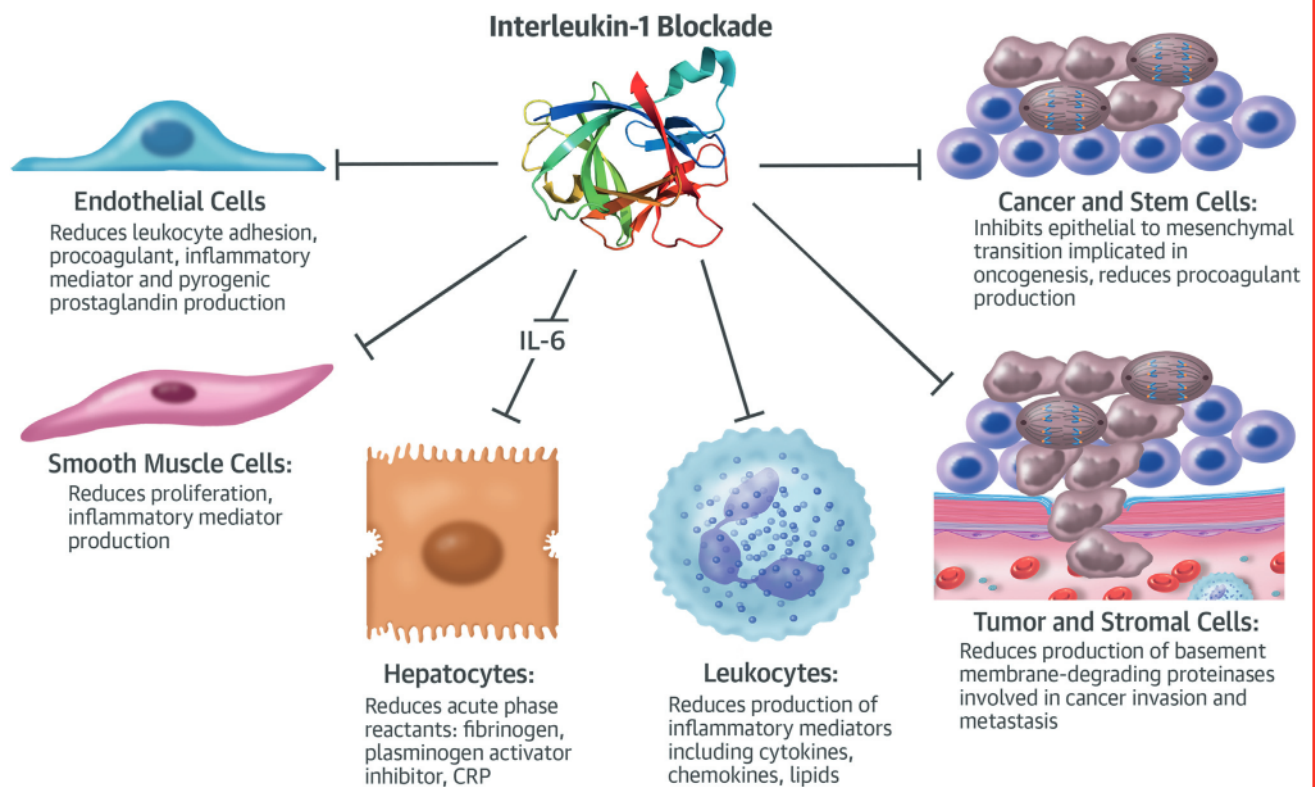
Considerable data implicate CD40 and its ligand CD154 in cardiovascular and metabolic diseases (97-101). Although monoclonal antibody strategies encountered thrombotic complications, a late-generation antisense oligonucleotide approach has promise as an approach to limiting the action of this signaling dyad (102). A small molecule inhibitor of CD40 interaction with its signal transducing partner TRAF also holds interest in this regard (103).

Many studies have implicated tumor necrosis factor (TNF) in inflammatory diseases including atherosclerosis (104,105). Like methotrexate, anti-TNF strategies have proven highly successful in certain rheumatologic and inflammatory diseases. However, anti-TNF strategies can adversely affect lipid profiles. Moreover, despite preclinical promise, trials that targeted TNF in patients with heart failure showed no benefit, rather a possible hazard (105). These considerations have limited interest in targeting TNF in cardiovascular patients.

Experimental evidence implicated the monocyte chemoattractant MCP-1 (CCL-2) and its receptor CCR-2 in atherogenesis (106-108). Currently, research regarding monocyte heterogeneity in cardiovascular diseases has flourished (109-112). In particular, a proinflammatory subset of monocytes recruited through the chemokine receptor CCR2 has proven functionally important in a number of cardiovascular conditions. As monoclonal antibodies that can neutralize CCR2 have entered clinical use, they also merit clinical evaluation to quell cardiovascular inflammation.

Any intervention that interferes with innate immunity, such as those delineated above, may increase susceptibility to infections and/or may impair tumor

CENTRAL ILLUSTRATION Some Effects of IL-1 Blockade on Cellular Functions



Libby, P. J Am Coll Cardiol. 2017;70(18):2278–89.

Interleukin (IL)-1 exerts many actions on cells that can contribute to pathogenesis diseases, including atherosclerosis, thrombosis, oncogenesis, and invasion and metastasis of tumors. Many of the effects IL-1 on hepatocytes, including the induction of the acute phase response, depend on the intermediary IL-6, a cytokine potentially induced by IL-1. Strong human genetic evidence implicates IL-6 as a causal factor for atherothrombosis. CRP = C-reactive protein.

surveillance. Therefore, the clinical applications of anti-inflammatory therapies require careful consideration of potential adverse effects. Indeed, CANTOS revealed a small but significant increase in fatal infections (an excess of approximately 1 per 1,000 patient-years) (76). Analysis of infection liability in the more than 6,700 patients exposed to canakinumab will inform regarding risk factors for infection and help to mitigate this risk. The decades of experience with anti-inflammatory interventions in rheumatologic and other diseases provide guidance in this regard, as we move toward clinical application in the cardiovascular arena of biological and other strategies to modulate the inflammatory response.

One might have expected an increase in cancer due to impaired tumor surveillance due to treatment with canakinumab, as anti-TNF strategies do entail a risk for lymphoma. However, CANTOS actually showed a substantial and canakinumab dose-dependent

reduction in fatal malignancy ($p = 0.0007$) (113). Canakinumab (300 mg every 3 months) produced a 67% fall in incidence of lung cancer and a 77% decrease in fatal lung cancer ($p = 0.0002$). The cancer benefit in this trial unlikely represents an effect on cancer initiation, although IL-1 may contribute to oncogenesis under some circumstances (114). Rather, IL-1 blockade may impede the invasion and metastasis of existing cancers. IL-1 can induce a key proteinase involved in cancer spread, matrix metalloproteinase (MMP)-2, implicated in breaching the basement membrane by cancers (Central Illustration) (115). IL-1 can also promote epithelial-to-mesenchymal transition implicated in tumorigenesis (116). Most cancer treatments entail cardiovascular risk. Canakinumab appears capable of reducing risk of cancer fatalities in the inflamed population studied while producing cardiovascular benefit rather than hazard.

Beyond the chronic phase of atherosclerosis in secondary prevention, inflammation participates pivotally in other clinical scenarios. Cytokines modulate the healing of acute ischemic myocardial injury experimentally (53). Therefore, some of the anticytokine strategies summarized above may foster beneficial healing after an ischemic insult in patients with ACS. For example, treatment with an anti-IL-1 β antibody limits mobilization of proinflammatory monocytes to the infarcted myocardium and improves left ventricular function following coronary artery ligation in mice (117). Data from more than 1,400 primary endpoint events in CANTOS, many of them ACS, will provide safety data to inform the use of canakinumab administration during ACS, a highly inflamed patient population excluded from CANTOS, which enrolled only individuals at least 30 days following an ACS. Interventions that target CCR2 also promote healthier healing of the ischemic myocardium (118).

CONCLUSIONS: ENTERING AN ERA OF TARGETING INFLAMMATION IN CARDIOVASCULAR DISEASES

We have entered an exciting era in which we can reap clinical benefits from decades of research of the participation of immune and inflammatory pathways in cardiovascular disease (8). Although extrapolation of preclinical study findings to humans requires considerable caution (119), the burden of unmet need and residual risk in our patients mandates careful consideration of novel approaches to targeting inflammatory pathways.

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KEY WORDS acute coronary syndromes, high-sensitivity C-reactive protein, interleukin-1, myocardial infarction

Attachment A-3

JACC REVIEW TOPIC OF THE WEEK

Inflammation, Immunity, and Infection in Atherothrombosis



JACC Review Topic of the Week

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ABSTRACT

Observations on human and experimental atherosclerosis, biomarker studies, and now a large-scale clinical trial support the operation of immune and inflammatory pathways in this disease. The factors that incite innate and adaptive immune responses implicated in atherogenesis and in lesion complication include traditional risk factors such as protein and lipid components of native and modified low-density lipoprotein, angiotensin II, smoking, visceral adipose tissue, and dys-metabolism. Infectious processes and products of the endogenous microbiome might also modulate atherosclerosis and its complications either directly, or indirectly by eliciting local and systemic responses that potentiate disease expression. Trials with antibiotics have not reduced recurrent cardiovascular events, nor have vaccination strategies yet achieved clinical translation. However, anti-inflammatory interventions such as anticytokine therapy and colchicine have begun to show efficacy in this regard. Thus, inflammatory and immune mechanisms can link traditional and emerging risk factors to atherosclerosis, and offer novel avenues for therapeutic intervention. (J Am Coll Cardiol 2018;72:2071-81)

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Considerable evidence supports the role of inflammation and immunity in atherosclerosis (1,2). The authors include panelists in a series of workshops convened in cooperation with

the National Heart, Lung, and Blood Institute to consider and weigh the evidence with regard to these topics. This discussion distills the proceedings of these multiple interactions.

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ABBREVIATIONS AND ACRONYMS

hsCRP = high-sensitivity
C-reactive protein

IL = interleukin

LDL = low-density lipoprotein

PAMP = pathogen-associated
molecular pattern

Th = helper T-cell subtype

TLR = toll-like receptor

Convergent streams of convincing data from animal experiments, observations on human atheromata, and clinical biomarker studies all support the importance of immune and inflammatory pathways in the pathogenesis of this disease. During much of the 20th century, research focused on cholesterol and subsequently lipoproteins as the key mechanism in establishing fatty lesions in arteries (3). The advent of a cell biological approach added to the biochemical discoveries related to cholesterol in the 1970s (4-6). Although low-density lipoprotein (LDL) certainly contributes causally to atherothrombosis, other lipoprotein fractions, non-lipid-related genetic variants, and lifestyle also influence this disease (7,8). Indeed, almost one-half of a population can harbor subclinical atherosclerosis without a high burden of traditional risk factors (9). Thus, elevated LDL levels alone cannot account for the entire burden of atherosclerosis.

The concept of atherosclerosis as a proliferative disorder of arterial smooth muscle cells gained prominence as a pathogenic pathway independent of cholesterol (10). Schemata of the pathogenesis of atherosclerosis posited a denuding injury to the endothelium followed by the deposition of platelets and release of the protein platelet-derived growth factor that would stimulate the migration and proliferation of smooth muscle cells (5,6). Extracellular matrix elaborated by these cells would entrap plasma-derived lipids, giving rise to the atheroma. Some viewed atherosclerosis as akin to leiomyomata, a benign tumor of smooth muscle cells arising by a monoclonal or monotypic pathway (11-13). Indeed, initial iterations of the “response to injury” hypothesis depicted atherosclerosis as a bland process, devoid of inflammation (5,6,14).

The advent of monoclonal antibody technology in the 1980s permitted more rigorous identification of the cell types that accumulate in human atherosclerotic plaque (15,16). These studies identified the foam cells in the atherosclerotic plaque as arising primarily from mononuclear phagocytes (Figure 1). Ironically, recent data suggest that smooth muscle cells may indeed give rise to foam cells through metaplasia, with cellular and molecular characteristics in common with mononuclear phagocytes (17). This concept unites the proliferative concept of atherogenesis with inflammatory pathways.

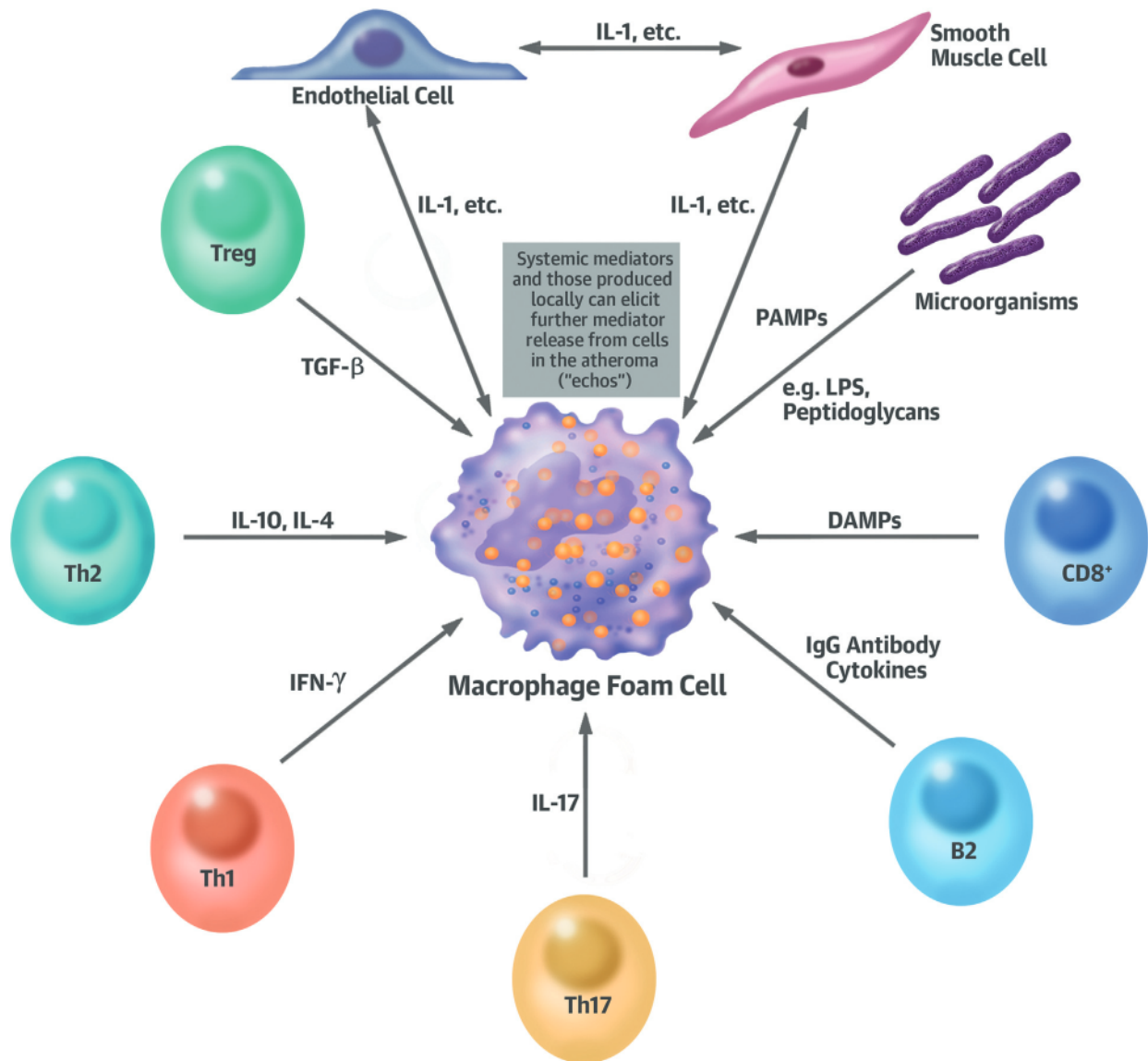
Soon after the unambiguous demonstration of macrophage markers on many foam cells in atheromata, Hansson’s group and others described the presence of a smaller population of T lymphocytes

within the plaque (16,18). Although the plaque T-cell population is scant in number, the expression of class II histocompatibility antigens on neighboring smooth muscle cells provided evidence for the functional activity of these lymphocytes in the arterial plaque (19,20). The induction of these molecules, critical in the afferent limb of the cellular immune response, depends in large measure on interferon gamma, a signature cytokine of helper T cells of the Th1 subtype (21). Far from being mere “fellow travelers,” the T cells in plaque thus appear to function immunologically. Such morphological observations in human plaque opened the door to a plethora of experimental studies which showed that adaptive immune responses modulate atherogenesis (22-25). These and other studies established that cells of the immune system, both the innate (macrophages) and adaptive (T cell and other lymphocytes) limbs, contribute to atherosclerosis (Figure 1).

Simultaneously with the identification of cells of the innate and adaptive immune systems in the atherosclerotic plaque, research progressed on the signals exchanged among the leukocyte invaders into the artery wall and the intrinsic vascular wall cells: smooth muscle and endothelium. Such interactions connect the immune cells to altered arterial biology. Cytokines (protein mediators of inflammation) mediate the exchange of signals between leukocytes and intrinsic arterial wall cells (26,27). The interleukins (ILs), so-called because they were originally believed to mediate cross-talk between leukocytes, can also arise from vascular smooth muscle and endothelial cells (28,29). The leukocytes and vascular cells in the plaque constitute the protagonists in inflammation during atherogenesis, and the cytokines provide the dialogue by which these actors communicate. A subset of cytokines, the chemokines, mediates migration of cells in the plaque (30,31). Chemokines participate in recruitment of the leukocytes and their directed migration from the luminal surface into the plaque; they can also stimulate smooth muscle cell migration.

We now recognize that the inflammatory and immune response can operate positively, to promote disease, or negatively, to modulate deleterious action and promote resolution or repair of lesions (Figure 1) (32). In addition to pro-inflammatory subsets of mononuclear phagocytes, reparative or less inflammatory populations also participate in the modulation of atherogenesis (33). Single-cell analyses indicate a much greater complexity of leukocyte subtypes than previously recognized (34-36). T cells not only incite inflammatory responses but can inhibit them (e.g., regulatory T cells, Th2 lymphocytes). B2 lymphocytes

FIGURE 1 Infection and Immunity in Atherogenesis



This figure depicts a trio of key cell types of the atheroma: endothelium, smooth muscle, and macrophage foam cells representative of the leukocytes found in plaques. These cells found within the atherosclerotic plaque can produce cytokines, notably interleukin (IL)-1, which can contribute to a positive feedback loop because IL-1 can induce its own gene expression in the source cell, an autocrine pathway, or activate neighboring cells through juxtacrine or paracrine pathways. Systemic mediators or these locally produced cytokines can elicit further mediator release from cells in the atheroma producing local echoes of systemic inflammation. The surrounding cells represent the lymphocytes that interact with cells within the atheroma and some main mediators by which they can modulate the local inflammatory and immune response within the plaque. Regulatory T cells (Treg) elaborate transforming growth factor beta (TGF- β), a mediator that exerts anti-inflammatory and pro-fibrotic actions on many cell types. The T-cell helper (Th) 2 lymphocytes can mute inflammatory responses and promote resolution or healing responses through the elaboration of IL-10 and IL-4. The Th1 lymphocytes can release interferon gamma (IFN- γ) that can potentially produce pro-atherogenic functions of the 3 major cell types depicted in the arterial plaque. The induction of class II major histocompatibility molecules on the surface of antigen-presenting cells in the plaque such as the macrophage can, in turn, enhance their ability to stimulate the afferent limb of the adaptive immune response. Th17 cells elaborate IL-17, which has mixed effects on atheromata, perhaps promoting inflammation but also augmenting fibrosis. B lymphocytes can also modulate atherosclerosis. B1 cells (not depicted here) can secrete natural immunoglobulin M antibodies that appear atheroprotective. Many such natural antibodies recognize epitopes associated with modified lipoproteins. B2 cells can elaborate cytokines and immunoglobulin G (IgG) antibodies that can stimulate atherogenesis, based on observations in mice. CD8 lymphocytes can kill virally infected cells, including those in the atheroma releasing damage-associated molecular patterns (DAMPs) that can augment inflammatory activation of many cell types through engagement of the toll-like receptors. Microorganisms themselves, as depicted by the bacillus in the diagram, can provide pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) or peptidoglycans that activate cells in the atherosclerotic plaque through engagement of the toll-like receptors. This complex network involves interactions between innate immune pathways and both humoral and cellular adaptive immunity.

tend to aggravate atherogenesis, whereas products of B1 lymphocytes exert antiatherogenic effects (37). A recognized subclass of B lymphocytes known as innate response activator B cells can aggravate atherogenesis in mice by augmenting Th1 responses, illustrating the links between cells that participate in humoral and T-cell-mediated immunity (38). Anti-inflammatory cytokines (e.g., IL-10, IL-4) tend to mitigate the pro-inflammatory actions of cytokines such as IL-1 and interferon gamma. Beyond anti-inflammatory adaptive and innate responses, we now recognize that lipid mediators of resolution can also regulate atherogenesis (39,40).

Accumulating evidence supports roles for myeloid cells in atherothrombosis (41). Mutations can occur in bone marrow stem cells with age that give rise to clones of leukocytes in peripheral blood. As expected, those who have these clones of mutant white blood cells have increased susceptibility to development of hematologic malignancies. Unexpectedly, people who have such leukocyte clones have a markedly increased incidence of cardiovascular events. This entity, known as clonal hematopoiesis of indeterminate potential (as few who have these clones will actually develop leukemia), constitutes a potent newly recognized risk factor for cardiovascular disease. These recent findings highlight another link between innate immune cells and atherothrombosis (42-44).

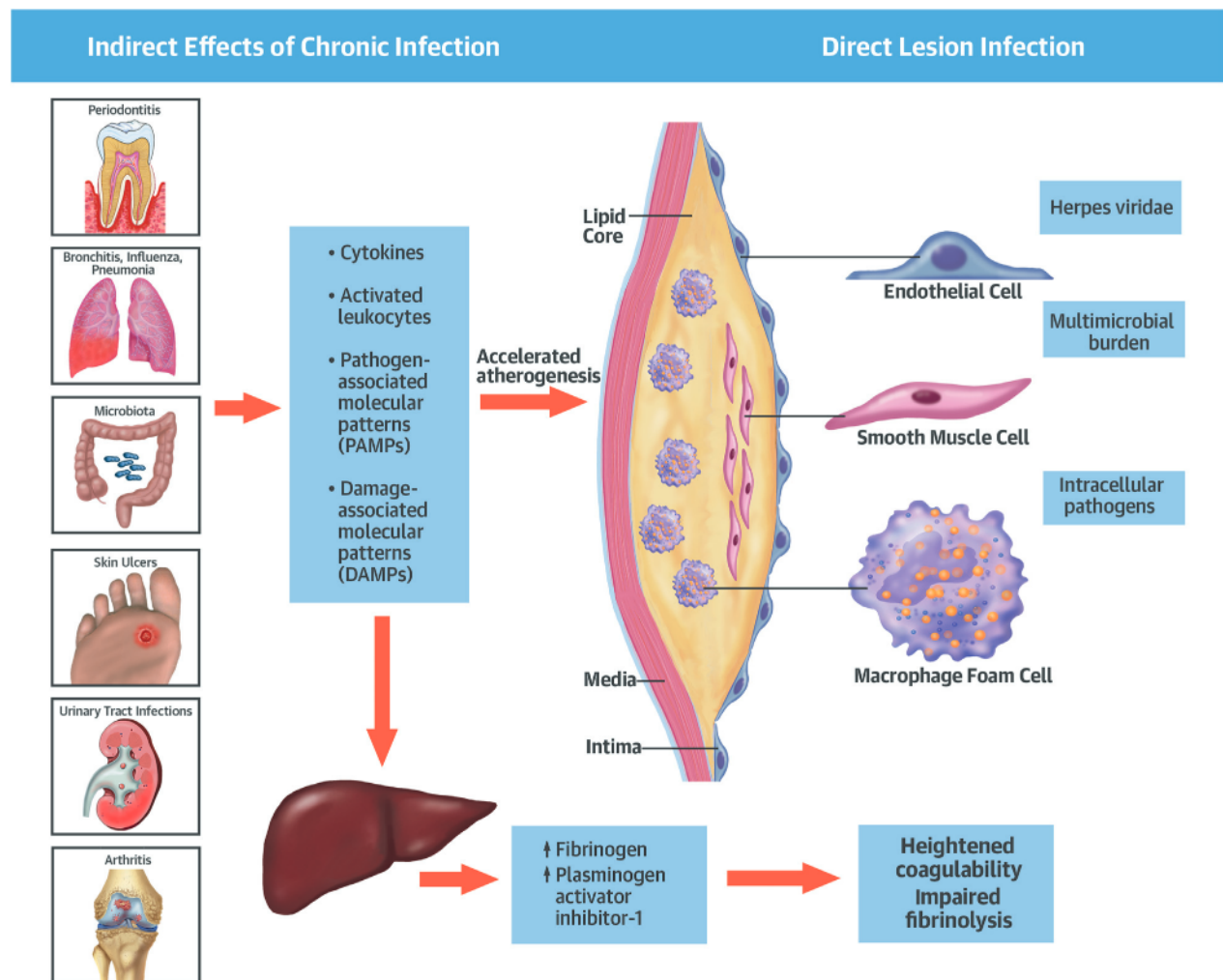
In sum, overwhelming evidence supports a complex, multilateral, and tightly regulated series of immune and inflammatory responses that initiate atherogenesis and engage in a “tug of war” during the phase of progression of atherosclerosis with competing positive and negative influences contributing to the prolonged incubation period of this disease. Ultimately, these pathways can regulate aspects of the plaque that lead to their disruption, providing a nidus for thrombosis (45,46). Inflammatory and immune mediators also influence coagulation and fibrinolysis, providing another dimension to their ability to modulate the complications of atherosclerosis (47). Rather than replacing or challenging traditional risk factors, the pathways of inflammation and immunity provide mechanistic explanations that connect these risk factors to altered behavior of vascular wall cells that give rise to the disease and its complications. Thus, the notion that inflammation, immunity, and infection can contribute to atherogenesis or trigger atherosclerotic events in no way challenges the concept that cholesterol contributes critically to disease development; rather, it adds another dimension to an extraordinarily complex pathobiological process.

WHAT TRIGGERS INFLAMMATION AND IMMUNITY IN ATHEROTHROMBOSIS?

Elucidation of immune and inflammatory pathways that function during atherogenesis does not illuminate the triggers that unleash their function. LDL can activate T cells, providing one link between a well-established traditional risk factor and adaptive immunity (48). Although a very large amount of literature supports the oxidation of LDL and its pro-inflammatory actions, antioxidant therapies have consistently failed to alter outcomes in humans with atherosclerosis. Thus, to date, the concept of LDL oxidation has not proven actionable in the clinic. Angiotensin II can act as a pro-inflammatory stimulus (49). Adaptive immunity also participates in experimental hypertension, linking high blood pressure with immune and inflammatory pathways (50). Visceral adipose tissue provides another potential stimulus to plaque inflammation through the elaboration of pro-inflammatory cytokines (51-53). These observations link obesity and insulin resistance to inflammatory pathways in arterial disease (54). Such examples illustrate how traditional risk factors can interface with the immune and inflammatory systems in ways that modulate atherogenesis.

The immune and inflammatory responses likely evolved primarily to protect the organism from infectious agents. Seeking triggers of these host defense mechanisms, investigators have expended considerable effort through the decades investigating the possible role of infectious agents in atherosclerosis and its complications (55-58). These studies identified markers of nucleic acid and antigens of viral and bacterial pathogens within atherosclerotic plaques. Moreover, bacterial products can stimulate vascular inflammation (59,60). In the extreme example, Gram-negative bacterial endotoxins strongly elicit inflammatory responses from endothelial cells, which explains much of the pathogenesis of septic shock (Figure 2) (28). Lower levels of endotoxemia indeed associate with cardiovascular risk (61-63). Seroepidemiological studies provided evidence that linked infections (notably with *Chlamydia pneumoniae*) with susceptibility to cardiovascular disease and atherosclerotic complications (57,64,65). However, prospective and better-controlled studies did not support many of the initial observational, seroepidemiological studies that linked infection to atherosclerosis (66,67). A wave of clinical trials, including rigorous and sufficiently powered investigations, examined whether antibiotic treatment could prevent cardiovascular

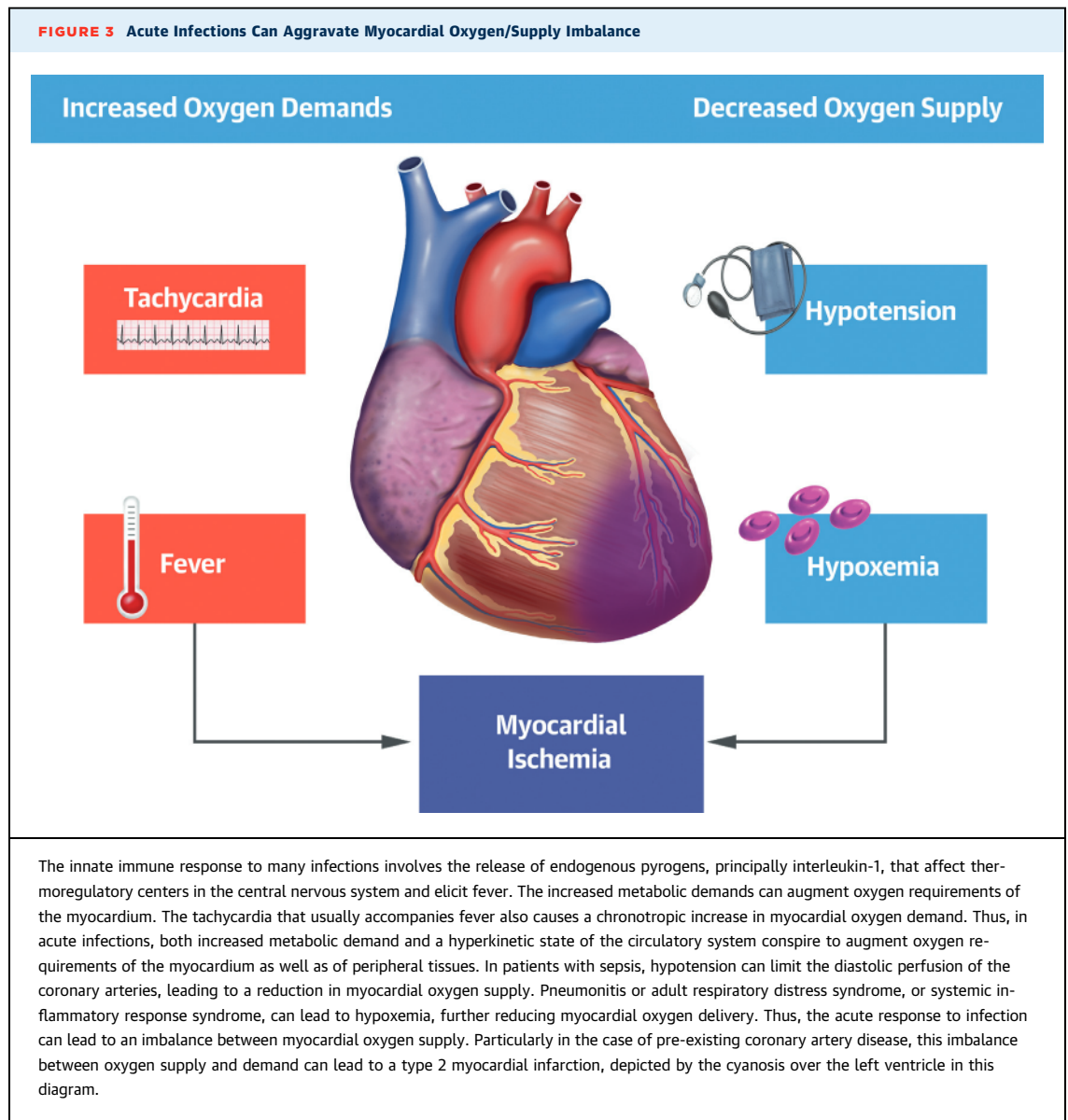
FIGURE 2 Chronic Infections Can Accelerate Atherogenesis and Set the Stage for Thrombotic Complications Directly and Indirectly



The **left side** of this diagram lists a number of examples of chronic infections or collections of microorganisms that can produce indirect effects on the cardiovascular system. For example, chronic infections can release cytokines, activate leukocytes, and elaborate pathogen-associated molecular patterns such as lipopolysaccharides or peptidoglycan components of bacterial cell walls. Tissue injury can produce and provoke the release of damage-associated molecular patterns. Cytokines, through their cognate receptors, and pathogen-associated and damage-associated molecular patterns, often through toll-like receptors, can contribute to the activation of cells involved in atherogenesis, including the intrinsic inhabitants of the normal artery wall, the endothelial and smooth muscle cells, or the leukocytes that accumulate in atherosclerotic lesions such as the macrophage foam cell. Activated white blood cells can also elaborate inflammatory mediators, including cytokines, lipid mediators, and reactive oxygen species that may enhance atherogenic functions of cells within the atheroma. Cytokines through the intermediary of interleukin-6 can elicit the acute-phase response from hepatocytes. Among the acute-phase reactants elaborated by hepatocytes during this response, fibrinogen can increase coagulability, and plasminogen activator inhibitor-1 can impair fibrinolysis. These changes in the fluid phase of blood can hasten the formation of thrombi and impair their resolution by inhibiting fibrinolysis. The **right side** of the diagram indicates various viral and microbial pathogens that studies have implicated in atherogenesis. The infection of endothelial and smooth muscle cell and of lesion-associated leukocytes can directly promote inflammation within the plaque.

events in patients with established atherosclerosis. The most rigorous and best-powered of these studies found no reduction in cardiovascular events with treatment with macrolides, such as azithromycin, or fluoroquinolones, such as gatifloxacin, in the

patients tested (68,69). Because macrolide use may associate with increased sudden death or ventricular tachyarrhythmias, their unwarranted use for cardiovascular prevention could cause hazards (70).

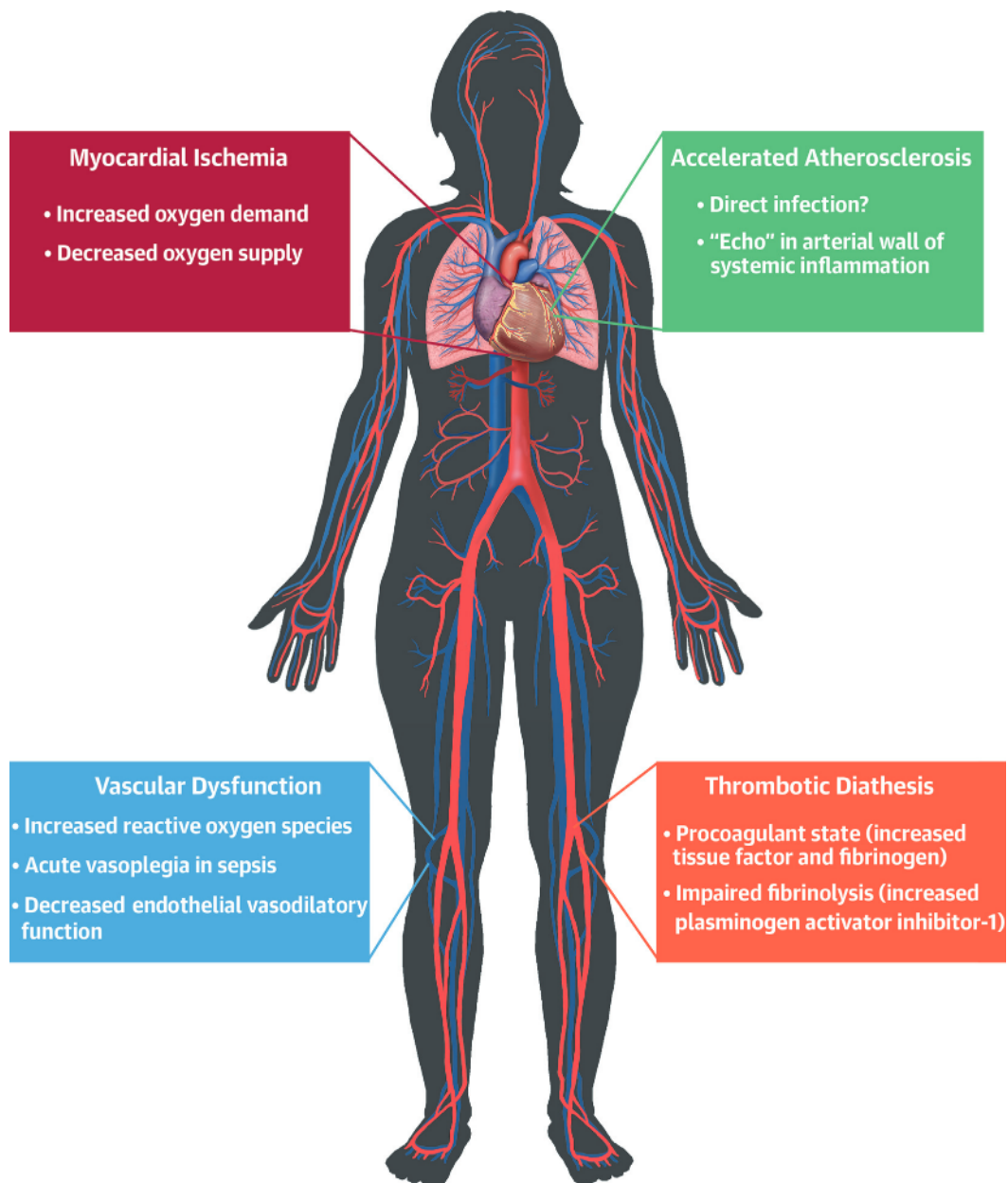


INFECTION AND ATHEROTHROMBOSIS: INDIRECT VERSUS DIRECT EFFECTS

Although direct microbial invasion does not seem to provide an actionable trigger for atherosclerosis, infection can still play a role in precipitating atherosclerotic events. Chronic infections in extravascular locations could provide a smoldering stimulus that contributes to inflammatory burden (71). Examples include periodontitis, bronchitis, urinary tract infection, infected cutaneous ulcers in patients with peripheral arterial disease, and diabetes mellitus. Infection at these sites could all provide niduses of inflammation remote from arteries that could evoke a systemic response that could accelerate

atherogenesis, reflected, for example, in modest elevations of C-reactive protein (Figure 2) (72-74). *C. pneumoniae* and certain microbial agents associated with periodontal disease in particular can elicit innate immune responses, aggravate experimental atherosclerosis, and associate with cardiovascular events (75-79). Azithromycin in particular concentrates in mononuclear phagocytes, the likely host to intracellular organisms such as *Chlamydia* species in the atheroma. However, antibiotic treatment may not effectively treat bacterial periodontitis because of an inability to penetrate the biofilms elaborated by oral microorganisms. *Helicobacter pylori*, a bacterium associated with gastric and duodenal ulcer disease, does not affect atherosclerosis in

CENTRAL ILLUSTRATION Acute and Chronic and Direct and Indirect Effects of Infection Can Augment Cardiovascular Risk



Libby, P. et al. J Am Coll Cardiol. 2018;72(17):2071-81.

The **left side** of this diagram depicts the effects of infections, generally acute, on aggravating myocardial ischemia (as detailed in [Figure 3](#)) and on producing vascular dysfunction in systemic and coronary arteries that can favor the development of cardiovascular events. The **right side** of the figure portrays how direct infection or echoes in the arterial wall of systemic or remote inflammation (as depicted in detail in [Figures 1 and 2](#)) can accelerate atherosclerosis. Both acute and chronic infections can heighten thrombotic risk by inducing a procoagulant state; for example, increasing tissue factor procoagulant production and fibrinogen elaboration by the hepatocyte (as shown in [Figure 2](#)) and impairing fibrinolysis by augmenting the expression of plasminogen activator inhibitor-1 as part of the acute-phase response. Thus, both acute and chronic infections can influence cardiovascular risk and infections remote from the artery, or potentially within the artery, and can thereby lead to augmented risk of cardiovascular events.

hypercholesterolemic mice, indicating some selectivity in microbial potentiation of traditional risk factors (80).

In some instances, bacterial products seeded into the systemic circulation from remote sites of infection could trigger a wave of acute inflammation by inflammatory cells as well as by products of native vascular cells that populate arterial lesions (81). We have dubbed this phenomenon the “echo” effect (Figures 1 and 2) (41). The increase in cardiovascular events and in thromboses in patients with pneumonia illustrates how remote infections can affect such outcomes (82). Experimentally, the local arterial inflammatory response to a systemic inflammatory stimulus derived from infectious organisms such as bacterial endotoxins can provide a greater local response in atherosclerotic arteries than in normal arteries (81). An example of such a stimulus is urosepsis, with leakage of endotoxin into the circulation from a bacterial source in the genitourinary tract.

We have recently gained an immense appreciation of the importance of the intestinal microflora in cardiometabolic disease (83,84). The astounding accumulation of bacteria and their products in the gastrointestinal tract provides a rich source of bacterial products such as endotoxins and heat-shock proteins, among others. In cases of impaired epithelial barrier function, bacterial products can leak into the circulation and provide another source of inflammatory stimuli that impinge on leukocytes lying in wait in atheromata or endothelial cells at sites of lesion formation. Such microbial products, pathogen-associated molecular patterns (PAMPs), activate innate immune receptors such as the toll-like receptors (TLRs) and provide stimuli for the activation of leukocytes and arterial cells within atheromata (Figure 2). Other microbial products such as trimethylamine oxide may also potentiate atherogenesis, as suggested by some, but not all, experimental and human observations (84,85).

Some stimuli derived from microorganisms can be strong (e.g., endotoxin engaging TLR4). Other stimuli can provide more subtle activation through the engagement of other innate immune receptors such as TLR2. Peptidoglycans can also serve as PAMPs (86,87). Other examples of bacterial PAMPs include lipoteichoic acid, which engages TLR2; viral and bacterial DNA, which can engage TLR9; peptidoglycans, which can engage TLR2; and mannans and beta-glucans associated with fungi, which can activate TLR2 and TLR4. PAMPs can also activate the nucleotide-binding and oligomerization domain-like receptors involved in the inflammasome that convert pro-IL-1-beta and pro-IL-18 into the active cytokines (88–91). Thus, although

the direct infection of the arterial lesion may not commonly drive atherogenesis, products of bacteria and other microorganisms in remote sites may elicit “echoes” from cells within lesions on both an acute or a chronic smoldering basis in a manner that can promote the evolution of lesions and their complication.

The responses to infection may also precipitate acute complications of atherosclerosis or amplify their consequences. For example, during sepsis, tachycardia and fever can lead to a hyperkinetic state that increases oxygen demands and predisposes to type 2 acute coronary syndromes (Figure 3) (56). Decreased oxygen supply due to hypertension and hypoxemia during sepsis can aggravate ischemic injury to the myocardium. In addition, the acute-phase reactants fibrinogen and plasminogen-activator inhibitor can promote thrombosis and impede endogenous fibrinolysis (Figure 2). Thus, although PAMPs can promote atherosclerotic lesion evolution generally in a chronic manner, the acute consequences of bacterial infections can augment myocardial oxygen requirements, decrease oxygen availability, promote clot formation, and impair the ability of the endogenous fibrinolytic system to clear thrombi when they form. Indeed, considerable recent observational and pathophysiological evidence supports the association between recent respiratory infections (92–96) or influenza (97) and atherosclerotic events. Indeed, large clinical trials are currently investigating the proposition that influenza vaccination can forestall cardiovascular events (98,99). Limiting influenza infections in vulnerable populations could remove a stimulus that elicits the inflammatory “echo” of systemic inflammation in atheromata (Figures 1 and 2) as well as the increased “demand” that can precipitate events (Figure 3).

CONCLUSIONS

Incontrovertible evidence now supports the importance of innate and adaptive immune pathways in atherogenesis. Moreover, infections may influence this disease process acutely, chronically, and directly or indirectly (Central Illustration). Although modulation of adaptive immunity has not yet reached clinical maturity as a therapeutic target, a number of strategies for vaccination are being investigated (100). The refinement of vaccination therapies for atherosclerosis in experimental studies continues to sustain interest in the clinical application of this approach (101). Targeting of innate immunity is reaching clinical maturity, with large-scale trials evaluating low-dose colchicine and anticytokine strategies in patients at risk for atherosclerotic events (102,103).

CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) showed that reducing inflammation by administering an anti-IL-1 beta antibody in men and women who had had a previous heart attack and residual inflammation despite standard-of-care therapy can reduce recurrent events (107,108). The anti-inflammatory therapy yielded a significant 15% reduction in the primary endpoint of “hard” major adverse cardiovascular events.

Biomarkers of the innate immune response, notably C-reactive protein (measured with a highly sensitive assay [hsCRP]), have entered clinical practice and have proven utility in targeting therapies to patients in ways that can effectively reduce their risk (109,110). In the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) primary prevention study, statin therapy was allocated on the basis of an hsCRP value above the median for the population (>2 mg/l) but with an LDL level <130 mg/dl. The statin-treated group had a 44% reduction in first-ever cardiovascular events. In secondary prevention, CANTOS allocated the anti-IL-1 antibody to patients with stable post-acute coronary syndromes who had an hsCRP value >2 mg/l despite effective statin therapy. Those CANTOS participants who achieved a reduction of hsCRP to <2 mg/l in response to the anti-inflammatory therapy had a >30% reduction in cardiovascular and all-cause mortality (111). These examples illustrate the potential of guiding therapy

according to inflammatory status assessed by biomarkers in trials and in clinical practice. Contemporary human genetic studies provide strong support for innate immune pathways in atherogenesis. For example, Mendelian randomization studies implicate the IL-6 pathway as a causal participant in the generation of atherosclerotic events (112,113).

Although direct infection may not be a common driver of atherogenesis, remote infections and bacterial products from extra-arterial infections or colonization may promote atherosclerosis on a chronic ongoing or episodic basis (Figure 2). Acute catastrophic bacterial infections such as Gram-negative sepsis can precipitate type 2 acute coronary syndromes (Figure 3). The decades of research into inflammatory and immune pathways implicated in atherosclerosis and its complications have begun to yield biomarkers that inform clinical practice. Further exploration of these pathways may identify new therapeutic targets to address the unacceptable burden of residual risk that persists beyond the management of traditional risk factors.

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