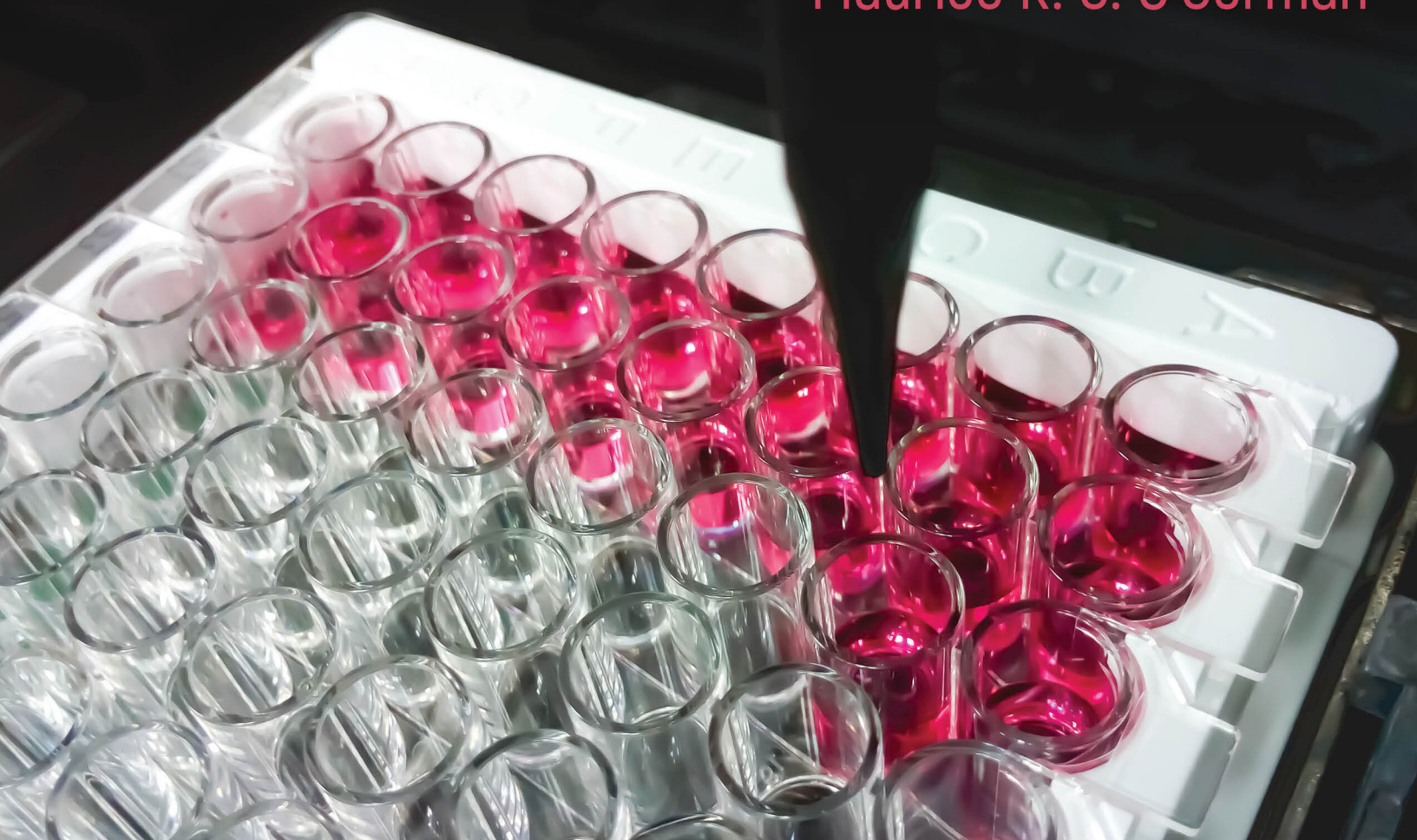
Ninth Edition

Manual of Molecular and Clinical Laboratory Immunology

Volumes 1–2

John L. Schmitz • Barbara Detrick
Maurice R. G. O'Gorman



Volume 1

Manual of Molecular and Clinical Laboratory Immunology

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9TH EDITION

EDITED BY

John L. Schmitz
University of North Carolina, School of Medicine
Chapel Hill, North Carolina

Barbara Detrick
Johns Hopkins University, School of Medicine
Baltimore, Maryland

Maurice R. G. O'Gorman
University of Southern California, Keck School of Medicine
Los Angeles, California

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Contributors

ROSHINI S. ABRAHAM
Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, Columbus, OH

MARIA E. AGUERO-ROSENFELD
Clinical Laboratories, Department of Pathology, New York University Langone Health, New York University Grossman School of Medicine, New York, NY

RENAN DE ALMEIDA AGUSTINELLI
Rheumatology Division, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil; Faculdade de Ciências Médicas de Santos, Santos, Brazil

IVONA AKSENTIJEVICH
Inflammatory Disease Section, National Human Genome Research Institute, NIH, Bethesda, MD

AHMAD AL-ATTAR
Department of Pathology, UMass Chan Medical School, Worcester, MA

THOMAS S. ALEXANDER
Incite Health Inc., Doylestown, PA; Northeast Ohio Medical University, Rootstown, OH

ASMA ALI
Department of Pediatrics, Mayo Clinic, Rochester, MN

CAROLINE R. ALQUIST
Hoxworth Blood Center, University of Cincinnati College of Medicine, Cincinnati, OH

BURT ANDERSON
Department of Molecular Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL

LUIS E. C. ANDRADE
Rheumatology Division, Escola Paulista de Medicina, Universidade Federal de São Paulo; Immunology Division, Fleury Medicine and Health Laboratories, São Paulo, Brazil

SARAH L. ANZICK
Research Technologies Branches, NIAID, NIH, Hamilton, MT

ROSA BACCHETTA
Division of Hematology, Oncology, Stem Cell Transplantation and Regenerative Medicine, Department of Pediatrics; Center for Definitive and Curative Medicine (CDCM), Stanford University School of Medicine, Stanford, CA

ANTONY BAKKE
Bakke Consulting, San Clemente, CA

HENRY H. BALFOUR, JR.
Departments of Laboratory Medicine & Pathology, and Pediatrics, University of Minnesota Medical School, Minneapolis, MN

GIUSEPPE BARBESINO
Thyroid Unit, Massachusetts General Hospital; Harvard Medical School, Harvard University, Boston, MA

SARA BARMETTLER
Department of Medicine, Massachusetts General Hospital, Boston, MA

MEAGAN BARNER
Kashi Clinical Laboratories, Portland, OR

MAREIKE BECKER
Department of Dermatology, University of Lübeck, Lübeck, Germany; Department of Pediatric Dermatology, Wilhelmstift Catholic Children's Hospital, Hamburg, Germany

JENNA R. E. BERGERSON
Laboratory of Clinical Immunology and Microbiology, NIAID, NIH, Bethesda, MD

MARK BERRONG
Duke University Medical Center, Department of Surgery, Durham, NC

ANGELIQUE BIANCOTTO
Precision Oncology and Flow Cytometry division, Sanofi, Vitry/Seine, France

LUCAS S. BLANTON
Department of Internal Medicine – Division of Infectious Diseases, University of Texas Medical Branch, Galveston, TX

CATERINA BODIO
Istituto Auxologico Italiano, IRCCS, Immunorheumatology Research Laboratory, Milan, Italy

MARIA ORIETTA BORGHI
Istituto Auxologico Italiano, IRCCS, Immunorheumatology Research Laboratory; Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

KAILEY E. BRODEUR
Division of Immunology, Boston Children's Hospital, Harvard Medical School, Boston, MA

MARY B. BROWN
Department of Infectious Diseases and Pathology, University of Florida College of Veterinary Medicine, Gainesville, FL

SARAH K. BROWNE
Altimmune, Gaithersburg, MD

YENAN T. BRYCESON
Center for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institutet; Division of Clinical Immunology and Transfusion Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden; Broegelmann Research Laboratory, Department of Clinical Science, University of Bergen, Bergen, Norway

CARRIE L. BUTLER
Department of Pathology & Laboratory Medicine, University of California, Los Angeles, Los Angeles, CA

AMANDA E. CALVERT
Division of Vector-Borne Diseases, U.S. Centers for Disease Control and Prevention, Fort Collins, CO

TESSA M. CAMPBELL
Center for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; Division of Clinical Immunology and Transfusion Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden

MIRANDA B. CARPER
Duke Human Vaccine Institute, Duke University School of Medicine, Durham, NC

PATRIZIO CATUREGLI
Department of Pathology, Johns Hopkins University School of Medicine, Johns Hopkins University, Baltimore, MD

ALMA-MARTINA CEPIKA
Division of Hematology, Oncology, Stem Cell Transplantation and Regenerative Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA

ANGELA CERIBELLI
Division of Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Milan, Italy; Department of Biomedical Sciences, Humanitas University, Milan, Italy

EDWARD K. L. CHAN
Department of Oral Biology, University of Florida, Gainesville, FL

SHANMUGANATHAN CHANDRAKASAN
Division of Bone Marrow Transplant, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA

LIANG CHEN
Division of Immunology, Boston Children's Hospital, Harvard Medical School, Boston, MA

XUEYAN CHEN
Translational Science and Therapeutics Division, Fred Hutchinson Cancer Center; Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA

TYSON CHIARO
McLendon Laboratories, UNC Health, Chapel Hill, NC

LAURA COOLING
Department of Pathology, University of Michigan, Ann Arbor, MI

ROSS L. COPPEL
Department of Microbiology, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia

CALEB CORNABY
Department of Pathology and Laboratory Medicine, Children's Hospital of Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA

MARC R. COUTURIER
Emerging Public Health Crises, Parasitology/Fecal Testing, and Infectious Disease Antigen Testing, ARUP Laboratories, Salt Lake City, UT

CLARKSON CRANE
Department of Pediatrics, University of California San Diego, La Jolla, CA

WILSON MELO CRUVINEL
Pontifícia Universidade Católica de Goiás, Goiânia, Brazil

TRACEY M. DAFONTE
Division of Pediatric Gastroenterology, Department of Pediatrics, MassGeneral Hospital for Children, Harvard Medical School; Center for Celiac Research and Treatment, Massachusetts General Hospital, Boston, MA

PRADEEP DAGUR
Flow Cytometry Core, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD

JAN DAMOISEAUX
Central Diagnostic Laboratory, Maastricht University Medical Center, Maastricht, The Netherlands

ADRIANA A. DE JESUS
Translational Autoinflammatory Diseases Section (TADS), Laboratory of Clinical Immunology and Microbiology, NIAID, NIH, Bethesda, MD

THOMAS N. DENNY
Duke Human Vaccine Institute, Duke University School of Medicine, Durham, NC

WILLIAM MARCIEL DE SOUZA
Department of Microbiology, Immunology, and Molecular Genetics, College of Medicine, University of Kentucky, Lexington, KY

JENNIFER DIEN BARD
Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles; Keck School of Medicine, University of Southern California, Los Angeles, CA

DANIEL DIGIACOMO
Department of Medicine, Massachusetts General Hospital, Boston, MA

BRADLEY DIXON
Children's Hospital Colorado; University of Colorado, School of Medicine, Aurora, CO

PRANAY DOGRA
Department of Translational Medicine Oncology, Genentech Inc., South San Francisco, CA

BRIAN F. DUFFY
Barnes-Jewish Hospital HLA Laboratory, St. Louis, MO

CULLEN M. DUTMER
Section of Allergy and Immunology, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO

ALLISON R. EBERLY
Department of Pathology & Immunology, Washington University School of Medicine in St. Louis, St. Louis, MO

DAVID E. ELLIOTT
Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Iowa Carver College of Medicine and the Iowa City Veterans Affairs Medical Center, Iowa City, IA

JOCELYN R. FARMER
Department of Medicine, Beth Israel Lahey Health, Burlington, MA

ALESSIO FASANO
Division of Pediatric Gastroenterology, Department of Pediatrics, MassGeneral Hospital for Children, Harvard Medical School; Center for Celiac Research and Treatment, Massachusetts General Hospital, Boston, MA

MARCELO FERNANDEZ-VINA
Department of Pathology, Stanford University School of Medicine, Stanford, CA

GUIDO FERRARI
Duke University Medical Center, Department of Surgery, Durham, NC

ALEJANDRO FERRER
Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN

LUIZ TADEU MORAES FIGUEIREDO
Virology Research Center, School of Medicine of Ribeirao Preto, University of São Paulo, Monte Alegre, Ribeirão Preto, SP, São Paulo, Brazil

WILLIAM G. FINN
Joint Venture Hospital Laboratories, Allen Park, MI

ASHLEY FRAZER-ABEL
University of Colorado, School of Medicine, Aurora, CO

ALEXANDRA F. FREEMAN
Laboratory of Clinical Immunology and Microbiology, NIAID, NIH, Bethesda, MD

HANS FRYKMAN
BC Neuroimmunology Laboratory and Neurocode Lab, University of British Columbia, Vancouver, British Columbia, Canada

DENNIS GALANAKIS
Departments of Medicine and Pathology, State University of New York, Stony Brook, NY

QI GAO
Memorial Sloan Kettering Cancer Center, Department of Pathology and Laboratory Medicine, New York, NY

AMBROSIA GARCIA
Immunology and Virology Quality Assurance Center (IVQAC), Duke Human Vaccine Institute, Duke University Medical Center, Durham, NC

KRYSTLE GARTH
University of Colorado Denver Anschutz Medical Campus, Aurora, CO

M. ERIC GERSHWIN
Division of Rheumatology/Allergy and Clinical Immunology, School of Medicine, University of California, Davis, Davis, CA

LAURA GILLIM
Medical Affairs, Labcorp, Burlington, NC

JOHN A. GOODFELLOW
Neuroimmunology Laboratory, Queen Elizabeth University Hospital, Glasgow, United Kingdom

PETER D. GOREVIC
Departments of Medicine and Pathology, State University of New York, Stony Brook, NY

FRANCESC GRAUS
Neuroimmunology Program, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

BRUCE GREIG
Clinical Hematopathology Laboratory, Vanderbilt Medical Laboratories, Vanderbilt University Medical Center, Nashville, TN

CLAUDIA GROSSI
Istituto Auxologico Italiano, IRCCS, Immunorheumatology Research Laboratory, Milan, Italy

AJAY GROVER
Department of Immunology and Flow Cytometry, Labcorp, Burlington, NC

LI GUO
Division of Hematology and Hematologic Malignancies, University of Utah School of Medicine, Salt Lake City, UT

ANNE HALPIN
Department of Laboratory Medicine and Pathology; Alberta Transplant Institute and Canadian Donation and Transplantation Research Program, University of Alberta, Edmonton, AB, Canada

YASUHITO HAMAGUCHI
Department of Dermatology, Kanazawa University, Ishikawa, Japan

ROBERT G. HAMILTON
Johns Hopkins Asthma and Allergy Center, Johns Hopkins University School of Medicine, Baltimore, MD

SHUHONG HAN
Division of Rheumatology, Allergy, & Clinical Immunology, University of Florida College of Medicine, Gainesville, FL

CURTIS A. HANSON
Division of Hematopathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

TOMOKO HASEGAWA
The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan

JILL J. HAUER
Molecular Otolaryngology and Renal Research Laboratories, Department of Otolaryngology, University of Iowa, Iowa City, IA; Department of Cellular and Molecular Medicine, University of California, San Diego; San Diego, CA

MICHELLE J. HICKEY
Departments of Pathology & Laboratory Medicine, University of California, Los Angeles, Los Angeles, CA

HARRY R. HILL
Department of Pathology, Pediatrics and Medicine, University of Utah, Salt Lake City, UT

MICHITO HIRAKATA
Medical Education Center, Graduate Medical Education Center, Keio University, Tokyo, Japan

CHANDLER C. HO
Molecular Pathology Laboratory, Stanford Medicine, Stanford, CA

SUZANNE HOFSTEDE-VAN EGMOND
Sanquin Diagnostic Services, Amsterdam, The Netherlands

KRISTIN A. HOGQUIST
Department of Laboratory Medicine & Pathology, University of Minnesota Medical School, Minneapolis, MN

STEVEN M. HOLLAND
Laboratory of Clinical Immunology and Microbiology, NIAID, NIH, Bethesda, MD

JOHN J. HOOKS
Immunology and Virology Section, National Eye Institute, National Institutes of Health, Bethesda, MD

D. CRAIG HOOPER
Department of Pharmacology, Physiology, and Cancer Biology, Department of Neurological Surgery, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

ELENA W. Y. HSIEH
Section of Allergy and Immunology, Department of Pediatrics; and Department of Immunology and Microbiology, University of Colorado School of Medicine, Aurora, CO

AMY P. HSU
Laboratory of Clinical Immunology and Microbiology, NIAID, NIH, Bethesda, MD

HOLLY R. HUGHES
Division of Vector-Borne Diseases, U.S. Centers for Disease Control and Prevention, Fort Collins, CO

SHELBY HUTCHERSON
Memorial Sloan Kettering Cancer Center, Department of Pathology and Laboratory Medicine, New York, NY

ANDREA ILLINGWORTH
Dahl-Chase Diagnostic Services, Bangor, ME

M. NEDIM INCE
Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Iowa Carver College of Medicine and the Iowa City Veterans Affairs Medical Center, Iowa City, IA

EMILIE JALBERT
University of Colorado Denver Anschutz Medical Campus, Aurora, CO

DRAGAN JEVREMOVIC
Division of Hematopathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

XIAOFAN JIA
Barbara Davis Center for Diabetes, University of Colorado School of Medicine, Aurora, CO

PAUL R. JOHNSON
Department of Clinical Laboratory Science, SUNY Upstate Medical University, Syracuse, NY

AMNA KAHN
Department of Pathology, Johns Hopkins University School of Medicine, Johns Hopkins University, Baltimore, MD

RICK KAPUR
Department of Experimental Immunohematology, Sanquin Research and Landsteiner Laboratory, Department of Immunohematology Diagnostics, Amsterdam, The Netherlands

ZAHRA KASHI
Kashi Clinical Laboratories, Portland, OR

ALF KASTBOM
Department of Biomedical and Clinical Sciences, Linköping University; Department of Rheumatology, Linköping University Hospital, Linköping, Sweden

GERSON DIERLEY KEPPEKE
Rheumatology Division, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil; Departamento de Ciencias Biomédicas, Facultad de Medicina, Universidad Católica del Norte, Coquimbo, Chile

DAVID F. KEREN
Department of Pathology, University of Michigan, Ann Arbor, MI

MICHAEL KIRSCHFINK
Institute of Immunology, University of Heidelberg, Heidelberg, Germany

VIJAYA KNIGHT
Section of Allergy and Immunology, Department of Pediatrics, University of Colorado School of Medicine, Immunopathology and Hematopathology Laboratory, Children's Hospital, Aurora, CO

LISA KOBRYNSKI
Division of Pediatric Allergy and Immunology, Emory University School of Medicine, Atlanta, GA

MIRA KOHORST
Department of Pediatrics, Mayo Clinic, Rochester, MN

ALEXANDRA E. KOVACH
Hematopathology, Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles; Keck School of Medicine, University of Southern California, Los Angeles, CA

DOUGLAS B. KUHNS
Clinical Services Program, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD

MASATAKA KUWANA
Department of Allergy and Rheumatology, Nippon Medical School, Tokyo, Japan

DAVID C. LAFON
Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham Heersink School of Medicine; University of Alabama at Birmingham Lung Health Center, Birmingham, AL

DIANA MARIA LANDONI
Escuela de Graduados, Facultad de Medicina, UdelaR (Universidad de la República), Montevideo, Uruguay

MONICA G. LAWRENCE
Division of Asthma, Allergy & Immunology, University of Virginia, Charlottesville, VA

TERRI LEBO
National Jewish Health Advanced Diagnostic Laboratories, National Jewish Health, Denver, CO

PUI Y. LEE
Division of Immunology, Boston Children's Hospital, Harvard Medical School, Boston, MA

SERENA J. LEE
Laboratory of Clinical Immunology and Microbiology, NIAID, NIH, Bethesda, MD

PATRICK S. C. LEUNG
Division of Rheumatology/Allergy and Clinical Immunology, School of Medicine, University of California, Davis, Davis, CA

JIN LI
Department of Physiology, University of Bern, Bern, Switzerland

QIZHAO LI
Department of Hematology, Qilu Hospital of Shandong University, Jinan, Shandong, China

RACHAEL M. LIESMAN
Department of Pathology and Laboratory Medicine, Medical College of Wisconsin, Milwaukee, WI

MARK D. LINDSLEY
Mycotic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, GA

CHRISTINE M. LITWIN
Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, SC

SHELDON E. LITWIN
Department of Internal Medicine Division of Cardiology, Medical University of South Carolina, Charleston, SC

CHANG LIU
Washington University in St. Louis School of Medicine, Department of Pathology and Immunology, Division of Laboratory and Genomic Medicine, St. Louis, MO

RENEE LIU
Department of Ophthalmology, Massachusetts Eye and Ear, Mass General Brigham; Harvard Medical School, Boston, MA

DEBRA LONG PRIEL
Clinical Services Program, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD

RAUL LOUZAO
Immunology and Virology Quality Assurance Center (IVQAC), Duke Human Vaccine Institute, Duke University Medical Center, Durham, NC

JOSE A. LUCAR
Division of Infectious Diseases, Department of Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC

CARRIE L. LUCAS
Department of Immunobiology, Yale University School of Medicine, New Haven, CT

EMILY M. MACE
Department of Pediatrics, Columbia University Irving Medical Center, New York, NY

CHINWE MADUBATA
Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, NY

HOLDEN T. MAECKER
Institute for Immunity, Transplantation, & Infection, Stanford University Medical School, Stanford, CA

ABHISHEK A. MANGAONKAR
Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN

MICHAEL P. MANNS
Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany

DAVID M. MANTHEI
University of Michigan, Department of Pathology, Ann Arbor, MI

IURI MARINOV
Flow Cytometry Unit, Institute of Haematology and Blood Transfusion, Prague, Czech Republic

JOHN PHILIP MCCOY JR.
Flow Cytometry Core, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD

PATRICIA A. MERKEL
Section of Allergy and Immunology, Department of Pediatrics, University of Colorado School of Medicine, Immunopathology and Hematopathology Laboratory, Children's Hospital, Aurora, CO

PIER LUIGI MERONI
Istituto Auxologico Italiano, IRCCS, Immunorheumatology Research Laboratory, Milan, Italy

KARIN P. MILLER
Hematopathology, Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles; Keck School of Medicine, University of Southern California, Los Angeles, CA

GERALD P. MORRIS
Department of Pathology, University of California San Diego, La Jolla, CA

BRUCE MOTYKA
Department of Pediatrics, Alberta Transplant Institute and Canadian Donation and Transplantation Research Program, University of Alberta, Edmonton, AB, Canada

ANN M. MOYER
Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

KAZUNORY MURATA
Memorial Sloan Kettering Cancer Center, Department of Pathology and Laboratory Medicine, New York, NY

MOON H. NAHM
Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham Heersink School of Medicine; Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL

STANLEY J. NAIDES
Labcorp, Burlington, NC

LAURA NARANJO
Immunology Department, Centre Diagnòstic Biomèdic, Hospital Clínic, Barcelona, Spain

DANIELLE NETTERE
Duke University Medical Center, Department of Surgery, Durham, NC

NGOC THUY T. NGUYEN
Cancer Innovation Laboratory, Center for Cancer Research, NCI, Frederick, MD

TIMOTHY B. NIEWOLD
Department of Medicine, Division of Rheumatology, Hospital for Special Surgery, New York, NY

ANDRRA NIMONI
Department of Medicine, Division of Rheumatology, Hospital for Special Surgery, New York, NY

MAURICE R. G. O'GORMAN
Departments of Pathology and Pediatrics, Children's Hospital of Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA

TERI OLDAKER
Oldaker Consulting, San Clemente, CA

KATHERINE L. OLSHAN
Division of Pediatric Gastroenterology, Department of Pediatrics, MassGeneral Hospital for Children, Harvard Medical School; Center for Celiac Research and Treatment, Massachusetts General Hospital, Boston, MA

HORATIU OLTEANU
Division of Hematopathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

S. MICHELE OWEN
National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA

BIJAL A. PARIKH
Department of Pathology & Immunology, Washington University School of Medicine in St. Louis, St. Louis, MO

MRINAL M. PATNAIK
Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN

DIANA PAULY
Department of Experimental Ophthalmology, Philipps University of Marburg, Marburg, Germany

XIAO PENG
Department of Genetic Medicine, Johns Hopkins University, Baltimore, MD; Center for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Germany

JONATHAN PEREZ
Department of Pathology, Johns Hopkins University School of Medicine, Johns Hopkins University, Baltimore, MD

LEENDERT L. PORCELIJN
Department of Experimental Immunohematology, Sanquin Research and Landsteiner Laboratory, Department of Immunohematology Diagnostics, Amsterdam, The Netherlands

CASSANDRA PORTH
Immunology and Virology Quality Assurance Center (IVQAC), Duke Human Vaccine Institute, Duke University Medical Center, Durham, NC

MIMI R. PRECIT
Department of Clinical Microbiology and Molecular Diagnostics, Labcorp Portland, Portland, OR Providence Health and Services Oregon Regional Laboratory, Portland, OR

DREW PROVAN
Department of Haematology, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

SHREY PUROHIT
Children's Hospital Colorado; University of Colorado, School of Medicine, Aurora, CO

RONALD L. RABIN
Center for Biologics Evaluation and Research, US FDA, Silver Spring, MD

ALEX J. RAI
Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, NY

RAJA RAJALINGAM
UCSF Immunogenetics and Transplantation Laboratory, Department of Surgery, University of California, San Francisco, CA

AMY RASLEY
Host-Pathogen Laboratory Group, Lawrence Livermore National Laboratory, Livermore, CA

SUSAN REALEGENO
Quest Diagnostics, San Juan Capistrano, CA

JOHAN REBETZ
Division of Hematology and Transfusion Medicine, Lund University, Lund, Sweden

ELAINE F. REED
Department of Pathology & Laboratory Medicine, UCLA Immunogenetics Center, Los Angeles, CA

WESTLEY H. REEVES
Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Florida, Gainesville, FL

RYAN F. RELICH
Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN

STEPHEN J. RICHARDS
Department of Hematology and Immunology, Leeds Institute of Medical Research at St James's, University of Leeds School of Medicine, Leeds, Yorkshire, United Kingdom

JOHAN RÖNNELID
Department of Immunology, Genetics and Pathology, Uppsala University; Department of Clinical Immunology and Transfusion Medicine, Uppsala University Hospital, Uppsala, Sweden

LINDSEY B. ROSEN
Laboratory of Clinical Immunology and Microbiology, NIAID, NIH, Bethesda, MD

SANDRA ROSEN-BRONSON
Medstar Georgetown University Hospital, Department of Pathology and Laboratory Medicine, Histocompatibility Laboratory, Washington, DC

MIKHAIL ROSHAL
Memorial Sloan Kettering Cancer Center, Department of Pathology and Laboratory Medicine, New York, NY

TAMAR S. RUBIN
Division of Pediatric Clinical Immunology and Allergy, University of Manitoba, Winnipeg, Manitoba, Canada

RAQUEL RUIZ-GARCÍA
Immunology Department, Centre Diagnòstic Biomèdic, Hospital Clínic; Neuroimmunology Program, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

LOUMA B. RUSTAM
Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Iowa Carver College of Medicine and the Iowa City Veterans Affairs Medical Center, Iowa City, IA

KEITH A. SACCO
Immunology Department, Barts Health NHS trust, London, United Kingdom

SHOMYSEH SANJABI
Department of Translational Medicine Oncology, Genentech Inc., South San Francisco, CA

MINORU SATOH
Department of Human, Information and Life Sciences, University of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan

ANKIT SAXENA
Immune Monitoring Flow Cytometry Shared Resource, Cancer Institute of New Jersey, Rutgers, New Brunswick, NJ

CAITLIN O. SCHEIN
Department of Clinical Pathology, Corewell Health East, William Beaumont University Hospital, Royal Oak, MI

HEINRICH SCHLUMS
Center for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; Division of Clinical Immunology and Transfusion Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden

ENNO SCHMIDT
Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany

JOHN L. SCHMITZ
Dept of Pathology & Laboratory Medicine, University of North Carolina, School of Medicine, Chapel Hill, NC

OSKAR SCHNAPPAUF
Department of Natural Sciences, University of Applied Sciences Bonn-Rhein-Sieg, Bonn, Germany

JOHN T. SCHROEDER
Department of Medicine, Division of Allergy and Immunology, Johns Hopkins University, Baltimore, MD

LEE SCHROEDER
University of Michigan, Department of Pathology, Ann Arbor, MI

R. HAL SCOFIELD
Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation; Departments of Medicine and Pathology, College of Medicine, University of Oklahoma Health Sciences Center; Medical and Research Services, US Department of Veterans Affairs Hospital, Oklahoma City, OK

ELISABETH SEMPLE
Division of Hematology and Transfusion Medicine, Lund University, Lund, Sweden

JOHN W. SEMPLE
Division of Hematology and Transfusion Medicine, Lund University, Lund, Sweden; Clinical Immunology and Transfusion Medicine, Office of Medical Services, Region Skåne, Lund, Sweden; Department of Pharmacology, University of Toronto, Toronto, Canada

ROSEMARY C. SHE
Department of Pathology, Keck School of Medicine of the University of Southern California, Los Angeles, CA

HESHAM M. SHEHATA
Department of Translational Medicine Oncology, Genentech Inc., South San Francisco, CA

MIN SHI
Division of Hematopathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

KILEEN L. SHIER
Quest Diagnostics, Chantilly, VA

JERRY W. SIMECKA
Department of Cell Biology and Immunology, University of North Texas Health Science Center, Fort Worth, TX

AMANDA K. SLAGLE
Molecular Otolaryngology and Renal Research Laboratories, Department of Otolaryngology; Graduate Program in Immunology, University of Iowa, Iowa City, IA

JAY E. SLATER
Center for Biologics Evaluation and Research, US FDA, Silver Spring, MD

PATRICIA SLEV
Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT

RICHARD J. H. SMITH
Molecular Otolaryngology and Renal Research Laboratories, Department of Otolaryngology; Graduate Program in Immunology, University of Iowa, Iowa City, IA

ANDREW L. SNOW
Department of Pharmacology and Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD

LUCIA SOBRIN
Department of Ophthalmology, Clinical Data Science, Massachusetts Eye and Ear, Mass General Brigham; Harvard Medical School, Boston, MA

REBECCA A. SOSA
Department of Pathology & Laboratory Medicine, University of California, Los Angeles, Los Angeles, CA

MEERA SRIDHARAN
Division of Hematology, Mayo Clinic, Rochester, MN

JASON E. STOUT
Division of Infectious Diseases and International Health, Department of Medicine, Duke University Medical Center, Durham, NC

MICHAEL BRAD STRADER
Center for Biologics Evaluation and Research, US FDA, Silver Spring, MD

D. ROBERT SUTHERLAND
Department of Medicine, University of Toronto, Oakville, Ontario, Canada

SHIN TANAKA
Department of Human, Information and Life Sciences, University of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan

MEI SAN TANG
Washington University in St. Louis School of Medicine, Department of Pathology and Immunology, Division of Laboratory and Genomic Medicine, St. Louis, MO

ELITZA S. THEEL
Division of Clinical Microbiology, Mayo Clinic, Rochester, MN

KATIE THOREN
Department of Pathology and Laboratory Medicine, University of Miami, Miami, FL

OLGA A. TIMOFEEVA
Medstar Georgetown University Hospital, Department of Pathology and Laboratory Medicine, Histocompatibility Laboratory, Washington, DC

ANTONIO TONUTTI
Division of Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital; Department of Biomedical Sciences, Humanitas University, Milan, Italy

ESZTER TOTH
Laboratory of Clinical Immunology and Microbiology, NIAID, NIH, Bethesda, MD

MARTHA TSALIKI
Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation; Departments of Medicine and Pathology, College of Medicine, University of Oklahoma Health Sciences Center; Medical and Research Services, US Department of Veterans Affairs Hospital, Oklahoma City, OK

RENEE TSOLIS
Department of Medical Microbiology and Immunology, University of California, Davis, Davis, CA

CARL TURESSON
Rheumatology, Department of Clinical Sciences, Malmö, Lund University; Department of Rheumatology, Skåne University Hospital, Malmö, Sweden

GULBU UZEL
Laboratory of Clinical Immunology and Microbiology, NIAID, NIH, Bethesda, MD

ANDRE VALCOUR
Labcorp, Burlington, NC

JULIO C. VALENCIA
Cancer Innovation Laboratory, Center for Cancer Research, NCI, Frederick, MD

MIRJAM VAN DER BURG
Department of Pediatrics, Laboratory for Pediatric Immunology, Willem-Alexander Children's Hospital, Leiden University Medical Center, Leiden, The Netherlands

PRIYA S. VERGHESE
Departments of Nephrology and Pediatrics, Northwestern University, Feinberg School of Medicine, Chicago, IL

PAUL A. WADSWORTH
Department of Pathology, Stanford University School of Medicine, Stanford, CA

KEN B. WAITES
Department of Pathology, University of Alabama at Birmingham, Birmingham, AL

DAVID H. WALKER
Department of Pathology, University of Texas Medical Branch, Galveston, TX

PAUL K. WALLACE
Roswell Park Comprehensive Cancer Center, Buffalo, NY; SciGro, Inc., Sedona, AZ

GUIQING WANG
Clinical Laboratories, Department of Pathology, New York University Langone Health, New York University Grossman School of Medicine, New York, NY

JEFFREY S. WARREN
Department of Pathology, University of Michigan Medical School, Ann Arbor, MI

ERIC T. WEIMER
Department of Pathology and Lab Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

ADRIANA WEINBERG
Department of Pediatrics, Medicine, and Pathology, University of Colorado Denver Anschutz Medical Campus, Aurora, CO

LORI J. WEST
Departments of Pediatrics, Surgery, Medical Microbiology and Immunology, and Laboratory Medicine and Pathology, Alberta Transplant Institute and Canadian Donation and Transplantation Research Program, University of Alberta, Edmonton, AB, Canada

KELLI W. WILLIAMS
Division of Pediatric Pulmonology, Allergy and Immunology, Medical University of South Carolina, Charleston, SC

HUGH J. WILLISON
School of Infection and Immunity, University of Glasgow, Glasgow, United Kingdom

MARIA ALICE VIEIRA WILLRICH
Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

BRENT L. WOOD
Pathology and Laboratory Medicine, Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA

SHUQIAN XU
Department of Hematology, Qilu Hospital of Shandong University, Jinan, Shandong, China

ZIYAN XU
Department of Pathology, Johns Hopkins University School of Medicine, Johns Hopkins University, Baltimore, MD

SHANGXIN (SHAUN) YANG
Department of Pathology and Laboratory Medicine, UCLA Health System, Los Angeles, CA

REBECCA YEE
Department of Pathology, George Washington University School of Medicine and Health Sciences, Washington, DC

HOWARD A. YOUNG
Cancer Innovation Laboratory, Center for Cancer Research, NCI, Frederick, MD

LIPING YU
Barbara Davis Center for Diabetes, University of Colorado School of Medicine, Aurora, CO

ROBERT ZAGORSKI
Center for Biologics Evaluation and Research, US FDA, Silver Spring, MD

FATIMA ZAMAN
Department of Pathology, Johns Hopkins University School of Medicine, Johns Hopkins University, Baltimore, MD

VALENTINA ZANFAGNIN
Department of Pathology, Keck School of Medicine of the University of Southern California, Los Angeles, CA

SOFIA ZAVALA
Division of Infectious Diseases and International Health, Department of Medicine, Duke University Medical Center, Durham, NC

BING MELODY ZHANG
Department of Pathology, Stanford University School of Medicine, Stanford, CA

MENGLEI ZHU
Memorial Sloan Kettering Cancer Center, Department of Pathology and Laboratory Medicine, New York, NY

HAOYANG ZHUANG
Division of Rheumatology, Allergy, & Clinical Immunology, University of Florida College of Medicine, Gainesville, FL

Acknowledgment of Previous Contributors

The *Manual of Molecular and Clinical Laboratory Immunology* is by its nature a continuously revised work which refines and extends the contributions of previous editions. Since its first edition in 1976, many eminent scientists have contributed to this important reference work. The American Society for Microbiology and its Publications Board gratefully acknowledge the contributions of all of these generous authors over the life of this *Manual*.

PREFACE

For almost 50 years, the *Manual of Molecular and Clinical Laboratory Immunology* (MMCLI) has been the principal resource for the laboratories, students, and professionals performing or interested in the clinical and technical details of diagnostic immunology testing. Since the last edition in 2016, the clinical laboratory has witnessed a global pandemic, the development and application of gene editing, and the widespread adoption of molecularly engineered cellular therapies, among other novel technical and clinical advancements in the diagnosis and treatment of infectious and immune diseases. This, the 9th edition of the MMCLI, continues the tradition of providing detailed clinical and technical information on technologies that are being utilized in the practice of medical and diagnostic immunology. This edition, with 119 chapters, has undergone substantial changes from the 8th edition to improve and update the utility of the *Manual*. The first major change is a reorganization of the content. Immunologic techniques are now combined into the first 36 chapters of the *Manual*. This change is intended to reduce duplicative information among technique-centric versus clinically oriented chapters. Second, all chapters have been updated with information on the latest technologies, some chapters have been deleted, and completely new chapters have been added. These updates were achieved with the recruitment of new section editors and authors and have led to the production of the most comprehensive and up-to-date resource available for laboratory testing and clinical information related to the diagnosis, evaluation, and monitoring of immune-mediated and immune system-related disorders.

Immunologic testing and new biomarkers continue to be developed and expand in scope and volume in parallel with the ever-increasing knowledge of the components and functions of the immune system in health and disease. The 9th edition serves as an important resource that combines details of immunologic methods with relevant clinical information to clarify the appropriate application and interpretation of tests for diagnosis, evaluation of treatment response, and patient management. This manual is appropriate for the laboratory director and the clinician seeking information on the selection, application, and interpretation of immunologic tests. It also benefits the laboratory manager and technologist by providing details on troubleshooting of methods, clinical application, interpretation, and test limitations. The content of this manual is also beneficial for the undergraduate, graduate, or professional student interested in laboratory immunology, given the breadth and depth of both clinical and technical information it provides.

The first portion of the 9th edition (chapters 1 to 36) is dedicated to descriptions of technologies practiced in the clinical immunology laboratory. To avoid duplication, this edition has extracted method-specific details from previous chapters and coalesced them into these first 36 chapters. Clinical chapters describing infectious diseases, inborn errors of immunity, hematologic malignancy, transplantation, systemic and organ-specific autoimmune disorders (chapters 37 to 119) now refer to the relevant method chapters for technical details. In some unique circumstances, detailed methodologic discussions are addressed in the clinical application chapters where the method is associated with a very specific application that is not specifically addressed in the methods chapters. The methods portion now provides more detailed coverage of immunoglobulin and T cell receptor gene technologies and their applications. Eight chapters highlight the technical aspects of traditional flow cytometry, rare event analysis, functional assays, and future cytometric technologies. Additional chapters on functional cellular immunologic assays have been expanded to include a chapter on interferon gamma release assays and a chapter on the assessment of cytotoxic T cell number and function. The methods portion now includes three chapters related to laboratory management, including up-to-date information on quality assurance, quality improvement, and quality management, areas which are becoming increasingly relevant in today's regulatory environment.

The second portion of the *Manual* encompasses clinical descriptions of specific immunologic diseases and specific clinical and diagnostic test applications. Broadly, these categories include infectious diseases, inborn errors of immunity (formerly referred to as primary immune deficiency disorders), allergic diseases, systemic autoimmune diseases, organ-specific autoimmune diseases, cancer (focus on hematologic malignancies), and transplantation immunology. New section editors and new authors have led to new and expanded content and removal of chapters related to testing that is no longer

relevant. Examples include removal of the chapter on *Helicobacter* infection due to the limited applicability of serologic testing, and the section on primary immunodeficiency has been completely updated to contain chapters that coincide with the International Union of Immunological Societies tables of classification for the inborn errors of immunity.

In the virology section, 3 chapters have been eliminated (respiratory viruses, gastroenteritis viruses, and prions). Two new chapters have been added, one on SARS-coronavirus-2 and a second on enteroviruses.

The explosion in our knowledge of rheumatic diseases is reflected in several expanded chapters highlighted in the section on systemic and organ-specific autoimmune disorders. Moreover, two new chapters have been added pertaining to Sjögren's syndrome and deficiency of adenosine deaminase 2.

In the organ-specific autoimmune diseases section, chapters have been significantly updated, and two new chapters, one on kidney disorders and one on blistering skin diseases, have been included.

Over the past decade, cytokine biology has radically expanded our opportunities to provide more innovative diagnostic testing and has stimulated exciting potential for the next generation of therapeutic applications for a variety of immune-mediated diseases. For example, the cytokine section updates the reader with specific chapters on the rapidly developing area of cytokine testing and the clinical consequences of anticytokine autoantibodies and interferonopathies.

The cancer section now includes four chapters that detail the diagnosis and monitoring of measurable residual disease in hematologic malignancies. The movement of these chapters from the methods to the clinical portion of the book is indicative of the current standards of practice for the diagnosis of monitoring of measurable residual disease in many hematologic malignancies. These chapters deal extensively with the flow-cytometric analysis of these malignancies related to both diagnosis and up-to-date information on the measurement of residual disease inclusive of informative figures highlighting relevant flow-cytometric analyses. Finally, the section on transplantation has been updated with chapters describing assessment of immune reconstitution and ABO testing.

With the completion of the 9th edition of the *Manual*, the editors recognize and thank all the section editors and chapter authors whose work contributed to this volume. Special thanks go to all the section editors for their expertise identifying and recruiting authors and their efforts in ensuring the submission and review of the chapters, and to the authors themselves, who delivered detailed and thorough state-of-the-art clinical and technical information. We also recognize our external reviewers, who assisted us in reaching the finish line. Lastly, a big thanks to Christine Charlip, Ellen Fox, Megan Angelini, and Ellie Tupper for their tireless work in guiding us through the publication process.

John L. Schmitz
Barbara Detrick
Maurice R. G. O'Gorman

Author and Editor Conflicts of Interest

Meagan Barner (coauthor on chapter 117) is an employee of Kashi Clinical Laboratories, which runs the MMDx assay.

Carrie L. Butler (coauthor on chapter 114) declares a conflict: UCLA holds a patent on non-HLA antibodies.

Jan Damoiseaux (author on chapter 85) reports consultancy and/or speakers fees from Werfen/Inova, ThermoFisher Scientific, Menarini, and Euroimmun.

Bradley Dixon (coauthor on chapter 12) has consulting agreements with Apellis Pharmaceuticals, Alexion Astra Zeneca Rare Disease, Arrowhead Pharmaceuticals, and Novartis Pharmaceuticals.

Pranay Dogra (coauthor on chapter 105) is an employee and stockholder of Roche.

Jocelyn R. Farmer (coauthor on chapter 67) is an ongoing consultant for Pharming and has received investigator-initiated research grants from Pfizer, Bristol Myers Squibb, and Pharming with no direct relation to the work presented.

Alessio Fasano (coauthor on chapter 97) is co-founder and stockholder of Alba Therapeutics, has a speaker agreement with Mead Johnson Nutrition, and has sponsored research with Pfizer.

Ashley Frazer-Abel (section editor and coauthor on chapters 9 and 12) consulting agreements with CSL Behring and Perceive Bio

Francesc Graus (coauthor on chapter 92) holds a patent licensed to Euroimmun for the use of IgLON5 in an autoantibody test, for which he receives royalties, and receives honoraria from MedLink Neurology for his role as associate editor.

Michelle J. Hickey (coauthor on chapter 114) declares a conflict: UCLA holds a patent on non-HLA antibodies.

Andrea Illingworth (coauthor on chapter 15) has served on advisory boards and taken part in speaking engagements for Alexion Pharmaceuticals (now part of Astra Zenica).

Zahra Kashi (coauthor on chapter 117) is the CEO and Lab Director of Kashi Clinical Laboratories, which runs the MMDx assay.

David F. Keren (section editor and coauthor on chapters 4, 5, and 8) is on the advisory boards of The Binding Site and Sebia.

Masataka Kuwana (coauthor on chapter 82) has received royalties from MBL, as well as consulting fees and/or honoraria from AbbVie, Asahi Kasei, Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Corbus, Chugai, Eisai, GSK, Horizon, Janssen, Mochida, Ono Pharmaceuticals, Mitsubishi Tanabe, and Nippon Shinyaku.

David C. LaFon (coauthor on chapter 23) is an employee of the University of Alabama at Birmingham, which has intellectual property rights on some multiplexed opsonophagocytosis assay reagents.

Monica G. Lawrence (coauthor on chapter 66) receives research funding via her institution from Takeda Pharmaceuticals and served on a medical advisory board for Enzyvant Therapeutics (now Sumitomo Pharma), which manufacturers cultured thymic tissue used in the treatment of congenital athymia (relationship not ongoing).

Chang Liu (coauthor on chapter 112) holds a patent on an HLA typing software package, ATHLATES; copyright on an HLA typing software package, ATHLON2; and declares an industry-funded research study via One Lambda/ThermoFisher.

Holden T. Maecker (author on chapter 20) is a member of the scientific advisory board of Cytek Biosciences.

Iuri Marinov (coauthor on chapter 15) has served on advisory boards and taken part in speaking engagements for Alexion Pharmaceuticals (now part of Astra Zenica).

Pier Luigi Meroni (coauthor on chapter 84) has received consultation fees from Werfen, Thermo Fisher.

Moon H. Nahm (coauthor on chapter 23) is an employee of the University of Alabama at Birmingham, which has intellectual property rights on some multiplexed opsonophagocytosis assay

(MOPA) reagents that were developed in Dr. Nahm's laboratory. Dr. Nahm is also a founder of Sunfire Biotechnologies, which performs MOPA.

Bijal A. Parikh (coauthor on chapter 55) is a member of the Cepheid Speaker's Bureau. This relationship is limited to the scope oncology testing.

Susan Realegeno (author on chapter 50) is employed by and has stock interests in Quest Diagnostics.

Elaine F. Reed (coauthor on chapter 114) declares a conflict: UCLA holds a patent on non-HLA antibodies.

Stephen J. Richards (coauthor on chapter 15) has served on advisory boards and taken part in speaking engagements for Alexion Pharmaceuticals (now part of Astra Zenica).

Shomyseh Sanjabi (coauthor on chapter 105) is an employee and stockholder of Roche.

Enno Schmidt (coauthor on chapter 102) has a scientific cooperation with Euroimmun, Lübeck, and holds patents with this company.

Hesham M. Shehata (coauthor on chapter 105) is an employee and stockholder of Roche.

Kileen L. Shier (author on chapter 57) is an employee and stockholder at Quest Diagnostics.

D. Robert Sutherland (coauthor on chapters 15 and 16) has served on advisory boards and taken part in speaking engagements for Alexion Pharmaceuticals (now part of Astra Zenica).

Priya S. Verghese (coauthor on chapter 51) is the principal investigator of an investigator-initiated study being sponsored by Eurofins, Viracor investigating CMV-specific T cell immunity in transplantation.

Kelli W. Williams (coauthor on chapter 66) serves on the steering committee and is a speaker for Pharming Healthcare (ongoing relationship) and participated in a medical advisory board for Sumitomo Pharma, which manufacturers cultured thymic tissue used in the treatment of congenital athymia (relationship not ongoing).

Molecular Methods *section* A

VOLUME EDITOR: JOHN L. SCHMITZ
SECTION EDITOR: ERIC T. WEIMER

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