

# Adrenocortical Carcinoma



Gary D. Hammer · Tobias Else  
Editors

# Adrenocortical Carcinoma

Basic Science and Clinical Concepts

 Springer

*Editors*

Gary D. Hammer, MD, Ph.D.  
Mille Schembechler Professor of Adrenal  
Cancer  
Director – Endocrine Oncology Program  
Director – Center for Organogenesis  
University of Michigan Health System  
University of Michigan

Tobias Else, MD  
Department of Internal Medicine  
Division of Metabolism, Endocrinology  
& Diabetes  
University of Michigan Health System  
University of Michigan

ISBN 978-0-387-77235-6 e-ISBN 978-0-387-77236-3  
DOI 10.1007/978-0-387-77236-3  
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2010934103

© Springer Science+Business Media, LLC 2011

All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer Science+Business Media, LLC, 233 Spring Street, New York, NY 10013, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden.

The use in this publication of trade names, trademarks, service marks, and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights.

While the advice and information in this book are believed to be true and accurate at the date of going to press, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

Springer is part of Springer Science+Business Media ([www.springer.com](http://www.springer.com))

# Preface

Adrenocortical carcinoma (ACC) is a disease that most physicians, including many endocrinologists, will rarely, if ever, diagnose or let alone treat during the course of their medical practice. Medical textbooks of endocrinology and oncology rarely dedicate an entire chapter to this disease entity. The pursuit of research and clinical excellence in uncommon diseases is extremely challenging because of a lack of research prioritization, nonexistent treatment guidelines and overall paucity of coordination between researchers and physicians. ACC is one such disease where no infrastructure for a unified research agenda and no consensus treatment guidelines had been developed.

While a number of international meetings over the past two decades have indeed focused on adrenal tumors in the context of hormone excess (Cushing's syndrome, hyperaldosteronism, and pheochromocytoma), few have exclusively catered to the science and clinical care of ACC and those afflicted with the disease. With only a single FDA-approved drug for ACC (mitotane – a derivative of the pesticide DDT), institutional experiences varied widely until recently when historic biases have slowly yielded to data-driven treatment strategies. A large part of the impetus for this push has come from Europe, where the availability of country-wide integrated networks for treatment has allowed a small number of centers in Italy, France, and Germany (among others) to develop specific expertise and specific treatment protocols for this rare disease.

In an attempt to facilitate coordination of global efforts, a consensus conference was organized and held at the University of Michigan in September 2003. At that meeting, an international group of physicians and scientists with research interest and clinical expertise in ACC set up initial guidelines for the diagnosis and treatment of ACC. Three principles emerged. Successful treatment of ACC demands coordinated care in the context of a multidisciplinary team dedicated to the disease. Future therapies for ACC need to be predicated on hypothesis-driven research based on a thorough analysis of tumor biology. Lastly, major advancement in the field demands national and international collaborative networks to facilitate analysis of large datasets and coordinate future clinical trials. The FIRM-ACT (First International Randomized Trial in locally advanced and Metastatic Adrenocortical Cancer Treatment) that coordinated over 35 ACC centers in a single multinational trial set precedence for the actualization of these principles. The Second

International Adrenal Cancer Symposium: Clinical and Basic Science held at the University of Michigan in March 2008 built upon the momentum of the 2003 consensus meeting and the successful development of a large international ACC network through the FIRM-ACT trial.

Over the past decade, the ACC research community has grown to a critical mass with new data emerging in the laboratory and clinic. In times of electronic publications we routinely rely on journal articles and expert reviews on both clinical and research topics. While such publications are informative, when approached by Springer about the possibility of editing such a textbook, we became convinced that the time had come to compile the accumulated clinical and basic science knowledge of 50 years of active research on this rare cancer into a concise medical textbook. The overall goal of this book is therefore to provide definitive reference material for scientists and clinicians, to introduce trainees to concepts of ACC management, and to stimulate further research, future collaborations, and networking.

As opposed to a solitary review article, a textbook with multiple chapters dedicated to discrete topics in the field provides contributors the opportunity to objectively review historic data and detail the current state of clinical care and research accomplishments. While this is a major advantage of a textbook, it is also a major challenge for a book that focuses solely on a rare cancer where data are scant. In editing this book, we tried to ensure that each individual chapter covers well-established knowledge in the area, but also allows room for expert opinion. Lastly, because ACC has been linked to several genetic disorders that usually escape discussion in a focused review of adrenal tumors, the various syndromes will be discussed in their entirety in separate chapters. The 32 Chapters of the 9 Sections are authored by the scientific and clinical leaders in the field.

With publication of this first edition, the editors want to extend special thanks to our colleagues within the ACC community, the contributors, Rachel, Todd and Lesley of the editorial staff at Springer Publishing House, and Lisa K. Byrd of the University of Michigan.

We are hopeful that this first edition of the textbook provides an intellectual platform for the continued coalescence and dissemination of knowledge on ACC in future editions. Both the authors and editors welcome comments and recommendations for improvement in writing or via electronic mail. The editors' and authors' institutional and e-mail addresses are given in the contributor's section.

Ann Arbor, Michigan  
November 2010

Gary Hammer  
Tobias Else

# Contents

<b>Part I</b>	<b>History of Adrenocortical Carcinoma Research and Clinical Care</b>	
<b>1</b>	<b>The History of Adrenocortical Carcinoma Treatment – A Medical Perspective</b> . . . . .	<b>3</b>
	David E. Scheingart	
<b>2</b>	<b>The History of Adrenocortical Carcinoma Treatment – A Surgical Perspective</b> . . . . .	<b>9</b>
	Norman W. Thompson	
<b>Part II</b>	<b>Epidemiology, Presentation and Diagnosis</b>	
<b>3</b>	<b>Epidemiology of Adrenocortical Carcinoma</b> . . . . .	<b>23</b>
	Martin Fassnacht and Bruno Allolio	
<b>4</b>	<b>Clinical Presentation and Initial Diagnosis</b> . . . . .	<b>31</b>
	Bruno Allolio and Martin Fassnacht	
<b>5</b>	<b>Diagnostic Approach to Incidentaloma</b> . . . . .	<b>49</b>
	Holger S. Willenberg and Stefan R. Bornstein	
<b>Part III</b>	<b>Imaging</b>	
<b>6</b>	<b>Computed Tomography/Magnetic Resonance Imaging of Adrenocortical Carcinoma</b> . . . . .	<b>67</b>
	Melvyn Korobkin, Anca M. Avram, and Hero K. Hussain	
<b>7</b>	<b>Functional Imaging of Adrenocortical Carcinoma</b> . . . . .	<b>85</b>
	Anca M. Avram and Stephanie Hahner	
<b>Part IV</b>	<b>Pathology</b>	
<b>8</b>	<b>Classical Histopathology and Immunohistochemistry</b> . . . . .	<b>107</b>
	Wolfgang Saeger	

<b>9 Cellular and Molecular Pathology of Adrenocortical Carcinoma</b> . . . . .	127
Tobias Else	
<b>Part V Genetic and Molecular Aspects</b>	
<b>10 Overview of Genetic Syndromes Associated with Adrenocortical Cancer</b> . . . . .	153
Tobias Else	
<b>11 Li–Fraumeni Syndrome</b> . . . . .	173
David Malkin	
<b>12 TP53 Molecular Genetics</b> . . . . .	193
Gerard P. Zambetti and Raul C. Ribeiro	
<b>13 Telomeres and Telomerase in Adrenocortical Carcinoma</b> . . . . .	207
Tobias Else and Peter J. Hornsby	
<b>14 Beckwith–Wiedemann Syndrome</b> . . . . .	227
Michael DeBaun and Jennifer Horst	
<b>15 The Insulin-Like Growth Factor System in Adrenocortical Growth Control and Carcinogenesis</b> . . . . .	235
Christian Fottner, Ina M. Niederle, and Matthias M. Weber	
<b>16 WNT/<math>\beta</math>-Catenin Signaling in Adrenocortical Carcinoma</b> . . . . .	263
Sébastien Gaujoux, Frédérique Tissier, and Jérôme Bertherat	
<b>Part VI Models of Adrenocortical Cancer</b>	
<b>17 Adrenocortical Stem and Progenitor Cells: Implications for Cancer</b> . . . . .	285
Joanne H. Heaton and Gary D. Hammer	
<b>18 Adrenocortical Cell Lines</b> . . . . .	305
Jeniel Parmar, Anita Kulharya, and William Rainey	
<b>19 Mouse Models of Adrenal Tumorigenesis</b> . . . . .	325
Felix Beuschlein	
<b>Part VII Therapies</b>	
<b>20 Overview of Treatment Options for Adrenocortical Carcinoma</b> . . . . .	343
Gary D. Hammer	
<b>21 Chemotherapy</b> . . . . .	351
Alfredo Berruti, Paola Sperone, Paola Perotti, Anna Ferrero, Luigi Dogliotti, and Massimo Terzolo	
<b>22 Mitotane</b> . . . . .	369
Massimo Terzolo, Arianna Ardito, Barbara Zaggia, Silvia De Francia, and Fulvia Daffara	



**23 Pharmacotherapy for Hormone Excess in Adrenocortical Carcinoma** . . . . . 383  
 Richard J. Auchus

**24 Surgery for Adrenocortical Carcinoma** . . . . . 403  
 James T. Broome, Barbra S. Miller, Paul G. Gauger,  
 and Gerard M. Doherty

**25 Radiation Therapy for Adrenocortical Carcinoma** . . . . . 427  
 Aaron Sabolch and Edgar Ben-Josef

**26 Follow-Up and Monitoring of Adrenocortical Carcinoma** . . . . . 443  
 Britt Skogseid and Gerard M. Doherty

**Part VIII Unique Cohorts and Future Perspectives**

**27 Aldosterone-Producing Adrenocortical Carcinoma** . . . . . 457  
 Anna Patalano, Maria V. Cicala, and Franco Mantero

**28 Adrenocortical Cancer in Children** . . . . . 467  
 Carlos Rodriguez-Galindo, Gerard P. Zambetti,  
 and Raul C. Ribeiro

**29 Genome-Wide Studies in Adrenocortical Neoplasia** . . . . . 483  
 Thomas J. Giordano

**30 New Strategies for the Treatment of Adrenocortical Carcinoma** . . . . . 493  
 Lawrence S. Kirschner

**Part IX Adrenal Cancer Networks and Registries**

**31 The Dutch Adrenal Network** . . . . . 517  
 Ilse G.C. Hermsen, Yvonne E. Groenen, and Harm R. Haak

**32 The ENS@T Initiative** . . . . . 521  
 Xavier Bertagna

**Index** . . . . . 533



# Contributors

**Bruno Allolio** Department of Internal Medicine I, Endocrine and Diabetes Unit, University of Würzburg, Josef-Schneider-Str. 2, 97080 Würzburg, Germany, allolio\_b@medizin.uni-wuerzburg.de

**Arianna Ardito** Department of Clinical and Biological Sciences, Medicina Interna 1, AOU San Luigi Gonzaga, University of Turin, Regione Gonzole, 10, 10043 Orbassano, Italy, arianna.ardito@gmail.com

**Richard J. Auchus** Division of Endocrinology and Metabolism, Department of Internal Medicine, UT Southwestern Medical Center Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA, richard.auchus@utsouthwestern.edu

**Anca M. Avram** Division of Nuclear Medicine/Radiology, University of Michigan Health System, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48105, USA, ancaa@umich.edu

**Edgar Ben-Josef** Department of Radiation Oncology, University of Michigan Health System, University of Michigan, 1500 East Medical Center Drive, Room UHB2C490, Ann Arbor, MI 48109-0010, USA, edgarb@med.umich.edu

**Alfredo Berruti** Oncologia Medica, Azienda Ospedaliero Universitaria San Luigi, Regione Gonzole, 10, 10043 Orbassano, Italy, alfredo.berruti@gmail.com

**Jérôme Bertherat** Endocrinology, Metabolism and Cancer Department, Institut Cochin, Descartes University, INSERM U567, CNRS UMR8104, Paris France; Reference center for rare adrenal disorders, Assistance Publique Hôpitaux de Paris, Hôpital Cochin, Paris Descartes University, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France, jerome.bertherat@cch.aphp.fr

**Xavier Bertagna** Endocrinology Department, Cochin Hospital, Paris, France; National Network COMETE, INCa, Paris, France; European Network for the Study of Adrenal Tumors (ENS@T), 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France, xavier.bertagna@cch.aphp.fr

**Felix Beuschlein** Department of Medicine, Endocrine Research, University Hospital Innenstadt, Ziemssenstr. 1, 80336 Munich, Germany, felix.beuschlein@med.uni-muenchen.de

**Stefan R. Bornstein** Department of Medicine, Carl Gustav Carus Medical School, University of Dresden, Fetscherstraße 74, 01307 Dresden, Germany, stefan.bornstein@uniklinikum-dresden.de

**James T. Broome** Vanderbilt Endocrine Surgery Center, Vanderbilt University, 597 Preston Research Building, 2220 Pierce Ave, Nashville, TN, USA, james.broome@vanderbilt.edu

**Maria V. Cicala** Division of Endocrinology, Department of Medical and Surgical Sciences, University of Padua, Via Ospedale 105, 35128 Padova, Italy, mariaverena.cicala@unipd.it

**Fulvia Daffara** Department of Clinical and Biological Sciences, Medicina Interna 1, AOU San Luigi Gonzaga, University of Turin, Regione Gonzole, 10, 10043 Orbassano, Italy, fulviaclaudia@libero.it

**Silvia De Francia** Department of Clinical and Biological Sciences, Farmacologia, AOU San Luigi Gonzaga, University of Turin, Regione Gonzole, 10, 10043 Orbassano, Italy, silvia.defrancia@unito.it

**Michael DeBaun** Division of Pediatric Hematology-Oncology, Department of Pediatrics, Washington University School of Medicine, 660 South Euclid Avenue, Box 8067, St. Louis, MO 63110-1093, USA, debaun\_m@kids.wustl.edu

**Luigi Dogliotti** Oncologia Medica, Azienda Ospedaliero Universitaria San Luigi, Regione Gonzole 10, 10043 Orbassano, Italy, luigi.dogliotti@unito.it

**Gerard M. Doherty** Department of Surgery, University of Michigan Health System, The University of Michigan, 2920 Taubman Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA, gerardd@umich.edu

**Tobias Else** Department of Internal Medicine – Division of Metabolism, Endocrinology & Diabetes, University of Michigan Health System, University of Michigan, Domino's Farms, Lobby C, Suite 1300, 24 Frank Lloyd Wright Drive, PO Box 451, Ann Arbor, MI 48106, USA, telse@med.umich.edu

**Martin Fassnacht** Department of Internal Medicine I, Endocrine and Diabetes Unit, University Hospital of Würzburg, Josef-Schneider-Str. 2, 97080 Würzburg, Germany, fassnacht\_m@medizin.uni-wuerzburg.de

**Anna Ferrero** Oncologia Medica, Azienda Ospedaliero Universitaria San Luigi, Regione Gonzole 10, 10043 Orbassano, Italy, anna.ferrero80@gmail.com

**Christian Fottner** Schwerpunkt Endokrinologie und Stoffwechselerkrankungen, I. Medizinische Klinik und Poliklinik, Universitätsmedizin, Johannes Gutenberg Universität Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany, fottner@endokrinologie.klinik.uni-mainz.de

**Paul G. Gauger** Department of Surgery, University of Michigan Health System, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA, pgauger@umich.edu

**Sébastien Gaujoux** Endocrinology, Metabolism and Cancer Department, Institut Cochin, INSERM U567, CNRS UMR8104, Paris, France; Department of Digestive and Endocrine Surgery, Assistance Publique Hôpitaux de Paris, Hôpital Cochin, Paris Descartes University, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France, sebastien.gaujoux@gmail.com

**Thomas J. Giordano** Departments of Pathology and Internal Medicine, University of Michigan Health System, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA, giordano@med.umich.edu

**Yvonne E. Groenen** Department of Internal Medicine, Máxima Medical Centre, Ds. Th. Fliednerstraat 1, PO Box 90052, 5600 PD Eindhoven, Leiden University Medical Centre, Leiden, The Netherlands, y.groenen@mmc.nl

**Stephanie Hahner** Department of Internal Medicine I, Endocrine and Diabetes Unit, University Hospital of Würzburg, Josef-Schneider-Str. 2, 97080 Würzburg, Germany, hahner\_s@medizin.uni-wuerzburg.de

**Gary D. Hammer** Endocrine Oncology Program – Comprehensive Cancer Center, Department of Internal Medicine – Division of Metabolism, Endocrinology & Diabetes, Department of Molecular & Integrative Physiology, Department of Cell & Developmental Biology, University of Michigan, 1528 BSRB, 109 Zina Pitcher Pl., Ann Arbor, MI 48109-2200, USA, ghammer@med.umich.edu

**Harm R. Haak** Department of Internal Medicine, Máxima Medical Centre, Ds. Th. Fliednerstraat 1, PO Box 90052, 5600 PD Eindhoven, Leiden University Medical Centre, Leiden, The Netherlands, h.haak@mmc.nl

**Joanne H. Heaton** Department of Internal Medicine, Division of Metabolism, Endocrinology & Diabetes, University of Michigan Medical School, 109 Zina Pitcher Place, 1680 BSRB, Ann Arbor, MI 48109, USA, heatonj@med.umich.edu

**Ilse G.C. Hermsen** Department of Internal Medicine, Máxima Medical Centre, Ds. Th. Fliednerstraat 1, PO Box 90052, 5600 PD Eindhoven, Leiden University Medical Centre, Leiden, The Netherlands, i.hermsen@mmc.nl

**Peter J. Hornsby** Department of Physiology and Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center, 15355 Lambda Drive, San Antonio, TX 78245, USA, hornsby@uthscsa.edu

**Jennifer Horst** Department of Pediatrics, Washington University School of Medicine, Washington University, One Brookings Drive, St. Louis, MO 63130, USA, horst\_j@kids.wustl.edu

**Hero K. Hussain** Department of Radiology, University of Michigan Health System, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48105, USA, hhussain@med.umich.edu

**Lawrence S. Kirschner** Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine and Department of Molecular Virology,

Immunology and Medical Genetics, The Ohio State University, Columbus Enarson Hall 154 W. 12th Avenue, Columbus, OH 43210, USA, lawrence.kirschner@osumc.edu

**Melvyn Korobkin** Department of Radiology, University of Michigan Health System, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48105, USA, korobkin@umich.edu

**Anita Kulharya** Department of Pediatrics, Pathology and Cytogenetics, Medical College of Georgia, 1120 15th Street, BG-1071, Augusta, GA 30912, USA, akulhary@mail.mcg.edu

**David Malkin** Division of Hematology/Oncology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, ON M5G 1X8, Canada, david.malkin@sickkids.ca

**Franco Mantero** Division of Endocrinology, Department of Medical and Surgical Sciences, University of Padua, Via Ospedale 105, 35128 Padova, Italy, franco.mantero@unipd.it

**Barbra S. Miller** Department of Surgery, University of Michigan Health System, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA, barbram@umich.edu

**Ina M. Niederle** Schwerpunkt Endokrinologie und Stoffwechselerkrankungen, I. Medizinische Klinik und Poliklinik, Universitätsmedizin, Johannes Gutenberg Universität Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany, niederle@1-med.klinik.uni-mainz.de

**Jeniël Parmar** Department of Physiology, Medical College of Georgia, 1120 15th Street Room CA3091, Augusta, GA 30912, USA, jparmar@students.mcg.edu

**Anna Patalano** Division of Endocrinology, Department of Medical and Surgical Sciences, University of Padua, Via Ospedale 105, 35128 Padova, Italy, anna.patalano@libero.it

**Paola Perotti** Oncologia Medica, Azienda Ospedaliero Universitaria San Luigi, Regione Gonzole, 10, 10043, Orbassano, Italy, oncotrial.sanluigi@gmail.com

**William Rainey** Department of Physiology, Medical College of Georgia, 1120 15th Street Room CA3094, Augusta, GA 30912, USA, wrainey@mail.mcg.edu

**Raul C. Ribeiro** Department of Oncology, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, USA, raul.ribeiro@stjude.org

**Carlos Rodriguez-Galindo** Department of Pediatric Oncology, Dana-Farber Cancer Institute and Children's Hospital, 44 Binney Street, Boston, MA 02115, USA, carlos\_rodriguez-galindo@dfci.harvard.edu

**Aaron Sabolch** Radiation Oncology, University of Michigan Medical School, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA, sabolch@umich.edu

**Wolfgang Saeger** Institute of Pathology of the Marienkrankenhaus, Alfredstraße 9, 22087 Hamburg, Germany, saeger.patho@marienkrankenhaus.org

**David E. Schteingart** Endocrine Oncology Program, Comprehensive Cancer Center, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA, dschtein@umich.edu

**Britt Skogseid** Department of Endocrine Oncology, Uppsala University Hospital, University of Uppsala, Akademiska sjukhuset/Uppsala, SE-751 85, Uppsala, Sweden, britt.skogseid@medsci.uu.se

**Paola Sperone** Oncologia Medica, Azienda Ospedaliero Universitaria San Luigi, Regione Gonzole 10, 10043 Orbassano, Italy, paola.sperone@email.it

**Massimo Terzolo** Department of Clinical and Biological Sciences, Medicina Interna 1, AOU San Luigi Gonzaga, University of Turin, Regione Gonzole, 10, 10043 Orbassano, Italy, terzolo@usa.net

**Norman W. Thompson** Surgery Emeritus Faculty, University of Michigan, Rm 2124C Taubman Health Care Center, 1500 East Medical Center Drive, Ann Arbor, MI 48105, USA, normant@umich.edu

**Frédérique Tissier** Endocrinology, Metabolism and Cancer Department, Institut Cochin, INSERM U567, CNRS UMR8104, Paris, France; Department of Pathology, Assistance Publique Hôpitaux de Paris, Hôpital Cochin, Paris Descartes University, Rue du Faubourg Saint-Jacques, 75014 Paris, France, frederique.tissier@cch-ap-hop-paris.fr

**Matthias M. Weber** Schwerpunkt Endokrinologie und Stoffwechselerkrankungen, I. Medizinische Klinik und Poliklinik, Universitätsmedizin, Johannes Gutenberg Universität Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany, mmweber@uni-mainz.de

**Holger S. Willenberg** Department of Endocrinology, Diabetes and Rheumatology, University Hospital Duesseldorf, Moorenstr. 5, D-40225 Duesseldorf, Germany, holger.willenberg@uni-duesseldorf.de

**Barbara Zaggia** Department of Clinical and Biological Sciences, Medicina Interna 1, AOU San Luigi Gonzaga, University of Turin Regione Gonzole, 10, 10043 Orbassano, Italy, barbara.zaggia@libero.it

**Gerard P. Zambetti** Department of Biochemistry, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, USA, gerard.zambetti@stjude.org