

Research and Perspectives in Alzheimer's Disease

T. Curran · Y. Christen (Eds.)

# Two Faces of Evil: Cancer and Neurodegeneration

FONDATION  
IPSEN  
POUR LA RECHERCHE  
THÉRAPEUTIQUE

 Springer

Research and Perspectives in Alzheimer's Disease

T. Curran · Y. Christen (Eds.)

# Two Faces of Evil: Cancer and Neurodegeneration

FONDATION  
IPSEN  
POUR LA RECHERCHE  
THERAPEUTIQUE

 Springer

# Two Faces of Evil: Cancer and Neurodegeneration

For further volumes:  
<http://www.springer.com/series/1175>

## RESEARCH AND PERSPECTIVES IN ALZHEIMER'S DISEASE

---

Thomas Curran • Yves Christen  
Editors

# Two Faces of Evil: Cancer and Neurodegeneration

 Springer

*Editors*

Thomas Curran, Ph.D., FRS  
The Children's Hospital of Philadelphia  
Department of Pathology  
and Laboratory Medicine  
Civic Center Boulevard 3501  
Philadelphia, PA 19104  
Pennsylvania  
USA  
currant@email.chop.edu

Yves Christen, Ph.D  
Fondation IPSEN pour la  
Recherche Therapeutique  
65 quai Georges Gorse  
92650 Boulogne-Billancourt  
Cedex  
France  
yves.christen@beaufour-ipsen.com

ISSN 0945-6066

ISBN 978-3-642-16601-3

e-ISBN 978-3-642-16602-0

DOI 10.1007/978-3-642-16602-0

Springer Heidelberg Dordrecht London New York

© Springer-Verlag Berlin Heidelberg 2011

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilm or in any other way, and storage in data banks. Duplication of this publication or parts thereof is permitted only under the provisions of the German Copyright Law of September 9, 1965, in its current version, and permission for use must always be obtained from Springer. Violations are liable to prosecution under the German Copyright Law.

The use of general descriptive names, registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

*Cover design:* WMXDesign GmbH, Heidelberg, Germany

Printed on acid-free paper

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

# Foreword

Homeostasis involves a delicate interplay between generative and degenerative processes to maintain a stable internal environment. In biological systems, equilibrium is established and controlled through a series of negative feedback mechanisms driven by a range of signal transduction processes. Failures in these complex communication pathways result in instability leading to disease. Cancer represents a state of imbalance caused by an excess of cell proliferation. In contrast, neurodegeneration is a consequence of excessive cell loss in the nervous system. Both of these disorders exact profound tolls on humanity and they have been subject to a great deal of research designed to ameliorate this suffering. For the most part, the topics have been viewed as distinct and rarely do opportunities arise for transdisciplinary discussions among experts in both fields. However, cancer and neurodegeneration represent *yin-yang* counterpoints in the regulation of cell growth, and it is reasonable to hypothesize that key regulatory events mediated by oncogenes and tumor suppressor genes in cancer may also affect neurodegenerative processes. This was the rationale for organizing the *Colloques Médecine et Recherche*, April 26, 2010 on the topic of *Two Faces of Evil: Cancer and Neurodegeneration*.

The presentations by the leaders of both fields were full of exciting unpublished data that reaffirmed the connection between the disciplines. Remarkably, genes that affect cell cycle progression and checkpoint control also play specific roles in postmitotic neurons that influence neurodegeneration. Many oncogenic signaling pathways have been expropriated to fulfill distinct functions in a range of biological situations. The complexity of the nervous system is such that evolution has usurped most molecular, biochemical and cellular regulatory mechanisms to support the formation, function and maintenance of neurons. The discussions at the meeting transcended traditional boundaries. Several new concepts were shared that will stimulate future research and perhaps contribute to better therapies for cancer patients as well as those struggling with the ravages of neurodegeneration.





## Acknowledgments

The editors would like to extend profound thanks to Jacqueline Mervaille and Sonia Le Cornec for their smooth organization of the meeting, despite *Eyjafjallajökull*, and to Astrid de Gérard for her efficient, gentle persistence in putting this book together.



# Contents

<b>Updating the Mammalian Cell Cycle: The Role of Interphase Cdk5 in Tissue Homeostasis and Cancer</b> .....	1
Mariano Barbacid	
<b>The Role of Cdk5 as a Cell Cycle Suppressor in Post-mitotic Neurons</b> .....	17
Karl Herrup	
<b>Actin-SRF Signaling in the Developing and Mature Murine Brain</b> .....	27
Alfred Nordheim and Bernd Knöll	
<b>The E3 Ubiquitin Ligase Ube3A Regulates Synaptic Function Through the Ubiquitination of Arc</b> .....	41
Eric C. Griffith, Paul L. Greer, and Michael E. Greenberg	
<b>Targeting Children’s Brain Tumors: Development of Hedgehog Pathway Inhibitors for Medulloblastoma</b> .....	57
Tom Curran	
<b>Primary Cilia as Switches in Brain Development and Cancer</b> .....	73
Young-Goo Han and Arturo Alvarez-Buylla	
<b>Nervous System Aging, Degeneration, and the p53 Family</b> .....	83
Freda D. Miller and David R. Kaplan	
<b>p53, a Molecular Bridge Between Alzheimer’s Disease Pathology and Cancers?</b> .....	95
Frédéric Checler, Julie Dunys, Raphaëlle Pardossi-Piquard, and Cristine Alves da Costa	

<b>RNA regulation in Neurodegeneration and Cancer</b> .....	103
Robert B. Darnell	
<b>Bridging Environment and DNA: Activity-Induced Epigenetic Modification in the Adult Brain</b> .....	113
Dengke K. Ma, Junjie U. Guo, Guo-li Ming, and Hongjun Song	
<b>Intrinsic Brain Signaling Pathways: Targets of Neuron Degeneration</b> .....	125
Harry T. Orr	
<b>The miRNA System: Bifurcation Points of Cancer and Neurodegeneration</b> .....	133
Kenneth S. Kosik, Pierre Neveu, and Sourav Banerjee	
<b>Molecular Mechanisms for the Initiation and Maintenance of Long-Term Memory Storage</b> .....	143
Sathyanarayanan Puthanveetil and Eric Kandel	
<b>Index</b> .....	161

# Contributors

**Arturo Alvarez-Buylla** Department of Neurological Surgery and The Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, University of California, San Francisco, CA 94143, USA, [abuylla@stemcell.ucsf.edu](mailto:abuylla@stemcell.ucsf.edu)

**Cristine Alves da Costa** IPMC and IN2M, UMR6097 CNRS/UNSA, Team Fondation pour la Recherche Médicale, Sophia-Antipolis, 06560, Valbonne, France

**Mariano Barbacid** Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández Almagro 3, 28029 Madrid, Spain, [barbacid@cniio.es](mailto:barbacid@cniio.es)

**Sourav Banerjee** Neuroscience Research Institute, Department Molecular Cellular Developmental Biology, University of California, Santa Barbara, CA 93106, USA

**Frédéric Checler** IPMC and IN2M, UMR6097 CNRS/UNSA, Team Fondation pour la Recherche Médicale, Sophia-Antipolis, 06560 Valbonne, France, [checler@ipmc.cnrs.fr](mailto:checler@ipmc.cnrs.fr)

**Tom Curran** Department of Pathology and Laboratory Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA, [currant@email.chop.edu](mailto:currant@email.chop.edu)

**Robert B. Darnell** Laboratory of Molecular Neuro-Oncology, The Rockefeller University, Box 226, 1230 York Avenue, New York, NY 10021, USA, [darnelr@rockefeller.edu](mailto:darnelr@rockefeller.edu)

**Julie Dunys** IPMC and IN2M, UMR6097 CNRS/UNSA, Team Fondation pour la Recherche Médicale, Sophia-Antipolis, 06560 Valbonne, France

**Michael E. Greenberg** Department of Neurobiology, Harvard Medical School, 220 Longwood Avenue, Boston, MA 02115, USA, [meg@hms.harvard.edu](mailto:meg@hms.harvard.edu)

**Paul L. Greer** Department of Neurobiology, Harvard Medical School, 220 Longwood Avenue, Boston, MA 02115, USA

**Eric C. Griffith** Department of Neurobiology, Harvard Medical School, 220 Longwood Avenue, Boston, MA 02115, USA

**Junjie U. Guo** Institute for Cell Engineering, Department of Neuroscience, Johns Hopkins University School of Medicine, 733 N. Broadway, BRB 759, Baltimore, MD 21205, USA

**Young-Goo Han** Department of Neurological Surgery and The Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, University of California, San Francisco, CA 94143, USA

**Karl Herrup** Department of Cell Biology and Neuroscience, Rutgers University, 604 Allison Road, Piscataway, NJ 08854, USA, herrup@biology.rutgers.edu

**Eric Kandel** Department of Neuroscience, Howard Hughes Medical Institute, Kavli Institute for Brain Sciences, Columbia University, New York, NY 10032, USA; The Scripps Research Institute, Scripps Florida, 130 Scripps Way, Jupiter, FL 33458, USA, erk5@columbia.edu

**David R. Kaplan** Department of Molecular Genetics, Cell Biology Programs, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada M5G 1L7

**Bernd Knöll** Neuronal Gene Expression Laboratory, Department of Molecular Biology, Interfaculty Institute for Cell Biology, University of Tübingen, Auf der Morgenstelle 15, 72076 Tübingen, Germany

**Kenneth S. Kosik** Neuroscience Research Institute, Department Molecular Cellular Developmental Biology, University of California, Santa Barbara, CA 93106, USA, kosik@lifesci.ucsb.edu

**Dengke K. Ma** Institute for Cell Engineering, Department of Neuroscience, Johns Hopkins University School of Medicine, 733 N. Broadway, BRB 759, Baltimore, MD 21205, USA; Department of Biology, Massachusetts Institute of Technology, 77 Massachusetts Ave., Room 68-441, Cambridge, MA 02139, USA

**Freda D. Miller** Developmental and Stem Cell Biology and Departments of Molecular Genetics and Physiology, University of Toronto, Toronto, ON Canada M5G 1L7

**Guo-li Ming** Institute for Cell Engineering, Department of Neuroscience, Department of Neurology, Johns Hopkins University School of Medicine, 733 N. Broadway, BRB 759, Baltimore, MD 21205, USA

**Pierre Neveu** Neuroscience Research Institute, Department Molecular Cellular Developmental Biology, University of California, Santa Barbara, CA 93106, USA

**Alfred Nordheim** Vertebrate Gene Expression and Organ Function, Department of Molecular Biology, Interfaculty Institute for Cell Biology, University of Tübingen, Auf der Morgenstelle 15, 72076 Tübingen, Germany, [alfred.nordheim@uni-tuebingen.de](mailto:alfred.nordheim@uni-tuebingen.de)

**Harry T. Orr** Institute of Translational Neuroscience, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55455, USA, [orrrx002@umn.edu](mailto:orrrx002@umn.edu)

**Raphaëlle Pardossi-Piquard** IPMC and IN2M, UMR6097 CNRS/UNSA, Team Fondation pour la Recherche Médicale, Sophia-Antipolis, 06560, Valbonne, France

**Sathyanarayanan Puthanveetil** Department of Neuroscience, Howard Hughes Medical Institute, Chevy Chase, MD USA; Department of Neuroscience, The Scripps Research Institute, Scripps Florida, 130 Scripps Way, Jupiter, FL 33458, USA, [sp2068@columbia.edu](mailto:sp2068@columbia.edu)

**Hongjun Song** Institute for Cell Engineering, Department of Neuroscience, Department of Neurology, Johns Hopkins University School of Medicine, 733 N. Broadway, BRB 759, Baltimore, MD 21205, USA, [shongju1@jhmi.edu](mailto:shongju1@jhmi.edu)