

Alzheimer's  
Disease

Cellular and Molecular  
Aspects of Amyloid  $\beta$   
Subcellular Biochemistry  
Volume 38

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# Alzheimer's Disease

## Cellular and Molecular Aspects of Amyloid $\beta$

### Subcellular Biochemistry Volume 38

Edited by

**J. Robin Harris**

*Institute of Zoology  
University of Mainz  
Mainz, Germany*

and

**Falk Fahrenholz**

*Institute of Biochemistry  
University of Mainz  
Mainz, Germany*

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## Contributors

**Christian Behl**, Institute for Physiological Chemistry &  
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**Peter Borghgraef**, Experimental Genetics Group, Department of Human  
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(IQUIFIB), CONICET, Cátedra de Química Biológica Patológica,  
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Bioquímica, Universidad de Buenos Aires, Junin 956, C113AAD,  
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**Ashley I. Bush**, Harvard Medical School and Massachusetts General  
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**Math P. Cuajungco**, Harvard Medical School and Massachusetts Eye and Ear Infirmary, Boston MA 02114, USA

**Ilse Dewachter**, Experimental Genetics Group, Department of Human Genetics, K.U.Leuven, B-3000 Leuven, Belgium

**Lisbell Estrada**, Protein Misfolding Disorders Laboratory, Department of Neurology, University of Texas Medical Branch, Galveston, TX, USA

**Gunter P. Eckert**, Department of Pharmacology, ZAFES, Biocenter University of Frankfurt, Germany

**Christopher Exley**, Birchall Centre for Inorganic Chemistry and Materials Science, Keele University, Staffordshire, ST5 5BG, UK

**Falk Fahrenholz**, Institute of Biochemistry, Johannes Gutenberg-University, Becherweg 30, Mainz D-55099, Germany

**Blas Frangione**, Department of Pathology, New York University School of Medicine, New York, NY 10016, USA

**Christopher, J. Frederickson**, NeuroBioTex, Inc. and University of Texas Medical Branch, Galveston TX 77550 USA

**Jorge Ghiso**, Department of Pathology, Room-TH432, New York University School of Medicine, 550 First Avenue, New York, NY 10016, USA

**Charles C. Glabe**, University of California, Irvine, Irvine, CA 92697, USA

**J. Robin Harris**, Institute of Zoology, University of Mainz, D-55099 Mainz, Germany

**Tobias Hartmann**, Center for Molecular Biology Heidelberg (ZMBH),  
University of Heidelberg, Im Neuenheimer Feld 282, D-69120  
Heidelberg, Germany

**Nibaldo C. Inestrosa**, FONDA-Biomedical Center, P. Catholic  
University of Chile, Santiago 114-D, Chile

**Vernon M. Ingram**, Department of Biology, M.I.T, 31 Ames Street,  
Cambridge, MA 02139, USA

**Hideyo Inouye**, Department of Biology, Higgins Hall 510,  
Boston College, 140 Commonwealth Avenue, Chestnut Hill,  
MA 02467-3811, USA

**Daniel A. Kirschner**, Department of Biology, Boston College, Chestnut  
Hill, MA 02467-3811, USA

**Elzbieta Kojro**, Institute of Biochemistry, Johannes Gutenberg-  
University, Becherweg 30, Mainz D-55099, Germany

**María Celeste Leal**, Instituto de Química y Físicoquímica Biológicas  
(IQUIFIB), CONICET, Cátedra de Química Biológica Patológica,  
Departamento de Química Biológica, Facultad de Farmacia y  
Bioquímica, Universidad de Buenos Aires, Junin 956, C113AAD,  
Buenos Aires, Argentina

**Nathaniel G. N. Milton**, Department of Clinical Neurosciences, Royal  
Free & University College Medical School, University College  
London, Rowland Hill Street, London NW3 2PF, UK

**Laura Morelli**, Instituto de Química y Físicoquímica Biológicas  
(IQUIFIB), CONICET, Cátedra de Química Biológica Patológica,  
Departamento de Química Biológica, Facultad de Farmacia y  
Bioquímica, Universidad de Buenos Aires, Junin 956, C113AAD,  
Buenos Aires, Argentina

**Werner E. Müller**, Department of Pharmacology, ZAFES, Biocenter  
University of Frankfurt, Frankfurt, Germany

**Francisco José Muñoz**, Unitat de Senyalització Cel lular, Departament  
de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra  
(UPF), Calle Dr Aiguader 80, 08003-Barcelona, Spain



**Agueda Rostagno**, Department of Pathology, New York University  
School of Medicine, New York, NY 10016, USA

**Juan Paulo Sagal**, FONDA-Biomedical Center, P. Catholic University  
of Chile, Santiago, Chile

**Montserrat Solé**, Unitat de Senyalització Cel·lular, Departament de  
Ciències Experimentals i de la Salut, Universitat Pompeu Fabra  
(UPF), 08003-Barcelona, Spain

**Claudio Soto**, Protein Misfolding Disorders Laboratory, Department of  
Neurology, University of Texas Medical Branch, Galveston, TX, USA

**Tom van Dooren**, Experimental Genetics Group, Department of Human  
Genetics, K.U.Leuven, B-3000 Leuven, Belgium

**Fred van Leuven**, Experimental Genetics Group, Department of Human  
Genetics, K.U.Leuven, Campus Gasthuisberg, O & N6, B-3000  
Leuven, Belgium

**Robert Vassar**, Department of Cell and Molecular Biology, The  
Feinberg School of Medicine, Northwestern University,  
303 E. Chicago Avenue, Chicago, IL 60611, USA

**W.G. Wood**, Department of Pharmacology, University of Minnesota  
School of Medicine, Minneapolis, USA

**Katsuhiko Yanagisawa**, National Institute for Longevity Sciences,  
Gengo 36-3, Morioka, 474-8522 Obu, Japan

## Preface

To understand Alzheimer's disease (AD) is one of the major thrusts of present-day clinical research, strongly supported by more fundamental cellular, biochemical, immunological and structural studies. It is these latter that receive attention within this book. This compilation of 20 chapters indicates the diversity of work currently in progress and summarizes the current state of knowledge.

Experienced authors who are scientifically active in their fields of study have been selected as contributors to this book, in an attempt to present a reasonably complete survey of the field. Inevitably, some exciting topics for one reason or another have not been included, for which we can only apologize.

Standardization of terminology is often a problem in science, not least in the Alzheimer field; editorial effort has been made to achieve standardization between the Chapters, but some minor yet acceptable personal / author variation is still present, *i.e.*  $\beta$ -amyloid/amyloid- $\beta$ ; A $\beta$ 42/A $\beta$ 1-42/A $\beta$ <sub>1-42</sub>!

The book commences with a broad survey of the contribution that the range of available microscopical techniques has made to the study of Alzheimer's amyloid plaques and amyloid fibrillogenesis. This chapter also serves as an Introduction to the book, since several of the topics introduced here are expanded upon in later chapters. Also, it is significant to the presence of this chapter that the initial discovery of brain plaques, by Alois Alzheimer, utilized light microscopy, a technique that continues to be extremely valuable in present-day AD research. Then follow 19 further chapters dealing with interesting areas of research that have a bearing upon

Alzheimer's disease. The authors present their own data within the context of a review of related work from others in their field of study.

Transgenic mouse models for AD are increasingly important and widely used, as is the understanding of the enzymology and biochemistry of amyloid  $\beta$  production from the amyloid precursor protein (APP) by the  $\beta$ - and  $\gamma$ -secretases, and the non-amyloidogenic APP cleavage products due to  $\alpha$ -secretases. Similarly, discussion of the enzymes responsible for the natural degradation of amyloid- $\beta$  is included. Oxidative stress in AD and the possible protective role of vitamin E have emerged as highly significant topics. Likewise, the role of the metals, aluminium copper and zinc in AD is thoroughly addressed, along with the possible value of metal chelation. Current concepts as to the fundamental importance of amyloid- $\beta$  oligomers *versus* A $\beta$  fibrillar deposits (diffuse and senile plaques) in the pathogenesis of AD is presented, along with the likely role of tissue and cellular cholesterol in the promotion of A $\beta$  fibrillogenesis, and Congo red binding to A $\beta$  fibrils.

Several naturally occurring human proteins have the ability to bind to A $\beta$  and are found in AD diffuse and senile plaques. Apolipoprotein E4, clusterin (ApoJ) and acetylcholinesterase are considered in depth. The direct effects of A $\beta$  on neuronal membranes, in terms of neuronal membrane fluidity changes and calcium ion transport are dealt with, then the role of amyloid inhibitors and  $\beta$ -sheet breaking drugs is included. The likely important beneficial effects of the cholesterol-lowering drugs, the statins, in lowering brain A $\beta$  and consequently the therapeutic prevention of AD by reducing A $\beta$  deposition in plaques is discussed thoroughly. Finally, an exciting new concept is advanced, namely the possible significance of phosphorylated A $\beta$  in Alzheimer's disease. From *in vitro* experiments A $\beta$  phosphorylation appears to increase the proportion of A $\beta$  oligomeric forms, an observation which correlates with the higher cytotoxicity of this species, compared to non-phosphorylated A $\beta$ .

The editors hope that this book will be of interest and value to both medical and scientific research communities working on AD, and to others with a more general interest in the understanding of this devastating neurodegenerative disorder of the elderly.

*Prof. J. Robin Harris*  
*Prof. Falk Fahrenholz*

University of Mainz  
August, 2004

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