Retinal Pharmacotherapeutics

Editors
Quan Dong Nguyen
Eduardo B. Rodrigues
Michel Eid Farah
William F. Mieler
Diana V. Do

Contents

Foreword: Miller, J.W.

Basic Sciences in the Retina
• Evolutionary Knowledge in Pharmacologic Treatments of Age-Related Macular Degeneration: Soubbrane Daguett, G.; Risard-Gasiorowski, S.; Massamba, N.
• Retinal Anatomy and Pathology: Gupta, M.P.; Herzlich, A.A.; Sauer, T.; Chan, C-C.
• Retinal Biochemistry, Physiology and Cell Biology: Smith, R.L.; Sivaprassad, S.; Chong, V.
• Ocular Angiogenesis: Vascular Endothelial Growth Factor and Other Factors: Rubio, R.G.; Adams, A.P.
• Ocular Immunity and Inflammation: Albini, T.A.; Davis, J.L.
• Complement Activation and Inhibition in Retinal Diseases: Kleinman, M.E.; Ambati, J.
• Genetics in Retinal Diseases: Riaz, M.; Baird, FN.

Animal Models and Routes for Retinal Drug Delivery
• Routes for Drug Delivery to the Retina: Topical, Transscleral, Suprachoroidal and Intravitreal Gas Phase Delivery: Yamada, N.; Olsen, T.W.
• Microspheres and Nanotechnology for Drug Delivery: Johannesson, G.; Stefansson, E.; Loftsson, T.
• Thermo-Responsive Hydrogels for Ocular Drug Delivery: Kang-Mieler, J.J.; Mieler, W.F.

Retinal Diseases Amenable to Pharmacotherapy
• Nonneovascular Age-Related Macular Degeneration: Michels, S.; Garhofer, G.
• Neovascular Age-Related Macular Degeneration: Shao, J.; Choudhary, M.M.; Schachat, A.P.
• Diabetic Retinopathy and Diabetic Macular Edema: Cohen, S.R.; Gardner, T.N.
• Retinal Vein Occlusion: Sawada, O.; Ohji, S.
• Retinal Detachment and Proliferative Retinopathy: Kwok, O.W.; Song, J.H.; Roh, M.I.
• Posterior Uveitis: Uy, H.S.; Yu-Keh, E.; Chan, P.S.
• Choroidal Neovascularization Secondary to Myopia, Infection, and Inflammation: Weber, M.L.; Heier, J.S.
• Ocular Infection: Endophthalmitis: Schwartz, S.G.; Flynn, H.W.Jr; Das, T.; Mieler, W.F.
• Treatment for Macular Intergelactasia Type 2: Charbel Issa, P.; Kupritz, E.H.; Heeren, T.F.C.; Holz, F.G.
• Neovascular Glaucoma: Havens, S.J.; Gulati, V.
• Retinal Hereditary and Degenerative/Dystrophic Diseases: Battaglia Parodi, M.; La Spina, C.; Corradetti, G.; Berichici, L.; Petruzzii, G.; Bandello, F.
• Routes for Drug Delivery to the Eye and Retina: Topical, Transscleral, Suprachoroidal and Intravitreal Gas Phase Delivery: Yamada, N.; Olsen, T.W.

Drugs and Mechanisms in Retinal Diseases
• Nonsteroidal Anti-Inflammatory Drugs in the Treatment of Retinal Diseases: Rodrigues, E.B.; Farah, M.E.; Mantovani Bottos, J., Bomm Aggio, F.
• Corticosteroids: Triamcinolone, Dexamethasone and Fluocinolone: Cáceres-del-Carpio, J.; Donato Costa, R.; Haider, A.; Narayanan, R.; Kuppermann, B.D.
• Therapeutic Monoclonal Antibodies and Fragments: Bevacizumab: Klein, A.; Loenvenstein, A.
• Therapeutic Monoclonal Antibodies and Fragments: Ranibizumab: Smith, A.G.; Kaiser, P.K.
• Biologic Therapies. Anti-Tumor Necrosis Factor α, Anti-Interleukins, Rituximab and Others: Bhatt, N.; Tucker, R.; Sen, H.N.; Nussenblatt, R.B.
• Immunomodulatory Therapy in Uveitis: Tomkincs-Netzer, O.; Talat, L.; Isometova, F.; Samy, A.; Lightman, S.
• Sirodlim for Retinal and Uveitic Diseases: Agarwal, A.; Rajagopalan, N.; Hassan, M.; Sadig, M.A.; Soliman, M.K.; Afridi, R.; Sepah, Y.J.; Nguyen, Q.D.
• The Protein Kinase C Inhibitor: Ruboxistaurin: Deissler, H.L.; Lang, G.E.
• Enukastat and Lampalizumab: Potential Therapeutic Options for Geographic Atrophy: Jack, L.S.; Sadig, M.A.; Do, D.V.; Nguyen, Q.D.
• Ocular Gene Therapy: Campbell, J.P.; McFarland, T.J.; Stout, J.T.
• Neuprotective and Retinal Diseases: Paulus, Y.M.; Campbell, J.P.
• Photostabilizers and Photodynamic Therapy: Verteportin: Battaglia Parodi, M.; La Spina, C.; Berichici, L.; Petruzzi, G.; Bandello, F.
• Chemotherapy for Malignant Intraocular Tumors: Shah, C.P.; Shields, C.L.; Shields, J.A.
• Antibiotics: Hariprasad, S.M.; Mieler, W.F.

Pharmacotherapeutics and Surgery
• Enzymatic Vitrectomy and Pharmacologic Vitrordynamics: Shah, A.R.; Trese, M.T.
• The Use of Vital Dyes during Vitreoretinal Surgery – Chromovitrectomy: Farah, M.E.; Maia, M.; Penha, F.M.; Rodrigues, E.B.

The Last Words
• Regulatory and Economic Considerations of Retinal Drugs: Shah, A.R.; Williams, G.A.
• Value-Based Medicine and Pharmacoeconomics: Brown, G.C.; Brown, M.M.

KARGER – Medical and Scientific Publishers
CH-4009 Basel, Switzerland
orders@karger.com, Fax +41 61 306 12 34
www.karger.com

From basic research to therapy
Ophthalmic Research

Journal for Translational and Clinical Research


Editorial Board

José Cunha-Vaz, Coimbra

Associate Editors

Age-Related Macular Degeneration
José-Alain Sahel, Paris

Anterior Segment
Marie-José Tassignon, Antwerp

Epidemiology
Cécile Delcourt, Bordeaux

Genetics
Bart Leroy, Ghent

Glaucoma
M. Francesca Cordeiro, London

Health Technology
Francisco Batel Marques, Coimbra

Imaging
Tunde Peto, London

Immunology and Infectious Diseases
Dorairajan Balasubramanian, Hyderabad

Inflammation
José Manuel Benitez del Castillo, Madrid

Medical Retina
Sobha Sivaprasad, London

Molecular and Cell Biology
Francisco Ambrósio, Coimbra

Neuro-Ophthalmology and Visual Function
Birgit Lorenz, Giessen

Oncology and Pathology
Edoardo Midena, Padua

Surgery
Yuichiro Ogura, Nagoya

Educational – ESASO
Bruno Falcomatà, Reggio Calabria
Maurizio Battaglia Parodi, Milan

EVIRC.net
Cecília Martinho, Coimbra

Editorial Board

J. Alio, Alicante
J. Ambati, Lexington, Ky.
A.J. Augustin, Karlsruhe
F. Bandello, Milan
A. Bringmann, Leipzig
T. Das, Hyderabad
D. Goldblum, Basel
G. Guarnaccia, Lugano
J. Hua, Boston, Mass.
T. Ishibashi, Fukuoka
J. Jonas, Mannheim
D. Lam, Guangzhou
C. Lobo, Coimbra

N. Osborne, Oxford
Y. Ozawa, Tokyo
M.J. Quadro, Coimbra
M. Rehak, Berlin
G. Richard, Hamburg
R.O. Schlingemann, Amsterdam
L. Schmetterer, Vienna
R. Silva, Coimbra
J. Smith, Adelaide, S.A.
P. Söderberg, Uppsala
J. Trevithick, London, Ont.
K. Tsubota, Tokyo
A. Wegener, Bonn
Guidelines for Authors

Submission

Only original papers written in English are considered and should be submitted using the online submission website:

www.karger.com/ore

or as an e-mail attachment (the preferred word-processing package is MS-Word) to the Editorial Office:

Editorial Office Ophthalmic Research
S. Karger AG
P.O. Box
CH-4009 Basel (Switzerland)
Tel +41 61 306 1358
Fax +41 61 306 1434
E-Mail ore@karger.com

Types of Papers

(1) The main body of papers to be published will be 'Original Papers' on experimental research. (2) 'Review Papers' of up to 30 manuscript pages will be published from invited authors and by direct submission. In both cases the manuscripts will be subject to peer reviewing. Review papers will be published free of charge. (3) 'Mini Reviews' of up to 10 manuscript pages (double-spaced, including an abstract of max. 200 words and references) should contain an easy-to-read literature overview on a specific topic. Papers are either invited or may be submitted for consideration. Please submit your mini review online. (4) 'Short Communications' of up to 3–4 pages dealing with new original concepts or technical approaches will be published at short notice. (5) Ophthalmic Research has a tradition in publishing Supplements' which can be published under the responsibility of guest editors. Requests for such supplements should be addressed to the Editor-in-Chief.

Conditions

All manuscripts are subject to editorial review. Manuscripts are received with the explicit understanding that they are not under simultaneous consideration by any other publication except in abstract form. Submission of an article for publication implies transfer of the copyright from the author to the publisher upon acceptance. Accepted papers become the permanent property of Ophthalmic Research and may not be reproduced by any means, in whole or in part, without the written consent of the publisher. It is the author’s responsibility to obtain permission to reproduce illustrations, tables, etc. from other publications. Research involving live human and animal subjects must have been approved by the author’s institutional review board. Ophthalmic Research requires that in the Methods section of their manuscript the authors state that they adhered to the tenets of the Declaration of Helsinki or the NIH statement for the use of Animals in Research.

Conflicts of Interest

Authors are required to disclose any sponsorship or funding arrangements relating to their research and all authors should disclose any possible conflicts of interest. Conflict of interest statements will be published at the end of the article.

Arrangement

Title page: The first page of each paper should indicate the title, the authors’ names, the institute where the work was conducted, and a short title for use as running head. Full address: The exact postal address of the corresponding author complete with postal code must be given at the bottom of the title page. Please also supply phone and fax numbers, as well as e-mail address.

Key words: Please supply 3–10 key words in English that reflect the content of the paper.

Abstract: Each paper needs an abstract of up to 200 words.

Footnotes: Avoid footnotes.

Tables and illustrations: Tables and illustrations (both numbered in Arabic numerals) should be sent in separate files. Tables require a heading and figures a legend, also in a separate file. Due to technical reasons, figures with a screen background should not be submitted. When possible, group several illustrations in one block for reproduction (max. size 180 × 223 mm). Black and white half-tone and color illustrations must have a final resolution of 300 dpi after scaling, line drawings one of 800–1200 dpi.

Color Illustrations

Online edition: Color illustrations are reproduced free of charge. In the print version, the illustrations are reproduced in black and white. Please avoid referring to the colors in the text and figure legends.

Print edition: Up to 6 color illustrations per page can be integrated within the text at CHF 960.00 per page.

References: In the text identify references by Arabic numerals [in square brackets]. Material submitted for publication but not yet accepted should be noted as [unpublished data] and not be included in the reference list. The list of references should include only those publications which are cited in the text. Do not alphabetize; number references in the order in which they are first mentioned in the text. The surnames of the authors followed by initials should be given. There should be no punctuation other than a comma to separate the authors. Preferably, please cite all authors. Abbreviate journal names according to the Index Medicus system. Also see International Committee of Medical Journal Editors: Uniform requirements for manuscripts submitted to biomedical journals. (www.icmje.org).

Examples


(b) Papers published only with DOI numbers: Theorardes TC, Boucher W, Spear K: Serum interleukin-6 reflects disease severity and osteoporosis in mastocytosis patients. Int Arch Allergy Immunol DOI: 10.1159/000063858.


Reference Management Software: Use of EndNote is recommended for easy management and formatting of citations and reference lists.

Digital Object Identifier (DOI)

S. Karger Publishing supports DOIs as unique identifiers for articles. A DOI number will be printed on the title page of each article. DOIs can be used in the future for identifying and citing articles published online without volume or issue information. More information can be found at www.doi.org.

Supplementary Material

Supplementary material is restricted to additional data that are not necessary for the scientific integrity and conclusions of the paper. Please note that all supplementary files will undergo editorial review and should be submitted together with the original manuscript. The Editors reserve the right to limit the scope and length of the supplementary material. Supplementary material must meet production quality standards for Web publication without the need for any modification or editing. In general, supplementary files should not exceed 10 MB in size. All figures and tables should have titles and legends and all files should be supplied separately and named clearly. Acceptable files and formats are: Word or PDF files, Excel spreadsheets (only if the data cannot be converted properly to a PDF file), and video files (.mov, .avi, .mpeg).

Author's Choice™

Karger's Author's Choice™ service broadens the reach of your article and gives all users worldwide free and full access for reading, downloading and printing at www.Karger.com. The option is available for a one-time fee of CHF 3,000.00, which is a permissible cost in grant allocation. More information can be found at www.karger.com/authors_choice.

NIH-Funded Research

The U.S. National Institutes of Health (NIH) mandates under the NIH Public Access Policy that final, peer-reviewed manuscripts appear in its digital database within 12 months of the official publication date. As a service to authors, Karger submits the final version of your article on your behalf to PubMed Central. For those selecting our premium Author’s Choice™ service, we will send your article immediately upon publishing, accelerating the accessibility of your work without the usual embargo. More details on NIH’s Public Access Policy are available at http://publicaccess.nih.gov/policy.htm

Self-Archiving

Karger permits authors to archive their pre-prints (i.e. pre-refereeing) or post-prints (i.e. final draft post-refereeing) on their personal or institution’s servers, provided the following conditions are met: Articles may not be used for commercial purposes, must be linked to the publisher’s version, and must acknowledge the publisher’s copyright. Authors selecting Karger’s Author’s Choice™ feature, however, are also permitted to archive the final, published version of their article, which includes copy-editing and design improvements as well as citation links.

Page Charges

There are no page charges for papers of 3 or fewer printed pages (including tables, illustrations and references). Each additional complete or partial page is charged to the author at CHF 325.00. The allotted size of a paper is equal to approx. 8 double-spaced manuscript pages (including abstract, tables, illustrations and references).

Proofs

Unless indicated otherwise, proofs are sent to the corresponding author and should be returned with the least possible delay. Alterations other than the correction of printer’s errors are charged to the author.

Reprints

Order forms and a price list are sent with the proofs. Orders submitted after the issue is printed are subject to considerably higher prices.
World Ophthalmology Congress®
of the International Council of Ophthalmology

Host: Sociedad Mexicana de Oftalmología
Co-Host: Pan-American Association of Ophthalmology

• XXXV International Congress of Ophthalmology
• XXXIII Congreso Mexicano de Oftalmología
• XXXII Pan-American Congress of Ophthalmology

Guadalajara | Feb 5-9

www.woc2016.org
Contents

See the journal website for contents
Nordic Congress of Ophthalmology
Aarhus, Denmark

Save the date
8-12 June 2016

Stay tuned at
www.nok2016.com

New!
For over 40 years the Karger Gazette has been distributed to a growing audience worldwide. Published in newspaper format, it highlights advances in biomedicine and clinical practice, introduces personalities, portrays research institutes and chronicles milestones in the history of Karger Publishers in a lively and readable style.

The new anniversary issue celebrates Karger’s 125 years as a medical publisher. It explores the STM publishing business in the digital age, offers short portraits of Karger’s journal and book series editors, and includes interviews with three renowned scientists who talk about their careers and how they define progress.

Register for a free print subscription or read it online at
www.karger.com/gazette
Medical Statistics has never been easier!

David E. Matthews
Vernon T. Farewell

Using and Understanding Medical Statistics
5th, revised and extended edition

The fifth revised edition of this highly successful book presents the most extensive enhancement since Using and Understanding Medical Statistics was first published 30 years ago. Without question, the single greatest change has been the inclusion of source code, together with selected output, for the award-winning, open-source, statistical package known as R. This innovation has enabled the authors to de-emphasize formulae and calculations, and let software do all of the 'heavy lifting'.

This edition also introduces readers to several graphical statistical tools, such as Q-Q plots to check normality, residual plots for multiple regression models, funnel plots to detect publication bias in a meta-analysis, and Bland-Altman plots for assessing agreement in clinical measurements. New examples that better serve the expository goals have been added to a half-dozen chapters. In addition, there are new sections describing exact confidence bands for the Kaplan-Meier estimator, as well as negative binomial and zero-inflated Poisson regression models for overdispersed count data.

The end result is not only an excellent introduction to medical statistics, but also an invaluable reference for every discerning reader of medical research literature.

Contents
Preface to the Fifth Edition
Prefaces to the Previous Editions
• Basic Concepts
• Tests of Significance
• Fisher’s Test for $2 \times 2$ Contingency Tables
• Approximate Significance Tests for Contingency Tables
• Some Warnings concerning $2 \times 2$ Tables
• Kaplan-Meier or 'Actuarial' Survival Curves
• The Log-Rank or Mantel-Haenszel Test for Comparing Survival Curves
• An Introduction to the Normal Distribution
• Analyzing Normally Distributed Data
• Linear Regression Models for Medical Data
• Binary Logistic Regression
• Regression Models for Count Data
• Proportional Hazards Regression
• The Analysis of Longitudinal Data
• Analysis of Variance
• Data Analysis
• The Question of Sample Size
• The Design of Clinical Trials
• Further Comments regarding Clinical Trials
• Meta-Analysis
• Epidemiological Applications
• Diagnostic Tests
• Agreement and Reliability

References
Subject Index

Karger – Medical and Scientific Publishers
CH-4009 Basel, Switzerland
orders@karger.com, f: +41 61 306 12 34
www.karger.com
This peer-reviewed online-only journal publishes original case reports covering the entire spectrum of ophthalmology, including prevention, diagnosis, treatment, toxicities of therapy, supportive care, quality-of-life, and survivorship issues. The submission of negative results is strongly encouraged. The journal will also accept case reports dealing with the use of novel technologies, both in the arena of diagnosis and treatment. Supplementary material is welcomed. The intent of the journal is to provide clinicians and researchers with a tool to disseminate their personal experiences to a wider public as well as to review interesting cases encountered by colleagues all over the world. Universally used terms can be searched across the entire growing collection of case reports, further facilitating the retrieval of specific information. Following the open access principle, the entire contents can be retrieved at no charge, guaranteeing easy access to this valuable source of anecdotal information at all times.
204 Glia-Mediated Retinal Neuroinflammation as a Biomarker in Alzheimer’s Disease
Madeira, M.H.; Ambrósio, A.F.; Santiago, A.R. (Coimbra)

169 Pharmacogenetic Effect of Complement Factor H Gene Polymorphism in Response to the Initial Intravitreal Injection of Bevacizumab for Wet Age-Related Macular Degeneration
Medina, F.M.C. (Campinas/Rio de Janeiro); Alves Lopes da Motta, A.; Takahashi, W.Y.; Carricondo, P.C. (São Paulo); dos Santos Motta, M.M. (Rio de Janeiro); Melo, M.B.; Vasconcellos, J.P.C. (Campinas)

181 Colour Vision in Stargardt Disease
Vandenbroucke, T. (Ghent); Buyl, R. (Brussels); De Zaeytijd, J.; Bauwens, M.; Uvijls, A.; De Baere, E. (Ghent); Leroy, B.P. (Ghent/Philadelphia, Pa.)

195 Complement Stimulates Retinal Pigment Epithelial Cells to Undergo Pro-Inflammatory Changes
Lueck, K. (Muenster/London); Busch, M. (Muenster); Moss, S.E.; Greenwood, J. (London); Kasper, M.; Lommatzsch, A.; Pauleikhoff, D.; Wasmuth, S. (Muenster)

212 Nitric Oxide Increases the Expression of Aquaporin-4 Protein in Rat Optic Nerve Astrocytes through the Cyclic Guanosine Monophosphate/Protein Kinase G Pathway

175 DNA Aptamer Raised against Advanced Glycation End Products Prevents Abnormalities in Electroretinograms of Experimental Diabetic Retinopathy
Maeda, S.; Matsui, T.; Ojima, A. (Kurume); Suematsu, M. (Kurume/Beppu); Kaseda, K. (Beppu); Higashimoto, Y.; Yamakawa, R.; Yamagishi, S. (Kurume)

222 Acknowledgement to Referees

Contents Vol. 54, 2015