UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOPEWELL PHARMA VENTURES, INC.,
Petitioner,

v.

MERCK SERONO SA,
Patent Owner.

Case IPR2023-00480
Patent 7,713,947

Case IPR2023-00481
Patent 8,377,903

DECLARATION OF NICHOLAS BODOR, Ph.D., D.Sc., d.h.c. (multi), HoF (multi)

MERCK 2054
HOPEWELL v MERCK
IPR2023-00481

I, Nicholas Bodor, declare as follows:

I. INTRODUCTION

1. I am over eighteen years of age, and I am competent to testify as to the matters set forth herein if I am called upon to do so.

2. I have prepared this Declaration for consideration by the Patent Trial and Appeal Board in the following *Inter Partes* Review proceedings: IPR2023-00480 ("'480 IPR") and IPR2023-00481 ("'481 IPR"). I understand that the subject of the '480 IPR is U.S. Patent No. 7,713,947 ("the '947 patent") and the subject of the '481 IPR is U.S. Patent No. 8,377,903 ("the '903 patent").

3. I am a named inventor of the PCT Application, WO 2004/087101, "Oral Formulations of Cladribine" ("BODOR PCT"), which I understand has been numbered Ex. 1022 in the '480 IPR and in the '481 IPR. I have been asked to provide a declaration as an inventor of the BODOR PCT.

4. I am being compensated for my time in preparing this declaration at my usual consulting rate of $1250.00/hour. My compensation is in no way contingent on the substance of my testimony or the outcome of this or any other proceeding. I have no interest in this proceeding.

5. I have personal knowledge of the facts stated herein and can testify competently to those facts.

II. BACKGROUND

6. I am currently a Graduate Research Professor Emeritus in the College of Pharmacy, University of Florida. My professional qualifications are stated more fully in my curriculum vitae, which is attached as Appendix A. Below is a brief summary of my relevant education, work experience, and other qualifications.

7. I received my B.S./M.S. degree in Organic Chemistry in 1959 from Bolyai University in Transylvania, and my Ph.D. degree in 1965 from the University of Babes-Bolyai, Cluj and the Romanian National Academy of Sciences.

8. I served as a Group Leader at the Pharmacochemical Research Institute in Romania until 1968. Thereafter, I received the R.A. Welch Fellowship at the University of Texas in Austin. From 1972 until 1978, I worked at the ALZA Laboratories in Lawrence, Kansas, which later became INTERx Research Corporation. During this time, I also served as an adjunct professor at the University of Kansas.

9. In 1979, I joined the University of Florida as Professor and Chairman of the Medicinal Chemistry Department. During my time at the University of Florida, I have held many appointments and served in many positions across the University, including Executive Director of the Center for Drug Discovery in the College of Pharmacy, Graduate Research Professor in the College of Pharmacy,

and Affiliate Graduate Research Professor in the Department of Chemistry in the College of Liberal Arts and the Department of Ophthalmology in the College of Medicine at the University.

10. In 2000, I accepted the role of Senior Vice President of Basic Research and Drug Discovery at IVAX Research, Inc. From 2000 to 2006, I served in various managing capacities at IVAX, including as Chief Scientific Officer of the IVAX Corporation, Managing Director of the IVAX Drug Research Institute, Budapest, Hungary, as well as President of the IVAX Research Institute. In 2006, after IVAX merged with Teva, I returned to the University of Florida and started Bodor Laboratories Inc., where I manage a small team who use a proprietary approach to drug design that leverages retrometabolic processes to create drugs that are safer, less toxic, and intrinsically better targeted than traditional drugs.

III. CLADRIBINE FORMULATION RESEARCH

11. When I joined IVAX in 2000, IVAX had obtained the rights to develop cladribine for the treatment of multiple sclerosis ("MS"), which had previously belonged to the SCRIPPS Research Institute ("SCRIPPS") and Johnson & Johnson ("J&J").

12. Cladribine is a chlorinated purine analog, 2-chloro-2'-deoxyadenosine ("2-CdA") compound. When I joined IVAX in 2000, cladribine was FDA

approved for the treatment of patients with hairy cell leukemia. It had not yet been approved for the treatment of other diseases, like multiple sclerosis.

13. As part of my role at IVAX, I was responsible for leading a team to investigate and develop an oral cladribine formulation suitable for use in Phase III clinical trials for MS patients.

14. My team at IVAX included my co-inventor of the BODOR PCT, WO2004/087101, Dr. Yogesh Dandiker, Dr. Stephen Marcus, and other team members.

15. In researching a potential cladribine formulation, my team at IVAX investigated different methods to maximize incorporation of cladribine into complexes with cyclodextrins. We had identified hydroxypropyl-β-cyclodextrin as a promising cyclodextrin for cladribine-cyclodextrin complexes for oral delivery of cladribine. My team focused on studying the conditions that would incorporate the most cladribine into the resulting complex as well as whether other cyclodextrins might form a complex that incorporated more cladribine.

16. The work that my team and I performed on cyclodextrin-cladribine complexes would ultimately result in our invention of an oral formulation of cladribine including a cladribine-cyclodextrin complex, as described in the BODOR PCT, WO 2004/087101.

17. After developing the cladribine-cyclodextrin complex described in the BODOR PCT, my team at IVAX performed pharmacokinetic and bioavailability studies of that oral formulation in non-human and human subjects. We conducted these studies using single doses of the oral cladribine formulation we developed, to compare its pharmacokinetic properties and bioavailability against prior intravenous formulations. My team at IVAX never treated a patient using multiple doses of cladribine. '480 Ex. 1022, 36:10-39:19; '481 Ex. 1022, 36:10-39:19. Thus, we never used or studied anything that could be described as a "dosing regimen."

A. IVAX AND SERONO PARTNERSHIP

18. Around 2002, IVAX entered into an exclusive worldwide product development and license agreement with Ares Trading, S.A., an affiliate of Serono, S.A., (collectively, "Serono") for the development and commercialization of an oral formulation of cladribine for the treatment of multiple sclerosis. Under this joint research and development agreement with Serono, IVAX was responsible for developing an oral formulation of cladribine. While IVAX developed an oral formulation of cladribine, Serono would develop a potential dose and dosing regimen, design and conduct Phase III clinical trials, obtain regulatory approval, and market and sell the final product for treating multiple sclerosis.

B. INVENTION OF THE COMPLEX CLADRIBINE-CYCLODEXTRIN COMPLEX

19. After my team and I began developing different oral formulations of cladribine, we first filed for a U.S. provisional patent application, U.S. Patent Application No. 60/458,922 ("'922 Provisional"), on March 24, 2003. The '922 Provisional was directed to particular cladribine-cyclodextrin complexes that IVAX had in development, including complexes isolated by freeze-drying (lyophilizing) cladribine and cyclodextrin. Ex. 2044, 1.[1] The '922 Provisional did not contain any proposed or suggested dosing regimen using cladribine formulations for treating MS. Ex. 2044, 1-18. I am the sole named inventor of the '922 Provisional.

20. IVAX also filed U.S. Application No. 60/484,756 ("'756 Provisional") on July 2, 2003. The '756 Provisional was directed to particular cladribine-cyclodextrin complexes that IVAX had in development. Ex. 2045, 1-2. The '756 Provisional did not contain any proposed or suggested dosing regimen using cladribine formulations for treating MS. Ex. 2045, 1-15. I am the sole named inventor of the '756 Provisional.

[1] All citations to Patent Owner's Exhibits are in reference to Patent Owner's exhibits filed contemporaneously in IPR2023-00480 and IPR2023-00481.

21. IVAX additionally filed U.S. Application No. 60/541,247 ("'247 Provisional") on February 4, 2004. The '247 Provisional was directed to oral formulations of cladribine that IVAX had in development. Ex. 2046, 1:3-5. In particular, it was directed to solid oral dosage forms containing an amorphous mixture of different cladribine-cyclodextrin complexes. Ex. 2046, 4:25-27. I am the sole named inventor of the '247 Provisional.

22. I understand that on March 25, 2004, IVAX also filed two provisional patent applications, both entitled "Cladribine Regimen for Treating Multiple Sclerosis." Both applications were cited in the BODOR PCT. '480 Ex. 1022, 23:24-29; '481 Ex. 1022, 23:24-29. I do not believe I or Dr. Dandiker are named as an inventor on either. I am not aware of the subject matter of either application. I am not aware of anyone at IVAX who was working on developing or researching a cladribine dosing regimen for treating MS, nor anyone at IVAX who invented a cladribine dosing regimen for treating MS. Counsel have provided me with an amendment from the prosecution history of U.S. Patent No. 8,785,415, which is a U.S. patent corresponding to the BODOR PCT. The amendment says:

> These were provisional applications which were abandoned without the filing of non-provisional applications based thereon. Further, they were not for inventions of the present inventors and belonged to a former assignee. They were not made available to the public. In the

> parent case, now patented (Application No. 12/986, 310), the sentence in question was deleted during prosecution, by an amendment made October 3, 2008. Accordingly, page 23 of the specification has been amended to delete the final sentence on page 23, consistent with the parent.

Ex. 2047, 10. I have no reason to doubt the amendment is accurate.

23. On March 26, 2004, IVAX filed the BODOR PCT Application, WO 2004/087101. The BODOR PCT named me and my colleague Dr. Dandiker as inventors. The BODOR PCT was directed to oral formulations of cladribine that IVAX had in development. In particular, it was directed to solid oral dosage forms containing an amorphous mixture of cladribine-cyclodextrin complexes.

24. The amorphous cladribine-cyclodextrin complexes described in the BODOR PCT contain an "amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex." '480 Ex. 1022, 14:12-14; '481 Ex. 1022, 14:12-14. Because this formulation contains both an inclusion complex and a non-inclusion complex of cladribine, it can be called a "complex cladribine-cyclodextrin complex." '480 Ex. 1022, 16:27; '481 Ex. 1022, 16:27. This complex cladribine-cyclodextrin complex can "be saturated with cladribine." '480 Ex. 1022, 14:16; '481 Ex. 1022, 14:16. This

allows "cladribine [to cyclodextrin] weight-ratios of from about 1:10 to 1:16." '480 Ex. 1022, 31:18-20; '481 Ex. 1022, 31:18-20. This composition can be created, for example, by adding cladribine to a dilute solution of cyclodextrin at elevated temperature until it is saturated and then freeze drying (lyophilizing) it. '480 Ex. 1022, 12-21, 26-33; '481 Ex. 1022, 12-21, 26-33.

25. I understand that certain disclosures in the '247 Provisional and the BODOR PCT are at issue in the *inter partes* review proceedings. Specifically, the BODOR PCT states:

> At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment.

'480 Ex. 1022, 23:15-20; '481 Ex. 1022, 23:15-20. The '247 Provisional contains similar language:

> At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for one week in the first month, repeated

for another week in the second month, followed by ten months of no treatment.

Ex. 2046, 20:6-10.

26. Neither myself nor my team, including Dr. Dandiker, developed, researched, or invented the above dosing regimen. Indeed, no one on my team at IVAX developed, researched, or invented any cladribine dosing regimen for treating MS. I do not consider this regimen to be my invention, and it was not claimed in the BODOR PCT or the corresponding U.S. patents, Nos. 7,888,328 and 8,785,415. Ex. 2069; Ex. 2029.

27. To the best of my knowledge, pursuant to the joint research and development agreement, Serono was responsible for any research and development regarding proposed dosing regimens to be used in Phase III clinical trials of the oral cladribine formulation that my team and I developed.

28. I understand that from 2002 to 2004, teams at IVAX and Serono regularly held joint team meetings discussing the progress of the cladribine project, and also communicated about the project via e-mail. Because Serono researchers were the only group in the IVAX-Serono collaboration working on proposed dosing regimens of cladribine for treating MS, it is highly likely that, prior to February 4, 2004, Serono communicated the above dosing regimen disclosed in the ’247 Provisional and BODOR PCT to other people at IVAX, including Dr.

Dandiker, Dr. Marcus, and others, through meetings and emails pursuant to the joint research and development agreement.

29. I am not aware of any evidence suggesting anyone at IVAX developed the regimen in the '247 Provisional and BODOR PCT. Nor am I aware of any evidence suggesting Serono did not communicate these regimens to other people at IVAX before February 2004.

30. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

31. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

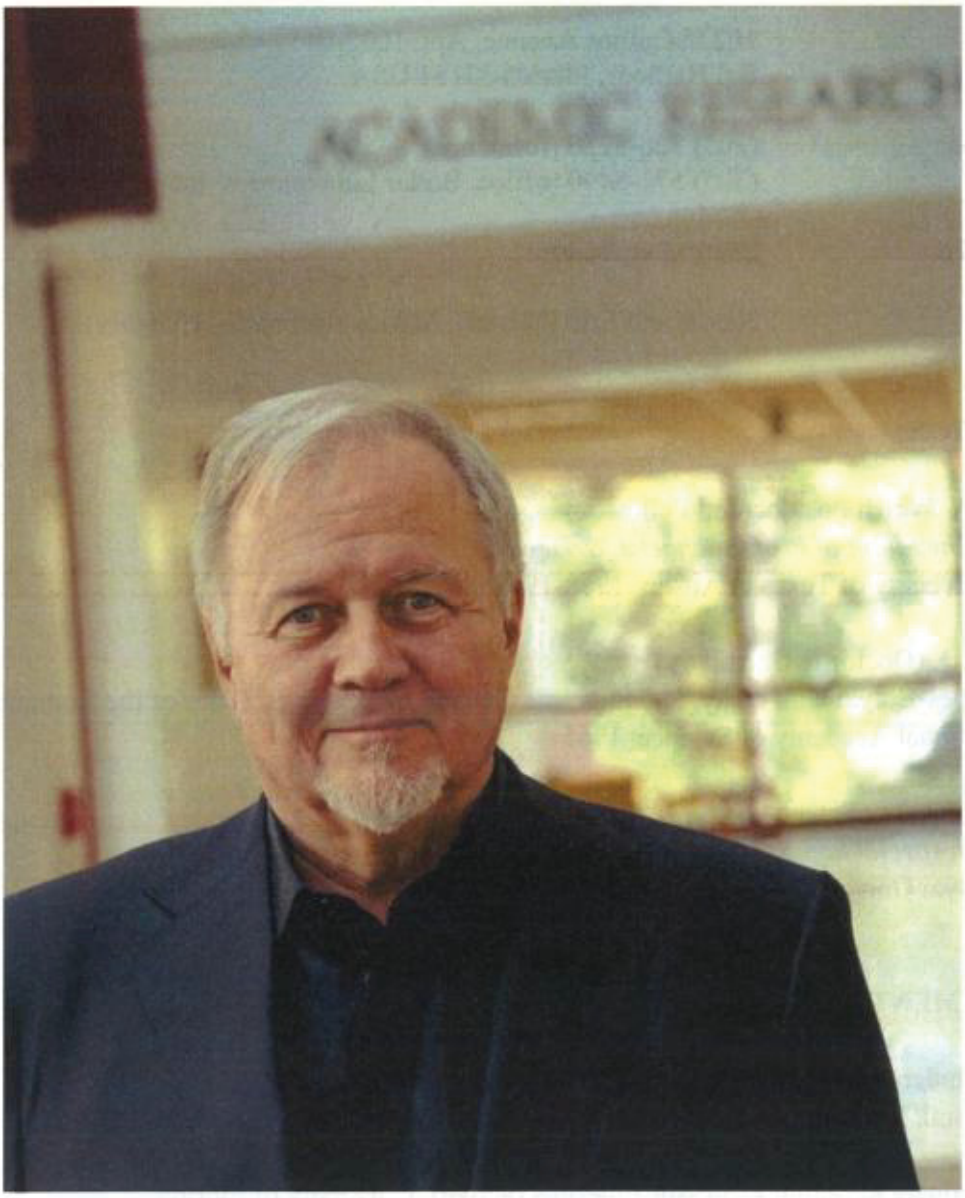
Dated: December 21, 2023 By: _____

Nicholas Bodor, Ph.D., D.Sc., d.h.c., HoF

APPENDIX A

Curriculum Vitae

Nicholas Bodor, Ph.D., D.Sc., d.h.c. (multi), HoF (multi)



Nicholas Bodor, Ph.D., D.Sc., d.h.c., HoF (multi)

CURRICULUM VITAE

Date of Birth:	February 1, 1939
Address:	10225 Collins Avenue, Apt. 1002-04 Bal Harbour, Florida 33154 USA
Telephone:	(305) 868-8250 (residence) (305) 571-8490 (office; Bodor Laboratories, Inc.)
Married To:	Sheryl Lee Bodor
Children:	Nicole and Erik (Miami); Miklós (Debrecen, Hungary)

EDUCATION:

- R.A. Welch Postdoctoral Fellow
  by invitation of Prof. Michael J. S. Dewar;
  University of Texas at Austin, 1968-1969; 1970-1972

- Ph.D. (Doctor in Chemistry)
  Babes-Bolyai University, and Supreme Council of Scientific Titles of the Romanian National Academy of Science, 1965

- Diploma in Science (B.S., M.S., Organic Chemistry)
  with special honors - straight A's throughout the five years;
  Bolyai University (Cluj, Romania), 1959

EMPLOYMENT:

- Founder and CEO, Bodor Laboratories, Inc.
  Miami, Florida; Founded in 2006

- Graduate Research Professor Emeritus (active), University of Florida
  Gainesville, Florida; since 2003

- Executive Director, University of Florida Center for Drug Discovery
  J. Hillis Miller Health Science Center, Gainesville, Florida; since 1990

- Affiliate Graduate Research Professor, Dept. of Ophthalmology
  University of Florida College of Medicine, Gainesville, Florida; since 1991

- Affiliate Professor, Dept. of Chemistry
  University of Florida College of Liberal Arts & Sciences
  Gainesville, Florida; since 1990

Previous:

- Chief Scientific Officer, IVAX Corporation
  Miami, Florida; 2003-2006

- Managing Director, IVAX Drug Research Institute, Ltd.
  Budapest, HUNGARY; 1999-2006

- President, IVAX Research Institute, Inc.
  Miami, Florida; 2002-2006

- Senior Vice President, Basic Research & Drug Discovery, IVAX Research, Inc.
  Miami, Florida; 2000-2006

- Graduate Research Professor, Dept. of Pharmaceutics, University of Florida
  College of Pharmacy, Gainesville, Florida; 1991-2003

- Graduate Research Professor, Dept. of Medicinal Chemistry, University of Florida
  College of Pharmacy, Gainesville, Florida; 1983-2003

- V Ravi Chandran PhD Professor in Drug Design and Targeting, University of Florida
  College of Pharmacy, Gainesville, Florida; 2000-2003

- Vice President and Director, Pharmatec, Inc.
  Alachua, Florida; 1983-1992

- Director, Center for Drug Design and Delivery, University of Florida
  J. Hillis Miller Health Science Center, Gainesville, Florida; 1986-1990

- Chairman, Dept. of Medicinal Chemistry, University of Florida
  College of Pharmacy, Gainesville, Florida; 1989-1990

- Professor (1979-1983) and Chairman (1979-1984), University of Florida
  Dept. of Medicinal Chemistry, J. Hillis Miller Health Center, Gainesville, Florida

- Adjunct Professor of Pharmaceutical Chemistry, University of Kansas
  Lawrence, Kansas; 1978-1980

- Adjunct Professor of Medicinal Chemistry, University of Kansas
  Lawrence, Kansas; 1974-1978

- Associate Director of Medicinal Chemistry, INTERx Research Corporation
  Lawrence, Kansas; 1973-1979

- Senior Research Scientist, ALZA Corporation
  Lawrence, Kansas; 1972-1973

- R.A. Welch Postdoctoral Fellow, University of Texas at Austin
  1968-1969 and 1970-1972

- Principal Investigator and Group Leader, Chemical-Pharmaceutical Research Institute
  Cluj, Romania; 1961-1968 and 1969-1970

- Research Investigator and Group Leader, "1 September" Factory
  Satu Mare, Romania; 1959-1961

ELECTED TO:

- Fellow, Council for Human Dignity (Hungary); 2005

- Fellow, the World Innovation Foundation; 2002

- Member, Dermatology Advisory Board, Glaxo Wellcome; 1997

- Member, Hungarian Academy of Sciences; 1995

- Fellow, American College of Clinical Pharmacology; 1991

- Fellow, American Association for the Advancement of Science; 1989

- Honorary Member, Panhellenic Association of Pharmacists; 1989

- Honorary Member, Hungarian Chemical Society; 1988

- Fellow, American Association of Pharmaceutical Scientists; 1986

- Fellow, Academy of Pharmaceutical Research and Science; 1983

AWARDS AND HONORS:

- Arany János Lifetime Achievement Award of the Hungarian Academy of Sciences, 2022.
- Inducted into the Academy of Science, Engineering & Medicine of Florida (ASEMFL) inaugural membership class; 2020
- Inducted into the Florida Inventors Hall of Fame; 2020
- Inducted into the American Chemical Society Hall of Fame (Medicinal Chemistry Division); 2012
- Commander's Cross of the Order of Merit of the Hungarian Republic - presented at the Hungarian Parliament during the national celebration of over 1,000 years of statehood and its Canonized first king, St. Stephen; 2010
- Fabinyi Prize, awarded by the Hungarian Chemical Society (given to eminent scientists living outside Hungary); 2010
- Distinguished Pharmaceutical Scientist Award, American Association of Pharmaceutical Scientists; 2007
- Honorary Doctor of Science Degree, University of Florida; 2005
- Gold Cross of Merit of the Hungarian Republic, awarded by Ferenc Madl, President of Hungary; March 31, 2004
- Volwiler Research Achievement, American Association of Colleges of Pharmacy; 1997
- Professorial Excellence Program Award, University of Florida; 1996
- Leo Friend Award, American Chemical Society; 1996
- The Nagai Foundation Tokyo Fellowship; 1994
- University of Florida Research Achievement Award; 1991
- Doctor Honoris Causa, Medical University of Debrecen, Hungary; 1990
- University of Florida Research Achievement Award; 1990
- Doctor Honoris Causa, Technical University of Budapest, Hungary; 1989

- American Pharmacists Association (APhA) Research Achievement Award in Pharmaceutical and Medicinal Chemistry; 1989
- American Association of Pharmaceutical Scientists Research Achievement Award (the first) in Medicinal and Natural Product Chemistry; 1988
- "The 1984 Florida Scientist of the Year"

OTHER ACADEMIC AND SCIENTIFIC RECOGNITIONS:

- *The Nicholas Bodor Distinguished Lectureship*, University of Florida; established 2014
- *The Nicholas Bodor Professor in Drug Discovery*, University of Florida; established 2007
- Appointed as Graduate Research Professor Emeritus upon retirement from the University of Florida; 2003
- Targeted brain delivery of neuropeptides (as published in *Science*, **257**, 1698-1700, 1992) cited as one of the top 10 medical advances of 1992 by the *Harvard Health Letter*, March 1993 issue
- Appointed Graduate Research Professor, University of Florida; 1983

SERVICE TO ACADEMIA AND INDUSTRY:

- Nominator of numerous successful award recognitions for international leaders in the pharmaceutical industry, including:
  - Prof. Yuichi Sugiyama, recipient of University of the Florida Doctor of Science degree *honoris causa*, 2012.
  - Dr. Phillip Frost, recipient of the University of Florida Doctor of Science degree *honoris causa*, 2015.
  - Prof. Thorsteinn Loftsson, recipient of the American Association of Pharmaceutical Scientists' Research Achievement Award in Physical Pharmacy and Biopharmaceutics, 2016.
- Organizing Member of the Association of Hungarian-American Academicians (AHAA), established in 2015 for US external members of the Hungarian Academy of Sciences (HAS)

- Member, Board of Directors, ALCHEM Laboratories Corp.; 1997-2015 (from inception, to sale to another entity)
- Member, Scientific and Medical Advisory Board, Oculis ehf.
- Chairman, Policy Committee of the Florida Center for Heterocyclic Compounds
- Member, Board of Trustees; ARKAT-USA
- Consultant, advisor or Board of Directors member for numerous major pharmaceutical companies and law firms (Taft Law, Schering-Plough, ONO Pharmaceutical Co., Otsuka Pharmaceutical Co., Xenon Vision, Inc., Oculis, Inc., Helene Curtis, Inc., etc.)
- Principal Investigator of numerous National Institutes of Health research grant awards
- Visiting Professor, Hoshi University, Tokyo Japan; 1995
- Visiting Professor, Assiut University, Assiut Egypt; 1984

LECTURES AND CONFERENCES:

- Invited speaker of more than 430 national and international symposia and special lectures (please see separate listing).
- Founder and Organizer of the *Retrometabolism Based Drug Design and Targeting Conference*; international series of symposia held biennially from 1997-2015 (a total of 10 events).
- Name Lectureships given: Hoechst-Roussel Lectureship in Chemistry, Somerville NJ, 1983; Hoshi University Diploma, Tokyo Japan, 1983; Bombay College of Pharmacy Silver Medal, Bombay India, 1984; Nichols Distinguished Symposium, American Chemical Society, Tarrytown NY, 1986; Sigma Xi Lectureship, 1987; University of Saskatchewan College of Pharmacy, Canada, 1998; The Högyes Lecture, Semmelweis University of Medicine, Budapest Hungary, 2000.

EDITORIAL BOARDS:

AAPS Journal
Advanced Drug Delivery Reviews
American Journal of Drug Delivery
Burger's Medicinal Chemistry, 6th Edition
Current Drugs
Current Medicinal Chemistry
Drug Design & Discovery
Expert Opinion on Drug Delivery
Journal of Ocular Pharmacology and Therapeutics
Journal of Pharmacology & Clinical Toxicology
Journal of Pharmacy and Pharmacology
Magyar Kemiai Folyoirat
Open Medicinal Chemistry Journal
Pharmaceutical Research
Pharmaceutical Science Communications
Pharmacy and Pharmacology Communications
STP Pharma Sciences

MEMBERSHIPS:

Academy of Pharmaceutical Scientists (APS)
American Association for the Advancement of Science (AAAS)
American Association of Colleges of Pharmacy (AACP)
American Association of Pharmaceutical Scientists (AAPS)
American Chemical Society (ACS)
American College of Clinical Pharmacology (ACCP)
American Epilepsy Society (AES)
American Pharmacists Association (APhA)
Association of Hungarian-American Academicians
Association for Ocular Pharmacology and Therapeutics (AOPT)
Controlled Release Society (CRS)
Hungarian National Academy of Sciences
International Council of Scientific Unions (ICSU)
International Scientific Advisory Panel of Oxford Molecular Group, PLC
International Union of Pure and Applied Chemistry (IUPAC)
New York Academy of Sciences
Sigma Xi
Worldwide Hungarian Medical Academy (WHMA)

PUBLICATIONS:

- Author/co-author of more than 530 publications (please see separate listing)

PATENTS:

- Inventor on more than 325 patents (please see separate listing)

GRADUATE AND POSTDOCTORAL SUPERVISON:

- Has supervised more than 50 doctoral students and 100 postdoctoral research fellows/associates

LANGUAGES:

- Fluent in English, Hungarian and Romanian;
  Read and write in French, Russian and German

LISTED IN:

American Scientist
Who's Who in America
Who's Who in Frontiers of Science
Who's Who in Science and Technology
Who's Who in Technology Today
Who's Who Worldwide (Platinum Edition)
Ki Kicsoda (Who's Who Worldwide – Hungarian Edition)

Nicholas Bodor, Ph.D., D.Sc., d.h.c. (multi), HoF (multi)

BIOGRAPHICAL SKETCH

Dr. Nicholas Bodor is a Graduate Research Professor Emeritus (active) at the University of Florida (UF) College of Pharmacy, Gainesville. He joined the university in 1979 as Professor and Chairman of the Medicinal Chemistry Department and was promoted to Graduate Research Professor in 1983. He was the Executive Director of the college's Center for Drug Discovery, founded by him in 1986. During his tenure at UF, Dr. Bodor has supervised the training of more than 50 doctoral students and over 100 postdoctoral level research associates and fellows. In February 2000, he took a leave of absence from his academic posts in order to accept a position as Senior Vice President of Basic Research and Drug Discovery at the IVAX Corporation. Dr. Bodor then served as Chief Scientific Officer of the IVAX Corporation, as well as President of the IVAX Research Institute. During this period, he simultaneously led Hungary's Institute for Drug Research (some 450 researchers) as its Managing Director until his retirement from IVAX in October 2005.

Dr. Bodor's main research interests include design of drugs with improved therapeutic index, design of new chemical delivery systems, computer-assisted drug design, drug transport and metabolism, and theoretical and mechanistic organic chemistry. He has published more than 530 research articles, has over 310 patents, and is on the editorial boards of numerous international scientific journals. An internationally recognized leader in drug discovery, design and delivery, he has introduced revolutionary, general, comprehensive drug design and drug targeting concepts known as *retrometabolic drug design* approaches. These concepts strategically combine chemical and enzymatic (metabolic) processes to achieve drug targeting and to produce safe drugs and safe environmental chemicals. The two major classes of the retrometabolic drug design concepts contain "*chemical drug targeting systems" (CDS)* and the *"soft drugs" (SD).* Each of these large classes contains various subclasses, based on the different design rules. The design concepts incorporated in the soft drug approaches were used by Dr. Bodor to develop a *general and comprehensive* program, including a *computerized expert system* which can be used to design all potential and possible metabolites and the corresponding safe active soft drugs or chemical delivery systems. The soft steroid Loteprednol Etabonate, designed by Dr. Bodor, is on the market in the U.S. and other countries. Other drugs designed by him using the retrometabolic concepts are in advanced clinical development.

Dr. Bodor received his B.S./M.S. degree in Organic Chemistry in 1959 at Bolyai University in Transylvania, and his Ph.D. degree in 1965 from the University of Babes-Bolyai, Cluj and the Romanian National Academy of Sciences. He was a Group Leader at the Pharmacochemical Research Institute in Romania until 1968, when he was offered an R. A. Welch Fellowship at the University of Texas in Austin, where he worked in the field of theoretical organic chemistry with Dr. Michael J. S. Dewar, the first Robert A. Welch Research Chair. In 1972 he became a Senior Research Scientist at ALZA Laboratories in Lawrence, Kansas, which later became INTERx Research Corporation, where he was Director of Research, as well as an Adjunct Professor at the University of Kansas until 1978.

Among his many honors, Dr. Bodor is an elected Fellow of the Academy of Pharmaceutical Sciences, American Association of Pharmaceutical Scientists, American Association for the Advancement of Science, and American College of Clinical Pharmacology. He is also an Honorary Member of the Hungarian Chemical Society and the Panhellenic Society of Pharmacists. Among other honors, Dr. Bodor has been named "The 1984 Florida Scientist of the Year" and received the

first AAPS Research Achievement Award in Medicinal and Natural Product Chemistry in 1988, as well as the APhA Research Achievement Award in Pharmaceutical and Medicinal Chemistry in 1989. In 1994 he was named the first recipient of the Nagai Foundation Tokyo International Fellowship. He was named by the American Chemical Society as the 1996 recipient of the Leo Friend Award in recognition of his article entitled, "Design of Biologically Safer Chemicals," published in *Chemtech*, October 1995. He is the first College of Pharmacy faculty member to receive a Professorial Excellence Award, given by the University of Florida in 1996. The AACP selected Dr. Bodor as the recipient of the 1997 Volwiler Research Achievement Award. In April 2000, he was named the V. Ravi Chandran Professor in Drug Design and Targeting of the UF College of Pharmacy, the first recipient of this endowed professorship. In February 2002, he was elected a Fellow of the World Innovation Foundation. An honorary Doctor of Science degree was conferred upon Dr. Bodor by the University of Florida in 2005. In 2007, the American Association of Pharmaceutical Scientists awarded Dr. Bodor with the Distinguished Pharmaceutical Scientist Award. Dr. Bodor was inducted in to the American Chemical Society's Hall of Fame, Medicinal Chemistry Division in August 2012. Additionally, he was named to the Florida Inventors Hall of Fame in 2020. He is an inaugural member (inducted in 2020) of the Academy of Science, Engineering & Medicine of Florida (**ASEM**-FL). Dr. Bodor received the title "Graduate Research Professor Emeritus" upon his retirement from the University of Florida in 2003 and remains an active part of its College of Pharmacy through, among other things, a Distinguished Professorship named the *Nicholas Bodor Professor in Drug Discovery* (established in 2007) and the *Nicholas Bodor Distinguished Lectureship* (introduced in 2014).

In addition to the honors above, Dr. Bodor has received the highest levels of recognition from his home country of Hungary for his scientific achievements and leadership of the Budapest-based Institute for Drug Research. In 1989 he received an honorary Doctor of Science degree from the Technical University of Budapest, and then was awarded the Doctor Honoris Causa degree from the Medical University of Debrecen in 1990. In 1995 he was elected to the Hungarian National Academy of Sciences. Ferenc Madl, President of Hungary, awarded Dr. Bodor the Gold Cross of Merit of the Hungarian Republic in 2004. In 2010 he received the prestigious Fabinyi Prize of the Hungarian Chemical Society, which is given to scientists living outside Hungary whose outstanding scientific accomplishment have contributed to the reputation of the HCS. In August 2010 at the national celebration of Hungary's over 1,000 years' statehood and its canonized first king, St. Stephen, Dr. Bodor was awarded at the Hungarian Parliament, the Commander's Cross of the Order of Merit of the Hungarian Republic, a prestigious award of civil merit. Dr. Bodor is also the 2022 recipient of the Arany János Lifetime Achievement Award of the Hungarian Academy of Sciences in recognition of his lifetime body of work in the sciences.

Dr. Bodor and his wife Sheryl call Miami their primary residence. He founded Bodor Laboratories, Inc. in 2006, and works there with his son Erik and daughter Nicole (who hold PhD/MBA and PhD degrees, respectively, in the relevant fields) to further develop his drug design strategies to the marketplace. His oldest son Miklós (an MD, PhD) is Chairman of the Clinical Pharmacology Department at the Medical University in Debrecen, Hungary.

Nicholas Bodor, Ph.D., D.Sc., d.h.c., HoF (multi)

SUMMARY OF SCIENTIFIC INTERESTS AND ACHIEVEMENTS

Combining an interest in a wide variety of scientific fields with a wealth of originality, Dr. Bodor has contributed to almost every conceivable aspect of the pharmaceutical sciences, including basic theory, practical drug discovery and development, to taking drugs designed by him through clinical development and FDA approval. His invention of the retrometabolic drug design concept is based on the mechanism of drug action in various tissues and aims at improving the therapeutic index to diminish unwanted side effects. This general concept uses drug metabolism information to design parent drugs whose metabolism and distribution can be controlled to target and eliminate the drug in order to increase efficacy and eliminate undesirable side effects. These approaches represent systematic methodologies that, in addition to thoroughly integrating structure-activity (SAR) and structure-property (SPR) relationships, structure-metabolism (SMR) relationships are also developed and used in the drug design. The retrometabolic drug design loop combines two complementary but distinctly different concepts, the (i) *chemical delivery systems* (CDS) and (ii) *soft drugs* (SD) approaches. In general, a CDS is *inactive* by design and is enzymatically *activated* stepwise to produce the active drug *only* (or preferentially) at the target site/organ. At the other end of the retrometabolic design loop are the soft drugs. A SD *is an active drug*, designed in such a way to be *deactivated* in a predictable and controllable way after it achieves its therapeutic role.

A striking example of a CDS introduced by Dr. Bodor is the *brain targeting of drugs* based on a redox targetor system, such as 1,4-dihydrotrigonelline↔trigonelline salt. The structurally similar, ubiquitous NAD^+↔NADH redox coenzyme system assures oxidation of the initial lipophilic drug targetor conjugate to the hydrophilic, still inactive quaternary form. Due to the unique architecture of the blood-brain barrier (BBB) this charged intermediate and is *locked-in* the brain, but is quickly eliminated from the whole body. Thus, further enzymatic liberation of the drug takes place essentially only in the brain, in a sustained manner.

Dr. Bodor's Soft Drug (SD) approach is particularly well-suited for applications in which a targeted effect is desired, but systematic side effects are to be avoided. One method of the soft drug principle is to apply the *inactive metabolite approach*. The design starts with an inactive metabolite of a known drug which is then chemically modified (activated) to produce an isosteric/isoelectronic analogue of the active drug which then, when applied at the site of need, will perform the desired function. However, when it is absorbed or reaches the systemic circulation, it will be deactivated to the very metabolite the design started from. By design this deactivation takes place by hydrolytic enzymes and avoids the usual oxidative metabolic processes. Dr. Bodor is sole inventor of the soft drug Loteprednol Etabonate, an ophthalmic corticosteroid that is used in suspensions against eye inflammation (for instance, after cataract surgery) and allergic diseases. His involvement carried through to all phases --- from design, through clinical development and FDA approval in 1998 for four different diseases. It is

currently sold in five different products (Lotemax™, Alrex™, Zylet™, as well as two subsequent Lotemax™ gel and ointment products), and a sub-micron formulation (Lotemax SM). It is considered one of the most important and safest eye drugs on the market. The FDA has also approved a 1% LE ophthalmic nanoparticle formulation for Inveltys™ by Kala Pharmaceuticals for the treatment of post-operative inflammation and pain, the first twice-daily ocular corticosteroid approved for this indication. The same company announced in January 2018 topline Phase III results for its nanoparticle formulation of Loteprednol Etabonate for treatment of dry eye disease. Together with a second generation of soft corticosteroids such as etiprednol dicloacetate, it is also being developed for a full spectrum of other possible applications, such as nasal spray for rhinitis, inhalation products for asthma, and topical cream for dermatological applications.

Another eye-specific drug invented by Dr. Bodor is betaxoxime, which is inactive when administered but becomes active in the eyes after converting, by design, an oxime into a ketone function, followed by its stereospecific reduction.

At the time of its introduction, the idea of designed-in metabolism represented a significant novelty and was against mainstream thinking of the time that instead focused on minimizing or entirely eliminating drug metabolism. Since then, Dr. Bodor's retrometabolic drug design concepts have ignited research in academia and industry. The importance of this field is reflected by the fact that its review in the 7th edition of *Burger's Medicinal Chemistry, Drug Discovery and Development* requires a full chapter with close to 200 chemical structures and 675 references and the book "*Retrometabolic Drug Design and Targeting*" (2012) is fully dedicated to the subject.

The novelty and importance of Dr. Bodor's CDS approach led to having its first applications published in *Science* in 1975, 1981 and 1983. Its later extension to the targeted brain delivery of neuropeptides by molecular packaging was listed as one of 1992's top 10 medical advances for medical progress by the *Harvard Health Letter*, based on an earlier 1992 *Science* article. Other types of CDSs invented by Dr. Bodor target drugs to the eye are of considerable interest as they allow site- and stereo-specific delivery of β-blockers by exploiting differential enzyme distributions. The administered, inactive β-amino-ketoxime is converted to the corresponding ketone by oxime hydrolase, an enzyme with preferential activity in the eye that was first identified by Dr. Bodor and then stereo-specifically reduced to the active alcohol form.

In addition to Loteprednol Etabonate, other drugs designed using the SD approach include soft β-blockers (Adaprolol, Esmolol/Breviblock™, Landiolol/Onoact™), soft opioid analgesics (Remifentanil/Ultiva™), soft Ca^{+}channel blockers (Clevidipine/Cleviprex™), soft soft E_2 analogs at Yale Univ., novel soft cytokine inhibitors at Janssen Pharm., soft immunosuppresants (soft cyclosporine A analogs at Enanta Pharm., soft tacrolimus analogs at Novartis); and soft benzodiazepines at GlaxosmithKline.

A compelling benefit of Dr. Bodor's concepts is that they have resulted in design of drugs that combine maximum effectiveness and safety, allowing a far greater number of patients to be treated by them. These concepts also allow design of drugs to fill previously-unmet needs. For example, Sofpironium Bromide, a topical soft anticholinergic designed by Dr. Bodor, is currently being developed in the USA for treatment of hyperhidrosis, a condition which currently lacks effective, well-tolerated and convenient treatment options. A New Drug Application (NDA) for this product was submitted to the FDA in September 2022. Marketing approval for Sofpironium Bromide in Japan was achieved in November 2020 and is currently sold there as ECCLOCK®. Additionally, Mavenclad®, a drug based on Dr. Bodor's US (and associated European and US) patent, "Oral Formulations of Cladribine," was approved in 2017 in the EU and Canada for treatment of highly active relapsing multiple sclerosis (RMS). Mavenclad® is designed to selectively target immune cells that trigger relapsing MS, while resetting the immune system. Using just two annual courses of treatment for a maximum of twenty days, it promotes long-term inhibition of harmful T- and B- cells, without continuous suppression of the immune system. Approval has since been received within the Middle East, Africa and Latin America, with US FDA approval granted in March 2019.

Dr. Bodor has published more than 530 research articles, many of them on drug design and formulation tools which have garnered high interest and use in the scientific community. In particular, four of his publications on novel models to predict Log P and Log W have been collectively cited more than 570 times. A pioneer of the use of MO calculations in drug design and delivery and the development and use of semi-empirical MO calculations in drug design, he defined novel computer-enabled systems to allow the design of soft drug and other improved drug candidates using rules-based and MO assessments. He is an innovator in the use of cyclodextrins and solubilizing excipients, and pioneered cyclodextrins for traditional and non-traditional (buccal) administration routes. He is an inventor on more than 270 patents, with numerous additional worldwide patent applications currently pending for such uses as treatment of hyperhidrosis, myopia, COPD and sialorrhea.

The progress in these various related fields has been reviewed biennially at an international series of symposia Dr. Bodor founded in 1997 entitled, *The Retrometabolism Based Drug Design and Targeting Conference*. He organized a total of ten of these meetings between 1997 and 2015; in addition to Florida, the venues have included Japan, Hungary and Austria.

Nicholas Bodor, Ph.D., D.Sc., d.h.c., HoF (multi)

INVITED PRESENTATIONS

1. March 1978, Lake Ozark, MO; 11th Higuchi Research Seminar.
2. May 1978, Osaka, JAPAN; Otsuka Pharmaceutical Co.
3. May 1978, Osaka, JAPAN; Kanebo, Ltd.
4. May 1978, Tokyo, JAPAN; Sankyo, Ltd.
5. June 1978, Aberdeen Proving Ground, MD; Edgewood Arsenal.
6. November 1978, Chicago, IL; Abbott Laboratories.
7. January 1979, Kalamazoo, MI; Upjohn Company.
8. March 1979, Lake Ozark, MO; Ayerst Laboratory.
9. April 1-6, 1979, Honolulu, HI; ACS/CSJ Computer Assisted Drug Design Symposium.
10. April 1979, Palo Alto, CA: Syntex Research.
11. June 1979, Raleigh, NC; Decontamination of Chemical Agents ARO Special Meeting.
12. November 1979, Philadelphia, PA; McNeil Laboratories.
13. November 1979, London, ENGLAND; Chemical Society – Royal Society.
14. November 1979, London, ENGLAND; University of London.
15. November 1979, Birmingham, ENGLAND; University of Birmingham.
16. February 1980, Bloomfield, NJ; Schering-Plough.
17. March 1980, Lake Ozark, MO; 13th Higuchi Research Seminar.
18. April 1980, Skokie, IL; G.D. Searle Co.
19. April 1980, Skokie, IL; APhA National Meeting.

20. August 24-29, 1980, Las Vegas, NV; ACS Symposium, "Soft Drugs: Strategies for Design of Safer Drugs."

21. August 1980, Las Vegas, NV; Gordon Research Conference on Medicinal Chemistry.

22. November 3-15, 1980, Reston, VA; ARO Conference on Defense Against Chemical Agents, "Acceleration of Deactivation of Chemical Agents."

23. December 8, 1980, Ann Arbor, MI; University of Michigan, "The Soft Drug Approach: Strategies for the Design of Safer Drugs."

24. December 9, 1980, Ann Arbor, MI; Warner Lambert, "The Soft Drug Approach: Strategies for the Design of Safer Drugs."

25. February 23, 1981, Washington, D.C.; National Institute for Aging, "Soft Drugs."

26. March 15-18, 1981, Lake Ozark, MO; 14th Higuchi Research Seminar.

27. April 12-17, 1981, Atlanta, GA; FASEB Symposium on Drug Center Systems, "The Prodrug Approach to Controlled Delivery."

28. August 3-7, 1981, New London, NH; Gordon Research Conference on Medicinal Chemistry.

29. August 25-28, 1981, Noordwijkerhout, THE NETHERLANDS; IUPAC-IUPHAR Symposium, "Strategy in Drug Research."

30. October 20-21, 1981, Indianapolis, IN; Lilly Research Company.

31. November 27-28, 1981, Montpellier, FRANCE; Clin Midy Research Center Symposium, "Drug Metabolism and Drug Design: Quo Vadis?"

32. December 6-14, 1981, Osaka, JAPAN; Otsuka Pharmaceutical Co.

33. December 7, 1981, Kyoto, JAPAN; Kyoto University.

34. January 10-11, 1982, Painesville, OH; Diamond Shamrock.

35. January 25, 1982, Clifton, NJ; American Cyanamid Company.

36. February 15-16, 1982, Hillside, NJ; Bristol Myers.

37. February 22, 1982, Boston, MA; Gillette Company.

38. March 15-17, 1982, Lake Ozark, MO; 15th Higuchi Seminar.

39. March 29, 1982, Painesville, OH; Diamond Shamrock.

40. March 31, 1982, Groton, CT; Pfizer Company.

41. April 1, 1982, Aberdeen Proving Ground, MD; Edgewood Arsenal.

42. May 6, 1982, Austin, TX; University of Texas.

43. May 25, 1982, Chicago, IL; Abbott Laboratories, "Brian-Specific Delivery of Drugs."

44. December 1982, Osaka, JAPAN; Fujisawa Pharmaceutical Co.

45. December 1982, Hiroshima, JAPAN; Umezawa Research Institute, "Brain-Specific Delivery of Drugs."

46. December 1982, Kyoto, JAPAN; University of Kyoto, "Soft Drugs."

47. March 13-16, 1983, Lake Ozark, MO; 16th Higuchi Research Seminar.

48. April 25, 1983, Skokie, IL; G.D. Searle.

49. May 6, 1983, San Francisco, CA; University of California at San Francisco.

50. September 29, 1983, Somerville, NJ; Hoechst-Roussel.

51. October 19, 1983, Gainesville, FL; University of Florida Frontiers of Science, "Strategies to Design Safe Drugs."

October 25-November 15, 1983, JAPAN:

52. Tokyo; Sankyo, Ltd.
53. Tokyo; Hoshi University, Special Lecture.
54. Tokyo; Snow Brand Milk Products.
55. Tokyo; Toyo Jozo Co., Ltd.
56. Osaka; Takeda Chemical Industries, Ltd.
57. Osaka; Fujisawa Pharmaceutical Co.
58. Osaka; Tanabe Co., Ltd.
59. Osaka; Sumitomo Company.
60. Osaka; Otsuka Pharmaceutical Co.
61. Osaka; Yoshitomi Company.

62. Hiroshima; Hiroshima University, Key Lecture at Drug Design and Metabolism Symposium.
63. Kyoto; ONO Pharmaceutical Co.
64. Kyoto; Kyoto University – Japanese Pharmaceutical Association.
65. Takata; Wakunaga Pharmaceutical Co.

66. December 7, 1983, Boston, MA; New England Nuclear.

67. December 8, 1983, Detroit, MI; Warner Lambert.

68. December 14,1983, Gainesville, FL; University of Florida Endocrinology Seminar.

69. January 1984, Assiut, EGYPT; University of Assiut Lecture Series.

70. January 1984, Milan, ITALY; Recordati Pharmaceutica e Chimica.

71. January 1984, Basel, SWITZERLAND; Sandoz, Inc.

72. January 28, 1984, Bombay, INDIA; Bombay College of Pharmacy, International Symposium Celebrating its 25th Anniversary.

73. February 1, 1984, New Delhi, INDIA; Indian Pharmaceutical Association Satellite Seminar on Advances in Drug Delivery Systems.

74. February 1984, Osaka, JAPAN; One Pharmaceuticals.

75. February 1984, Osaka, JAPAN; Yoshitomi Company.

76. February 1984, Osaka, JAPAN; Fujisawa Pharmaceutical Co.

77. March 11-14, 1984, Lake Ozark, MO; 17th Higuchi Research Seminar.

78. April 19, 1984, Arlington, VA; NIH Special Study Section on "Boronate, Redox and Related Compounds as Vital Reagents."

79. May 15, 1984, Boston, MA; American Chemical Society, NE Section, Invited Lecture.

80. July 26, 1984, Miami, FL; Key Pharmaceuticals.

81. July 30-August 3, 1984, New London, NH; Gordon Conference on Medicinal Chemistry.

82. August 26-31, 1984, Philadelphia, PA; American Chemical Society Symposium on Drug Design and Discovery.

83. September 27, 1984, Gainesville, FL; University of Florida Department of Chemistry.

84. October 28-31, 1984, Philadelphia, PA; American Pharmaceutical Association Academy of Pharmaceutical Sciences Symposium on Theory and Application of Bioreversible Carriers to Drug Design.

85. November 1, 1984, West Chester, PA; SmithKline and Beckman Corporation.

86. November 9, 1984, Gainesville, FL; Engineering Advisory Council.

87. February 21-22, 1985, Austin, TX; University of Texas.

88. March 10-13, 1985, Lake Ozark, MO; 18th Higuchi Research Seminar.

89. March 18, 1985, Tokyo, JAPAN; Tokyo University – Pharmaceutical Society of Japan (Divisional).

90. March 19, 1985, Tsukuba, JAPAN; Eisai Company.

91. March 20, 1985, Osaka, JAPAN; Takeda Pharmaceutical Co.

92. March 21, 1985, Osaka, JAPAN; Sumitomo Pharmaceutical Co.

93. March 22, 1985, Hiroshima, JAPAN; Hiroshima University – Pharmaceutical Society of Japan (Divisional).

94. March 23, 1985, Osaka, JAPAN; ONO Pharmaceutical Co.

95. March 25, 1985, Tokushima, JAPAN; Otsuka Pharmaceutical Co.

96. March 26, 1985, Kyoto, JAPAN; Biwako Research Institute.

97. March 27, 1985, Osaka, JAPAN; Nihon Medi-Physics.

98. April 21-25, 1985, Anaheim, CA; Federation of American Societies for Experimental Biology (FASEB).

99. May 7, 1985, Cincinnati, OH; Proctor & Gamble.

100. May 8, 1985, Raleigh-Durham, NC; Burroughs-Welcome.

101. May 30, 1985, Magnolia, AR; Medicinal Chemistry Symposium.

102. June 10, 1985, Budapest, HUNGARY; National Academy of Science.

103. June 20, 1985, Milan, ITALY; Recordati Industria Chimica e Farmaceutica S.P.A.

104. June 24, 1985, Geneva, SWITZERLAND; Arcopharma.

105. July 4, 1985, London, ENGLAND; The Institute of Cancer Research and London University College Hospital.

106. July 22-25, 1985, Plymouth, NH; Gordon Conference on Drug Metabolism.

107. September 16, 1985, Philadelphia, PA; McNeil Pharmaceutical Co.

108. September 17, 1985, Kingsport, TN; Eastman Chemical Co.

109. September 25, 1985, Belfast, IRELAND; Queen's University of Belfast, Symposium on Prodrugs, Biochemical Society.

110. September 27, 1985, Reykjavik, ICELAND; University of Iceland.

111. September 30, 1985, Copenhagen, DENMARK; Lunbeck A/C.

112. October 1, 1985, Helsingborg, SWEDEN; Leo Pharmaceuticals.

113. October 3, 1985, London, ENGLAND; University College Hospital.

114. November 7, 1985, Kalamazoo, MI; Upjohn Company.

115. December 3, 1985, Rochester, NY; Eastman Kodak Company.

116. March 9-12, 1986, Lake Ozark, MO; 19th Higuchi Research Seminar.

117. April 4, 1986, Tarrytown, NY; ACS Nichols Distinguished Symposium.

118. May 19, 1986, Edgewood, MD; Edgewood Arsenal Conference.

119. May 20, 1986, Baltimore, MD; Nova Pharmaceutical Co.

120. June 15-19, 1986, Chapel Hill, NC; ACS Medicinal Chemistry Symposium.

121. July 29-August 13, 1986, Budapest, HUNGARY; Conference on the Role of Hungarians in Science and Technology in the World; National Academy of Science of Hungary; Central Research Institute for Drug Research.

122. August 15, 1986, Budapest, HUNGARY; Chinoin Pharmaceutical Co.

123. September 12, 1986, Castres Cedex, FRANCE; Pierre Fabre Research Center.

124. September 14-18, 1986, West Berlin, GERMANY; IX International Symposium on Medicinal Chemistry.

125. September 19, 1986, Helsingborg, SWEDEN; Leo Pharmaceutical Co.

126. September 29-30, 1986, Tokushima, JAPAN; Otsuka Research Institute.

127. October 1, 1986, Hiroshima, JAPAN; Hiroshima University.

128. October 2, 1986, Osaka, JAPAN; Takeda Chemical Industries.

129. October 3, 1986, Osaka, JAPAN; Sumitomo Pharmaceutical Co.

130. October 4, 1986, Kyoto, JAPAN; Kyoto University.

131. October 6, 1986, Tokyo, JAPAN; Hoshi University and Kanto Division of Japanese Pharmaceutical Society.

132. October 7, 1986, Tokyo, JAPAN; Tokyo University.

133. October 7, 1986, Tokyo, JAPAN; Snow Brand Milk Industries.

134. October 8, 1986, Tsukuba, JAPAN; Eisai Company.

135. October 8, 1986, Tsukuba, JAPAN; Tsukuba Research Institute.

136. October 9, 1986, Osaka, JAPAN; Fujisawa Pharmaceuticals.

137. October 10, 1986, Osaka, JAPAN; ONO Pharmaceutical Co.

138. November 2-6, 1986, Washington, D.C.; American Association of Pharmaceutical Scientists.

139. November 18-21, 1986, Edgewood, MD; Edgewood Arsenal Conference.

140. January 12-15, 1987, New York, NY; New York Academy of Sciences.

141. February 10, 1987, Gainesville, FL; Sigma Xi, "Concepts to Design Safer Drugs."

142. March 14-18, 1987, Lake Ozark, MO; 20th Higuchi Research Seminar.

143. March 30-April 3, 1987, Washington, D.C.; Federation of American Societies for Experimental Biology (FASEB).

144. April 2, 1987, Milan, ITALY; Recordati Industria Chimica e Farmaceutica S.P.A.

145. April 3, 1987, Paris, FRANCE; Delagrange, Inc.

146. April 3-13, 1987, Budapest, HUNGARY; Institute for Drug Research and Hungarian Academy of Sciences.

147. April 20-21, 1987, Bloomfield, NJ; Schering Corporation.

148. May 20-23, 1987, Frankfurt, GERMANY; Hoechst AG and Cassella Riedel Pharma GmbH.

149. June 4-7, 1987, Boston, MA; American Association of Pharmaceutical Scientists.

150. June 7-12, 1987, Madison, NJ; Residential School in Medicinal Chemistry of Drew University.

151. June 23-25, 1987, Washington, D.C.; NIH Special Study Section.

152. July 29, 1987, New York, NY; Pfizer Co.

153. August 3-7, 1987, New London, NH; Gordon Conference on Medicinal Chemistry.

154. September 21, 1987, Takasaki, JAPAN; Upjohn Company.

155. September 22, 1987, Tokyo, JAPAN; Eisai Company.

156. September 24, 1987, Osaka, JAPAN; Takeda Pharmaceutical Co.

157. September 25, 1987, Osaka, JAPAN; ONO Pharmaceutical Co.

158. September 26, 1987, Hiroshima, JAPAN; Hiroshima University.

159. September 28, 1987, Osaka, JAPAN; Osaka University.

160. September 29, 1987, Tokushima, JAPAN; Otsuka Pharmaceutical Co.

161. October 17, 1987, Budapest, HUNGARY; Chinoin Pharmaceutical Co.

162. October 22, 1987, Munich, GERMANY; Cyanamid Company.

163. October 22, 1987, Frankfurt, GERMANY; Hoechst AG.

164. October 23, 1987, Frankfurt, GERMANY; Merck.

165. October 26, 1987, London, ENGLAND; May & Baker.

166. November 17-20, 1987, Edgewood, MD; 1987 Scientific Conference on Chemical Defense Research.

167. December 2-7, 1987, Honolulu, HI; JUC PHARM SCI '87.

168. December 10, 1987, Raleigh, NC; Burroughs-Wellcome and Glaxco.

169. December 17, 1987, Beaverton, OR; Tektronix.

170. February 3-4, 1988, Chicago, IL; Hayes & Griffith.

171. February 7-9, 1988, New York, NY; Pfizer Co.

172. February 25-27, 1988, Austin, TX; Dewar Symposium.

173. March 12-16, 1988, Lake Ozark, MO; 21st Higuchi Research Seminar.

174. March 16-18, 1988, Lexington, KY; University of Kentucky.

175. April 26, 1988, Palo Alto, CA: Syntex.

176. April 27, 1988, Palo Alto, CA; Alza.

177. April 28, 1988, San Francisco, CA; Genentech.

178. May 6, 1988, Gainesville, FL; College of Pharmacy Development Advisory Board.

179. May 29-June 4, 1988, Jerusalem ISRAEL; International Conference on Pharmaceutical Science, 'Structure-Pharmacokinetic Relationships,"

180. June 22, 1988, Philadelphia, PA; HGP, Inc.

181. July 14, 1988, Newark, NJ; Johnson & Johnson.

182. August 12-19, 1988, Budapest, HUNGARY; Xth International Symposium on Medicinal Chemistry.

183. October 24-25, 1988, Newark, NJ; Johnson & Johnson.

184. October 30-November 3, 1988, Orlando, FL; Annual Meeting of the American Association of Pharmaceutical Scientists (AAPS).

185. January 27, 1989, Miami, FL; Schering-Plough Corporation.

186. March 12-15, 1989, Lake Ozark, MO; 22nd Higuchi Research Seminar.

187. April 8-11, 1989, Anaheim, CA; APhA Annual Meeting.

188. May 11-16, 1989, Thessaloniki, GREECE; Aristotelian University Postgraduate Seminar on Medicinal Chemistry.

189. May 29-30, 1989, Osaka, JAPAN; ONO Pharmaceutical Co.

190. May 31-June 1, 1989, Tokushima, JAPAN; Otsuka Pharmaceutical Co., Ltd.

191. June 2, 1989, Tokyo, JAPAN; Upjohn Company.

192. August 12-19, 1989, Budapest, HUNGARY; XIth International Symposium on Medicinal Chemistry.

193. August 21-25, 1989, Budapest, HUNGARY; Conference, The Role of Hungarians in the Scientific & Technological Progress of the World, "Recent Advances in the Design of Safer Drugs."

194. September 14-15, 1989, Bethesda, MD; APhA End-of-Summer Symposium, "Chemically Designed Targeted Drug Delivery System."

195. September 20-21, 1989, Morgantown, WV; West Virginia University Dept. of Chemistry Symposium, "Site-Specific Chemical Delivery System."

196. October 22-26, 1989, Atlanta, GA; American Association of Pharmaceutical Scientists Annual Meeting, "Concepts in the Design of Safer Drugs."

197. November 3-7, 1989, Phoenix, AZ; Preuss Foundation Seminar, "Role of the BBB in the Therapy of Brain Tumors,"

198. November 23, 1989, Kyoto, JAPAN; ONO Pharmaceutical Co., "Site-Specific Drug Delivery."

199. November 24, 1989, Osaka, JAPAN; Otsuka Pharmaceutical Co., Ltd., "Soft Drugs."

200. November 27, 1989, Tokyo, JAPAN; Japan Tobacco Company, "Novel Strategies in Drug Design."

201. December 1, 1989, London, ENGLAND; IBC Conference on Recent Advances I Site-Specific Chemical Delivery Systems, "Role of Prodrugs and Soft Drugs in Drug Delivery and targeting Systems."

202. December 4, 1989, Debrecen, HUNGARY, Medical University of Debrecen, Redox Systems of Drugs to the Brain."

203. December 11-15, 1989, Maui, HI; American College of Neuropsychopharmacology, "Clinical Utilization of Redox Drug Combinations."

204. February 12-14, 1990, Memphis, TN; College of Pharmacy, University of Tennessee, "Novel Strategies to Design Safer Drugs."

205. February 15-16, 1990, Cleveland, OH; College of Pharmacy, Case Western University, "Site-Specific Chemical Delivery Systems."

206. February 25-28, 1990, Reno, NV; AAPS Western Regional Meeting, "Brain-Specific Delivery of Peptides and Related Compounds."

207. March 1, 1990, Palo Alto, CA; Syntex Co., "Novel Strategies in Drug Design and Delivery."

208. March, 10-14, 1990, Lake Ozark, MO; Higuchi Research Seminar, "Delivery of Peptides to the Brain."

209. March 31-April 8, 1990, Bath, ENGLAND; The Biochemical Society, "Design Strategies for Safer Drugs."

210. July 1-6, 1990, Amsterdam, THE NETHERLANDS; XIth International Congress of Pharmacology, "Drug Targeting by Site-Specific Chemical Delivery Systems."

211. July 16-18, 1990, Tokyo, JAPAN; Fifth Japanese-American Conference on Pharmacokinetics and Biopharmaceutics, "Novel Site-Specific Chemical Drug Delivery Systems."

212. July 18-19, 1990, Kyoto, JAPAN; ONO Pharmaceutical Co., "Brain Delivery of Peptides."

213. July 22-23, 1990, Tokushima, JAPAN; Otsuka Pharmaceutical Co., "Brain Delivery of Neuropeptides and Related Compounds."

214. July 25-26, 1990, Osaka, JAPAN; Fujisawa Pharmaceutical Co., "Delivery of Peptides to the Brain."

215. July 26, 1990, Osaka, JAPAN; Nihon Medi-Physics, "Technetium Chelates."

216. August 22, 1990, Debrecen, HUNGARY; Hungarian Pharmaceutical Society, "Recent Advances in the Design of Safer Drugs."

217. August 23, 1990, Budapest, HUNGARY; Federation of European Biochemical Societies, "Recent Advances in Site-Specific Chemical Delivery Systems."

218. November 4-8, 1990, Las Vegas, NV; AAPS Annual Meeting, "Pharmacological Evaluation of Alprenolone Oxime - A New Potential Antiglaucoma Agent."

219. February 6, 1991, Gainesville, FL; University of Florida College of Medicine, Division of Cardiovascular Medicine, "Roundtable Discussion: A New Site-Specific Endovascular Drug Delivery Catheter System."

220. April 4, 1991, Charleston, SC; AAPS Regional Meeting, "Topical Drug Targeting by Chemical Delivery Systems and Soft Drugs."

221. April 9, 1991, Osaka, JAPAN; Takeda Chemical Industries, Ltd., "Recent Advances in Chemical-Enzymatic Targeting of Drugs."

222. April 10, 1991, Osaka, JAPAN; Otsuka Pharmaceutical Co., Ltd., "Recent Advances in Chemical-Enzymatic Targeting of Drugs."

223. April 11-12, 1991, Osaka, JAPAN; ONO Minase Research Institute.

224. April 15, 1991, Tokyo, JAPAN; Eisai Tsukuba Research Laboratories.

225. April 16, 1991, Tokyo, JAPAN; Japan Tobacco Company, "Novel Soft Drugs."

226. April 18, 1991, Suwon, SOUTH KOREA; Ajou University, "Design of Soft Drugs."

227. April 19, 1991, Suwon, SOUTH KOREA; Korean Drug Delivery Symposium, "Brain-Specific Drug Delivery."

228. April 22, 1991, Suwon, SOUTH KOREA; Korea Research Institute of Chemical Technology, "Design of Soft Drugs."

229. May 6, 1991, Dallas, TX; Alcon Laboratories, Inc., "Enzymes in the Eye."

230. May 10, 1991, Gainesville, FL; Florida School of Applied Molecular Orbital Theory, "Molecular Orbitals and Drug Design."

231. May 21, 1991, Jamaica, NY; St. John's University College of Pharmacy and Health Related Professions, "Chemical-Enzymatic Drug Targeting."

232. June 6, 1991, San Diego, CA: Gensia Pharmaceutical Co., "Metabolism-Based Drug Design."

233. June 7, 1991, La Jolla, CA: Agouron Pharmaceutical Co., "Rational Design of Drugs Based on Metabolic Considerations."

234. July 8-13, 1991, Amsterdam, THE NETHERLANDS; Controlled Release Society Symposium, Chemical Delivery Systems for Brain Targeting of Drugs."

235. July 12, 1991, Basel, SWITZERLAND; F. Hoffmann-La Roche AG, "Strategies to Design Safer Drugs."

236. July 24, 1991, Tampa, FL; Bausch & Lomb, Inc.

237. August 17-22, 1991, Budapest, HUNGARY; 33rd IUPAC Congress, "Drug Discovery by Retrometabolism – Concepts and Applications."

238. September 30-October 1, 1991, East Brunswick, NJ; Technology Management Group Conference on Pharmaceutical Markets in Imaging Agents and Related Products, "Targeted Chemicals for Imaging (Brain and Heart)."

239. October 13-16, 1991, Atlanta, G; American College of Clinical Pharmacology Meeting, "Topical Drug Targeting by Chemical Delivery and Soft Drugs."

240. October 30, 1991, Gainesville, FL; UF College of Pharmacy Honors Seminar Course in Pharmaceutical Research, "Metabolism-Based Drug Design."

241. November 226-28, 1991, Tokyo, JAPAN; ONO Pharmaceutical Co.

242. November 28, 1991, Itami, JAPAN; Senju Pharmaceutical Company, Drug Design Based on Retrometabolism Concepts."

243. November 29, 1991, Osaka, JAPAN; Otsuka Pharmaceutical Co., Ltd.

244. December 6, 1991, London, ENGLAND; IBC Conference-Drug Delivery III, "Drug Targeting by Chemical Delivery and Soft Drugs."

245. January 22-24, 1992, Gainesville, FL; UF Short Course on Surface Science in Pharmaceutical Technology, "Drug Targeting by Chemical Delivery and Soft Drugs."

246. February 8-12, 1992, King of Prussia, PA; CAChe Scientific Conference, "Chemistry by Design."

247. March 26-27, 1992, Baltimore, MD; Johns Hopkins Oncology Center, "Novel Methods of Drug Design."

248. May 15, 1992, Tokushima, JAPAN; Otsuka Pharmaceutical Co., "Recent Advances in Retrometabolic Drug Design."

249. May 18, 1992, Osaka, JAPAN; Japan Tobacco Company.

250. May 19, 1992, Itami, JAPAN; Senju Research Company.

251. May 20, 1992, Kyoto, JAPAN; ONO Pharmaceutical Co.

252. May 24-29, 1992, Jerusalem, ISRAEL; Second Jerusalem Conference on Pharmaceutical Sciences and Clinical Pharmacology, "Chemical-Enzymatic Approaches to Drug Targeting: Retrometabolism Concepts."

253. May 25, 1992, Rehovot, ISRAEL; Pharmos, Ltd.

254. June 1-4, 1992, Budapest, HUNGARY; Hungarian Academy of Sciences, "Recent Results in Retrometabolic Drug Design."

255. June 8-10, 1992, Tarrytown, NY; Conference on Topical Glucocorticoids with Increased Benefit/Risk Ratio, "Chemical Variability of Glucocorticoid Molecules: Application of the Soft Drug Concept to Topical Anti-inflammatory Agents."

256. July 22-24, 1992, Washington, D.C.; NIH Drug Discovery Groups for Alzheimer's Disease, "Brain Targeting of Peptides."

257. August 12, 1992, Miami, FL; IVAX Corporation, "Novel Soft Drugs."

258. September 10, 1992, Madrid, SPAIN; 12th World Computer Congress, "Computer-Aided Drug Design: A Neural Network Approach."

259. September 15-17, 1992, Washington, D.C.; American Colleges of Clinical Pharmacology, "Development of New Corticosteroids."

260. September 18, 21 and 23, 1992, Gainesville, FL; (UF) Frontiers of Human Knowledge (university-wide honors course), "Drug Design and Discovery Based on Retrometabolism Concepts."

261. October 9-11, 1992, Leiden, THE NETHERLANDS; Symposium on Drug Transport to the Brain: Concepts and Strategies, "The Application of Chemical Delivery Systems for Brain Targeting of Drugs."

262. October 13-14, 1992, Gainesville, FL; UF Faculty Honors Course, "In Search of Magic Bullets."

263. November 15-19, 1992, San Antonio, TX; AAPS Annual Meeting, "Brain Targeting of Peptides."

264. November 19-20, 1992, Fort Worth, TX; Alcon Laboratories, Inc., "Chemical Delivery Systems for the Eye."

265. December 1, 1992, Chicago, IL; Helene Curtis, Inc., "Novel Soft Anticholinergic Compounds."

266. February 20-22, 1993, Miami, FL; IVAX Corporation, "Soft Drugs for the Treatment of Asthma."

267. February 24, 1993, Raleigh, NC; Cato Research, Ltd., "Soft Steroids for the Treatment of Colitis."

268. March 5-8, 1993, Amelia Island, FL; Pharmos Corp., "Soft Ophthalmic Drugs."

269. April 20-21, 1993, Garden City, NY; 35th Annual Pharmacy Congress, "Application of Retrometabolic Approaches for Design of Novel Ophthalmic Drugs."

270. June 5-8, 1993, Washington, D.C.; United States Patent Office, "Novel Anionic Delivery System."

271. June 20-25, 1993, Edmonton, Alberta CANADA; 13th American Peptide Symposium, "Delivery of Peptides into the Central Nervous System by Sequential Metabolism."

272. July 23-24, 1993, Szeged, HUNGARY; International Workshop on Molecular Mechanism Regulating the Permeability of the Blood-Brain Barrier, "Strategies for Opening the Gateway to the Brain."

273. July 28-29, 1993, Rockville, MD; NIDA Technical Review Meeting on Opiate Pharmacotherapy, "Targeting Drugs to the Brain by Sequential Metabolism."

274. August 6, 1993, Bethesda, MD; NIH Drug Discovery Group Meeting, "Discovery of Novel Drugs for Alzheimer's Disease: Project 3—Neuropeptides."

275. August 8-10, 1993, Novia, MI; Symposium on Ocular Pharmacology, "The Application of Soft Drug Concepts to the Design of Ophthalmic Drugs."

276. August 22-27, 1993, Chicago, IL; 206th Annual Meeting of the American Chemical Society, "Brain Targeting of Peptides via Sequential Metabolism."

277. September 2-4, 1993, Kyoto, JAPAN; International Symposium on Delivery of Protein Drugs – the Next 10 Years, "Peptide Delivery to the Brain by Sequential Metabolism."

278. September 6, 1993, Kobe, JAPAN; Senju Pharmaceuticals.

279. September 7, 1993, Tokyo, JAPAN; Japan Tobacco Company.

280. September 10,1993, Tsukuba, JAPAN; Upjohn Pharmaceuticals, Ltd., "Soft Drugs Concept."

281. September 28-29, 1993, Bethesda, MD; NIDA Technical Review Meeting on Membranes and Barriers: Targeted Drug Delivery, "Retrometabolic Approaches to Drug Targeting."

282. October 22, 25 and 27, 1993, Gainesville, FL; (UF) Frontiers of Human Knowledge (university-wide honors course), "Drug Design and Discovery Based on Retrometabolism Concepts."

283. November 22-24, 1993, London, ENGLAND; IBC Drug Delivery 4, "Site-Specific Drugs by Chemical Transformations."

284. December 2-3, 1993, Washington, D.C.; IBC Meeting on Allergic Disease and Asthma, "Soft Drugs: A Retrometabolic Drug Design Concept."

285. April 23, 1994, Tokyo, JAPAN; Hoshi University Lecture Meeting on Comprehensive Cyclodextrins, "Recent Studies on Cyclodextrins and their Use in Drug Delivery and Targeting."

286. April 25-28, 1994, Tokyo, JAPAN; 7th International Cyclodextrins Symposium, "Optimization of Drug Targeting by Combinations of Chemical Delivery Systems and Cyclodextrins."

287. June 20-25, 1994, Edmonton, Alberta CANADA; 13th American Peptide Symposium, "Delivery of Peptides into the Central Nervous System by Sequential Metabolism."

288. July 28-29, 1994, Rockville, MD; NIDA Technical Review Meeting on Opiate Pharmacotherapy, "Targeting Drugs to the Brain by Sequential Metabolism."

289. August 21-25, 1994, Washington, D.C.; 208th American Chemical Society National Meeting, "Design of Biologically Safer Drug Based on Retrometabolic Concepts."

290. September 2-4, 1994, Kyoto, JAPAN; International Symposium Delivery of Protein Drugs – The Next 10 Years," Peptide Delivery to the Brain by Sequential Metabolism."

291. September 28-29, 1994, Rockville, MD; NIDA Technical Review Meeting on Membranes and Barriers: Targeted Drug Delivery, "Retrometabolic Design Approaches to Drug Targeting."

292. November 14-19, 1994, Buenos Aires, ARGENTINA; XV Pan American Congress of Pharmacy and Biochemistry, "Retrometabolic Drug Design Concepts."

293. December 7, 1994, Budapest, HUNGARY; National Academy of Sciences, "Retrometabolic Drug Design Concepts."

294. December 9, 1994, Budapest, HUNGARY; Technical University of Budapest, "Computer-Assisted Drug Design."

295. December 10, 1994, Budapest, HUNGARY; Gedeon Richter Works, "Soft Steroids."

296. December 12, 1994, Debrecen, HUNGARY; Medical University of Debrecen, "Novel Safe Ophthalmic Drugs."

297. January 26-29, 1995, New Orleans, LA; AOPT Annual Meeting, "Sequential Bioactivation of Methoxime Analogs of β-Adrenergic Antagonists in the Eye."

298. April 2-7, 1995, Anaheim, CA; 209th National Meeting of the American Chemical Society, "Optimization of Drug Targeting by Cyclodextrins."

299. April 10-13, 1995, Amelia Island, FL; 3rd Suncoast Workshop on the Neurobiology of Aging, "The Application of the Molecular Packaging Methods to Brain Targeting of TRH Analogs."

300. April 28-30, 1995, San Diego, CA; Houghten Pharmaceutical Co.

301. May 5, 1995, Birmingham, AL; University of Alabama Vision Research Center Visiting Scholar Program, "Retrometabolic Approaches for the Design of Novel Ophthalmic Drugs."

302. May 19-20, 1995, Thessaloniki, GREECE; 4th Conference in Advanced Medicinal Chemistry, "Retrometabolic Drug Design Concepts in Drug Targeting."

303. July 6-7, 1995, Hiroshima, JAPAN; 11th Annual Meeting of Japan Drug Delivery Systems Society, "Drug Targeting by Chemical and Enzymatic Retrometabolic Approaches to the Brain and Eye."

304. July 17, 1995, Heidelberg, GERMANY; BioResearch, BASF/Pharma Knoll Pharmaceuticals, "Chemical-Enzymatic Targeting of Drugs."

305. September 1-10, 1995, Tokyo, JAPAN; Hoshi University Visiting Professorship, several lectures of drug design.

306. September 3-8, 1995, Tokyo, JAPAN; AFMC International Medicinal Chemistry Symposium, Plenary Session, "Targeted drug Delivery to the Brian Using Chemical Delivery Systems."

307. September 11-13, 1995, Kobe, JAPAN; Academy of Pharmaceutical Science and Technology, Plenary Session, "Computer-Assisted Design of Targeted Drugs Based on Retrometabolic Concepts."

308. September 14, 1995, Osaka, JAPAN; Fujisawa Pharmaceutical Co., Ltd., "Optimal Combination of Chemical-Enzymatic and Physical Drug Targeting Approaches."

309. September 20, 1995, Osaka, JAPAN; ONO Pharmaceutical Co., Ltd., "Retrometabolic Drug Design Approaches and Computer Assisted Design of New Drugs."

310. September 22, 1995, Osaka, JAPAN; Takeda Chemical Industries, Ltd., "Retrometabolic Drug Design Approaches."

311. September 28-October 1, 1995, Geneva, SWITZERLAND; International Symposium on Experimental and Clinical Ocular Pharmacology and Pharmaceutics, Plenary Session, Retrometabolic Design Concepts in Ophthalmic Drug Discovery."

312. October 2, 1995, Milan, ITALY; BioResearch, BASF Pharma/Knoll Pharmaceutical Co., "Brain Targeting of Drugs."

313. October 6, 1995, SINGAPORE; The National University of Singapore, "Design and Development of Soft Drugs."

314. October 12, 1995, Ako, JAPAN; Otsuka Pharmaceutical Co., Ltd., "Design of Safer Ophthalmic Drugs."

315. November 1, 1995, Gainesville, FL; Frontiers of Science, "Designing Targeted Drugs for the Brain and Eye."

316. November 14, 1995, Budapest, HUNGARY; Induction into the Hungarian Academy of Sciences, Plenary Session, "The Chemical and Enzymatic Basis of the Retrometabolic Drug Design Approaches."

317. December 4-5, 1995, Ann Arbor, MI; Parke-Davis, Retrometabolic Drug Design Approaches."

318. February 5, 1996, Budapest, HUNGARY; Gedeon Richter, Ltd., "Brain Targeting Chemical Works of Gedeon Richter."

319. February 9, 1996, Frankfurt, GERMANY; Drug Targeting Symposium, German Chemical Society, "Drug Targeting Based on Retrometabolic Drug Design Approaches."

320. April 1, 1996, Budapest, HUNGARY; 8th International Cyclodextrin Symposium, "Recent Studies on the Use and Structure of Cyclodextrin Complexes."

321. April 19, 1996, Gainesville, FL; University of Florida Department of Neuroscience, "Retrometabolic Approaches to Drug Design and Targeting."

322. July 4, 1996, SINGAPORE; The National University of Singapore, "Recent Advances in Retrometabolic Drug Design."

323. July 9, 1996, Osaka, JAPAN; Senju Pharmaceutical Co., "Novel Antiglaucoma Drugs."

324. August 28, 1996, New York, NY; Forest Laboratories, "Soft Drugs."

325. September 5-12, 1996, Budapest, HUNGARY; Institute for Drug Research, Ltd., "Issues in Drug Development."

326. October 27-31, 1996, Seattle WA; AAPS Annual Meeting & Exposition, "Drug Targeting Based on Retrometabolic Drug Design Approaches."

327. November 18-20, 1996, Gainesville, FL; UF Pharmacy Honors Seminar, "In Search of Magic Bullets, "Retrometabolism-Based Drug Design."

328. January 20-22, 1997, Ispra, ITALY; Data Management in Computer-Aided Drug Design Workshop Joint Research Centre, "Computer-Assisted Design of New Drugs Based on Retrometabolic Concepts."

329. January 23-25, 1997, Brussels, BELGIUM; Janssen Pharmaceutica, "The Application of Chemical Delivery Systems for Brain Targeting of Drugs."

330. March 20, 1997, Gainesville, FL; UF College of Pharmacy National Development Advisory Board, "Issues in Drug Discovery and Targeting."

331. April 3, 1997, Austin, TX; University of Texas at Austin College of Pharmacy, "Design of Safer Drugs Using Retrometabolic Approaches."

332. April 13-17, 1997, San Francisco, CA; National Meeting of the American Chemical Society, "Design of Biologically Safer Chemicals."

333. May 6-9, 1997, Amelia Island, FL; 1st Drug Optimization via Retrometabolism Conference, (Founder and Organizer), "Retrometabolic Drug Design Concepts."

334. May 23-24, 1997, St. Petersburg, FL; Glaxo Dermatology Advisory Board Meeting, "Overview of the Soft Molecule Concept."

335. June 17, 1997, Raleigh, NC; Glaxo Wellcome, Inc.; Retrometabolic Drug Design Approaches."

336. July 9-12, 1997, Gdansk, POLAND; 6th International Symposium on Molecular Aspects of Chemotherapy, "Retrometabolic Approaches for Drug Targeting."

337. September 4, 1997, Budapest, HUNGARY; Chemical Works of Gedeon Richter, "Design of Soft Drugs."

338. September 8, 1997, Frankfurt, GERMANY; ASTA Medica, "Design of Soft Drugs."

339. September 11-14,1997, Munich, GERMANY; 2nd International Symposium on Experimental and Clinical Ocular Pharmacology and Pharmaceutics," Targeted Drug Delivery to Retina via Systemic Routes."

340. September 27-30, 1997, Chicago, IL; Abbott laboratories, Acceptance of Volwiler Research Achievement Award, "Retrometabolic Drug Design and Targeting Concepts."

341. October 22-24, 1997, Bethesda, MD; 3rd Annual Meeting of the Association for Ocular Pharmacology and Therapeutics, "Targeted Drug Delivery to Retina via Systemic Routes."

342. October 27-28, 1997, Arlington, VA; IBC's 7th Annual Conference on Asthma & Allergy, "Design of Soft Corticosteroids."

343. November 11, 1997, Budapest, HUNGARY; Institute for Drug Research, Ltd., 'Drug Development Concepts."

344. November 17 and 19, 1997, Gainesville, FL; UF Honors Seminar in Pharmacy Research, College of Pharmacy, "Retrometabolism-Based Drug Design: Making Magic Bullets Better and Safer."

345. January 14, 1998, Osaka, JAPAN; Santen Pharmaceutical Co., Ltd.; "Design of Safer Ophthalmic Drugs by Retrometabolic Approaches."

346. January 16, 1998, Hiroshima, JAPAN; Hiroshima University School of Medicine, "Design of Safer Ophthalmic Drugs Using Retrometabolic Approaches."

347. January 27,1998, Gainesville, FL; UF Department of Neuroscience, "Brain Targeting of Neuropharmaceuticals by Chemical Delivery Systems."

348. March 2, 1998, Miami, FL; IVAX Corporation, "Retrometabolic Drug Design and Targeting Approaches."

349. March 26-27, 1998, Saskatchewan, CANADA; University of Saskatchewan College of Pharmacy, "Retrometabolic Approaches for Drug Design & Targeting."

350. April 4-11, 1998, Budapest, HUNGARY; Institute for Drug Research, Ltd., "The Past and Future of Drug Discovery Research."

351. May 6, 1998, Budapest, HUNGARY; Institute for Drug Research, Ltd., "Recent Advances in Retrometabolic Drug Design."

352. May 25-28, 1998, Paris, FRANCE; 2nd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology (Invited Speaker and Session Chair), "Brain Targeting of Basic Amino Acids and their Redox Analogs Containing Peptides."

353. May 31-June 3, 1998, Santiago de Compostela, SPAIN; 9th International Symposium on Cyclodextrins (Invited Speaker and Session Chair), "The Effect of 2-Hydroxypropyl-β Cyclodextrin on the Solubility, Stability and Brain Targeting of Chemical Delivery Systems for Neuropeptides."

354. June 9-11, 1998, Tokyo JAPAN; Challenges for Drug Delivery and Pharmaceutical Technology (Invited Speaker and Session Chair), "Retrometabolic Drug Design Approaches."

355. July 16-20, 1998, Budapest, HUNGARY; Institute for Drug Research, Ltd., "Neuropeptide Targeting to the Brain."

356. July 28-August 3, 1998, Reykjavik, ICELAND; University of Iceland, "Soft Drug Approach in Drug Design."

357. October 19-23, 1998, Debrecen, HUNGARY; Medical University of Debrecen Scientific Symposium to Celebrate its 80th Anniversary, "Retrometabolic Concepts for the Design of Safer Drugs."

358. October 28, 1998, Gainesville, FL; UF Honors Seminar in Pharmacy Research, College of Pharmacy, "Retrometabolism-Based Drug Design: Making Magic Bullets Better and Safer."

359. January 4-31, 1999, Budapest, HUNGARY; Institute for Drug Research, Ltd., and the Hungarian Academy of Sciences, "Computer Drug Design" and "Computer-Assisted Design of Soft Drugs."

360. March 23-April 2, 1999, Budapest, HUNGARY; Institute for Drug Research, Ltd., and the Technical University of Budapest, "Retrometabolism-Based Drug Design" and "Graduate Education at the University of Florida."

361. April 18-20, 1999, Dresden GERMANY; Technical University of Dresden, "Chemical Approaches in the Design of Targeted Drugs."

362. April 25-30, 1999, Jerusalem, ISRAEL; 7th European Congress of Biopharmaceutics & Pharmacokinetics and the 5th Congress of the European Federation of Pharmaceutical Sciences (Invited Speaker and Session Co-Chair), "Drug Targeting Using Retrometabolic Approaches."

363. May 11-14, 1999, Amelia Island, FL; 2nd Retrometabolism-Based Drug Design and Targeting Conference (Founder and Organizer), "Recent Advances in Retrometabolic Drug Design."

364. May 20-21, 1999, Monroe, LA; AAPS-SRDG 2nd Annual Meeting (Keynote Address), "Drug Targeting Using Retrometabolic Approaches."

365. May 24, 1999, Groton, CT; Pfizer Central Research, "Retrometabolic Drug Design and Targeting" and "Computational Approaches to Retrometabolic Drug Design and Targeting."

366. June 2, 1999, New Brunswick NJ; Bristol-Myers Squibb, "Computer-Assisted Design of New Drugs Based on Retrometabolic Concepts" and "Recent Advances in Retrometabolic Design Approaches."

367. September 2-7, 1999, Beerse, BELGIUM; Janssen Pharmaceuticals, "Computational Approaches to Retrometabolic Drug Design and Targeting."

368. September 21, 1999, Tampa, FL; Bausch & Lomb, "Novel Soft Steroids for Ophthalmic Use."

369. September 23-30, 1999, Budapest, HUNGARY; Institute for Drug Research, Ltd., "Computer-Assisted Soft Drug Design."

370. October 25 & 27, 1999, Gainesville, FL; UF Honors Seminar in Pharmacy Research, College of Pharmacy, "Retrometabolic Design."

371. November 14-18, 1999, New Orleans, LA; AAPS Annual Meeting and Exposition, "Retrometabolic Approaches for Drug Design and Targeting."

372. February 18, 2000, Lisbon, PORTUGAL; 3rd International Symposium on Ocular Pharmacology & Therapeutics (ISOPP), "The Creation of a Site Active (Soft) Steroid."

373. July 7, 2000, Paris, FRANCE; 27th International Symposium on Controlled Release of Bioactive Materials, "Cyclodextrins and Brain Delivery."

374. August 29, 2000, Philadelphia, PA; Rohm & Haas Co., "Retrometabolic Drug Design and Targeting."

375. October 23 & 25, 2000, Gainesville, FL; UF Honors Seminar "in Search of Magic Bullets", College of Pharmacy, "Retrometabolic Design."

376. November 1, 2000, Indianapolis, IN; AAPS Annual Meeting and Exposition, "Retrometabolic Approaches to the Design of Ophthalmic Drugs."

377. November 13-16, 2000, Budapest, HUNGARY; Semmelweis University of Medicine, "The Högyes Lecture."

378. November 22, 2000, Osaka, JAPAN; Takeda Chemical Industries, Ltd., "Recent Results in Retrometabolic Drug Design."

379. February 8, 2001, Atlanta, GA; IBC 9th Annual Conference on Alzheimer's Disease, "Brain-Targeting of Drugs and Neuropeptides."

380. March 31, 2001, Tempe, AZ; Muro Asta Medica Investigator Meeting on Loteprednol Etabonate Nasal Spray, "Design of Loteprednol – A Soft Corticosteroid."

381. March 28, 2001, Basel, SWITZERLAND; Roche Pharmaceuticals, Ltd., "Design of Retrometabolism-Based and Specific Receptor-Oriented Drugs."

382. March 28, 2001, Basel, SWITZERLAND; Novartis Pharma, "Design of Retrometabolism-Based and Specific Receptor-Oriented Drugs."

383. April 17, 2001, Hawthorne, NY; Taro Pharmaceuticals USA Inc., "Design of Loteprednol Etabonate, A Novel Soft Steroid."

384. May 13-16, 2001, Amelia Island, FL; 3rd Retrometabolism-Based Drug Design and Targeting Conference (Founder and Organizer), "Design of a New Class of Soft Corticosteroids."

385. May 31, 2001, Stockholm, SWEDEN; Stockholm University, "Recent Advances in Retrometabolic Drug Design and Targeting Approaches."

386. October 25-28, 2001, San Francisco, CA; Foundation Fighting Blindness Meeting on Drug Delivery: Focusing on the Posterior Segment of the Eye, "Design of Novel Ophthalmic Drugs Using Retrometabolic Principles."

387. November 5 & 7, 2001, Gainesville, FL; UF Honors Seminar in Pharmacy Research, College of Pharmacy, "Retrometabolic Design – Magic Bullets."

388. February 13, 2002, Budapest, HUNGARY; Institute for Drug Research, Ltd., Scientific Retreat, "Retrometabolic Drug Design."

389. February 24-March 1, 2002, Ventura, CA; Drug Carriers in Medicine & Biology (Gordon Research Conference), "Brain Drug Delivery via Redox Carriers."

390. March 6-8, 2002, Gainesville, FL; 3rd Annual Heterocyclic Conference, "The Use of Dihydropyridine Pyridinium Salt Redox System for Development of Brain-Specific Drugs."

391. April 4-11, 2002, Taormina, SICILY; 6th Eilat Conference on New Antiepileptic Drugs, "Talampanel."

392. May 5-8, 2002, Reykjavik, ICELAND, 11th International Cyclodextrin Symposium, "Theoretical Insights into the Formation, Structure and Energetics of Some Cyclodextrin Complexes."

393. October 30 & November 1, 2002, Gainesville, FL; UF Honors Seminar in Pharmacy Research, College of Pharmacy, "Retrometabolic Design."

394. February 20, 2003, Budapest, HUNGARY; Institute for Drug Research, Ltd. Annual Scientific Meeting, "Drug Design and Discovery."

395. May 11-14, 2003, Palm Coast, FL; 4th Retrometabolism-Based Drug Design and Targeting Conference (Founder and Organizer), "Soft Corticosteroids: Design Considerations and Recent Advances."

396. February 5-6, 2004, Tokyo, JAPAN; Metabolism & Membrane Transport in Drug Discovery and Development Conference (MMT3D), "Retrometabolic Approaches in Drug Design and Targeting."

397. February 9, 2004, Osaka, JAPAN; Takeda Chemical Industries, Ltd., "Computer-Assisted Drug Design"; "Novel Approaches to Treat Sepsis"; Use of AMPA Antagonists for Treatment of Neurological Diseases" (three lectures).

398. February 18, 2004, Budapest, HUNGARY; Institute for Drug Research, Ltd. Annual Scientific Meeting, "Design of Novel Soft Steroids" and "Recent Advances in Talampanel" (two lectures).

399. May 8-13, 2004, Sardinia, ITALY; Eilat VII Conference on New Antiepileptic Drugs, "Talampanel."

400. May 17-19, 2004, Budapest, HUNGARY; Hungarian Biochemical Society Meeting, "Retrometabolic Drug Design, CDS and Soft Drugs."

401. June 12-17, 2004, Honolulu, HI; Controlled Release Society 31st Annual Meeting, "Drug Targeting to the Brain by Chemical-Enzymatic Approaches."

402. November 7-11, 2004, Baltimore, MD; AAPS Annual Meeting, "Insights for Drug Design Based on Metabolic Activity of the Eye – Soft Drugs and Chemical Delivery Systems."

403. February 17, 2005, Budapest, HUNGARY; 5th Retrometabolism-Based Drug Design and Targeting Conference (Founder and Organizer), "Overview of and Recent Advances in Retrometabolic Drug Delivery."

404. June 21-23, 2005, Budapest, HUNGARY; Institute for Drug Research Talampanel Investigator's Meeting, "History of Talampanel – Pre-Clinical & Toxicology."

405. September 26-28, 2005, Siófok, HUNGARY; 1st BBB Conference on Pharmaceutical Sciences, "Etiprednol Dicloacetate: Design and Development of a New Soft Steroid."

406. October 23-26, 2005, Sarasota, FL; 37th Annual Meeting of the Hungarian Medical Association of America, "Anti-inflammatory Soft Glucocorticoids. The Design and Development of Two Generations of New, Safer Drugs."

407. November 5-10, 2005, Nashville, TN; 2005 AAPS Annual Meeting and Exposition, "Can Peptides Ever Become Drugs? – Targeted Delivery of Peptides."

408. May 2, 2006, Biberach, GERMANY; Boehringer Ingelheim Research Institute, "Soft Steroids in Asthma and COPD."

409. September 5, 2006, Reykjavik, ICELAND; University of Iceland; "Design and Activity of Two Classes of Soft Steroids."

410. October 29-November 3, 2006, San Antonio, TX; AAPS Annual Meeting and Exposition, "Targeted Drug Delivery by Sequential Metabolism."

411. June 4, 2007, Göd, HUNGARY; 6th Retrometabolism-Based Drug Design and Targeting Conference (Founder and Organizer), "Transporter Enhanced Soft Corticosteroid Activity."

412. June 9, 2007, Munich, GERMANY; 6th Global Gator Meeting (University of Florida), "Safe Targeted Drugs by Retrometabolic Design: Soft Drugs and Chemical Delivery Systems."

413. August 5-10, 2007, Torino, ITALY; 41st IUPAC Congress, "Recent Developments in Retrometabolic Drug Design and Targeting Strategies."

414. November 10-15, 2007, San Diego, CA; AAPS Annual Meeting and Exposition – Special Lecture as Recipient of Distinguished Pharmaceutical Scientist Award, "Retrometabolic Drug Design and Targeting Strategies: Chemical Delivery Systems (CDS)."

415. April 24-26, 2008, Orlando, FL; Bausch & Lomb, Keynote Lecture and Symposium Honoring the 10th Anniversary of Loteprednol Etabonate, "Retrometabolic Drug Design" and "Discovery and Development of LE" (two lectures).

416. April 22, 2009, Nutley, NJ; Hoffman-La Roche, Inc., "Retrometabolic Drug Design."

417. May 10-13, 2009, Villas of Grand Cypress (Orlando), FL; 7th Retrometabolism-Based Drug Design and Targeting Conference (Founder and Organizer), "Recent Advances in Retrometabolic Drug Design (RMDD) and Development."

418. September 8-11, 2010, Primosten, CROATIA; 5th Central European Conference "Chemistry Towards Biology," "Retrometabolic Design: Soft Drugs and Chemical Delivery Systems."

419. March 8, 2011, Cambridge, MA; Novartis Institutes for Biomedical Research, "Drug Targeting by Chemical-Enzymatic Delivery Systems."

420. May 22-25, 2011, Sopron, HUNGARY; Hungarian Chemical Society National Conference Plenary Lecture as Recipient of Fabinyi Prize, "From Remote Substituent Effects to Retrometabolic Drug Design – 50 Years of Research in Chemistry."

421. June 2, 2011, Graz, AUSTRIA; 8th Retrometabolism-Based Drug Design and Targeting Conference (Founder and Organizer), "Recent Advances in Retrometabolic Design Concepts."

422. January 16-18, 2012, Tokyo, JAPAN; International Symposium on Past, Present and Future of Molecular Pharmacokinetics, "Transporters in Retrometabolic Drug Design."

423. May 12-15, 2013, Villas of Grand Cypress (Orlando), FL; 9th Retrometabolism-Based Drug Design and Targeting Conference (Founder and Organizer), "Recent Advances in Retrometabolic Drug Design (RMDD) and Targeting."

424. October 17-21, 2015, Orlando, FL; 10th Retrometabolism-Based Drug Design and Targeting Conference (Founder and Organizer); in conjunction with 20th North American ISSX Meeting, "Second Generation of Soft Steroids."

425. January 29, 2016, Newport Beach, CA; Association of Hungarian-American Academicians Scientific Meeting, "Retrometabolic Drug Design."

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Approximately 20 patent applications are pending as of August 2023.

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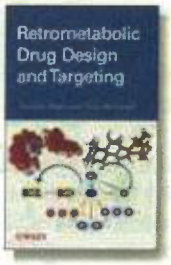
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Retrometabolic Drug Design and Targeting

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About this Book

Innovative approach to drug design that's more likely to result in an approvable drug product

Retrometabolic drug design incorporates two distinct drug design approaches to obtain soft drugs and chemical delivery systems, respectively. Combining fundamentals with practical step-by-step examples, *Retrometabolic Drug Design and Targeting* gives readers the tools they need to take full advantage of retrometabolic approaches in order to develop safe and effective targeted drug therapies. The authors, both pioneers in the fields of soft drugs and retrometabolic drug design, offer valuable ideas, approaches, and solutions to a broad range of challenges in drug design, optimization, stability, side effects, and toxicity.

Retrometabolic Drug Design and Targeting begins with an introductory chapter that explores new drugs and medical progress as well as the challenges of today's drug discovery. Next, it discusses:

- Basic concepts of the mechanisms of drug action
- Drug discovery and development processes
- Retrometabolic drug design
- Soft drugs
- Chemical delivery systems

Inside the book, readers will find examples from different pharmacological areas detailing the rationale for each drug design. These examples set forth the relevant pharmacokinetic and pharmacodynamic properties of the new therapeutic agents, comparing these properties to those of other compounds used for the same therapeutic purpose. In addition, the authors review dedicated computer programs that are available to support and streamline retrometabolic drug design efforts.

Retrometabolic Drug Design and Targeting is recommended for all drug researchers interested in employing this newly tested and proven approach to developing safe and effective drugs.

Nicholas Bodor. A Chemist from Transylvania in the American Chemical Society's Hall of Fame

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Most contributions of chemists to Medicinal Chemistry consist in discovering or inventing one or several new medicinal drugs. Very few chemists open up new methods for finding many medicinal drugs; Professor Nicholas Bodor (Nick to his friends) is such a chemist.

He was born in Satu Mare on February 1, 1939 in a family of Hungarian ethnicity. On the paternal side one can trace the roots of his Transylvanian family to the 14th century, and to the 16th century on the maternal side. From early childhood he showed exceptional qualities. He started school when he was 5 years old, two years ahead of all his classmates, and graduated first in his class at the age of 15. Based on a tough competition (180 candidates for 20 places), he was accepted in 1954 as a 15-year-old student to a five-year program as a Research Chemist at the Chemistry Faculty of the Bolyai University. All his studies had been in the Hungarian language, but in 1959 when he graduated as an organic chemist with an exceptional *red diploma*, Ceausescu's chauvinistic dictatorship closed the Bolyai University, unifying it with the Romanian counterpart (Babes Bolyai University) and discontinued courses in Hungarian.

As a result, Nick lost the promised academic position at the Bolyai University and started to work at a factory producing enameled products (dishes, stoves, etc.) in Satu Mare. He went through hard training to be an industrial engineer. In 1961, however, he was accepted at the Chemical Pharmaceutical Research Institute in Cluj (CPRI-Cluj), a subsidiary of the main Institute in Bucuresti. Because he wanted to continue his studies, he had to be accepted to the Russian-modeled doctorate (*aspirantura*). At that time, there were only two professors with the right to train aspirantura students in organic chemistry — professors Costin Nenitzescu and Eugen Angelescu, both in Bucuresti (nobody had this right in Cluj). Nick was accepted by Professor Angelescu at the end of 1961 (mainly due to the rare *red diploma* and a personal interview), while he was still working full time at the CPRI-Cluj. Soon afterwards Professor Alexandru Silberg, who taught organic chemistry at the Babes Bolyai University in Cluj, received the right to supervise doctoral students and he became the new supervisor for Nick's doctoral research. After having finished with the mandatory oral examinations in a year, he started working on the research project, a subject he himself had selected (Isonitrosation of Substituted Nitrobenzenes, Application of the Hammett-Taft Equation) and approved by the new supervisor. Soon afterwards, quite fortunately, the Soviet-style aspirantura was converted into an Academy doctorate. At the research institute Nick had a very heavy workload. He was supposed to work only seven hours a day because of *dangerous work*. — and it was indeed, as they did not even have fume hoods. Thus, he would check out at 2:00 p.m. and immediately checked-in to start his thesis work. He worked alone every day until about 10:00 p.m. The research progressed smoothly and by 1964 he had typed (in the Romanian language) the Doctoral Thesis and the 50-page summary. The summary was sent out to some 100 selected chemists in the country. The rule was to have three Committee Members/Reviewers; two of the three had to be members of the Romanian Academy; all three had to be from different institutes in different cities.

Thus, as one of the three referees, I met Nick for the first time and this is how our friendship started. He defended his thesis (in Romanian) in January 1965, and the title *Doctor in Chimie* was approved in unanimity. The process continued with further review at the Romanian Academy of Science, and then by the Supreme Committee of Scientific Titles (such tight controls existed because at that time in Romania a significant monthly stipend was paid in addition to the salary for those who heldthe degree).

At the CPRI-Cluj Nick was responsible for many, mostly synthetic, projects. He published his first paper in 1964 in *Rev. Roumaine Chim.* in English [1] demonstrating a novel mechanism (opposite to the published work by the Syntex group) of direct iodination of 20-oxopregnanes, followed by four papers based on his thesis. However, in addition to the multiple synthetic chemical work, he was also interested in the theoretical and mechanistic aspects of organic chemistry. He was fascinated by Derek Barton's *Conformational Analysis* (Nobel Prize work) and the six brilliant papers published by M. J. S. Dewar in *J. Am. Chem. Soc.* on *The electronic basis of organic chemistry*. Nick wrote a few papers on the *Remote Effects* that had been discussed by Dewar in one of his papers. Nick did not like the demonstration of separation of substituent effects and provided an alternate proof. He sent the manuscript to Michael Dewar, who subsequently invited Nick to work at University of Texas in Austin, offering to him an R. A. Welch postdoctoral fellowship. When he asked for permission to leave, the authorities in Romania did not reply. However, due to the 1968 uprising in Czechoslovakia, he was provided an opportunity through some influential friends to be allowed to go to the University of Texas. However, he had to promise though to return in one year, which he did. Working with Michael Dewar was very rewarding and successful. Nick arrived in Austin in November 1968 and by February 1969 a joint paper was submitted to be published in *Tetrahedron* [2]. After his return to Romania, Michael Dewar invited Nick again, and he joined him in Austin in 1970. This time he did not return to Romania, and was thus sentenced *in absentia* according to the standard procedure for *defectors from the socialist regime*. Michael Dewar's semiempirical computational methods for organic substances based on molecular orbital

quantum-chemical parameters determined from empirical data were in full development [3]. In two years, Nicholas Bodor and Michael J. S. Dewar published eleven joint papers, mostly in the *Journal of the American Chemical Society*. Nick also published several papers without Dewar but with other post-doctoral students of Dewar such as Nenad Trinajstiæ from Croatia, or with Emil Pop from CPRI-Cluj, in Romania.

During this period Nick met and married Sheryl, his wife for 45 years. In order to take care of his family, Nick had to move to a different position. He accepted an offer from Professor Higuchi (University of Kansas at Lawrence, Kansas), who had started a research company, INTERx. This main job was to invent new *prodrugs* (a misnomer - predrug would be a better name for a molecule that after administration changes to an improved structure by a chemical reaction, possibly due to enzymes at the desired site). After one year he was promoted to Director of Research. In this position he authored some 70 patents and numerous publications (about 50), including his first *Science* paper [4].

In 1978 Nick was approached by the new Dean of the College of Pharmacy at the University of Florida and offered a position there as a Full Professor (a rare occurrence for a young researcher) and subsequently in half a year was named Chair of the Department of Medicinal Chemistry. He is now a Graduate Research Professor Emeritus (active) at the College of Pharmacy, University of Florida (UF) in Gainesville. In 1979 Nick received the first of a long line of NIH Grants. He built a group of coworkers that at some point consisted of up to 75 members of vastly different backgrounds. More than 50 doctoral students and more than 100 postdoctoral fellows were trained by him. He is also Executive Director of the College's Center for Drug Discovery that he founded in 1986.

Here one needs a brief digression for describing the concepts of *synthon*, and *retrosynthetic (or disconnection) approach*. At present, about 100 million chemical structures are known and recorded in the *Chemical Abstracts Service* (CAS) of the American Chemical Society, the vast majority of these are organic compounds obtained in the search for new medicinal drugs. Up until the 1970s, in order to find whether a chemical structure was new, one had to spend days in the library leafing through *Chemical Abstracts Indexes* and looking at possible IUPAC names for the particular isomer with the analytically found molecular structure. Nowadays, this only takes minutes thanks to chemical applications of graph theory that deal with molecular graphs (hydrogen-depleted graphs with vertices for atoms and edges for covalent bonds). The graphs have to be assembled directly on the computer screen with the CAS SciFinder Program. Thus, without words or names, the structure is directly found and chemistry is thus the best documented science. Of course, when using words, chemistry is not different from other sciences. Molecular graphs can be cut in various ways, and computer programs first introduced by E. J. Corey (1990 Nobel Prize for Chemistry) show all possibilities for the assembly of smaller units (*synthons*) into a target molecule - this is the r*etrosynthetic (or disconnection) approach*.

In the late 1970s Nicholas Bodor applied a similar concept that includes enzyme-catalyzed reactions occurring in living cells, and invented the retrometabolic drug design system [5]. It is based on the mechanism of drug action in various tissues and it aims at improving the therapeutic index and diminish unwanted side effects. It combines two complementary concepts, namely (i) *chemical delivery systems* (CDS) with (ii) *soft drugs* (SD). In general, *a CDS is inactive* by design and is enzymatically *activated* stepwise to produce the active drug *only* (or preferentially) at the target site/organ. At the other end of the retrometabolic design loop are the soft drugs. A *SD is an active drug*, designed in such a way to be *deactivated* in a predictable and controllable way after it achieves its therapeutic role. One method of the soft drug principles of Dr. Bodor is to apply the *inactive metabolite approach*. According to this, the design starts with an inactive metabolite of a known drug which is then chemically modified (activated) to produce an isosteric/isoelectronic analogue of the active drug which then, when applied at the site of need, will perform the desired function. However, when it is absorbed or reaches the systemic circulation, it will be deactivated to the very inactive metabolite the design started from. By design this deactivation takes place by hydrolytic enzymes and avoids the usual oxidative metabolic processes. On the other side of the retrometabolic drug design loop are the CDSs. A striking example for a CDS introduced by Bodor is the *brain targeting of drugs* based on a redox targetor system, such as 1,4-dihydrotrigonelline$\leftrightarrow$trigonelline salt. The structurally similar, ubiquitous $NAD^+ \leftrightarrow$NADH redox coenzyme system assures oxidation of the initial lipophilic drug targetor conjugate to the hydrophilic, inactive quaternary form, which is due to the unique architecture of the blood-brain barrier (BBB), is *locked-in* the brain, but is eliminated fast from the whole body. Thus, further enzymatic liberation of the drug takes place essentially only in the brain, in a sustained manner. The first successful brain delivery-targeting of neuropeptides was accomplished by Bodor by combining the above redox targetor system with strategically selected amino acid *spacers* and large lipophilic modifiers, called *molecular packaging* undergoing *sequential metabolism*, a general method applied now to a variety of neuropeptides, which was highlighted by the *Harvard Health Letters* as one of the top ten discoveries of 1992. Other types of CDSs invented by Dr. Bodor target drugs to the eye, to the lungs and to specific receptors.

Among hundreds of drugs found worldwide through Nick's methodology and his computerized expert system, one should mention the soft drug Loteprenol Etabonate, an ophthalmic corticosteroid invented by Nick that is used in suspensions against eye inflammation (for instance, after cataract surgery) and allergic diseases. It was approved in 1998 and is sold in five different products. It is one of the most important and safest eye drugs. Another eye-specific drug invented by Nick is betaxoxime, which is inactive when administered but becomes active in eyes after converting, by design, an oxime into a ketone function, followed by its stereospecific reduction.

Nick organizes the biennial Retrometabolism Based Drug Design and Targeting Conference. In addition to Florida, meetings in this international series have also taken place in Japan, Hungary and Austria. He has authored or co-authored 520+ papers and over 200 patents. More than half of these patents were assigned to the University of Florida.

The first two companies that he founded were Pharmatec (which went public in1985) and Xenon Vision in1986, both with participation of the University of Florida. In 1999 he accepted a position at IVAX Corp., a world-wide pharmaceutical company (some 12,500 employees) as its Chief Scientific Officer. He was for several years President of the IVAX Research Institute, Inc. and Managing Director of the IVAX Drug Research Institute in Budapest, Hungary (formerly the Central

Pharmaceutical Research Institute of Hungary) with a leave of absence from the University of Florida. After IVAX merged with Teva in 2006, he returned to UF and additionally started Bodor Laboratories Inc. where he works today with both his son Erik and daughter Nicole to continue development of his new technologies. One current project focuses on Sofpironium Bromide, a soft anticholinergic invented by Nick with unique structure and properties which has recently shown success in a Phase IIb study for the treatment of hyperhidrosis, a medical condition with significant unmet needs.

Nicholas Bodor has been honored by numerous awards, among which are:

- Member of the Hungarian Academy of Sciences (1995)
- Fellow of the American Academy of Pharmaceutical Sciences (1983)
- Fellow of the American Association of Pharmaceutical Scientists (1986)
- Fellow of the American Association for the Advancement of Science (1989)
- Fellow of the American College of Clinical Pharmacology (1991)
- Honorary Member of the Panhellenic Society of Pharmacists (1989)
- Fellow of the International Nagai Foundation Tokyo (1995)
- AACP Volwiler Research Achievement Award (1997)
- AAPS Distinguished Pharmaceutical Scientist Award (2007)
- Florida Scientist of the Year (1984)
- Doctor Honoris Causa, University of Florida (2005)
- Doctor Honoris Causa, Technical University of Budapest (1989)
- Doctor Honoris Causa, Medical University of Debrecen (1990)
- Fabinyi Prize of the Hungarian Chemical Society, given to eminent scientists living outside Hungary (2010)
- Gold Cross of Merit of the Hungarian Republic (2004)
- Commander's Cross of the Order of Merit of the Hungarian Republic (2010)
- Hall of Fame of the American Chemical Society (2012)

In addition, a Distinguished Professorship named the *Nicholas Bodor Professor in Drug Discovery*, was established at the University of Florida in 2007. Furthermore, a Nicholas Bodor Distinguished Lectureship was introduced in 2014.

Dr. Emil Pop, who had been his fellow researcher at CPRI-Cluj, was invited by Nick to Gainesville, Florida, to work first at the University of Florida and then at Pharmatec/Pharmos as Director of Chemistry. Later, Nick helped Dr. Pop to established his successful synthesis company, Alchem Corp. (Dr. Pop passed away recently). For about the last 15 years, Professor Bodor has also supported two scholarships at two high schools in Romania, his alma mater in Satu Mare and at the Bolyai College in Tirgu Mures, awarding annually a diploma and significant monetary support to the best student in chemistry.

I believe that Professor Nicholas Bodor's remarkable activity deserves to be better known and appreciated by Romanian chemists.

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Loteprednol etabonate for inflammatory conditions of the anterior segment of the eye: twenty years of clinical experience with a retrometabolically designed corticosteroid

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REVIEW

Check for updates

Loteprednol etabonate for inflammatory conditions of the anterior segment of the eye: twenty years of clinical experience with a retrometabolically designed corticosteroid

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ABSTRACT

Introduction: Topical corticosteroids are an important pharmacotherapy for the management of various inflammatory conditions affecting the anterior segment of the eye. However, medications in this class are associated with well-known risks including increased intraocular pressure (IOP) and development of cataracts. The topical corticosteroid loteprednol etabonate (LE) was developed with the specific intention of minimizing these side effects.

Areas covered: The focus of this review is to examine published efficacy and safety data for LE, a drug engineered to undergo rapid metabolism to inactive metabolites with the goal of improved safety. Two decades of clinical research focused on LE formulations are reviewed, including the use of LE in combination with tobramycin. The cumulative body of experience affirms the concept that the molecular design of LE confers certain safety benefits without compromising the desired anti-inflammatory efficacy of a topical corticosteroid.

Expert opinion: Loteprednol etabonate is a mainstay for topical therapy of a wide variety of commonplace and niche conditions of the ocular surface and the anterior segment, including in the healing post-operative patient. Its versatility and safety allow eye care providers to recommend both acute induction as well as chronic maintenance therapy with appropriate follow-up.

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Anterior segment; cataract; dry eye; conjunctivitis; intraocular pressure; loteprednol etabonate; ocular surface disease; post-operative ocular inflammation; retrometabolic drug design; uveitis

1. Introduction

Ophthalmic corticosteroids elicit numerous potent anti-inflammatory effects and are a standard of care for the management of anterior segment inflammation. Loteprednol etabonate (LE) is an ocular corticosteroid that was engineered with the goal of maintaining robust and effective corticosteroid anti-inflammatory activity while minimizing typical risks associated with this class of medication, notably elevated intraocular pressure (IOP) and cataract formation [1]. Although the chemical structure of LE shares many similarities with other corticosteroids, its molecular configuration was purposefully designed with the goal of improved safety without sacrificing anti-inflammatory effectiveness.

LE ophthalmic suspension 0.5% and 0.2% formulations were first approved by the US Food and Drug Administration in 1998. Since then, additional formulations have been developed, including an ointment, a tobramycin combination suspension, and a gel approved in 2012, all at a concentration of 0.5%. Over the past two decades, these formulations have been studied in a variety of anterior segment inflammatory conditions.

The purpose of this review was to describe the rationale for the development of LE, the first retrometabolically designed topical corticosteroid to be commercially marketed, and provide an overview of published preclinical and clinical data, including safety data with regard to IOP elevation and cataract formation. Studies were identified through medical literature searches performed in PubMed through September 2017 using the term 'loteprednol etabonate' and limited to English-language reports. Bibliographies of identified publications were also scanned. All identified clinical studies which used a commercially marketed formulation of LE were included.

2. Retrometabolic drug design

For the treatment of anterior segment inflammatory conditions, administration of corticosteroids via the topical route is generally favored, given that distribution of systemically delivered medications into ocular tissues is limited by the blood–retinal barrier. Through topical application, drug delivery to the anterior segment is maximized while systemic effects, such as suppression of the hypothalamic-pituitary-adrenal-axis, are minimized. However, topical ophthalmic corticosteroid use can result in ocular complications including IOP elevations, posterior subcapsular cataract formation with long-term use, secondary infection, and delays in corneal wound healing [2–5]. The possibility of lessening the risks of adverse events (AEs) with topical corticosteroid use became apparent as research revealed that some of the unwanted effects of corticosteroids are mediated through lingering genomic-level activity of the

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Article highlights

- Loteprednol etabonate (LE) is a topical ophthalmic corticosteroid retrometabolically engineered to undergo rapid local metabolism into inactive metabolites with the goal of improved safety, including a lower risk of elevated intraocular pressure (IOP), relative to other ocular corticosteroids.
- Preclinical research confirmed a high level of corticosteroid-related efficacy and potency with LE, along with low aqueous humor concentrations of unmetabolized drug and little evidence of IOP elevation in animal models.
- Over the past two decades, a large body of clinical research has accumulated with various formulations of LE which include a suspension, an ointment, a combination product with tobramycin, and a recently introduced gel.
- Clinical studies have demonstrated the effectiveness of LE in various ocular inflammatory diseases (giant papillary conjunctivitis, seasonal allergic conjunctivitis, vernal keratoconjunctivitis, anterior uveitis, blepharokeratoconjunctivitis, dry eye disorders) and for control of postoperative inflammation and pain following cataract surgery and refractive surgeries.
- The risk of clinically significant IOP elevation with LE has been shown to be low (similar to that observed with vehicle) and significantly less than with other ocular corticosteroids, even in patients known to be steroid responders.
- Based on extensive experience accumulated over the past two decades, combined with the clinical flexibility offered by various formulation options, LE has become a trusted and versatile ophthalmic corticosteroid option.

This box summarizes key points contained in the article.

corticosteroid-glucocorticoid receptor (GR) complex beyond that responsible for eliciting the desired anti-inflammatory effects [6].

The concept of retrometabolic drug design, introduced by Bodor and colleagues in the 1970s [7], entails a process of designing a compound that will achieve a desired pharmacologic action followed by rapid metabolism into inactive metabolites to avoid unwanted effects. The process begins with identifying a metabolite of the reference compound that has no apparent pharmacologic activity and structurally modifying that molecule into an isosteric/isoelectronic analog (Figure 1) [8]. Thus, drugs can be purposefully designed to have a lower risk for AEs, while retaining a potency that is comparable to the reference compound. It is critical that the new compound have sufficient metabolic stability to reach its intended receptor and produce the intended pharmacological outcome. Also, and of equal importance, there must be a balance between pharmacokinetic and pharmacodynamic attributes of the drug such as solubility, lipophilicity, distribution into tissues, receptor binding, and metabolic deactivation rate. Bodor originally used the term 'soft drug design' to underscore the improved safety profile of compounds designed through this process, but that term was later replaced, in large part, by the more descriptive term 'retrometabolic drug design.'

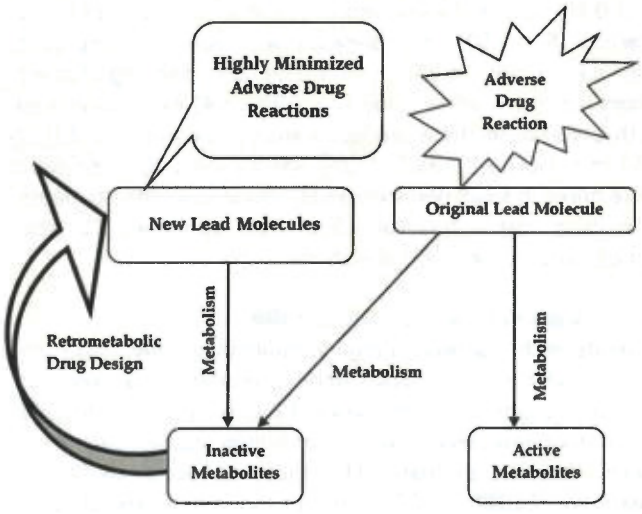


Figure 1. Concept of retrometabolic drug design in which a new lead molecule is reverse-engineered based on an inactive metabolite of a previous leading compound (adapted with permission from reference [9]).

As the basis for corticosteroid retrometabolic engineering, Bodor used Δ1-cortienic acid, an inactive metabolite of prednisolone acetate (PA). Bodor and colleagues created a series of analogs by chemical substitutions that preserved desirable corticosteroid anti-inflammatory activity while ensuring efficient metabolism to inactive metabolites, thus reducing the potential for AEs. The developmental steps have been reviewed in greater detail elsewhere [6]. Bodor and colleagues synthesized more than 100 molecules derived from the Δ1-cortienic acid structure, the most promising of which was LE [10]. Prednisolone, like many other corticosteroids, has a ketone group at the carbon-20 (C-20) position; the LE molecule has a 17β-chloromethyl ester at the C-20 position in place of the ketone group (Figure 2) [11], as well as a 17α-etabonate moiety. The expected consequence of the modification was that LE would be rapidly de-esterified to its inactive carboxylic acid metabolite after eliciting the desired pharmacologic activity. A number of other desirable characteristics contributed to the identification of LE as the most promising molecule for further development, including a high degree of lipophilicity in order to enhance penetration across biological membranes [12], evidence of potent GR binding affinity approximately 4.3-fold greater than that of dexamethasone [13], and a therapeutic index markedly greater (more than 20-fold) than other corticosteroids (hydrocortisone 17α-butyrate, betamethasone 17α-valerate, clobetasone 17α-propionate) [7]. The placement of an ester group at the C-20 position had the added benefit of lessening the risk of cataract formation compared to C-20 ketone-based steroids [14,15]. C-20 ketone steroids can form Schiff base intermediates with lysine residues of lens protein and eventual stable amine-substituted adducts following Heyns rearrangement; C-20 ester steroids, in contrast, do not form such adducts [14].

3. Preclinical and pharmacokinetic studies

Numerous preclinical investigations demonstrated that the pharmacologic characteristics of LE are, in fact, consistent with those anticipated by Bodor when he designed the molecule. In rabbit models, the highest concentrations of LE were detected in the cornea and conjunctiva, followed by the iris/ciliary body, and much lower levels in the aqueous humor (100-fold lower than corneal concentrations) [13,16]. Studies in human subjects noted measurable levels of LE in tear fluid through 24 h after instillation [17] and plasma levels of LE and

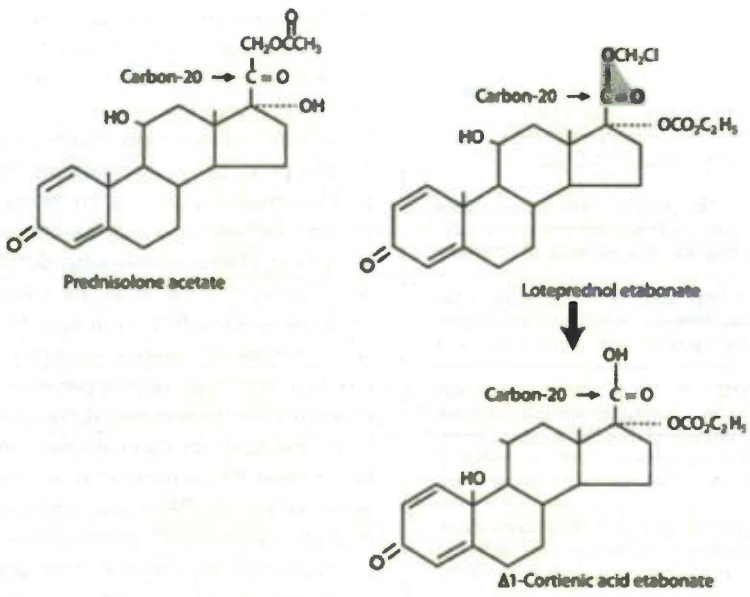


Figure 2. Prednisolone-based structure and metabolic fate of loteprednol etabonate. The ketone group at the prednisolone carbon-20 (C-20) position is replaced by a 17B-chloromethyl ester (indicated in gray) in the LE molecule. LE undergoes rapid de-esterification to the inactive Δ1-cortienic acid after exerting its effect. (Reproduced from reference [11] with permission of John Wiley and Sons).

its major (inactive) metabolite, Δ1-cortienic acid, below the level of quantification (1 ng/mL) [18], indicating a low risk of systemic exposure. The observed low aqueous humor levels of LE highlighted the possibility that this novel corticosteroid might pose little risk for IOP elevation, and rabbit studies confirmed this assumption [19]. In animal models of ocular disease and human cell tissue studies, LE demonstrated similar or greater anti-inflammatory activity as other glucocorticoids as measured by greater GR migration to the nucleus (a marker for comparing drug efficacy) relative to PA or fluorometholone [20] and reductions in cytokine and prostaglandin E2 release comparable to dexamethasone [21]. Preclinical and pharmacologic data with LE have been reviewed in greater detail elsewhere [6].

4. Clinical studies

All 5 formulations of LE (suspension [0.2% and 0.5%], 0.5% ointment, 0.5% gel, 0.5% suspension combined with tobramycin 0.3%) have undergone randomized, controlled, clinical safety and efficacy trials. Available published clinical study experience with LE is reviewed in the following paragraphs by formulation. Randomized, controlled, clinical trials for the major therapeutic usage categories of ocular inflammatory diseases and management of postoperative inflammation and pain are also outlined in Tables 1 and 2, respectively.

4.1. LE suspension

4.1.1. Giant papillary conjunctivitis

Giant papillary conjunctivitis (GPC), an ocular allergic condition most often seen in contact lens (CL) wearers, is characterized by papillary hypertrophy, mucous discharge, itching, redness, and foreign body sensation [22]. Several clinical trials evaluated the use of LE 0.5% suspension for CL-associated GPC. In one double-masked 4-week trial, patients treated with LE 0.5% QID demonstrated significantly reduced papillae severity vs. vehicle as early as day 7 and at each weekly visit through the final visit on day 28 (all $P \leq 0.02$) [23]. Patients in the LE group were given higher ratings in the investigator global assessment vs. placebo-treated patients ($P = 0.017$); patient ratings were not significantly different for LE vs. placebo, but favored LE. In two other similarly designed, double-masked studies, patients with GPC were assigned therapy with LE suspension 0.5% QID for 6 weeks while continuing CL use [24,25]. Both studies noted a significantly greater proportion of patients with an improvement in papillae of at least one severity grade among patients treated with LE vs. placebo ($P \leq 0.001$) and a greater improvement in itching with LE vs. placebo ($P \leq 0.001$). CL tolerance was marginally improved with LE in one study ($P = 0.053$) [25] and significantly improved in the other study ($P = 0.002$) [24] when compared with placebo. In these studies, transient increases in IOP of ≥10 mm Hg from baseline (considered clinically important) were noted in small percentages (3–7%) of LE-treated patients. It is likely that a reservoir effect from continued CL wear contributed to these IOP elevations.

4.1.2. Seasonal allergic conjunctivitis

Patients with seasonal allergic conjunctivitis (SAC) typically display symptoms of ocular itching, redness, and excessive tear production that can range from mild to severe [26]. Three double-masked placebo-controlled studies, each of 6-weeks duration, evaluated LE either as prophylaxis [27] or treatment [26,28] of SAC. In the prophylaxis study, LE 0.5% QID treatment was initiated prior to the allergy season (asymptomatic patients) [27]. Composite severity grades for itching and bulbar conjunctival injection (BCI) and

Table 1. Randomized, controlled, clinical studies of loteprednol etabonate for ocular inflammatory diseases.

Study	Study Treatment(s) and Duration[a]	Efficacy Findings	Safety Findings: IOP	Safety Findings: Other
Giant Papillary Conjunctivitis				
[23]	4 weeks LE 0.5% suspension QID (n = 57) vs. placebo QID (n = 56)	(i) LE reduced papillary severity score ($P \leq 0.02$ vs. placebo, days 7, 14, 21, and 28) (ii) Change in papillae AUC vs. placebo −13.4 vs. −7.5 ($P < 0.001$) (iii) Investigators global assessment better with LE ($P = 0.017$ vs. placebo)	IOP remained stable in LE-treated group, but decreased in placebo group (difference between groups, $P < 0.05$ at Day 21)	No treatment-related adverse ocular changes No infection of external ocular tissues or evidence of steroid-induced keratopathy or uveitis
[24]	6 weeks LE 0.5% suspension QID (n = 111) vs. placebo QID (n = 109)	(i) Reduced papillary severity at final visit: LE 75%; placebo 50% ($P < 0.001$) (ii) Reduced itching at final visit LE 92%; placebo 76% ($P = 0.001$) (iii) Improved lens tolerance at final visit: LE 84%; placebo 66% ($P = 0.002$ vs. placebo)	↑ IOP (≥10 mm Hg at ≥1 visit): 3% for LE group; 0% for placebo ($P = 0.099$) One patient discontinued LE early at week 5 due to elevated IOP (28 mm Hg OD and 30 mm Hg OS)	Discontinuations due to AEs (other than ↑ IOP): (i) 3 in LE group (flu-like symptoms, severe headache, taste perversion) (ii) 3 in placebo group (nausea and dizziness, corneal ulcer, twitching eyes) Other signs/symptoms were similar in both treatment groups No serious AEs
[25]	6 weeks LE 0.5% suspension QID (n = 110) vs. vehicle QID (n = 113)	(i) Reduced papillary severity at final visit: LE 78%; vehicle 51% ($P = 0.001$) (ii) Reduced itching at final visit: LE 95%; vehicle 81% ($P < 0.001$) (iii) Improved lens tolerance at final visit: LE 87%; vehicle 77% ($P = 0.053$)	↑ IOP (≥10 mm Hg): 7% vs. 0% n = 8 for LE n = 0 for vehicle 3 LE-treated patients discontinued treatment early due to elevated IOP (max of 24–38 mm Hg)	1 LE and 1 vehicle patient discontinued treatment due to conjunctivitis Other signs/symptoms were similar in both treatment groups No serious AEs reported
Seasonal Allergic Conjunctivitis				
[27]	*Prophylaxis* 6 weeks LE 0.5% suspension QID (n = 146) vs. vehicle QID (n = 147)	(i) Reduced composite of itching and BCI ($P = 0.001$ vs. vehicle) (ii) Investigators global assessment ($P < 0.001$ vs. vehicle)	↑ IOP (≥10 mm Hg): n = 0 (0%) for LE n = 2 (1.4%) for vehicle 1 LE-treated patient discontinued treatment early due to elevated IOP (24 mm Hg)	Discontinuations due to AEs (other than ↑ IOP): (i) 3 in LE group (ocular irritation, headache, rhinitis, flu symptoms, atrial fibrillation) (ii) 6 in vehicle group (2 patients with ocular allergic reactions, 2 patients with nonocular pain, viral keratitis, rhinitis) Other symptoms were similar in both treatment groups; no untoward ocular signs other than those of allergic conjunctivitis
[26]	*Treatment* 6 weeks LE 0.2% suspension QID (n = 66) vs. vehicle QID (n = 67)	(i) Reduced BCI ($P = 0.006$ vs. vehicle) and itching ($P = 0.034$ vs. vehicle) at 2 weeks (ii) Investigator global assessment at week 2 better: LE 79%; vehicle 47% ($P < 0.001$)	No ↑ IOP (≥10 mm Hg) 1 LE-treated patient discontinued early (week 1) due to IOP 9 mm Hg above pre-study baseline	≥1 AE: 68% vs. 90% ($P = 0.002$) Discontinuations due to AEs (other than ↑ IOP): (i) 1 in LE group (headache) (ii) 2 in vehicle group (severe itching, viral conjunctivitis) No serious AEs reported
[28]	*Treatment* 6 weeks LE 0.2% suspension QID (n = 67) vs. vehicle QID (n = 68)	(i) Reduced BCI, itching at 2 weeks: LE 80%; vehicle 44% ($P \leq 0.008$) (ii) Investigator global assessment at week 2 better ($P < 0.001$ vs. vehicle)	↑ IOP (≥10 mm Hg): n = 1 (1.5%) for LE n = 1 (1.5%) for vehicle 1 vehicle patient discontinued early due to elevated IOP (30 [right eye]/35 [left eye] mm Hg)	Patients with no AEs: 36% (LE) vs. 19% (vehicle) ($P = 0.035$) Discontinuations due to AEs (other than ↑ IOP): (i) 1 in LE group (hospitalized after unrelated motor vehicle accident) (ii) 1 in vehicle group (spasm on instillation of drop) No serious AEs reported

(*Continued*)

Table 1. (Continued).

Study	Study Treatment(s) and Duration[a]	Efficacy Findings	Safety Findings: IOP	Safety Findings: Other
[29]	*Conjunctival Allergen Challenge Model* Day of allergen challenge, 1 drop LE 0.2% (n = 20) or olopatadine 0.1% (n = 20) or vehicle (n = 10). (LE group given 2-week 'load' QID prior to challenge)	Assessments at 10, 15, and 20 min following allergen challenge: (i) Itching relief and redness prevention greater with olopatadine vs. LE at all time points ($P \leq 0.034$). No significant difference between LE and vehicle.	Mean IOP in the LE 0.2% group increased significantly from 14.65 at baseline to 16.25 after 14 days ($P < 0.001$) (Olopatadine only given as 1 drop)	No AEs reported in any group
[30]	*Treatment* 2 weeks LE 0.2% suspension QID (n = 151) vs. olopatadine 0.1% solution BID (n = 149)	(i) Reduced BCI, itching at week 2 in both groups ($P \leq 0.0006$ in favor of LE)	No ↑ IOP (≥10 mm Hg)	≥1 AE: 3.3% LE vs. 1.3% olopatadine ≥1 ocular AE: 2.0% LE vs. 1.3% olopatadine (P = NS) Ocular AEs (i) 1 LE patient each with: swollen eyelid (led to discontinuation), instillation-site abnormal sensation, instillation-site stinging (ii) 1 olopatadine patient each with epidemic hemorrhagic conjunctivitis (led to discontinuation), vision blurred Nonocular AEs: (i) 2 LE patients: 1 with both sinusitis and nasal septum deviation (considered serious, led to discontinuation), 1 with fibula fracture (ii) None in olopatadine group
[31]	*Treatment* 2 weeks LE 0.5% suspension QID (n = 20) or olopatadine HCl 0.1% BID (n = 20) or emedastine difumarate 0.05% BID (n = 20), or AT TID (n = 20)	(i) All active treatment groups significantly ($P < 0.05$) more effective than AT against ocular signs and symptoms at 2 weeks. No differences between active treatments	IOP not evaluated	AE data not reported (no indication evaluated). No clinically significant changes in visual acuity; no changes in fundus oculi in any group
Vernal Keratoconjunctivitis				
[32]	LE 0.5% suspension or prednisolone acetate 1% or fluorometholone acetate 0.1% (each group, n = 20 patients/40 eyes) 2 weeks, QID	(i) All active treatment groups produced significant ($P < 0.001$) improvement in signs and symptoms from baseline to Week 4. LE similar to prednisolone, but significantly better than fluorometholone ($P < 0.01$) for all signs/symptoms except chemosis (all treatments similar) (ii) LE and prednisolone groups had similar mean visual acuity improvements, both higher compared with fluorometholone (P = 0.02)	Significantly ($P < 0.001$) elevation in mean IOP in prednisolone group only after day 3. 3 patients in prednisolone group dc/d study because of IOP elevation in Week 2	No other AEs reported in any group
Anterior Uveitis				
[33]	6 weeks LE 0.5% suspension (n = 36) vs. prednisolone 1% (n = 34). Regimen: Days 0–7: 8 times/day Days 8–14: 6 times/day Days 15–21: QID Days 21+: tapered according to severity of uveitis	Patients with resolution (score of 0) by the final on-treatment visit (LOCF), LE vs. prednisolone: (i) ACC: 74 vs. 88% (P = NS) (ii) Flare: 71 vs. 81% (P = NS) (iii) Pain: 79 vs. 81% (P = NS)	↑ IOP (≥10 mm Hg): n = 0 (0%) for LE n = 1 (2.9%) for prednisolone	No patients discontinued from study because of AEs No serious AEs reported

(*Continued*)

Table 1. (Continued).

Study	Study Treatment(s) and Duration[a]	Efficacy Findings	Safety Findings	
			IOP	Other
[33]	4 weeks LE 0.5% suspension (n = 84) vs. prednisolone 1% (n = 91) Regimen: Days 0–7: Hourly, up to 16 times/day Days 8–14: Every 2 h, up to 8 times/day Days 15–21: QID Days 22–25: BID Dats 26–28: QD	Patients with resolution (score of 0) by the final on-treatment visit (LOCF), LE vs. prednisolone: (i) ACC: 72 vs. 87% (P = 0.015) (ii) Flare: 66 vs. 82% (P = 0.017) (iii) Pain: 90 vs. 85% (P = NS)	↑ IOP (≥10 mm Hg): n = 1 (1.2%) for LE n = 6 (6.6%) for prednisolone	Discontinuations due to AEs (other than ↑ IOP): (i) 2 in LE group (cystoid macular edema/ decreased visual acuity, various ocular symptoms) (ii) 2 in prednisolone group (interstitial keratitis, increase in age-related macular degeneration) Otherwise, no serious AEs reported
Blepharokeratoconjunctivitis (BKC) or Blepharitis				
[47]	(BKC) 2 weeks LE 0.5%/tobramycin 0.3% QID (n = 138) vs. dexamethasone 0.1%/tobramycin 0.3% QID (n = 138)	(i) Mean change [SD] in reduced composite signs and symptoms at day 15 (−15.2 [7.3] vs. −15.6 [7.7], P = NS) (ii) Investigator global assessment: 43.6 vs. 40.9% cured (P = NS)	↑ IOP (≥10 mm Hg): n = 0 for LE/T n = 1 (0.7%) for DM/T Mean IOP increase at day 7 (−0.1 mm Hg vs. 0.6 mm Hg, P = 0.04), day 15 (−0.1 mm Hg vs. 1.0 mm Hg, P = 0.01), and overall (1.6 mm Hg vs. 2.3 mm Hg, P = 0.02)	≥1 ocular AE: 2.9 vs. 6.5% (P = NS) (i) LE/T group: 1 subject each (allergic conjunctivitis, eye irritation, eye pain, increased IOP) (ii) DM/T group: 1 subject each (decreased lacrimation, foreign body sensation; 2 subjects (punctate keratitis); 5 subjects (increased IOP) No serious ocular AEs reported 4 subjects (2.9%) in each group reported a non-ocular AE (no infections) 2 subjects in the LE/T group discontinued due to AEs (1 each headache, allergic conjunctivitis) No clinically relevant findings/differences between treatment groups related to visual acuity or biomicroscopy
[48]	(BKC) 2 weeks LE 0.5%/tobramycin 0.03% QID (n = 180) vs. dexamethasone 0.1%/tobramycin 0.3% QID (n = 177)	(i) Improvement from baseline in composite signs and symptoms severity at day 15 in both groups (P < 0.0001 vs. baseline) (ii) Mean change [SD] in reduced composite signs and symptoms at day 15 (−11.6 [4.6] vs. −12.4 [4.7], P = NS)	↑ IOP (≥10 mm Hg): n = 6 (3.4%) for LE/T n = 13 (7.3%) for DM/T (P = NS) One eye in DM/T group experienced IOP ≥30 mm Hg Mean IOP increase at day 15: 1.33 mm Hg vs. 2.43 mm Hg (P = 0.004)	≥1 ocular AE: 13.0 vs. 23.2% (1 case bacterial keratitis in LE group) Nonocular AEs: (i) LE/T group: 1 subject each (mild nausea, moderate spinal disorder, mild headache, mild alopecia) (ii) DM/T group: 1 subject each (mild nausea, mild nasopharyngitis, mild dizziness) No serious AEs reported
[51]	(Blepharitis, pediatrics) LE 0.5%/tobramycin 0.3% (n = 72) or vehicle (n = 36) QID for 7 days followed by BID for 7 days along with warm compresses BID throughout the study	(i) Efficacy findings from this study were unclear due to improvements in all treatment groups	Mean IOP and IOP changes from baseline were not different between LE/T and vehicle treatment groups at any study visits No ↑ IOP (≥10 mm Hg)	No serious ocular AEs were reported; ≥1 treatment-emergent ocular AE: LE group – 3 (4.2%); vehicle – 2 (5.6%) ≥1 treatment-emergent nonocular AE: LE group – 6 (8.3%); vehicle – 2 (5.6%) No AEs reported
[50]	(BKC) LE 0.5%/tobramycin 0.3% BID (n = 20), dexamethasone 0.1%/tobramycin 0.3% BID (n = 20) for 3–5 days	Scores at 3–5 days of treatment, DM/T vs. LE/T: Ocular surface (1.8 vs. 3.4), blepharitis (0.9 vs. 1.35), discharge (0.2 vs. 0.6), and conjunctivitis (0.15 vs. 0.6) (all $P \leq 0.025$) Corneal punctate epithelial keratopathy scores were not significantly different between treatments	No differences between groups for IOP findings	No clinically meaningful changes in visual acuity
[51]	(BKC, pediatrics) 2 weeks LE 0.5%/tobramycin 0.3% QID (n = 34), LE 0.5% QID (n = 35), Tobramycin 0.3% QID (n = 34), or vehicle QID (n = 34)	(i) Efficacy findings from this study were unclear due to improvements in all treatment groups	IOP not evaluated	No serious ocular AEs were reported; ≥1 ocular AE: LE/T group – 1 (2.9%); LE – 4 (11.4%); T – 0; vehicle – 0; ≥1 non-ocular AE: LE/T – 2 (5.9%); LE – 6 (17.1%), T – 6 (17.6%); vehicle – 5 (15.2%)

(*Continued*)

Table 1. (Continued).

Study	Study Treatment(s) and Duration[a]	Efficacy Findings	Safety Findings	
			IOP	Other
Dry Eye Disorders				
[34]	(Keratoconjunctivitis sicca) 4 weeks LE 0.5% suspension QID (n = 32) vs. vehicle QID (n = 34)	(i) Reduced hyperemia at week 2 and week 4 (P = 0.0473 vs. vehicle) (ii) Subset analysis showed reduced central corneal staining, nasal bulbar conjunctival hyperemia, and lid margin injection at some visits (P < 0.05 vs. vehicle)	No ↑ IOP (≥10 mm Hg) No significant change in mean IOP	≥1 treatment-related AE: 16.7 vs. 23.5% (treatment-related ocular AEs included increased burning, redness, blurring of vision, foreign body sensation) No clinically significant changes in visual acuity or treatment-related abnormalities on slit-lamp examination, lens examination, or fundoscopy No treatment-related serious AEs
[35]	(Meibomian gland dysfunction) 2 months LE 0.5% suspension QID following eyelid scrubs with warm compresses BID (Group I; n = 34) vs. eyelid scrubs with warm compresses only BID (Group II; n = 36)	(i) Significantly lower levels of IL-6 (P = 0.007), IL-8 (P = 0.001), and IL-1β (P = 0.030) in Group I vs. Group II (ii) Significantly longer TBUT (P = 0.014) and lower (better) staining scores (cornea, conjunctiva, DEWS, Oxford) (P < 0.05) in Group I vs. Group II (iii) Significantly larger improvements in lid margin abnormality (P = 0.018) and meibum quality (P < 0.001) in Group I vs. Group II at 2 months compared to baseline (iv) Significant improvements in expressibility (P = 0.019), ocular irritation symptom score (P < 0.001), and MGD stage (P < 0.001), Group I vs. Group II at 2 months	No significant difference in mean IOP between groups at each time point. No ↑ IOP (≥10 mm Hg)	Authors noted there were no serious AEs; no other AE information provided
[36]	(Dry eye syndrome [DES]/GVHD) LE 0.5% suspension BID (n = 38 patients; n = 76 eyes) vs. tCSA 0.05% BID (n = 37 patients; n = 74 eyes) Treatment starting 1 month prior to, and for 12 months after, hematopoietic stem cell transplant	(i) Similar rates of DES incidence (P = 0.22) and progression (P = 0.41) between groups (ii) Significant increase in tear osmolarity for LE compared to tCSA at 12 months (P = 0.08) (iii) 38% rate of disease progression with tCSA compared to 26% rate with LE at 12 months	No difference between groups in IOP change from baseline to 12 months (P = 0.70) No ↑ IOP (≥10 mm Hg from baseline)	Mean visual acuity remained stable in both treatment groups
[37]	(Chronic dry eye disease) LE 0.5% suspension or AT QID for 2 weeks, followed by tCSA BID with either LE or AT BID for another 6 weeks LE group, n = 57 AT group, n = 55	(i) LE pretreatment significantly reduced tCSA stinging (P < 0.05) (ii) LE group demonstrated significantly greater OSDI improvement than AT. (iii) Onset of effectiveness was achieved after 15 days of LE + tCSA compared with 45 days for AT + tCSA	Mean IOP did not change in either treatment group	Ocular AE profiles were similar between treatment groups The most common ocular AEs were eye pain (LE, 7.0%; AT, 2.6%), reduced visual acuity (LE, 5.3%; AT, 3.2%), conjunctival hyperemia (LE, 5.3%; AT, 2.6%), and IOP increased (LE, 5.3%; AT, 1.3%) No cataract, hypotony, posterior capsular opacification, or surgical wound complications reported
[65]	(Mild-to-moderate dry eye) Treatment groups: 1) LE gel BID for 12 weeks (n = 36) 2) LE gel BID weeks 1–4, along with tCSA BID week 3–12 (n = 33) 3) tCSA BID for 12 weeks (n = 33)	(i) At 12 weeks, all treatments improved signs and symptoms of dry eye compared with baseline (P < 0.05)	IOP >21 mm Hg, n = 2: 1 each in LE and LE + tCSA groups at week 12	Few AEs (all ocular) with any of the 3 treatments, including burning, stinging, discomfort on instillation Biomicroscopy/ophthalmoscopy findings unremarkable No serious AEs

ACC: anterior chamber cells; AE: adverse event; AT: artificial tears; BCI: bulbar conjunctival injection; BID: twice daily; BKC: blepharokeratoconjunctivitis; DES: dry eye syndrome; IOP: intraocular pressure; GVHD: graft versus host disease; LE: loteprednol etabonate; LOCF: last observation carried forward; NS: not significant; QD: once daily; QID: four times daily; tCSA: topical cyclosporine A.

[a]N values represent number of randomized patients unless indicated otherwise.

Adapted from [6] with permission of Hindawi.

Table 2. Randomized, controlled, clinical studies of loteprednol etabonate for postoperative inflammation.

Reference	Procedure, treatment duration, study treatments[a]	Efficacy	Safety Findings: IOP	Safety Findings: Other
[41,43]	Postoperative cataract surgery with intraocular lens implantation; 2 weeks LE 0.5% suspension QID (n = 109 [ITT population]) vs. vehicle QID (n = 113 [ITT population])	(i) Resolution of ACI at final visit: 64 vs. 29% (P < 0.001 vs. vehicle) (ii) Treatment failure rate: 6% vs. 30% (P < 0.001 vs. vehicle) (iii) Investigator global assessment of treatment effect (P < 0.001 vs. vehicle) (iv) Grade 0 (no pain) at final visit: 85 vs. 54% (P = 0.003)	↑ IOP (≥10 mm Hg) n = 3 (2.8%) for LE n = 0 for vehicle Mean IOP decreased in both groups	≥1 AE: 58 vs. 80% (P < 0.001) Discontinuations due to AEs: (i) 2 in LE group (ocular inflammation, chest pain in patient with history of cardiovascular disease) (ii) 3 in vehicle group (ocular inflammation) Other serious AEs included: (i) 2 in LE group (endophthalmitis, myocardial infarction) (ii) 1 in vehicle group (cystoid macular edema)
[42,43]	Postoperative cataract surgery with intraocular lens implantation; 2 weeks; LE 0.5% suspension QID (n = 102) vs. vehicle QID (n = 101)	(i) Resolution of ACI at final visit: 55 vs. 28% (P < 0.001) (ii) Treatment failure rate: 7 vs. 32% (P < 0.001 vs. vehicle) (iii) Investigator global assessment of treatment effect (P < 0.001 vs. vehicle) (iv) Grade 0 (no pain) at final visit: 83 vs. 59% (P = 0.018)	↑ IOP ≥10 mm Hg) n = 0 for LE n = 1 (1.0%) for vehicle	≥1 AE: 54 vs. 75% (P = 0.002) 4 patients (all in vehicle group) discontinued due to AEs 1 patient in LE group hospitalized due to itching of arms, legs, and trunk; fatigue; and leg cramps
[55]	Postoperative cataract surgery with intraocular lens implantation; 2 weeks; LE 0.5% ointment QID (n = 404) vs. vehicle QID (n = 401) [2 studies]	(i) Resolution of ACI at day 8: 27.7 vs. 12.5% (P < 0.0001) (ii) Grade 0 (no pain) at day 8: 75.5 vs. 43.1% (P < 0.0001) (iii) Need for rescue medication: 27.7 vs. 63.8% (P < 0.001)	↑ IOP (≥10 mm Hg): n = 3 (0.7%) for LE n = 1 (0.2%) for vehicle Mean IOP decreased in both groups	≥1 ocular AE: 47.2 vs. 78.0% (P < 0.0001) Most common ocular AEs with LE were anterior chamber inflammation, photophobia, corneal edema, conjunctival hyperemia, eye pain, and iritis (all but corneal edema and photophobic, P < 0.05 vs. vehicle) ≥1 nonocular AE: 5.2 vs. 4.5% (P = NS) 3 subjects in vehicle group discontinued early due to a serious AE 1 serious ocular AE of cystoid macular edema in LE group No differences between treatment groups in visual acuity or dilated fundoscopy results Slit lamp results either comparable between treatment groups or favored LE
[58]	Postoperative cataract surgery with intraocular lens implantation; 2 weeks; LE 0.5% gel QID (n = 203) vs. vehicle QID (n = 203)	(i) Resolution of ACC at day 8: 30.5 vs. 16.3% (P < 0.001) (ii) Grade 0 (no pain at day 8): 72.9 vs. 41.9% (P < 0.001) (iii) Need for rescue medication: 42.4 vs. 71.9%	↑ IOP (≥10 mm Hg): n = 1 (0.5%) for LE; n = 1 (0.5%) for vehicle No significant difference between groups in mean change in IOP	≥1 ocular AE: LE – 18.7%; vehicle – 21.7% (P = NS) ≥1 drug-related ocular AE: LE – 4.4%; vehicle – 6.9% ≥1 nonocular AE: LE – 4.4%; vehicle – 4.4% (none considered treatment related) Treatment-emergent serious AEs: (i) 1 in LE group (cystoid macular edema) (ii) 3 in vehicle group (cystoid macular edema, bronchitis and exacerbated systolic congestive heart failure in same patient) No notable differences between treatment groups in visual acuity or dilated fundoscopy results Few patients in LE group had worsening ocular signs on biomicroscopy, and findings generally favored LE over vehicle

(*Continued*)

Table 2. (Continued).

Reference	Procedure, treatment duration, study treatments[a]	Efficacy	Safety Findings: IOP	Safety Findings: Other
[59]	Postoperative cataract surgery with intraocular lens implantation; 2 weeks; LE 0.5% gel QID (n = 206) vs. vehicle QID (n = 201)	(i) Resolution of ACC at day 8: 31.1 vs. 13.9% (P < 0.001) (ii) Grade 0 (no pain at day 8): 75.7 vs. 45.8% (P < 0.001) (iii) Need for rescue medication, 30.1 vs. 61.2% (statistical significance not published)	↑ IOP (≥10 mm Hg): n = 0 for LE; n = 1 (0.5%) for vehicle	≥1 ocular AE: LE – 16.0%; vehicle – 28.9% (P = 0.002) ≥1 drug-related ocular AE: LE – 2.4%; vehicle – 7.5% ≥1 nonocular AE: LE – 5.8%; vehicle – 2.5% (P = NS; potential drug-related in LE group included facial rash and dry mouth) Serious AEs: (i) 3 in LE group (diverticulitis, cholecystitis, and myocardial infarction) (ii) 2 in vehicle group (dehydration and hypokalemia in same patient) With exception of change from baseline in visual acuity significant worse in vehicle group at Day 8 (P = 0.032), no notable differences between treatment groups in visual acuity or dilated fundoscopy results Few patients in LE group had worsening ocular signs on biomicroscopy, and findings generally favored LE over vehicle
[44]	Postoperative cataract surgery with intraocular lens implantation; 30 days; LE 0.5% suspension (n = 30) vs. ketorolac tromethamine 0.5% (n = 30); each QID for 1 week, then BID through 30 days	(i) Both treatments equally improved cell and flare, conjunctival inflammation graded by slit lamp (ii) Similar improvements in visual acuity	No between-group difference in IOP at any time point	No AEs reported in either group
[45]	Postoperative cataract surgery; LE 0.5% suspension (n = 48) or prednisolone acetate 1% (n = 45) QID for 3 weeks after surgery	(i) Control of inflammation was equivalent between treatment groups by assessment of cell and flare grading 1, 3, 7, and 21 days postoperatively	1 patient (2.2%) in the prednisolone group had ↑ IOP (≥10 mm Hg) 7 days after surgery considered drug-related; 2 patients (2.2%) had ↑ IOP (≥10 mm Hg) 1 day after surgery (treatment group not indicated) Mean change in IOP was numerically higher in the prednisolone acetate group than in the LE group (P = NS)	5 patients (3 [6.7%] prednisolone acetate group, 2 [4.2%] LE group) reported AEs during the course of the study
[63]	Phacoemulsification cataract surgery; difluprednate (n = 30 eyes) or LE gel (n = 30 eyes) QID for 3 days preoperatively; QID for 1 week postoperatively, then BID for 1 week	(i) Both treatments were equally effective in reducing inflammation (ii) Both treatment had a similar effect on postoperative visual recovery	At day 1 visit, ↑ IOP (≥10 mm Hg): n = 8 eyes (26.7%) for LE; n = 9 eyes (30.0%) for difluprednate; no patients with ↑ IOP at any other visit IOP changes were reportedly similar between the two treatment groups	↑ retinal thickness developed in 0 patients in LE group and 2 patients (6.7%) in difluprednate group
[46]	Photorefractive keratectomy; n = 62 patients; 1 eye of each assigned to LE 0.5% suspension or fluorometholone 0.1% for 3 months (QID month 1, TID month 2, BID month 3)	(i) Both treatments equally effective with regard to visual acuity, manifest refraction, corneal haze, ocular discomfort and redness (ii) No visually significant corneal haze in either treatment group	No ocular hypertension in either group (IOP rise of >10 mm Hg or IOP >21 mm Hg) No significant differences between groups in IOP elevation	

(*Continued*)

Table 2. (Continued).

Reference	Procedure, treatment duration, study treatments[a]	Efficacy	Safety Findings: IOP	Safety Findings: Other
[62]	Photorefractive keratectomy; n = 132 patients (261 eyes) randomized to: LE 0.5% gel (n = 114 eyes) QID for 1 week TID for 3 weeks BID for 1 month QD for 1 month OR Prednisolone 1% (n = 147 eyes) QID for 1 week BID for 3 weeks [Switch to fluorometholone] TID for 1 month BID for 1 month	(i) Similar incidence of haze (LE, 2.6% [3/114 eyes]; Prednisolone/fluorometholone, 4.8% [7/147 eyes]; P = 0.37) (ii) At 3 months, similar uncorrected visual acuity (LE, −0.078 ± 0.10; Prednisolone/fluorometholone, 0.075 ± 0.09; P = 0.83)	Clinically significant ↑ IOP (≥10 mm Hg over baseline or IOP >21 mm Hg): 1.8% (2/114 eyes) in the LE group; 4.1% (6/147 eyes) in the prednisolone group (difference not statistically significant)	

ACI: anterior chamber inflammation; AE: adverse event; BID: twice daily; BKC: blepharokeratoconjunctivitis; IOP: intraocular pressure; LE: loteprednol etabonate; NS: not significant; QID: four times daily; tCSA: topical cyclosporine A; TID: three times daily.

[a]N values represent patients unless indicated otherwise.

Adapted from [6] with permission of Hindawi.

investigator global assessments significantly favored LE 0.5% treatment ($P \leq 0.001$) compared with placebo during periods of peak pollen counts. Two patients (1.4%; n = 143) in the placebo group had an IOP increase ≥10 mm Hg compare to none in the LE group (0%; n = 145). The efficacy of LE 0.2% QID in patients exhibiting ocular signs and symptoms of SAC was evaluated in 2 similarly designed studies [26,28]. In both trials, BCI and itching were reduced by a greater extent with LE compared with placebo at day 14 ($P \leq 0.034$) and investigator global assessments at week 2 favored LE over placebo ($P < 0.001$). Across both studies, IOP elevations ≥10 mm Hg over baseline were noted in 1 (0.8%) LE-treated patient and 1 (0.7%) placebo-treated patient.

LE 0.2% suspension was compared with a dual-acting antihistamine mast-cell stabilizer, olopatadine HCl 0.1% solution, and with placebo for inhibiting early-phase allergic responses after conjunctival allergen challenge (CAC) in a double-masked, randomized study of 50 subjects with a history of allergic conjunctivitis [29]. Subjects in the LE study arm were treated with a 14-day 'loading' regimen (QID), while subjects randomized to olopatadine and placebo treatments received placebo QID for 14 days. On day 15, study medication was instilled 15 min prior to the CAC. At all 3 assessment time points (10, 15, and 20 min after challenge), improvements in itching and redness were better with olopatadine compared with LE ($P < 0.05$). Mean IOP in the LE 0.2% group increased from baseline (14.7 mm Hg) to 14 days (16.3 mm Hg) ($P < 0.001$). The authors acknowledged that a limitation of this study was its focus on the acute-phase reaction only rather than late-phase, in which corticosteroids are most effective.

Two environmental studies compared LE and olopatadine in patients with SAC, including a 2-week investigator-masked study in Chinese patients with SAC [30] which found LE 0.2% superior to olopatadine for improving BCI and ocular itching from baseline ($P \leq 0.0006$). There were no clinically significant increases from baseline in IOP (≥10 mm Hg). In the other active-comparator study (also investigator-masked), Chinese children (ages 5–10 years) with SAC were randomized to bilateral treatment with olopatadine hydrochloride 0.1% twice a day (BID), emedastine difumarate 0.05% BID, LE 0.5% QID, or artificial tears (AT) for 14 ± 2 days [31]. On both days 8 and 15, all active treatments were found to be more effective than AT ($P < 0.05$) in reducing signs (conjunctival papillae, follicle, conjunctival congestion, edema) and symptoms (itching, photophobia, blinking) of SAC. However, no difference was observed among active treatments, possibly due to the sample size (n = 20 per treatment) and short duration of the study.

4.1.3. Vernal keratoconjunctivitis

Vernal keratoconjunctivitis (VKC) is a particularly severe form of ocular allergy which typically requires management with topical corticosteroids. The use of LE 0.5% was compared against PA 1% or fluorometholone 0.1% in an investigator-masked randomized study, each administered QID for 28 days [32]. Based on the evaluation of major signs and symptoms of VKC (itching, redness, tearing, foreign body sensation,

burning, hyperemia, chemosis, Trantas dots, and corneal pannus formation, each graded 0 [none] to 3 [severe]), LE and PA produced similar and significant ($P < 0.001$) improvement from baseline, and both were better ($P < 0.01$) than fluorometholone for all measures except chemosis. Mean IOP was significantly elevated in the PA group only (Week 1 through Week 4).

4.1.4. Anterior uveitis

LE 0.5% was compared with PA 1% for the treatment of acute anterior uveitis in two randomized, double-masked studies [33]. In one study, both treatments were instilled 8 times per day for the first week, 6 times per day for the second week, QID for the third week, and then tapered according to the severity of the uveitis up to a total of 42 days of treatment. In the second and shorter study, treatment started with hourly administration (up to 16 times daily) for the first week, then every 2 h (up to 8 times per day) for the second week, QID for the third week, finally tapering down to QD by day 28. In each study, LE and PA both substantially reduced signs (anterior chamber cell [ACC] and flare) and symptoms (pain, photophobia) of uveitis from baseline to 28 days. In study 1, no statistical differences were observed between LE and PA in the proportion of patients with resolution of ACC, flare, pain, and photophobia by the last on-treatment visit (last observation carried forward) and at each individual study visit. In the second and larger study, more patients achieved resolution of cell and flare by the last visit (last observation carried forward) with PA compared with LE ($P \leq 0.017$); however, there were no significant differences between treatments noted at individual study visits. Numerically but not statistically, greater percentages of patients experienced resolution of pain and photophobia with LE as compared to PA. Across both studies, IOP increases ≥10 mm Hg over baseline were noted in 1 (0.8%) LE- and 7 (5.6%) PA-treated patients.

4.1.5. Dry eye disorders

LE has been studied as a treatment for a variety of dry eye disorders [34–36], as well as induction therapy to reduce stinging associated with topical cyclosporine therapy for dry eye disease [37,38]. A 1-month randomized, double-masked, vehicle-controlled pilot study assessed the efficacy of LE suspension 0.5% QID in patients with dry eyes related to delayed tear clearance [34]. The primary objective variable, composite corneal staining, did not improve significantly with either treatment, while the primary subjective variable, severity of worst baseline symptom (visual analog scale), improved similarly from baseline in both groups ($P < 0.0001$). Among a cohort of patients with moderate or worse inflammation associated with dry eye, significant differences ($P < 0.05$) were noted at some visits in central corneal staining, nasal bulbar conjunctival hyperemia, and lid margin injection between the LE- and vehicle-treated groups. There were no instances of clinically significant IOP elevations during the month-long treatment.

A randomized, controlled, investigator-masked trial evaluated tear cytokine levels and clinical outcomes in patients with meibomian gland dysfunction (MGD) treated BID with eyelid scrubs and warm compresses alone or in combination with LE QID for 2 months [35]. The group using adjunctive LE demonstrated greater improvements from baseline in almost every clinical outcome evaluated, including TBUT, ocular surface epitheliopathy (staining), eyelid margin abnormality, meibum quality, expressiblity, ocular irritation, and MGD stage compared with eyelid scrubs and warm compresses alone ($P < 0.05$). The group using adjunctive LE also demonstrated significantly lower levels of the interleukins IL-6, IL-8, and IL-1ß (all $P < 0.05$ vs. non-LE group). There were no significant IOP increases in either group.

A prospective, randomized trial compared LE with topical cyclosporine 0.5% emulsion (tCSA) to prevent and treat graft versus host disease-related dry eye syndrome (DES) in patients undergoing hematopoietic stem cell transplant [36]. Patients were randomized to LE 0.5% BID or tCSA 0.05% BID starting 1 month before transplantation. After 12 months, rates of DES incidence and progression were similar between the two groups ($P = 0.22$ and $P = 0.41$, respectively; log-rank test). Kaplan–Meier analysis revealed a numerically lower rate of new DES development in the LE versus the tCSA group (79 vs. 90%), as well as a numerically lower rate of DES progression among patients who had DES at the beginning of the study (26 vs. 38%). There were no IOP elevations ≥10 mm Hg above baseline.

While tCSA (Restasis®) is indicated and effective for keratoconjunctivitis sicca (dry eye) patients [39], stinging is a common and sometimes treatment-limiting adverse reaction [40]. A retrospective analysis assessed clinical signs and symptoms and medication tolerability of patients who received LE 0.5% BID for 2–16 months prior to tCSA therapy initiation for chronic dry eye disease (CDED) compared with patients who did not receive LE induction therapy [38]. Of 36 patients in the induction therapy group, 2 (5.5%) reported significant stinging, leading to discontinuation in 1 patient (2.8%). In the group that did not receive LE pretreatment, 8 (22%) developed stinging, leading to discontinuation in 3 (8.3%) patients. Between group differences were significant for severe stinging ($P < 0.02$) and for tCSA discontinuation because of severe stinging ($P < 0.04$). There were no significant IOP elevations in the LE induction group, defined as 2 consecutive visits with an IOP increase ≥6 mm Hg from baseline.

In a later double-masked study, patients with CDED were randomized to treatment with either LE ($n = 61$) or AT ($n = 57$) QID for 2 weeks, followed by tCSA BID coupled with initial therapy (LE or AT) BID for 6 more weeks [37]. Compared to the AT group, patients using LE pretreatment experienced significantly less stinging on initial tCSA instillation ($P < 0.05$). In both treatment groups, Ocular Surface Disease Index (OSDI) outcomes improved significantly, but this was achieved earlier with LE (15 days) compared with AT (45 days). The LE group, but not the AT group, demonstrated significant improvements in other outcomes at day 60 (Schirmer test, central corneal staining, lissamine green staining). Mean IOP was not significantly increased in either group.

4.1.6. Postoperative inflammation following cataract surgery

The efficacy and safety of LE suspension 0.5% for the management of postoperative inflammation were assessed in two identical randomized, double-masked, vehicle-controlled trials in patients having cataract surgery with IOL implantation

[41,42]. In both studies, patients instilled LE 0.5% suspension or vehicle starting the day after surgery, QID for 14 days. Resolution of anterior chamber inflammation was greater with LE compared with vehicle ($P < 0.001$) in both studies. Based on pooled findings for pain resolution, a greater percentage of LE-treated patients reported no pain at the final visit compared with vehicle-treated patients (84 vs. 56%; $P < 0.05$) [43]. Following surgery, mean IOP decreased in both groups. Three patients in the LE group (1.4%) experienced an IOP elevation ≥10 mm Hg, all of which resolved and one of which was related to uveitis.

A randomized, double-masked study compared LE 0.5% suspension and the non-steroidal anti-inflammatory ketorolac tromethamine 0.5% in 60 patients undergoing routine phacoemulsification with posterior chamber IOL implantation [44]. Starting on postoperative day 1, study medication was instilled QID for one week then BID through Day 30. There were no observed differences between treatments for any signs or symptoms of postoperative inflammation, and no difference in mean IOP.

In an investigator-masked, comparative case series, the efficacy of LE 0.5% suspension versus PA 1% suspension was evaluated for the control of postoperative inflammation in patients undergoing routine cataract surgery [45]. Patients were randomized to receive LE or PA QID for 3 weeks after surgery, as well as bromfenac 0.09% BID and besifloxacin 0.6% QID for 2 weeks after surgery. Based on 3-week postsurgical assessments of visual acuity, IOP, and ACC and flare intensity findings, the authors concluded that LE and PA provided similar levels of inflammation control, but that LE resulted in less IOP fluctuation.

4.1.7. Photorefractive keratectomy

Topical corticosteroids are often used to mitigate corneal haze and myopic regression following photorefractive keratectomy (PRK). In an investigator-masked study involving 62 patients undergoing PRK, patients were randomly assigned to treatment with LE 0.5% in one eye and fluorometholone in the other eye following surgery, each instilled QID for one month, then tapered to three times a day (TID) and BID during the next 2 months [46]. Three months postoperatively, there was no significant corneal haze noted and no significant differences between treatment groups in any other assessments: visual acuity, manifest refraction, IOP, or ocular discomfort/redness after drug instillation.

4.2. Combination LE/tobramycin suspension

LE 0.5%/tobramycin 0.3% ophthalmic suspension (LE/T) is indicated for inflammatory ocular conditions where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. Two investigator-masked studies compared LE/T with dexamethasone 0.1%/tobramycin 0.3% (DM/T) suspension in patients with blepharokeratoconjunctivitis (BKC), each administered QID for 2 weeks [47,48]. In both studies, both combinations markedly improved the signs and symptoms of BKC from baseline to day 14, with no significant differences between treatments. In one study, IOP increased 5–9 mm Hg from baseline in 7.1% of 136 LE/T-treated patients and 14.4% of 137 DM/T-treated patients; additionally, one patient (0.7%) in the DM/T group had an IOP increase from baseline of ≥10 mm Hg [47]. In the other study [48], mean IOP was higher at all three follow-up visits in DM/T-treated versus LE/T-treated patients (all $P \leq 0.0186$). Twice as many DM/T-treated patients developed IOP increases ≥10 mm Hg compared with LE/T-treated patients (7.3 vs. 3.4%; $P = 0.0958$); one case of IOP elevation ≥30 mm Hg was noted in the DM/T group [48]. A subsequent pooled analysis of data for blepharitis signs only from these two trials [49] found LE/T was effective in lessening blepharitis severity, with full resolution of signs in approximately half of patients after 15 days of treatment. While LE/T and DM/T demonstrated similar efficacy, LE/T appeared to have a clear safety advantage with regard to IOP response.

One additional randomized, double-masked study compared LE/T and DM/T in 40 patients with BKC, using shorter (3–5 days) and reduced (BID) dosing [50]. Severity scores evaluated after 3–5 days of treatment indicated greater improvement (lower severity) of symptoms with DM/T compared with LE/T for ocular surface (1.8 vs. 3.4), blepharitis (0.9 vs. 1.35), discharge (0.2 vs. 0.6), and conjunctivitis (0.15 vs. 0.6) (all $P \leq 0.025$). Corneal punctate epithelial keratopathy severity improved in both treatment groups but was not significantly different between treatments at post-treatment assessment. No AEs were reported and no differences were observed in IOP findings between treatments. These findings should be interpreted cautiously, given the reduced dosing and short duration of treatment with both combinations.

Two randomized, multicenter, double-masked, parallel-group safety studies of LE/T were conducted in pediatric subjects aged 0–6 years [51]. In the first study, 108 pediatric subjects with lid inflammation (blepharitis) were treated with warm compresses BID 2 weeks along with LE/T or vehicle (QID for the first week and BID for the second week). In the second study, 137 subjects were randomized to LE/T, LE, tobramycin, or vehicle instilled QID for 14 days for blepharoconjunctivitis. Few ocular AEs, none serious, were reported during either study, and the investigators concluded LE/T appeared safe when used short term in pediatric subjects.

In a retrospective study, medical records were compared for 40 post-strabismus surgery patients who were managed postoperatively with LE/T ($n = 20$) or DM/T ($n = 20$) TID for 3 weeks [52]. There were no statistical differences between treatment groups for assessments of discomfort, chemosis, conjunctival hyperemia, or conjunctival gap size, and IOP measurements were within normal limits for both groups at all time points.

4.3. LE ointment

A preservative-free LE ointment 0.5% formulation became available in 2011. Ointment formulations may be beneficial for patients with tremors or arthritis as well as others who may have trouble instilling drops into their eyes [53], and remain on the ocular surface significantly longer than ophthalmic solutions, making them particularly suitable for nighttime use [54].

The use of LE ointment 0.5% QID over 2 weeks for the management of post-cataract surgery pain and inflammation

was evaluated in 2 randomized, double-masked, vehicle-controlled studies (N = 805) [55]. In an analysis of pooled data from the two studies, findings at Day 8 revealed complete resolution of anterior chamber inflammation and absence of pain in significantly more LE-treated patients compared to vehicle-treated patients (both $P < 0.0001$). Rescue medication use and ocular AEs occurred in fewer patients treated with LE compared with those who received vehicle. With both treatments, mean IOP decreased from baseline, with no significant difference in IOP increases ≥10 mm Hg between the LE (n = 3, 0.7%) and vehicle (n = 1, 0.2%) groups.

Pterygium, an exposure-related eye disease, is a wing-shaped growth that extends from the bulbar conjunctiva onto the cornea. They typically, but not exclusively, occur on the nasal side, and can be unilateral or bilateral [56]. Excision is indicated in cases with compromised vision. In a published review of the role of LE ointment as part of post-pterygium surgery management, the authors concluded that LE ointment is safe and effective for this indication [56]. At present, there have been no prospective clinical studies of LE post-pterygium surgery.

4.4. LE gel

The latest formulation of LE 0.5% is a non-settling gel first marketed in 2012. The gel has a unique rheological nature that allows it to be instilled as a viscous drop, after which it transitions to a fluid state on the surface of the eye, and also contains polycarbophil, a mucoadhesive polymer designed to prolong ocular surface retention time. LE was detected in tear fluid for 24 h following gel instillation in both rabbits and human volunteers [17]. LE gel has a homogenous composition, and, compared with LE suspension, a lower concentration of the preservative benzalkonium chloride (0.003% vs. 0.01%), a more physiologic pH, (6.5 vs. 5.5) and does not need to be resuspended by shaking prior to administration [57].

The safety and efficacy of LE gel in the treatment of postoperative inflammation and pain following uncomplicated cataract surgery were demonstrated in two randomized, double-masked placebo-controlled clinical trials [58,59]. Patients were randomized to LE 0.5% gel or vehicle QID for 14 days following surgery. In an integrated analysis of 813 patients involved in these studies, significantly more LE gel-treated patients showed complete resolution of ACC and reported being pain free at postoperative days 8 and 15 compared to vehicle-treated patients ($P < 0.001$) [60]. Across both studies, transient IOP increases ≥10 mm Hg occurred in 2 (4.9%) LE-treated patients and 1 (2.5%) vehicle-treated patient [60]. Other side effects were typically mild to moderate and reported less frequently with LE gel than with vehicle.

The postoperative use of LE gel 0.5% (most commonly prescribed QID for 7–14 days) following laser-assisted *in situ* keratomileusis (LASIK) or PRK surgery was evaluated in a retrospective study. This study demonstrated that the gel was safe and effective for patients undergoing these procedures [61]. No increase from baseline in mean IOP was observed in either LASIK or PRK eyes postoperatively ($P \geq 0.33$), and IOP elevations ≥10 mm Hg were observed in only 2 of 108 PRK patients (1.9%). More recently, LE 0.5% gel was evaluated in an investigator-masked study in 132 patients (262 eyes) undergoing PRK randomized to one of the following regimens: (1) LE 0.5% gel QID for the first week, TID for three weeks, BID for one month, then QD for one month; or (2) PA 1% QID for one week, then BID for three weeks, then switched to fluorometholone 0.1% suspension given TID for one month, BID for one month, then stopped [62]. Over the 3-month postsurgical follow-up, the incidence of haze was similar between the LE (2.6%) and PA/fluorometholone (4.8%) groups (P = 0.43). Refractive outcomes were considered excellent in both groups, and mean postoperative logMAR uncorrected visual acuity was similar between groups. Clinically significant IOP increases (≥10 mm Hg over baseline or any IOP >21 mm Hg) occurred in a smaller, albeit not significantly, percentage of eyes treated with LE (1.8%) vs. PA/fluorometholone (4.1%).

LE gel 0.5% (n = 30) was compared with difluprednate 0.05% (n = 30) for decreasing inflammation and improving vision recovery after phacoemulsification cataract surgery in an investigator-masked study [63]. All patients instilled assigned medication QID 3 days preoperatively and one week postoperatively, then BID for one week. Both treatments reduced inflammation equally and postoperative visual recovery was similar between treatments ($P > 0.05$). Although significant IOP elevations (≥10 mm Hg from baseline and ≥21 mm Hg) were noted 1 day after surgery in 30.0% of difluprednate and 26.7% of LE patients, all IOPs returned to baseline by the 1-month visit, and there was no difference in mean IOP between groups during the study. Patients with baseline IOP >21 mm Hg or vision-compromising ocular pathology were excluded from this cataract study.

The use of LE gel 0.5% was compared with PA 1% after Descemet membrane endothelial keratoplasty (DMEK) for the purposes of preventing corneal transplant rejection [64]. A total of 167 patients (233 eyes) were treated with PA 1% QID for the first postoperative month, at which point they were randomized to LE gel 0.5% or continued use of PA for the next 11 months. Both treatments were administered QID during the second and third months, TID during month 4, BID in month 5, and QD until the end of month 12. There were no immunologic rejection episodes in either treatment group. IOP elevations (IOP ≥24 mm Hg or increase of ≥10 mm Hg over the preoperative baseline level) occurred more than twice as often in the PA group than in the LE group (25 vs. 11%; P = 0.013).

LE gel 0.5% appeared safe and effective for dry eye in a small, exploratory study where patients with mild or moderate dry eye were randomized to one of three treatments: LE gel BID for 12 weeks (n = 36), LE gel BID for weeks 1–4 with the addition of tCSA BID for weeks 3–12 (n = 33), or tCSA BID for 12 weeks (n = 33) [65]. All three treatments reduced signs (fluorescein and lissamine green staining, tear film breakup time [TFBUT], Schirmer score) and symptoms (OSDI, DEQ-5, Comfort Index) of dry eye relative to baseline after 12 weeks ($P < 0.05$). At week 2, LE gel plus tCSA showed a treatment benefit versus tCSA alone for improvement from baseline in total OSDI (P = 0.022), while LE gel alone and LE gel plus tCSA showed a treatment benefit versus tCSA for OSDI visual function domain questions 6–9 ($P \leq 0.041$). At week 4, treatment differences were noted in favor of LE gel versus tCSA for hyperemia (by keratography) and TFBUT ($P \leq 0.04$). One patient each in the LE and LE plus tCSA groups had an IOP >21 mm Hg, both at week 12.

In an open-label study, 30 patients with MGD and evaporative dry eye were treated with LE gel 0.5% BID for 30 days [66]. At the end of treatment, TFBUT increased by 44.3% ($P = 0.005$). Other findings included a 52% decrease in corneal staining ($P = 0.006$), a 47.5% decrease in conjunctival staining ($P = 0.002$), a 31.9% decrease in MGD signs ($P < 0.001$), and a mean improvement in OSDI of at least 1 severity level ($P = 0.004$).

5. IOP effects

While topical ocular corticosteroids have undisputed benefits with regard to managing ocular inflammation, elevated IOP is a class concern. Published data on the effects of short-term (<28 days duration) and long-term (28 days up to 2 years duration) LE use on IOP were recently reviewed [67]. Pooled short-term data demonstrated a cumulative incidence of clinically significant IOP elevations (≥10 mm Hg from baseline) of 0.8% (14/1725 subjects); among long-term studies, the cumulative incidence was 1.5% (21/1386 subjects). Analysis of pooled data from controlled studies found a similar rate of clinically significant IOP elevation with LE versus vehicle [0.6% (9/1407) vs. 0.4% (6/1365); $P = 0.646$], but significantly lower rates compared with PA [3.4% (10/291) vs. 11.3% (33/292); $P < 0.001$] and compared with DM/T [1.8% (9/491) vs. 5.2% (25/485), $P = 0.008$] (Figure 3).

Studies in known steroid responders have confirmed that LE has a low propensity for eliciting IOP elevations in this high-risk population [68,69]. Bartlett et al. conducted a double-masked, randomized, cross-over study in 14 known steroid-responders treated with either LE 0.5% suspension or PA 1% QID for 42 days and then crossed-over to the other treatment after a washout period. Treatment with LE did not significantly impact mean IOP over the study, while PA resulted in a significant mean IOP elevation at each post-baseline visit [68]. Holland retrospectively reviewed 30 post-penetrating keratoplasty and post-keratolimbal allograft patients who, after having an IOP increase with PA 1%, demonstrated a reduction in IOP after switching to LE 0.5% suspension with continued treatment for a median period of 20 weeks [69].

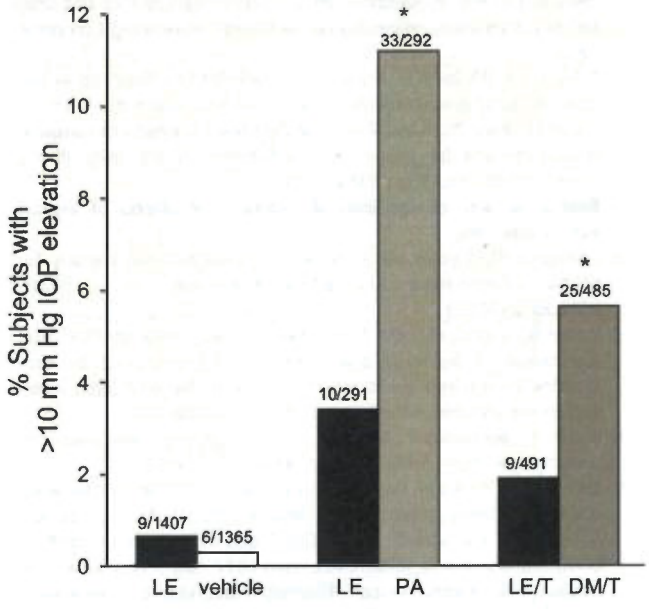


Figure 3. Cumulative rates of clinically significant IOP elevation in head-to-head studies (Reproduced from [67] with permission of Springer Nature).

The proportion of subjects with IOP elevation ≥10 mm Hg from baseline in studies of LE suspension and gel formulations compared to vehicle (10 studies) or PA 1% (5 studies) and of LE/T vs. DM/T (4 studies). *$P < 0.01$ vs. comparator, *DM/T* dexamethasone 0.1%/tobramycin 0.3% suspension, *LE* loteprednol etabonate, *LE/T* loteprednol etabonate 0.5%/tobramycin 0.3% suspension, *IOP* intraocular pressure, *PA* prednisolone acetate.

6. Cataract formation

Manabe and colleagues demonstrated that PA and other C-20 ketone steroids can form covalent bonds, or adducts, with lens protein, whereas nonketolic analogs are unable to form such adducts [14]. Because LE was designed with an ester rather than a ketone group at the C-20 position, its chemical structure is not conducive to forming such covalent adducts. However, it is possible that other, or as yet unknown, corticosteroid-induced mechanisms of cataractogenesis exist [2].

A study that assessed the long-term safety (>12 months) of LE 0.2% (given once to 4-times/day) in the treatment of seasonal and perennial allergic conjunctivitis did not suggest a potential for cataract formation even after more than 36 months of follow-up in some patients [70]. A review of global postmarketing AE data reported through October 2016, reflecting an estimated distribution of 85 million units of LE, revealed 12 voluntary reports of cataract formation in patients using LE (any formulation) since 1998, although causality cannot be established by such reports [71].

7. Conclusions

The principles of retrometabolic drug design were applied in the development of LE, a corticosteroid with a C-20 ester which replaces the C-20 ketone that is characteristic of PA. This substitution, as well as the 17α-etabonate moiety, makes possible the necessary balance between *in vivo* solubility and lipophilicity, distribution into ocular tissues, binding to the GR, and the rate of de-esterification into an inactive metabolite. Preclinical and clinical studies confirm that LE is a safe and effective option for the treatment of a number of ocular inflammatory conditions including GPC, SAC, anterior uveitis, blepharokeratoconjunctivitis, keratoconjunctivitis sicca, and postoperative pain and inflammation therapy following PRK, LASIK, and cataract surgery with IOL implantation. In the pediatric population, LE has been shown to be safe for short-term therapy in patients 0–6 years of age with blepharitis and blepharoconjunctivitis. The substantial volume of data accumulated over the past two decades provides clinical evidence that the retrometabolic design of the LE molecule has, in fact, resulted in a compound that is clinically effective but with a lower propensity to cause AEs seen with other ocular corticosteroids, notably IOP elevation and cataract formation.

8. Expert opinion

Steroids remain the most potent topical, injectable, depot implantable, and systemically administered pharmaceutical agents available for controlling ocular inflammation, and LE appears to one of

the safest in the entire class. The combination of efficacy and safety often renders a 'smart steroid' designation, while efficacy purported to be less than other steroids such as difluprednate somewhat inaccurately recalls the 'soft steroid' moniker, a label originally coined to reflect better safety. In reality, as demonstrated in both tightly controlled animal model experiments and human trials, LE performs with admirable potency for a variety of indications compared to other topical steroids [20,33,45,47–50,52,62–64], the nonsteroidal anti-inflammatory ketorolac [44], and tCSA [36,65]. However, the rapid metabolism responsible for the improved safety of LE could result in slightly lower efficacy relative to other corticosteroids in cases of particularly severe, acute inflammation as suggested by one of two studies in acute anterior uveitis [33]. Enhanced drug delivery with submicron [72] or mucus-penetrating [73] LE particles may, in the future, increase the ocular penetration and thus potential efficacy of a given concentration of topical LE.

Promising investigational chemical entities including SEGRAs (selective GR agonists) [74] and aldehyde trap strategies [75] target the enviably established combination of efficacy and safety enjoyed by LE, but their approval awaits additional randomized, controlled human trial data. Although safety has always been the premier LE asset, versatility bespeaks a deep portfolio in clinical practice. LE has become a preferred ocular surface anti-inflammatory agent for a multitude of acute and chronic conditions seen routinely in comprehensive ophthalmology, primary care optometry as well as referral corneal external disease practices. For numerous clinicians, LE is a favored agent for more severe and chronic forms of ocular surface disease, including blepharitis, dry eye and allergy, particularly when multiple etiologies converge upon the same patient and chronic therapy is indicated. Personalized medicine and genomic profiling may provide considerable foresight regarding efficacy and safety for any anti-inflammatory class prior to prescription, further refining medication selection as well as permitting higher doses for appropriate patients and organ targets.

For surgical patients with preexisting ocular surface disease, elevated IOP, so-called steroid responders, and candidates with cataract and glaucoma anticipating MIGS (micro-incisional glaucoma surgery), LE very often rises to most preferred agent. With the perceived enhanced potency of gel and ointment formulations, many surgeons and their management teams are also recommending off-label reduced frequency regimens, or more rapid medication weaning when compared to the suspension formulation.

Finally, LE works hand in hand with partnered pharmaceuticals to create clinically viable induction and maintenance strategies. In dry eye, LE becomes the initial fast onset potent agent for induction therapy, followed by long term prescription tCSA maintenance therapy [37]. Many patients with controlled chronic anterior uveitis patients benefit from continuous low-dose LE maintenance therapy to avoid recurrent attacks following treatment of acute disease with a different topical steroid. Thus, LE versatility is expressed by numerous clinical indications, a diverse spectrum of responsive disease states, targeted therapy for numerous commonplace and niche surgical procedures, as well as applicability for both initiation and maintenance therapy. More than two decades after first approval, LE remains a mainstay for eye care providers and a balanced treatment solution for patients.

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Declaration of interest

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