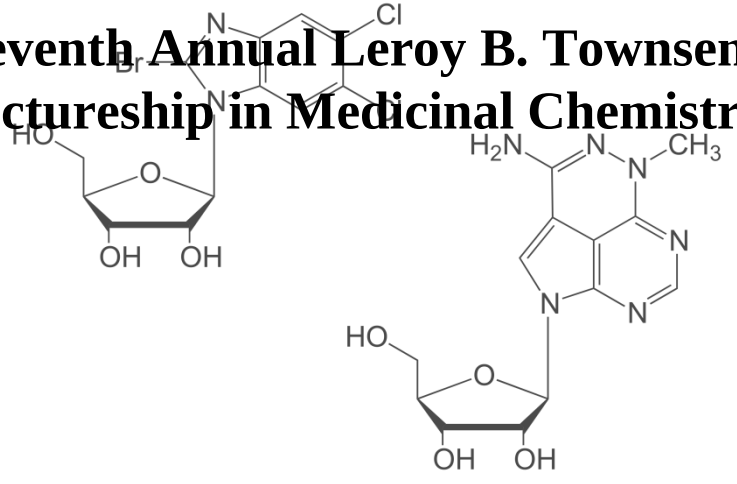
University of Michigan
College of Pharmacy
Department of Medicinal Chemistry

Eleventh Annual Leroy B. Townsend Lectureship in Medicinal Chemistry



Leah N. Makley, Ph.D.

Chief Scientific Officer, Director
Viewpoint Therapeutics; San Francisco, California

"Development of a Medical Treatment for Cataracts Based on a Pharmacological Chaperone of α-Crystallin"

Thursday, May 19, 2016
2:00 p.m.
2548 C.C. Little Building

Schedule of Events

2:00 p.m. to 3:30 p.m. - Symposium

Introduction Dr. George A. Garcia

Lecture Dr. Leah N. Makley

Post Lecture Discussion

Outstanding Graduate Student Awards Presentation

(MedChem students, please gather for group photo)

4:00 p.m. to 7:00 p.m. - Picnic

4:15 p.m.
Hors d'oeuvres and drinks

5:00-6:30 p.m.
Dinner, Catered by Weber's Inn

7:00 p.m.
Nature House closed, grounds open until 8:00 p.m.

Location: Leslie Science and Nature Center, Nature House
1831 Traver Rd.

Leah N. Makley, Ph.D.

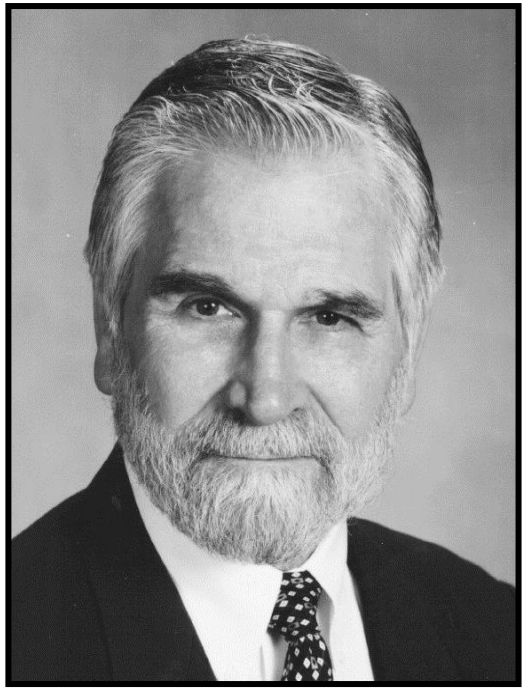
Chief Scientific Officer, Director;
Viewpoint Therapeutics, San Francisco, California

Leah is currently serving as Chief Scientific Officer of ViewPoint Therapeutics, a pre-clinical stage Biotechnology startup developing novel therapeutics for diseases of protein misfolding, including cataracts. She founded ViewPoint in 2014 to continue to develop her Ph.D. thesis research with Jason Gestwicki, currently an Associate Professor of Pharmaceutical Chemistry at UCSF. ViewPoint is a virtual company operating out of the JLABS/QB3@953 incubator. The company was founded in 2014 and has raised a total of $4.3MM from venture investors and non-dilutive grant funding. Leah received her B.S. in biochemistry from the University of Dayton in 2009 and her Ph.D. in Medicinal Chemistry from the University of Michigan in 2014.

"Development of a Medical Treatment for Cataracts Based on a Pharmacological Chaperone of α-Crystallin"

Abstract

The molecular chaperone αB-crystallin helps to maintain the transparency of the crystallin lens. The mutation R120G promotes its misfolding and aggregation, resulting in hereditary, early-onset cataracts. We tested the hypothesis that R120G αB-crystallin ligands could prevent or reverse its aggregation, using *in vitro* studies with recombinant protein and R120G αB-crystallin knock-in mice. We conducted a high-throughput screen at the University of Michigan Center for Chemical Genomics to identify a class of small molecules that directly bind to R120G αB-crystallin. The binding interaction was verified using biolayer interferometry and nuclear magnetic resonance, and structure-activity relationships of a small library of analogues were characterized. The anti-aggregation properties of an optimized compound were characterized by electron microscopy and light scattering assays using recombinant protein. To assess the effects on lens transparency, an eyedrop solution of the lead compound or a vehicle-only control was administered to R120G αB-crystallin knock-in mice for two or four weeks. Slit lamp biomicroscopy was used to qualitatively assess lens transparency, and complemented by measurements of lens protein solubility. In heterozygous R120G cryAB +/- mice, 28 of 33 mice (85%) exhibited improved lens transparency, while 7 of 9 (78%) of homozygous R120G cryAB -/- mice were improved. Conversely, a negative control molecule had no effect on lens transparency in three R120G cryAB -/- animals. The solubility of α-crystallins increased by 63% in the treated relative to the vehicle-only control eyes, and total lens protein solubility increased by 16 ± 5% (n=7). Similar activity was observed in knock-in mice expressing a different mutation in αA-crystallin and in aged wild type mice, suggesting that this mechanism may extend to age-related cataracts. Lastly, human lenses from cataract surgery patients or tissue banks containing grade 1 to grade 4 cataracts were treated *ex vivo* by soaking in a solution of the lead compound. Total lens protein solubility increased by an average of 18% (n=7). In conclusion, topical administration via eyedrop was found to reverse crystallin protein aggregation and correct lens transparency in the R120G αB-crystallin genetic model of cataract, and preliminary data suggest the activity may extend to age-related cataract. These observations suggest a potential pharmacological treatment modality. Ongoing work will continue to evaluate the efficacy, pharmacokinetics, safety, and mechanism of action of the intervention.



Leroy B. Townsend, Ph.D.

Albert B. Prescott Professor Emeritus of Medicinal Chemistry,
College of Pharmacy
Professor Emeritus of Chemistry, College of LS&A
University of Michigan

Professor Leroy B. Townsend

Professor Leroy B. Townsend has had a long and distinguished career as a heterocyclic and nucleoside chemist. While his leadership and expertise in those areas is internationally renowned, he is also very knowledgeable in many aspects of biology, biochemistry and virology. His ability to learn quickly and apply biological principles has led to the design and synthesis of many new and unique compounds. Professor Townsend, along with his students and collaborators has published over 500 papers since his first publications in 1962 with his mentor R. K. Robins. Each of these publications has reported sound efforts in synthetic organic chemistry with many applied to problems in infectious diseases and cancer. He is the holder of over 95 patents and is active and conscientious in transferring technology developed in his laboratories.

In addition to his very active research program he is also dedicated to the field of Medicinal Chemistry. Professor Townsend has held virtually every office in the American Chemical Society, Division of Medicinal Chemistry and the International Society of Heterocyclic Chemistry. He was the founder or co-founder of scientific societies, the author and editor of several book series, editorial board member for numerous journals and study section chair or member for many organizations, e.g. National Institutes of Health, The American Cancer Institute, The World Health Organization, etc. For this work he has received numerous awards including The Smissman Bristol-Meyers Squibb, The Ernest H. Volwiler, etc. and honorary degrees from The Universite de Montpellier Langedoc, Montpellier, France and The University of Nebraska.

Previous Symposia

2015 **Anthony R. Porcari, PharmD., Ph.D. (1999)**
"Recent advances in the treatment of venous thromboembolism: the role of new oral anticoagulants (NOACs)"

2014 **Geoffrey C. Hoops, Ph.D. (1989)**
"Probing the Enzymatic Activity of the Rv0045c Esterase from M. Tuberculosis: A Research Model for Undergraduate Biochemistry Education"

2013 **Gloria Komazin-Meredith, Ph.D. (2003)**
"*Methylenecyclopropane Analogues of Nucleosides as Broad Spectrum Anti-Herpes Agents*"

2012 **Jane V. Aldrich, Ph.D. (1983)**
"Peptidic Ligands for Kappa Opioid Receptors – Potential for Drug Development"

2011 **Thomas Renau, Ph.D. (1994)**
"From Lead Discovery to Medical Affairs: A Journey through Drug Discovery and Development"

2010 **Deborah Heyl-Clegg, Ph.D. (1991)**
"Understanding the Role of Human Islet Amyloid Polypeptide (hIAPP) Fragments in Pancreatic Cell Membrane Damage in Type 2 Diabetes"

2009 **Jamey Weichert, Ph.D. (1985)**
"Molecular Diapeutics-New Targeting Approaches to Cancer Detection and Treatment"

2007 **Kristjan S. Gudmundsson, Ph.D. (1996)**
"Tetrahydrocarbazoles as Potential Agents for Treatment of Papillomavirus Infection"

2006 **William P. Malachowski, Ph.D. (1993)**
"IDO in Sickness and in Health: Promoting Antitumor Immune Responses"

2005 **Thomas L. Cupps, Ph.D. (1982)**
"Development of a Novel Alpha 2-Adrenoceptor Agonist: Discovery to Commercial Scale."