BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Annelise E. Barron, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): AEBarron

POSITION TITLE: W.M. Keck Associate Professor of Bioengineering

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Washington, Seattle, Washington	B.S. *cum laude*	1990	Chemical Engineering
University of California, Berkeley, California	Ph.D.	1995	Chemical Engineering
ACLARA BioSciences, Inc., Hayward, California	Postdoc	1995	Molecular Biotechnology
University of California, San Francisco, CA / Chiron	Postdoc	1996	Pharmaceutical Chemistry

A. Personal Statement

I am a tenured Associate Professor of Bioengineering at the Stanford University School of Medicine. My diverse research accomplishments and recent discovery of sequence-specific LL-37 binding to the Aβ amyloid peptide make me uniquely able to blaze a trail with an NIH Pioneer project, investigating an entirely novel Alzheimer's Disease mechanistic hypothesis. I have been working in peptide biophysics since 1996, and over the past 7 years have published a number of *in vivo* mouse studies (as are part of the proposed research), however, this is a new direction for me: investigating the novel idea that Alzheimer's-associated peptide Aβ accumulates in the brain as the result of chronic underexpression of a natural binding partner, the human innate immune peptide LL-37. Thus, as opposed to removing Aβ, an effective prevention of (or treatment for) Alzheimer's could be upregulating LL-37 expression. We have shown that LL-37 binds tightly and sequence-specifically to Aβ, blocking Aβ fibril formation. I am ready to lead molecular biophysical, bioanalytical and *in vivo* studies that explore this hypothesis. Previously, I have served as PI for multiple NIH R01 grants, with diverse topics in peptide biophysics, protein biomimicry, and bioanalysis; including two competitively renewed R01s, one of which was an NIH PECASE. I have 147 peer-reviewed publications (H-index 43), and have mentored and graduated 38 Ph.D. students. My ideas related to LL-37 and amyloid diseases were recognized by an invitation to the 2015 Nobel Symposium on this topic in Stockholm, Sweden. I have proven my ability to establish productive collaborations related to innate immune peptides, as shown by these publications:

1. E. De Lorenzi, M. Chiari, R. Colombo, M. Cretich, L. Sola, R. Vanna, P. Gagni, F. Bisceglia, C. Morasso, J.S. Lin, M. Lee, P.L. McGeer, **A.E. Barron** (2017) Evidence that the human innate immune peptide LL-37 may be a binding partner of amyloid-beta and inhibitor of fibril assembly. *J. Alzheimer's Disease*. 59, 1213-1226. PMID: 28731438
2. M. Lee, **A.E. Barron**, E. McGeer, P.L. McGeer (2015) Human antimicrobial peptide LL-37 induces glial-mediated neuroinflammation. *Biochemical Pharmacology*. 94(2): 130-41. PMID: 25686659
3. A.M. Czyzewski, H. Jenssen, C.D. Fjell, M. Waldbrook, N.P. Chongsiriwatana, E. Yuen, R.E.W. Hancock, **A.E. Barron** (2016) *In vivo*, *in vitro*, and *in silico* characterization of peptoids as antimicrobial agents. *PLoS One* 11 (2) e0135961. PMID: 26849681
4. T. Fülöp, R.F. Itzhaki, B.J. Balin, J. Miklossy, **A.E. Barron** (2018) Role of microbes in the development of Alzheimer's disease: state of the art - An international symposium presented at the 2017 IAGG congress in San Francisco. *Frontiers in Genetics: Genetics of Aging.* Review. **In Press**, accepted Aug. 21, 2018. doi: Front. Genet. | doi: 10.3389/fgene.2018.00362

B. Positions and Honors

Positions and Employment

1990 – 1995 Graduate Student and Ph.D. Candidate (Research and Teaching Assistant), U.C. Berkeley, Dept. of Chemical Engineering. *Advisors:* Profs. Harvey W. Blanch & David S. Soane *Thesis:* Capillary electrophoresis of DNA in uncrosslinked polymer solutions: Experiment and Theory

1995 – 1995 Postdoctoral Researcher, ACLARA BioSciences. *Mentor:* Dr. Herbert H. Hooper, Vice President and Director of Research. *Project focus:* Synthesis and study of novel polyacrylamides with tunable LCST "volume phase transitions" for DNA sequencing by capillary electrophoresis

1996 – 1996 NIH-NRSA Postdoctoral Fellow, University of California, San Francisco, Dept. of Pharmaceutical Chemistry. *Mentors:* Prof. Ken A. Dill (UCSF), Dr. Ronald N. Zuckermann (Chiron Corp.). Synthesis, purification, and spectroscopic study of helical peptidomimetic poly-*N*-substituted glycines (peptoids)

1997 – 2003 Assistant Professor (tenure-track), Northwestern University, Dept. of Chemical Engineering

2003 – 2006 Associate Professor (tenured), Northwestern University, Dept. of Chemical & Biological Engineering, with a courtesy appointment in Chemistry (Organic Division)

2006 – 2007 Full Professor (tenured), Northwestern University, Department of Chemical & Biological Engineering, with courtesy appointment in Chemistry (Organic Division)

2007-present W.M. Keck Associate Professor (tenured), Stanford University, Department of Bioengineering, Schools of Medicine and of Engineering

Other Experience and Professional Memberships

2004 – 2007 Director, Northwestern University's NIH/NRSA Predoctoral Training Program in Biotechnology

2004 – 2007 Member, Scientific Advisory Committee to the Director of the NIH (Dr. Elias Zerhouni)

2005 – 2006 Permanent Member, NIH Instrumentation and Systems Development Study Section

2006 – 2007 *Ad Hoc* Member, Biomolecular Materials and Processes (BMAP) Committee of the National Research Council (NRC), National Academies of Science (co-authored a report on this topic)

2006 – 2007 NIH Director's Liaison to the NIH Director's Council of Public Representatives

2006 – 2010 Permanent member, NIH Synthetic & Biological Chemistry B Study Section

2006 – 2007 Full Member, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, IL

2008-present Member, Stanford University Comprehensive Cancer Center

2009-present Mentoring Faculty Member, Graduate Program in Biophysics, Stanford University

2009-2010 Scientific Program Chair and Conference Organizer, 26th International Symposium on Microscale Bioseparations (MSB 2011), held May 1-5, 2011, San Diego, CA. (~250 attendees)

2010-2013 Associate Chair for Graduate Studies, Department of Bioengineering, Stanford University

2011 Participant, 2011 Gordon Conferences on (1) Antimicrobial Peptides, (2) Atherosclerosis

2015 Invited Participant, Nobel Symposium: "Amyloid: A multifaceted player in human health and disease", Stockholm, Sweden (June 10-11, 2015)

2018-2020 Member, Executive Board of Directors, Lawrence Berkeley Laboratory, Molecular Foundry

Honors

1986-1990 National Merit Scholar, Recipient of Associated Four-Year Undergraduate Scholarship

1986 National Hispanic Scholar

1986 Tektronix Foundation Undergraduate Merit Scholarship

1987, 1988 University of Washington Undergraduate Merit Scholarship (two consecutive years)

1989 H.K. Benson Chemical Engineering Tuition Scholarship

1990-1993 U.C. Berkeley Chancellor's Minority Pre-doctoral Fellowship

1993 Outstanding Graduate Student Instructor Award, U.C. Berkeley Dept. of Chemical Engineering

1994 Dow Excellence in Teaching Award, U.C. Berkeley Department of Chemical Engineering

1994 Matheson Fellowship in Chemical Engineering

1994 Univ. of CA Minority Dissertation Year Fellowship

1998-1999 Beckman Young Investigator Award

1999 Presidential Early Career Award for Scientists and Engineers (through NIH/NHGRI)

2002 DuPont Young Professor Award

2002 Camille Dreyfus Teacher-Scholar Award

2005 Thiele Lecturer in Chemical Engineering at the University of Notre Dame

2003-2012 Invited lectures at 10 Gordon Research Conferences: Analytical Chemistry, 2003; Microfluidics, Physics and Chemistry of, 2005; Bioorganic Chemistry, 2005; Elastomers, Networks & Gels, 2005; Peptides, Chemistry & Biology of, 2006; Biointerface Science, 2006; Colloidal, Macromolecular, and

Polyelectrolyte Solutions, 2006; Organic Structures and Properties, 2006; Antimicrobial Peptides, 2007, Bioinspired Materials, 2012

2008 Invited lecturer, National Academy of Engineering Japan-America Frontiers of Engineering Symposium, Kobe, Japan, November 16-19, 2008. Topic: "Ultra-fast DNA sequencing"

2010 Keynote lecture, 26th Int'l Symposium on Microscale Bioseparations, Prague, Czech Repub.

2011 Invited lecture, American Society for Biochemistry & Molecular Biology (April 2011, Wa. D.C.)

2011 Advisor/Site Visitor. Biosciences Division, Lawrence Berkeley National Labs, CA, April 2011

2012 Named Virginia Tech's 2012 "NanoBio Scholar"; gave a series of three lectures over three days

2012 Invited lecturer, 2012 Peptide Engineering Meeting (Atlanta, GA, October 3, 2012)

2014 Keynote Lecturer, CE Pharm 2014—*Capillary Electrophoresis (CE) in the Biotechnology and Pharmaceutical Industries: 16th International Symposium* (Seattle, WA, October 12-14, 2014)

2015 Invited Participant, Nobel Symposium: "Amyloid: A multifaceted player in human health and disease", Stockholm, Sweden (June 10-11, 2015)

2017 Invited Lecture, IAGG 2017 World Congress of Gerontology and Geriatrics, Symposium on the Role of Microbes in Alzheimer's Disease, *Evidence that the Human Innate Immune Peptide LL-37 may be a Binding Partner of Amyloid-β and Inhibitor of Fibril Assembly*, San Francisco, CA, July 24, 2017.

2018 Plenary Lecture, Molecular Foundry, Lawrence Berkeley National Laboratory, March 6, 2018. *Peptoid mimics of lung surfactant proteins: Helical peptoids that associate naturally with phospholipids.*

2018 Plenary Lecture, Int'l Meeting on Antimicrobial Peptides, Edinburgh, Scotland, Sept. 4, 2018. *Balanced Expression of Yin/Yang Innate Immune Peptides, LL-37 and Aβ, May Prevent Alzheimer's Disease*

C. Contributions to Science

1. *Antimicrobial peptide mimics:* One of the most important classes of natural weapons against infection in humans are **antimicrobial peptides**, employed by immune cells to control the growth of pathogenic bacteria, inactivate viruses, and kill infected and cancerous host cells. Inspired by the broad-spectrum activity of these natural human antibiotics, my laboratory created a family of stable, non-natural mimics of antimicrobial peptides based on "peptoids" (sequence-specific *N*-substituted glycines), to determine their biophysical mechanism(s) of action, and test their ability to kill resistant strains of bacteria. This work was funded by NIH NIAID grant R01 AI072666 (3/15/07–2/28/12) on which I was sole PI. The project was successful, as evidenced by the publications below. It was through this work that I discovered the unique properties of LL-37, which seeded the current research project.

    a. Intracellular biomass flocculation as a key mechanism of rapid bacterial killing by cationic, amphipathic antimicrobial peptides and peptoids", N.P. Chongsiriwatana , J.S. Lin , R. Kapoor, M. Wetzler, J.A.C. Rea, M.K. Didwania, C.H. Contag, **A.E. Barron**, *Nature Scientific Reports* (2017) 7: 16718, pp. 1-15.
    b. Antimicrobial peptoids effective against Pseudomonas aeruginosa biofilms. Kapoor R, Wadman MW, Dohm MT, Czyzewski AM, Spormann AM, **Barron AE.** 2011. *Antimicr Agents Chemother* 55, 3054-3057.
    c. *In Vivo*, *In Vitro*, and *In Silico* Characterization of Peptoids as Antimicrobial Agents. Czyzewski AM, Jenssen H, Fjell CD, Waldbrook M, Chongsiriwatana NP, Yuen E, Hancock REW, **Barron AE**. 2016, *PLoS ONE*, 11 (2): e0135961. doi:10.1371/journal.pone.0135961. PMCID: 26849681
    d. Peptoids that mimic the structure, function, and mechanism of helical antimicrobial peptoids, N.P Chongsiriwatana, J.A. Patch, A.M. Czyzewski, M.T. Dohm, A. Ivankin, D. Gidalevitz, R.N. Zuckermann, **A.E. Barron**, *Proc. Natl. Acad. Sci. USA* (2008) 105, 2794-2799. PMCID: PMC2268539

2. *Biomimetic lung surfactant protein mimics*: Infants born prematurely require "lung surfactant"—a complex mixture of surface-active proteins with lipids and cholesterol—to take their first breath. This substance, which greatly reduces pulmonary surface tension, is expensive and in limited supply; to date, only first-world countries have access to it, to save premature infants. The surface-active proteins that enable its function cannot be expressed in bacteria; when isolated from natural sources (such as minced calf lungs) they tend to misfold and aggregate, shortening shelf life and increasing expense. My laboratory successfully created conformationally and proteolytically stable mimics of lung surfactant proteins B and C, as well as an ideal biomimetic lipid mixture, and formulated a stable biomimetic surfactant, which has been successfully tested in animals. This project was funded by NIH NHLBI grant 2 R01 HL067984 (3/15/06 - 3/14/11) on which I was sole PI.

a. Biomimetic N-terminal alkylation of peptoid analogues of surfactant protein C. Brown NJ, Dohm MT, Bernardino de la Serna J, **Barron AE**. Biophys J. 2011, 101, 1076-1085. (Cover Image)
b. Effective *in vivo* treatment of acute lung injury with helical, amphipathic peptoid mimics of pulmonary surfactant proteins. Czyzewski AM, McCaig LM, Dohm MT, Broering LA, Yao LJ, Brown NJ, Didwania MK, Lin JS, Lewis JF, Veldhuizen R, **Barron AE**, *Nature Scientific Reports* (2018) 8, *6795*
c. Simple helical peptoid analogues of lung surfactant protein B. Seurynck SL, Patch JA, **Barron AE**. Chemistry & Biology. 2005, 12, 77-88.
d. Helical peptoid mimics of lung surfactant protein C. Wu CW, Lee KYC, **Barron AE**. Chemistry & Biology. 2003, 10, 1057-1063.

3. *Hydrogels for Culture and Transplantation of Stem Cells and Pancreatic β-Islets*: In a series of collaborative projects, my laboratory provided advanced hydrogel materials for clinicians seeking technology to allow the successful transplantation of stem cells for wound healing applications, or pancreatic islet cells for the treatment of Type I diabetes. Various types of water-soluble polymer systems were used as the bases for these biomimetic hydrogels, and we found multiple useful materials tailored to stem cells and/or islets.

    a. A tunable silk-alginate hydrogel scaffold for stem cell culture and transplantation, K. Ziv, H. Nuhn, Y. Ben-Haim, L.S. Sasportas, P.J. Kempen, T.P. Niedringhaus, M. Hrynyk, R. Sinclair, **A.E. Barron**, S.S. Gambhir. *Biomaterials* (2014) 35 (12): 3736-3743.
    b. The incorporation of extracellular matrix proteins in protein polymer hydrogels to improve encapsulated beta-cell function, L.N. Beenken-Rothkopf, L.S. Karfeld-Sulzer, N.E. Davis, R. Forster, **A.E. Barron**, M.J. Fontaine. *Annals of Clinical and Laboratory Science* (2013) 43 (2): 111-121.
    c. Encapsulation of protein microfiber networks supporting pancreatic islets, J.A. Steele, **A.E. Barron**, E. Carmona, J. Halle, R.J. Neufeld. *J. Biomedical Materials Research Part A* (2012) 100A (12): 3384-3391.
    d. Enhanced function of pancreatic islets co-encapsulated with ECM proteins and mesenchymal stromal cells in a silk hydrogel, N.E. Davis, L.N. Beenken-Rothkopf, A. Mirsoian, N. Kojic, D.L. Kaplan, **A.E. Barron**, M.J. Fontaine *Biomaterials* (2012) 33 (28): 6691-6697.

4. *ELFSE (End-Labeled Free-Solution Electrophoresis)*: In work completed in 2012, now being developed by IntegenX, Inc. for forensic genotying, my laboratory developed a novel, bioconjugate approach to DNA sequencing and genotyping involving chemical tethering of genetically engineered protein "drag-tags" to DNA sequencing or genotyping fragments. Protein-DNA conjugation, with our uniquely designed protein drag-tags, allows DNA to be analyzed efficiently by capillary or microchip electrophoresis in free solution, in the absence of a viscous gel material, which is difficult to load into capillaries. This project was funded by NIH NHGRI grant R01 HG002918-01 (9/1/03–8/31/07), on which I was sole PI, and was successful in achieving its goals:

    a. A 265-base DNA sequencing read by capillary electrophoresis with no separation matrix", J.C. Albrecht, J.S. Lin, **A.E. Barron** *Analytical Chemistry* (2011) 83 (2): 509-515
    b. Simultaneous detection of 19 K-ras mutations by free-solution conjugate electrophoresis of ligase detection reaction products on glass microchips, J.C. Albrecht, A. Kotani, J.S. Lin, S. Soper, **A.E. Barron** *Electrophoresis* (2013) 34 (4): 590-597.
    c. Monodisperse, 'Highly' positively charged protein polymer drag-tags generated in an intein-mediated purification system used in free-solution electrophoretic separations of DNA, X.X. Wang, J.C. Albrecht, J.S. Lin, **A.E. Barron** *Biomacromolecules* (2012) 13 (1): 117-123
    d. Free-solution electrophoretic separations of DNA-drag-tag conjugates on glass microchips with no polymer network and no loss of resolution at increased electric field strength, *Electrophoresis* J.C. Albrecht, M.B. Kerby, T.P. Niedringhaus, J.S. Lin, X.X. Wang, **A.E. Barron** (2011) 32 (10): 1201-1208

Complete List of Published Works in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40560232/?sort=date&direction=descending

D. Additional Information: Research Support

Ongoing Research Support

Research Contract Shamloo (PI), Barron (Co-PI) 5/1/18 - 11/1/20
Funder: TEDCO, Tulalip Tribal Economic Development Corporation
Title: "Efficacy & Mechanism of Action of Cannabinoids for the Treatment of Alzheimer's Disease and Addiction"
The major goal of this project is to determine the efficacy, in a rat model of addiction to self-administered opiates, and a 5XFAD mouse model of Alzheimer's Disease, of treatment with cannabinoids extracted from *Cannabis Sativa* flowers. We will initially determine which innate immune pathways are activated by a complex mixture of cannabinoids, and then identify particular cannabinoids most active in affecting innate immune gene expression pathways.

Stanford PTA # 1186088-1-DPDRN (Barron) 9/1/2015–8/30/2019
Stanford Deans of Medicine and of Engineering
Title: Support of Barron laboratory research
The major goal of this project is to investigate a new hypothesis that the human innate immune cathelicidin peptide, LL-37, plays a key role in the initiation and progression of Alzheimer's Disease.

Completed Research Support (relevant to this application)

Stanford PTA # 1111236-377-JHACT Barron (PI) 7/1/2016–12/31/2017
Children's Health Research Institute (CHRI), Stanford School of Medicine
Title: "*Biomimetic treatment of pediatric ear infections with antimicrobial peptide mimics and surfactants"*
P.I. Barron, Annelise E. (Co-Investigator, Contag, Christopher H.)
This project is aimed at developing a new treatment for recurring pediatric ear infections, or *otitis media*, using a biomimetic surfactant formulation comprising peptoid analogues of the human antimicrobial peptide LL-37. The grant funds an animal study, using chinchillas and bioluminescent bacteria, to test these novel treatments.

Ampetoids as Biostable Functional Mimics of Antimicrobial Peptides (Barron)
NIH/National Institute of Allergy and Infectious Disease 1 R01 AI072666 3/15/07 - 2/28/12
Create and study biostable, biomimetic oligo-*N*-substituted glycine analogues of antimicrobial peptides. This project is related to the current proposal, as it involved comparative studies of innate immune peptides such as LL-37.

OVERLAP: There is no scientific or budgetary overlap of these funded projects with the present application.