BIOGRAPHICAL SKETCH

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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 w/ Biophys/Biochem Minor
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 Stanford University School of Medicine. My research accomplishments in the original invention and study of antimicrobial peptoids make me uniquely suited to lead the proposed research tasks. One of our most important natural weapons against infection as humans are **antimicrobial peptides**, employed by epithelia and immune cells to control the growth of pathogenic bacteria and inactivate viruses. Inspired by the potent activity of these natural peptide antibiotics and the relative rarity of bacteria gaining resistance to them, we created a family of biostable, non-natural mimics of antimicrobial peptides based on sequence-specific **peptoids** (oligo-*N*-substituted glycines). We have made 80 different peptoid sequences, testing the best compounds' ability to kill 49 different strains of bacteria and fungi (including many resistant strains). We studied their mechanism(s) of action (proving that they are true mimics of natural antimicrobial peptides). The work was funded by NIH NIAID R01 AI072666 (3/15/07–2/28/12) on which I was sole PI. Since 2007, we published 25 papers on this topic. Since 2012, the problem of multi- and extensively resistant (MDR/XDR) pathogens has grown more serious; and more, new classes of antibiotics are needed. Thus, this project is timely and important. I have previously served as PI for multiple NIH R01s, with diverse topics in protein biomimicry, peptide biophysics, and bioanalysis; including two competitively renewed R01s, one of which was an NIH PECASE. I have 147 peer-reviewed publications (H-index 44), and I have graduated 38 Ph.D. students. A few relevant/significant papers are:

1. Intracellular biomass flocculation as a key mechanism of rapid bacterial killing by cationic, amphipathic antimicrobial peptides and peptoids", Chongsiriwatana NP, Lin JS, Kapoor R, Wetzler M, Rea JAC, Didwania MK, Contag CH, **Barron AE**, 2017, *Nature Scientific Reports* 7: 16718, 1-15.
2. 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.
3. *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

4. 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

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)

2015-present Reviewer, Arnold O. and Mabel Beckman Foundation, Beckman Young Investigator Program

2017 NSF Panelist and Proposal Reviewer, National Science Foundation, Division of Chemistry, Biopolymer Synthesis Panel, January 26-27, 2017. NSF Lead: Scott Rychnovsky, Ph.D.

2017-2018 *Ad Hoc* NIH Study Section member, NIH CSR, BMBI Study Section, June 8-9, 2017, Washington DC; NIH CSR, MIRA Study Section, October 12-13, 2017, Bethesda, MD; NIH CSR, CMT Study Section, June 12-13, 2018, San Francisco, CA

2018-2020 Member, User Executive Committee, Molecular Foundry, Lawrence Berkeley Nat'l Laboratory

2018-present Affiliated Faculty Member, Stanford University Wu Tsai Neurosciences Institute

2018-present Editorial Board Member: *Nature Scientific Reports, Journal of Alzheimer's Disease*

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 Nat’l Laboratory, March 6, 2018. *Peptoid mimics of lung surfactant proteins: Helical Peptoids That Associate Naturally With Phospholipids.*
2018	Plenary Lecture, International 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. <u>*Biomimetic lung surfactant protein mimics*</u>: 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**, *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.

2. *Antimicrobial Peptide Involvement in Alzheimer's Disease:* My laboratory recently discovered sequence-specific binding of the human antimicrobial peptide LL-37 to the Aβ amyloid peptide, opening a vista to an entirely novel Alzheimer's Disease mechanistic hypothesis. We have studied this interaction extensively *in vitro*, and will continue to do so, while now pursuing *in vivo* studies in the 5XFAD model of Alzheimer's Disease. Specifically, we are investigating the novel idea that Alzheimer's-associated peptide Aβ accumulates in the brain as the result of chronic under-expression of a natural binding partner, the human innate immune peptide LL-37; which also allows brain infections. Thus, as opposed to removing Aβ, an effective prevention of (or treatment for) Alzheimer's may be upregulating LL-37 expression. We have shown *in vitro* that LL-37 binds tightly and sequence-specifically to Aβ, blocking Aβ fibril formation.

   a. Evidence that the human innate immune peptide LL-37 may be a binding partner of amyloid-beta and inhibitor of fibril assembly. 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) *J. Alzheimer's Dis*. 59, 1213-1226. PMID: 28731438
   b. Human antimicrobial peptide LL-37 induces glial-mediated neuroinflammation. M. Lee, **A.E. Barron**, E. McGeer, P.L. McGeer (2015) *Biochemical Pharmacology*. 94(2): 130-41. PMID: 25686659
   c. 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. Review. T. Fülöp, R.F. Itzhaki, B.J. Balin, J. Miklossy, **A.E. Barron** (2018) *Frontiers in Genetics: Genetics of Aging.* Vol. 9, article 362. 10 September 2018 | https://doi.org/10.3389/fgene.2018.00362
   d. *In vivo*, *in vitro*, and *in silico* characterization of peptoids as antimicrobial agents. A.M. Czyzewski, H. Jenssen, C.D. Fjell, M. Waldbrook, N.P. Chongsiriwatana, E. Yuen, R.E.W. Hancock, **A.E. Barron** (2016) *PLoS One* 11 (2) e0135961. PMID: 26849681

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

Discovery Innovation Fund Barron (PI) 10/1/2019–9/30/2024
Stanford Medical Center Development

Title: "P. gingivalis involvement in Alzheimer's Disease: in vitro, in vivo murine and human studies"
The major goal of this project is to investigate the hypothesis that stable upregulation of the innate immune cathelicidin (CRAMP in mice, LL-37 in humans) can prevent or treat infection-associated Alzheimer's Disease.

Stanford SPARK program Santa Maria (PI), Barron (Co-PI) 1/7/2019 - 1/6/2020
Title: Synthetic Antimicrobial Peptoids for the Treatment of Chronic Suppurative Otitis Media

The major goal of this project ($35,000 in funding for 1 year) is to do initial testing of Barron lab antimicrobial peptoids in the Santa Maria lab mouse model of Chronic Suppurative Otitis Media (ear infections).

Research Contract Shamloo (PI), Barron (Co-PI) 5/1/2018 - 11/1/2020
Funder: TEDCO, Tulalip Tribal Economic Development Corporation
"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 Indica* 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.

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
"*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 3/15/2007 - 2/28/2012
Create and study biostable, biomimetic oligo-*N*-substituted glycine analogues of antimicrobial peptides. This project is related to this 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.