Annelise E. Barron, PhD
Associate Professor
Bioengineering

One Ellipsoid to Control them all - Peptoid Anti-infectives that are Antiviral, Antibacterial & Antifungal and Well-tolerated in the Lung

Annelise E. Barron is the W.M. Keck Associate Professor of Bioengineering at Stanford University.

The broad theme of the Barron lab is the study and biomimicry of natural host defense peptides (antimicrobial peptides). We study the molecular biophysics and mechanisms of LL-37—a centrally important human host defense peptide—and its involvement in Alzheimer's dementia (via LL-37 dysregulation and degradation by pathogen virulence factors). Alzheimer's dementia can be caused by (or at least, accompanied by) cerebral infections, a phenomenon now receiving renewed attention given recent discoveries. We are also working to develop biostable peptoid mimics of LL-37 as therapeutics that can combat antibiotic-resistant infections. Finally, we are working to mimic lung surfactant proteins that facilitate the delivery of therapeutics to the lungs, treat bacterial and viral pneumonia, or prevent or treat ventilator-associated acute lung injury.

We are currently putting efforts into better understanding the pathogenic mechanisms of Covid-19, as relates to dysregulation of innate immunity; understanding why certain minority populations seem to be more strongly affected by Covid-19 infections; and developing therapeutic approaches to both preventing and treating severe Covid-19.

Dr. Barron was trained as a chemical engineer at the University of Washington (B.S.) and U.C. Berkeley (Ph.D., under the mentorship of Prof. Harvey W. Blanch), and was a Pharmaceutical Chemistry postdoc with Prof. Ken A. Dill (UCSF) and Dr. Ronald N. Zuckermann (Chiron Corp.). She has served on the faculty at Stanford since 2007, and prior to that, served on the Chemical & Biological Engineering faculty of Northwestern University in Evanston, IL for 10 years (1997-2007). Dr. Barron has been awarded the NIH Pioneer Award (2020), the Presidential Early Career Award for Scientists & Engineers (PECASE) through NIH / NHGRI (1999), the Beckman Young Investigator Award (1999), and the Camille Dreyfus Teacher-Scholar Award (1998), among other awards. Dr. Barron was the youngest scientist ever to serve on the Scientific Advisory

Committee to the Director of the NIH, under Dr. Elias Zerhouni. She has more than 172 publications and a current H-index of 45 (Web of Science, All Databases), and serves on the advisory boards of several biotechnology companies. She is proud to be 1/4 Quechua (the Native American people of Bolivia), 1/4 Hispanic, 1/4 Swedish, 1/4 English, and 100% American.

Abstract: Viral infections, such as those caused by SARS-CoV-2 and Influenza A, affect millions of people each year. Few antiviral drugs can effectively treat these infections. The standard approach in the development of antiviral drugs involves the identification of a unique viral target, followed by the design of an agent that addresses that target. Antimicrobial peptides (AMPs) represent a novel source of potential antiviral drugs. AMPs can inactivate numerous different enveloped viruses through disruption of their viral envelopes. Yet the clinical development of AMPs as antimicrobial therapeutics has been hampered by a number of factors, especially their enzymatically labile structure as peptides. We report the antiviral potential of peptoid mimics of AMPs (sequence-specific N-substituted glycine oligomers). These peptoids have the advantage of being insensitive to proteases, and exhibit increased bioavailability. Our results demonstrate that several peptoids exhibit potent in vitro antiviral activity against SARS-CoV-2 and Influenza virus when incubated prior to infection. Thus, they have direct effects on the viral structures, which appear to render the viral particles non-infective. Visualization by cryo-EM shows viral envelope disruption similar to what is observed in AMP activity against other viruses. Furthermore, we observe no cytotoxicity against human primary cultures of epithelial cells. Results suggest a biomimetic mechanism, likely due to the differences between the phospholipid head group makeup of viral envelopes and host cell membranes, thus underscoring the potential of this class of molecules as safe and effective broad-spectrum antiviral agents. Furthermore, in recent work we have found some of the same peptoids to be effective against both bacterial and fungal pathogens that commonly co-occur in pneumonia in ICU patients. We discuss how and why differing molecular features between ten different peptoid candidates may affect both antiviral activity and selectivity, specifically, the self-assembly of the most effective peptoids into discrete micellar structures such as ellipsoidal micelles comprising ~100 peptoid molecules per micelle. Remarkably, some of these same peptoids with broad-spectrum activity against respiratory viruses are also active against a broad array of pathogenic bacterial and fungal organisms, offering the possibility of a truly novel therapeutic approach to treating polymicrobial lung infections.