BIOGRAPHICAL SKETCH

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NAME: Arnold S. Bayer, MD

eRA COMMONS USER NAME (credential, e.g., agency login): ABAYER705

POSITION TITLE: Investigator, Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center
Professor of Medicine; Adult Infectious Diseases – UCLA School of Medicine

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
Temple University School of Med. Phila, Penn.	MD	1970	Medicine
Thomas Jefferson Univ Hospital – Phila, Penn	Intern/Resid	1970-1973	Internal Medicine
Harbor-UCLA Med. Center, Torrance, CA	Sr. Resident	1973-1974	Internal Medicine
Harbor-UCLA Med. Center, Torrance, CA	ID Fellow	1974-1977	Infectious Diseases
West LA VA Medical Center, Los Angeles, CA	Research Post-Doc	1977-1980	Infectious Diseases

A. Personal Statement. My labs focus on bacterial pathogenesis, with a particular emphasis on pathogens causing vascular infections (e.g.,endocarditis). This includes *Staph. aureus*, enterococci and viridans group streptococci. We specifically study the adaptations these pathogens undergo at a cellular level to avoid innate host defenses, focusing on cationic antimicrobial peptides from white blood cells and platelets, as well as cationic clinical antimicrobials such as daptomycin and vancomycin (as in this proposal). My lab has devoted the last 20 years to studying the mechanisms by which the staphylococci and enterococci develop adaptive resistance to host defense peptides, and the last 15 years dovetailing those mechanistic investigations with those related to daptomycin-resistance. I serve as a PI on two current NIH RO-1's, both dealing with antibiotic resistance in key gram-positive pathogens, the viridans group streptococci and MRSA. The former grant deals with mechanisms of daptomycin-resistance in viridans streptococci, while the latter deals with resensitization of MRSA to B-lactam agents. I am also a sub-contract PI on another RO-1 (Rose – Univ of Wisc), and a co-I on an additional RO-1 (Xiong – Lundquist Institute). I serve an overall role in study design of *in vitro*, *ex vivo* and animal experimental investigations, as well as in data interpretation and manuscript formulations; in addition, I direct the animal endocarditis studies in my lab.

Ongoing and recently completed grant projects:

"Development of lysins for the treatment of invasive Pseudomonas aeruginosa infections"

"S*ystems Immunobiology of Antibiotic-Persistent MRSA Infection"*

"Bicarbonate-mediated enhancement of beta-lactam-MRSA killing: Mechanisms and Clinical Translatability"

"The role of purine biosynthesis and stringent response in persistent MRSA endovascular infections"

"Mechanisms and circumvention of daptomycin resistance in Streptococcus mitis"

"Mechanisms of penicillin-binding protein inhibition to optimize cationic peptide anti-MRSA treatment"

"Resensitization of MRSA to β-lactam antibiotics following preexposures to phage lysin CF-301 in experimental rabbit endocarditis"

"Efficacy of Gram-Negative Lysins in an Experimental Rabbit Model of Right-Sided *Pseudomonas aeruginosa* (PA) Endocarditis (IE)"

"Eradication of in vivo S. aureus Biofilms with Phage Lysin CF-301 in Experimental MRSA IE"

"Mitigating Resistance & Virulence in MRSA"

The following **4 peer-reviewed** publications (selected from **>300 overall and >30 relevant publications**) highlight and globally represent my experience and qualifications for this project related to **antimicrobial resistance** and **efficacy in key Gram-positive pathogens,** especially MRSA:

Bayer AS, T Schneider, H-G Sahl. Mechanisms of daptomycin resistance in *Staphylococcus aureus*: role of the cell membrane and cell wall. Annals of the New York Academy of Sciences 1277:139-158, Jan 2013. PMID: 23215859. PMCID: PMC3556211.

Mishra NN, S-J Yang, L Chen, C Muller, A Saleh-Mghir, S Kuhn, A Peschel, MR Yeaman, CC Nast, BN Kreiswirth, A-C Crémieux, **AS Bayer**. Emergence of daptomycin resistance in daptomycin-naïve rabbits with methicillin-resistant *Staphylococcus aureus* prosthetic joint infection is associated with resistance to host defense cationic peptides and *mprF* polymorphisms. PloS One. Aug 19; 2013; 8(8):e71151. PMID 23990934. PMCID: PMC3747195.

Yang SJ, NN Mishra, A Rubio, **AS Bayer.** Causal role of single nucleotide polymorphisms (SNPs) within the *mprF* gene of *Staphylococcus aureus* in daptomycin resistance. Antimicrob Agents Chemother. 57:5658-5664, Nov 2013. PMID: 24002096. PMCID: PMC3811309.

Mishra NN, T.T. Truc, R. Seepersaud, C. Garcia-de-la-Maria[f], K. Faull, A. Yoon, J.M. Miro, M.J. Rybak, **A.S. Bayer**, C.A. Arias, P.M. Sullam. Perturbations of phosphatidate cytidylyltransferase (CdsA) mediate daptomycin resistance in *Streptococcus mitis* by a novel mechanism. Antimicrob Agents Chemother. 2017. 61(4):1-13; e02435-16; PMID: 28115347; PMCID: PMC536570361.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

Senior Investigator – LA Biomedical Research Institute	2000-present
Junior Investigator – LA Biomedical Research Institute	1981-1999
Distinguished Professor – UCLA School of Medicine	20010-present
Professor of Medicine (in Residence) - UCLA School of Medicine (Above Scale)	2001-present
Associate Professor of Medicine (in Residence) - UCLA School of Medicine	1986-2001
Associate Program Director Infectious Disease Harbor-UCLA Med. Ctr.	1981-present
Assistant Professor of Medicine (in Residence) - UCLA School of Medicine	1980-1985
Faculty, Internal Medicine- Harbor-UCLA Medical Center	1980-present

Other Experience and Professional Memberships.

The Lundquist Institute Research "Hall of Fame" (*Legends*)	Elected 2017
Vice Chair-then-Chair Gordon Research Conference on "Staphylococci"	2001-2005
Charter Member – NIH-NIAID-NARSA	1999-2014
Council Member - ISCVID	1995-present
Western Association of Physicians	1986-present
Fellow, American College of Chest Physicians	1981-present
Fellow, Infectious Disease Soc of America	1980-present
Fellow, American College of Physicians	1979-present
Member- American Society for Microbiology	1976-present

C. Contribution to Science

1. **Immune complex nature of infective endocarditis (IE).** It had been proposed for many years that many of the clinical and laboratory manifestations of IE were immune-mediated. However, there had been minimal direct evidence in this regard. My lab was able to measure circulating immune complexes (**CICs**) in the serum of patients with IE and confirm their frequency in such patients. In addition, using the levels of CICs, we were able to sero-differentiate non-IE from IE in bacteremic patients. Moreover, we were able to link CIC formation with certain specific IE-related syndromes. These studies were all done by me during my ID Fellowship and post-doctoral tenure.

   Relevant Publications:

   a. **Bayer AS**, Theofilopoulos AN, Eisenberg R, Dixon FJ, Guze LB. Circulating immune complexes in infective endocarditis. N Engl J Med.295:1500-1505, Dec 1976. PMID: 995157.
   b. **Bayer AS**, Theofilopoulos AN, Eisenberg R, Friedman SG, Guze LB. Thrombotic thrombocytopenic purpura-like syndrome associated with infective endocarditis. A possible immune complex disorder. JAMA. 238:408-410, Aug 1977. PMID: 141532.
   c. **Bayer AS**, Theofilopoulos AN, Tillman DB, Dixon FJ, Guze LB. Use of circulating immune complex levels in the serodifferentiation of endocarditic and nonendocarditic septicemias. Am J Med. 66:58-62, Jan 1979. PMID: 420250.
   d. **Bayer AS**, Theofilopoulos AN, Dixon FJ, Guze LB. Circulating immune complexes in experimental streptococcal endocarditis: a monitor of therapeutic efficacy. J Infect Dis. 139:1-8. Jan 1979. PMID: 438528.

2. **Pathogenesis and mechanisms of antibiotic resistance in endovascular infections**. My lab next explored the pathogenesis of IE, using *Pseudomonas aeruginosa* as the model organism and the rabbit model of IE. Importantly, we were able to show that the capacity of this organism to produce the antibiotic-protective biofilm, mucoid exopolysaccharide, was an oxygen-denependent phenomenon (higher in the increased oxygen content on the left-side vs right-side of the heart); this explained, at least in part, the more facile capacity to eradicate this organism from cardiac vegetations in right-sided vs left-sided IE. In addition, using this same IE model, were able to demonstrate that PMNs within cardiac vegetations on the right-side (but not the left-side) of the heart were able to down-modulate intracardiac pseudomonal densities. Finally, we confirmed that aminoglycoside-resistant pseudomonal variants emerging during unsuccessful therapy of experimental IE were electron transport mutants which abrogated aminoglycoside uptake. These studies were all directed by me and supervised as the lab director.

   Relevant Publications:

   a. Parr TR Jr, **Bayer AS**. *Mechanisms of aminoglycoside resistance in variants of Pseudomonas aeruginosa* isolated during treatment of experimental endocarditis in rabbits. J Infect Dis. 158:1003-1010, Nov 1988. PMID: 3141520.
   b. **Bayer AS**, Yih J, Chiu CY, Nast CC. Pathogenic effects of monocytopenia, granulocytopenia and dexamethasone on the course of experimental *Pseudomonas aeruginosa* endocarditis in rabbits. Chemotherapy. 1989;35:278-288, 1989. PMID: 2504546.
   c. **Bayer AS**, O'Brien T, Norman DC, Nast CC. Oxygen-dependent differences in exopolysaccharide production and aminoglycoside inhibitory-bactericidal interactions with *Pseudomonas aeruginosa*--implications for endocarditis. J Antimicrob Chemother. 23:21-35, Jan 1989. PMID: 2501267.

3. **Interaction of host defense peptides from platelets and staphylococci in the innate immunity against endovascular infections.** Over the past 20 years, my lab has focused on the mechanisms of staphylocidal killing and resistance to host defense cationic antimicrobial peptides (**HDPs**) from mammalian platelets in the context of endovascular infections. These studies have ranged from the identification and characterizations of the overall family of platelet HDPs, to their mechanisms of killing straphylococci, to the countermeasures employed by staphylococci to resist HDP-mediated killing, to the interplay of these metrics on clinical outcomes of such infections.

Relevant Publications:

a. Wu T, Yeaman MR, **Bayer AS**. *In vitro* resistance to platelet microbicidal protein correlates with endocarditis source among bacteremic staphylococcal and streptococcal isolates. Antimicrob Agents Chemother. 38:729-732, April 1994. PMID: 8031037. PMCID: PMC284533.
b. Yeaman MR, **Bayer AS**, Koo SP, Foss W, Sullam PM. Platelet microbicidal proteins and neutrophil defensin disrupt the *Staphylococcus aureus* cytoplasmic membrane by distinct mechanisms of action. J Clin Invest. 1998 Jan 1;101:178-187, Jan 1998. PMID: 9421480. PMCID: PMC508554.
c. Kupferwasser LI, Yeaman MR, Shapiro SM, Nast CC, **Bayer AS**. *In vitro* susceptibility to thrombin-induced platelet microbicidal protein is associated with reduced disease progression and complication rates in experimental *Staphylococcus aureus* endocarditis: microbiological, histopathologic, and echocardiographic analyses. Circulation. 2002. 105:746-752, 2002. PMID: 11839632.
d. Xiong YQ, **Bayer AS**, Elazegui L, Yeaman MR. A synthetic congener modeled on a microbicidal domain of thrombin- induced platelet microbicidal protein 1 recapitulates staphylocidal mechanisms of the native molecule. Antimicrob Agents Chemother. Nov 2006; 50:3786-3792, PMID: 16954324. PMCID: PMC1635186.

4. **Mechanisms, circumvention and prevention of daptomycin resistance in gram-positive coccal endovascular pathogens, with particular emphasis on *Staphylococcus aureus*.** As noted in my Personal Statement above in section A, since 2008, my lab has focused on this issue of daptomycin resistance, especially in MRSA. We have identified many of the genetic correlates of this resistance phenotype, particularly focusing on gain-in-function mutations within the *mprF* and *dlt* operons. We have also catalogued the large range of phenotypic perturbations associated with daptomycin-resistance, spanning a multiplicity of cell membrane abnormalities (surface charge; fluidity; daptomycin binding; phospholipid mislocalizations) as well as cell wall modifications (including walls; increased wall teichoic acid synthesis; and excess d-alanylation). Lastly, we have shown a rather consistent "cross-resistance" profile between daptomycin-resistance and HDPs. These studies were all co-directed by me and co-supervised as the Pathogenesis Lab director in close collaboration with the Yeaman lab in our group.

   Relevant publications (see section A above).

5. **Bicarbonate-mediated suppression of B-lactam resistance in MRSA.** My lab recently discovered and microbiologically characterized a novel phenomenon termed "bicarbonate-mediated resensitization of B-lactam susceptibility in MRSA". In this arena, exposure of a substantial proportion of MRSA strains to physiologic and supra-physiologic bicarbonate concentrations renders them "susceptible" in vitro to standard B-lactam agents (e.g., oxacillin; cefazolin). This sensitization phenomenon translated *in vivo* in experimental MRSA infections, such as endocarditis. The mechanisms involved in this phenomenon are multifactorial, but appear to depend heavily on impacts of bicarbonate on the genetic regulation of production, localization, maturation and functionality of the predominant PBP of MRSA strains, PBP2a. These studies were all directed by myself, under an existing NIH RO-1 grant.

   Relevant publications:

   a. SC Ersoy, HF Chambers, RA Proctor, A Rosato, S Farah, NM Mishra, YQ Xiong, **Bayer AS**. Impact of bicarbonate on PBP2a maturation and functionality in methicillin-resistant *Staphylococcus aureus* (MRSA). Antimicrobial Agents & Chemotherapy 02621-20; March 2021; PMID: 33649115.
   b. SC Ersoy, Rose WE, Patel R, Proctor RA, Chambers HD, Harrison EW, Pak Y, **Bayer AS**. A combined phenotypic-genotypic predictive algorithm for *in vitro* detection of bicarbonate: β-lactam sensitization among methicillin-resistant *Staphylococcus aureus* (MRSA). Antibiotics (Basel). 10:1089; Sept 2021; PMID: 34572671.
   c. SC Ersoy, Hanson BM, Proctor RA, Arias CA, Tran T, Chambers HF, **Bayer AS**. Impact of bicarbonate-β-lactam exposures on methicillin-resistant *Staphylococcus aureus* (MRSA) gene

expression in bicarbonate-β-lactam-responsive vs. non-responsive strains. Gene. (in press 10/21).

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=bayer+as