BIOGRAPHICAL SKETCH

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NAME: Prince, Alice

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

POSITION TITLE: Professor of Pediatrics (with tenure)

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)	END DATE MM/YYYY	FIELD OF STUDY
Wellesley College, Wellesley, MA	BA	06/1971	Molecular Biology
Columbia University,College of Physicians & Surgeons, New York, NY	MD	06/1975	Medicine
Babies Hospital/Columbia University, New York, NY	Resident	06/1978	Internship and Residency in Pediatrics
Columbia University Health Sciences, New York, NY	Postdoctoral Fellow	06/1980	Infectious Diseases/Microbiology
MGH-Harvard Medical School, Boston, MA	Postdoctoral Fellow	06/1981	Infectious Diseases

A. Personal Statement

My laboratory studies the pathogenesis of bacterial infection, specifically how clinically important pathogens, such as S. aureus, Pseudomonas aeruginosa and Klebsiella pneumoniae activate host immune signaling, especially in the lung. As an Infectious Diseases pediatrician, I am especially attuned to the host-pathogen interaction and have embraced a multidisciplinary approach toward understanding the pathogenesis of pneumonia over the course of decades of NIH funded research, including a current R35 award. I actively participate in a variety of national and international efforts, reviewing grants and manuscripts, organizing and chairing meetings such as the Gordon Conference on Respiratory Infection and less well publicized but equally important, local Pediatric ID and Bacterial Pathogenesis meetings for the greater NY and Connecticut area. Ongoing studies are exploring how immunometabolomic signaling can be used to prevent/treat infection. While an appropriate inflammatory response is critical to eradicate infection, innate immune signaling often results in inflammation-associated damage. Many pathogens adapt to the airways, altering their metabolic activity in response to the environmental niche at the site of infection. These host-adapted pathogens have substantially different properties than many of the laboratory isolates from bloodstream infections. Antimicrobial agents, even those that are highly active, are often inadequate in the treatment of pulmonary infection. Our goal is to identify innate clearance mechanisms that could be manipulated to enhance eradication of these pathogens, using longitudinal collections of sequenced clinical isolates to determine how airway pathogens adapt to the lung, and specifically how the organisms alter their metabolism in response to the host. A major focus of my work is education and mentoring; my lab hosts trainees at all stages of education who help to shape the direction of our research. As the Chief of Pediatric Infectious Diseases, I am directly involved in many aspects of graduate education that include my participation in Scholarly Oversight Committees and advising newly trained physician scientists. My expertise in bacterial pathogenesis as well as in clinical medicine has made me a sought after member of thesis committees and PhD defenses.

1. Wong Fok Lung T, Charytonowicz D, Beaumont KG, Shah SS, Sridhar SH, Gorrie CL, Mu A, Hofstaedter CE, Varisco D, McConville TH, Drikic M, Fowler B, Urso A, Shi W, Fucich D, Annavajhala MK, Khan IN, Oussenko I, Francoeur N, Smith ML, Stockwell BR, Lewis IA, Hachani A, Upadhyay Baskota S, Uhlemann AC, Ahn D, Ernst RK, Howden BP, Sebra R, Prince A. Klebsiella

pneumoniae induces host metabolic stress that promotes tolerance to pulmonary infection. Cell Metab. 2022 May 3;34(5):761-774.e9. PubMed Central PMCID: PMC9081115.

2. Riquelme SA, Lozano C, Moustafa AM, Liimatta K, Tomlinson KL, Britto C, Khanal S, Gill SK, Narechania A, Azcona-Gutiérrez JM, DiMango E, Saénz Y, Planet P, Prince A. CFTR-PTEN-dependent mitochondrial metabolic dysfunction promotes *Pseudomonas aeruginosa* airway infection. Sci Transl Med. 2019 Jul 3;11(499) PubMed Central PMCID: PMC6784538.
3. Parker D, Ahn D, Cohen T, Prince A. Innate Immune Signaling Activated by MDR Bacteria in the Airway. Physiol Rev. 2016 Jan;96(1):19-53. PubMed Central PMCID: PMC4698397.
4. Cohen TS, Prince A. Cystic fibrosis: a mucosal immunodeficiency syndrome. Nat Med. 2012 Apr 5;18(4):509-19. PubMed Central PMCID: PMC3577071.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2015 -	John M. Driscoll, Jr. MD and Yvonne T. Driscoll MD Professor of Pediatrics, Columbia University, Chief, Division of Pediatric Infectious Diseases
1997 -	Professor of Pediatrics (with tenure), Columbia University, (in Pharmacology), New York, NY
1988 - 1997	Assoc. Prof of Pediatrics, Columbia University, New York, NY
1981 - 1988	Asst. Prof Medicine/Microbiology, Columbia University, New York, NY

Honors

2018	Dean's Distinguished Lecturer in Clinical Science, Columbia University
2017	Outstanding Investigator Award, NHLBI
2015	John M. Driscoll, Jr and Yvonne T. Driscoll Professor of Pediatrics, Columbia University
2000	Charles Bohmfalk Award , Columbia University
1997	Fellow, American Society for the Advancement of Science
1994	Member, American Society for Clinical Investigation
1987	Charles Lubin Research Scholar, Cystic Fibrosis Foundation

C. Contribution to Science

1. Metabolic susceptibility to infection - Exactly why some individuals are highly susceptible to infection by specific bacteria is poorly understood yet central to strategies to prevent severe infection such as pneumonia. We have used cystic fibrosis as a model to establish how abnormalities in an ion channel, CFTR, generates a metabolic milieu in the airway that is especially conducive to P. aeruginosa infection, the major airway pathogen causing life limiting pulmonary infection in CF patients. Over the course of many years with increasingly sophisticated methodologies, we demonstrated that clinical isolates of P. aeruginosa accrue mutations in metabolic genes in response to the succinate-dominated airway metabolome in CF. Succinate, which generates proinflammatory signaling, as well as itaconate, an anti-oxidant and anti-inflammatory metabolite, are readily consumed by P. aeruginosa, but few other pathogens. Growth in succinate skews bacterial metabolism toward the production of biofilm, the extracellular polysaccharides that render bacteria resistant to phagocytosis and clearance. We established that CFTR is linked to PTEN, the phosphatase that regulates PI3K and cellular metabolism, and in the absence of membrane associated CFTR, inadequate amounts of PTEN are functioning to suppress inflammatory signaling through NF-kB. We have similarly established the immunometabolic bases for the pathogenesis of S. aureus infection in CF and are actively studying how the metabolic stress induced by another common airway pathogen, K. pneumoniae, enables it to recruit an anti-inflammatory immune response.

    a. Riquelme SA, Liimatta K, Wong Fok Lung T, Fields B, Ahn D, Chen D, Lozano C, Sáenz Y,

Uhlemann AC, Kahl BC, Britto CJ, DiMango E, Prince A. Pseudomonas aeruginosa Utilizes Host-Derived Itaconate to Redirect Its Metabolism to Promote Biofilm Formation. Cell Metab. 2020 Jun 2;31(6):1091-1106.e6. PubMed Central PMCID: PMC7272298.

b. Riquelme SA, Lozano C, Moustafa AM, Liimatta K, Tomlinson KL, Britto C, Khanal S, Gill SK, Narechania A, Azcona-Gutiérrez JM, DiMango E, Saénz Y, Planet P, Prince A. CFTR-PTEN-dependent mitochondrial metabolic dysfunction promotes *Pseudomonas aeruginosa* airway infection. Sci Transl Med. 2019 Jul 3;11(499) PubMed Central PMCID: PMC6784538.

c. Riquelme SA, Hopkins BD, Wolfe AL, DiMango E, Kitur K, Parsons R, Prince A. Cystic Fibrosis Transmembrane Conductance Regulator Attaches Tumor Suppressor PTEN to the Membrane and Promotes Anti Pseudomonas aeruginosa Immunity. Immunity. 2017 Dec 19;47(6):1169-1181.e7. PubMed Central PMCID: PMC5738266.

d. Cohen TS, Prince A. Cystic fibrosis: a mucosal immunodeficiency syndrome. Nat Med. 2012 Apr 5;18(4):509-19. PubMed Central PMCID: PMC3577071.

2. Pathogenesis of S. aureus infection – S. aureus is a major pulmonary pathogen implicated in CF lung disease, in primary infection in well hosts, and as an important cause of fatal infection in the setting of influenza. We have characterized several specific interactions between staphylococcal virulence factors and host immune signaling cascades. These include the activation of TNF signaling by protein A, as well as the induction of ADAM-17 and EGFR signaling through the same ligand. Using selective depletion studies in transgenic mice, we demonstrated that alveolar macrophages are critical for successful outcome from MRSA infection, and that they are specifically depleted in the early stages of MRSA pneumonia, as they undergo necroptosis in response to MRSA toxins. We have also initiated longitudinal studies S. aureus from chronically infected patients to follow genetic and epigenetic changes accrued by the organisms to facilitate long term human infection. Our recent studies using longitudinal isolates of S. aureus from CF patients demonstrates metabolic adaptation over the course of infection, consistent with the organisms reliance upon glycolysis to generate ATP.

   a. Tomlinson KL, Lung TWF, Dach F, Annavajhala MK, Gabryszewski SJ, Groves RA, Drikic M, Francoeur NJ, Sridhar SH, Smith ML, Khanal S, Britto CJ, Sebra R, Lewis I, Uhlemann AC, Kahl BC, Prince AS, Riquelme SA. Staphylococcus aureus induces an itaconate-dominated immunometabolic response that drives biofilm formation. Nat Commun. 2021 Mar 3;12(1):1399. PubMed Central PMCID: PMC7930111.

   b. Gabryszewski SJ, Wong Fok Lung T, Annavajhala MK, Tomlinson KL, Riquelme SA, Khan IN, Noguera LP, Wickersham M, Zhao A, Mulenos AM, Peaper D, Koff JL, Uhlemann AC, Prince A. Metabolic Adaptation in Methicillin-Resistant *Staphylococcus aureus* Pneumonia. Am J Respir Cell Mol Biol. 2019 Aug;61(2):185-197. PubMed Central PMCID: PMC6670030.

   c. Prince A, Wang H, Kitur K, Parker D. Humanized Mice Exhibit Increased Susceptibility to Staphylococcus aureus Pneumonia. J Infect Dis. 2017 May 1;215(9):1386-1395. PubMed Central PMCID: PMC5853420.

   d. Kitur K, Parker D, Nieto P, Ahn DS, Cohen TS, Chung S, Wachtel S, Bueno S, Prince A. Toxin-induced necroptosis is a major mechanism of Staphylococcus aureus lung damage. PLoS Pathog. 2015 Apr;11(4):e1004820. PubMed Central PMCID: PMC4399879.

3. Opportunistic pathogens activate innate immune defenses - Many of the bacterial pathogens that cause health care-associated pneumonia, in patients with COPD or following SARS CoV-2 or influenza infection, have specifically adapted to the conditions and metabolites in the human airway. These pathogens readily undergo metabolic adaptation to exploit or even metabolize the immunometabolites released by immune cells. We found that S. aureus virulence can be directly attributed to the induction of type I IFNs in the lung, and that mice lacking the receptors for either type I (IFNAR) or type III IFNs (IL-28R) have a significantly improved outcome. The interferons are also important in the epithelial responses to carbapenem-resistant K. pneumoniae also induce both IFN lambda and IL-22, which shares the same IL-10 receptor, and have major effects on the integrity of

the respiratory epithelium. In ongoing studies of the epidemic ST258 carbapenem resistant K. pneumonias, we have identified a novel genetic element, not found in more conventional Klebsiellae, that significantly boost the metabolic activity of these organisms within the lung. Such host-adapted bacteria are able to alter their metabolic activity to cope with the oxidants released by immune cells and by their own metabolic activity. These adaptive changes include the production of extracellular polysaccharides that promote intractable infection. Strategies to block bacterial metabolic adaptation are being tested to prevent pneumonia

a. Wong Fok Lung T, Charytonowicz D, Beaumont KG, Shah SS, Sridhar SH, Gorrie CL, Mu A, Hofstaedter CE, Varisco D, McConville TH, Drikic M, Fowler B, Urso A, Shi W, Fucich D, Annavajhala MK, Khan IN, Oussenko I, Francoeur N, Smith ML, Stockwell BR, Lewis IA, Hachani A, Upadhyay Baskota S, Uhlemann AC, Ahn D, Ernst RK, Howden BP, Sebra R, Prince A. Klebsiella pneumoniae induces host metabolic stress that promotes tolerance to pulmonary infection. Cell Metab. 2022 May 3;34(5):761-774.e9. PubMed Central PMCID: PMC9081115.
b. Ahn D, Wickersham M, Riquelme S, Prince A. The Effects of IFN-λ on Epithelial Barrier Function Contribute to Klebsiella pneumoniae ST258 Pneumonia. Am J Respir Cell Mol Biol. 2019 Feb;60(2):158-166. PubMed Central PMCID: PMC6376406.
c. Ahn D, Peñaloza H, Wang Z, Wickersham M, Parker D, Patel P, Koller A, Chen EI, Bueno SM, Uhlemann AC, Prince A. Acquired resistance to innate immune clearance promotes *Klebsiella pneumoniae* ST258 pulmonary infection. JCI Insight. 2016 Oct 20;1(17):e89704. PubMed Central PMCID: PMC5070956.
d. Parker D, Ahn D, Cohen T, Prince A. Innate Immune Signaling Activated by MDR Bacteria in the Airway. Physiol Rev. 2016 Jan;96(1):19-53. PubMed Central PMCID: PMC4698397.

4. S aureus is the major cause of human skin and soft tissue infection. We have examined in detail the response of human keratinocytes to S. aureus, and established the roles of some major signaling cascades in host defense. The activation of necroptosis, a RIPK1/MLKL mediated mechanism of cell death functions to limit the inflammatory damage invoked by staphylococcal toxins, eliminating immune cells as well as keratinocytes that participate in inflammation. We have demonstrated that S. aureus infection imposes an hypoxic stress on keratinocytes that respond by metabolic reprogramming to use glycolysis to generate ATP. The staphylococci, in the context of human skin, similarly must be capable of glycolysis to persist in the milieu of the skin. Ongoing studies are examining the importance of small colony variants in persistent skin infection, their metabolic adaptation to skin, and how this is affected by the metabolic changes observed in diabetes.

a. Wong Fok Lung T, Monk IR, Acker KP, Mu A, Wang N, Riquelme SA, Pires S, Noguera LP, Dach F, Gabryszewski SJ, Howden BP, Prince A. Staphylococcus aureus small colony variants impair host immunity by activating host cell glycolysis and inducing necroptosis. Nat Microbiol. 2020 Jan;5(1):141-153. PubMed PMID: 31686028.
b. Acker KP, Wong Fok Lung T, West E, Craft J, Narechania A, Smith H, O'Brien K, Moustafa AM, Lauren C, Planet PJ, Prince A. Strains of Staphylococcus aureus that Colonize and Infect Skin Harbor Mutations in Metabolic Genes. iScience. 2019 Sep 27;19:281-290. PubMed Central PMCID: PMC6700416.
c. Kitur K, Wachtel S, Brown A, Wickersham M, Paulino F, Peñaloza HF, Soong G, Bueno S, Parker D, Prince A. Necroptosis Promotes Staphylococcus aureus Clearance by Inhibiting Excessive Inflammatory Signaling. Cell Rep. 2016 Aug 23;16(8):2219-2230. PubMed Central PMCID: PMC5001919.
d. Parker D, Planet PJ, Soong G, Narechania A, Prince A. Induction of type I interferon signaling determines the relative pathogenicity of Staphylococcus aureus strains. PLoS Pathog. 2014 Feb;10(2):e1003951. PubMed Central PMCID: PMC3930619.