BIOGRAPHICAL SKETCH

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NAME: Ann M. Arvin, MD

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

POSITION TITLE: Professor of Pediatrics and Microbiology & Immunology

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
Brown University, Providence, RI	BA	1966	Philosophy
University of Pennsylvania, Philadelphia, PA	MD	1972	Medicine
University of California, San Francisco		1975	Pediatric Residency
Stanford University, Department of Medicine, Stanford, CA		1978	Postdoctoral Fellowship

A. Personal Statement

The focus of my research in virology and immunology is on the molecular mechanisms of varicella zoster virus pathogenesis, including VZV glycoprotein functions, T cell tropism, innate immune control of VZV and neurotropism in human cell models *in vitro* and in the SCID mouse model of VZV infection *in vivo.*

B. Positions and Honors

Positions and Employment

1978-89 Assistant-Associate Professor of Pediatrics, Stanford University School of Medicine
1989-Present Lucile Salter Packard Professor of Pediatrics (Infectious Diseases) and Professor of Microbiology & Immunology

Other Experience and Professional Memberships

2007-11: NIAID Director's Advisory Council
2011-13: American Association for the Advancement of Science, Section on Medical Sciences, Chair-elect/Chair
2014- : National Academy/NRC Committee on Science, Technology and Law, National Academy of Science

Honors

1981-1984 National Institute of Allergy and Infectious Diseases: New Investigator Award
1984-1989 National Institute of Allergy and Infectious Diseases: Research Career Development Award
2016- National Institute of Allergy and Infectious Diseases: MERIT Award

2003 National Academy of Medicine (Institute of Medicine)
2009 Fellow, American Association for Advancement of Science
2012 Fellow, American Academy of Microbiology
2012 Fellow, American Academy of Arts and Sciences

C. Contributions to Science. My research has focused on VZV immunity and pathogenesis beginning with my earliest publications showing the critical role of VZV T cell immunity in varicella and live vaccine efficacy. Subsequently, we focused on molecular mechanisms of VZV pathogenesis, based primarily on our proficiency with generating VZV recombinants with targeted mutations in viral genes and promoters and our development of the SCID mouse model with human tissue xenografts. Significant contributions are described by category below, highlighting VZV glycoprotein studies as most relevant to this proposal and summarizing key reports

related to each of our areas of interest in VZV virology. In each case, my role has been to directly oversee the design, conduct and interpretation of the experiments and the publication of the findings. An invited overview of our work on molecular mechanisms of VZV pathogenesis appeared in Nature Reviews Microbiology, 2014.

1. VZV glycoproteins. Our studies of VZV glycoprotein functions in pathogenesis encompass many reports, culminating in four recent papers that describe their critical domains and contributions to VZV virulence in skin and T cells. We described the unique characteristics of VZV gE compared to other herpesvirus gE proteins which make gE an essential protein in VZV whereas it is dispensable in these viruses (PNAS, 2010). Our first study of gH structure-function identified domain-specific roles for cell fusion and skin pathogenesis (PNAS, 2011). Other important discoveries about VZV pathogenesis are that human T cells are resistant to VZV glycoprotein-induced cell fusion and that effective regulation of cell fusion is critical for pathogenesis in skin. Hyperfusogenic gB and gH mutants show reduced pathogenicity and functions that modulated cell fusion were mapped to gB and gH cytoplasmic domains. In recent papers relevant to this proposal, we identified the αV integrin subunit as a VZV entry mediator (J Virol. 2016) and we showed that dysregulating gB-mediated fusion alters both the VZV and host cell gene transcriptome and dramatically accelerates cell fusion.

a). Oliver SL, Brady JJ, Sommer MH, Reichelt M, Sung P, Blau HM, Arvin AM. An immunoreceptor tyrosinebased inhibition motif in varicella-zoster virus glycoprotein B regulates cell fusion and skin pathogenesis. Proc Nat Acad Sci,.110:1911-6, 2013. PMCID: PMC3562845.

b). Yang E, Arvin AM, Oliver SL. The cytoplasmic domain of varicella-zoster virus glycoprotein H regulates syncytia formation and skin pathogenesis. PLoS Pathogens. 10(5):e1004173, 2014. PMCID: PMC4038623.

c). Yang E, Oliver S/Arvin AM*. The glycoprotein B cytoplasmic domain lysine cluster regulates varicella zoster virus cell-cell fusion and infection. J Virol, The glycoprotein B cytoplasmic domain lysine cluster regulates varicella zoster virus cell-cell fusion and infection. J Virol. 16;91(1). pii: e01707-16. PMCID: PMC5165221.

d). Oliver S, Yang E, Arvin AM. Dysregulated glycoprotein B mediated cell-cell fusion disrupts varicella-zoster virus and host gene transcription during infection. J Virol. 16;91(1). pii: e01613-16, 2016. PMCID: PMC5165202.

2. Innate immunity. In addition to studies of the VZV regulatory and kinase proteins as virulence factors in T cells and skin, several of these proteins contribute to the manipulation of host cells so that VZV replication is enhanced and host response mechanisms are disarmed. We found that two of these, IE62 and the ORF61 protein, were expressed in the nuclei of infected cells at the earliest time point after viral entry. Notably, IE62 blocks the interferon pathway at the initial step of its activation and ORF61 protein plays a critical role in disrupting the architecture of PML nuclear bodies that are a first line of defense against replication by many viruses and are highly upregulated by IFN-α. Our work demonstrated that SUMOylation of ORF61 is essential for this function and that it is ORF61 SUMO-mediated disruption of the PML-NB structure rather than degradation of PML protein that is critical for replication. Conversely, we identified a novel intrinsic barrier to VZV replication mediated by binding of the PML-IV isoform to the VZV ORF23 capsid protein which results in entrapment of newly formed capsids in the nuclei of infected cells. Because of our SCID mouse model, we were able to document that this process occurs in differentiated human cells infected in vivo. Notably, the same mechanism was shown to sequester aberrant proteins associated with neurodegenerative diseases. Our approach also made it possible to demonstrate that VZV induces STAT3 activation and that pSTAT3 has proviral functions for pathogenesis of VZV infection as it was known to have for oncogenic herpesviruses. We recently showed that VZV activates CREB and this host cell manipulation is necessary for VZV skin pathogenesis *in vivo (*J Virol, 2016), age affects VZV replication in human skin (J Virol, 2018) and type I and type II interferons have differential effects on VZV.

a). Reichelt M, Wang L, Sommer M, Perrino J, Nour AM, Sen N, Baiker A, Zerboni L, Arvin AM. Entrapment of viral capsids in nuclear PML cages is an intrinsic antiviral host defense against varicella-zoster virus. PLoS Pathogens. 7:1001266, 2011. PMCID: PMC3033373.

b). Sen N, Che X, Zerboni L, Rajamani J, Ptacek, J, Arvin AM. Signal transducer and activator of transcription 3 (STAT3) and survivin induction by varicella-zoster virus promote replication and skin pathogenesis. Proc Nat Acad Sci., 109:600-5, 2012. PMCID: PMC3258638.

c). François S, Sen N, Mitton B, Xiao X, Sakamoto KM, Arvin A. Varicella-zoster virus activates CREB and inhibition of the pCREB-p300/CBP- interaction inhibits viral replication in vitro and skin pathogenesis in vivo. J Virol. 2 12;90(19):8686-97, 2016. PMCID: PMC5021407.

d). Sen N, Sung P, Panda A, Arvin AM. Distinctive roles for type I and type II interferons and interferon regulatory factors in the host cell defense against varicella-zoster virus. J Virol 2018 Aug 8. pii: JVI.01151-18. doi: 10.1128/JVI.01151-18. [Epub ahead of print]

3. T cell tropism. Key publications include our early report detecting VZV genomic DNA in peripheral blood lymphocytes from children with varicella, followed by experiments in the SCID mouse model showing VZV tropism for T cells infected in vivo and proving that VZV through the mouse circulation, trafficked across the

human capillary endothelial cells and released virus into skin xenografts, where infection then progressed over 10-21 days to produce cutaneous lesions. Most recently, as will be pursued in our new work, we showed that VZV infection of tonsil T cells resulted in activation of cell signaling pathways and remodeling of surface proteins to enhance properties of skin trafficking, regardless of the basal state and T cell subpopulations that were infected.

a). Moffat J, Stein MD, Kaneshima H, Arvin AM. Tropism of varicella-zoster virus for human CD4+ and CD8+ T-lymphocytes and epidermal cells in SCID-hu mice. J Virol, 69:5236-42, 1995. PMCID: PMC189355.

b). Ku CC, Zerboni L, Ito H, Wallace M, Graham B, Arvin AM. Transport of varicella-zoster virus to skin by infected CD4 T cells and modulation of viral replication by epidermal cell interferon-a. J Exp Med, 200:917-925, 2004. PMCID: PMC2213285. *Selected for Editor's Choice, Science*

c). Sen N, Mukherjee G, Sen A, Bendall SC, Sung P, Nolan GP, Arvin AM. Single-cell mass cytometry analysis of human tonsil T cell remodeling by varicella zoster virus. Cell Reports. 24;633-45, 2014. PMCID: PMC4127309

4. Neurotropism. Given the insights about VZV pathogenesis that were obtained from studies of T cell and skin tropism in the SCID mouse model, we elected to develop the model to encompass investigations of VZV neurotropism by creating dorsal root ganglion xenografts and evaluating VZV infection in differentiated neural tissues in vivo. Among the unexpected and important observations was that VZV infects both satellite cells and neurons, in contrast to HSV-1, which is restricted to neurons. Further, VZV had the capacity to induce fusion between satellite cells and neurons in DRG xenografts, as observed in clinical reports of VZV ganglion infection from patients with active zoster at the time of death. This model revealed unexpected consequences of mutations in gE and gI functional domains, resulting in prolonged productive infection instead of transitioning to persistence. In work now been corroborated by two other labs, we showed that what had been thought to represent continued expression of some VZV proteins during latency can be attributed to cross-reactivity of antibody reagents with blood group A determinants, with the important implication that new hypotheses about mechanisms of VZV latency are needed.

a). Zerboni L, Ku C, Jones C, Zehnder J, Arvin AM. Varicella-zoster virus infection of human dorsal root ganglia in vivo. Proc Nat Acad Sci. 102:6490-6495, 2005. PMCID: PMC1088374.

b). Zerboni L, Reichelt M, Jones CD, Zehnder JL, Ito H, Arvin AM. Aberrant infection and persistence of varicella-zoster virus in human dorsal root ganglia in vivo in the absence of glycoprotein I. Proc Nat Acad Sci.104:14086-91, 2007. PMCID: PMC1955823.

c). Reichelt M, Zerboni, L, Arvin AM. Mechanisms of varicella-zoster virus neuropathogenesis in human dorsal root ganglia. J Virol. 82:3971-83, 2008. PMCID: PMC2292995.

d). Zerboni L, Sobel R, Lai M, Triglia R, Steain M, Abendroth A, Arvin AM. Apparent expression of varicella zoster virus proteins in latency resulting from reactivity of murine and rabbit antibodies with human blood group A determinants in sensory neurons. J Virol. 86:578-83, 2012. PMCID: PMC3255922.

5. VZV regulatory and kinase proteins in replication and skin and T cell pathogenesis. Our lab has investigated the contributions of several of the VZV proteins that are components of the virion tegument and have regulatory activity, or both. We have been particularly interested in the two viral kinases encoded by ORF47 and ORF66. A notable finding is that the ORF66 kinase is important for VZV T cell tropism but its deletion or a point mutation in a kinase domain has little impact on replication and lesion formation in skin. Such a mutant could be an effective 2nd generation live attenuated vaccine because our earlier work demonstrated that the current vaccine retains full capacity to infect T cells, thus explaining its poor attenuation and capacity to cause a varicella-like infection in immunocompromised children In both cases, mutations that disrupt the kinase function have limited effects in tissue culture, demonstrating the importance of defining VZV virulence determinants in differentiated primary human cells.

a). Moffat J, Zerboni L, Sommer MH, Heineman TC, Cohen J, Kaneshima H, Arvin A. The ORF47 and ORF66 putative protein kinases of varicella-zoster virus determine tropism for human T cells and skin in the SCID-hu mouse. Proc Nat Acad Sci. 95:11969-74, 1998. PMCID: PMC21749.

b). Besser J, Ikoma M, Fabel K, Sommer MH, Zerboni L, Grose C, Arvin AM. Differential requirement for cell fusion and virion formation in the pathogenesis of varicella-zoster virus infection in skin and T cells. J Virol. 78:13293-305, 2004. PMCID: PMC524993.

c). Schaap-Nutt A, Sommer M, Che X, Zerboni L, Arvin AM. ORF66 protein kinase function is required for T-cell tropism of varicella-zoster virus in vivo. J Virol, 80:11806-16, 2006. PMCID: PMC1642581. *Selected for Editor's Spotlight*

d). Khalil MI, Che X, Sung P, Sommer MH, Hay J, Arvin AM. Mutational analysis of varicella-zoster virus (VZV) immediate early protein (IE62) subdomains and their importance in viral replication. Virology. 492:82-91, 2016. PMCID: PMC4826839.

A complete list of my published work is available at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/ann.arvin.1/bibliography/41139115/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R37 AI020459 (Arvin) MERIT Award 02/15/2016- 01/31/21
NIH/NIAID
Varicella zoster virus: T Cell/Skin tropisms and immunity
The major goals of this project are to analyze VZV effects on T cell signaling pathways, T cell protein synthesis and T cell gene expression at single cell level and to carry out functional analyses of the contributions of VZV proteins to T cell tropism and skin infection.

Recently Completed

R01 AI102546 (Arvin) 06/01/2012-05/31/2018
NIH
Varicella-zoster virus: Molecular controls of cell fusion-dependent pathogenesis
The pathogenesis of varicella-zoster virus (VZV) overcomes the usual constraint against fusion between fully differentiated host cells to form multinucleated polykaryocytes during replication in skin and sensory ganglia. Our hypothesis is that this process, which is critical for VZV pathogenesis, is regulated by a gB-dependent intracellular signaling function. This novel concept is based on our observation that preventing tyrosine phosphorylation of the gB cytoplasmic domain (gBcyt) leads to anomalies in cell-cell fusion and syncytia formation. We will investigate the role of the gBcyt in modulating cell-cell fusion via intracellular signaling pathways during the production of syncytia observed in VZV-infected cells in vitro and the fusion of epidermal cells in skin and neuron-satellite cells in sensory ganglia associate with VZV virulence in vivo.

R56 AI116857 (Arvin) 09/01/2015-08/31/2016
NIH
The Role of the LAT Locus in HSV-1 Infection of Human Skin Xenografts in vivo
HSV-1 latency is characterized by the production of long non-coding RNAs called LATs. This grant explores our new findings that LATs are critical for HSV-1 infection of skin.

Project 120443 (Arvin) 06/15/2015-11/30/2016
Pfizer
Evaluation of the effects of Tofacitinib on Varicella-zoster virus (VZV) infection of human skin xenografts in the severe combined immunodeficiency (SCID) model mouse. The major goal of this grant is to determine whether tofacitinib enhances the capacity of VZV to replicate and form lesions in human skin xenografts *in vivo.*

R01 AI89716 (Arvin) 03/01/2011-02/28/2016
Subcontract University of Iowa
NIH/NIAID
Autophagy and ER stress during Varicella virus infection
The goal of this subcontract was to test autophagy markers in VZV-infected skin.