BIOGRAPHICAL SKETCH

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NAME: Vance, Russell E.

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POSITION TITLE: HHMI Investigator and Professor of Immunology & Molecular Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Queen's University, Kingston, Ontario, Canada	B.Sc.	1994	Biochemistry
Queen's University, Kingston, Ontario, Canada	M.A.	1995	Philosophy of Science
University of California, Berkeley	Ph.D.	2000	Immunology
Harvard Medical School; Lab of John Mekalanos	Postdoc	2000-2003	Microbiology
Harvard Medical School; Lab of William Dietrich	Postdoc	2003-2006	Genetics

A. Personal Statement

My training and expertise are in the areas of microbiology, immunology and mouse genetics. My lab has made several contributions to our understanding of the molecular basis by which pathogens are detected by the innate immune system. In particular, our studies have helped establish the concept that vertebrate immune sensors respond to the virulence activities of pathogens. My lab is known primarily for our work on inflammasomes and the cGAS–STING pathway. Inflammasomes are multiprotein complexes that initiate inflammation via the recruitment and activation of the Caspase-1 protease. We demonstrated that NAIP proteins, members of the NLR superfamily, form inflammasomes upon direct recognition of flagellin and other bacterial proteins [1]. We also found that direct proteolysis by the anthrax lethal factor protease is sufficient to activate the NLRP1B inflammasome, and solved the decade long mystery of the underlying biochemical mechanism of NLRP1B activation [2]. In separate work, we also discovered a novel cytosolic immunosurveillance pathway that detects unique bacterial signaling molecules called cyclic-di-nucleotides [3]. We used mouse mutagenesis to identify the host protein STING as essential for the response to cyclic-di-nucleotides, and provided biochemical proof that STING is the cytosolic cyclic-di-nucleotide receptor [3]. This discovery proved significant as it later helped provide a key signaling link in the innate cytosolic DNA sensing pathway. We currently focus on several bacterial pathogens including *Legionella pneumophila*, *Shigella flexneri*, and *Mycobacterium tuberculosis*. We developed the first physiological oral mouse infection model for Shigella [4]. We also recently discovered a new pathway for interferon induction in cells that responds to virulence factors produced by viruses [5].

1. Kofoed EM, **Vance RE** (2011) Innate immune recognition of bacterial ligands by NAIPs determines inflammasome specificity. Nature 477(7366):592-5 (PMC3184209).
2. Sandstrom A, Mitchell PS, Goers L, Mu EW, Lesser CF, **Vance RE** (2019) Functional degradation: A mechanism of NLRP1 inflammasome activation by diverse pathogen enzymes. Science pii: eaau1330. doi: 10.1126/science.aau1330 (PMC6532986).
3. Burdette DL, Monroe KM, Sotelo-Troha K, Iwig JS, Eckert B, Hyodo M, Hayakawa Y, **Vance RE** (2011) STING is a direct innate immune sensor of cyclic-di-GMP. Nature Sep 25;478(7370):515-8 (PMC3203314).
4. Mitchell PS, Roncaioli JL, Turcotte EA, Goers L, Chavez RA, Lee AY, Lesser CF, Rauch I, **Vance RE** (2020) NAIP-NLRC4-deficient mice are susceptible to shigellosis. Elife Oct 19;9:e59022. doi: 10.7554/eLife.59022. (PMC7595732).
5. Gaidt MM, Morrow A, Fairgrieve MR, Karr JP, Yosef N, **Vance RE** (2021) Self-guarding of MORC3 enables virulence factor-triggered immunity. Nature Dec;600(7887):138-142. doi: 10.1038/s41586-021-04054-5. Epub 2021 Nov 10. PMID: 34759314 (PMC in process).

B. Positions, Scientific Appointments, and Honors

Positions & Scientific Appointments

2014–	Professor, Division of Immunology & Pathogenesis, UC Berkeley
2013–	Investigator, Howard Hughes Medical Institute
2013–	Director, Cancer Research Laboratory
2012-2014	Associate Professor, Division of Immunology & Pathogenesis, UC Berkeley
2006-2012	Assistant Professor, Division of Immunology & Pathogenesis, UC Berkeley

Honors

2023	Co-Chair, Keystone Conference on Innate Immunity (Snowbird, UT)
2022	Co-Chair, Midwinter Conference of Immunologists (Asilomar, CA)
2021	Departmental Teaching Excellence Award (Molecular & Cell Biology, UC Berkeley)
2021	Streilein Lecture (Dept. of Immunology, University of Texas Southwestern Medical Center)
2020	William B. Coley Award for Basic and Cancer Immunology (Cancer Research Institute)
2019	Howard Ricketts Lecturer (Department of Microbiology, University of Chicago)
2018–	NIH R37 (MERIT) Award
2017	Fellow of the American Academy of Microbiology
2013–	Howard Hughes Medical Institute Investigator
2012	The Diane Taylor Lectureship in Microbiology (University of Alberta)
2011	Merck Irving S. Sigal Memorial Award (from the American Society for Microbiology)
2009–2015	Burroughs Wellcome Fund Investigator in the Pathogenesis of Infectious Disease
2008–2012	Cancer Research Institute Investigator Award
2008–2009	Hellman Family Fund Faculty Award (UC Berkeley)
2006–2008	NIH K22 Career Development Award
2004–2006	NIH NRSA Ruth L. Kirschstein Postdoctoral Fellowship
2001–2004	Damon Runyon Cancer Research Fund Postdoctoral Fellowship
2000	Harold Weintraub Award (for an Outstanding PhD Thesis)
1995–2000	Howard Hughes Medical Institute Predoctoral Fellowship

C. Contributions to Science

1. Identification of the molecular basis of STING activation by cyclic-di-nucleotides (CDNs).
We discovered that mammalian cells trigger an interferon response upon detection of cyclic-di-nucleotides (CDNs) in their cytosol [1a]. We showed that the interferon response induced by CDNs is indistinguishable from that induced by cytosolic recognition of viral or bacterial DNA. In collaboration with the Portnoy Lab, we used random ENU mutagenesis in mice to identify a novel mouse mutant, called *goldenticket*, that fails to produce interferon in response to CDNs or *Listeria monocytogenes*. By genetic mapping, sequencing, and complementation, we found *goldenticket* mice harbor a null mutation in a gene encoding STING, a protein previously shown to function as a signaling adaptor protein in the interferon response to DNA. *Goldenticket* (*Sting*$^{-/-}$) mice are now in widespread use in many laboratories internationally. By biochemical approaches, we then identified that the host CDN receptor is STING itself [1b]. Our work became of great significance when it provided a missing link between the cytosolic DNA sensor, cGAS, discovered by the Chen group, and the STING signaling adaptor. We demonstrated that cGAS produces a 2'-linked CDN that specifically activates human STING [1c]. In more recent work, we identified and functionally and structurally characterized cGAS and STING homologs in the sea anemone *Nematostella vectensis*, demonstrating the deep evolutionary conservation of this pathway [1d]. Taken together, our work has provided fundamental insights into the molecular basis by which nucleic acids are sensed in the cytosol.

a. McWhirter SM, Barbalat R, Monroe KM, Fontana MF, Hyodo M, Joncker NT, Ishii KJ, Akira S, Colonna M, Chen ZJ, Fitzgerald KA, Hayakawa Y, **Vance RE** (2009) A host type I interferon response is induced by cytosolic sensing of the bacterial second messenger cyclic-di-GMP. Journal of Experimental Medicine Aug 31;206(9):1899-911 (PMC2737161).
b. Burdette DL, Monroe KM, Sotelo-Troha K, Iwig JS, Eckert B, Hyodo M, Hayakawa Y, **Vance RE** (2011) STING is a direct innate immune sensor of cyclic-di-GMP. Nature Sep 25;478(7370):515-8 (PMC3203314).
c. Diner EJ, Burdette DL, Wilson SC, Monroe KM, Kellenberger CA, Hyodo M, Hayakawa Y, Hammond MC, **Vance RE** (2013) The innate immune DNA sensor cGAS produces a noncanonical cyclic dinucleotide that activates human STING. Cell Reports May 30;3(5):1355-61 (PMC3706192).
d. Kranzusch PJ, Wilson SC, Lee AS, Berger JM, Doudna JA, **Vance RE** (2015) Ancient origin of cGAS-STING reveals mechanism of universal 2',3' cGAMP signaling. Mol Cell 59(6): 891-903 (PMC4575873).

2. Discovery of a cytosolic flagellin-sensing inflammasome pathway and its importance in resistance to *Legionella pneumophila* and *Shigella flexneri* infection.

In the late 1980s, it was discovered that the intracellular bacterial pathogen *Legionella pneumophila* is unable to replicate efficiently in macrophages from the C57BL/6 mouse strain, but is able to replicate ≥1000-fold in macrophages from the A/J mouse strain. Classic genetic studies determined that restriction of *L. pneumophila* replication requires a single genetic locus on mouse chromosome 13 that contains a cluster of *Naip* genes. By homology, NAIP proteins were identified as members of the Nucleotide-binding domain/Leucine-rich Repeat-containing (NLR) superfamily, but the function of NAIPs was unknown. Over the course of a decade, our work established NAIP proteins as cytosolic innate immune sensors of bacterial proteins, including flagellin [2a-2c]. Our work culminated in the cryo-EM structure of NAIP bound to flagellin, a structure that represented the first structure of a full-length NLR as well as the first structure of an NLR bound to a ligand [2c]. Taken together, our work is significant because it demonstrated that NAIP proteins are required for specific recognition of bacterial ligands, and because we provided the first biochemical evidence for ligand-dependent oligomerization of any mammalian NLR protein.

Most recently, our work on the NAIP-NLRC4 inflammasome has been in the context of *Shigella flexneri*. *Shigella* is a human adapted pathogen that causes approximately 200,000 human deaths per year, but does not cause disease in wildtype mice. The lack of a mouse model of *Shigella* has been a major impediment to studies of its *in vivo* pathogenesis mechanisms, as well as to the development of a Shigella vaccine. We discovered that the reason mice are resistant to *Shigella* is because the mouse (but not human) NAIP-NLRC4 inflammasome detects *Shigella* and mediates the expulsion of *Shigella*-infected intestinal epithelial cells back into the gut lumen [2d]. After oral infection, NAIP-NLRC4-deficient mice exhibit all the hallmarks of human disease and thus represent the first physiological and genetically tractable oral infection model for *Shigella*.

a. Ren T, Zamboni DS, Roy CR, Dietrich WF, **Vance RE** (2006) Flagellin-deficient *Legionella* mutants evade caspase-1- and Naip5-mediated macrophage immunity. PLoS Pathogens Mar;2(3):e18 (PMC1401497).
b. Kofoed EM, **Vance RE** (2011) Innate immune recognition of bacterial ligands by NAIPs determines inflammasome specificity. Nature Aug 28;477(7366):592-5. (PMC3184209).
c. Tenthorey JL, Haloupek N, López-Blanco JR, Grob P, Adamson E, Hartenian E, Lind NA, Bourgeois NM, Chacón P, Nogales E, **Vance RE** (2017) The structural basis of flagellin detection of NAIP5: a strategy to limit pathogen immune evasion. Science, 358(6365):888-893. (PMC5842810).
d. Mitchell PS, Roncaioli JL, Turcotte EA, Goers L, Chavez RA, Lee AY, Lesser CF, Rauch I, **Vance RE** (2020) NAIP-NLRC4-deficient mice are susceptible to shigellosis. Elife Oct 19;9:e59022. doi: 10.7554/eLife.59022. (PMC7595732).

3. Identification of novel inflammasome functions and the NLRP1 inflammasome mechanism.

Inflammasomes are now appreciated as critical innate immune sensors and activators of the Caspase-1 protease. Although pyroptosis and cytokine processing were widely assumed to be the major signaling outputs of inflammasomes, we demonstrated that induction of inflammatory lipid mediators (eicosanoids) is a third important inflammasome signaling output *in vivo* [3a]. We demonstrated that inflammasome-dependent induction of eicosanoids produces rapid vascular leakage that can be lethal within <30 minutes. We have also demonstrated unique inflammasome functions in epithelial cells [3b]. We also demonstrated that a distinct inflammasome, containing the NLRP1B protein, is activated by direct proteolysis by the anthrax lethal factor protease [3c]. We recently elucidated a 'functional degradation' model that explains how proteolysis of NLRP1 leads to its activation [3d]. Together our results have established several new functions for inflammasomes in innate immunity.

a. von Moltke J, Trinidad NJ, Moayeri M, Kintzer AF, Wang SB, van Rooijen N, Brown CR, Krantz BA, Leppla SH, Gronert K & **Vance RE** (2012) Rapid induction of inflammatory lipid mediators by the inflammasome in vivo. Nature Oct 4;490(7418):107-11 (PMC3465483).
b. Rauch I, Deets KA, Ji DX, von Moltke J, Tenthorey JL, Lee AY, Philip NH, Ayres JS, Brodsky IE, Gronert K, **Vance RE** (2017) NAIP-NLRC4 Inflammasomes Coordinate Intestinal Epithelial Cell Expulsion with Eicosanoid and IL-18 Release via Activation of Caspase-1 and -8. Immunity Apr 18;46(4):649-659 (PMC5476318).
c. Chavarría-Smith J, Mitchell PS, Ho AM, Daugherty MD, **Vance RE** (2016) Functional and evolutionary analyses identify proteolysis as a general mechanism for NLRP1 inflammasome activation. PLoS Pathogens 12(12):e1006052 (PMC5142783).
d. Sandstrom A, Mitchell PS, Goers L, Mu EW, Lesser CF, **Vance RE** (2019) Functional degradation: A mechanism of NLRP1 inflammasome activation by diverse pathogen enzymes. Science Mar 14. pii: eaau1330. doi: 10.1126/science.aau1330. [Epub ahead of print] PMCID PMC6532986.

4. Identification of "patterns of pathogenesis" as a major mechanism of innate immune activation.
A major theme of our work is that the innate immune system can distinguish bacterial pathogens from harmless commensal microbes by detection of the virulence factors produced by pathogens (but not by harmless microbes). In a review written by myself, Ralph Isberg, and Dan Portnoy, we referred to this mode of innate immune activation as detection of 'patterns of pathogenesis' [4a]. This review has been influential, but unfortunately, there have been relatively few examples of this mode of pathogen detection worked out in molecular detail. Our work has provided several examples of how patterns of pathogenesis can be detected by the innate immune system. One early discovery was our finding that blockade of protein synthesis—a common 'pattern of pathogenesis' of several pathogens, including *L. pneumophila*—induces a robust cytokine transcriptional response in the host [4b, 4c]. The host response is characterized by induction of IL-23, GMCSF, and IL-1α, the latter which appears to be especially critical to the *in vivo* response to *L. pneumophila*. More recently, we have extended the concept of "patterns of pathogenesis" to viruses. We identified a novel innate immune sensing pathway that detects an important HSV-1 virulence factor called ICP0. We found that the enzymatic activity of ICP0 triggers a robust type I interferon response via the ubiquitin-mediated degradation of a nuclear body protein called MORC3 [4d].

a. **Vance RE**, Isberg RR, Portnoy DA (2009) Patterns of pathogenesis: discrimination of pathogenic and nonpathogenic microbes by the innate immune system. Cell Host Microbe Jul 23;6(1):10-21 (PMC2777727).
b. Fontana MF, Banga S, Barry KC, Shen X, Tan Y, Luo ZQ, **Vance RE** (2011) Secreted bacterial effectors that inhibit host protein synthesis are critical for induction of the innate immune response to virulent Legionella pneumophila. PLoS Pathogens Feb;7(2):e1001289 (PMC3040669).
c. Barry KC, Ingolia NT, **Vance RE** (2017) Global analysis of gene expression reveals mRNA superinduction is required for the inducible immune response to a bacterial pathogen. eLife. Apr 6;6. pii: e22707. (PMC5407856).
d. Gaidt MM, Morrow A, Fairgrieve MR, Karr JP, Yosef N, **Vance RE** (2021) Self-guarding of MORC3 enables virulence factor-triggered immunity. Nature Dec;600(7887):138-142. doi: 10.1038/s41586-021-04054-5. Epub 2021 Nov 10. PMID: 34759314.

5. Identification of the molecular function of CD94/NKG2A on mouse NK cells
As a graduate student in David Raulet's Lab, I investigated how NK cells are activated by abnormal host cells. The missing self hypothesis states that NK cells survey cells for normal expression of MHC class I molecules and attack cells that have downregulated MHC class I (e.g., as a consequence of viral infection or transformation). In the mouse, it had been shown by Yokoyama and colleagues that the Ly49 family of receptors were MHC specific inhibitory receptors on NK cells. However, Ly49 receptors did not fully account for the ability of NK cells to be inhibited by target cell MHC class I. I cloned a second family of MHC class I-specific inhibitory receptors in the mouse, the heterodimeric CD94/NKG2 receptors. In a series of papers [5a-d], I showed that these receptors recognize a nonclassical MHC class I molecule called Qa-1^b. Qa-1 primarily presents a single peptide which is derived from the cleaved signal sequence of classical MHC class I molecules. My results therefore provided an indirect mechanism by which NK cells could survey cells for normal expression of classical MHC class I molecules.

a. **Vance RE**, Tanamachi DM, Hanke T, Raulet DH (1997) Cloning of a mouse homolog of CD94 extends the family of C-type lectins on murine natural killer cells. Eur J Immunol Dec;27(12):3236-41.
b. **Vance RE**, Kraft JR, Altman JD, Jensen PE, Raulet DH (1998) Mouse CD94/NKG2A is a natural killer cell receptor for the nonclassical major histocompatibility complex (MHC) class I molecule Qa-1(b). Journal of Experimental Medicine Nov 16;188(10):1841-8 (PMC2212405).
c. **Vance RE**, Jamieson AM, Raulet DH (1999) Recognition of the class Ib molecule Qa-1(b) by putative activating receptors CD94/NKG2C and CD94/NKG2E on mouse natural killer cells. Journal of Experimental Medicine Dec 20;190(12):1801-12 (PMC2195720).
d. **Vance RE**, Jamieson AM, Cado D, Raulet DH (2002) Implications of CD94 deficiency and monoallelic NKG2A expression for natural killer cell development and repertoire formation. Proc Natl Acad Sci U S A. Jan 22;99(2):868-73 (PMC117397).

Link to full publication list: https://www.ncbi.nlm.nih.gov/myncbi/russell.vance.1/bibliography/public/