## BIOGRAPHICAL SKETCH

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NAME: OFFRINGA, Ite A.

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

POSITION TITLE: Associate Professor of Surgery and of Biochemistry and Molecular 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 |
|---|---|---|---|
| University of Leiden, The Netherlands | B.S. | 05/1983 | Biology |
| University of Leiden, The Netherlands | M.S. | 05/1985 | Molecular Biology |
| University of Leiden, The Netherlands | Ph.D. | 05/1991 | Medical Biochemistry |
| Harvard University, Boston, MA | Postdoctoral Fellowship | 01/1996 | Molecular Biology |

### A. Personal Statement

Dr. Offringa is an expert in clinical and experimental aspects of lung diseases, epigenomic analyses, the use of animal models of lung cancer, and biosensors. She has led/participated in many interdisciplinary collaborations with clinicians, epidemiologist and biostatisticians, including her work on identifying DNA methylation-based markers for early detection of non-small cell lung cancer, a collaborative project with the NIH/NCI Early Detection Research Network. Dr. Offringa's lab was also responsible for a number of analyses for the Environment and Genetics in Lung cancer Etiology (EAGLE) study of the Genetic Epidemiology Branch at NCI. Dr. Offringa's lung cancer research inspired a focus on the epigenetic basis of normal lung development, as well as other non-cancer lung diseases, and led to a longtime collaboration with expert pulmonologist Dr. Borok and stem cell expert Dr. Firth. Dr. Offringa's lab also investigates small cell lung cancer-associated autoimmune responses, using a powerful genetically engineered SCLC mouse model, and recently identified a molecular alteration believed to be the trigger of at least one type of autoimmune response seen in SCLC patients. The modification is currently being used to develop a new therapy. Besides her research interests, Dr. Offringa has a strong interest in science education. She brought science into the high school classroom for many years, and routinely speaks at STEM field informational sessions for high school students an undergraduates. She currently mentors a Bravo Medical Magnet High School URM student from the STAR/EHA program, which mentors students in their junior and senior years providing real lab experience. Dr. Offringa has mentored clinical and postdoctoral fellows and students at all levels, including high school, Master's and PhD students for twenty years. She has participated in the Bridging the Gaps summer program, which bring URM students to research labs at USC during the summer, since the program's inception. Dr. Offringa's commitment to education is further exemplified by her role as Associate Director (2007) and Director (2008-present) of UCS's umbrella program PIBBS (Programs in Biomedical and Biological Sciences), which recruits high quality PhD applicants to USC. By 2017-2018, we were able to recruit 25% URM matriculating PhD students (10% African American, 15% Latino). As PIBBS director, Dr. Offringa mentors 20-30 first year PhD students each year, as they rotate through three labs of their choice. In addition, she has developed and teaches a scientific writing class to first year PhD students. This class prepares students for their F31 fellowship-format written qualifying exam. Many students use this as the basis for their own F31 application, which they submit with support from the Graduate Affairs office. In June 2015, Dr. Offringa was appointed as Associate Dean for Graduate Affairs, in which capacity she oversees the education of all PhD students at the Keck School of Medicine.

## B. Positions and Honors

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|---|---|
| 1985 -1991 | Graduate Student/T.A., Dept. Medical Biochemistry, Univ. of Leiden, The Netherlands. |
| 1991-1996 | Postdoctoral Fellow, Dept. Microb. and Mol. Genet., Harvard Medical School, Boston, MA, |
| 1996-2004 | Assistant Professor of Surgery and of Biochem. & Mol. Biology., Univ. S. California, LA, CA |
| 2004-present | Associate Professor of Surgery and of Biochem. & Mol. Biology, Univ. S. California, LA, CA. |
| 2008-present | Director, Programs in Biomedical and Biological Sciences |
| 2015-present | Associate Dean for Graduate Affairs (PhD students) |

**Other Experience and Professional Memberships**

| | |
|---|---|
| Ongoing | Reviewer for a large number of professional journals |
| 1999-present | Member, American Association for Cancer Research |
| 2005 | Ad hoc Reviewer NIH Experimental Therapeutics III Cluster Meeting |
| 2007 | Ad hoc member NIH Special Emphasis Panel Shared Instrumentation Grant Program |
| 2007 | Ad hoc member NIH/NCI study section Cancer Genetics |
| 2007-2008 | Associate Director, Program in Biomedical and Biological Sciences |
| 2007-present | Member Canary Foundation Early Detection Lung Team |
| 2008-2011 | Member, NIH/NCI study section Cancer Genetics |
| 2008-present | Director, Program in Biomed. and Biological Sciences, USC; Scientific Advisory Board ALCMI |
| 2009-present | Reviewer, Fondazione CARIPLO, Italy, European Union |
| 2009-present | Reviewer, British Lung Cancer Foundation |
| 2011-present | Reviewer, MRC Univ of Cambridge Clinician Scientist Fellowships; Assoc Editor BMC Cancer |
| 2012 | Ad hoc reviewer NIH/NCI Provocative Questions |
| 2015 | Ad hoc reviewer, NIH/NCI Fellowship proposals |

**Honors**

| | |
|---|---|
| 1985 | M.Sc., University of Leiden, The Netherlands, *cum laude* |
| 1993-1996 | American Cancer Society Fellowship, Harvard Medical School, Boston, MA. |
| 1996-1997 | Medical Faculty Women's Association Award |
| 1996-1997 | American Cancer Society Pilot Project Award |
| 1997-1998 | Zumberge Research and Innovation Fund Award |
| 1997, 2001 | Wright Foundation Awards |
| 2002 | STOP Cancer special Marcia Israel Curley Award |
| 2003 | Whittier Foundation Translational Research award for lung cancer |
| 2006-2008 | Mesothelioma Applied Research Foundation award |
| 2006-2007 | Kazan Foundation award |
| 2006-2008 | Joan's Legacy award |
| 2008-2010 | Whittier Award: Development of new tools for genome-wide DNA methylation analysis |
| 2013-2014 | Whittier Award: Development of a companion diagnostic for all lung cancer subtypes |
| 2014 | New England Biolabs Passion in Science Award for my lung cancer research |

## C. Contribution to Science

(Offringa lab members in the publications are underlined, collaborators on this proposal italicized)

My bibliography URL: https://www.ncbi.nlm.nih.gov/myncbi/ite.laird-offringa.1/bibliography/public/

*I have listed the five areas that best illustrate my research areas, my dedication to innovation and detailed investigation, and some of the more unusual expertise we have in molecular analyses. In the citations, my lab members are underlined.*

**1) Generation of epigenomic profiles from purified human alveolar epithelium, as it transitions from one cell type to another and applications of this data.**

*With our USC collaborators, we described for the first time dynamic epigenomic profiling of differentiating primary human epithelial cells. We show we can characterize epigenomes from primary human alveolar type 2 and type 1 cells. In contrast to many labs using tissue samples containing mixed cell populations or cell lines (often cancerous ones), we used highly purified populations of primary human epithelial cells derived from remnant transplant lung. Partnering with epidemiologists, we have also integrated DNA methylation data we had collected for population-based lung cancer/exposure studies with other epigenetic marks from our primary epithelial cells, to publish the first study of meQTLs in lung tissue. We have also integrated risk SNPs and alveolar epigenomes.*

- Marconett CN, Zhou B, Rieger ME, Selamat SA, Dubourd ME, Fang X, Lynch SE, Stueve TR, Siegmund KD, Berman, BP, Borok Z, **Laird-Offringa IA**. Integrated transcriptomic and epigenomic

analysis of primary human lung epithelial cell differentiation. **PLoS Genet**. 2013. 9(6):e1003513. PMID: 23818859; PMCID: PMC3688557.

- Stueve, TR, Marconett, CN, Zhou B, Borok Z, **Laird-Offringa IA.** The Importance of detailed epigenomic profiling of different cell types within organs. **Epigenomics** 2016 8:817-29. PMID:28854564
- Shi, J, Marconett CN, Duan J, Hyland PL, Li P, Wang Z, Wheeler W, Zhou B, Campan M, Lee DS, Huang J, Zhou W, Triche T, Amundadottir L, Warner A, Hutchinson A, Chen PH, Chung BS, Pesatori AC, Consonni D, Bertazzi PA, Bergen AW, Freedman M, Siegmund KD, Berman BP, Borok Z, Chatterjee N, Tucker MA, Caporaso NE, Chanock SJ, **Laird-Offringa IA**, Landi MT. Characterizing the genetic basis of methylome diversity in histologically normal human lung tissue. **Nature Commun**. 2014, 5:3365. PMID:24572595; PMCID: PMC3982882.
- Yang C, Stueve TR, Yan C, Rhie SK, Mullen DJ, Luo J, Zhou B, Borok Z, Marconett CN, **Offringa IA**. Positional integration of lung adenocarcinoma susceptibility loci with primary human alveolar epithelial cell epigenomes. **Epigenomics**. 2018,10(9):1167-1187. doi: 10.2217/epi-2018-0003. PMID:30212242

**2) The identification of epigenetic events in lung adenocarcinoma development.**

*We were the first to show, in abstracts and talks, that premalignant precursor lesions to lung adenocarcinoma could be profiled for multiple DNA methylation markers, and could shed light on the sequential acquisition of DNA methylation changes during lung adenocarcinoma development, demonstrating the feasibility of analyzing DNA methylation in tiny lung lesions. Our poster (1st item below) came several months later, and our manuscript, which underwent very hefty bioinformatics scrutiny by us was, not published until 2011 (see below, second publication listed). The next paper is the first major paper in the field in which genome-wide DNA methylation in lung adenocarcinoma and adjacent non-tumor lung are integrated with RNA expression data to identify epigenetic cancer driver genes. We are pursuing several of these as cancer drivers in lung adenocarcinoma.*

- Galler, JS, Kerr, KM, **Laird-Offringa, IA**. DNA methylation changes in developing lung adenocarcinoma. 12th World Conference on Lung Cancer, International Association for the Study of Lung Cancer, Seoul, Korea (2007). Poster presentation.
- Selamat SA, Galler JS, Joshi AD, Fyfe MN, Campan M, Siegmund KD, Kerr KM, **Laird-Offringa IA**. DNA methylation changes in atypical adenomatous hyperplasia, adenocarcinoma in situ, and lung adenocarcinoma. **PLoS One**. 2011. 6(6):e21443. PMID: 21731750; PMCID: PMC3121768.
- Selamat SA, Chung BS, Girard L, Zhang W, Zhang Y, Campan M, Siegmund KD, Koss MN, Hagen JA, Lam WL, Lam S, Gazdar AF, **Laird-Offringa IA**. Genome-scale analysis of DNA methylation in lung adenocarcinoma and integration with mRNA expression. **Genome Res**. 2012. 22(7):1197-1211. PMID: 22613842; PMCID: PMC3396362.
- Luo J, Chimge NO, Zhou B, Flodby P, Castaldi A, Firth AL, Liu Y, Wang H, Yang C, Marconett CN, Crandall ED, **Offringa IA**, Frenkel B, Borok Z. CLDN18.1 attenuates malignancy and related signaling pathways of lung adenocarcinoma in vivo and in vitro. **Int J Cancer**. 2018,143:3169-3180. PMID:30325015

**3) Using of epigenetics and transcriptomics to gain mechanistic insight in lung development and differentiation, as well as environmental effects.**

*Detailed mechanistic insights into lung development and differentiation requires in depth analysis of gene expression and the layers of epigenetic information that underlie gene expression profiles. We have partnered with the laboratory of Dr. Borok, providing epigenetic and transcriptomic analysis in the investigation of cell-specific gene regulation in the lung. We have also studies the effects of environmental exposures on lung epigenomes, showing that epigenetic changes seen in population-based studies could be replicated in vitro.*

- Li G, Flodby P, Luo J, Kage H, Sipos A, Gao D, Ji Y, Beard LL, Marconett CN, DeMaio L, Kim YH, Kim KJ, **Laird-Offringa IA**, Minoo P, Liebler JM, Zhou B, Crandall ED, Borok Z. Knockout mice reveal key roles for claudin 18 in alveolar barrier properties and fluid homeostasis. **Am J Respir Cell Mol Biol**. 2014. 51(2):210-222. PMID: 24588076; PMCID: PMC4148039.
- Liebler JM, Marconett CN, Juul N, Wang H, Liu Y, Flodby P, **Laird-Offringa IA**, Minoo P, Zhou B. Combinations of differentiation markers distinguish subpopulations of alveolar epithelial cells in adult lung. **Am J Physiol Lung Cell Mol Physiol**. 2016 310(2):L114-120. PMID: 26545903.
- Flodby P, Li C, Liu Y, Wang H, Marconett CN, **Laird-Offringa IA**, Minoo P, Lee AS, Zhou B. GRP78 Regulates ER Homeostasis and Distal Epithelial Cell Survival During Lung Development. **Am J Respir Cell Mol Biol**. 2016 Jan 27. [Epub ahead of print]. PMID: 26816051.

- Stueve TR, Li WQ, Shi J, Marconett CN, Zhang T, Yang C, Mullen D, Yan C, Wheeler W, Hua X, Zhou B, Borok Z, Caporaso NE, Pesatori AC, Duan J, **Laird-Offringa IA**, Landi MT. (2017) Epigenome-wide analysis of DNA methylation in lung tissue shows concordance with blood studies and identifies tobacco smoke-inducible enhancers. **Hum Mol Genet***,* 2017. 26:3014-3027, PMID: 28854564.

**4) Establishing the basis of small cell lung cancer-associated autoimmunity and application of this knowledge to the development of immunotherapy.**

*Using a genetically engineered mouse model of small cell lung cancer, we determined that, just like human SCLC patients, a subset of mice develop paraneoplastic autoimmunity against neuronal ELAVL antigens. We recently provided strong evidence that isoaspartylation is the trigger of this type of autoimmune response. Based on the improved survival of SCLC patients with anti-ELAVL4 autoimmune response, this sets the stage for the development of immunotherapy for a disease that has seen little therapeutic improvement in the last 30 years, and has an abysmal 5-year survival of 6%. Our findings form the basis for a new therapeutic strategy.*

- Kazarian M, **Laird-Offringa IA**. Small cell lung cancer-associated autoantibodies: potential applications to cancer diagnosis, early detection, and therapy. **Mol Cancer**. 2011 Mar 30;10:33. doi: 10.1186/1476-4598-10-33. Review. PMID:21450098
- Kazarian M, Calbo J, Proost N, Carpenter CL, Berns A, **Laird-Offringa IA**. Immune response in lung cancer mouse model mimics human anti-Hu reactivity. **J Neuroimmunol.** 2009 Dec 10;217(1-2):38-45. doi: 10.1016/j.jneuroim.2009.08.014.PMID:19765830
- Pulido MA, DerHartunian MK, Qin Z, Chung EM, Kang DS, Woodham AW, Tsou JA, Klooster R, Akbari O, Wang L, Kast WM, Liu SV, Verschuuren JJ, Aswad DW, **Laird-Offringa IA**.Isoaspartylation appears to trigger small cell lung cancer-asociated autoimmunity against neuronal protein ELAVL4. **J Neuroimmunol.** 2016 Oct 15;299:70-78. doi: 10.1016/j.jneuroim.2016.09.002. PMID:27725125
- Pulido MA, DerHartunian MK, Sehgal P, **Laird-Offringa IA**. Data on isoaspartylation of neuronal ELAVL proteins. **Data Brief.** 2016, 9:1052-1055. PMID:27924291

**5) Using of kinetics studies to understand nucleic acid/protein interaction.**

*Detailed mechanistic insights into molecular interactions requires accurate measurement of association/ dissociation rates. I realized the importance of kinetics when data from a Nature paper others had published was not reproducible in my hands. I realized the authors had a dissociation artifact. I brought a surface plasmon resonance biosensor into my lab to measure real-time binding interactions and have used it ever since. The first paper describes one of our most interesting findings. The next paper, by world experts in this technology, cite work from our lab as top notch, in the top few percent of well-executed studies. The other papers illustrate our recent application of surface plasmon resonance to gain an understanding of a variety of systems. We continue be at the forefront this methodology, having recently acquired a state-of-the-art DRX2 switchsense biosensor.*

- Katsamba PS, Myszka DG, **Laird-Offringa IA**. Two functionally distinct steps mediate high affinity binding of U1A protein to U1 hairpin II RNA. **J Biol Chem**. 2001. 276(24):21476-21481. PMID: 11297556.
- Rich RL, Myszka DG. Grading the commercial optical biosensor literature-Class of 2008: “the Mighty Binders”. **J Mol Recognit**. 2010. 23(1):1-64. Review. PMID:20017116.
- Chen Y, Bates DL, Dey R, Chen PH, Machado AC, **Laird-Offringa IA**, Rohs R, Chen L. DNA binding by GATA transcription factor suggests mechanisms of DNA looping and long-range gene regulation. **Cell Rep**. 2(5):1197-1206. PMID: 23142663; PMCID: PMC3978094.
- Law MJ, Lee DS, Lee CS, Anglim PP, Haworth IS, **Laird-Offringa IA.** The role of the C-terminal helix of U1A protein in the interaction with U1hpII RNA. **Nucleic Acids Res**. 2013. 41(14):7092-7100. PMID: 23703211; PMCID: PMC3737524.

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## D. Research Support

**Ongoing Research Support**

**U54 CA233465** Florida-California Cancer Research, Education and Engagement Center (CaRE$^2$). Carpten and Stern USC DPs, *Offringa USC PI for Research and Education Core.* 09/19/2018-08/31/2023

*This tri-university partnership project is aimed at addressing cancer health disparities, both in its research as well as in the training of underrepresented minority researchers. Dr. Offringa is the USC head of the research and education core.*

**TRDRP Award** Laird-Offringa (PI) 07/01/2017-06/30/2020*
Tobacco-Related Disease Research Program (University of California) "Functional lung cancer risk SNP identification & mechanism"
T*his project is aimed at determining the functional SNPS that predispose to lung cancer.*
**No cost extension approved for 1 year.*

**R35 Merit Award** Zea Borok, PI. Laird-Offringa, co-investigator. 2017-2024.
Beyond the barrier: alveolar epithelial cell biology in health and disease.
*Laird-Offringa lab role is assisting with epigenetics and bioinformatics.*

**Completed Proposals (last three years)**
**Whittier Foundation** *Translational Pilot Project* Laird-Offringa (PI) 02/01/2016-06/30/2018
"Application of State-of-the-Art DNA Methylation Detection to Lung Cancer Patient Follow Up; Developing a Broad Companion Diagnostic for all Lung Cancer Types"
*My lab's research in this project is aimed at using DNA methylation signatures we have developed to track response to therapy and recurrence in lung cancer patients.*

**V Foundation Grant** Laird-Offringa (PI) 10/31/2013-10/30/2018
"Developing Immunotherapy for Small Cell Lung Cancer Using Novel Modified Antigens"
*My lab's role is to develop a mouse model for immunotherapy for SCLC based on a novel modification we have identified on SCLC antigens (data in a manuscript in preparation).*

**BAPP-15-121814** Laird-Offringa (PI) 07/2015-09/2017
California Community Foundation "Training young lung cancer researchers"
*The goal of this project is support the training of PhD students in lung cancer research.*

**Concept Award** Laird-Offringa (PI) 02/01/2014-01/31/2016
Department of Defense
"Combining linkage disequilibrium SNPs and epigenomic data from primary lung epithelium to identify true lung cancer risk SNPs and their mechanism of action"
*This was a pilot project to demonstrate the feasibility of purifying three cell types from one lung, to obtain epigenomic profiles from distinct purified cell types from one lung, and to implement strategies to obtain epigenomic information with fewer cells, such as use of the ATACseq technology to identify nucleosome free regions for the genome.*

**Ming Hsieh Institute** *Research Grant* Camarero (PI) 01/01/2016-12/31/2016
Laird-Offringa (Co-Investigator)
"Development of novel PD1/PD-L1 antagonists using novel cys-knotted proteins"
*We provide expertise with and execution of experiments with lung cancer mouse models and surface plasmon resonance analysis (an area where we have world-class expertise) for the primary PI.*

**1R01HL114094** Laird-Offringa (contact PI), Borok (DPI) 09/23/2011-06/30/2017
NIH "Epigenetic profiling of human alveolar epithelial cells in health and disease"
This project is aimed at elucidating the epigenetic basis of alveolar epithelial cell phenotype and differentiation, and requires the timed collection of epigenomes from differentiating AT2 cells.
*My lab's role is obtaining and interpreting the epigenomes, carrying out all the bioinformatics analyses and much of the molecular biology.*

**Ming Hsieh Institute** *Research Grant* **Camarero (PI)** Offringa (Co-Investigator) 07/01/2018-06/30/2019
"Oral Bioavailabilty and In Vivo Activity against Lung Cancer of Cyclotide Based Agonists of the Tumor Suppressor p53 Pathway"
*We provide expertise with and execution of experiments with lung cancer mouse models and biosensor analysis (an area where we have world-class expertise) for the primary PI.*