

**BIOMEDICAL & VETERINARY SCIENCES
GRADUATE PROGRAM**



ANNOUNCES

The Doctor of Philosophy Seminar and Examination of

Margaret Ann Nagai-Singer
**“Protective or Problematic? Investigating the role of
the innate immune receptor NLRX1 as a tumor
suppressor or promoter in breast and pancreatic
cancer.”**

**Wednesday, October 19th, 2022
3:00PM**

VMCVM Classroom 100

<https://viriniatech.zoom.us/j/84623074135>



Bio

Margaret was born and raised in Valparaiso, Indiana, where she spent her time playing basketball, singing in choir, and helping on the family farm. With a passion for agriculture, she received her Bachelor's Degree in Animal Science from the University of Tennessee at Martin (UTM) in 2018. Through the UTM University Scholars program, she conducted a 2-year research project on different feeding strategies for piglets to maximize their health and growth. During her Intro to Immunology course, she decided that the immune system would be really cool to study and decided to pursue graduate programs that would allow her to do so. She moved to Blacksburg with her husband Will in Spring 2019 when they both began their PhD programs. As a lab member in Dr. Coy Allen's lab, she has been studying the role of an immune signaling protein, NLRX1, in the context of breast and pancreatic cancer. Margaret has also been able to revisit her animal science skills through many projects in the lab involving pig models. With an interest in and passion for science policy, Margaret was also selected as a 2021 COVES Fellow – a state-level science policy fellowship where she worked with the Virginia Department of Forestry investigating the role that forests play in water quality and quantity. In her spare time, Margaret works on several advocacy projects, annoys her friends about registering to vote, and loves to spend time with her dog Peanut.

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Lay Language Abstract

Inflammation, which is characterized by redness, heat, pain, swelling, and sometimes loss of function, is a critical way in which our bodies fight infections and repair tissue damage. However, chronic inflammation occurs when our bodies are unable to turn inflammation off and can result in cancerous mutations. Therefore, the successful resolution of inflammation is critical to maintaining inflammatory balance and has previously been dubbed the “Goldilocks Conundrum”. The immune system houses a class of cellular signaling proteins called pattern recognition receptors (PRRs), which often function to turn inflammation on.

However, a unique PRR in the NOD-like receptor (NLR) family called “NLRX1” functions to turn inflammation off and therefore plays an important role in preventing damaging chronic inflammation. NLRX1 has historically been studied in the context of infectious diseases, but because NLRX1 is involved in inflammation and because inflammation is a critical factor of cancer, its role as a tumor suppressor or tumor promoter has recently become an area of interest. NLRX1 has also been found to regulate biological pathways beyond inflammation that are also important for cancer initiation and progression. Interestingly, depending on the type and subtype of cancer, NLRX1 can either be tumor promoting or tumor suppressing.

Here, we investigate the role of NLRX1 in two deadly cancers: triple-negative breast cancer (TNBC) and pancreatic cancer. In a mouse mammary tumor model that highly mimics TNBC, we discovered that NLRX1 is protective against disease burden when NLRX1 is expressed in healthy, non-tumor cells. NLRX1 exerts its protection through impacting the immune cells recruited to the tumor, limiting the ability of the tumor cells to leave the original tumor and spread throughout the body in the process known as metastasis, and suppressing the formation of a favorable tumor metastasis environment in the lung. Conversely, when NLRX1 is instead expressed by the mammary tumor cells, NLRX1 promotes disease burden by helping tumor cells leave the original tumor and spread throughout the body. This indicates that the role of NLRX1 in TNBC is highly dependent on cellular context, including if the cell is healthy or cancerous. Conversely, in mouse pancreatic cancer cells, we found that NLRX1 expression by the tumor cells is protective against cancer-associated characteristics. Together, this research indicates that the role of NLRX1 can be highly variable based on the cell and tumor type. This is critical information for drug development initiatives so therapies can be developed that turn NLRX1 on or off in the appropriate cell type and in the appropriate disease.

Publications

1. Morrison HA, Eden K, Mounzer C, **Nagai-Singer MA**, Liu Y, Wade P, Allen IC. NLRX1 Deficiency Increases Susceptibility towards Gut Microbiome Dysbiosis and is Further Exacerbated by Adherence to a Gluten-free Diet. *Frontiers in Immunology*. (2022). doi: 10.3389/fimmu.2022.882521.
2. Imran KM, **Nagai-Singer MA**, Brock RM, Nastaran A, Davalos RV, Allen IC. Improving immune system engagement following irreversible electroporation targeting pancreatic cancer. *Frontiers in Oncology*. (2022). doi: 10.3389/fonc.2022.853779.
3. Ivester HM, Tupik JD, **Nagai-Singer MA**, Allen IC. Chapter: Methods to Evaluate Virus-Mediated Acute Lung Inflammation. *Methods in Cell Biology*. (2022). doi: 10.1016/bs.mcb.2021.12.021.
4. **Nagai-Singer MA**. Virginia Department of Forestry 2021 COVES Fellowship Report. *Virginia Department of Forestry*. (2021).
5. Hendricks-Wenger A, Arnold L, Gannon J, Simon A, Singh N, Sheppard H, **Nagai-Singer MA**, Imran K, Lee K, Clark-Deener S, Bryon C, Edwards M, Larson M, Rossmeisl J, Coutermarsh-Ott S, Eden K, Dervisis N, Klahn S, Tuohy J, Allen IC, Vlasisavljevich E. Histotripsy Ablation in Preclinical Animal Models of Cancer and Spontaneous Tumors in Veterinary Patients: A Review. *Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*. (2021). doi: 10.1109/tuffc.2021.3110083
6. Hendricks-Wenger A, Aycok K, **Nagai-Singer MA**, Gannon J, Lorenzo M, Coutermarsh-Ott S, Uh K, Farrell K, Beitel-White N, Clark-Deener S, Tuohy JL, Vlasisavljevich D, Davalos R, Lee K, Allen IC. Establishing a Human Pancreatic Cancer SCID-Like Porcine Model. *Scientific Reports*. (2021). doi:10.1038/s41598-021-87228-5
7. Tuohy JL, Byer BJ, Royer S, Keller C, **Nagai-Singer MA**, Regan DP, Seguin B. Evaluation of Myogenin and MyoD1 as Immunohistochemical Markers of Canine Rhabdomyosarcoma. *Veterinary Pathology*. (2021). doi: 0.1177/0300985820988146
8. **Nagai-Singer MA**, Hendricks-Wenger A, Brock RM, Morrison HA, Tupik JD, Coutermarsh-Ott, S, Allen IC. Using Computer-based Image Analysis to Improve Quantification of Lung Metastasis in the 4T1 Breast Cancer Model. *Journal of Visualized Experiments*. (2020). doi: 10.3791/61805.
9. **Nagai M**. Ali Safiabadi Tali: Lasers are great for cats, Star Wars duels, and... cellular biology! *Virginia Tech Center for Communicating Science*. (2020). https://communicatingscience.isce.vt.edu/research-stories/Ali_SafiabadiTali.html
10. Tupik JD, **Nagai-Singer MA**, Allen IC. To protect or adversely affect? The dichotomous role of the NLRP1 inflammasome in human disease. *Molecular Aspects of Medicine*. (2020). doi: 10.1016/j.mam.2020.100858

11. **Nagai-Singer MA**, Morrison HA, Allen IC. NLRX1 is a Multifaceted and Enigmatic Regulator of Immune System Function. *Frontiers in Immunology*. (2019). doi: 10.3389/fimmu.2019.02419.
12. **Nagai-Singer MA**, Woolls MK, Leedy K, Hendricks-Wenger A, Brock RM, Coutermarsh-Ott S, Imran KM, Tupik JD, Fletcher EJ, Brown DA, Allen IC. The Dichotomous Role of NLRX1 in Triple-Negative Breast Cancer Is Dictated by Cellular Context. [In Preparation for Journal of Experimental Medicine]
13. **Nagai-Singer MA**, Woolls MK, Leedy K, Morrison HA, Allen IC. NLRX1 attenuates cancer-associated phenotypes in murine pancreatic tumor cells. [In Preparation for ImmunHorizons]

Presentations

1. “NLRX1 exacerbates aggressive properties of triple-negative breast cancer cells *in vitro* and *in vivo*.” **Nagai-Singer MA**, Woolls M, Imran KM, Tupik JD, Fletcher E, Allen IC. Southeastern Immunology Symposium, Duke University, Durham NC, June 11 2022. Poster.
2. “X’ploring the multifaceted functions of NLRX1 in triple-negative breast cancer.” **Nagai-Singer MA**, Woolls M, Imran KM, Tupik JD, Fletcher E, Allen IC. American Association of Immunologists IMMUNOLOGY2022, Portland OR, May 9 2022. Poster.
3. “Protective or Problematic? Uncovering the contradictory functions of NLRX1 in triple-negative breast cancer.” **Nagai-Singer MA**, Woolls M, Imran KM, Tupik JD, Fletcher E, Allen IC. 2022 ICTAS Doctoral Scholars Poster Session, Blacksburg VA, April 22 2022. Poster.
4. “Understanding the role of NLRX1 in triple-negative breast cancer.” **Nagai-Singer MA**. BMVS Research in Progress, Blacksburg VA, April 20 2022. Oral presentation.
5. “Helpful or Harmful? Uncovering the contradictory functions of NLRX1 in triple-negative breast cancer.” **Nagai-Singer MA**, Woolls M, Imran KM, Tupik JD, Fletcher E, Allen IC. 38th Annual GPSS Research Symposium, Virtual, March 23 2022. Poster. **Honorable Mention Poster**
6. “X’ploring the contradictory function of NLRX1 on epithelial-mesenchymal transition in triple-negative breast cancer.” **Nagai-Singer MA**, Woolls M, Imran KM, Tupik JD, Fletcher E, Allen IC. Virginia Tech Cancer Research Alliance Retreat, Roanoke VA, March 18 2022. Poster.
7. “NLRX1 demonstrates tumor suppressive abilities in pancreatic cancer cells.” **Nagai-Singer MA**, Allen IC. 2021 Commonwealth of Virginia Cancer Research Conference, Richmond VA, November 20 2021. Oral presentation.

8. "NLRX1 can suppress or promote breast cancer tumor growth and lung metastasis in a cell-dependent manner." **Nagai-Singer MA**, Hendricks-Wenger A, Fletcher E, Imran KM, Morrison HA, and Allen IC. American Association of Immunologists IMMUNOLOGY2021 Conference Poster Session, Virtual, May 12 2021. Poster.
9. "Protective or Problematic? Investigating the cell-specific role of NLRX1 in triple-negative breast cancer." **Nagai-Singer MA**, Hendricks-Wenger A, Fletcher E, Imran KM, Morrison HA, and Allen IC. 2021 ICTAS Doctoral Scholars Poster Session, Blacksburg VA, April 30 2021. Poster.
10. "Cancer Immunology: Investigating the Role of NLRX1 in pancreatic cancer." **Nagai-Singer, MA**. BMVS Research in Progress, Virtual, March 3 2021. Oral presentation.
11. "Investigating the role of NLRX1 as a potential tumor suppressor in triple-negative breast cancer." **Nagai-Singer MA**, Hendricks-Wenger A, Fletcher E, Imran KM, Morrison HA, and Allen IC. Virginia-Maryland College of Veterinary Medicine 31st Annual Research Symposium, Virtual, March 25 2021. Poster.
12. "A Cancer Conundrum: NLRX1 can suppress or promote breast cancer disease burden based on cell type." **Nagai-Singer MA**, Hendricks-Wenger A, Fletcher E, Imran KM, Allen IC. 2021 Virginia Tech Graduate Student Assembly Research Symposium, Virtual, March 23 2021. Oral presentation. **1st Place 10 Minute Oral Presentation**
13. "From Arabidopsis to Animals: How one plant lead to the discovery of a potential tumor suppressor." **Nagai-Singer MA**. Zhang Lab Summer Communication, Virtual, July 27 2020. Oral presentation.
14. "Destination Mitochondria: The roadmap to understanding NLRX1 as a tumor suppressor." **Nagai-Singer MA**, Allen IC. 2020 Virginia Tech Graduate Student Assembly Research Symposium, Virtual, April 15 2020. Oral presentation. **2nd Place Flash Talk**
15. "NLRX1 potentially suppresses tumorigenesis by modulating mitochondrial function in murine cancer cells." **Nagai-Singer MA**, Brock RM, Davis G, Brown D, Allen IC. Virginia-Maryland College of Veterinary Medicine 30th Annual Research Symposium, Blacksburg VA, November 6 2019. Poster.
16. "Determining the immunological effects of NLRX1 on Murine Breast Cancer Cells and Tissues." **Nagai-Singer MA**, Allen IC. 2019 ICTAS Doctoral Scholars Poster Session, Blacksburg VA, April 19 2019. Poster.
17. "Determining the immunological effects of NLRX1 on Murine Breast Cancer Cells and Tissues." **Nagai-Singer MA**, Allen IC. 12th Annual Life Science Forum of Southwest Virginia, Blacksburg VA, April 3 2019. Poster.

Examination Graduate Committee

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