

BIOMEDICAL & VETERINARY SCIENCES

GRADUATE PROGRAM



ANNOUNCES

The Doctor of Philosophy Seminar and Examination of

Holly Ann Morrison

**"Dysregulation of Noncanonical NF- κ B Signaling in
Gastrointestinal Diseases"**

Friday, August 11th, 2023

10:00AM

VMCVM, Classroom 100



Bio

Holly Morrison was born in Reykjavik, Iceland, where she lived for the first few years of her life. Once her dad concluded his service in the U.S. Navy and her parents moved back to the USA, one of the first places they called home was Christiansburg, VA before settling in Roanoke, VA. Early on, Holly's childhood dream was to attend the VA-MD College of Veterinary Medicine. After graduating from high school as valedictorian, Holly attended a small private liberal arts college for undergrad at Roanoke College in Salem, VA, where she graduated with her B.S. in Biology and Environmental Studies Cum Laude and with college honors distinction/departmental honors.

At Roanoke College, Holly realized her passion for biomedical research while conducting her first independent research project analyzing the skin microbiomes in horses afflicted with pressure ulcers ("bed sores") at Rood & Riddle Equine Hospital in Lexington, KY. This work inspired her to pursue her PhD at the VA-MD College of Veterinary Medicine, where she joined Dr. Irving Coy Allen's Laboratory and continued to make strides in making research findings that could benefit both human and veterinary medicine. Her doctoral work focuses on dysregulated inflammation and impaired immune responses given impaired levels of the NIK protein in the gastrointestinal tract. Additionally, Holly devotes her time mentoring other aspiring scientists through her alma mater's Maroon Mentor program, directly advising her own undergrad(s) in the laboratory, and by volunteering at disadvantaged school districts inspiring children under 12 years old that their future in science is attainable and as big as they dream. Outside of the laboratory, Holly is an avid runner, mountain biker, and loves her golden retriever Lily.

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VMCVM Office of Research and Graduate Studies

Lay Language Abstract

Redness, swelling, heat, pain, and loss of function – these are the five signs of inflammation. Under normal physiological conditions, inflammation is the body's conserved evolutionary response by serving as the first line of defense against infections propagated by foreign invaders like pathogens (i.e. bacteria, viruses, fungi), while also signaling to the immune system to resolve tissue damage. Therefore, properly maintained pro-inflammatory signaling is critical to ensuring a healthy state. However, an imbalance in pro- and anti-inflammatory signaling elicits a long-term, low-grade form of inflammation termed “chronic inflammation”. Unresolved chronic inflammation can persist for several months or even years and further predisposes patients to various chronic inflammatory conditions and even inflammation-induced cancer. The NF- κ B cellular signaling mechanism is a central regulator of inflammation and can be activated upon either the canonical NF- κ B or noncanonical NF- κ B pathways. In comparison to its canonical counterpart, the noncanonical NF- κ B is vastly understudied, especially in regards to gastrointestinal health. A unique feature of the noncanonical NF- κ B pathway is the required stabilization of the NF- κ B-inducing Kinase (NIK) protein, which is required for further propagation of this signaling network.

Lay Language Abstract continued

As evidenced by our culmination of works, we reveal that Noncanonical NF- κ B signaling is critical to gut health, as it maintains a precise cellular signaling mechanism within the gastrointestinal tract by properly maintaining pro- and anti-inflammatory signaling. Additionally, downstream implications include regulation of cell division and activation of cell death to elicit a proper damage response. Within this dissertation, we evaluate the understudied noncanonical NF- κ B pathway in various chronic inflammatory diseases of the gut including Eosinophilic Esophagitis (upper GI tract), Celiac Disease/Non-Celiac Gluten Sensitivities (small intestine), Inflammatory Bowel Disease (entire intestine/large intestine), and an inflammatory subtype of colorectal cancer Colitis-Associated Colorectal Cancer (large intestine). Through the use of murine models bearing deletions of genes related to noncanonical NF- κ B signaling (esp. NIK), cell models, and the generation of “mini-organs” organoids from isolated intestinal stem cells, we are able to model the involvement of NIK and noncanonical NF- κ B signaling in maintaining gastrointestinal health. Clinical relevancy of these findings was further evaluated by quantifying noncanonical NF- κ B signaling levels in human biopsies. Culminating our work, we find noncanonical NF- κ B signaling to be context-specific in driving disease. Finally, we conclude this work by suggesting the promise of NIK as a potential candidate for disease biomarkers and target for future drug development.

Publications

Morrison HA, Trusiano B, Rowe AJ, Allen IC. Negative Regulatory NLRs Mitigate Inflammation via NF- κ B Pathway Signaling in Inflammatory Bowel Disease. *Biomed J.* 2023 Jun 13;100616. doi: 10.1016/j.bj.2023.100616. Epub ahead of print. PMID: 37321320.

Imran KM, Tintera B, **Morrison HA**, Tupik JD, Nagai-Singer MA, Ivester H, Council-Troche M, Edwards M, Coutermarsh-Ott S, Byron C, Clark-Deener S, Uh K, Lee K, Boulos P, Rowe C, Coviello C, Allen IC. Improved Therapeutic Delivery Targeting Clinically Relevant Orthotopic Human Pancreatic Tumors Engrafted in Immunocompromised Pigs Using Ultrasound-Induced Cavitation: A Pilot Study. *Pharmaceutics.* 2023 May 24;15(6):1585. doi: 10.3390/pharmaceutics15061585. PMID: 37376034; PMCID: PMC10302458.

Nagai-Singer MA, **Morrison HA**, Woolls MK, Leedy K, Imran KM, Tupik JD, Allen IC. NLRX1 functions as a tumor suppressor in Pan02 pancreatic cancer cells. *Front Oncol.* 2023 Jun 5;13:1155831. doi: 10.3389/fonc.2023.1155831. PMID: 37342194; PMCID: PMC10277690.

Morrison HA*, Liu Y*, Eden K*, Nagai-Singer MA, Wade PA, Allen IC. NLRX1 Deficiency Alters the Gut Microbiome and Is Further Exacerbated by Adherence to a Gluten-Free Diet. *Front Immunol.* 2022 Apr 28;13:882521. doi: 10.3389/fimmu.2022.882521. PMID: 35572547; PMCID: PMC9097893.

*Authors share co-authorship

Callahan V, Hawks S, Crawford MA, Lehman CW, **Morrison HA**, Ivester HM, Akhrymuk I, Boghdeh N, Flor R, Finkielstein CV, Allen IC, Weger-Lucarelli J, Duggal N, Hughes MA, Kehn-Hall K. The Pro-Inflammatory Chemokines CXCL9, CXCL10 and CXCL11 Are Upregulated Following SARS-CoV-2 Infection in an AKT-Dependent Manner. *Viruses.* 2021 Jun 3;13(6):1062. doi: 10.3390/v13061062. PMID: 34205098; PMCID: PMC8226769.

Publications

Nguyen VQ*, Eden K*, **Morrison HA***, Sammons MB, Knight KK, Sorrentino S, Brock RM, Grider DJ, Allen IC, Sorrentino D. Noncanonical NF- κ B Signaling Upregulation in Inflammatory Bowel Disease Patients is Associated With Loss of Response to Anti-TNF Agents. *Front Pharmacol.* 2021 Jun 10;12:655887. doi: 10.3389/fphar.2021.655887. PMID: 34177575; PMCID: PMC8223059. *Authors share co-authorship

Hendricks-Wenger A, Aycock KN, Nagai-Singer MA, Coutermarsh-Ott S, Lorenzo MF, Gannon J, Uh K, Farrell K, Beitel-White N, Brock RM, Simon A, **Morrison HA**, Tuohy J, Clark-Deener S, Vlaisavljevich E, Davalos RV, Lee K, Allen IC. Establishing an immunocompromised porcine model of human cancer for novel therapy development with pancreatic adenocarcinoma and irreversible electroporation. *Sci Rep.* 2021 Apr 7;11(1):7584. doi: 10.1038/s41598-021-87228-5. PMID: 33828203; PMCID: PMC8027815.

Dillon KM, **Morrison HA**, Powell CR, Carrazzone RJ, Ringel-Scaia VM, Winckler EW, Council-Troche RM, Allen IC, Matson JB. Targeted Delivery of Persulfides to the Gut: Effects on the Microbiome. *Angew Chem Int Ed Engl.* 2021 Mar 8;60(11):6061-6067. doi: 10.1002/anie.202014052. Epub 2021 Jan 29. PMID: 33511734; PMCID: PMC7967250.

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. *J Vis Exp.* 2020 Oct 2;(164). doi: 10.3791/61805. PMID: 33074250.

McDaniel DK, Ringel-Scaia VM, **Morrison HA**, Coutermarsh-Ott S, Council-Troche M, Angle JW, Perry JB, Davis G, Leng W, Minarchick V, Yang Y, Chen B, Reece SW, Brown DA, Cecere TE, Brown JM, Gowdy KM, Hochella MF Jr, Allen IC. Pulmonary Exposure to Magnéli Phase Titanium Suboxides Results in Significant Macrophage Abnormalities and Decreased Lung Function. *Front Immunol.* 2019 Nov 28;10:2714. doi: 10.3389/fimmu.2019.02714. PMID: 31849940; PMCID: PMC6892980.

Publications

Nagai-Singer MA, **Morrison HA**, Allen IC. NLRX1 Is a Multifaceted and Enigmatic Regulator of Immune System Function. *Front Immunol.* 2019 Oct 11;10:2419. doi: 10.3389/fimmu.2019.02419. PMID: 31681307; PMCID: PMC6797603.

Morrison HA, Eden K, Rothschild DE, Qin Y, Wade PA, Rowe AJ, Mounzer C, Stephens MC, Hanson KM, Brown SL, Holl EK, Allen IC. NF- κ B Inducing Kinase Attenuates Colorectal Cancer by Regulating Noncanonical NF- κ B Mediated Intestinal Epithelial Cell Regeneration. [In Submission - CMGH Cellular and Molecular Gastroenterology and Hepatology]

Morrison HA, Hoyt KJ, Mounzer C, Ivester HM, Barnes BH, McGowan EC, Allen IC. Expression Profiling Identifies Key Genes and Biological Functions Associated with Eosinophilic Esophagitis in Human Patients. [In Review -Frontiers in Allergy]

Presentations

ORAL PRESENTATIONS

“Intestinal Epithelial Cells Are the Root Cause of Colorectal Cancer Following Loss of NIK Protein”, Biomedical & Veterinary Sciences Research Symposium, Blacksburg, VA, March 2023.

“Diminished Noncanonical NF- κ B Signaling Induces Colitis-Associated Colorectal Cancer Susceptibility Upon De-differentiation of Epithelial Cells”, American Association of Immunologists Annual Meeting, Portland, OR May 2022. Trainee Abstract Award

“Inflammation-induced Tumorigenesis: Loss of NIK Protein in Intestinal Epithelial Cells Causes Susceptibility to Colorectal Cancer”, Roanoke College Biology Department, Salem, VA, March 2022. Invited Talk

“You’ve Got a Friend in Me: NIK Protein Protects Against Cancer”, Virginia Tech Nutshell Games, Blacksburg, VA, March 2022.

“NIK the Friendly Protein Protects Against Cancer”, Flip the Fair – Melrose Library Branch, Roanoke, VA, February 2022. Top Presenter Award

“NF- κ B Inducing Kinase (NIK) Deletion Results in Accumulation of Intestinal Epithelial Cells Increasing Susceptibility to Colitis-associated Colorectal Cancer via Top-down Tumorigenesis”, Commonwealth of Virginia Cancer Research Conference, Richmond, VA, Nov. 2021. Popular Award

“Noncanonical NF- κ B Signaling Critical to Regulating Intestinal Stem Cell Niche and Implications Increase Susceptibility to Colitis-Associated Colorectal Cancer”, Biomedical & Veterinary Sciences Research Symposium, Blacksburg, VA, March 2021.

“Translation from Pets to People and People to Pets”, iTHRIV Event, Blacksburg, VA, February 2021. Invited Talk

Presentations

“Redness, Swelling, and Heat, oh my! Inflammation Results in Cancer Development”, Virginia Tech Graduate School Assembly Research Symposium, Blacksburg, VA, March 2020. **Bronze Award**

“Growing Mini Organs to Study the Development of Colorectal Cancer”, Nutshell Games, Blacksburg, VA, November 2019.

“Inflammation, Tumorigenesis, and the Stem Cell Niche: Unraveling the Role of the Noncanonical NF- κ B Signaling Pathway in Colitis-Associated Colorectal Cancer”, Biomedical & Veterinary Sciences Research Symposium, Blacksburg, VA, November 2019.

“Noncanonical NF- κ B Signaling: Inflammation, Mutations, and Colorectal Cancer oh my!”, Biomedical & Veterinary Sciences Research Seminar, Blacksburg, VA, September 2019.

“Noncanonical NF- κ B Signaling in Inflammatory Bowel Disease Associated with Anti-TNF Therapy Responsiveness in Human Patients”, Virginia Tech Graduate School Assembly Research Symposium, Blacksburg, VA, March 2019. **Silver Award**

POSTER PRESENTATIONS

Morrison, H. A., A. Rowe, K. Eden, D. E. Rothschild, K. Baumgarner, S. Brown, E. Holl, I. C. Allen. “Loss of NF- κ B Inducing Kinase Increases Susceptibility to Colorectal Cancer Via Top-Down Tumorigenesis Following Diminished Regenerative Capacity off Stem Cell Niche”, The Global Stem Cell Event, Boston, MA, June 2023

Morrison, H. A., A. Rowe, K. Eden, D. E. Rothschild, K. Baumgarner, S. Brown, E. Holl, I. C. Allen. “Deletion of NIK Increases Susceptibility to Colorectal Cancer through Diminished Intestinal Epithelial Cell Regeneration”, Biomedical & Veterinary Sciences Research Symposium, Blacksburg, VA, March 2023. **Outstanding Poster Presentation**

Presentations

Morrison, H. A., K. M. Imran, R. M. Brock, N. Alinezhadbalalami, K. N. Aycock, B. Tintera, R. V. Davalos, I. C. Allen. “Immune Checkpoint and DNA Damage Repair Pathways Mitigate the Effects of Irreversible Electroporation on Pancreatic Cancer, Virginia College of Osteopathic Medicine Research Day, Blacksburg, VA, February 2023. **3rd Place Graduate Student – Biomedical Research**

Morrison, H. A., A. Rowe, K. Eden, D. E. Rothschild, K. Baumgarner, S. Brown, E. Holl, I. C. Allen. “NF- κ B Inducing Kinase (NIK) Attenuates Top-Down Tumorigenesis During Colorectal Cancer by Regulating Epithelial Cell Proliferation-Differentiation Axis”, Virginia College of Osteopathic Medicine Research Day, Blacksburg, VA, February 2023.

Morrison, H. A., A. Rowe, K. Eden, K. Baumgarner, S. Brown, J. Hagar, E. Holl, I. C. Allen. “NF- κ B Inducing Kinase (NIK) Attenuates Top-Down Tumorigenesis During Colorectal Cancer by Regulating Intestinal Epithelial Cell Regeneration and Differentiation”, Wake Forest Baptist Comprehensive Cancer Center’s Signaling and Biotechnology Retreat, Floyd, VA November 2022.

Morrison, H. A., E. Russ, N. Mikhalkevich, S. Iordanskiy. “MicroRNAs as a Potential Countermeasure for Acute Radiation Syndrome to Repopulate Radiation-Depleted Neutrophils”, Uniformed Services University of the Health Sciences, Bethesda, MD, August 2022. **Highest Scoring Poster**

Morrison, H. A., A. Rowe, K. Eden, K. Baumgarner, S. Brown, J. Hagar, E. Holl, I. C. Allen. “Diminished Noncanonical NF- κ B Signaling Induces Colitis-Associated Colorectal Cancer Susceptibility Upon De-differentiation of Epithelial Cells”, American Association of Immunologists Annual Meeting, Portland, OR May 2022. **Trainee Abstract Award**

Morrison, H. A. “The Guardian of the Gut: NIK Protein Critical for Protecting Against Colorectal Cancer”, Virginia Tech Graduate School Assembly Research Symposium, Blacksburg, VA March 2022.

Presentations

Morrison, H. A., A. Rowe, K. Eden, K. Baumgarner, S. Brown, E. Holl, I. C. Allen. “Loss of Noncanonical NF- κ B Signaling in Intestinal Epithelial Cells Increases Susceptibility to Colitis-associated Colorectal Cancer”, Virginia Tech Cancer Alliance Retreat, Roanoke, VA, March 2022.

Morrison, H. A., Y. Liu, K. Eden, M. A. Nagai-Singer, P. A. Wade, I. C. Allen. “NLRX1 is Critical for Maintaining Gut Microbiome Symbiosis Following Adherence to a Gluten-free Diet”, Virginia College of Osteopathic Medicine Research Day, Blacksburg, VA, February 2022.

Morrison H. A., A. Rowe, K. Baumgarner, K. Eden, D. Rothschild, E. Holl, J. Hagar, S. Brown, I. C. Allen. “NF- κ B Inducing Kinase Critical for Gastrointestinal Homeostasis: Dysregulation of Noncanonical NF- κ B Pathway Implicated in Colitis-Associated Colorectal Cancer”, Virginia College of Osteopathic Medicine Research Day, Blacksburg, VA, February 2021.

Morrison H. A., C. Mounzer, K. Eden, K. Baumgarner, S. Brown, E. Holl, I. C. Allen. “Inflammation-Induced Tumorigenesis: Diminished Noncanonical NF- κ B Signaling is Associated with the Pathogenesis of Colitis-associated Colorectal Cancer”, American Association of Immunology Conference, May 2020. *Event canceled due to COVID-19 pandemic*

Morrison H. A., K. Eden, D. Rothschild, C. Mounzer, K. Baumgarner, E. Holl, S. Brown, I. C. Allen. “Inflammation-induced Tumorigenesis: Non-canonical NF- κ B Pathway Controls Gastrointestinal Homeostasis in the Pathogenesis of Colorectal Cancer”, Virginia College of Osteopathic Medicine Research Day, Blacksburg, VA, February 2020. **1st Place in Graduate Student – Biomedical Research**

Morrison H. A., K. Eden, D. Rothschild, M. Stephens, S. Brown, E. Holl, I. C. Allen. “Elucidating the Role of the Noncanonical NF- κ B Signaling Pathway in Inflammation-Induced Carcinogenesis: Pathway Controls Stem Cell Niche in Colonic Mucosa”, Southeastern Immunology Symposium, Atlanta, GA, June 2019.

Presentations

Morrison H. A., K. Eden, M. Stephens, I. C. Allen. “Inflammation-induced Carcinogenesis Paradox: Noncanonical NF- κ B Pathway Controls Stem Cell Niche”, Virginia Drug Discovery Rx Symposium, Roanoke, VA, May 2019.

Outstanding Graduate Student Presentation

Morrison H. A., Stephens M., K. Eden, V. Q. Nguyen, D.R. Sorrentino, S. Sorrentino, R. M. Brock, M. Lang, D. J. Grider, I. C. Allen. “Newfound Role for Noncanonical NF- κ B Signaling in Inflammatory Bowel Disease: Gene Expression Levels Serve as a Proxy for Predicting Anti-TNF Therapy Responsiveness”, American Association of Immunology Conference, San Diego, CA, May 2019.

Morrison H. A., K. Eden, D. Rothschild, S. Brown, E. Holl, I. C. Allen. “Noncanonical NF- κ B Controls Stem Cell signatures in the Colonic mucosa and Affects susceptibility to Inflammation-induced Carcinogenesis”, American Association of Immunology Conference, San Diego, CA, May 2019.

Morrison H. A., Stephens M., K. Eden, I. C. Allen. “Noncanonical NF- κ B Signaling Upregulation in IBD Patients and Contributes to Decreased Anti-TNF Treatment Response”, Life Science Forum of Southwest Virginia, Blacksburg, VA, April 2019.

Awards and Academic Achievements

- **Best Oral Presentation**, VT Graduate School Assembly Research Symposium Oral Presentation, Blacksburg, VA (2023)
- **Virginia Tech Travel Fund Program Award**, \$300 (2023)
- **Outstanding Poster Presentation**, Biomedical & Veterinary Sciences Research Symposium, Blacksburg, VA (2023)
- **Third Place - Biomedical Graduate Student Research**, Edward Via College of Osteopathic Medicine Research Day, Blacksburg, VA (2023)
- **Stanford University PRISM Program Travel Fund**, \$2,500 (2022)
- **Highest Scoring Poster**, USUHS Research Day, Bethesda, MD (2022)
- **American Association for Immunologists (AAI) Trainee Abstract Award**, Portland, OR (2022)
- **Top Presenter**, Flip the Fair, Melrose Branch Library, Roanoke, VA (2022)
- **Popular Award**, Commonwealth of Virginia Cancer Research Conference Oral Presentation, Richmond, VA (2021)
- **Bronze Award**, VT Graduate School Assembly Research Symposium Oral Presentation, Blacksburg, VA (2020)
- **First Place - Biomedical Graduate Student Research**, Edward Via College of Osteopathic Medicine Research Day, Blacksburg, VA (2020)
- **Outstanding Graduate Student Presentation**, Virginia Drug Discovery Rx Symposium, Roanoke, VA (2019)
- **Silver Award**, VT Graduate School Assembly Research Symposium Oral Presentation, Blacksburg, VA (2019)

Examination Graduate Committee

Major Advisor/Chair:

Irving Allen, PhD, MBA

Full Professor

Department of Biomedical Sciences and Pathobiology

VA-MD College of Veterinary Medicine

Virginia Tech

Graduate Advising Committee Members:

Clayton Caswell, PhD

Associate Professor

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Xin Luo, PhD

Full Professor

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Department of Microbial Infection and Immunity

The Ohio State University College of Medicine



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