Doctoral Dissertation Defense Announcement

“Interleukin 13 Signaling Specifically to Macrophages Promotes Recovery after Myocardial Infarction”

Santiago Alvarez Argote
Candidate for Doctor of Philosophy
Physiology
School of Graduate Studies
Medical College of Wisconsin

Committee in Charge:
Caitlin C. O’Meara, PhD (Mentor)
Allison J. Kriegel, PhD
Justin L. Grobe, PhD
Calvin B. Williams, PhD
Ronald J. Vagnozzi, PhD

Date: Tuesday, Oct 24, 2023
Time: 10:00 AM (CST)
Defense Location: Bolger Auditorium
Zoom: https://mcw-edu.zoom.us/j/94814851601?pwd=ZE1HSlV0S095NXhQN2xPSlkrTHk5Zz09
**Graduate Studies:**

- Reading and Research
- Boundaries of Science and Medical Practice
- Current Topics in Physiology
- Special Topics in Physiology
- Advanced Respiratory Physiology
- Advanced Renal Physiology
- Advanced Cardiovascular Physiology
- Advanced Endocrine Physiology
- Physiological Genomics
- Cellular and Molecular Immunology
- Grant Writing
- Biostatistics Health Sciences
- Ethics & Integrity in Science
- Seminar
- Research Ethics Discussion Series
- Doctoral Dissertation
Dissertation

“Interleukin 13 Signaling Specifically to Macrophages Promotes Recovery after Myocardial Infarction”

There is great interest in identifying signaling pathways that promote cardiac repair after myocardial infarction (MI). Prior studies suggest a beneficial role for IL13 signaling in neonatal heart regeneration, while in adult wild type (Wt) mice, systemic IL13 stimulation results in improved cardiac functional recovery after injury. However, the cell types mediating cardiac regeneration and improved functional recovery are unknown. Interestingly, even though cardiomyocytes (CM) play a central role in cardiac regeneration, CM-specific IL13/IL4Rα stimulation fails to improve functional recovery in adult mice. Thus, it remains unclear the cellular mechanism by which IL13/IL4Rα signaling promotes functional recovery post-MI.

Considering prior literature implicates a beneficial role for IL13 signaling in neonatal heart regeneration and in adult heart post infarct, the goal of my thesis is to identify the cell type(s) responding to this cytokine to mediate beneficial outcomes following cardiac injury. Initially, I targeted IL13 signaling in mice by testing ischemic heart injury in a mouse model that is globally depleted of the IL13 receptor subunit, IL4Rα. IL4Rα knock out (IL4RαKO) mice showed exacerbated ischemic heart failure after MI, and while IL4Rα is expressed in virtually all cell types in the heart, I found that cardiac macrophages had the highest expression of this receptor.

Macrophages are the most abundant leukocyte in the heart during homeostasis and after injury, and play a central role in myocardial recovery post-MI. Thus, I hypothesized that macrophage IL13/IL4Rα signaling was the cellular mechanism behind exacerbated heart failure in IL4RαKO mice and improved functional recovery after systemic IL13 administration in Wt mice. Consequently, I targeted macrophage IL13/IL4Rα signaling by using a mouse model whereby IL4Rα is depleted in macrophages (IL4RαMacKO).

IL13 was highly produced in the neonatal heart and accordingly and IL4RαMacKO neonates showed a strong deficit in functional recovery post MI indicating that IL13 signaling directly to macrophages mediates cardiac repair in neonates. Interestingly, IL13 expression declined precipitously in the adult heart and accordingly, untreated IL4RαMacKO adult mice displayed only a moderate effect post-MI. Nevertheless, after systemic IL13 administration, wildtype mice showed improved functional recovery post-MI while
IL4Rα^MacKO^ mice did not improve cardiac function in response to IL13, demonstrating that macrophages are the main cellular mechanism mediating beneficial effects of IL13. Surprisingly, systemic IL13 stimulation in IL4Rα^MacKO^ mice not only failed to improve cardiac function post MI, but resulted in aggravated mortality, worsening cardiac function, and exaggerated scars compared to vehicle treatment alone, suggesting that IL13 is acting on yet another cell type to aggravate heart failure after MI.

IL13 stimulation modified the cardiac macrophage response post-MI and resulted in the appearance of completely novel macrophage subgroup in the heart. These IL13-stimulated macrophages have a phenotype that is clearly beneficial in the recovering heart. As they are less inflammatory than other macrophages but are highly phagocytic and have high expression of matrix remodeling markers. Moreover, these IL13-induced macrophages seem to have a local effect in the heart ameliorating cardiac inflammation post-MI.

In summary, we elucidate a strongly pro-reparative role for IL13 signaling directly to macrophages following cardiac injury. While this pathway is active in pro-regenerative neonatal stages, re-activation of macrophage IL13 signaling is required to promote cardiac functional recovery in adults and could be potentially targeted to modulate ischemic heart failure development in human patients.
Curriculum Vitae
Santiago Alvarez Argote M.D.
Graduate Student- PhD Candidate
Dr. Caitlin O’Meara Laboratory
Department of Physiology
Medical College of Wisconsin

General Information
Name: Santiago
Last Name: Alvarez Argote
Date of birth: October 18th of 1988
Marital status: In a relationship
Nationality: Colombian
Current mailing address: 2555 N Oakland Ave, Apt 304
City/State: Milwaukee, WI
Zip code: 53211
Phone number: +1 773 9878244
Professional email: salvarez@mcw.edu
Personal email: salvarez88@gmail.com

Education
2018 – present
Medical College of Wisconsin, WI.
Degree expected: Ph.D. in Physiology and translational research.
Thesis Advisor: Caitlin C. O’Meara, Ph.D.
Thesis Title: Interleukin 13 signaling mediates cardiac recovery after myocardial infarction exclusively acting on macrophages.
Description/Skills obtained: Greatly improved and developed skills such as independent worker, critical and independent thinking, problem-solving, leadership, time management, team playing, and to thrive under pressure. I learned to apply the scientific method, to develop a hypothesis based on a clinical problem and background knowledge, and to design and develop a set of experiments that will test that hypothesis effectively. I mastered skills such as flow cytometry, cell sorting and flow cytometry analysis. Greatly improved skills such as whole animal physiological experiments, echocardiography in rodents, and survival surgeries and procedures in rodents such as myocardial infarction, and intravenous and intraperitoneal injections. Enhanced skills such as statistical analysis, scientific writing, and public speaking at scientific conferences.

2005 – 2012
University of Valle, Cali, Colombia
Degree: M.D.
Description/Skills obtained: Completed basic coursework, clinical clerkships, and sub internships as a medical student at the University of Valle, Colombia. Developed skills such as active listening, communication, leadership, problem-solving, critical, and independent thinking, to pay attention to details, to keep up in a fast-paced environment, and to thrive under pressure by actively participating in patient care along with other health care professionals. Additionally, developed medical and clinical knowledge that allows me to see better "the bigger picture" while planning a research project and to identify areas that lack a clear pathophysiological understanding and would drastically benefit from additional translational research. I also developed compassionate skills by dealing with patients with severe diseases that would benefit minimally from anything beyond palliative care.

Professional Experience
2017 – 2018
Medical College of Wisconsin, WI: Research technologist I. (12 months)
Supervisor: Matthew R. Hodges, Ph.D.
Description/Skills obtained: I studied the neuro-control of breathing in different pathophysiological conditions, focusing on a bronchopulmonary dysplasia project. I improved skills such as independent working, team playing, active listening, critical thinking, problem-solving, time management and to thrive under pressure. Performed a wide variety of whole animal in-vivo physiological experiments, including whole-body plethysmography, electromyography, oximetry, and blood gases analysis. Greatly improved research skills such as western blotting, bright field and immunofluorescence
staining, imaging, and analysis. I also contributed to projects studying sudden infant death syndrome and a rat model with mutations in the potassium channel Kir 4.1/5.1 with inducible seizures.

2015 – 2016  **Comfenalco Hospital, Cali, Colombia:** General medicine physician in the emergency department.  
**Supervisor:** Janeth David, MD. (12 months)  
**Description/Skills obtained:** Worked as a general medicine physician in the emergency department of a high-complexity hospital in Cali, Colombia. Improved skills such as independent working, team playing, active listening, communication, leadership, problem solving, to keep up in a fast-paced environment. Treated patients with a wide variety of diseases, including acute coronary syndromes, COPD, diabetes, GI bleeding, etc. Performed bedside procedures such as tracheal intubation. This experience solidified my knowledge of many pathophysiological processes and allowed to put into action the medical knowledge gathered throughout my medical and surgical training.

2013 - 2014  **Mayo Clinic, MN:** Research Trainee (12 months)  
**Supervisor and mentor:** Carlos B. Mantilla, M.D., Ph.D.  
**Description/Skills obtained:** Research trainee at Drs. Sieck & Mantilla laboratory at the Mayo clinic. I led the research project that studied diaphragm functional and respiratory impairment after spinal cord trauma. Improved and developed skills such as independent worker, time management, critical thinking, problem solving, and to thrive under pressure. Learned and mastered rodent microsurgical techniques such as cervical laminectomy and spinal cord contusions, and diaphragm electrode placement. Learned in vivo physiological experiments such as motor and behavior assessment, whole-body plethysmography, and diaphragm electromyography recording and analysis. Developed data and statistical analysis skills, and greatly improved my scientific writing skills.

**Additional training**

**June 2022**  **45th Annual Course in Flow Cytometry, Madison, WI, June 2022:** Attendee.  
**Description/Skills obtained:** Attendee at the 45th annual course in flow cytometry in Madison, WI. Attended seminars about basic principles in flow cytometry and participated in hands-on small group sessions that taught advanced techniques such as spectral flow cytometry, intracellular signaling, antigen presentation and flow cytometry of extracellular vesicles.

2014 – 2015  **Universidad de Antioquia, Medellin, Colombia:** General surgery internship. (12 months)  
**Program director:** Álvaro Sanabria, M.D., Ph.D., FACS  
**Description/Skills obtained:** I completed the first year of postgraduate training in general surgery. I performed advanced patient care in critical care, general hospital floor and ambulatory settings. Improved skills such as critical thinking, leadership, problem-solving, communications, time management, to keep up in a fast-paced environment and thrive under pressure. Performed bedside surgical procedures such as chest tube placement and central IV placement. Improved teaching skills by multiple presentations to medical students, my surgical team and the general surgery department about surgical diseases and treatments. Active participation in emergency and non-emergency surgical cases such as laparoscopic appendectomies, cholecystectomies, hernia repairs, etc.

**Observership and Clerkships**

**March 2022**  Observership in internal medicine. Medical College of Wisconsin, Milwaukee-WI.  
**July 2012**  Clerkship in cardiothoracic surgery. Mayo clinic, MN.  
**May – June 2012**  Clerkship in general surgery. Emory school of medicine, GA.  
**April 2012**  Observership in colorectal surgery. University of Miami Leonard M. Miller, FL.  
**July 2011**  Observership in surgical oncology. University of Miami Leonard M. Miller, FL.  

**Awards and Recognitions**

**Oct 2022**  MCW cardiovascular research center retreat. First place poster presentation. Milwaukee, WI.
May 2022  Weinstein cardiovascular research student travel award. Marseilles, France.

August 2021  MCW graduate student travel award. Milwaukee, WI.

**Publications in Peer Reviewed Journal Articles**


**Alvarez-Argote S**, Almeida VA, Buday S, and O'Meara CC. IL4Rα Blockade Exacerbates Heart Failure in Mice and Humans after Ischemic Heart Disease. *In preparation.*


**National and International Oral Presentations**

**Alvarez-Argote S**, Paddock S, Flinn MA, and O'Meara CC. Interleukin 13 Signaling to Macrophages Promotes Recovery after Myocardial Infarction in Mice. BCVS. Boston, MA. August 2023. *Accepted for oral presentation.*

**Alvarez-Argote S.**, O'Meara CC. Interleukin 4 And 13 Signaling in Macrophages Regulates Neonatal Cardiac Regeneration. BCVS. Virtual meeting. August 2021.


**National and International Poster Presentations**

Alvarez-Argote S., O'Meara CC. IL4/13 Signaling on Macrophages Promotes Recovery after Myocardial Infarction in Mice. Cardiovascular research center retreat, Milwaukee, WI. October 2022.


Alvarez-Argote S., O'Meara CC., IL4/13 signaling depletion in macrophages impairs cardiac function after myocardial infarction in neonatal mice. Regional cardiovascular research symposium. Chicago, IL. March 2022.

Alvarez-Argote S., Paddock S., O'Meara CC. Interleukin 4 and 13 Signaling in Myeloid Cells Regulates Cardiac Regeneration. BCVS. Virtual meeting. July 2020.

Alvarez-Argote S., Paddock S., O'Meara CC., IL4 and IL13 promote cardiac regeneration after cardiac injury in neonatal mice. Cardiovascular research center retreat. Milwaukee, WI. October 2019.


**Academic and Professional Memberships**
American Heart Association, 2019 - Present
American Association for the Advancement of Science, 2019 - 2021

**Volunteering Experience**
February 2022 – December 2023
Saturday clinic for the uninsured, Milwaukee-WI: Medical student mentor
*Supervisor:* Rebecca C. Lundh, MD.

February – May 2017
Forster and Hodges laboratories. Medical College of Wisconsin, Milwaukee, WI: Observer
*Supervisor:* Bert V. Forster, PhD.

February – March 2017
Aurora St. Luke’s Medical Center, Milwaukee-WI: Emergency department liaison.

May 2010
Rotary group, Cali, Colombia: Medical student volunteer

**Language Proficiency**
*Spanish:* Native speaker
*English:* Advanced level

**Professional References**
Caitlin C. O'Meara, Ph.D. comeara@mcw.edu
Mathew R. Hodges, Ph.D. mhodges@mcw.edu
Michaela Patterson, Ph.D. mpatterson@mcw.edu
Yi-Guang Chen, Ph.D. yichen@mcw.edu
Calvin B. Williams, M.D., Ph.D. cbwillia@mcw.edu