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Memo

To: CAAIF Membership
From: Andrea Waserman, Managing Director, CAAIF
Date: November 9, 2024
Re: **2024 CAAIF Research Grants and Fellowships**

BACKGROUND:
Thus far, together with our partners, CAAIF has distributed $413,000 this year with another $90,000 to be distributed by the end of the year totaling $503,000 in research funds in 2024. Below is a list of all Awards that have been distributed thus far. There are still two grants left to be distributed in 2024.

CAAIF RESEARCH FELLOWSHIP IN IMMUNODEFICIENCY SUPPORTED BY TAKEDA CANADA

Awardee: Dr. Roopa Hebbandi Nanjundappa
Project Title: *Exploring the Role of Type III IFNs and IFNL Receptor Variants in Common Variable Immunodeficiency*
Amount: $50,000
Lay Summary: Interferons are proteins that play a crucial role in our immune system's response to infections. Type III interferons, also known as IFNλ, are particularly important for fighting viral and bacterial infections, especially at barrier surfaces like the lungs and gut. These interferons work by binding to specific receptors on epithelial cells, which then trigger a signaling pathway leading to the expression of genes that fight off infections. Recent research has shown that besides battling infections, IFNλs also have a role in autoimmune diseases and inflammatory conditions. However, their involvement in a particular immune deficiency called Common Variable Immune Deficiency (CVID) remains poorly understood. CVID is characterized by a weakened immune system, leading to recurrent infections, autoimmune diseases, and an increased risk of cancer. In this study, we aim to investigate how IFNλs contribute to the development of complications in CVID. We hypothesize that abnormalities in IFNλ signaling may lead to the autoimmune and inflammatory complications seen in CVID patients. To test this hypothesis, we will measure IFNλ levels in the serum samples of CVID patients and healthy individuals. Then, we will see how immune cells from CVID patients respond to IFNλ. Overall, this research will define the role of IFNλs in CVID and provide valuable insights into the underlying mechanisms of this complex immune disorder. Ultimately, our findings may lead to new therapeutic strategies for managing CVID and related autoimmune conditions.

CASP-CAAIF RESEARCH GRANT IN HEREDITARY ANGIOEDEMA (HAE)

Awardee: Dr. Adil Adatia
Project Title*: Intravenous use of concentrated C1 inhibitor for on demand treatment of hereditary angioedema*
Amount: $50,000
Lay Summary: Hereditary angioedema (HAE) is a genetic disease that causes periodic attacks of swelling in the bowels, hands/feet, and throat. In this disease, patients are deficient in a protein normally found in the bloodstream called C1 inhibitor. C1 inhibitor can

be collected from blood donors and used to treat HAE. Acute attacks of swelling are treated by giving intravenous (IV) infusions of C1 inhibitor. Swelling episodes can also be prevented by giving twice weekly injections of C1 inhibitor into the fatty tissue underneath the skin (subcutaneous).
There are two C1 inhibitor blood products currently available in Canada. Berinert is approved for IV use for acute swelling attacks, whereas Haegarda is approved for subcutaneous use for attack prevention. However, these two formulations are nearly identical in composition. If Haegarda could also be used IV for acute attacks, patients could carry only one C1 inhibitor product, which could simplify therapy for patients and improve HAE treatment cost-effectiveness.
In this study, we will enroll patients receiving IV Haegarda for acute attacks and collect data on effectiveness and side effects. We hypothesize that IV Haegarda will provide safe and effective treatment for acute attacks in patients with HAE.

This award was jointly funded by the Canadian Allergy, Asthma and Immunology Foundation (CAAIF), Canadian Angioedema Scholarship Program (CASP) and Biocryst Canada.

CAAIF-CLA-CRRN RESEARCH STUDENTSHIP

Awardee: Nadia Suray Tan
Project Title*:* Role of B cells in mediating inflammation, autoimmunity and clinical symptoms in respiratory diseases
Amount: $33,000

Lay Summary: Asthma is a common lung disorder where patients experience difficulty breathing, and corticosteroids are the standard treatment to reduce the inflammatory cells causing these symptoms. However, in some patients, neither corticosteroids nor expensive targeted antibody therapies work, leaving them symptomatic and unwell, which significantly adds to healthcare costs. We believe that these patients may have a different type of inflammation in their lungs that is not addressed by current therapies. One possibility is the development of autoimmunity, where rogue antibodies are generated as part of ongoing inflammation. These antibodies attack the body's own tissues, causing further inflammation.
B cells, a type of immune cell, generally produce antibodies. They can either protect the body from infections or, in some cases, contribute to autoimmune diseases by attacking the body's tissues. Regulatory B cells help prevent the production of rogue antibodies, particularly during times of high inflammation. We have observed that severe asthma patients with airway autoimmunity have a distinct profile of B cells compared to those without. Our project aims to explore the role of B cells, in the development of airway autoimmunity in severe asthma patients with uncontrolled symptoms.

This award is funded by the Canadian Allergy, Asthma and Immunology Foundation, Canadian Lung Association and the Canadian Respiratory Research Network.

GRADUATE STUDENT AWARDS IN ASTHMA

Awardee: Nadia Abzan, PhD Candidate
Project Title: *Development of 3D in vitro lung airway models to investigate the role of hypoxia in airway remodeling in asthma*
Amount: $30,000

Lay Summary: Asthma is a chronic inflammatory lung disease, and subepithelial fibrosis (SF) is one of its hallmarks. This fibrosis is caused by excessive accumulation of extracellular matrix (ECM) proteins – especially collagen type I. This makes the airways become thickened and obstructed, leading to tissue stiffening and a reduction in lung function. Obstructed airway reduces oxygen supply to the tissues. Evidence shows that low oxygen concentration in the lungs (known as "hypoxia") regulates the production of ECM proteins (such as collagen type I), enzymes, etc.
The interactions between the ECM and tissue-resident cells, the mechanisms driving ECM alternations in asthma, and the role of oxygen in this process are poorly understood. This research will be the first to integrate two novel technologies, multimodal Raman microspectroscopy and Second Harmonic Generation (RM-SHG), and high-resolution Nonlinear Optical Microscopy (NLOM) to understand fundamental mechanisms associated with low oxygen levels (hypoxia) and ECM alternation in asthma.

This award was jointly funded by Asthma Canada and the Canadian Allergy, Asthma and Immunology Foundation (CAAIF).

GRADUATE STUDENT AWARDS IN ASTHMA

Awardee: Courtney Marshall, PhD Candidate
Project Title: *Sex as a biological variable in immunomodulation of airway inflammation by Innate Defence Regulator (IDR) peptides*
Amount: $5,000
Lay Summary: Asthma is the most common chronic respiratory disease affecting nearly 3 million Canadians including children. Around 15% patients do not respond to available steroid therapies and represent the major burden of asthma accounting for annual healthcare costs of $2B. Also, common steroid therapies can increase the risk of lung infections, which can make asthma worse. New therapies are urgently needed that can alleviate steroid-unresponsive disease without compromising the ability to resolve infections.
There is a clear sex bias in asthma, for example adult females experience greater disease severity and are more likely to develop steroid-resistance, compared to males. These sex-related differences are largely ignored during drug development. Effective development of new treatments must consider the differences in disease and response to therapy between females and males.
This study focuses on new molecules known as innate defence regulator (IDR) peptides, which can control both inflammation and infection. We have shown that IDR peptides improve breathing capacity in an animal model of asthma, and control cellular processes linked to steroid unresponsiveness. This project aims to develop IDR peptides as a new therapy for asthma, by examining the effects in both females and males concurrently. This research will directly support the development of a new IDR peptide-based therapy for asthma, by taking into consideration how the treatment affects females compared to males. It is entirely possible that we will need to develop sex-specific treatment protocols to provide the most efficient care for asthma sufferers.
Insight into the fibrotic responses in asthma with an unprecedented level of spatial and biochemical specificity will drive the identification of biomarkers active in disruptive airway remodelling and support therapeutic development minimizing the formation of scar tissue observed through the excessive burden of SF.

This award was jointly funded by Asthma Canada and the Canadian Allergy, Asthma and Immunology Foundation (CAAIF).

GRADUATE STUDENT AWARDS IN ASTHMA

Awardee: Mojdeh Matloubi, PhD Candidate
Project Title*: Investigating the role of airway epithelial cell (AEC)-derived semaphorin3E in chronic type-2 high and steroid-resistant type-2 low models of asthma*
Amount: $27,000
Lay Summary: Asthma is a major health concern in Canada, while inhaled corticosteroids (ICS) are the first-line treatment for persistent asthma, some patients have a poor response to these drugs. This condition is known as steroid-resistant asthma (SRA), with type 2-low (neutrophilic) asthma being a major phenotype of SRA. Understanding the mechanisms behind this resistance is crucial for developing better treatments.
Our research focuses on Semaphorin3E, a protein that our lab has found to reduce asthma severity in preclinical models. Sema3E decreases airway sensitivity, inflammation, and lung tissue scarring. Healthy human lungs naturally produce Sema3E, primarily from airway epithelial cells (AECs). However, in severe asthma cases, Sema3E levels are lower, correlating with decreased lung function, indicating its role in maintaining lung health.
Using two chronic (type-2 high) eosinophilic and (type-2 low) neutrophilic asthma models, we aim to study the effects of AEC-derived Sema3E on asthma. We will also compare the impact of Sema3E with dexamethasone, and explore the combination of both treatments.

This award was jointly funded by Asthma Canada and the Canadian Allergy, Asthma and Immunology Foundation (CAAIF).

GRADUATE STUDENT AWARDS IN ASTHMA

Awardee: Ali Mozaffaripour , MSc Candidate
Project Title: *Evaluating small-airways remodeling and response to therapy in patients with severe asthma using 129Xe MRI ventilation texture features.*
Amount: $7,500
Lay Summary: Asthma is a chronic lung disease characterized by airway remodelling, chronic inflammation, airway wall thickening, and lumen narrowing. Several clinical tools exist to help diagnose and monitor airway dysfunction. However, these approaches provide measurements that are relatively insensitive to small-airways dysfunction and its associated patchy ventilation which is believed to drive asthma symptoms and worsening. To address this gap, our project proposes the use of pulmonary functional MRI with inhaled hyperpolarized 129Xe gas. This method has shown promise in previous studies for detecting airway dysfunction with high sensitivity. By tracking small-airways abnormalities, we have an opportunity to enhance our understanding of how the airways respond to asthma therapy. This information will help focus new treatments targeting small-airway abnormalities which we think will lead to better asthma patient outcomes overall. 129Xe MR images will be analyzed using texture analysis—an image analysis technique to determine if the patterns in the MRI reveal abnormalities in lung ventilation due to asthma. By employing machine learning models to these texture features, we aim to identify which are most indicative of changes in the airways, potentially outperforming traditional clinical measurements. This information will be vital in guiding improved treatments for asthma, leading to better patient outcomes.

This award was jointly funded by Asthma Canada, the Canadian Allergy, Asthma and Immunology Foundation (CAAIF) and the Canadian Institutes of Health Research's Institute of Circulatory and Respiratory Health (CIHR-ICRH).

GRADUATE STUDENT AWARDS IN ASTHMA

Awardee: Ikebek Peter, MSc Candidate
Project Title: *Exploring the molecular interactions between early-onset asthma and cow's milk allergy*
Amount: $15,000
Lay Summary: Childhood asthma and food allergies frequently occur together, affecting millions of children globally. Studies show that 4-8% of asthmatic children also have food allergies, and about 50% of children experiencing allergic reactions with respiratory symptoms have food allergies. Despite this common overlap, the reasons behind this connection or how these conditions influence each other at a molecular level remain poorly understood. This study aims to uncover the molecular link between cow's milk allergy (CMA) and worsening asthma symptoms.
We hypothesize that specific components of cow's milk proteins, when broken down during digestion, release fragments that trigger allergic pathways, potentially exacerbating asthma. By focusing on cow's milk as a model system, the aim is to gain insights that can be applied to other food allergies as well. Utilizing advanced computational tools and bioinformatics techniques, this research seeks to identify and analyze these specific protein fragments, simulate digestion processes, and examine how they interact with the immune system. Additionally, a machine learning model will be developed based on data from children with CMA. This model will then be used to help us predict if other milk alternatives or food proteins might also worsen asthma symptoms.
The goal is to improve quality of life for affected children by better understanding how CMA may worsen asthma. Our findings could lead to improved risk prediction, more targeted treatments, and personalized dietary advice for children with both conditions.

This award was jointly funded by Asthma Canada, the Canadian Allergy, Asthma and Immunology Foundation (CAAIF) and the Canadian Institutes of Health Research's Institute of Circulatory and Respiratory Health (CIHR-ICRH).

GRADUATE STUDENT AWARDS IN ASTHMA

Awardee: Sam Tcherner, MSc Candidate
Project Title: *An evaluation of gas-exchange abnormalities in moderate-severe asthma over time*
Amount: $7,500
Lay Summary: Asthma is a disease that inflames and narrows the airways, so treatments usually focus on relieving airway symptoms. However, new research suggests that other parts of the lungs, like blood vessels and the alveoli where gas exchange takes place, might also be involved in asthma. Studies indicate that lung blood vessels may change in severe asthma, similar to serious heart disease. We aim to understand the role of these pulmonary blood vessels and areas of gas exchange in asthma patients.
Using hyperpolarized 129Xe magnetic resonance imaging (MRI) and spectroscopy, we can visualize and measure gas exchange and ventilation in the lungs. We plan to evaluate 129Xe MR gas-exchange measurements in a large group of asthma patients with varying severity and age-matched healthy individuals. We will also follow a subset of moderate-to-severe asthma patients over time to see how their gas-exchange measurements change with treatment.
While gas-exchange abnormalities and blood flow changes are known in many diseases including COVID-19, few studies have examined gas-exchange in asthma with large participant groups. This project will be the first large-scale investigation to explore whether

gas-exchange and blood vessel abnormalities are linked in asthma. By comparing healthy individuals with asthma patients and observing changes over time with treatment, we aim to confirm these gas-exchange abnormalities, potentially establishing them as a new treatable trait in asthma beyond the airways.

This award was jointly funded by Asthma Canada, the Canadian Allergy, Asthma and Immunology Foundation (CAAIF) and the Canadian Institutes of Health Research's Institute of Circulatory and Respiratory Health (CIHR-ICRH).

CAAIF-CSACI FOOD ALLERGY RESEARCH GRANT

Awardee: Dr. Alberto Caminero
Project Title: *Exploiting microbial allergen metabolism to improve oral immunotherapy safety and outcomes*
Amount:$50,000
Lay Summary: Peanut (PN) allergy is the most prevalent food allergy in Canadian children and the major culprit of food-induced anaphylaxis. There is no cure for food allergy and the standard medical advice is allergen avoidance. However, there is a high rate of accidental exposures.
Oral immunotherapy (OIT) is the only treatment for food allergies that can change the way the immune system responds to allergens. It works by giving patients tiny amounts of the food they are allergic to help them become less sensitive. However, OIT often causes side effects, particularly in PN-allergic patients, and rarely results in the immune system being able to fully tolerate the food. Thus, therapeutic interventions improving OIT safety and outcomes are needed.
The use of bugs (bacteria) with beneficial properties (probiotics) has been proposed in OIT. Our central hypothesis is that probiotics can improve OIT outcomes through efficient digestion of food allergens. We will characterize PN-degrading bugs with probiotic-like characteristics (Lactobacillus) and evaluate their capacity to reduce allergenicity. The beneficial properties of these bacteria will be tested in animal models of OIT.
Our goal is to design probiotic combinations with the potential to increase OIT safety and adherence in high-risk allergic patients through allergen digestion. Our proposal can potentially help patients in achieving a safe and successful OIT. Moreover, the probiotic can be used for PN removal in the household environment and food preparation industry. This approach is key to avoid PN cross-contamination to other foods and reduce accidental exposures, a major concern in allergy.

CAAIF-CSACI FOOD ALLERGY RESEARCH GRANT

Awardee: Dr. Lisa Reynolds
Project Title: *Investigating the impact of intrapartum antibiotic prophylaxis on the development of oral tolerance to food antigens in early life*
Amount:$50,000
Lay Summary: To stop the rise in new cases of food allergies we need to understand factors that contribute to allergy development. In people with food allergies the immune system becomes activated after being exposed to the problem food, causing allergy symptoms. This inappropriate immune activation often begins in infancy, where the system fails to learn *not* to become active after eating that particular food. In healthy people who do not have allergies a process occurs called 'oral tolerance', where after eating different foods, their immune system essentially learns not to mount an allergic reaction to these same foods later in life. Oral tolerance starts to develop early in life, as soon as we get exposed to different foods through breast milk and through the introduction of solid foods. We have learned a lot about the immune cell types involved in oral tolerance development

from experimental studies in mice, however, much of this knowledge comes from studies of *adult* mice, not from *young* mice. The immune system functions differently in young animals as it is still developing, and exposure to breastmilk impacts cell types involved in oral tolerance.
One factor that may impact the process of oral tolerance development is exposure to antibiotics: pregnant females in North America are commonly given intravenous antibiotics prior to and during labour (intrapartum antibiotic prophylaxis). We will use model models to investigate whether this type of early life antibiotic exposure impact's the infant's ability to develop oral tolerance to food substances during early life.

CAAIF-CSACI RESEARCH GRANT IN ALLERGY & CLINICAL IMMUNOLOGY

Awardee: Dr. Matthew Swarski
Project Title: *Exploring the Utility of 3-Bromotyrosine , a Urinary Biomarker, in assessing Disease Activity in Pediatric Eosinophilic Esophagitis: A Pilot Study*
Amount:$50,000
Lay Summary: Eosinophilic esophagitis (EoE) is a disease characterized by inflammation in the esophagus from eosinophils, which are a type of white blood cell. Symptoms may vary with age and include food refusal, vomiting, abdominal or chest pain, difficulty swallowing, and food impaction. The incidence and prevalence of EoE in the pediatric and adult population is sharply growing. Parents of patients with eosinophilic gastrointestinal disorders (which includes EoE) perceived their children to have significantly lower emotional and school health-related quality of life scores than youth with a variety of chronic conditions including cystic fibrosis, epilepsy, and type 1 diabetes mellitus. Long-term sequelae of EoE can include esophageal strictures leading to food impactions and may require serial dilatations. The gold standard for diagnosis, management, and monitoring of EoE is through serial esophageal biopsies. There are heightened risks to frequent endoscopies in pediatrics due to the need for general anesthesia with each endoscopy. These repeat procedures put extra strain on endoscopic resources in an healthcare system where wait times are already long. Previous research has determined that there are urine and serum biomarkers that are associated with disease activity. The primary objectives of this pilot study is to explore the use of urine 3-bromotyrosine levels and serum cytokine levels as biomarkers of disease activity as measured from esophageal biopsies, visual changes in the esophagus during endoscopy, and patient symptoms measured in a previously-validated score. At McMaster University, approximately 70 patients are followed at the Pediatric Eosinophilic Esophagitis Clinic. These patients undergo upper endoscopy with biopsies approximately every 6-12 months to re-evaluate their disease activity. We anticipate that 50 patients will agree to study recruitment. With a study duration of 2 years, it is estimated that 100-200 urine samples, serum samples, and symptom surveys will be collected. The urine samples will be analyzed at McMaster University which has the appropriate facilities and expertise to conduct a metabolomics study. The cytokine levels will be sent to a McMaster-associated laboratory in British Columbia. Clinical data will be collected prospectively as well as from the patient medical record which will include demographics, disease progression and therapies, endoscopic findings, and biopsy results. Statistical analysis will be performed in collaboration with a statistician at McMaster University. We intend to develop a scoring system based on urine and serum cytokine levels as a predictor of eosinophilic-predominant inflammation in the esophagus. This novel validation study can strengthen Canada's reputation as a nation committed to cutting edge translational research which will directly improve the quality of life of patients with EoE by decreasing their need for frequent, invasive testing.

CAAIF-CSACI RESEARCH GRANT IN ALLERGY & CLINICAL IMMUNOLOGY

Awardee: Dr. Manali Mukherjee
Project Title: *Investigating the role of regulatory B cells in severe asthma patients with airway autoimmunity*
Amount: $50,000
Lay Summary: Asthma is a common lung disorder where patients experience difficulty breathing, and corticosteroids are the standard treatment to reduce the inflammatory cells causing these symptoms. However, in some patients, neither corticosteroids nor expensive targeted antibody therapies work, leaving them symptomatic and unwell, which significantly adds to healthcare costs. We believe that these patients may have a different type of inflammation in their lungs that is not addressed by current therapies. One possibility is the development of autoimmunity, where rogue antibodies are generated as part of ongoing inflammation. These antibodies attack the body's own tissues, causing further inflammation. B cells, a type of immune cell, generally produce antibodies. They can either protect the body from infections or, in some cases, contribute to autoimmune diseases by attacking the body's tissues. Regulatory B cells help prevent the production of rogue antibodies, particularly during times of high inflammation. We have observed that severe asthma patients with airway autoimmunity have a distinct profile of B cells compared to those without. Specifically, a reduction in a type of regulatory B cell, known as CD5+ B cells, has been noted in these patients. Our project aims to explore the role of B cells, particularly regulatory B cells, in the development of airway autoimmunity in severe asthma patients with uncontrolled symptoms.