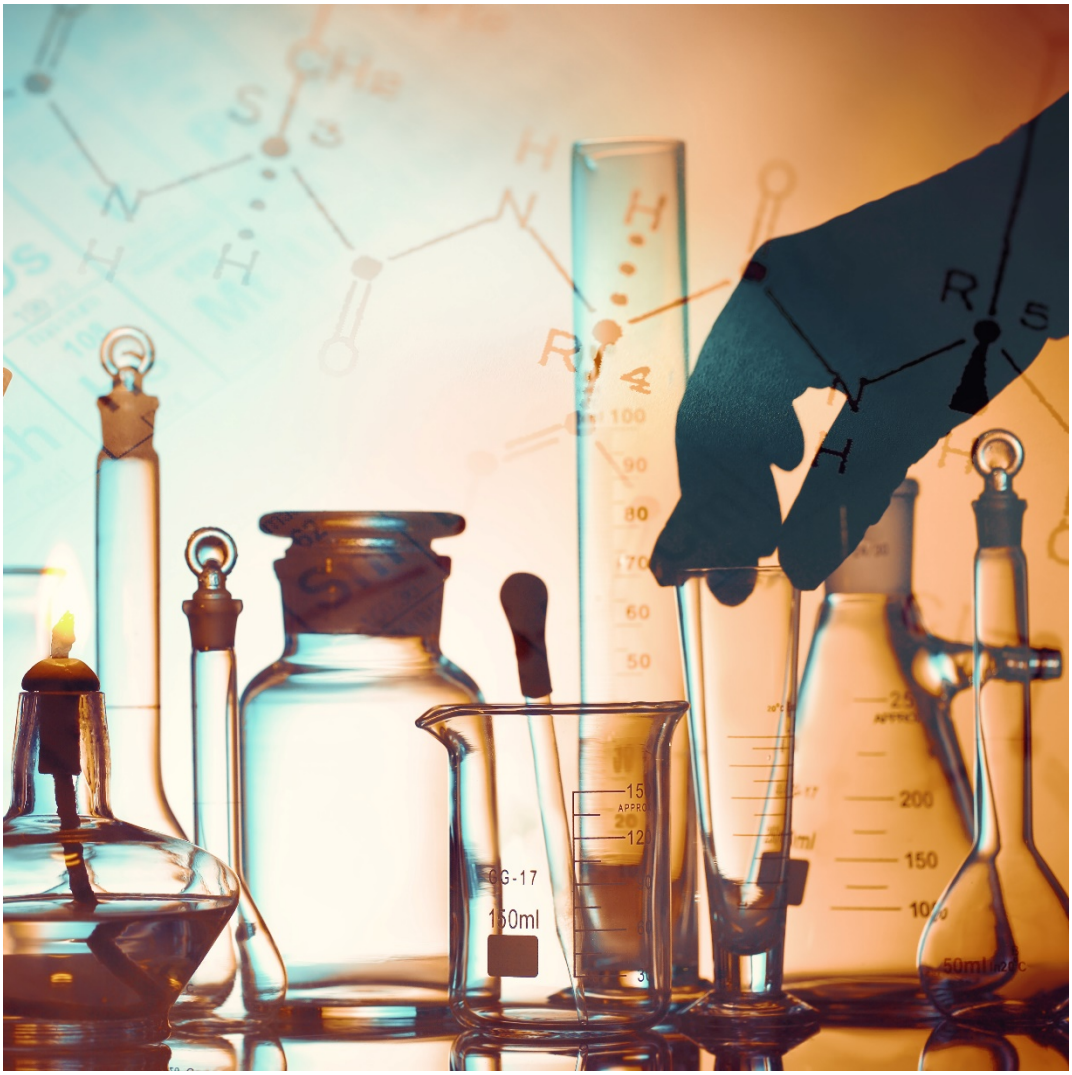
Office of Dietary Supplements Scholars Symposium

February 22, 2022



Program & Abstracts

National Institutes of Health
Office of Dietary Supplements

NIH Office of Dietary Supplements Research Scholars Symposium *Virtual*

Tuesday
February 22, 2022
10:00 a.m. – 2:00 p.m. ET

Agenda

10:00 a.m.	Welcome *Joseph M. Betz, Acting Director of the Office of Dietary Supplements*
10:05 a.m.	Overview of the ODS Scholars Program *Patricia A. Haggerty, Director of Grants and Extramural Activities, ODS*
10:15 a.m.	Complement activates an autocrine Vitamin D system that recruits a defined transcription factor network to shut down pro-inflammatory programs of Th1 cells *Daniel Chauss, NIDDK*
10:45 a.m.	The role of oleic acid supplement on reducing the risk of brain tumor formation in mice *Adrian Lita, NCI*
11:15 a.m.	Impact of taurine on the gut microbiota in health and disease *Apollo Stacy, NIAID*
11:45 a.m.	Modulation of epigenome and cellular pathways in the aging retina by diet and micronutrient supplementation *Anupam Mondal, NEI*
12:15 p.m.	Break
12:45 p.m.	Maternal prenatal omega-3 supplementation and infant obesity and atopic outcomes *Danielle Stevens, NICHD*
1:15 p.m.	Dietary supplementation reference material development at the National Institute of Standards and Technology *Hugh V. Hayes, NIST*
1:45 p.m.	Wrap-up *Patricia A. Haggerty, ODS*
2:00 p.m.	Adjourn

Abstracts

Scholar: Daniel Chauss
Mentor: Ben Afzali

Complement activates an autocrine Vitamin D system that recruits a defined transcription factor network to shut down pro-inflammatory programs of Th1 cells

Background: Pro-inflammatory CD4+ T helper (Th)1 cells clear pathogens effectively but cause excessive tissue injury if not shut down appropriately. The complement (C') system both induces Th1 differentiation and their shutdown, but the mechanisms regulating orderly shutdown remain unknown.

Hypothesis: C' receptor engagement recruits transcriptional regulators essential to Th1 shutdown.

Methods: Multi-modal profiling of activated, or patient-derived Th cells, psoriatic skin, and SARS-CoV2-infected tissues was carried out by epigenome profiling, RNAseq, network modeling, phospho-arrays, confocal, and regulator knockdown.

Results: C' receptor signaling induced the vitamin D (VitD) receptor (VDR) and CYP27B1, the enzyme that activates VitD, allowing T cells to both fully activate and respond to VitD. Active VitD shut down IFN-γ production by Th1 cells and induced IL-10. This was mediated by activation of IL-6 production by T cells and signaling through STAT3. Mechanistically, VitD reprogrammed the Th1 transcriptomes by forming super-enhancers and recruiting a transcription factor (TF) network consisting of VDR, c-JUN, STAT3, and BACH2. We mapped genome-wide targets of these TFs by CUT&RUN/Tag. As proof of principal, psoriatic skin treated with VitD induced BACH2 in Th cells, and genetic deficiency of either BACH2 or STAT3 inhibited IL-10 produced in response to VitD. Bronchoalveolar lavage fluid of COVID-19 patients, a C'-rich environment, showed excessive Th1 skewing and perturbation of the VitD-regulated program of genes.

Conclusion: We identified a C'-recruited autocrine VitD system as key to Th1 shutdown and indicate the potential for adjunct therapy with VitD in hyper-inflammatory syndromes, e.g., COVID-19.

Scholar: Adrian Lita
Mentor: Miorara Larion

The role of oleic acid supplement on reducing the risk of brain tumor formation in mice

The use of dietary supplements has dramatically increased as an approach to maintain health and prevent disease such as cancer. Previous associations of olive oil intake with decreased cancer risk were correlative and masked by the presence of additional components such as phenols which are usually present in olive oil. Moreover, there is no comprehensive study of olive oil and risk of brain tumors. In this proposal we plan to elucidate whether or not oleic acid, the main monounsaturated fatty acid present in olive oil provides a protective role in preventing or delaying tumor growth in vivo and the mechanisms associated with this. The general hypothesis for this proposal is that omega-9 fatty acid supplements have a protective role against tumor initiation and maintenance, due to its pro-apoptotic effects. This hypothesis is based on evidence that oleic acid is inducing apoptosis of brain tumor cells that have a metabolic defect induced by mutations in isocitrate dehydrogenase gene. In this proposal, however, we plan to study the effect oleic acid on healthy mice and mice that are healthy and taking the supplements but then, are inoculated after a period of 14 days or longer with tumor

cells. This will test the hypothesis that presence of oleic acid in the diet of healthy mice is sufficient to attend large amount of oleic acid in the brain and prevent tumor formation. It will also allow us to look for mechanisms by which oleic acid induces a lipidome that is unfavorable for tumor growth. We are applying LC/MS metabolomics profiling to determine the lipid changes in the plasma as well as brain tissue and to quantify oleic acid in different organs and blood in order to determine its bioavailability and mechanism of action in preventing the initiation of brain tumors. At the end of this study, we expect to have a complete understanding of the mechanism by which oleic acid protects the normal brain and prevents/delays the tumor initiation. The completion of this proposal would inform on mechanisms by which oleic acid provides health benefits towards acquisition of a devastating disease such glioma. This topic is of high interest in both basic research and clinical community since gliomas are very aggressive brain tumors with no known dietary risk factors. Due to the focus of my proposal and the applicability in the clinical settings, I feel that the Office of Dietary Supplement's call is an excellent fit for my proposal.

Scholar: Apollo Stacy
Mentor: Yasmine Belkaid

Impact of taurine on the gut microbiota in health and disease

Intestinal infections are a major health burden for which antibiotics can be a life-saving therapy. Antibiotics, however, cause collateral damage to the gut microbiota, a first line of defense against gut pathogens, and moreover, the growing spread of antibiotic resistance has rendered many of these drugs ineffective. Therefore, an appealing alternative to antibiotics is to leverage the microbiota's intrinsic defenses, defined as colonization resistance. Towards this goal, one potential strategy is to nourish the gut microbiota with prebiotics, or dietary supplements that serve as microbial nutrients. However, the identification of novel prebiotics is hindered by the gut microbiota's vast metabolic diversity. Recently, I developed a preclinical model to unveil nutrients that the host deploys to enhance colonization resistance. Using this approach, I discovered that an amino acid-like molecule, taurine, can be co-opted as a dietary supplement to enhance host resistance to pathogens. Collectively, my preliminary studies support a model where the microbiota degrades taurine to sulfide, and sulfide in turn inhibits aerobic respiration, a highly efficient growth strategy widely exploited by gut pathogens. While my data strongly support dietary taurine as being sufficient to stimulate sulfide production, I have yet to demonstrate that this function is indeed required for enhanced colonization resistance. Furthermore, the impact of taurine-derived sulfide on the gut microbiota, including aerobic respiration by its own community members, has not been fully explored. Thus, my central hypothesis is that taurine-driven sulfide production by the microbiota inhibits aerobic respiration in the gut, not only by gut pathogens but also by the gut microbiota. To test my hypothesis, I propose to establish two gnotobiotic (defined) communities, one with and one without the ability to produce sulfide from taurine. With these two communities, I will be able to disentangle the impact of taurine and taurine-derived sulfide on the gut microbiota in health (Aim 1) and on a defined gut pathogen (Aim 2). This work is directly in line the Office of Dietary Supplements' mission ("to strengthen knowledge and understanding of dietary supplements…to foster an enhanced quality of life and health") and has important implications for the development of novel therapeutic approaches to combat foodborne and multidrug-resistant pathogens based on dietary supplementation.

Scholar: Anupam Mondal
Mentor: Anand Swaroop

Modulation of epigenome and cellular pathways in the aging retina by diet and micronutrient supplementation

The etiology of aging is multifaceted. At old age, many cellular processes lose fidelity, leading to functional aberrations and elevated disease risk. In the aging retina, epigenomic changes are a key hallmark that can modify gene regulation and initiate damage including mitochondrial dysfunction. Clinical trials and epidemiological studies have found diet and nutrients moderate aging related pathologies including age-related macular degeneration, however the mechanisms underlying such strategies remain obscure. We hypothesize that nutrients modulate the aging phenotype through epigenomic reprogramming. Therefore, in this proposal we aim to characterize the epigenomic and mitochondrial responses to dietary interventions in the mice retina for up to 12 months commencing at one year of age. Our study design involves diet regimens formulated to contain the Age-Related Eye Disease Study Research (AREDS 1 and 2) supplements, vitamin B supplements, Mediterranean diet or high fat diet. We will analyze the retinal transcriptome, DNA methylome and chromatin accessibility landscapes from control and treated animals at 12, 18 and 24 months of age. By integrating the multi-omics analysis with retinal structure and function assays, we propose to deduce the modalities of nutrient mediated epigenome reprogramming in the context of aging. The anticipated findings from these studies should enhance our understanding of how diet composition influences health through molecular interactions.

Scholar: Danielle Stevens
Mentor: Pauline Mendola

Maternal prenatal omega-3 supplementation and infant obesity and atopic outcomes

Maternal nutritional exposures during pregnancy are hypothesized to have a lifelong impact on offspring chronic disease risk. Studies suggest that prenatal nutritional exposure to omega-3 may prevent the development of atopy and obesity, with some population subgroups benefitting more from supplementation than others. The goal of the proposed study is to examine the association between omega-3 supplementation during pregnancy and early indicators of offspring obesity and atopy. To achieve this goal, we leveraged existing data and biospecimens from the B-WELL-Mom study, a prospective pregnancy cohort following 311 women with and 107 women without asthma throughout pregnancy and the postpartum and their offspring using in-person assessments and questionnaires, chart abstractions, and daily diaries. Exposure was maternal usual dietary intake of omega-3 from up to five ASA-24 dietary assessments combined with daily diary measures of omega-3 supplementation during pregnancy. Outcomes were infant obesity measures (weight [grams], lean and fat mass [grams], percent fat mass) obtained from an in-person exam and air displacement plethysmography at birth and 4 months, and infant atopic measures (wheeze, cough, asthma, food allergy, or eczema) obtained via maternal report at 4 months. G-computation was used to target population contrasts in the mean/risk for our infant outcomes by potential prenatal omega-3 supplement interventions, controlling for maternal characteristics. In the short-term, the proposed study will provide information to inform studies of fetal programming mechanisms and omega-3 supplementation during pregnancy. In the long-term, the proposed study will inform clinical guidelines for supplementation and dietary intake of omega-3 intake during pregnancy, thereby reducing chronic disease risk and improving population health.

Scholar: Hugh V. Hayes
Mentor: Catherine A. Rimmer

Dietary supplementation reference material development at the National Institute of Standards and Technology

The National Institute of Standards and Technology (NIST), in collaboration with the National Institutes of Health, Office of Dietary Supplements (NIH, ODS) has developed suites of Reference Materials (RMs) for dietary supplements. These RMs promote experimental rigor and support manufacturing quality control efforts by including value assignments for targeted organic and/or inorganic compounds. As dietary supplement consumption continuously increases worldwide, RMs are critical for method validation to ensure accurate product labeling and consumer safety. This talk will highlight the tools at NIST for dietary supplement analysis which includes calibration RMs, matrix based RMs, and quality assurance programs.