W_TEMP_5002: Nutrient Bioavailability--Phytonutrients and Beyond

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Statement of Issues and Justification

Diet, including nutrients and bioactive components, plays a vital role to improve health and reduce the burden of chronic diseases. This research project includes a team of trans-disciplinary scientists with expertise in biomolecular, clinical, community, and international nutrition. This scientific team will continue to engage in collaborative research at the intersection of basic science and research translation. Of specific focus, the team is addressing critical issues concerning the bioavailability of and mechanisms by which bioactive food components mediate human health, and by extension, evidence-based dietary recommendations that can increase a healthy lifespan. The team will accomplish project goals by testing a myriad of complementary sub-hypotheses that employ various experimental and clinical models to yield expected long-range outcomes that can enhance the health of individuals, communities, and the global population by reducing the risk of malnutrition-associated morbidity and mortality. Indeed, there are numerous chronic diseases and developmental disorders for which risk may be modified by bioactive compounds in our diet. Together, team members define interactions among essential nutrients and non-essential health-promoting nutrients in relation to human health outcomes. This effort requires transdisciplinary approaches to advance knowledge that will lead to effective preventative and therapeutic dietary strategies, especially in vulnerable groups and with consideration of inter-individual responses to dietary factors. Factors determining the absorption/bioavailability and targeted mechanism of actions will be addressed through preclinical and translational approaches in this multi-state effort. A major outcome of this approach is to establish the foundation for evidence-based dietary recommendations for communities and individuals.

Nutrition is a central scientific premise for the promotion of optimal health, including the prevention, treatment and management of disease. The relationship between food, nutrition and health, however, is complex, dynamic, multi-faceted across the entire biopsychosocial framework, and highly affected by biological as well as environmental, socioeconomic, cultural and behavioral factors (US Dietary Guidelines 2020-2025). Global population growth, cultural, and economic factors also mediate access to healthy foods. The complex network of factors contributes to malnutrition, which not only considers deficient intakes of bioactive food components but also consequences of overnutrition or excess intakes. Malnutrition, in all its forms, includes undernutrition (wasting, stunting, and underweight), inadequate vitamins or minerals, and overweightness/obesity (overnutrition) that result in diet-related non-communicable diseases. Importantly, susceptibility to environmental factors, as well as age, gender, race and disease-state may influence bioavailability and absorption of micronutrients.

Both developed and emerging economies experience rising levels of chronic diseases such as obesity, type 2 diabetes, and cardiovascular diseases (Anderson et al., 2019). The etiology of each of these diseases is complex and varied, but a unifying concept is that bioactive food components, and by extension dietary patterns, play a fundamental role to regulate disease risk. Epidemiological evidence suggests phytochemical intake is associated with reduced risk of developing chronic diseases (Xiao & Bai, 2019), however we remain limited in our ability to establish evidence-based nutrition recommendations to achieve optimal health because of their limited bioavailability, complex structure, specificity to influence biomarkers and/or health outcomes, and they often have broad biological targets that influence multiple biomolecular and/or physiological responses (Manach et al., 2009).

Members of this group are expected to advance nutrition knowledge through the application of well-established approaches and experimental techniques, but also through the implementation of novel and innovative tools. These collective approaches are critical to account for the bioavailability and diversity of dietary phytochemicals and their biological activities that often occur with wide inter-individual variability. For addressing bioavailability, examples of novel approaches include: (i) the use of exosomes as carriers of nutrients/phytochemicals that are regulated in their release of these compounds; (ii) the application of nanoparticles and prebiotic fibers to enhance the bioavailability and absorptive efficiency across the intestinal barrier; (iii) the development of transgenic mouse and cell culture systems to assess the bioavailability of exosomes and their cargo in milk; and ; and (iv) the use of site-specific intestinal viral knockdown approaches to determine localized receptor effects. Our team is actively examining a broad number of dietary constituents including, but not limited to, folate, exosomes present in milk and their RNA cargos, phospholipids, zinc, fat-soluble nutrients (vitamins A, D, E, K), various carotenoids, isothiocyanates, polyphenols, and citrus monoterpenes; all of which have important roles in human health and protection against chronic disease.

Alterations in energy metabolism such as obesity, diabetes, and atherosclerosis contribute to the development of cardiovascular disease, the leading cause of death in the United States. Our transdisciplinary approach tackles these conditions with diverse strategies including dietary and behavioral interventions, discovery and characterization of novel bioactive constituents of foods, and the evaluation of the molecular mechanisms behind the effects of (phyto)nutrients in health. Efforts to mitigate the clinical consequences of cardiometabolic disorders are not only warranted, but provide significant promise to achieve healthspan. Outcomes of these studies will help to control the undesirable biological changes including inflammation, fat accumulation, and oxidative distress responses – that can promote alterations in energy metabolism. Others enlisted on this multi-disciplinary team focus their scientific attention on cancer chemoprevention because it is the second leading cause of death in the United States, and ~40% of Americans are estimated to receive a cancer diagnosis in their lifetime (American Cancer Society, 2022). Goals of these investigators are not only to identify and characterize health-promoting dietary constituents and their metabolites, but also their anti-inflammatory and anti-neoplastic functions that can improve intestinal health and alleviate cancer risk or serve as adjuvant therapy for standard-of-care treatments. Chronic inflammation, aging, specific morbidities, dietary patterns, and specific bioactive food components have been associated with improved or decreased brain health. There are more than 600 diseases of the nervous system, such as brain tumors, epilepsy, Parkinson's disease and neural tube defects (NTD) as well as less familiar ones such as frontotemporal dementia (Essa et al., 2016). There is also evidence supporting an interrelationship of poor cognitive health and other disorders. For example, cognitive dysfunction has been recognized as a complication of obesity-associated nonalcoholic fatty liver disease, probably caused by neuroinflammation (Kjærgaard et al., 2021). Proper diet can also play an important role in building and maintaining bone mass throughout life, primarily by providing bone-building nutrients and by influencing absorption and retention of these nutrients. Our team will continue long-standing scientific inquiry on calcium and isoflavones and will expand into other nutrients and bioactive compounds including vitamin D, vitamin K, milk exosomes, and fermentable carbohydrates (i.e., fructooligosaccharides). Application of new and novel techniques and approaches to assess the impact of dietary interventions on bone outcomes through the collaborative and complementary expertise within the research group will afford an unprecedented opportunity for research in this area.

The overarching goal of our Multi-state efforts is to achieve research translation for broad-based nutrition recommendations that can help achieve healthspan for Americans and persons worldwide. However, our team also recognizes that conventional ‘one-size-fits-all’ recommendations have substantial limitations for achieving this goal. Precision nutrition is the conceptual framework that addresses the constellation of integrated factors to influence healthspan and well-being throughout life. Members of this interdisciplinary team are leaders in the application of multi-omics technologies (e.g., (meta)genomics, transcriptomics, metabolomics) towards the study of (phyto)nutrients, including the regulation of their bioavailability and their bioactive functions that thwart disease. For example, the metabolites generated by bacterial populations of the gut microbiota are increasingly recognized for the favorable or unfavorable influences on the pathogenesis of disease and the success of therapeutic intervention. Our team members integrate approaches to study the complex connections of thousands of data points generated through the assessment of metagenomic, metabolomic, and/or transcriptomic signatures of gut bacteria and the human host in disease and with relation to precision nutrition benefits of phytonutrients. These approaches are critical for understanding why different individuals and persons of different races or ethnic groups respond differently to intervention, have different health risks despite similar diets, and will ultimately permit an understanding of the unique biological factors that can predict successful treatment or reduction of risk for chronic diseases.

Importance of Work: There is a need to further understand the independent and interactive role of nutrients and bioactive food constituents in promoting optimal health. Our goal is to provide a clear understanding of the factors that determine their bioavailability and mechanisms of action. This will establish the foundation for evidence-based dietary recommendations to stakeholders that ultimately affect the health of our nation and the world. The opportunity for our experts to share knowledge, techniques and resources is central to achieving our collective goal in a timely, resource-efficient, and strategic manner. Our transdisciplinary approach thereby rapidly advances our understanding of health-promoting dietary approaches having the potential for broader impact on human health, which will be made possible through this multi-state collaboration.

Technical Feasibility of Studying Bioavailability and Bioactivity of Food Components: This W4002 Multi-state group is an extremely diverse group of nutrition scientists across the continental US and Hawaii who have complementary expertise and access to specialized resources. These characteristics uniquely position our Multi-state group to identify the mechanisms and bioavailability of (phyto)nutrients and other bioactive food components. All of the proposed projects involve established methodologies in the respective investigators' laboratories and through this collaborative effort, are feasible (see related work from W4002 and our previous groups). W4002 researchers have established a national and international prominence to study the mechanisms and bioavailability of nutrients and dietary bioactive components important in chronic disease prevention. We have extensive experience in pharmacokinetic modeling of nutrients, bioavailability studies in preclinical models and humans, integrative multi-omics studies, as well as significant expertise in the study of chronic diseases in relation to malnutrition and metabolic disorders in translational models. Our approaches span novel "bench-to-bedside" and "clinic-to-community" innovations to favorably impact the health and welfare of our stakeholders. Many of the proposed methodologies were pioneered by previous W4002 members and will be leveraged in this multi-state effort.

Advantages of a Multi-State Effort for the Study of Bioavailability and Bioactivity of Dietary Bioactive Components: This multi-state effort will provide the vehicle for collaborative efforts towards the investigation of mechanisms at the molecular/cellular level and directly translate these benefits to susceptible populations. The effort and scope of our research would not be possible without the collaborative expertise of each multi-state station. Indeed, defining the bioavailability and bioactivity of dietary bioactive components requires a transdisciplinary approach to achieve research translation. The input of each station enlisted on this project will promote synergy to address knowledge gaps of importance to human health by combining efforts and expertise, and sharing resources unique to each individual station that will support the expected successful completion of this multistate effort. The issues to be addressed and benefits gained are expected to exceed those achieved by any single station, thus potentiating national and global impact. Researchers in this group collaborate routinely, either formally through competitive proposals, sharing authorship on peer-reviewed publications, and presenting invited seminars at each other's academic institute, or less formally by sharing research protocols and/or resources that can benefit other team members. Since the health issues of this project are addressed through complementary, multi-disciplinary approaches, there is little to no concern of scientific duplication among members' respective institutes. Our members will also produce innovative, state of the art methodologies for understanding the metabolism and roles for dietary bioactive constituents that can promote human health. The breadth and depth of expertise (from basic science to human population studies to outreach/extension) among faculty at major land-grant universities facilitates translational studies. Knowledge gained from W4002 collaborative activities will be disseminated to the scientific community and relevant stakeholders thereby having maximal benefit to public health. Importantly, efforts and focus specific to W4002 are not duplicated in any other multi-state project.

Impact of Research/Endpoints: We expect the multidisciplinary, translational research driven by the W4002 investigators to have significant impact on human health, which will be identified as measurable, scientifically rigorous endpoints. At the broadest level, outcomes of this research will result in evidence-based strategies using foods and/or their dietary bioactive compounds to contribute to optimal health and reduce chronic disease risk. Specifically, expected outcomes will help to establish novel biomarkers for nutrient status, (re)define dietary requirements for Americans, especially specialized and vulnerable cohorts that likely have unique metabolic requirements. Without the research to be undertaken by this multistate group, our understanding of the metabolism and mechanistic role of these health-promoting dietary agents will be significantly hampered. Other endpoints for the W4002 group include collaborative research grants, publications, the organization of scientific meetings, and efforts directed at public outreach and support of local extension leaders in developing important educational materials that translate our research findings.

This multi-state team of researchers are a transdisciplinary team spanning fields of agriculture, food science and technology, molecular/cellular nutrition, clinical nutrition and population health. Together, the team is able to address key issues relevant to food and its bioactive compounds and human health, both in the United States and across the globe.

This research is innovative and novel in that it utilizes a translational approach to understand the role of dietary bioactive compounds, especially those consumed as a "whole food" on optimal health. The collaboration among basic, clinical, epidemiological and extension faculty from diverse academic institutions across the United States affords the opportunity to advance scientific understanding of the role of, and requirements for, nutrients and bioactive food components in maintaining optimal health. Further, our robust scientific interactions, which are possible through this collaborative agreement, afford an opportunity to translate research findings to public health practice in a time and cost-efficient manner.

National Information Management and Support System (NIMSS) Search: A NIMSS search with the keyword “bioavailability” returned 12 active projects. There are no similar regional projects therefore supporting a critical need for multidisciplinary research through this Multi-state project. A recent review of active multi-state projects suggests only one project has the potential for overlap with our efforts, W5122” Beneficial and adverse effects of natural chemicals on human health and food safety.” However, there are several important distinctions between the projects. First, the planned project focuses on dietary constituents to achieve optimal health whereas W5122 addresses issues related to environmental toxicology, cancer, foodborne toxins, and antimicrobials. Our project focuses much more heavily on micronutrients and health-promoting phytochemicals, and with direct consideration of research translation, compared to the W5112. Also, food safety/toxicology is the central theme of their research and is not represented in the focus of our project. Moreover, issues regarding global health, bioavailability and potential interactions among food, nutrients and processing are not addressed by the W5112 group. Without question, the information derived from the proposed research is innovative and unique, and the proposed dissemination of information to both the scientific community and lay public will provide part of the framework on which future nutrient recommendations can be based. Table 1 outlines a list of proposed nutrients and phytochemicals for initial analysis, their biomarkers and endpoints/clinical outcomes.

Related, Current and Previous Work

W4002 researchers have collaborated to make significant contributions towards understanding the role of nutrients and bioactive food components in health. These efforts focused on optimizing health in vulnerable populations domestically and globally. To continue this work, our team will focus on examining bioavailability of dietary bioactives (i.e., nutrients and non-nutrient beneficial compounds), identifying human and environmental factors that affect their absorption and metabolism, and innovative approaches to improve bioavailability and delivery. An important goal is to understand the mechanism of action of bioactives. This group has advanced these areas with multi-disciplinary and translational approaches that span *in vitro* and animal models and human populations using both laboratory-based and bioinformatics/computational methodologies.

1. **Absorption and Metabolism Modeling**

W4002 scientists have developed state of the art techniques to assess the bioavailability and metabolism of several bioactives. These techniques address interactions within the gut microbiome, nutrient bioavailability, and metabolism. Novel methods include use of rare and stable isotopes to precisely monitor nutrients or bioactives, its uptake, distribution into plasma and elimination in urine and feces across different life stages and physiological conditions. We can examine alterations in nutrient metabolism during different physiological conditions, including malnutrition and inflammation. Kinetic modeling and compartmental analysis will be used to assess vitamin, mineral and bioactive turnover rates and metabolism (IN, NE, OR, OH). Bone turnover rates will be used to evaluate predictors of bone formation and resorption during growth and age-related bone loss (IN, OR). OH is also active in developing liquid chromatography–mass spectrometry (LC-MS) methods to facilitate the translation of preclinical studies in rodent models into clinical efficacy for the management of cardiometabolic disorders. Similar approaches have been employed in OR, where LC-MS methodologies for isothiocyanate assessment have been developed to understand differences in the bioavailability of isothiocyanates from supplements vs cruciferous vegetable sources.

2. **Development and validation of methods for assessing status and bioavailability of nutrients and bioactive food components**

Methods are in development to assess nutrient/bioactive bioavailability and to validate them in different conditions and life stages. NE has developed new technologies to assess the bioavailability and distribution of milk exosomes and their RNA cargos in mice. These technologies include the use of mice expressing fluorophore-labeled exosomes in milk, transgenic cell culture systems that secrete genetically engineered milk exosomes, and species-specific polymerase chain reaction (PCR) protocols. OR has utilized zebrafish models to understand the transgenerational impact of zinc status on developmental processes, susceptibility to environmental stresses and chronic disease. OR is also utilizing machine learning methods to help predict dietary intake patterns from models and pre-existing metabolomic data.

3. **Innovative use of model systems for nutrient and bioactive food component bioavailability**

AZ, KS, NY and OR have used *in vitro* digestion/Caco-2, rats and chicken models to study zinc, iron and vitamin A bioavailability. The microbiota of the pig gastrointestinal (GI) tract is comparable to that of the human GI tract, making the pig a suitable animal model for the study of microbiota-health interactions. CA-D has developed pig models with pre-weaning and post-weaning piglets, which allow us to determine how nutrient bioavailability, health, behavior, and brain development are influenced by dietary essential nutrients (i.e., amino acids, micro minerals), bioactives, and other food supplements during healthy or disease challenge conditions. CA-D has used neonatal piglets as a translational model of human infants to study dietary iron bioavailability and metabolism and determine the effects of dietary iron overexposure and prebiotics on gut development and gut microbiota. The CA group customized a programmable automatic milk delivery system that precisely controls feeding rate and nutrient profiles for their animals. The piglet model and the precise milk feeding system are great tools to evaluate infant nutrition. CA-D has also established a pathogen-challenge model to evaluate the antimicrobial activities of bioactive food components, novel feed additives, and micronutrients. This model allows us to test dietary strategies that enhance host resilience and alleviate enteric bacterial infections.

4. **Precision Nutrition- Factors that influence absorption, distribution, metabolism, and excretion (ADME)**

4A. Subgroup differences (age, gender, race, disease-state)

OH is investigating the influence of obesity-related disorders (e.g. metabolic syndrome, nonalcoholic steatohepatitis) on the bioavailability and pharmacokinetics of vitamin E and green tea catechins. Completion of these studies is expected to provide critical knowledge to guide dietary recommendations to effectively manage these disorders that are characterized by inflammatory stress. OR is examining the impact of aging on micronutrient absorption, metabolism and distribution, especially in the context of age-related immune dysfunction.

4B. Microbiome

NE is assessing the interactions between dietary exosomes and the gut microbiome. OH is examining the benefits microbial catechin metabolites that are potentially responsible for the anti-inflammatory activity of green tea. In OR, the impact of age on the microbiome and subsequent impact on age-related changes in nutrient use related to cruciferous vegetable bioactives is an emerging area of research. IN is assessing complex interactions of dietary bioactives, gut bacteria, and the host in chronic inflammation models to better harness the anti-inflammatory potential of food to promote gut health and has developed germ-free and gnotobiotic mice models to study intestinal inflammation. PA has established a rabbit model with chronic intestinal and liver inflammation and a pig model to study the gut microbiome during development of low-grade inflammation. AZ has established a postprandial time course study to model short chain fatty acid production from the gut microbiome in several tissue sites of rats. The interactions of microbiota and host are also assessed in pig models developed in CA to explore the importance of gut microbiome on regulating the overall intestinal health in piglets and young children and in transgenic germ-free mice to evaluate the interactions between dietary indoles and the microbiome. CT has investigated the effect of the gut microbiome between healthy and obesity conditions on the production of blackcurrant metabolites that may exert anti-inflammatory effects. OK is investigating carotenoids in regulation of gut microbiome in mice.

4C. Environmental interactions

AZ is investigating the interaction between noise pollution and sleep on metabolic dysfunction. OR is investigating the interaction of micronutrient deficiencies, like zinc with susceptibility to arsenic toxicity. This work is being investigated using in vitro models, in vivo rodent and zebrafish models, and in human populations with high risk for zinc deficiency and arsenic well-water contamination.

4D. Food Sources and Processing

The food and nutrition industries are constantly seeking strategies that expand healthy alternatives for consumers. Encapsulation is a promising technology to incorporate and deliver bioactives, nutrients and flavors in foods. There are many encapsulation strategies using synthetic or natural materials, but their influence on bioavailability is not fully understood. FL is using legume-based nanoaggregates capable of protecting and dispersing fat-soluble compounds. KS has investigated the impact of extrusion on micronutrient bioavailability. HI has studied the effects of pre-harvest factors and processing on the bioavailability of carotenoids from crops such as papaya and taro. HI has also explored the effects of biopolymer-phytochemical interactions and their implications on physicochemical stability and subsequent delivery. OR discovered differences in bioavailability from whole food sources compared to individual supplements and have determined that food processing alters bioactive bioavailability.

5. **Bioavailability of nutrients and bioactive food components**

5.A. Vitamins and Minerals

5.A.1. Vitamin E

Less than 10% of Americans meet the estimated average requirements for dietary vitamin E (Maras et.al., 2004) and populations with inflammation are especially susceptible to inadequate vitamin E status. Therefore, continued studies in OH are aimed at assessing vitamin E absorption, distribution, and metabolism in healthy individuals and cohorts of increased chronic disease risk. OH has utilized LC-MS techniques to assess vitamin E absorption and pharmacokinetics. UC-D has constructed a kinetic model of human vitamin E distribution and metabolism. These stations will collaborate to extend their observations for future dietary recommendations.

5.A.2. Carotenoids and Vitamin A

Carotenoids are responsible for the vibrant orange and yellow colors of carrots, and sweet potato. PA found that carotenoid concentrations were inversely correlated with obesity and triglyceride levels and positively correlated with high density lipoprotein (HDL) levels in Mexican-American youth (n = ~570). In addition, the investigators found that these correlations between may be influenced by genetic factors. KS is examining the bioavailability of vitamin A from food products made with different commodities (corn, soybean, sorghum, and cowpea and fortified rice). CT has studied protective roles of the carotenoid astaxanthin in nonalcoholic fatty liver disease prevention. OK is exploring the protective roles of carotenoids in chronic inflammation using type 2 diabetic mice.

5.A.3. Calcium and Vitamin D

Vitamin D absorption often low, partially due to limited micellarization in the gut, especially from products that do not control particle size. FL is designing and evaluating nanoparticles to increase vitamin D bioavailability, especially for populations with chronic disease (i.e., chronic kidney disease). RI is evaluating whether serum vitamin D concentrations are associated with serum lead concentrations among pregnant women at high risk for lead exposure. It is possible that a vitamin D deficiency increases bone turnover during pregnancy, releasing lead that has been stored in the bone over years of lead exposure. This research will provide new insight into mechanisms related to how vitamin D may affect circulating levels of lead in pregnant women.

5.B.3. Iron

Iron deficiency is the most common micronutrient deficiency globally and is the primary cause of anemia. KS is examining the bioavailability of iron from food products made from different commodities. Research in CA-D aims to understand regulation of iron metabolism in early life and how iron deficiency and excess affect growth, development (e.g. neuronal development, cognitive functions, gut development), gut microbiota, and host resilience to infections in a piglet model. CA-D has shown that early postnatal iron deficiency altered dendritic complexity of hippocampal neurons and iron excess affected brain metabolism by enhancing purine catabolism. CA-D is investigating the influence of iron deficiency and iron excess on intestinal stem cell proliferation and gut microbiome and whether the adverse effects of dietary iron overexposure on gut microflora can be reverted by the presence of pre- and synbiotics.

5.B.4. Zinc

Zinc deficiency is a highly prevalent deficiency across the world, yet there is still no reliable human biomarker for zinc deficiency. Research in OR has established that damage to DNA is one of the early hallmarks of zinc deficiency in humans, that precedes decreases in zinc plasma zinc. Zinc deficiency has an important impact on health, affecting processes important in growth and development, bone health, immune function, cancer prevention and many others. Work in OR in zinc nutrition and metabolism examines factors that affect bioavailability and health parameters in both model systems and in populations at risk for zinc deficiency.

5.C. Bioactive Food Components

5.C.1. Polyphenols- Green tea catechins, flavonoids, anthocyanins, stilbenoids, cranberry phenolics

Research in OH suggests that green tea extract regulates intestinal lipid absorption, lipid metabolism and may serve as a dietary strategy to attenuate the development of nonalcoholic fatty liver disease. Continued studies in OH are evaluating the bioavailability, metabolism, and mechanisms of green tea catechins in animal models of obesity. Other polyphenol-rich foods (soy, plum, blueberries and blackcurrant) were studied for their protective role in ameliorating bone loss (IN), obesity (ME) and/or nonalcoholic fatty liver disease (CT). ME has studied the effect of anthocyanins and phenolic acids from wild blueberries on chronic diseases. *In vitro* and pre-clinical studies have shown that phenolic acid extracts from wild blueberries promote speed of wound closure, revascularization, re-epithelialization, and attenuate inflammation. IN found that baked anthocyanin-rich purple-fleshed potatoes significantly suppressed colon tumor proliferation in rodents. IN also established rodent colitis models to study the role of anthocyanins and fiber-anthocyanin complexes in improving the barrier function and reducing the intestinal inflammation. Recently PA found that purple-fleshed potatoes prevent and reverse high-fat diet induced inflammation and oxidative stress markers in a pig model. CA-D has tested several phytochemicals extracted from seasonings with promising effects on diarrhea incidence of weaned pigs. OR has studied the effects of isoliquiritigenin, a phenolic compound found in licorice root, on bone metabolism. Licorice root is often consumed by older women based on the belief that, as a botanical estrogen, it attenuates menopausal symptoms, including weight gain and bone loss. We showed that dietary isoliquiritigenin reduced bone resorption *in vivo* and osteoclast differentiation *in vitro,* by mechanisms likely differing from actions of estrogen.

5.C.2. Isothiocyanates/indole-3-carbinol

Isothiocyanates and indoles (sulforaphane and indole-3-carbinol) from cruciferous vegetables have been studied for their potential health benefits (cancer prevention, anti-inflammatory activity). However, their bioavailability in humans is relatively unknown. OR developed sensitive mass spectrometry methods to better understand the distribution of sulforaphane and indole-3-carbinol and their respective metabolites using pre-clinical models and human subjects. OR also studied effects of whole foods versus supplement sources and found that supplements that lack myrosinase, a key enzyme the helps release sulforaphane, have lower bioavailability. Several cancer clinical trials are also underway to test the effects of sulforaphane supplementation.

5.C.3. Bioactive fatty acids

CT found that milk bioactives can alleviate effects of obesity. Clinical trials are underway, which may lead to value-added use of inexpensive dairy co-products rich in milk bioactives that would normally be discarded. Research at CA-D observed that butyric acid derivatives have strong *in vitro* antimicrobial and anti-inflammatory benefits. Research with a disease challenged pig model confirmed that these derivatives can enhance disease resistance of newly weaned pigs by reducing diarrhea and enhancing intestinal integrity. Results can be translated to human research for preventing diarrheal illness. A study in progress in RI suggests that omega-3 fatty acid intake may reduce lead absorption among pregnant women at high risk for exposure.

5.C.4. Bioactive proteins and peptides

Milk proteins have beneficial impacts on gut health, however it is unclear the extent to which milk proteins are bioavailable. Research in OR examines milk protein digestion in infants and adults. We have examined the survival of milk and recombinant antibodies across the digestive tract of infants and differences in survival of peptides in the stomach of preterm and term infants. Recombinant antibodies do not survive within the term and preterm infant digestive tract, but to some extent, milk antibodies do. This demonstrates that milk antibodies are uniquely resistant to digestion, which allows them to exert their protective functions within the gut.

5.C.5. Pre- and Probiotics

CA-D has verified that several probiotic *Bacillus* strains can aid against pathogenic *E. coli* infection and promote intestinal health of young pigs. The potential mechanisms include modulating the host immune responses and promoting the growth of beneficial microbes in the gut. The most striking effects of prebiotics is their ability to reshape the composition of gut microbiota in the host. CA-D research discovered a novel oligosaccharide polymer that reduces diarrhea in young pigs, which can be translated to pediatric diarrheal illness.

5.C.6. Exosome and RNA cargos

NE has discovered that exosomes and their RNA cargos do not exclusively originate in endogenous synthesis but can also be absorbed from foods such as bovine milk and chicken eggs.

6. **Factors that modulate absorption and metabolism**

6.A. Optimizing delivery systems

Nanotechnology has tremendous potential to make high quality, nutritious foods. While nanoparticles are ubiquitous in nature and our food supply, the directed use of nanotechnology in foods is yet to reach its potential and limitations exist. Among suitable nanomaterials, legume proteins offer advantages but new technologies must undergo rigorous characterization with further stability, efficacy, and sensory evaluation before their widespread use in food applications. ME is developing a nanoparticle carrier that encapsulates wild blueberry bioactives for transdermal slow-release delivery. FL is evaluating the efficacy of vitamin D in patients with late stages of chronic kidney disease using legume-based nano-aggregates.

6.B. Nutrient-Gene interactions

NE has shown that dietary depletion of exosomes and their RNA cargos elicit impaired spatial learning and memory, loss of fecundity, changes in the gut microbiome, aberrant purine metabolism, changes in immune function, and changes in the hepatic and muscle transcriptome. These phenotypes are consistent with effects of dietary exosomes in Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways in human peripheral blood mononuclear cells and murine liver, brain, skeletal muscle and placenta and milk/egg (exosome) feeding studies. The ability to study complex food/metabolic interactions that determine nutrient/phytochemical availability is an additional strength of W4002. Previous work in OH and IN have established the role of salivary enzymes and gut microbes on phytochemical metabolism and bioavailability.

Summary

Table 1 shows specific expertise of each station member and Table 2 includes a summary of proposed collaborations. This team is a unique group of researchers with an interest in advancing the science to define the role of dietary bioactives for optimal human health. Our group includes experts in a wide variety of compounds – an appropriate approach since food is a complex and integrated mix of nutrients and bioactives. Our technological expertise is diverse and includes cell culture, tissue culture, animal models, imaging, epidemiology and clinical trials. This diversity provides fertile ground for informal and formal collaborations. The collaborative activity of our group has allowed us to impact the fields of agriculture, food, and health through high-impact publications, presentations and stakeholder outreach and engagement.

Objectives

1. Determine the bioavailability (absorption, distribution, metabolism, elimination) of nutrients and bioactive food components.
2. Determine the efficacy and mechanisms of action of nutrients and dietary bioactive compounds towards improved health. Comments: We have also included specific expertise each station member brings to this collaborative effort (Table 1). A summary of proposed collaborations and interactions are listed (Table 2). This W4002 team is a unique group of researchers with an interest in advancing the science in defining the role of dietary bioactive compounds for optimal human health. This group includes experts in a wide variety of nutrients and dietary bioactive components – an appropriate approach given that the food we eat is a complex and integrated mixture of nutrients and bioactives. Further, the research technological expertise of our group is also diverse and includes expertise in biomolecular techniques, integrated multi-omics approaches, and applied sciences methodologies that incorporate cell/tissue culture models, experimental studies in rodents, epidemiological approaches, and controlled clinical trials towards a goal of research translation. This diversity provides fertile ground for collaborations in the form of informal conversations as well as formal and collaborative grant proposal development. The value of collaborative activity of the W4002 Multi-state group has allowed its members, or teams they are a part of, to obtain more than $54 million in extramural funding and over 340 scientific publications during the past 4 years (10/1/2017-9/30/2021).

Methods

Objective 1: Determine the bioavailability (absorption, distribution, metabolism, elimination) of nutrients and bioactive food components.

1. Absorption and Metabolism Modeling

Methods to model absorption and metabolism include the use of rare and stable isotopes for isothiocyanates, lutein (OR) and vitamin E (OH). The use of these isotopes will allow W4002 scientists to precisely monitor each nutrient, its uptake, distribution into plasma and elimination in urine & feces across different life stage and physiological conditions, including physical activity. Our methods also allow us to monitor alterations in nutrient metabolism during different physiological conditions, including malnutrition, inflammation, and physical activity. Some of the proposed studies in zebrafish allow us to quantifiably measure the effect of gut microbial metabolism on the physiological effects of dietary polyphenols. NE will study the absorption and distribution of bovine milk exosomes and their RNA and protein cargos in mice and humans with a particular focus on the blood/brain barrier and placental transfer. This group has developed sophisticated approaches to understanding transport rates, pool sizes, and metabolism parameters using isotopic tracers, kinetic modeling and compartmental analysis as well as statistical models. These approaches will continue to allow us to understand metabolism of bioactive compounds such as labeled compounds bioactives derived from cruciferous vegetables and zinc. Modeling will be used to predict outcomes and design experiments to test predicted outcomes. OH will also examine inflammation and host-microbial interactions on green tea catechin bioavailability using newly established LC-MS methods. Studies will also consider time-dependent changes in catechin pharmacokinetics following chronic ingestion along a trajectory of clinical translation of an anti-inflammatory dietary strategy to address the growing concern of metabolic disorders on human health outcomes. Similar studies by OH are also planned to redefine human dietary requirements of vitamin E and novel recommendations for specialized cohorts including those with chronic disease. These studies will leverage deuterium-labeled alpha-tocopherol in conjunction with LC-MS analytical approaches to assess dose-response relationships of alpha-tocopherol on vitamin E status.

2. Development and validation of methods for assessing status and bioavailability of nutrients and bioactive food components

Methods are under development to assess nutrient and bioactive bioavailability and to validate them in different conditions. In FL, scientists are leveraging the functionality of photonic crystal biosensors for the determination of biomarkers of iron deficiency (i.e. ferritin and soluble transferrin receptor). Studies will be focused on enhancing the number of assays (e.g., retinol binding protein, C-reactive protein) conducted on a single drop of sample, which can be easily measured with the use of a reading apparatus based on smartphone technology, as well as their validation by measuring total allowable error (systematic and random) using established clinical cutoffs. Using the same development paradigm, focus will be also given to the development of low-cost applications (paper-based assays) for the determination of micronutrients (e.g., Fe, Zn, vitamin A) in fortified foods. These sensing applications will be useful of monitoring efforts of populations at risk of micronutrients deficiencies as well as of the quality of foods. KS is working to use an enhanced simulated digestion system to evaluate iron bioaccessibility (Brodkorb et al. 2019) that mimics the oral, gastric, and small intestinal phases of digestion. Rats have been criticized as a model for iron bioavailability, but work in KS has found rats to be more advantageous than believed by some. Thus, the plan is to continue to use this model and discuss their relevance compared to other commonly recommended model systems.

Zebrafish models are a premier model used by toxicologists to study development, but have been underutilized to examine the impact of dietary compounds on developmental and transgenerational processes. Zebrafish will be utilized to examine the influence of bioactives such as zinc and polyphenols across the lifespan in OR. For polyphenols, these studies will address the hypothesis that the gut microbiome catalyzes the production of specific, water-soluble metabolites called urolithins from dietary ellagitannins (OR).

Owing to similarity in digestive physiology and brain morphometry and comparable brain growth dynamic, the domestic pig had been recognized to be a valuable model for pediatric nutrition and neurodevelopment. Research will continue at UC-D to validate the pig model with pre- and post-weaning pigs and to evaluate the efficacy of dietary bioactive components and elucidate their mechanisms of action. AZ will use a rodent model to address whether the increase in overall feeding in response to environmental noise exposure is due to a compensatory reduction in absorption or metabolism. NE will develop a PCR-based technology that distinguishes bovine and human microRNAs that differ by as little as one nucleotide. NE will also develop the following transgenic mice to study the bioavailability of bovine milk exosomes and their RNA and protein cargos: 1) microRNA sensor mice (to assess the tissue delivery of microRNAs), 2) TSG101 conditional knockout mice to study the re-packaging of cargos from milk exosomes into endogenous exosomes, and 3) exosome and cargo tracking mice, which will allow to study the trafficking and cargos of exosomes in murine milk and tissues. The mouse will be used to assess roles of exosomes in obesity and colon cancer, obesity and heart disease, and substance abuse disorders.

3. Factors that influence ADME

Subgroup differences (age, gender, race, disease-state)
Elderly individuals have high susceptibility to micronutrient deficiencies. Researchers in OR will examine age-related differences in zinc absorption and cellular transport in aged mice and zebrafish, and their impact on inflammation and immune function.

Microbiome
The influence of age-related alterations in the microbiome on response to bioactive supplementation and susceptibility to stress will be examined in OR using mouse models and human feeding studies. OR has developed novel MS methodologies for microbial metabolites and integration methods for microbiome and metabolomic data. NE will study the effects of exosomes in bovine milk on the microbiome at four levels: 1) changes in microbial communities, 2) selection of microbes in murine and human fecal samples in exosome-defined minimal media, 3) selection of mutations in microorganisms in exosome-defined minimal media, 4) the roles of microbial RNA cargos in bovine milk exosomes, and 5) milk exosome-dependent changes in the quantity and quality of extracellular vesicles secreted by the gut microbiome. MA will also conduct the study determining the role of microbiome in metabolisms of bioactive compounds and their bioactivities using a rodent model. AZ will perform comparative analyses of the efficacy of different plant-based fibers on altering the gut microbiome and impacting energy and glucose homeostasis, as well as cardiovascular health, use state of the art in-vivo cardiometabolic assessments in mice and rats. UC-D will compare immune cell differentiation (specifically CD4+ T cell subsets and macrophage polarization) between SPF and germ-free mice administered dietary indoles. Causal inference approaches will be used to predict bacteria species responsible for modulating indole-immune crosstalk. Predictions will be experimentally tested by monocolonization studies.

Environmental interactions
Susceptibility to environmental toxins such as air and water pollutants may influence bioavailability and absorption of micronutrients such as zinc. In OR we will utilize cell culture and animal models (mouse and zebrafish) to examine the impact of polycyclic aromatic hydrocarbons and arsenic exposure on zinc metabolism and transport. It is unknown whether noise pollution, which reduces sleep, increases risk for chronic disease and reduces brain function by modifying nutrient bioavailability equally across gender and lifespan. Work in AZ will use an animal model (rat) to test whether sleep loss due to noise exposure reduces memory and increases weight gain by reducing nutrient bioavailability important for brain function. Along with other factors, persistent environmental contaminants have been positively associated with development of chronic disease, particularly obesity and type 2 diabetes. In addition, it was recently reported the interaction of dietary fat and low doses of pesticides on development of obesity and insulin resistance.

Nutrient/gene interactions
The influence of polymorphisms in glutathione-s-transferases and cytochrome P450, and non-coding RNA expression on bioavailability of phytochemicals found in cruciferous vegetables will also be examined in OR. NE will focus on exosome/RNA-dependent gene pathways that play roles in spatial learning and memory and purine metabolism and pathways that link the gut microbiome with human metabolism. CT studies the role of carotenoids, such as astaxanthin, in the regulation of histone deacetylases for the prevention of obesity and its associated conditions.

Processing
A number of approaches can be used to improve bioavailability. For instance, extrusion is a technique that may improve the bioavailability of minerals by decreasing antinutritional factors. In KS, this technique will be leveraged to produce products with increased bioavailability. Nutrients and bioactives with low polarity require dispersion in biliary micelles before absorption in the small intestine. Reduction and homogenization of particle size of different bioactive molecule formulations can enhance their incorporation into biliary micelles, and thus, their absorption in the gut. This enhanced absorption could reduce the amount of bioactive used in food formulations, which instead saves resources, reduce negative effects of bioactives on important food attributes, and limit the potential for toxicity. Scientists at FL and HI will continue with the design and evaluation of different encapsulation and emulsification techniques aimed at enhancing the bioaccessibility and bioavailability of nutrients and bioactives. Chemical and physical processes such as pH shifting, high power ultrasound, microfluidization, freeze and spray drying will be used to design products with superior functionalities, especially for the incorporation of non-polar molecules such as vitamins A, D, and E, resveratrol and lutein.

Objective 2. Determine the efficacy and mechanisms of action of nutrients and dietary bioactive compounds towards improved health.

Obesity and metabolic diseases

CVD
OH is a leader in conducting postprandial studies examining acute hyperglycemia-mediated impairments in vascular endothelial function (VEF). Clinical studies show that postprandial hyperglycemia (PPH) transiently impairs VEF in an oxidative stress-dependent manner that decreases nitric oxide bioavailability, and that dietary interventions can either effectively limit the hyperglycemia stimulus and/or downstream oxidative stress responses that otherwise impair VEF. Planned studies in normoglycemic adults and those with prediabetes will utilize ultrasound-based flow-mediated dilation of the brachial artery to examine bioactive proteins of dairy foods and eggs and dietary phytochemicals (vitamin E, green tea catechins) in regulating postprandial VEF. These studies aim to establish evidence-based recommendations to prevent the accumulation of transient insults to the vascular endothelial that would be expected to contribute to long-term CVD risk.

Cancer
Cruciferous vegetable intake has been associated with decreased incidence of both prostate and breast cancer. OR researchers are examining the impact of bioactive compounds derived from cruciferous vegetables on genetic and epigenetic mechanisms leading to suppression of cancer cell growth. Clinical and biological samples from the clinical trials using broccoli sprout extracts in OR are being used to evaluate the role of cruciferous vegetables and their constitutive bioactive food components (OR) in reducing breast cancer recurrence and prostate cancer risk.

Obesity
NE has developed a transgenic mouse that will allow to track study the trafficking of endogenous exosomes from adipose tissue to the colon and mammary glands, and collect the exosomes for cargo analysis. The mouse will be used to study the effects of obesity on colon and breast cancer, and the role of exosomes in increasing cancer risk in obesity. AZ will use rodent models to test whether environmental factors modify obesity risk and worsen cognition by increasing efficiency of energy utilization and reducing sensitivity to neuropeptides that promote memory and normal energy homeostasis.

Diabetes, Metabolic Syndrome, Fatty Liver Disease
OH has been active investigating anti-inflammatory activities of green tea catechins in obese models of NASH. Evidence suggests that green tea catechins attenuate hepatic NFkB-mediated liver injury through a mechanism involving the gut-liver axis that limits gut-derived endotoxin translation to the portal circulation to prevent hepatic TLR4/NFkB activation to protect against NASH. OH will lead collaborative efforts to conduct studies examining green tea catechins in modulating gut microbiota composition and metabolomic responses that otherwise disrupt enterocyte signaling leading to impaired tight junction protein expression. Translational studies in humans will also examine the extent to which controlled feeding of green tea regulates gut health in relation to improved microbiota composition using non-invasive probes that effectively evaluate gut barrier permeability. Metabolomics studies in both preclinical and clinical models are expected to identify catechins and/or microbial-derived catechin metabolites that are functionally responsible for improvements in gut health in relation to attenuating hepatic inflammatory responses leading to hepatic injury. CT has will study the role of carotenoids and NAD precursors in the prevention and therapy for NAFLD and alcoholic hepatitis via the modulation of bioenergetics and inflammatory/fibrogenic pathways using cell-type specific gene knockout mice.

Gut Health
CA-D and MA will focus on determine the impact of dietary bioactive components, such as, plant extracts, on gut health and physiology with in vitro cell culture models and pig as well as rodent models. Dual benefits will be generated from this work for utilizing the bioactive food components to improve both animal and human gut health. At OR, scientists are investigating whether members of the gut microbiome in zebrafish hydrolyze ellagitannins from pomegranates to urolithins. Urolithins are associated with anti-inflammatory, improved vascular function, lowered blood pressure, and increased efficiency of muscle contraction. NE will study the effects of exosomes in bovine milk on the microbiome at five levels: 1) changes in microbial communities, 2) selection of microbes in murine and human fecal samples in exosome-defined minimal media, 3) selection of mutations in microorganisms in exosome-defined minimal media, 4) quorum sensing, and 5) the roles of microbial RNA cargos in bovine milk exosomes. OSU is examining how various milk proteins, peptides and oligosaccharides affect the gut microbiome, immune protein profile and gastrointestinal symptoms in the elderly, people with lactose intolerance and people with irritable bowel syndrome. OSU is also examining how these components affect key gut cells including enterocytes and macrophages.

Immunity and Inflammation
Chronic inflammation is a common precursor to many chronic disease states. W4002 researchers are examining the impact of bioactive food components on mitigating inflammatory processes. OR is examining the interaction among the microbiome, immunity and zinc status. A particular focus is on identifying bioactive food components to mitigate age-related chronic inflammation in mouse models and in humans. More research will be conducted at UC-D and MA to examine the influences of bioactive components on gut and systemic inflammation caused by infectious diseases. Research will focus on the regulation of both gut microbiome and immunity. NE will study the activation of toll-like receptors (TLRs) receptors by RNAs, encapsulated in bovine milk exosomes, in murine TLR reporter cells and TLR reporter mice; the latter will be challenged with influenza A virus to elicit a strong TLR response.

Malnutrition

The immediate cause of malnutrition includes an inadequate nutrient intake or a specific disease condition that limits the consumption, absorption and utilization of nutrients. In low-resource settings, soil-transmitted helminths (STHs) and food and waterborne protozoans (FWPs) are among the most widespread infectious agents afflicting millions of people worldwide, particularly in marginalized, low-income and resource-constrained regions. At KS and FL, scientists will focus on the design, development and evaluation of enhanced food formulations for emergency relief. In FL, these new food formulas will provide critical nutrients (e.g., omega-3 polyunsaturated fatty acids (PUFAs), through enhanced blends of nutrients of superior quality and absorption profile, while directly addressing STHs and FWPs infections through the functional dispersion of bioactive compounds. This work will transform the ability of world agencies (USAID, WHO, WFP, FAO) to better address undernutrition during emergency episodes or for food supplementation programs. In KS, work will focus on determining the bioavailability of iron from different food aid products such as fortified-blended foods and fortified rice. Results from this work should better inform food aid providers and distributors. UC-D will keep exploring high quality protein food ingredients, which will help to reduce hunger and malnutrition related to protein deficiency.

Neurological Health

Aging, specific morbidities, dietary patterns and specific bioactive food components have been associated with improved or decreased brain function, as evidenced by changes in cognition, memory and learning. W4002 scientists propose to study dietary compounds, including zinc, iron, polyphenols, the zebrafish model (OR), rodent model (AZ), and pig model (UC-D) to determine the effect on behavior, learning, memory and various other measures of cognitive function. These studies will investigate the effects of these dietary bioactive compounds on the brain and plasma metabolome, as well as the fecal microbiome, and their association with these behavioral phenotypes and physical performance. NE will study the transfer of bovine milk exosomes and their RNA cargos across the blood-brain barrier and their roles in spatial learning and memory, and prevention of seizures.

Bone

In OR more research will be conducted to determine the effects of nutrients (e.g., zinc), whole foods (e.g., walnuts), and bioactive food components (e.g., isoliquirtogenin) on bone health using rodent models. In addition, OR will be examining the role of bone marrow adipose tissue, an understudied adipose depot, in regulating bone metabolism, energy balance, and hematopoiesis. Collaborating investigators will utilize existing and yet to be developed data sets from cohort studies and clinical trials to assess the relationship between nutrients/ bioactive food components and disease outcomes and/or surrogate biomarkers of disease risk. Scientists are quantifying mineral and their ratios from National Health and Nutrition Examination Survey (NHANES) and risk of blood pressure and indices of bone health (IN).

Measurement of Progress and Results

Outputs

- Output 1: Additional collaborative projects
- Output 2: Research data
- Output 3: Peer-reviewed publications
- Output 4: Presentations and posters at scientific meetings
- Output 5: Data sharing
- Output 6: Outreach presentations or publications for non-scientific organizations
- Output 7: Annual meeting
- Output 8: Students advised and postdocs trained

Outcomes or Projected Impacts

- Impact 1: Collaborating researchers will have access to shared datasets to test hypotheses related to the role of our targeted bioactive food constituents
- Impact 2: Collaborations to translate in vitro and animal studies to human populations
- Impact 3: Collaborative support in grant development to assure optimal research design particularly in regard to bioactive food constituent measurements
- Impact 4: Shared methodologies regarding measurement of health outcomes and improved human health
- Impact 5: Support for the development of outreach materials that translate research findings for broad based consumption and improved healthcare
- Impact 6: Increased knowledge of the bioactivity of nutrients and dietary bioactive components and their underlying protective mechanisms
- Impact 7: Increased knowledge of biomarkers and determinants of ADME of dietary bioactive components
- Impact 8: Development and publication of models for determining bioactivity and bioavailability of nutrients and other dietary bioactive components
- Impact 9: Building a highly skilled workforce in human nutrition

Milestones

(**1**):Milestone 1: Establish and verify models of bioavailability for bioactive food components involved in improved health (including lysine, iron, zinc, calcium, potassium, vitamin D, B vitamins, vitamin E, vitamin A, exosomes, RNA and plant compounds such as nitrate, flavonoids and isothiocyanates).

(**2**):Milestone 2: Determine the efficacy and mechanisms of action of nutrients and dietary bioactive compounds

(**3**):Milestone 3: Identify and quantify the impacts of factors that affect absorption, digestion, metabolism and excretion (ADME) of nutrients and bioactives

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Outreach Plan

All members of this multistate group will engage in various outreach activities. The type of activity will depend on each member’s expertise and environment. For example, some members will make presentations to professional organizations and the lay public, or will have appearances on local TV and radio stations. Other members will offer research and education opportunities for high school students and teachers. All members will disseminate their research findings through publications in science journals, presentations at science meetings, and through invited seminars. Group members will adhere to the practice of making manuscripts available in the public domain no later than 12 months after publication.

We also plan to invite extension specialists to our next annual meeting scheduled, so that they can learn about the research we’re conducting and there can be discussions on what information is ready for dissemination to the audiences they serve. We hope to continue to try to engage others in our future meetings including extension, industry, and biomedical researchers. If funding and logistics allow, we may also be able to host a symposium, minisymposium, session or something similar at the American Society for Nutrition’s annual conference, Institute for Food Technologists conference, and/or the Food & Nutrition Conference Expo.

Organization/Governance

The recommended Standard Governance for multistate research activities includes the election of a Chair, a Secretary, who will become the chair the following year. Typically the chair hosts the annual meeting. All officers are to be elected for two-year terms (1 year Secretary, 1 year Chair) to provide continuity. Administrative guidance will be provided by an assigned Administrative Advisor and a CSREES Representative.

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Land Grant Participating States/Institutions

NY,AZ,NE,RI,CT,HI,OR,ME,CA,IL,MO,KS,IN,OH

Non Land Grant Participating States/Institutions

Participation

Participant	Is Head	Station	Objective	Research						Extension	
				KA	SOI	FOS	SY	PY	TY	FTE	KA
Amengual Terrasa, Jaime	Yes	Illinois - University of Illinois	1,2	701 702 724	6020 6020 6020	1010 1040 1010	0.20	0.40	0.40	0	0
Blesso, Christopher		Connecticut -Storrs	2	702	3270	1010	0.20	1.00	0.00	0	0
Bruno, Richard	Yes	Ohio - Ohio State University	1,2	702 702 702	1899 2234 3450	1010 1010 1010	0.15	0.00	0.00	0	0

Participant	Is Head	Station	Objective	Research						Extension	
				KA	SOI	FOS	SY	PY	TY	FTE	KA
Dallas, David		Oregon - Oregon State University	1,2	702	5010	1010	0.15	0.00	0.00	0	0
Duca, Frank		Arizona - University of Arizona	1,2	302 305 702	3840 3840 4010	1010 1020 1100	0.10	0.00	0.00	0	0
Ho, Kacie		Hawaii - University of Hawaii	1	502	5010	2000	0.10	0.00	0.00	0	0
Ho, Emily	Yes	Oregon - Oregon State University	1,2	702	2234	1010	0.15	0.00	0.00	0	0
Iwaniec, Urszula		Oregon - Oregon State University	1,2	702	5010	1010	0.15	0.00	0.00	0	0
Ji, Peng		California -Davis : University of California, Davis	1,2	302 305	3510 3840	1010 1040	0.10	0.00	0.00	0	0
Klimis-Zacas, Dorothy		Maine - University of Maine	1,2	702	1120	1010	1.00	0.00	0.00	0.5	702
Lee, Ji-young	Yes	Connecticut -Storrs	1,2	702 702	1129 1129	1040 1010	0.10	0.00	0.00	0	702
Lindshield, Brian L	Yes	Kansas - Kansas State University	1,2	702	6099	1010	0.10	0.00	0.00	0	0
Liu, Yanhong		California -Davis : University of California, Davis	2	302 311	3510 5230	1010 1090	0.10	0.00	0.00	0	0
Natarajan, Sathish Kumar		Nebraska - University of Nebraska	2	702 724 724	1219 1219 1219	1000 1010 1030	0.10	0.00	0.00	0	0
Oaks, Brietta		Rhode Island - University of Rhode Island	2	702	5010	1010	0.50	0.00	0.00	0	0
Reddivari, Lavanya	Yes	Indiana - Purdue University	1,2	702 701	2410 2410	1040 1010	0.15	0.00	0.00	0	0
SanGiovanni, John Paul		Arizona - University of Arizona	1,2	702	7220	1010	0.10	0.00	0.00	0	0
Somavat, Pavel	Yes	Missouri - University of Missouri	2	501 501 502 502 711 711	5010 5010 5010 5010 5010 4099	1510 2020 1510 2020 1510 1510	0.10	0.00	0.00	0	0

Participant	Is Head	Station	Objective	Research						Extension	
				KA	SOI	FOS	SY	PY	TY	FTE	KA
Tako, Elad		New York -Ithaca : Cornell University	1,2	701 702 704 502	5010 5010 5010 5010	1010 1010 1010 1010	0.10	0.00	0.00	0	0
Teske, Jennifer A	Yes	Arizona - University of Arizona	1,2	703 724	3840 3840	1010 1010	0.10	0.00	0.00	0	0
Yang, Jinzeng	Yes	Hawaii - University of Hawaii	1,2	702 702	1030 1010	1040 1010	0.30	0.00	0.00	0	0
Zempleni, Janos	Yes	Nebraska - University of Nebraska	1,2	702	3450	1010	0.10	10.00	0.50	0	0

Combined Participation

Combination of KA, SOI and FOS	Total SY	Total PY	Total TY
502-5010-1010	0.03	0	0
701-5010-1010	0.03	0	0
702-5010-1010	0.03	0	0
704-5010-1010	0.03	0	0
703-3840-1010	0.05	0	0
724-3840-1010	0.05	0	0
302-3840-1010	0.03	0	0
305-3840-1020	0.03	0	0
702-4010-1100	0.03	0	0
702-3450-1010	0.1	10	0.5
702-5010-1010	0.5	0	0
702-1219-1000	0.03	0	0
724-1219-1010	0.03	0	0
724-1219-1030	0.03	0	0
702-1129-1010	0.05	0	0
702-1129-1040	0.05	0	0
702-3270-1010	0.2	1	0
502-5010-2000	0.1	0	0
Grand Total:	**4.15**	**11.40**	**0.90**

Combination of KA, SOI and FOS	Total SY	Total PY	Total TY
702-2234-1010	0.15	0	0
702-5010-1010	0.15	0	0
702-5010-1010	0.15	0	0
702-1120-1010	1	0	0
302-3510-1010	0.05	0	0
311-5230-1090	0.05	0	0
701-6020-1010	0.07	0.4	0.4
702-6020-1040	0.07	0.4	0.4
724-6020-1010	0.07	0.4	0.4
501-5010-1510	0.02	0	0
501-5010-2020	0.02	0	0
502-5010-1510	0.02	0	0
502-5010-2020	0.02	0	0
711-4099-1510	0.02	0	0
711-5010-1510	0.02	0	0
702-6099-1010	0.1	0	0
701-2410-1010	0.08	0	0
702-2410-1040	0.08	0	0
302-3510-1010	0.05	0	0
305-3840-1040	0.05	0	0
702-1010-1010	0.15	0	0
702-1030-1040	0.15	0	0
702-1899-1010	0.05	0	0
702-2234-1010	0.05	0	0
702-3450-1010	0.05	0	0
702-7220-1010	0.1	0	0
Grand Total:	**4.15**	**11.40**	**0.90**

Program/KA	Total FTE
0	0
0	0
0	0
0	0
0	0
0	0
702	0
0	0
0	0
0	0
0	0
0	0
702	0.17
0	0
0	0
0	0
0	0
0	0
0	0
0	0
0	0
0	0
Grand FTE Total:	**0.5**