BIOGRAPHICAL SKETCH

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NAME: Mary Ann Lila

eRA COMMONS USER NAME (credential, e.g., agency login): MA_LILA

POSITION TITLE: David H. Murdock Distinguished Professor and Director, Plants *for* Human Health Institute

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE	Completed	FIELD OF STUDY
University of Illinois-Urbana	B.Sc.	05/1978	Horticultural Sciences
University of Illinois-Urbana	M.Sc.	05/1980	Plant Pathology
University of Wisconsin-Madison	Ph.D.	05/1984	Plant Biology

A. Personal Statement

Over the past two decades, my research has centered on bioactive phytochemical constituents, particularly polyphenolic/flavonoid phytoactives, their capacity to mitigate immunosuppression and inflammation, and the differential efficacies that these compounds exert in individual human subjects. The primary emphases in my team are (1) rigorous structural characterization of phytochemicals and metabolites (2) elucidation of phytochemical interactions that potentiate benefits for human health maintenance, (3) development of functional ingredients that stabilize the bioactive properties of these otherwise ephemeral constituents, (4) individualized responses of subjects to phytoactive agents (tentatively as a consequence of their differential intestinal microbiota profiles, which condition the production of active catabolites), and (5) interpretation of the bioavailability/bioaccessibility of phytoactive metabolites. In this project, I will capitalize on our expertise in flavonoid characterization, intervention preparation and metabolomics in human fluids. I will serve as project director to coordinate the complementary roles of each of the investigators in this project.

B. Positions and Honors

Positions:

1984–1995 Assistant & Associate Professor, Department of Natural Resources & Environmental Sciences, University of Illinois
1991–1992 Visiting Professor, Laboratoire de Phytogenetique Cellulaire, Université de Lausanne, Switzerland
1995-2008 Professor, Department of Natural Resources & Environmental Sciences, Joint appointment, Division of Nutritional Sciences, University of Illinois
1997– 2000 Associate Director, Functional Foods for Health Program, University of Illinois
1999 Visiting Senior Scientist, Plant & Food Research Ltd. (a Crown Research Institute). Palmerston North, New Zealand
2001-2003 Interim Department Head, Natural Resources & Environmental Sciences, University of Illinois
2003–2005 Assistant Dean for Research, College of ACES, University of Illinois
2005–present Vice President, Global Institute for BioEXploration (GIBEX)
2006–2007 Interim Associate Dean for Research, College of ACES, University of Illinois
2007-2008 Director, ACES Global Connect (the international arm of the College of ACES), University of Illinois
2008-present Director, Plants for Human Health Institute, and David H. Murdock Distinguished Professor, Food Bioprocessing and Nutrition Sciences Department, North Carolina State University

Professional Activities & Honors:

1987-1988 Lilly Endowment Teaching Fellowship
1994–1998 Elected National Correspondent, International Association of Plant Biotechnology
1995 Young Faculty Research Excellence Award, College of ACES

1997	AMOCO Award for Innovation in Undergraduate Instruction
1997–1998	ESCOP Leadership Development Fellowship
1997–1998	CIC Academic Leadership Fellowship
1998-1999	Fulbright Senior Scholar Fellowship (in New Zealand)
2000–2002	President, Society for In Vitro Biology
2000–2002	CIES Fulbright Australasia Panel (panel Chair 2002)
2001	Paul A. Funk Recognition Scholarship Award, College of ACES
2003	Elected Fellow, Society for In Vitro Biology
2007	Spitze Land Grant Professorial Career Award, College of ACES
2008–2011	Council for Agricultural Science and Technology (CAST) Board Member
2010-present	David H. Murdock Distinguished Professorship
2020	Babcock-Hart Award, Institute of Food Technologists

Professional Memberships: American Society for Nutrition, Fulbright Association (Lifetime Member & Senior Scholar Fellow), Gamma Sigma Delta, Groupe Polyphenols, INAF (Institut sur la nutrition et les aliments fonctionnels)/International Scientific Advisory Committee, Institute of Food Technologists, International Association of Plant Biotechnology, International Workshop on Anthocyanins (Scientific Advisory Board), Society for In Vitro Biology

C. Contributions to Science

1. Polyphenolic flavonoid compounds have exerted clear anti-inflammatory bioactivities in numerous *in vitro* and *in vivo* trials, but clinical evidence to support the ability to improve performance/alleviate stress-induced immunosuppression and inflammation coincident with strenuous exercise was minimal. Our collaborative team was first to demonstrate that flavonoid intervention prior to and during strenuous exercise produced **gut-derived polyphenolic signatures in plasma and urine** that contributed to immunomodulatory benefits as well as elevated ketogenesis into the resting/recovery period post-exertion, with reciprocal modulation of gut microbiota profile and functionality. I was primary or co-investigator in these studies.

a. Nieman, David C., Nicholas D. Gillitt, Amy M. Knab, R. Andrew Shanely, Kirk L. Pappan, Fuxia Jin, Mary Ann Lila. 2013. Influence of a polyphenol-enriched protein powder on exercise-induced inflammation and oxidative stress in athletes: a randomized trial using a metabolomics approach. *PLoS ONE* 8(8): e72215. doi:10.1371/journal.pone.0072215 PMC3744465 PMID 23967286
b. Nieman, David, Sivapriya Ramamoorthy, Colin Kay, Courtney Goodman, Christopher Capps, Zach Shue, Nicole Heyl, Mary H. Grace, Mary Ann Lila. 2017. Influence of ingesting a flavonoid-rich supplement on the metabolome and concentration of urine phenolics in overweight/obese women. *Journal of Proteome Research* 16:2924-2935. DOI: 10.1021/acs.jproteome.7b00196 PMID: 28631923
c. Nieman, David C., Colin D. Kay, Atul S. Rathore, Mary H. Grace, Renee C. Strauch, Ella H. Stephan, Camila A. Sakaguchi, Mary Ann Lila. 2018. Increased plasma levels of gut-derived phenolics linked to walking and running following 2-weeks flavonoid supplementation. *Nutrients* 10:1718. doi:10.3390/nu10111718 PMID: 30423955
d. Nieman, David C., Nicholas Gillett, Guan-Yuan Chen, Qibin Zhang, Wei Sha, Colin D. Kay, Preeti Chandra, Kristin L. Kay and Mary Ann Lila. 2020. Blueberry and/or banana consumption mitigate cytochrome P450 oxylipin generation during recovery from 75-Km cycling: A randomized trial. *Frontiers In Nutrition* (Sport and Exercise Nutrition Section) 7:121. doi: 10.3389/fnut.2020.00121 PMID: 32850939

2. Food allergies have a detrimental impact on quality of life, can present life-threatening consequences and are of increasing public health concern. Various food allergies are responsible for approximately 125,000 emergency room visits and 53,700 episodes of anaphylaxis each year in the USA alone. The allergic reaction or adverse immune response always occurs in response to certain allergens (allergenic proteins) within a food which are recognized by sensitive individuals as harmful foreign material. Segments of the allergenic edible proteins (epitopes) bind and cross-link to allergen-specific immunoglobulin E (IgE) antibodies on mast cell and basophil surfaces, triggering the downstream cascades responsible for the allergic response. There is intense interest in developing therapeutic strategies that could alleviate the danger and severity of IgE-mediated *or* immune cell mediated allergic reactions. Initially using allergenic peanut proteins to develop the novel strategy, I have served as primary investigator in development of stable (food grade) binding of natural fruit/vegetative plant-derived phytochemical constituents to allergenic epitopes on the proteins to create **protein-phytoactive particles which will attenuate allergic reactions** to protein-rich foods. I was PI for all.

a. Plundrich, Nathalie, Mike Kulis, Brittany L. White, Mary H. Grace, Rishu Guo, A. Wesley Burks, Jack P. Davis and Mary Ann Lila. 2014. Novel strategy to create hypoallergenic peanut protein-polyphenol edible matrices for oral immunotherapy. *Journal of Agricultural and Food Chemistry* 62:7010-7021. doi: 10.1021/jf405773b. PMID: 24758688
b. Plundrich, Nathalie, Brittany L. White, Lisa L. Dean, Jack P. Davis, E. Allen Foegeding, Mary Ann Lila. 2015. Protein-polyphenol interactions in hypoallergenic edible peanut matrices and their stability during simulated pepsin digestion. *Food & Function* 6:2145-2154. doi:10.1039/C5FO00162E PMID:26007692
c. Bansode, Rishipal, Priscilla Randolph, Nathalie Plundrich, Mary Ann Lila, Leonard Williams. 2019. Peanut protein-polyphenol aggregate complexation suppresses allergic sensitization to peanut by reducing peanut-specific IfE in C3H/HeJ mice. *Food Chemistry* 299:125025. doi.org/10.1016/j.foodchem.2019.125025
d. Plundrich, Nathalie, Bethany Cook, Sheila Maleki, Denis Fourches and Mary Ann Lila. 2019. Binding of peanut allergen Ara h 2 with *Vaccinium* fruit polyphenols. *Food Chemistry* 284:287-295. doi.org/10.1016/j.foodchem.2019.01.081

3. A mounting body of *in vitro*, *in vivo*, epidemiological and clinical evidence strongly supports that bioactive phytochemicals (phytoactives) including flavonoids, carotenoids, and alkaloids, whether administered in foods or as pharmaceuticals, are uniquely able to interface with human therapeutic targets in order to combat chronic disease or improve metabolic performance. While the presence, concentrations, and combinations of the key phytoactive compounds are generally correlated to a degree of health protection, paradoxically, they appear to be only poorly absorbed and to have very limited bioavailability in animals including humans. My research has addressed the apparent disconnect between **bioaccessability/bioavailability** of phytoactives, and their efficacy and mechanisms of action by 1) developing a novel radiolabel and stable isotope-labeled tracking system to deliberately synthesize and label phytoactive chemicals in rigorously-controlled cell and organ cultures of functional plant donors, and 2) using an artificial gastrointestinal (GIT) system and *in vitro* digestive models to track the metabolic fate of ingested phytoactives, alone or in a food ingredient matrix. ^{14}C or ^{13}C-labeled phytoactive purified compounds and/or interactive mixtures administered to rodent models fitted with subcutaneous and jugular probes were automatically sampled for blood, interstitial fluid, urine and feces, and tracked via scintillation counting and accelerator mass spectrometry, allowing deposition into bone and liver to be determined. Artificial GIT studies demonstrated that **phytoactive compound integrity and bioefficacy was protected when delivered in protein-polyphenol colloidal aggregate complexed food matrices**. These studies provided direct evidence for the distribution and structural integrity of ingested phytoactives and metabolites. I served as primary investigator or co-investigator for all of these studies.

a. Moran, Nancy E., Randy B. Rogers, Chi-Hua Lu, Lauren E. Conlon, Mary Ann Lila, Steven K. Clinton, John W. Erdman, Jr. 2013. Biosynthesis of highly enriched ^{13}C-lycopene for human metabolic studies using repeated batch tomato cell culturing with ^{13}C-glucose. *Food Chemistry* 139:631-639. http://dx.doi.org/10.1016/j.foodchem.2013.01.016 PMC3621112
b. Ribnicky, David M., Diana E. Roopchand, Andrew Oren, Mary Grace, Alexander Poulev, Mary Ann Lila, Robert Havenaar, Ilya Raskin. 2014. Effects of a high fat meal matrix and protein complexation on the bioaccessibility of blueberry anthocyanins using the TNO gastrointestinal model (TIM-1). *Food Chemistry* 142:349-357. http://dx.doi.org/10.1016/j.foodchem.2013.07.073 PMC4072317
c. Lila, Mary Ann, Britt Burton-Freeman, Mary H. Grace, Willy Kalt. 2016. Unraveling anthocyanins bioavailability. *Annual Reviews Food Science & Technology* 7:17.1–17.19 doi:10.1146/annurev-food-041715-033346 PMID: 26772410
d. Hoskin, Roberta, Jia Xiong, Mary Ann Lila. 2019. Comparison of berry juice concentrates and pomaces and alternative plant proteins to produce stable spray dried protein-polyphenol food ingredients. *Food & Function* 10:6286-6299. doi:10.1039/c9fo01587f

4. In tandem with the work described above, our team has explored the mechanisms by which flavonoids, particularly anthocyanins, with **different chemical structures differentially affect efficacies** related to metabolism, cardiometabolic health, and metabolic syndrome. I was PI or co-PI on all of this work.

a. Overall, John, Sierra Bonney, Mickey Wilson, Arnold Beermann III, Mary H. Grace, Debora Esposito, Mary Ann Lila, Slavko Komarnytsky. 2017. Metabolic effects of berries with structurally diverse anthocyanins. *International Journal of Molecular Sciences* 18: 422. PMID: 28212306, PMCID: PMC5343956. doi:10.3390/ijms18020422

b. Skates, Emily, John Overall, Katie Dezego, Mickey Wilson, Debora Esposito, Mary Ann Lila, Slavko Komarnytsky. 2018. Berries containing anthocyanins with enhanced methylation profiles are more effective at ameliorating high fat diet-induced metabolic damage. *Food & Chemical Toxicology* 111:445-453. PMID: 29196236. https://doi.org/10.1016/j.fct.2017.11.032
c. Grace, Mary H., Jia Xiong, Debora Esposito, Mark Ehlenfeldt. Mary Ann Lila. 2019. Simultaneous LC_MS quantification of anthocyanins and non-anthocyanin phenolics from blueberries with widely divergent profiles and biological activities. *Food Chemistry* 227:336-346. doi.org/10.1016/j.foodchem.2018.10.101 PMID: 30502155.

5. A common axiom in my laboratory team is: "*It doesn't matter how efficacious, potent or health-relevant a food component or natural product may be – if you can't get people to eat it, the discovery will not do any good*". A considerable body of research has identified and characterized the health-protective constituents in functional fruit and vegetable crops, yet the bioactive potential of many of these ephemeral phytochemicals is severely attenuated with processing or even storage. Relatively little attention has focused on effective strategies to deliver efficacious health-relevant levels of phytoactive compounds in shelf-stable ingredient formats available for convenient functional foods, especially for consumers who do not have ready access to, or cannot incorporate perishable, bulky fruit and vegetable produce into daily diets, including military personnel, or rural village populations in the developing world. My research team succeeded in **development and delivery of pharmacologically-relevant levels of phytoactive compounds** (equivalent to 1-2+ servings from fruit and vegetable sources) concentrated within relatively small, easily transported volumes of dry powered (high protein phytoactive-fortified flour) or concentrated liquid ingredient formats which are chimeric colloidal aggregate complexes of edible proteins and phytoactive constituents. These highly stable aggregate matrices maintain anti-inflammatory and anti-diabetic properties over long-term storage even under harsh conditions. I served as PI or co-PI on these projects.

a. Schneider, Margaret, Debora Esposito, Mary Ann Lila, E. Allen Foegeding. 2016. Formation of whey protein-polyphenol meso-structures as a natural means of creating functional particles. *Food & Function* 7:1306-1308. doi: 10.1039/C5FO01499A PMID:26857696
b. Lila, Mary Ann, Maggie Schneider, Amy Devlin, Nathalie Plundrich, Scott Laster, E. Allen Foegeding. 2017. Polyphenol-enriched berry extracts naturally modulate reactive proteins in model foods. *Food & Function* 8:4760-4767. doi: 10.1039/C7FO00883J PMID 29192707
c. Foegeding, E.A., Nathalie Plundrich, Margaret Schneider, Caroline Campbell, Mary Ann Lila. 2017. Protein-polyphenol particles for delivering structural and health functionality. *Food Hydrocolloids* 72:163-173. doi.org/10.1016/j.foodhyd.2017.05.024
d. Xiong, Jia, Yu Hsuan Chan, Thirumurugan Rathinasabapathy, Mary H. Grace, Slavko Komarnytsky and Mary Ann Lila. 2020. Enhanced stability of berry pomace polyphenols delivered in protein-polyphenol aggregate particles to an in vitro gastrointestinal digestion model. *Food Chemistry* 331: 127279. doi: 10.1016/j.foodchem.2020.127279

Complete List of Published Works:
https://scholar.google.com/citations?hl=en&user=cLInZr8AAAAJ&view_op=list_works&sortby=pubdate

D. Additional Information: Research Support

Ongoing Research Support

USDA NIFA ANNH #201804720 Dunlap (PI) 08/2018-07/2021
Back to the river: the science behind Alaska's traditional subsistence lifestyle
Goal of this project is introduction of STEM-relevant bioexploration tools and culturally-relevant sled dog nutrition analysis in outreach to Native AK youth in a series of workshops coincident with annual fish camps
Role: Co-I, NCSU subcontract PI

USDA NIFA CBG #201938821-29115 Kobayashi (PI) 12/2018-11/2021
Collaborative evaluation of saffron (*Crocus sativa*) as a high value culinary and medicinal niche crop
The goals of this project are to determine saffron adaptation as domestic crop in controlled environments and to gauge the relative potency and bioavailability of saffron bioactive metabolites from domestic and international sources
Role: Co-I, NCSU subcontract PI

FFAR #534667 Lila (PI) 11/2017-10/2021.
Closing the gap in delivery of fruit and vegetable benefits
Goals of this Foundation for Food and Agriculture Research transdisciplinary project are to apply functional phenotyping and genetic mapping to target nutrient and phytoactive *content* and *bioavailability* in functional crops and products, to bridge the gap between dietary habits and nutrient/bioactive absorption/metabolism.
Role: PI

USDA NIFA SCRI CAP 562417-09879 Iorizzo (PD) 09/2019-08/2023
Leveraging genetic/genomic resources to enable development of *Vaccinium* with improved quality attributes
Goal of this multi-institutional initiative is to develop advanced breeding and genomic resources targeting phytoactive components of berries relevant to human health and quality
Role: Co-PI

USDA SBIR 2020-00824. Plundrich (PI) 09/2020-05/2021
Stabilization and recovery fruit phytoactives from waste streams
The goal of this small business innovation research project is to develop advanced multi-frequency microwave technology for the extraction (of polyphenolics) and pasteurization (of protein-polyphenol aggregated matrices) to stabilize ingredient innovations
Role: Academic PI

Recently Completed Research Support
USDA NIGA CBGP 570942-02469 Williams (PD) 10/2015-09-2019
Retraining the immune system: Mitigating allergic responses using hypoallergenic peanut protein-polyphenol aggregates
The scope of this project explored a novel therapeutic strategy to reduce danger and severity of the allergic reaction to peanuts in sensitive patients, developing a peanut protein-polyphenol chimeric colloidal aggregate as a highly controlled, predictive oral immunotherapy reagent.
Role: Co-I, NCSU subcontract PI

NIH NCCIH 1 RO1 A008754-01 Weaver (PD) 09/2014-10/2019
Berries and Bone
The goal of this project was to determine the acute bioavailability of phytoactive polyphenolics in dietary berry interventions, efficacy for skeletal protection and promotion of microbiome diversity.
Role: Co-I

Pending Research Support
NSF IUCRC Lila (PD) 01/2021-12/2022
Center for Biopotency, Bioavailability and Personalized Nutrition Innovation
This Industry/University Cooperative Research Center addresses industry priorities in validation and efficacy testing for ingredients, products and interventions.
Role: PD

NIH NIAID R21 Lila (PI) 07/2021-06/2023
Inhibition of peanut protein antigenicity via food-grade proanthocyanidin binding
The goal of this effort is to establish complete structural elucidation of novel peanut protein-proanthocyandin colloidal aggregate complexes, and to determine potentiating (additive/synergistic) mechanisms of action for allergy attenuation, as a prelude to future utilization in oral/sublingual immunotherapy and hypoallergenic functional foods.
Role: PI

NIH RO1 Lila (PI) 01/2021-12/2025 (**this proposal**)
Age-related cognitive changes: Effects of combined flavonoid intake and exercise mediated by the gut microbiome
Goal to explore dynamic interactions of exercise & flavonoid intake on microbiome-mediated cognitive change
Role: PI