



THE UNIVERSITY *of*  
NORTH CAROLINA  
*at* CHAPEL HILL

**NUTRITION  
RESEARCH  
INSTITUTE**

**IMPACT REPORT FY17**



## **Steven H. Zeisel, MD, PhD**

*Director*

Nutrition Research Institute

University of North Carolina at Chapel Hill

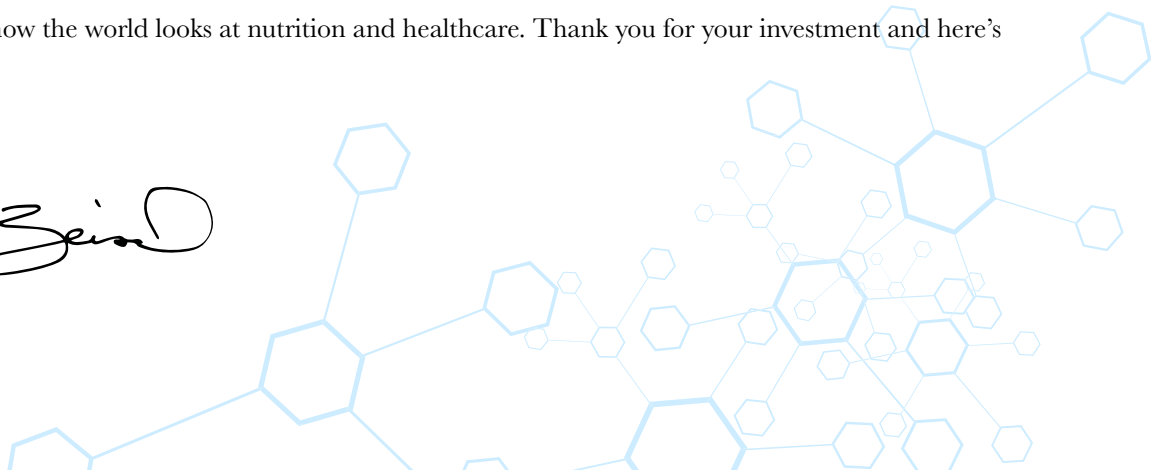
Dear Friends,

Nutrition is fast being recognized as a major player in whether we are ill or well. People everywhere are taking interest in controlling their own health by eating what works best for them. Progressive companies are implementing nutrition-based wellness programs for their employees because they know that a healthy workforce is the best assurance of a healthy bottom line.

At the Nutrition Research Institute, we have dedicated our careers to exploring the potential of precision, or personalized, nutrition for unlocking optimal health. Precision nutrition is the study of why people differ in our metabolism and nutritional needs, and the use of this information to target the right nutrition to each individual. With your support this past year, we continued to make exciting nutrition discoveries (pp. 6-8), which will become the guidance healthcare professionals need to help you, their patients.

Our research is changing how the world looks at nutrition and healthcare. Thank you for your investment and here's to a healthy future.

Sincerely,



## Mission

The NRI is leading research in precision nutrition by developing an understanding of how our genes, the bacteria in our gut, and our environment create differences in our metabolism that affect our individual requirements for and responses to nutrients.

## Guiding Scientific Premise

Each of us is metabolically unique. The NRI is dedicated to finding out how these differences affect an individual's health so that current one-size-fits-all dietary guidelines can be replaced with customized nutritional recommendations and actions to improve a person's health and quality of life. With NRI's discoveries, physicians and dietitians will soon be able to create diet and exercise plans customized to your unique needs.

## Nutrigenomics and Metabolomics

In Nutrigenomics, we study common variations in the spelling of our genetic code and in the “switches” that turn our genes on and off, and relate these to differences in our metabolism and nutrition needs. The gene tests we are developing will allow gene-guided recommendations for individual nutrition.

**Nutrigenomics and Metabolomics:**  
*New Tools to Detect Individual Differences in Metabolism*

With Metabolomics, we can measure thousands of metabolites in blood or other tissues using a single, small sample. This makes possible a complete view of our metabolism that was not possible before. Now, we can add to gene tests the ability to see what the changes in genes are doing to our metabolism, and use this to make metabolomic-guided recommendations for individual nutrition.

The Nutrition Research Institute is an international leader in both of these new fields of science.

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EATUNIQUELY

# PIONEERS



Saroja Voruganti, PhD  
Faculty

**18** Faculty Members



Rodrigo San Cristobal  
Faculty Fellow

**2** Visiting Scholars



Eneda Pjetri, PhD  
Postdoctoral Fellow

**13** Postdoctoral Fellows



Grant Canipe  
Graduate Student

**11** Graduate Students



Baba Mas  
Research Technician

**26** Research Staff



Carolyn Harris  
Executive Assistant  
to the Director

**14** Administrative Staff



Allison Hunt  
Intern

**25** Interns

True pioneers of science, our team of faculty investigators, supporting scientists, lab technicians, and administrative staff are forging new lines of inquiry and methodology in the study of human nutrition.

**4**

**109**  
Faculty & Staff



## Precision Nutrition & Health/Disease

Carol Cheatham, PhD  
Stephen Hursting, PhD  
Natalia Krupenko, PhD  
Sergey Krupenko, PhD  
Philip May, PhD  
Katie Meyer, ScD

Susan Smith, PhD  
Natalia Surzenko, PhD  
Jomari Torres, MD  
Manya Warriar, PhD  
Saroja Voruganti, PhD

## Nutrigenomics

Brian Bennett, PhD  
Folami Ideraabdullah, PhD  
Martin Kohlmeier, MD, PhD  
Steven Zeisel, MD, PhD

## Metabolomics

Wimal Pathmasiri, PhD  
Delisha Stewart, PhD  
Susan Sumner, PhD

# KEY FINDINGS

## 1. Folate gene responsible for optimal neurodevelopment.

When a gene important for metabolizing the vitamin folate is deleted in mice, it causes specific learning problems. In people, naturally occurring mutations to this gene are associated with increased risk for bipolar disorder and schizophrenia. Continuing research will help us understand how to adjust diet and nutrition for optimal neurodevelopment.

## 2. Essential fatty acid ratios, not only quantity, are important for the brain.

Cognitive performance in children is dependent not only on getting sufficient amounts of omega-6 and omega-3 fatty acids, but also on their ratio. Best performance was observed at different ratios depending on age, with children ages 7-9 requiring the lowest  $\omega$ -6 :  $\omega$ -3 ratio and the children ages 10-12 needing the highest ratio. These findings indicate ongoing differences in nutritional needs for healthy brain development throughout childhood.

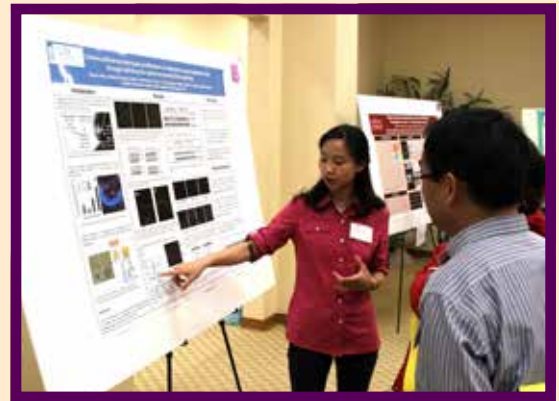
## 3. Effects of prenatal alcohol exposure differ by gender.

Prenatal alcohol exposure is detrimental for both boys and girls, but the effects differ slightly between genders, with boys showing lower survival rates and girls showing more cognitive impairment. Such differences could provide clues as to exactly how alcohol exerts its damaging effects in early development.

Citations on page 8.

## 4. Eggs are great for some populations, but maybe not all.

In contrast to previous studies linking egg consumption with cardiovascular disease (CVD) risk, new research suggests that, at least for healthy middle-aged adults, eggs and other choline-rich foods do not increase risk.



## 5. Obesity-related cancers respond well to calorie restriction.

Most studies on the association of obesity with breast cancer risk have focused on the estrogen receptor-positive form of the disease. Research now clearly extends this relationship to HER2-positive breast cancer and supports the anti-cancer effects of calorie-restricted diets.

## 6. Generations affected when vitamin D is too low.

Maternal vitamin D deficiency can alter gene expression during critical periods of fetal development in ways that are heritable. This means that effects such as abnormal body weight can be seen not only in the immediate offspring, but also in the next generation as well.

# KEY FINDINGS

## 6. A metabolic imbalance may lead to certain liver tumors.

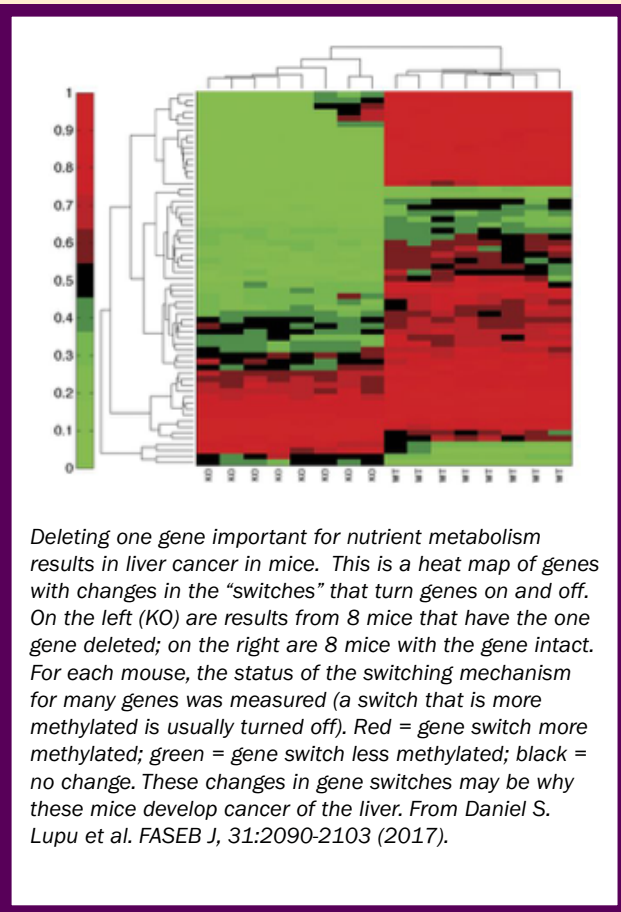
Deletion of the *Bhmt* gene in mice impairs metabolism of the dietary nutrient betaine, setting off a metabolic chain reaction that ultimately changes methylation, and consequently expression, of a different set of genes. Ultimately, these changes in gene expression lead to tumors. Variants in the *BHMT* gene are common in humans, and may be associated with certain liver cancers.

## 8. Environmental toxins cause epigenetic changes across generations.

Prenatal exposure to the plasticizer DEHP can cause behavioral changes in mice that extend multiple generations, even when the initial exposure is at very low levels. These findings point to the need for detailed research into how these changes occur and are passed through multiple generations.

## 9. Who is susceptible to obesity?

A gene mutation may hold the answer. While obesity is a consequence of caloric intake (diet) exceeding caloric output (exercise), the precise relationship between what you eat and how many calories you absorb has a genetic component. The association of common inherited spelling variations in the *PEX1* gene with obesity could help identify who will be more susceptible to obesity and lead to novel approaches to prevention.



*Deleting one gene important for nutrient metabolism results in liver cancer in mice. This is a heat map of genes with changes in the “switches” that turn genes on and off. On the left (KO) are results from 8 mice that have the one gene deleted; on the right are 8 mice with the gene intact. For each mouse, the status of the switching mechanism for many genes was measured (a switch that is more methylated is usually turned off). Red = gene switch more methylated; green = gene switch less methylated; black = no change. These changes in gene switches may be why these mice develop cancer of the liver. From Daniel S. Lupu et al. FASEB J, 31:2090-2103 (2017).*

# CITATIONS



## Key Findings

- 1. Deletion of one allele of Mthfd1 (methylenetetrahydrofolate dehydrogenase 1) impairs learning in mice.** Pjetri E, Zeisel SH. *Behav Brain Res*, 332:71-74 (2017).
- 2. Executive functions and the  $\omega$ -6-to- $\omega$ -3 fatty acid ratio: a cross-sectional study.** Sheppard KW, Cheatham CL. *Am J Clin Nutr*, 105:32-41 (2017).

**3. Who is most affected by prenatal alcohol exposure: boys or girls? May PA,** Tabachnick B, Hasken JM, Marais AS, de Vries MM, Barnard R, Joubert B, Cloete M, Botha I, Kalberg WO, Buckley D, Burroughs ZR, Bezuidenhout H, Robinson LK, Manning MA, Adnams CM, Seedat S, Parry CDH, Hoyme HE. *Drug Alcohol Depend*, 177:258-267 (2017).

**4. Microbiota-dependent metabolite trimethylamine N-oxide and coronary artery calcium in the Coronary Artery Risk Development in Young Adults study (CARDIA).** Meyer KA, Benton TZ, Bennett BJ, Jacobs DR, Lloyd-Jones DM, Gross MD, Carr JJ, Gordon-Larsen P, Zeisel SH. *J Am Heart Assoc*, 5:e003970 (2016).

**5. Energy balance modulation impacts epigenetic reprogramming, ER $\alpha$  and ER $\beta$  expression, and mammary tumor development in MMTV-neu transgenic mice.** Rossi EL, Dunlap SM, Bowers LW, Khatib SA, Doerstling SS, Smith LA, Ford NA, Holley D, Brown PH, Estecio MR, Kusewitt DF, deGraffenried LA, Bultman SJ, Hursting SD. *Cancer Res*, 77:2500-2511 (2017).

**6. Maternal vitamin D depletion alters DNA methylation at imprinted loci in multiple generations.** Xue J, Schoenrock SA, Valdar W, Tarantino LM, Ideraabdullah FY. *Clin Epigenetics*, 8:107 (2016).

**7. Altered methylation of specific DNA loci in the liver of Bhmt-null mice results in repression of Iqgap2 and F2r12 and is associated with development of preneoplastic foci.** Lupu DS, Orozco LD, Wang Y, Cullen JM, Pellegrini M, Zeisel SH. *FASEB J*, 31:2090-2103 (2017).

**8. Direct and transgenerational effects of low doses of perinatal di-(2-ethylhexyl) phthalate (DEHP) on social behaviors in mice.** Quinnes KM, Harris EP, Snyder RW, Sumner SS, Rissman EF. *PLoS One*, 12:e0171977 (2017).

**9. Exome sequencing reveals novel genetic loci influencing obesity-related traits in Hispanic children.** Sabo A, Mishra P, Dugan-Perez S, Voruganti VS, Kent JW Jr, Kalra D, Cole SA, Comuzzie AG, Muzny DM, Gibbs RA, Butte NF. *Obesity (Silver Spring)*, 25:1270-1276 (2017).





Natalia Surzenko, PhD, is working to understand how genetic and dietary deficiencies of the nutrient choline in the mother affect neuronal growth in the developing fetus. Pictured are cultured neurons from the cortex of a mouse brain. Axons and dendrites are colored in magenta, nuclei in blue, and a specific class of neurons in green.

# PUBLICATIONS

**Transcriptome profiling identifies ribosome biogenesis as a target of alcohol teratogenicity and vulnerability during early embryogenesis.** Berres ME, Garic A, Fientke GR, Smith SM. *PLoS ONE*, 12:e0169351 (2017).

**Genetic variation underlying renal uric acid excretion in Hispanic children: the Viva La Familia Study.** Chittoor G, Haack K, Mehta NR, Laston S, Cole SA, Comuzzie AG, Butte NF, Voruganti VS. *BMC Med Genet*, 18:6 (2017).

**Metabolites as biomarkers of adverse reactions following vaccination: a pilot study using nuclear magnetic resonance metabolomics.** McClenathan BM, Stewart DA, Spooner CE, Pathmasiri WW, Burgess JP, McRitchie SL, Choi YS, Sumner SCJ. *Vaccine*, 35:1238-1245 (2017).

**Guide and position of the International Society of Nutrigenetics/Nutrigenomics on personalized nutrition: Part 2 - Ethics, challenges and endeavors of precision nutrition.** Kohlmeier M, De Caterina R, Ferguson LR, Görman U, Allayee H, Prasad C, Kang JX, Nicoletti CF, Martinez JA. *J Nutrigenet Nutrigenomics*, 9:28-46 (2016).

**CerS6 is a novel transcriptional target of p53 protein activated by non-genotoxic stress.** Fekry B, Jeffries KA, Esmailniakooshkghazi A, Ogretmen B, Krupenko SA, Krupenko NI. *J Biol Chem*, 291:16586-16596 (2016).

**Trimethylamine N-oxide, the microbiome, and heart and kidney disease.** Zeisel, SH, Warriar, M. *Annu Rev Nutr*, 37:157-181 (2017).

**Guide for current nutrigenetic, nutrigenomic, and nutriepigenetic approaches for precision nutrition involving the prevention and management of chronic diseases associated with obesity.** Ramos-Lopez O, Milagro FI, Allayee H, Chmurzynska A, Choi MS, Curi R, De Caterina R, Ferguson LR, Goni L, Kang JX, Kohlmeier M, Marti A, Moreno LA, Pérusse L, Prasad C, Qi L, Reifen R, Riezu-Boj JI, San-Cristobal R, Santos JL, Martínez JA. *J Nutrigenet Nutrigenomics*, 10:43-62 (2017).

**Modeling of interactions between functional domains of ALDH1L1.** Horita DA, Krupenko SA. *Chem Biol Interact*, pii: S0009-2797(17)30398-8 (2017).

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Peer-Reviewed  
Publications

**Energy balance and obesity: what are the main drivers?** Romieu I, Dossus L, Barquera S, Blottière HM, Franks PW, Gunter M, Hwalla N, Hursting SD, Leitzmann M, Margetts B, Nishida C, Potischman N, Seidell J, Stepien M, Wang Y, Westerterp K, Winichagoon P, Wiseman M, Willett WC, IARC working group on Energy Balance and Obesity. *Cancer Causes Control*, 28:247-258 (2017).

**Metabolic reprogramming by folate restriction leads to a less aggressive cancer phenotype.** Ashkavand Z, O'Flanagan C, Hennig M, Du X, Hursting SD, Krupenko SA. *Mol Cancer Res*, 15:189-200 (2017).

**Blueberry consumption affects serum uric acid concentrations in older adults in a sex-specific manner.** Cheatham CL, Vazquez-Vidal I, Medlin A, Voruganti VS. *Antioxidants (Basel)*, 5 pii: E43 (2016).

**Metabolomics analysis of hormone-responsive and triple-negative breast cancer cell responses to paclitaxel identify key metabolic differences.** Stewart DA, Winnike JH, McRitchie SL, Clark RF, Pathmasiri WW, Sumner SJ. *J Proteome Res*, 15:3225-3240 (2016).

**Breast cancer genetic and molecular subtype impacts response to omega-3 fatty acid ethyl esters.** Chen CH, Fabian C, Hursting S, deGraffenried LA. *Nutr Cancer*, 68:1021-1033 (2016).

# HONORS

## Awards



**NRI Director Steven H. Zeisel, MD, PhD**, received the highest honor bestowed by the American Society for Nutrition by being elected to its Class of 2017 Fellows.



**Carol L. Cheatham, PhD**, has been selected to join the Education Board at the American Health Council, America's leading organization in health awareness and advancement.



**Martin Kohlmeier, MD, PhD**, received the Circle Award from the North Carolina Dietetics Association. This award is presented annually to someone outside the profession who demonstrates outstanding support and contribution to the profession of dietetics.



**Philip May, PhD**, achieved a milestone when four decades of his work on fetal alcohol spectrum disorders resulted in the first and only diagnostic criteria endorsed by the National Institute on Alcohol Abuse and Alcoholism.

## Presentations

**NRI faculty members were invited to give more than 60 presentations at academic conferences or scientific meetings, including:**

- National Institutes of Health, Bethesda, MD
- American Diabetes Association Annual Meeting, San Diego, CA
- Metabolomics Society Meeting, Dublin, IE
- International Society of Exposure Sciences, Utrecht, NL
- International Conference on Homocysteine & One Carbon Metabolism, Aarhus, DK
- International Workshop on Enzymology and Molecular Biology of Carbonyl Metabolism, Girona, ES

# EDUCATION



## NGx Workshop

To help prepare for a future when personalized nutrition is used to manage everyone's health, the NRI held the second **Nutrigenetics, Nutrigenomics and Precision Nutrition Workshop** in Kannapolis, NC, May 21-25. Nearly 100 graduate students, post-doctoral fellows, clinicians and industry researchers attended from around the world. The workshop promoted understanding of diet-genome interactions through lectures and applied sessions.

## Days of Discovery

**Girl Scout Troop 757 and Concord (NC) High School's Theory of Knowledge** students each spent a morning learning about careers in nutrition research and scientific methods used in NRI labs. They experienced hands-on activities using the western blot, cell culture, and gel electrophoresis.

*"Through direct interaction with the scientists, the scouts saw how science degrees translate into both interesting and rewarding careers."*

- Pricia Orage, Troop 757 leader



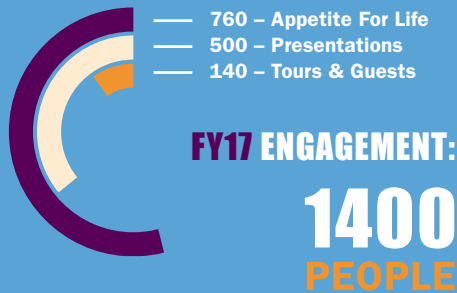
## Student Housing

For 100 years, Kannapolis was home to Cannon Mills. Its workers lived in company-built and -owned houses. With help from the Kannapolis Rotary Club, which raised \$63,500 through a four-year fundraising effort, and support from UNC Chapel Hill, UNC General Administration, and the state of North Carolina, we purchased and renovated five of those historic properties on one block, turning them into a new housing option for NRI graduate students.

# ENGAGEMENT

## Appetite For Life

Our nutrition research is difficult work, but we make it easy to digest with free, public presentations geared to the nonscientist. This year, more than 760 community members learned from NRI scientists and guest speakers about food allergies, obesity and breast cancer, Mediterranean diets, food cravings, brain-healthy nutrients, and nutrigenomics, the backbone of the NRI's research. Nearly 100 guests visited active NRI laboratories and heard directly from scientists about their investigations through our series of summer guided tours.



## Presentations

NRI faculty and staff members spoke on behalf of the NRI to:

- A.L. Brown HS Class of '66 50th Reunion
- Holistic Health Network, Charlotte Chapter
- Kannapolis Rotary Club
- North Carolina Medical Society Alliance
- Rowan Rotary Club
- Sun City Carolina Lakes Lifelong Learning Club

## Partnerships

We were grateful partners with a variety of organizations to provide cooking mini-classes, nutrition talks, and corporate receptions for additional community members.

- Restaurant 46
- Castle & Cooke, North Carolina
- Dole Nutrition Institute
- Johnson & Wales University - Charlotte campus
- Just Fresh Restaurants
- NC State University

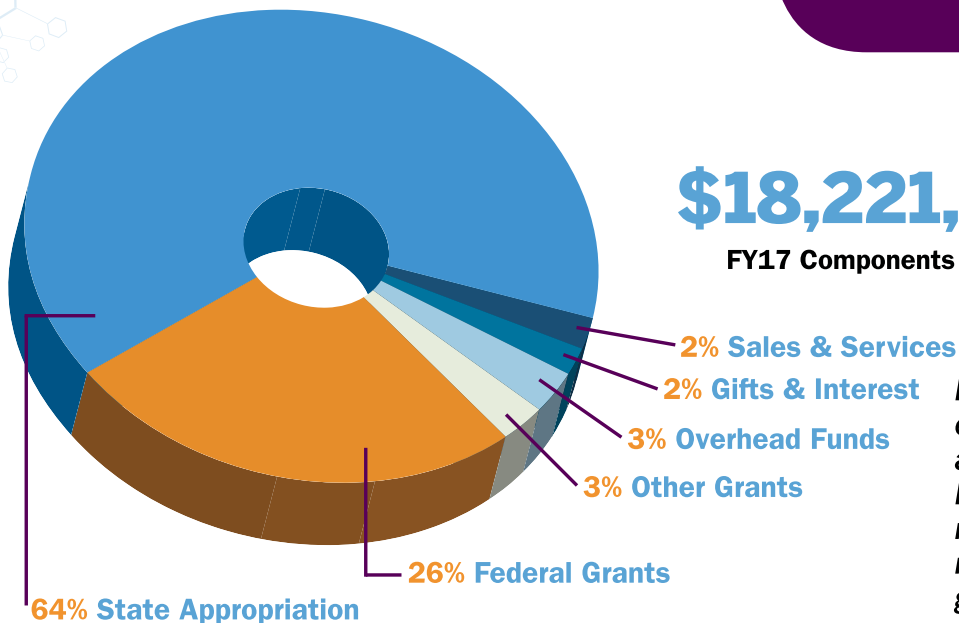


Chef Mark Allison,  
Director of Culinary Nutrition  
Dole Nutrition Institute

# GIVING

*"We praise the work being done at NRI and hope its campaign to enlighten the public, share research among scientists, and garner financial support will result in healthier American and global beneficiaries."*

-George & Lela Herzog



## \$18,221,610

FY17 Components of Support

*Donor gifts provide crucial funds for exploring new ideas to prove they are worthy of larger federal funding. Donations also make possible our recruitment of the world's best minds in nutrition science. Your gifts make all the difference to our success. Thank you.*

## Corporate & Foundation

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## Individual

### Visionary

**\$10,000 and more**

Gregory & Melissa Alcorn  
Byron Bullard  
Jeffery Hughes & Jana Harrison  
Fred & Alice Stanback  
Steven & Susan Zeisel

### Futurist

**\$5,000 - \$9,999**

Jolee & John Fennebresque, Jr.  
Erika Gantt  
Karen & David Harper  
Charles Kinsey  
David H. Murdock  
Tom E. Smith

### Innovator

**\$1,000 - \$4,999**

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Fred & Laura Brown  
William & Ann Cannon  
Chris Cope  
Arthur Gallagher  
Iris Granek  
Jason & Laura Holt

Douglas Kelling  
Diane Laval  
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Hugh & Mary Margaret Morrison  
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Jo Anna Stephens  
Phyllis Wingate  
James Woodward

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**\$500 - \$999**

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Eric Winter  
Kim Wojnowich  
Kristen Woodward  
Christina Zannieri

*"I would like to see a greater focus on the role of nutrition in the treatment of general and chronic health issues. I am happy to know that my support of this research will improve nutrition-focused resources in medical school curriculum and continuing education for medical doctors."*

-Jeff Adams, 2017 donor

*Discovering How To Personalize Nutrition*

*...For Every Body*

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