LINUS PAULING INSTITUTE

OREGON STATE UNIVERSITY
RESEARCH NEWSLETTER

SPRING-SUMMER 2017

INSIDE: LPI Conference Announcement ►

THE HEALTHY YOUTH PROGRAM

Working to advance healthspan for youth and families

The foundation for a healthy lifespan is laid in childhood, as a balanced diet provides essential nutrients for healthy development and growth. As part of the Linus Pauling Institute's public outreach mission, the Healthy Youth Program is dedicated to translating the scientific discoveries on vitamins, minerals, phytochemicals, and healthy eating patterns into meaningful information for the public. Working in the Corvallis community since 2009, we have developed several nutrition education programs that are evidence-based, hands-on, and community-centered — all promote healthy food choices for children and their families.

Food choices — healthy ones or not — develop early in life and become difficult to change once we reach adulthood. Consistent nutrition education throughout the school years provides children with the information and skills to make lasting, healthy food choices. A logical place to focus nutrition education efforts is in schools, yet is this realistic? Nutrition education is not included in state standardized tests, so the average time devoted to teaching nutrition and dietary behavior in elementary school is only 4.6 hours *over an entire school year*.

To gauge teachers' perceptions on this topic, we implemented a cross-sectional survey of Oregon elementary school classroom teachers about nutrition education programs. Overall, we were encouraged that 97% of teachers rated nutrition education in elementary school to be at least 'somewhat important,' and more than half agreed that

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Oregon State University
Linus Pauling Institute

Jan Frederik Stevens, Ph.D.
Professor and Interim Director
Linus Pauling Institute

FROM THE DIRECTOR

We are pleased to present this Spring/Summer edition of the Linus Pauling Institute's Research Newsletter. We have many new developments to share with you, such as the latest news on our research findings, accomplishments of our students, the activities of the Healthy Youth Program (on the cover), and the program for this summer's Diet and Optimum Health conference in Corvallis, Oregon.

As you may recall from our previous newsletter, we are moving forward in an ever-changing research environment. While we stay on course with our mission and our research focus on vitamins, minerals, and phytochemicals, now more than ever it will take a multidisciplinary approach to reach our goals. We are now collaborating with colleagues throughout Oregon State University and academic institutions in the region to complement our expertise.

Today's federal funding climate is the toughest I have seen in my 15 years at Oregon State University. The national competition for federal grants is fierce, by some called 'hypercompetition' for the federal research budgets. Our strategy is not to simply wait for better times. To better position the Institute to face competition, I decided to give faculty who submit a grant application additional funds to generate proof-of-concept data requested by grant review panels or for professional grant-writing support. Most LPI faculty have already taken advantage of this 'submission premium' to strengthen their proposals.

Our approach is beginning to pay off: Our faculty are submitting more proposals than last year, and they are receiving better scores with each new submission cycle.

Through a collaboration with investigators from the University of Nebraska, LPI investigators Drs. Fritz Gombart and Arup Indra won a subaward on a four-year R01 grant from the National Institutes of Health. Dr. Victoria Drake, Manager of the Micronutrient Information Center (MIC), has received a grant from a large nutraceutical company, making it possible for her and her team to update several micronutrient articles and other materials to be published on the MIC website. Congratulations to all!

Over the past several months, we have also begun reorganizing the LPI Core Laboratories. These facilities were established to meet the needs of researchers over a decade ago. As research priorities have changed over time, reorganization is needed to stay competitive. Although the original priorities of these labs remain intact, we are expanding in the areas of analytical chemistry (such as metabolomics, see the article on page 12), new animal models, and human clinical research. The new core labs will be named 'Biological Models and Translational Research Core' and the 'Analytical Services Core.' Most importantly, they will have a broader scope and greater flexibility to assist faculty and allocate resources where needs are most urgent.

In this issue of the newsletter, we highlight news from the research and outreach programs. Dr. Maret Traber and her co-workers discovered that vitamin E pharmacokinetics is different between normal, healthy individuals and those with metabolic syndrome. Please read the article on why that might just have an impact on your health. Dr. Claudia Maier, LPI adjunct faculty, and I present an update on the metabolomics research at the LPI – a field pioneered by Dr. Linus Pauling himself.

If you have followed the news

The Biological Models and Translational Research Core in the Linus Pauling Institute includes the facilities and staff for conducting human clinical trials. Three such trials are currently underway, with more to come.

lately, you will have noticed that intravenously administered vitamin C has reached the media headlines as a cancer therapeutic — we will update you on the research in this field. And, as you have already seen on the cover, we will tell you about the efforts of the Institute's Healthy Youth Program to bring nutrition education to elementary school children, setting a trajectory for a healthy diet into adulthood.

Stephen Lawson decided to retire last June. With the LPI since its inception at OSU 20 years ago, he had worked directly with Dr. Pauling at the Linus Pauling Institute of Science and Medicine in California. Steve enjoyed writing and editing the Research Newsletter, corresponding with friends of the LPI, introducing LPI research and outreach activities to the public, assisting with the design of the new Linus Pauling Science Center and, at long last, seeing its completion in 2011. But discussing his many activities over the years would fill this entire issue and beyond. In our article on page 6, we take a moment to celebrate Steve's many contributions over the past 40 years with our Institute. On behalf of the entire LPI faculty, staff, and students, I express my sincere gratitude to Steve for everything he has done for the Institute. We wish him all the best as a retiree!

Now I would like to introduce LPI's new Director of Development, Amanto Marcotulli, J.D., who joined the OSU Foundation in November 2016. Amanto served in similar roles at the University of California, San Francisco, and at the University of California, Berkeley. Prior to fundraising, he served as a public defender, solo practitioner, and recruiting manager. In the few months I have worked with him, I have discovered that he has an amazing ability to explain complex scientific topics in simple, clear terms without losing the essence of the complexity.

We look forward to working with Amanto and hope that you reach out to speak with him yourself sometime soon.

Lastly, save the date, if you haven't done so already: The 2017 Diet and Optimum Health conference will be held on September 13-16, 2017, at the CH2M Hill Alumni Center in Corvallis, Oregon. This year's conference, chaired by Dr. Maret Traber, will have a tribute to Dr. Balz Frei, who directed the LPI from 1997 to 2016. The scientific program has been set, and details can be found on our website. If you are an LPI graduate or lifelong friend of the Institute, don't forget to sign up for the LPI alumni reception during the conference!

Jan Frederik Stevens, Ph.D.
Professor and Interim Director

Continued from cover — The Healthy Youth Program

educational programs may improve students' food choices at least in the short term and possibly in the long term.

However, as one might expect, implementing nutrition education programs in schools presents several challenges. Barriers noted by teachers included competing academic expectations (52% of survey respondents), a lack of available time (48% of respondents), and a lack of suitable curricula (36% of respondents). Also, about half of these teachers thought that getting parents involved would be one key to establishing an effective program.

Not surprisingly, teachers also noted that unless the food environment in school cafeterias reflects what is being taught, nutrition education will have a limited impact on students' food choices. Following up on this, we sent a second survey to Oregon elementary school foodservice personnel, also on the topic of nutriton education. All of those who responded thought that nutrition education in elementary schools is at least somewhat important, and most thought that school cafeterias should be involved for program success. Three-quarters of school foodservice personnel were interested in nutrition education training, but, similar to teachers, they noted barriers for incorporating nutrition education programs into the school cafeteria. These included cost, time, and the staff available to take on these roles.

To learn more about the Healthy Youth Program at the Linus Pauling Institute, visit: lpi.oregonstate.edu/healthyyouth or send us an email at hyp@oregonstate.edu

As an established partner with Corvallis schools, the LPI's Healthy Youth Program has found that children are much more likely to eat healthfully when they are involved in growing and preparing the food. To this end, nutrition messages presented in our programs are woven into cooking and garden-based activities where children, as active learners, become truly invested in the outcome of a meal or rewards of a harvest. Our long-term goal is to set the stage for future generations to make lasting, healthy food choices; we accomplish this by involving children in all aspects of food preparation, from soil to seed to plate.

Reinforcing nutrition messages provided during the school day, Healthy Youth Program educators work with K-12th graders in school gardens managed by our staff. Teachers involved in garden activities appreciate the inherent links garden-based education has to academic standards, and students appreciate the opportunity to learn outdoors. Harvests are taken directly to the school kitchens, where the colorful and fresh fruit and vegetables enliven cafeteria salad bars. Signs posted near these offerings boast messages like "Grown by YOU!" or "From your school garden!," inspiring ownership, and ultimately consumption.

With constraints on teachers during school hours, the Healthy Youth Program also offers after-school cooking courses that combine cooking/food preparation, kitchen safety, tasting, and food/nutrition knowledge. *Fresh Grown Cooking for Kids* and *Master Chefs* are two of our courses designed for elementary and middle school students, respectively, offered regardless of family income level. Both courses meet once per week for two hours and include a nutrition lesson followed by 60 to 90 minutes of hands-on cooking in small teams of three-to-four participants. Each team makes two or three healthy recipes each week, and importantly, time is spent sharing the meal and talking about the experience.

Ingredients emphasize whole grains, minimally added sugars, and abundant fresh fruit and vegetables that are often harvested on-site from the school gardens. During the off-season, you can find *Master Chefs* participants starting microgreen seeds in the HYP-managed school greenhouse in week one of their session. The kids harvest these greens to use in a cooking competition, a much-anticipated activity in the final class of this six-week program.

The goals of the cooking classes are to teach participants how to prepare a variety of healthy, complete meals; expose participants to new and familiar healthy foods; teach participants basic kitchen safety skills and nutrition knowledge; and, overall, to promote healthy food choices for children and their families by boosting children's confidence in the kitchen to make scratch cooking fun, tasty, and rewarding. A preliminary evaluation of both courses indicate that these course goals are being achieved. The changes go beyond our data, as we are witnessing changes in the food behaviors of children; it is not uncommon to hear a child shout, "I *love* kale!" at the end of a lesson.

The Centers for Disease Control and Prevention (2014) cdc.gov/healthyschools
Perera et al. J Educ Pract. 6 (2015)
Perera et al. J Health Edu Res Dev. 3 (2015)

Join the Linus Pauling Institute for the

Diet and Optimum Health Conference 2017

September 13–16 | Corvallis, OR

Featuring

- A Tribute to Balz Frei
- Dietary Components and the Microbiome
- Update on Vitamin E
- Bioactives and Cancer Prevention
- All-day Symposium on IV Vitamin C
- A Free Public Session on Sat., September 16th

lpi.oregonstate.edu/DOH

STEPHEN LAWSON

40 years of service and an entire career dedicated to the Linus Pauling Institute

Stephen Lawson

"Working at the Linus Pauling Institute of Science and Medicine and the Linus Pauling Institute at Oregon State University has been an extraordinary experience."

— STEPHEN LAWSON, 2017

It is with mixed feelings that we announce that Stephen Lawson has retired from the Linus Pauling Institute. Many who contacted the Institute over the last few decades knew something of Steve: He worked at LPI for many years longer than anyone else and was an integral part of its success over its history.

A graduate of Stanford University, Steve joined the Linus Pauling Institute of Science and Medicine (LPISM) in California in 1977. Initially, his work at the Institute with Linus Pauling focused on several projects with vitamin C, including the role of vitamin C in the prevention of skin cancer and potential interactions between vitamin C and cancer chemotherapeutic drugs.

Later, as a co-director of the Laboratory for Research in Gene Regulation in the late 1980s, Steve developed a technique for using two-dimensional gel electrophoresis to profile proteins involved in cancer metastasis. He also studied the effects of phytic acid, a substance found in grain and plant seeds, on blood lipids and tumor growth in rats, resulting in a patent for its use in inhibiting cancer growth.

From 1988 to 1991, Steve served as executive assistant to the president, Emile Zuckerkandl — who developed the concept of molecular evolution with Pauling — and, in 1991, as executive officer.

In 1993 he was appointed chief executive officer and grappled with financial, legal, zoning, and other critical issues facing the Institute, and successfully negotiated several remunerative research and corporate contracts.

In 1996 he organized the move of the Institute to Oregon State University. "Dr. Pauling was aware and supportive of our discussions to move LPI to Oregon State University and continue the mission of orthomolecular medicine," says Lawson. "He would certainly be pleased to know that important research in metabolomics — a field he and colleagues pioneered in the late 1960s — and on essential minerals like zinc; phytochemicals; and vitamins C, D, and E has been conducted at LPI."

At the new Linus Pauling Institute, Steve served as our administrative officer and editor of the Research Newsletter, helping to preserve institutional memory. Steve also assisted in recruiting Balz Frei as the new director of the LPI and served as the director's advisor until they both retired in 2016.

Steve was critically involved in LPI's fundraising and strategic, long-term planning. He also served on the steering and art committees for OSU's Linus Pauling Science Center, the current home of the Institute, and, for many years, on the Campus Planning Committee and the Student Health Advisory Board.

Over the years he has authored or co-authored many papers, including those published in the *Journal of Virology, Carcinogenesis, Gynecologic Oncology,* the *Journal of Orthomolecular Medicine,* the *Proceedings of the National Academy of Sciences, Nutrition Research,* the *Journal of Applied Nutrition*, the *American Journal of Clinical Nutrition,* and the *Journal of Anesthesia History*, among others.

Yet, all of these accomplishments only barely touch on Steve's life at the Institute. He often speaks of many happy afternoons in the LPISM spent identifying mineral specimens and crystals with Dr. Pauling and Zelek Herman, Pauling's collaborator in theoretical chemistry. Or the occasions when Pauling would ask him to take on special assignments, like writing a review of *Vitamin C and Cancer: Medicine or Politics?* by Evelleen Richards for a journal publication.

"Once," he recollects, "Dr. Pauling stopped by my office to tell me that he had an idea about a new method to fabricate superconductive material... incredibly thin fibrils of conductive metal, such as tin, clad in nonconductive glass." Pauling asked Steve to help set up a small lab to see if they could make this material, hoping the licensing of a patent might provide a high revenue stream to fund research in orthomolecular medicine at the Institute.

Steve and Zelek bought a furnace, blowtorch, and supplies and started working away, melting and pulling the tin and glass in the method outlined by Dr. Pauling. "He joined us occasionally in the lab and wielded the blowtorch," Lawson recalls, "When we finally succeeded, we rushed excitedly to his apartment and showed him the material. He was gleeful and gave us each beautiful pyrite crystals in appreciation."

Most people are unaware that Steve set up the Institute's first cell culture laboratory. His recollections of these experiences provide a fascinating window into the LPISM, and how innovation triumphed in the days before modern cell culture was the norm.

Steve's commitment to the Institute and the memory of Linus Pauling, as well as his advocacy for orthomolecular medicine, is present in

Stephen Lawson *(left)* **with Linus Pauling** *(right)*

everything he has accomplished over the years. He participated in many film projects about Linus Pauling and orthomolecular medicine, including the 2011 production "Linus Pauling" by Oregon Public Broadcasting for the *Oregon Experience* program.

Steve also served on the Select Advisory Committee for the Linus Pauling Exhibition, an exhibit honoring Pauling's positive, long-term influence on society, visited by millions of people worldwide. Moreover, Steve has been an integral member of OSU's Pauling Heritage Committee, a group organized to recognize the wide impact of Pauling's life and work and how it is reflected on the Oregon State University campus.

Steve annotated and added an afterword to the 20th anniversary edition of Linus Pauling's bestseller *How to Live Longer and Feel Better*, published in 2006. He recently contributed a preface discussing anticancer mechanisms to the new 21st-Century Edition of *Cancer and Vitamin C* by Ewan Cameron and Linus Pauling, as well as an appendix that summarizes recent research on intravenous vitamin C as adjunctive therapy for cancer, to be published soon.

Steve often gave lectures on orthomolecular medicine or Linus Pauling to graduate students in nutrition or medicine; undergraduate students in the School of History, Philosophy, and Religion; other student, professional, and civic groups; and at scientific or medical conferences. In late April, he was inducted into the Orthomolecular Medicine Hall of Fame, joining scientists and physicians like Linus Pauling, Ewan Cameron, Bruce Ames, Roger Williams, and Abram Hoffer.

To conclude in Steve's own words: "I feel particularly fortunate to have been so closely associated with Linus Pauling and LPI for so long and cherish the time I spent learning about the critical contributions of science to society and how science can be the source of so much fun and satisfaction."

Stephen Lawson currently holds a courtesy appointment at Oregon State University and can still be reached through the Linus Pauling Institute.

INTRAVENOUS VITAMIN C AND CANCER

After nearly 40 years, where does the science stand on this therapy?

Linus Pauling was very interested in the value of vitamin C in treating cancer. Clinical research with his colleague Ewan Cameron in the 70s demonstrated that large doses of oral and intravenous (IV) vitamin C were helpful in increasing the survival time and improving the quality of life of terminal cancer patients. When follow-up studies by the Mayo Clinic using only oral vitamin C did not show any benefit, many cancer researchers doubted the value of vitamin C therapy, and the research slipped out of the mainstream.

About 10 years ago, studies at the NIH with Dr. Mark Levine revitalized cancer research with vitamin C. His group confirmed that high concentrations of vitamin C do indeed kill cancer cells in culture. Studies in animals show that vitamin C infusions can slow tumor growth. A number of studies are now underway to characterize the molecular anticancer mechanisms of vitamin C and optimal protocols for administration. However, there is plenty of work to be done before vitamin C can be accepted as a mainstream therapy for cancer.

Yet, as clinical researchers try to understand why and how much vitamin C can help fight against cancer, thousands of people worldwide are using it as a primary treatment or adjunctive therapy. Therefore, we believe a review of the current state of intravenous vitamin C as a cancer therapy may be useful for those who wish to know where the science stands on this treatment:

It is generally safe: Results from controlled clinical trials indicate that IV vitamin C is generally safe and well tolerated in most prescreened cancer patients. In fact, there are very few contraindications for vitamin C in intravenous form. However, there is still the potential for side effects: those with existing kidney disease, history of kidney stones, or glucose-6-phosphate dehydrogenase deficiencies should take particular caution.

It is not the same as taking a supplement: The therapeutic effect of vitamin C in cancer patients has mainly

been demonstrated through IV administration or direct infusion, not by taking supplements. Concentrations of vitamin C in the blood are the key: formulations of oral vitamin C — even those that claim to boost bioavailability — do not increase blood vitamin C levels to a point that would produce the same anticancer effect. IV administration allows concentrations of vitamin C in the blood to reach at least 100 times higher than taking oral supplements.

Hydrogen peroxide is likely important: Researchers have found that high concentrations of vitamin C can produce hydrogen peroxide in the vicinity of a cancer cell. The hydrogen peroxide interferes with functions in many cancer cells, leading to their death. Cancer cell death cannot be achieved by directly administering hydrogen peroxide because enzymes in the blood would remove any hydrogen peroxide formed before it could reach tissues. Also, taking large amounts of hydrogen peroxide by mouth is not safe and would not target cancer cells.

The working hypothesis is that high levels of vitamin C may reach the spaces where removal enzymes are absent, allowing a reaction with oxygen, production of hydrogen peroxide, and its transport into cells. This causes a cascade of reactions that ultimately can kill cancer cells. Other mechanisms have also been proposed regarding how vitamin C might slow tumor growth and cause cell death that do not involve hydrogen peroxide, so it is possible that multiple mechanisms are at play.

It can be combined with some cancer therapies; not with others: Studies have found that intravenous vitamin C treatments can alleviate fatigue or decrease other side effects of some chemotherapeutic drugs, thereby improving the quality of life of cancer patients. Some drugs have been shown to work better in combination with vitamin C. On the other hand, vitamin C may interact with other drugs to limit how well they work or even exacerbate side effects. Thus, it is *extremely important* to talk to a physician before combining IV vitamin C with any drug. Of course, any administration of an injection or infusion of vitamin C should only be performed under the direct supervision of a qualified health professional.

IV vitamin C is not a miracle agent for all cancers: Research has shown that some cancers are not affected by the use of IV vitamin C, especially cancer cells that are resistant to hydrogen peroxide. Researchers are trying to find ways of overcoming those barriers, but progress in this area is slow and needs more funding to continue.

Bottom-line: Overall, vitamin C infusions are a promising approach to fighting some types of cancer, but much more work still needs to be done to determine how and when they should be used. It is still too early for the Linus Pauling Institute to make general recommendations about IV vitamin C to cancer patients. Clinical trials are currently underway at centers around the world to provide answers to important questions about this therapy.

Chen et al. Proc Natl Acad Sci. USA 102 (2005)
Ma et al. Sci Transl Med. 6 (2014)
Schoenfeld et al. Cancer Cell. 31 (2017)

For those who want to know more about the subject, we recommend the new edition of *Cancer and Vitamin C* by Cameron and Pauling that discusses anticancer mechanisms and summarizes the recent clinical research. Contact the Institute for more details.

GETTING ENOUGH VITAMIN E?

Studying metabolic syndrome may lead to new recommendations for vitamin E

Vitamin E, a fat-soluble antioxidant, plays a supporting role in immune function, wound healing, vision, and neurologic function. Estimates are that 90% of Americans do not eat enough vitamin E-rich foods to meet published requirements. Despite its importance, people who don't consume enough vitamin E still seem to be healthy. Are the requirements wrong?

Maret Traber, Ph.D., Ava Helen Pauling Professor at the Linus Pauling Institute, believes that people are not getting enough vitamin E and are, in fact, not as healthy as they think. The extent of the problem, especially in people with underlying health conditions, may be worse than has been appreciated by most nutrition professionals. Research from her laboratory has demonstrated that measuring the amount of vitamin E you consume, or even the amount in your blood stream, might not give you a complete picture of vitamin E status. Her new studies show there might be a better way to tell if you are eating enough vitamin E.

First, some background on how vitamin E moves through the body: After you eat something containing vitamin E — be it a handful of almonds, some vegetable oil, a few cups of spinach, or a supplement — the vitamin E, along with the fat in your meal, gets absorbed and sent through the blood stream to the liver. The liver is the guardian, picking out those molecules needed for life and sending those back into the blood stream. It also sorts out and removes the things you don't need in your body. Thus, the liver works as a sorting facility, keeping the good and excreting the useless or potentially toxic.

Here, one form of vitamin E named alpha-tocopherol is special: A transfer protein found in the liver rescues alpha-tocopherol and sends it — along with dietary fats — back into the blood stream for delivery to tissues. Other forms of vitamin E, like tocotrienols, don't get this special treatment.

Because of this distribution system, measuring alpha-tocopherol levels in the blood gives doctors and researchers a good understanding if someone is deficient. Under normal circumstances, if vitamin E levels in the blood are low, the person is not consuming enough. If levels are high, it probably means enough vitamin E is reaching the tissues where it needed the most.

However, this is not always the case. A problem arises when fat is not taken up into tissues normally. This occurs in hyperlipidemia or hypercholesterolemia, where triglycerides and cholesterol particles circulate in the blood at abnormally high levels. Where the fats go, the vitamin E follows. "It's a micronutrient that's going along for the ride," says Dr. Traber.

To study this in more detail, Dr. Traber, along with her collaborators at The Ohio State University, decided to look at persons with metabolic syndrome (see sidebar). Although blood levels of vitamin E in these individuals are apparently normal,

Dr. Traber and her colleagues were concerned. This syndrome is associated with high levels of inflammation and increased oxidative stress — could these problems increase the amount of vitamin E they need?

The scientists gave volunteers specially tagged alpha-tocopherol to eat so that the vitamin E could be followed in the circulation. This molecular tag let them follow the vitamin E they provided and also the fate of that vitamin, such as vitamin E catabolites that are excreted in the urine.

In participants with metabolic syndrome compared with healthy individuals, the tagged vitamin E was not only poorly absorbed but also disappeared from the blood stream more slowly. Upon analysis, this odd behavior gave clues that something peculiar was happening to this tagged vitamin E in the body.

Traber explains: "In metabolic syndrome, tissues are rejecting fat because they already have enough. In the process, they also reject vitamin E. So even though the tissues are facing serious oxidative stress, the delivery of vitamin E to them is being impaired. Our research shows that people with metabolic syndrome need about 30-50 percent more vitamin E than those who are generally healthy."

When vitamin E intake is higher than the body needs, the extra is eliminated. This is a catabolic process that starts by step-wise removal of the carbons on the long tail found on a tocopherol molecule. The product of this elimination process is a molecule called CEHC. The advanced laboratory tests conducted by Dr. Traber's group showed that people with metabolic syndrome eliminated less CEHC than healthy people.

In other words, those with metabolic syndrome were showing signs that they weren't getting the vitamin E they needed.

Traber is now touting CEHC as a biomarker of vitamin E status — a way for researchers, and potentially physicians (if the future testing confirms the outcomes) to know if vitamin E levels in the body are adequate. Traber hopes that future support of this research will help determine if this molecule can be clinically measured to validate a person's low vitamin E levels in tissues.

The unfortunate conclusion to this set of experiments is that the people with metabolic syndrome are showing signs of needing much more vitamin E. It is not yet clear if eating more vitamin E-rich foods is the best solution for those with metabolic syndrome — but a balanced diet is certainly a good start. Of course, supplementation may be a good way for many people to get enough vitamin E, and the Linus Pauling Institute recommends taking a daily multivitamin supplement, which usually contains close to the recommended levels of vitamin E. The Traber lab is hoping to work with other research participants with lipid dysregulation in the future, to see if this problem may affect more people than this small study would indicate.

Mah et al. Am J Clin Nutr. 102 (2015)
Traber et al. Am J Clin Nutr. 105 (2017)
Grundy et al. Circ. 112 (2005)

What is Metabolic Syndrome?

Metabolic syndrome is a combination of medical conditions that places you at increased risk for several chronic diseases.

How is Metabolic Syndrome Diagnosed?

You have metabolic syndrome if you have three or more of the following risk factors, or are taking medication to control them:

- Abdominal obesity (waist size ≥ 40 inches for men or ≥ 35 inches for women)
- High serum triglycerides (triglycerides greater than 150 mg/dL)
- High blood pressure (blood pressure of 130/85 mm Hg or higher)
- High blood glucose (fasting blood glucose above 100 mg/dL)
- Low HDL cholesterol (HDL levels < 40 mg/dL for men or < 50 mg/dL for women)

What is the Impact of Metabolic Syndrome?

Metabolic syndrome can increase your risk for cardiovascular disease, type 2 diabetes, insulin resistance, Alzheimer's disease, and non-alcoholic fatty liver disease. Fatty liver can progress into cirrhosis,hepatocellular carcinoma, and potentially death.

How is Metabolic Syndrome Prevented?

- Eat a healthy diet rich in fruit, vegetables, fish, and whole grains
- Keep sugar intake low (less than 10% of calories)
- Get regular physical activity
- Achieve and maintain a healthy body weight
- Do not smoke
- Get regular medical checkups

For more information, see the Micronutrient Information Center: http://lpi.oregonstate.edu/mic

METABOLOMICS IN THE NEW MILLENNIUM

Although 'metabolomics' or 'metabolic profiling' find their roots in the previous millennium, they are still in development to become mature techniques.

Claudia Maier, Ph.D.
LPI Adjunct Faculty

Jan Frederik Stevens, Ph.D.
Professor and Interim Director
Linus Pauling Institute

What is Metabolomics?

Metabolites are small organic molecules: intermediates in biochemical processes or end-products of series of pathways of reactions that have occurred somewhere in the body. First coined in the late 1990s, 'metabolomics' is the study of these small molecules. By analyzing metabolites in cells, blood, urine, or other biological fluids, researchers can monitor the biochemical processes that are occurring. Certain molecules or patterns of metabolites may be indicators of health or disease. Other molecules may be produced in response to an intervention, such as a dietary supplement.

Is metabolomics really the latest addition to the spectrum of 'omics' tools?

Linus Pauling and Arthur Robinson are credited by many sources, including Wikipedia, as pioneers in the field of metabolomics. In 1974, they published a paper in the journal, *Clinical Chemistry* (vol. 20, pp. 961-5), entitled "Techniques of Orthomolecular Medicine," reporting on research they had been conducting since the late sixties. They defined their term 'orthomolecular diagnosis' as 'the process of determining and evaluating the concentrations of the substances normally present in the human body.' Initially, they were trying to identify substances in urine that quantitatively correlated with specific diseases or physiological status. This is actually nearly identical to how metabolomics is used today (see sidebar).

Pauling and Robinson hypothesized that information on the health status of people can be derived from the analysis of as many metabolites as possible. To support their case, they showed a pattern of amino acids found in the urine that was characteristic of women taking birth control pills. In another study, they failed to detect a urinary metabolomics pattern that correlated with the grade-point average in male Stanford students, as one might anticipate.

Dr. Pauling's early exploratory work suffered from many technological limitations of the analytical equipment and the lack of databases to identify metabolites. In the 1990s, the widespread introduction of liquid chromatography coupled to electrospray mass spectrometry greatly improved the ability to detect polar metabolites in plasma and urine. Since that time, high-resolution accurate mass detectors have found universal use in metabolome research. In the mid-2000s, several large metabolome databases were developed that can be accessed online, notably METLIN and the Human Metabolome Database (HMDB).

Yet, despite all of these technical and bioinformatics advancements, we are still not able to identify the majority of metabolites in a given biological sample. Most metabolomics laboratories around the world have the ability to identify hundreds of metabolites in a given sample; however, the mammalian metabolome consists of an estimated 2,500-3,500 metabolites.

The Linus Pauling Institute has a long history of being able to quantify vitamins and markers of oxidative stress. With funding from the National Institutes of Health, Oregon State University, and generous gifts from private donors, we have established a state-of-the-art infrastructure for metabolomics research over the past eight years. The Institute owns a quadrupole time-of-flight mass spectrometer — a device that allows us to determine mass and abundance of metabolites with sufficient accuracy to calculate their chemical formula. The Biomolecular Mass Spectrometry Center at OSU operates three additional mass spectrometers that are also suitable for metabolomics research. Software tools have allowed us to build our own

in-house library that consists of more than 650 metabolites commonly found in mammals. We can identify tiny amounts of metabolites from a variety of biological samples both quickly and efficiently.

For additional support, we call upon OSU bioinformaticians and biostatisticians, notably LPI Principal Investigator Gerd Bobe, Ph.D., to help us evaluate enormous amounts of data generated by our metabolomics platforms, the first step in interpreting their functional meaning. With this wealth of metabolomics data, we have already made several discoveries of how vitamins and dietary phytochemicals work and how environmental stressors affect human metabolism; see https://goo.gl/fV26XK for our current list of metabolomics publications.

The LPI is committed to invest further in "new and emerging 'omics' technologies" to advance research in human health and disease, healthspan, and cancer prevention. New directions in metabolomics research focus on the use of stable-isotope tracers. Functionally identical to the naturally occurring molecules of interest, stable isotope-labeled metabolites have heavier atoms, allowing them to be distinguished from the naturally occurring metabolites by mass. Their fate in a biological system can be followed with mass spectrometry by monitoring what metabolites carry the additional mass.

Our faculty are using metabolic tracers to study the dysregulation of metabolic pathways in diverse diseases and to examine the fate of vitamins and dietary phytochemicals in mammalian systems.

LPI investigators seek to determine what dietary supplements and functional foods are able to restore distinct physiological pathways that are disrupted in disease states or altered by aging. LPI will continue to conduct sophisticated metabolomics research with the most modern technologies available to advance micronutrient research aimed at improving human health.

LPI/OSU Mass Spectrometry & Metabolomics Group

From left-to-right:
Back row: Fred Stevens, Joseph Beckman, Elizabeth Axton, Bayissi Bading Taika (Gabon), Jeff Morré, Claudia Maier, Liping Yang, Fereshteh Zandkarimi (Iran), Ines Paraiso (France), Jaewoo Choi, Cristobal Miranda;

Front row: David Yu, Armando Alcazar Magana (Mexico), Johana Revel (France), Manual García-Jaramillo (Spain), Supatcha Kubglomsong (Thailand).

Foreign exchange students and postdoctoral researchers are identified with their country of origin.

LPI GRADUATE STUDENTS

Graduate students are key to the success of the Linus Pauling Institute and research at Oregon State University. In this and future issues of the newsletter, we will highlight our students and their achievements at the Institute.

Melissa McDougall

Ph.D. Candidate in Nutrition in the College of Public Health and Human Sciences

Melissa had the science bug at a very young age. Eventually that developed into an interest in cellular biology. After obtaining her bachelor's degree in molecular and cellular biology with an emphasis in neuroscience, Melissa came to Oregon State University to pursue a Ph.D. working with Dr. Maret Traber, investigating the role of vitamin E in the body (see p. 10). Her focus is on vitamin E in the brain, from beneficial functions in early development to those found during old age. She is currently working to elucidate the effects of vitamin E deficiency on brain function using zebrafish.

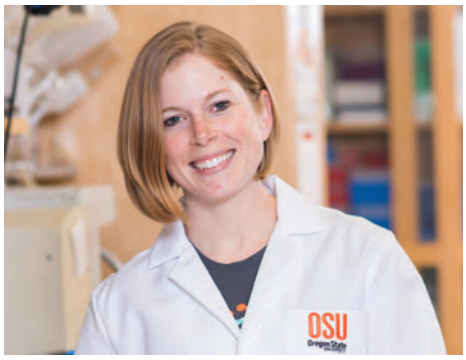
Melissa's hard work has paid off in multiple fellowships over the years, and she is currently a Marion T. Tsefalas Graduate Fellowship awardee. This generous financial support has helped propel her research forward in the last few years at the LPI. Her research projects have earned her several awards, including a Young Investigator Award from the Society for Free Radical Biology and Medicine, as well as a Travel Award from the American Society for Biochemistry and Molecular Biology.

Bayissi Bading Taika

Ph.D. Candidate in Pharmacy, Pharmacology and Postgraduate Medicine

Bayissi is a visiting graduate student and Ph.D. candidate at the University of Hertfordshire in London/UK, working in the laboratory of Dr. Fred Stevens. Her project involves bioactives from a shrub native to Gabon and Central Africa called *Tabernanthe iboga*. Alkaloid compounds from this plant may be useful in treating obesity and type 2 diabetes.

With a background in molecular biology, cellular biology, biochemistry, and pharmacology from University Paul Sabatier in France, Bayissi was awarded a grant from the Gabon Oregon Center, which gave her the opportunity to work with Dr. Stevens' lab and develop her mass spectrometry skills, along with pharmacology training. She is currently in the final year of her Ph.D. program.



Elizabeth Axton

Ph.D. Candidate in Pharmaceutical Sciences and Environmental and Molecular Toxicology

Elizabeth grew up in small rural town in northern California, where science careers were undervalued. Always interested in the natural world, she developed a keen interest in metabolomics (see p. 12) after her undergraduate years at the University of California, Davis. This interest drove her to Oregon State University, specifically to work with Dr. Fred Stevens.

Currently, she is using metabolomics to explore the biological effects of nitrates, and she has followed the interactions of vitamin C, nitroglycerin, and effects on the cardiovascular system. Elizabeth was recently awarded first place at the annual Environmental and Molecular Toxicology Research Day at Oregon State University for a presentation on her work. She also received a Science Communication Fellowship and a Food Science and Nutrition Scholarship. Like Dr. Pauling, she is committed to bringing communication and outreach into her science career.

DEVELOPMENTS

Dear Friends,

Most of you who have read our newsletter over the years are familiar with our wonderful faculty researchers. However, did you know that the Institute is also home to many student researchers? In fact, we have 15 undergraduate researchers and 8 graduate researchers, many of whom are Ph.D. candidates.

In this issue, we feature some of our student researchers so that you can get a sense of the caliber of their work and the contributions they make towards advancing the cutting-edge science taking place here at Linus Pauling Institute. Our faculty takes great pride in mentoring young researchers who are just starting their careers because educating the next generation of citizen scientists is an integral part of our mission. And make no mistake, these students play a vital role in advancing our research goals.

As a public institution, Oregon State University is committed to offering students access to a high-quality education regardless of their financial background, and this commitment is shared by all of us at the Institute. Many of our student researchers come from humble backgrounds — just like Dr. Pauling did — but once they step into our labs, they become integral members of a world-class research team.

These students have their own accomplishments and awards, but the size and number of funding opportunities are limited. Many of our brilliant students work their way through school, and their families often make great sacrifices to help them graduate. Sadly, there are times when research funding falls short and support for these students disappears — they simply can't afford to pay for tuition, books, or living expenses and work an unpaid position in the laboratory at the same time. When this happens, our research gets held back and students miss out on important learning opportunities.

For these reasons, we have established the Balz Frei Endowed Fellowship Fund (in honor of our former director) to support graduate students. I hope that you will consider making a gift to this fund. Your generosity will support LPI's research and help hard-working students launch their careers.

Please contact me to learn more about the Balz Frei Endowed Fellowship, or if you would like to set up your own named scholarship fund at LPI. Who knows, maybe one of the students that you help will become a Nobel Laureate!

Sincerely,

Amanto Marcotulli

Amanto is the new Director of Development for the Linus Pauling Institute at the OSU Foundation. If you would like to know more about how to work with Amanto to support the LPI and its research goals, you can contact him at Amanto.Marcotulli@osufoundation.org or call at (503) 553-3400.

Amanto Marcotulli, J.D.
Director of Development

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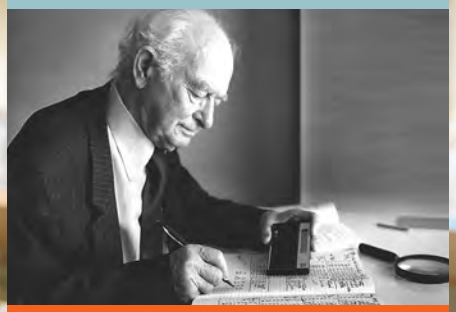

A LASTING LEGACY

You can create a legacy of your own by providing opportunities for future researchers. Gifts in support of students or research projects at the Linus Pauling Institute can be made at any time. To learn the many ways you can help support the LPI, please contact the OSU Foundation at 1-800-354-7281, write to the Institute, or go online: **osufoundation.org/GiveToLPI**

New research updates from the Linus Pauling Institute. LOOK INSIDE ►