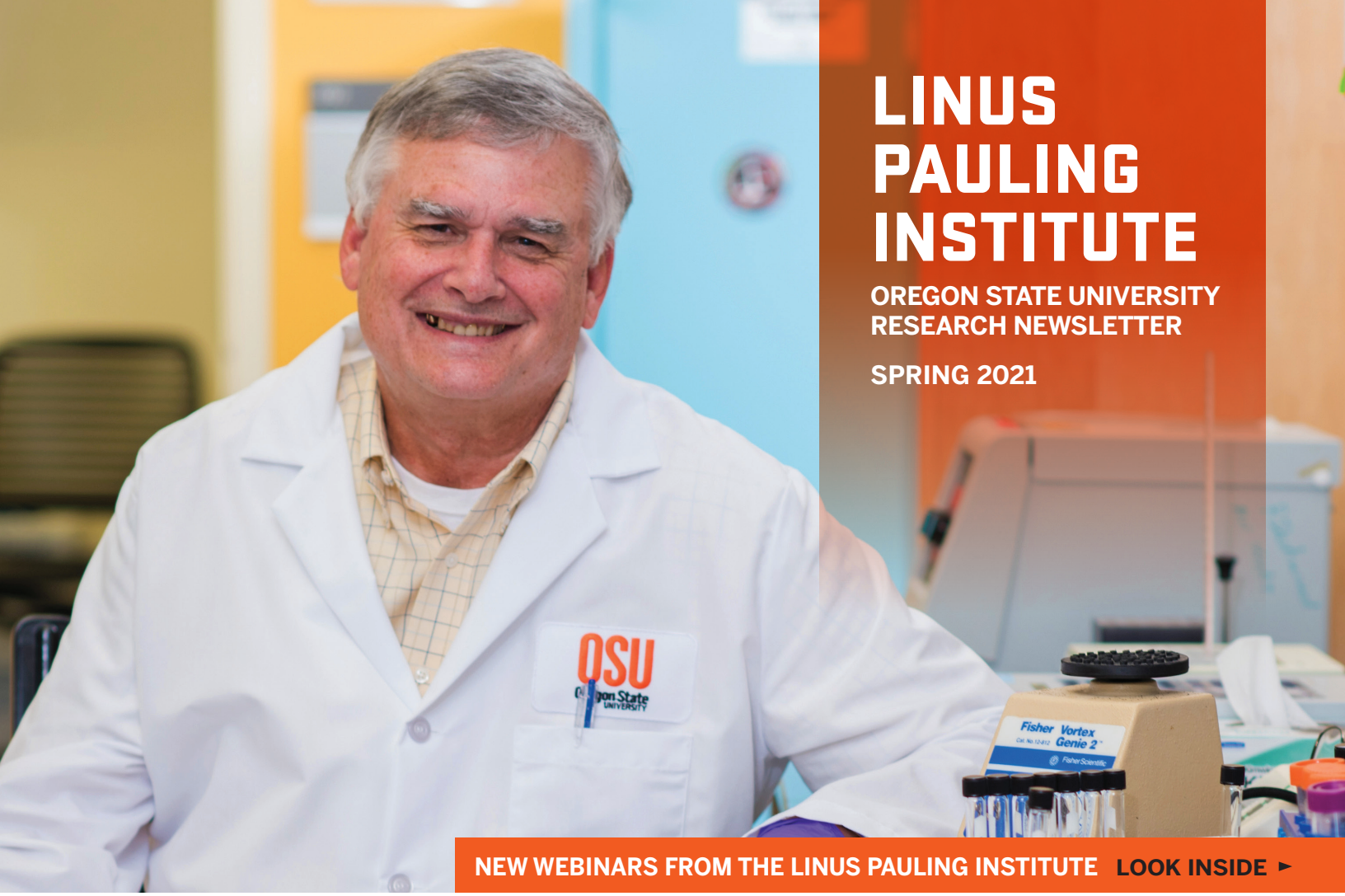

LINUS PAULING INSTITUTE

OREGON STATE UNIVERSITY
RESEARCH NEWSLETTER

SPRING 2021

NEW WEBINARS FROM THE LINUS PAULING INSTITUTE LOOK INSIDE ►

Photo credit: Hannah O'Leary

EAT, LIVE – EAT, DIE:

An Interview with Dr. David E. Williams

Each year, Oregon State University names two University Distinguished Professors. This is the highest honor granted to professors at the University.

Previous University Distinguished Professors at the Linus Pauling Institute include Drs. Donald Reed (1990), George Bailey (1995), Balz Frei (2010), and Joseph Beckman (2013).

Dr. David E. Williams, the Helen P. Rumbel Professor for Cancer Prevention at the Linus Pauling Institute, joined the ranks of University Distinguished Professors at the Institute in 2020.

We sat down with Dr. Williams to discuss his career achievements, which include discovering how certain dietary compounds might cause or prevent cancer.

Much of your career has focused on dietary indoles. What are they, and how did you start working with them?

When we talk about dietary indoles, we are referring to indole-3-carbinol, which is also known as I3C. Cruciferous vegetables contain a compound called glucobrassicin. When we chew these vegetables, an enzyme in the plant cells called myrosinase reacts with glucobrassicin to form I3C.

I began working with I3C with Dr. Roderick Dashwood and the late Dr. George Bailey, two cancer investigators at the Linus Pauling Institute. We wanted to know how I3C and other plant compounds might be protective against certain carcinogens, making them dietary anticarcinogens.

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Linus Pauling Institute

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Endowed Chair and Director,
Linus Pauling Institute

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Why a Healthy Immune System Needs Vitamin D
lpi.pub/VitaminD2021

FROM THE DIRECTOR

We are excited to celebrate the 25th anniversary of the Linus Pauling Institute at Oregon State University with a series of virtual events.

In February, we held our first webinar of 2021. *Vitamin C and Health: New Frontiers* featured four world-renowned experts, including the Institute's Dr. Maret Traber. A summary of the discussion can be found on pages 6 and 7.

In May, Dr. Adrian Gombart, the Institute's expert on vitamin D and immune function, presented our second webinar, *Why a Healthy Immune System Needs Vitamin D*. Given the latest research on the COVID-19 pandemic, this topic was especially pertinent and well received.

Our next webinar, *Why You and Your Dog Can't Find Your Keys: This is Your Brain on Aging*, will be July 8 (see below). Presented by Dr. Kathy Magnusson, this webinar will address the changes our brains go through when we age – both good and bad – and how diet and lifestyle can improve brain function.

Additionally, we will host a series of scientific webinars this fall in place of our in-person biennial Diet and Optimum Health conference. These sessions will contain more technical content and will focus on the role of nutrition in three areas: healthy aging, gut health and the microbiome, and immunity. Please visit **lpi.pub/DOHonline** for future updates and additional details.

Finally, I am proud to share that the Linus Pauling Institute raised more than $13,000 during Dam Proud Day – the annual day of giving for Oregon State University. Most donations went to the Caron and Donald Reed Fellowship Fund, which supports young scientists at the Institute.

This is a very exciting year for the Institute, and we are looking forward to sharing our science with all of you in celebration.

Sincerely,
Emily Ho

LPI STUDENT HIGHLIGHT

Graduate students at the Linus Pauling Institute must complete and successfully defend their dissertation to fulfill the requirements of a PhD program. Their success is also that of the Institute and all of the donors who supported their work.

We will feature research projects of graduate students supported by Linus Pauling Institute fellowships. We begin with Dr. Brian Head, our most recent graduate from the laboratory of Dr. Maret Traber.

Photo credit: Hannah O'Leary

A DEVELOPING BRAIN NEEDS VITAMIN E

By Brian Head, PhD

Vitamin E is necessary for embryonic development of all vertebrates. As a fat-soluble antioxidant, vitamin E helps prevent the oxidation of fatty acids in the cell. This is especially important for cell membranes rich in polyunsaturated fatty acids, which are abundant in the nervous system.

Normally, embryonic development is a highly regimented process: the order of events is very tightly controlled to carefully construct groups of cells that will eventually become the organs and bodily structures. Without vitamin E, this process breaks down.

Using a zebrafish embryo model, I discovered that vitamin E is necessary for proper development during a very critical window: the first 24 hours after fertilization. In humans, this corresponds to the first three weeks after fertilization.

My work indicates that embryos without vitamin E experience unchecked oxidative damage. This places a heavy burden on other antioxidant systems like vitamin C and glutathione.

To continue functioning, cells must spend their precious energy reserves to maintain these antioxidants. Energy is a very limited resource in young embryos, so this is a very costly process.

We believe that the zebrafish embryo senses the lack of vitamin E with a protein complex called mTOR. This is an important signaling protein at the nexus of redox balance, energy status, and cell survival.

Embryos without vitamin E do not turn on their mTOR pathway at the right time, and most don't survive. Embryos that do survive have severely delayed or disrupted nervous system development.

Adequate vitamin E is critical throughout our lifespan. I expect that future research on vitamin E will show how it is necessary for protecting an adult brain, especially as we progress into old age.

I am grateful to have received both the **Mark Sponenburgh** and **Marion T. Tsefelas Endowed Fellowships** from the Linus Pauling Institute. With these fellowships, I did not have to take time from my project to seek out other funding to support my position. Instead, I was able to spend more time in the lab studying critically timed events in embryonic development.

I hope that other graduate students at the Institute will get similar opportunities.

Dr. Head started a new position at the National Institutes of Health. He currently works in the National Institute of Child Health and Human Development studying lipoprotein metabolism, cholesterol transport, and other rare genetic defects.

Fellowships at the Linus Pauling Institute help us foster the next generation of nutrition scientists.

If you are interested in supporting the future of graduate student education, please go to **lpi.pub/Donate**

For more information, contact **Andrew.Norwood@osufoundation.org**

Photo credit: Hannah O'Leary

Continued from cover

Your first cancer studies were in trout. Why use a fish model?

At that time, it was standard practice to conduct carcinogen studies in rodents. But these trials typically used very high doses of carcinogens. It was the most effective way to study tumor formation in a small group of animals.

But those high doses did not reflect "normal" human exposures. The doses used were quite excessive, and toxicologists had to extrapolate down to a relevant range for typical human exposure levels. It was a lot of guesswork.

"To perform low-dose carcinogen trials, you need a large number of animals. With rodents, this is prohibitively expensive."

"Our first trial with trout used 40,000 animals, and we were able to increase the sensitivity of tumor detection by 50 times that observed in other animal models."

Dr. Bailey suggested using trout, where the large number of animals allowed us to use significantly lower, more realistic carcinogen doses.

We could also do dietary intervention studies with trout. In other words, we could ask whether dietary factors could help prevent or modify the development of cancer. It turned out that I3C was one such compound.

You then moved from fish to mice, creating a transplacental cancer prevention model. Can you explain that work in more detail?

When this work began, we knew that carcinogens given to a pregnant animal could be carried to the developing offspring. A maternal carcinogen exposure just days before birth could result in severe and often fatal cancers in the pups.

We were attempting something different in our cancer studies: to see if a maternal diet could protect offspring from carcinogens. Could anticarcinogens derived from food protect the expectant mother and the developing fetus?

I'm pleased to say that these animal trials were very successful. Some compounds that we tested were highly protective for the young mouse pups.

I am still amazed by the fact that the developing pups that never ate these anticarcinogen compounds themselves could be protected by the components of their mother's diet.

And dietary indoles played a starring role in this model as well?

I3C was the most protective of all of the compounds we tested. Chlorophyll and green tea extracts also seemed to be moderately protective, but the effects of the latter might have been related to the caffeine content.

Now you are working with diindolylmethane or DIM. What is DIM, and how is it formed?

DIM is essentially two I3C molecules joined together. It is only formed when two I3C molecules come together in an acidic environment like your stomach.

In general, only a modest amount of DIM is created in these reactions. There are estimates that about 40% of the I3C that you consume reacts to form DIM.

Recently, you transitioned from animal models into trials in people. Has this given you any new insights about DIM?

Right now, we're looking at the metabolism of DIM in our clinical study volunteers. We're hoping to find clues about how it might counteract the effects of carcinogen exposure.

To do this, our trials used a DIM supplement. I thought it was prudent to use a dose commonly used in supplement products. Our estimates are that a person would need to eat more than 20 pounds of Brussels sprouts to obtain a similar amount of DIM from food.

It's always tricky using compounds from plants for studies in humans or animals because metabolism complicates the picture. Our bodies don't often leave these compounds alone. Instead, they treat them as something foreign and transform them into metabolites that the body can handle using some sort of detoxification or elimination mechanism.

This is why I think it is premature to recommend taking DIM supplements. Since the research in this area is not complete, we don't know if DIM metabolites have biological activity – it's impossible to predict what effect they may have. We need to take the time to do these trials in human volunteers first.

Do you have any suggestions for anyone trying to get more DIM in their diet by eating cruciferous vegetables?

I would say that the best advice is to eat them as raw as possible. Myrosinase is easily destroyed by heat. Some light cooking like steaming is okay, but any heavy cooking can destroy the enzyme.

This enzyme isn't just important for the formation of I3C from glucobrassicin. It also reacts with glucoraphanin to form sulforaphane, which also has anticancer properties. Just one more reason to eat cruciferous vegetables.

Dr. Williams presented a retrospective review of his scientific career when accepting his University Distinguished Professor award. The video recording can be viewed at: lpi.pub/williams

READER QUESTIONS

Q. **A few years ago, the LPI recommended taking lipoic acid and acetyl-L-carnitine for brain health and memory. I have used it for years and watch for updates on this work. Your Winter 2021 issue addressed a study using only lipoic acid. Is research continuing on the combination?** *—K.S. via email*

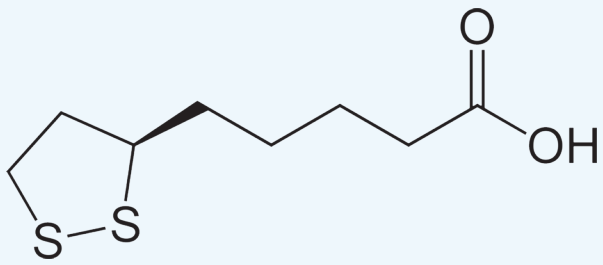
A. There are indications that the combination of lipoic acid and acetyl-L-carnitine has some benefits for older animals, but at the time of this writing, these studies have not progressed into human clinical trials.

Our recently published trial on lipoic acid was designed to explore the benefits of lipoic acid on energy metabolism but not specifically in older adults.

While the Institute continues to have an interest in this combination of supplements, we await funding opportunities to conduct studies in older adults. For more information about lipoic acid, acetyl-L-carnitine, and the current state of the research, please stay tuned for Dr. Tory Hagen's webinar later this year (date TBD).

Q. **The structure you show as alpha-lipoic acid does not indicate that it's the *R*-form, as captioned, because the bond attaching the ring to the chain is a simple line segment, not a wedge or any other means of depicting the stereochemistry at the ring carbon where the chain is attached.** *—H.W. via email*

A. You are absolutely right! The accurate structure for *R*-alpha-lipoic acid is below.



VITAMIN C AND HEALTH: NEW FRONTIERS

On February 27, the Linus Pauling Institute celebrated Linus Pauling's birthday with an online forum on vitamin C and health. This webinar was hosted by the Institute's Director, Dr. Emily Ho, and moderated by our vitamin C expert, Dr. Alexander Michels.

At this event, four of the world's top experts on vitamins and health (see below) answered questions about the new frontiers in vitamin C research and also addressed some questions that remain unanswered about how vitamin C works in the body.

Here, we present several key takeaways from the forum to give you insight into the current state of vitamin C research. We strongly encourage you to check out the video at **lpi.pub/VitCWebinar2021**. Transcripts of the event, copies of the slides, and some of the answers to attendee questions are available upon request.

Vitamin C supplement formulation is not a crucial factor.

In terms of absorption of dietary supplements, there is little difference in what type of vitamin C formulation you take, despite claims by vitamin manufacturers.

During the webinar, Dr. Anitra Carr noted that the absorption of vitamin C from synthetic sources is equivalent to that from natural sources. Additionally, Dr. Jeanne Drisko noted that there is some evidence that liposomal vitamin C is slightly better absorbed than other supplemental forms, but the differences are small.

Supplement formulation may matter if you experience heartburn after taking vitamin C supplements. In this case, look for products labeled as "buffered." These products have less acid and are therefore more gentle on the stomach.

Anitra Carr, PhD

Associate Professor
Director, Nutrition in Medicine Research Group
University of Otago, Christchurch

Dr. Carr worked at the Linus Pauling Institute as an American Heart Association postdoctoral fellow under the mentorship of former Institute Director, Dr. Balz Frei. While at the Institute, she and Dr. Frei authored several of high-impact publications on the role of vitamin C in human health and disease.

Upon returning to the University of Otago, Dr. Carr continued her research on vitamin C. She is particularly interested in the roles of vitamin C in the prevention and treatment of infection and cancer.

Jeanne Drisko, MD, CNS, FACN

Riordan Professor of Orthomolecular Medicine
Director Emeritus of Integrative Medicine
University of Kansas Medical Center

Dr. Drisko helped build the Integrative Medicine department at the University of Kansas Medical Center. She facilitated many of the studies to test the safety and efficacy of intravenous vitamin C in the treatment of cancer and infectious disease.

Dr. Drisko is a strong advocate for complementary and alternative medicine. She has a wealth of experience using intravenous vitamin C in cancer patients and has repeatedly demonstrated its benefits.

Oral vitamin C supplements cannot mimic intravenous vitamin C infusions.

Intravenous vitamin C bypasses the vitamin C absorptive control mechanisms in the small intestine. Dr. Jeanne Drisko emphasized that no amount of oral supplements can produce the same plasma concentrations of vitamin C as IV infusion.

A single intravenous infusion results in blood concentrations of vitamin C that are at least 50 times higher than that achieved with oral supplements. The unique benefits of intravenous vitamin C are due to the very high concentrations in the blood.

How does this work? Although there is much work that needs to be done, it appears that the high blood concentrations of vitamin C lead to the production of hydrogen peroxide. This is presumed to be an important factor for the effects of IV vitamin C in the body.

With intravenous vitamin C, the dose matters.

Clinical trials have explored the use of intravenous vitamin C to treat various diseases, including cancer, sepsis, and other infections. However, work in these areas has shown mixed results.

One reason we do not have a clear answer is the varied amounts of vitamin C given in these infusion trials. As Drs. Drisko and Fowler discussed, the dose of vitamin C and the timing of its administration are likely key determinants of a trial's success.

There is much we still do not know.

Dr. Maret Traber commented that limited funding opportunities have slowed vitamin research, leading many to believe that vitamin C has a limited impact on health. Our experts agree this couldn't be further from the truth. There is still much more to be discovered about vitamin C.

Alpha "Berry" Fowler, III, MD

William Taliaferro Thompson Professor of Medicine
Division of Pulmonary Disease and Critical Care Medicine
Virginia Commonwealth University

Dr. Fowler's research focuses on ways to mitigate the lung and vascular inflammation that occurs in acute respiratory distress syndrome (ARDS) and sepsis.

Dr. Fowler recently directed a multicenter trial using high-dose intravenous vitamin C to treat acute lung injury in critically ill patients with sepsis; he reviewed the results of this trial during the webinar. Dr. Fowler is also studying intravenous vitamin C as a treatment for COVID-19-related lung injury.

Maret Traber, PhD

Ava Helen Pauling Professor, Linus Pauling Institute
Professor, College of Public Health and Human Sciences
Oregon State University

Dr. Traber's research interests lie in the functions and properties of vitamin E, a major fat-soluble antioxidant in the body. Her work seeks to better define the interplay between vitamin C and vitamin E in health and disease.

Dr. Traber has long sought to better understand the effects of low vitamin E status. Currently, her focus is on embryonic brain development (see page 3).

Oregon State University
Linus Pauling Institute

LINUS PAULING INSTITUTE RESEARCH NEWSLETTER

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INSIDE: THE LINUS PAULING INSTITUTE'S WEBINAR ON VITAMIN C AND HEALTH

CREATE A LEGACY OF HEALTH

WE CAN IMPROVE LIVES FOR GENERATIONS TO COME with our research and outreach programs. Continuing the Pauling legacy, the Linus Pauling Institute seeks to discover and share the new ways that nutrition can help people everywhere achieve the best of health.

What will your legacy be?

Would you like to learn more about how thoughtful legacy planning can help you:

- Create a tax-wise estate plan that is healthy for both you and your family?
- Support the charities you love, while maintaining healthy assets?
- Consider a charitable gift that creates a healthy income for life?

If yes, please join our ***Create Your Legacy*** **webinar on July 21 at 10 AM PDT.** Register online at **lpi.pub/Legacywebinar**

For more details on the webinar, contact Andrew Norwood: 503-936-0086 or **Andrew.Norwood@osufoundation.org**

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