



LINUS PAULING INSTITUTE

OREGON STATE UNIVERSITY
RESEARCH NEWSLETTER

FALL-WINTER 2017

The new director of the Linus Pauling Institute is announced. **LOOK INSIDE ►**

BROCCOLI AND LONG NON-CODING RNAs

EXPLORING NOVEL ROUTES OF EPIGENETIC REGULATION THROUGH NUTRITION

By **Laura M. Beaver, Ph.D.** and **Emily Ho, Ph.D.**

If you only take away one message from this article, it would be this: Eat more broccoli.

Everyone knows that broccoli is good for you. It is low in calories, packed with fiber and a variety of micronutrients, and is a part of the cruciferous vegetable family (see page 5). However, there is more to broccoli than this: And we want to share our exciting new discoveries about broccoli that may help convince you to put more of it on your plate.

Here we discuss sulforaphane, a phytochemical your body can obtain from consuming broccoli, and how it may relate to cancer prevention. This is through changing the expression of genes that were, until recently, thought of as *junk*.

In the past, researchers believed that the DNA and RNA in our cells had only one known

function: providing instructions to make protein. “Junk DNA” is a term that applies to the DNA sequences that do not code for protein and therefore considered unimportant, just random junk found in chromosomes. However, some of these DNA sequences provide the code for RNA molecules that can be found in cells. There are multiple types of this ‘non-coding’ RNA, and in this article we will explore a class of these RNA molecules termed long non-coding RNA or **lncRNA**.

Although these RNAs do not produce proteins, there are thousands of lncRNAs in the human genome (and likely many more still to be discovered). Interestingly, lncRNAs tend to be tissue specific; for example, lncRNA1 is found only in the prostate, while lncRNA2 is found only in the brain and spinal cord. But because lncRNAs are often expressed at much lower levels than most other RNAs that code for functionally significant proteins in the body, they have largely been ignored. Further, genes that code for lncRNAs are not as conserved from one species to the next, which is a traditional sign of “important” DNA within the cell.

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FROM THE DIRECTOR



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

“This past year, the combined LPI faculty trained 34 graduate students, 29 postdocs and visiting scholars, and 57 undergraduate students in their laboratories.”

— Jan Frederik Stevens, Ph.D.

Fall has come to Oregon, after a very productive summer for the Linus Pauling Institute. This September, the LPI hosted the ninth biennial Diet and Optimum Health conference (see page 6). Over 180 participants from more than a dozen countries came to hear from a select group of recognized experts in the areas of molecular nutrition, vitamins, lipid metabolism, and gut microbiota. At the conference banquet, we celebrated the 20th anniversary of the LPI at Oregon State University with an amazing gift from Joahn H. Facey, we honored Director Emeritus Dr. Balz Frei with the LPI Prize for Health Research, and we welcomed the new Director of the Linus Pauling Institute, Dr. Richard van Breemen. Overall, it was an extremely successful event.

With summer now over, more than 25,000 students have returned to campuses in Corvallis and Bend for a new academic year at OSU. Many students are now seeking health-related research opportunities in LPI laboratories to gain hands-on experience and to strengthen their applications for admission to graduate school, medical school, or other professional healthcare programs. This past year, the combined LPI faculty trained 34 graduate students, 29 postdocs and visiting scholars, and 57 undergraduate students in their laboratories. In this newsletter, LPI students Yang Zhang, Bharath Sunchu, and Lea Sophie Ullrich are telling their stories on page 14.

The reorganization of the LPI Core Laboratories I mentioned in the previous newsletter is now complete. Focusing on metabolomics, bioinformatics, and metabolic phenotyping, with strong ties to clinical and translational research, we are positioning ourselves better for federal funding opportunities. With help from Oregon State University’s Research Office, the College of Public Health and Human Sciences, and the College of Pharmacy, we are now operating a Promethion metabolic phenotyping system in our Biological Models and Translational Research Core. Dr. Kate Shay has more in this newsletter on what this system can do to foster research on metabolic health and physical activity (see page 11).

Federal grants are still difficult to obtain. LPI faculty have applied for more grants this past year than the year before. Six LPI proposals seeking support from the National Institutes of Health (NIH) scored in the top 15% nationally, and three of these were selected for funding. Two of the NIH award winners, LPI Principal Investigators Viviana Pérez and Kathy Magnusson, plan to study cellular aging in the brain and what it means for our understanding of Alzheimer’s disease. See more about Dr. Pérez’s work and their grant in this newsletter, starting on page 8.

And now for the “Changing of the Guard”:

It gives me great pleasure to announce that the next director, Richard van Breemen, Ph.D., will start his appointment in January 2018. By way of introduction, Dr. van Breemen, currently a Professor of Medicinal Chemistry and Pharmacognosy at the University of Illinois at Chicago, is one of the foremost leaders in the qualitative and quantitative analysis of botanicals and dietary supplements using mass spectrometry techniques. Dr. van Breemen and his group have developed innovative methods for chemical analysis of botanicals and novel technologies for rapid identification of bioactive compounds in botanicals and dietary supplements.

This area of research is important because dietary supplements may be harmful to human health if they interact with drug-metabolizing enzymes and if they contain toxic natural products due to herbal misidentification or due to adulteration with cheaper but harmful ingredients.

For the past seven years, Dr. van Breemen has directed the NIH Center for Botanical Dietary Supplements Research in Chicago, which has a focus on botanical dietary supplements used by women seeking alternatives to hormone therapy for relief of menopausal symptoms. His group will continue studying the safety and efficacy of dietary supplements at the LPI. All of us at the Institute support Dr. van Breemen, and we are looking forward to working with him and his group. Please feel free to contact Dr. van Breemen in the coming months,



The four directors of the Linus Pauling Institute (from left to right): Dr. Don Reed, Dr. Balz Frei, Dr. Fred Stevens, and Dr. Richard van Breemen

and you will undoubtedly be hearing much more from him and his group in the spring.

Our Executive Assistant, Barbara McVicar, has announced her retirement from the Linus Pauling Institute. Barbara has been with the Institute for nearly all of its history at Oregon State University, serving all three directors to date: Donald Reed (1996-1997), Balz Frei (1997-2016), and me. With such an astounding career at LPI, her contributions to our success are difficult to summarize. Dr. Frei once wrote: "It is not an exaggeration to say that neither my own effectiveness and accomplishments as LPI Director nor the rapid progress of the Institute itself would have been possible without Barbara."

For over two decades, we have relied upon Barbara for all the Institute's needs. Her commitment and initiative show clearly in her tireless efforts to help us achieve success. Reflecting upon a career

at LPI, Barbara has seen the Institute change from humble beginnings at OSU after leaving Palo Alto. One of her favorite parts of the job was being able to help you – the reader – when you call or email looking for answers to a question, more information, or just a friendly ear. All of us will miss her presence at the front desk at the LPI. I encourage everyone to read more of her recollections about her time at the Institute on page 12.

Barbara's last day working for the Institute is at the end of this year. Although that day is fast approaching, we have her successor in training: Caitlyn Reilley, formerly a volunteer worker with our Healthy Youth Program, is learning many of Barbara's daily duties. Caitlyn is also a recent graduate of OSU's College of Public Health and Human Sciences, and thus is very familiar with the University and LPI. For those of you who have interacted with

Barbara over the years, please introduce yourself to Caitlyn when you call or email.

Finally, I would like to thank you all for your support in my time as interim director. It has been an honor and privilege to serve the LPI in this role, and I am pleased with the successes we have achieved in my short tenure in this office. Though I am stepping aside, I am not going far. I will resume my academic activities as professor, principal investigator, and journal editor. You will continue to see advances and developments from my laboratory in the future.

Sincerely,

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



Laura M. Beaver, Ph.D.
LPI Investigator



Emily Ho, Ph.D.
Professor, School of Biological & Population Health Sciences; Endowed Director, Moore Family Center for Whole Grain Foods, Nutrition & Preventive Health; LPI Principal Investigator

Then came a turning point: the discovery that individual lncRNAs were found to have specific functions. These functions could be diverse, such as creating subcellular structures or regulating the expression of genes that code for proteins, but lncRNAs may have critical roles in cells. Furthermore, recent advances in RNA sequencing led to the discovery that lncRNAs are dysregulated in many diseases, including cancer, and may be key components of epigenetic regulatory networks.

with genes that regulate cell cycle, signal transduction, and metabolism – all important players in cancer development. So, we took a step further and explored the role of just one of these lncRNAs called LINC01116, an RNA that is relatively high in aggressive prostate cancer cells and also in other types of cancer cells. Sulforaphane treatment appeared to do exactly what we expected: It decreased the expression of LINC01116 about 50% compared to untreated cells. Artificially reducing the levels of this lncRNA shows that LINC01116

Compounds from the food that we eat have the potential to alter the expression of lncRNAs, and this may play a role in our health.

–Laura M. Beaver, Ph.D.

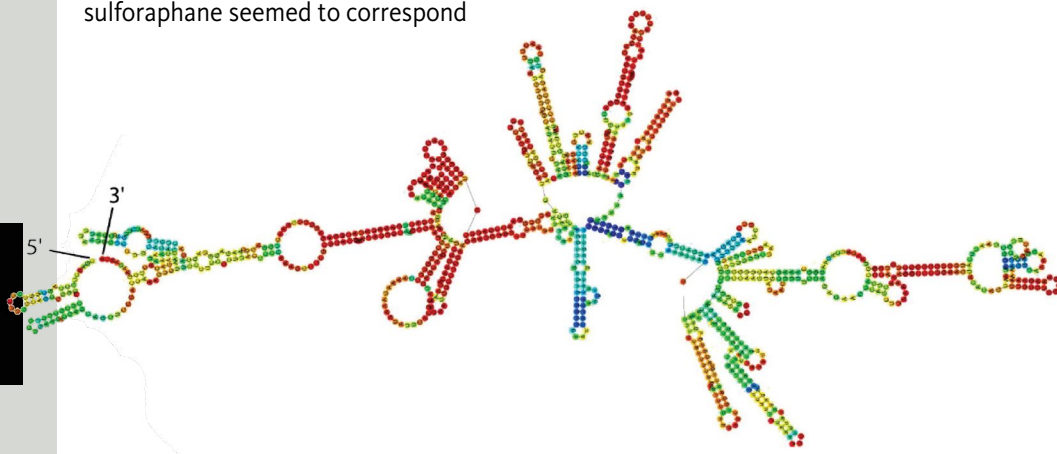
As it turns out, some of these non-coding RNAs aren't junk after all.

This is when our laboratory began to explore the possibility that lncRNAs might also have a role in cancer prevention. We did this using sulforaphane because it can prevent and suppress cancer in animal models. Sulforaphane is toxic to prostate cancer cells in culture, but non-toxic in normal (non-cancerous) prostate cells. Using RNA sequencing, we tested the hypothesis that sulforaphane changes the expression of cancer-associated lncRNAs in human prostate cancer cells. Interestingly, the treatment altered the expression of about 100 different lncRNAs and even normalized the expression of some lncRNAs that were dysregulated in prostate cancer.

participates in regulating the expression of some genes involved in glycolysis, autophagy, and chromatin structure. These studies also showed that reducing LINC01116 levels decreased the ability of prostate cancer cells to grow and form colonies. This is a positive outcome in cancer, where you want to inhibit the ability of the cells to grow or invade new areas of the body.

Although we still are unsure about exactly how LINC01116 functions in cells, our work suggested that it might form a folded structure (see image below) that interacts with the DNA of potential target genes by creating an RNA-DNA triplex, and this may influence how neighboring genes are activated.

The lncRNAs that changed with sulforaphane seemed to correspond



Graphical representation of LINC01116. This is one of the possible configurations the molecule could adopt that would allow it to interact with proteins and DNA.

Even as our work in prostate cancer was progressing, a parallel story was developing in labs of our collaborators with respect to colon cancer. The research began with the sequencing of RNA from sulforaphane-treated human colon cancer cells and non-cancerous colon cells. With sulforaphane treatment, a non-coding RNA named NMRAL2P increased dramatically, also appearing to have an anti-cancer function. NMRAL2P appears to be under the control of Nrf2, a master regulatory protein in stress response and aging. Further, NMRAL2P regulates the expression of a gene called NQO1, which participates in the protection of cells against oxidative stress. By manipulating NMRAL2P levels, we found evidence that sulforaphane has cancer suppressive properties in colon cancer cells in part through NMRAL2P.

Our findings highlight some of the exciting new ideas that have been emerging about non-coding RNA. The first is that lncRNAs are promising new targets that could be manipulated for cancer prevention. The second is that compounds from the food that we eat have the potential to alter the expression of lncRNAs, and this may play a role in our health. Eating cruciferous vegetables is associated with a decreased risk of cancer in some studies – is this through the involvement of lncRNAs?

We thus arrive back at our take-home message: Please eat more broccoli, broccoli sprouts, Brussels sprouts, bok choy, cabbage, or any other cruciferous vegetable that appeals to you. Most of them are reasonably priced, easy to find, and taste pretty good. For many reasons, including the production of sulforaphane, they are generally good for your health. Enjoy!

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Beaver, LM et al., J Nutr Biochem. **42** (2017) doi: 10.1016/j.jnutbio.2017.01.001
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THE HEALTH BENEFITS OF CRUCIFEROUS VEGETABLES

FROM THE MICRONUTRIENT INFORMATION CENTER

Nutrients and phytochemicals in cruciferous vegetables like broccoli synergistically contribute to health promotion. Broccoli is healthful for many reasons: It is a good source of vitamins (like folate, vitamin C, and vitamin K), minerals (magnesium and potassium), and dietary fiber. Like other cruciferous vegetables, broccoli also contains glucosinolates that can form sulforaphane – an isothiocyanate that may have cancer-fighting properties – and many other bioactive compounds.

Glucosinolate compounds are the source of the bitter taste found in broccoli and other cruciferous vegetables. Glucoraphanin, a glucosinolate, can be converted to sulforaphane. This only happens when the vegetable is chewed or chopped, because an enzyme released from the plant is necessary for the process. Cooking the vegetables inactivates the enzyme needed for this conversion, but light cooking (i.e., steaming for no more than 5 minutes) will preserve some of the enzyme activity.

Cruciferous vegetables are a family of *Brassica* vegetables that also includes

Brussels sprouts, bok choy, cabbage, cauliflower, kale, arugula, horseradish, radishes, turnips, watercress, and wasabi. High intakes of cruciferous vegetables have been associated with lower risks of cardiovascular disease and several site-specific cancers, including prostate, stomach, colorectal, bladder, lung, kidney, pancreatic, and breast cancer. However, the evidence supporting these effects is not particularly strong due to the nature of the studies that were conducted. Thus, this topic requires more research.

Learn more about cruciferous vegetables and their bioactive compounds in these recently updated articles in the LPI Micronutrient Information Center:

lpi.oregonstate.edu/mic/food-beverages/cruciferous-vegetables

lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/isothiocyanates

lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/indole-3-carbinol

DIET AND OPTIMUM HEALTH 2017

THE LINUS PAULING INSTITUTE'S 9TH BIENNIAL CONFERENCE



The Linus Pauling Institute held the Diet and Optimum Health conference on the Oregon State University campus in Corvallis from September 13-16, 2017. The conference featured 39 speakers from many different countries, presenting in 13 different sessions around the central theme of the conference: Innovative Approaches to Improving Health.

The conference started with **A Tribute to Balz Frei**, a session dedicated to our director from 1997-2016. Dr. John Keaney, who worked with Dr. Frei before he came to the Linus Pauling Institute, started the session with a background on vitamin C and its roles in protecting the vasculature. Dr. Roderick Dashwood, formerly of the Linus Pauling Institute, then spoke about his projects on dietary indole compounds and sulforaphane from cruciferous vegetables – work influenced by Dr. Frei's involvement. Lastly, Dr. Helmut Sies, LPI Prize award winner from 2013, talked about the “Redox Code,” detailing electron reaction systems prominently featured in Dr. Frei's work over the past few decades.

Components of our diet that promote or inhibit the growth of beneficial bacteria in the colon were outlined in **Dietary Components and the Microbiome**. **The Metabolism of Bioactives** continued this theme, focusing on how polyphenolic compounds may be altered by an interplay

of our microbiome and our cells, transforming them into a number of different molecules with properties that we are just beginning to explore. The impact bioactives may have on human health was elucidated further in **Bioactives and Cancer Prevention**, with a focus specifically on modifying epigenetic signals.

Lipid Metabolism challenged our views on how fats behave in the body, including the benefits of medium-chain fatty acids and how lipid oxidation might trigger a newly described form of cell death. Next, **An Update on Vitamin E**, with three presentations followed by a round-table discussion, was dedicated to understanding new roles and requirements of this poorly understood lipid-soluble vitamin.

Nutrition and Brain Health had a diverse set of talks that investigated various aspects of the diet on cognitive function, including the impact of certain herbal supplements, high-fat diets, and vitamin C deficiency. The oxidation of a mitochondria-specific phospholipid, cardiolipin, was also indicated as a target for therapies in traumatic brain injury.

The Linus Pauling Institute was particularly excited to host the last full day of the conference: an all-day session on vitamin C, addressing **Mechanisms of Vitamin C in Cancer, Intravenous Vitamin C Therapy in Cancer, and Intravenous Vitamin C Therapy in Sepsis**. These sessions built upon Linus Pauling's seminal work with vitamin C starting in the 1970s, extending out into the mainstream, but they also covered new frontiers that expounded on the theories of Pauling and many other early vitamin C pioneers. The case reports of individuals who

had their lives changed by intravenous vitamin C therapy were particularly moving and served as a validation of the power behind this fascinating molecule.

The final session of the conference was the free public session, focusing on cancer prevention and treatment, and featuring Drs. Emily Ho and Jeanne Drisko. Dr. Ho spoke of her work with sulforaphane (see front page) and dietary approaches to cancer prevention, and Dr. Drisko focused on the history and modern use of intravenous vitamin C in cancer treatment.

The LPI's Young Investigator Award, given to graduate students and postdoctoral researchers, went to four outstanding young scientists: Yang Zhang from the Linus Pauling Institute (featured on page 14), Shilpy Dixit from Vanderbilt University, Martin Pearce from Oregon State University, and Geoffrey Sasaki from The Ohio State University.

Major conference donors included LivOn Labs, Bayer AG, TishCon Corporation, Nu Skin/Pharmanex, and DSM Nutritional Products. We would also like to highlight the support of Ms. Karen Sharples from Vancouver, Washington, who has supported many of our conferences, as well as our long-time supporter, the Oxygen Club of California.

Thanks to all who participated in and attended the conference this year. The next Diet and Optimum Health conference will be held in 2019.

Diet and Optimum Health consisted of 13 sessions focusing on many innovative approaches to improving health. A full conference program, with videos, photos, and sponsors can be found at lpi.oregonstate.edu/DOH

LINUS PAULING INSTITUTE PRIZE FOR HEALTH RESEARCH

The 2017 Linus Pauling Institute Prize for Health Research was awarded to Dr. Balz Frei, in honor of his dedication to micronutrient and phytochemical research. A respected name in many fields, Dr. Frei's contributions total over 350 published articles, which together have been cited by his peers more than 23,000 times. Papers noted by his colleagues include:

- *Ascorbate is an outstanding antioxidant in human blood plasma* (1989)
- *Vitamin C prevents metal ion-dependent initiation and propagation of lipid peroxidation in human low-density lipoprotein* (1995)
- *Increase in circulating products of lipid peroxidation (F₂-isoprostanes) in smokers. Smoking as a cause of oxidative damage* (1995)
- *Does vitamin C act as a pro-oxidant under physiological conditions?* (1999)
- *Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions* (2003)

As the director of the Linus Pauling Institute, Dr. Frei grew the Linus Pauling Institute from a small group of only six people into a robust, thriving research enterprise with 12 principal investigators supported by a team of dozens of students, scientists, and staff. Thanks to his direction, the Linus Pauling Institute has become a respected name in molecular nutrition. In addition to the scientific accomplishments, under his leadership LPI established a 105,000-square-foot facility with modern laboratories, cutting-edge technologies, and the space needed for LPI researchers to interact and innovate.

And last, but not least, Dr. Frei established two outreach programs at the Linus Pauling Institute: the Healthy Youth Program and Micronutrient Information Center. The Healthy Youth Program is dedicated to implementing knowledge on healthful eating and a healthy lifestyle in local

communities. Currently it has partnerships with many community organizations, including local hospitals, allowing it to reach upwards of 1,200 children and families in just this past year.

The Micronutrient Information Center is a website that disseminates freely available, evidence-based information on vitamins, minerals, phytochemicals, and other dietary factors in health and disease. Averaging more than one million visitors annually, this website is read by people around the globe. Currently available in English and Spanish, it soon will be translated into Japanese.

“Doing basic research is important, but it is equally important to come out of the ivory tower and really help people make the right decisions regarding the use of diet and dietary supplements for their health.”

–Balz Frei, Ph.D.

Although his early career focused on vitamin C and atherosclerosis, Dr. Frei and his lab team at the LPI made important inroads into the mechanistic actions of phytochemicals and polyphenols. Under his leadership, LPI researchers broke new ground in research on catechins in tea, quercetin in onions, sulforaphane in broccoli, and xanthohumol in hops, just to name a few. Their findings have generated new knowledge for preventing pathological conditions, such as cancer, metabolic syndrome, neurodegenerative disease, and cardiovascular disease.

With the 2017 Linus Pauling Institute Prize for Health Research, we recognize Dr. Frei's tireless efforts to build and transform the field of micronutrient research into what it has become today, and helping to advance the field of molecular nutrition into the 21st century.



Dr. Balz Frei at the 2017 Diet and Optimum Health conference.

The Linus Pauling Institute Prize for Health Research is awarded in recognition of innovation and excellence in research relating to the roles of vitamins, essential minerals, and phytochemicals in promoting optimum health and preventing or treating disease, and the roles of oxidative and nitrative stress and antioxidants in human health and disease. The prize also recognizes successful efforts to disseminate and implement knowledge on diet, lifestyle, and health to enhance public health and reduce suffering from disease.

The award was presented to Dr. Frei during the Diet and Optimum Health conference this year, surrounded by his friends and family. Many speakers who spoke in other sessions also mentioned the impact that Dr. Frei had on their personal and professional lives. Dr. Fred Stevens, interim director of the Linus Pauling Institute, made the award presentation; the video of the award ceremony and tributes to Balz Frei are available online at lpi.oregonstate.edu/frei

COMBATING CELLULAR SENESCENCE

A NEW FUNCTION DISCOVERED FOR RAPAMYCIN, A COMPOUND THAT MAY HELP SLOW AGING

By Alexander Michels, Ph.D.



Dr. Viviana Pérez and her team (pictured: Bharath Sunchu) research the basic biology of aging on a cellular level.

When cells accumulate significant damage, they typically initiate a process of cell death. Depending on the type of cell and the amount and nature of the damage involved, this is usually an orderly process, and neighboring cells do not suffer any untoward consequences. However, there are times when a damaged cell does not initiate this process – instead, it stops cell division in an attempt to survive the damage. This is known as cellular senescence.

The problem is that senescent cells are not always quietly active inside organs – they can secrete a number of pro-inflammatory molecules that alter the proper function of healthy, adjacent cells. Researchers refer to this as the **senescence-associated secretory phenotype, or SASP**.

In other words, they become noisy neighbors.

Senescent cells aren't all bad – they can play important roles in the body (see sidebar on page 9). Yet, SASP-positive cells increase in tissues as we get older, so the process of cells turning toward senescence is broadly linked to aging. And, an increase in cellular senescence has been linked with

cardiovascular disease, diabetes mellitus, and cancer, among other age-related diseases.

Viviana Pérez, Ph.D., a member of the Healthy Aging Program at the Linus Pauling Institute, focuses on finding ways to prevent or delay senescence as a possible route for preventing disease. Her research group focuses on a compound called rapamycin.

Rapamycin, also called Sirolimus, is found in bacteria and was initially investigated for its use as an anti-fungal treatment. However, it was later discovered that rapamycin had potent anti-inflammatory and anti-proliferative properties that allowed it to be widely used to prevent tissue rejection in transplant patients. It is also approved for use in treating a rare, progressive lung disease.

Rapamycin became a compound of interest in aging research because it can mimic the effects of dietary restriction, which in some animals has been proven to extend their lifespan. It also has a clear role in combating cellular senescence in animals.

“Increases in cellular senescence are associated with aging. The associated inflammation can set the stage for a wide

variety of diseases, including cancer, heart disease, diabetes, and neurological disease, such as dementia or Alzheimer's,” Dr. Pérez explains. “In laboratory animals when we clear out senescent cells, they live longer and have fewer diseases. And rapamycin can have similar effects.”

Laboratory mice that have received rapamycin have demonstrated increased fitness, less decline in physical activity with age, improved cognition and cardiovascular health, less cancer, and a longer life.

Researchers had previously determined one mechanism of action for rapamycin in preventing SASP: It boosts the activity of Nrf2, a master regulator protein that can induce the expression of up to 200 genes responsible for cell repair, detoxification of carcinogens, protein and lipid metabolism, and antioxidant protection. The culmination of these Nrf2-driven processes reduce levels of SASP in laboratory models.

Dr. Pérez's group has now discovered a new mechanism for rapamycin in stopping cellular senescence. They concluded – in two newly published studies – that rapamycin reduces SASP separate from

a pathway involving Nrf2. This route of rapamycin's action could cause a direct reduction of inflammatory markers in cells, preventing senescence formation when damage occurs. However, at present the use of rapamycin to help prevent human disease is limited due to the side effects, like insulin resistance, that can occur.

Dr. Pérez has now brought her work on senescence to neurological disease in a newly funded grant from the National Institutes of Health's National Institute on Aging. This 5-year grant will support Dr. Pérez's work on determining the impact cellular senescence plays in the development of **Alzheimer's disease** in newly developed animal models.

In part of the grant, Dr. Pérez and her collaborators will develop a new animal model for investigating the role senescent cells play in Alzheimer's disease. In this model, the senescent cells that naturally develop in the brain or other tissues can be removed by administering a specific compound to the animals.

Dr. Pérez's collaborators in San Antonio will assist by monitoring changes in memory and behavior in these animals. In the LPI, Dr. Kathy Magnusson will help evaluate synaptic function in the isolated brain tissue. If the team determines that the disease stops or slows when the senescent cells are removed, it provides evidence for their theory that Alzheimer's or other neurological conditions may be treated by targeting senescent cells in the body. They also plan to measure the impact of compounds like rapamycin that are purported to limit the negative effects of senescent cells.

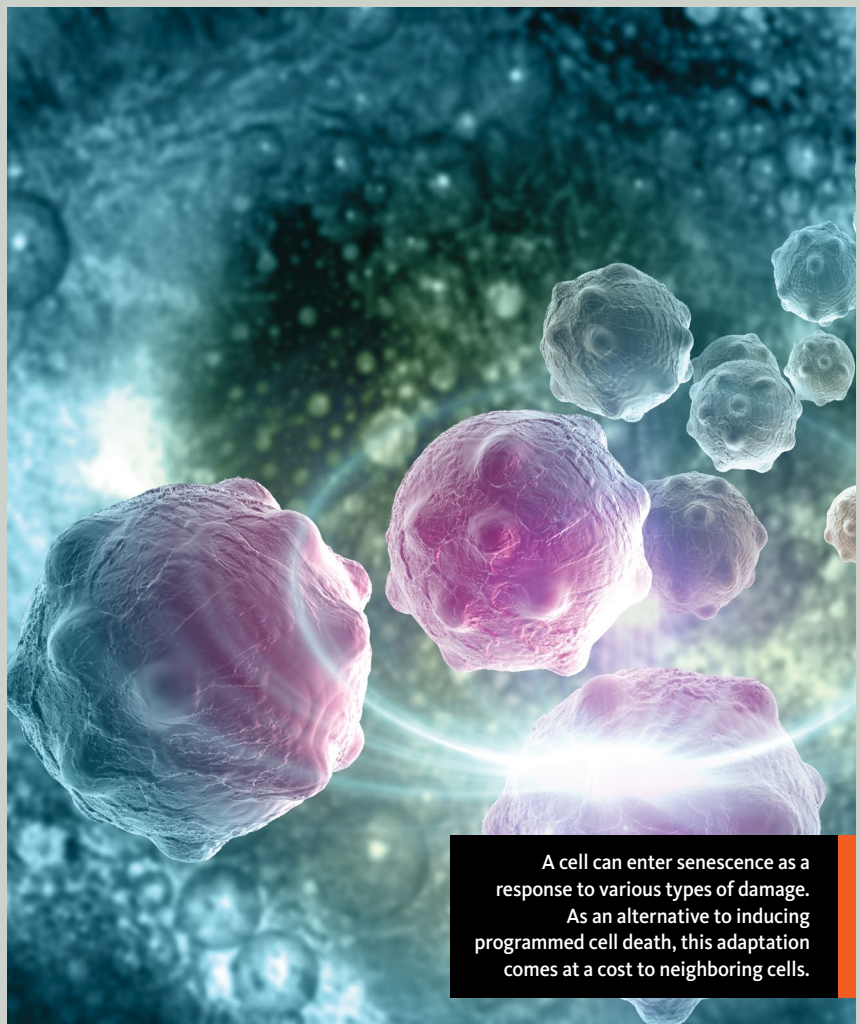
The hope is that this will eventually lead to new breakthroughs in treating a variety of neurological diseases in humans. "We know that cells in the brain can be damaged by SASP," explains Dr. Pérez. "Since these cells help protect neuronal function and health, rapamycin could lead us toward a new approach to treating Alzheimer's disease in the future."

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Wang, R et al., Aging Cell. **16** (2017) doi: 10.1111/ace1.12587

Wang, R et al., Exp Gerontol. **94** (2017) doi: 10.1016/j.exger.2017.01.026



A cell can enter senescence as a response to various types of damage. As an alternative to inducing programmed cell death, this adaptation comes at a cost to neighboring cells.

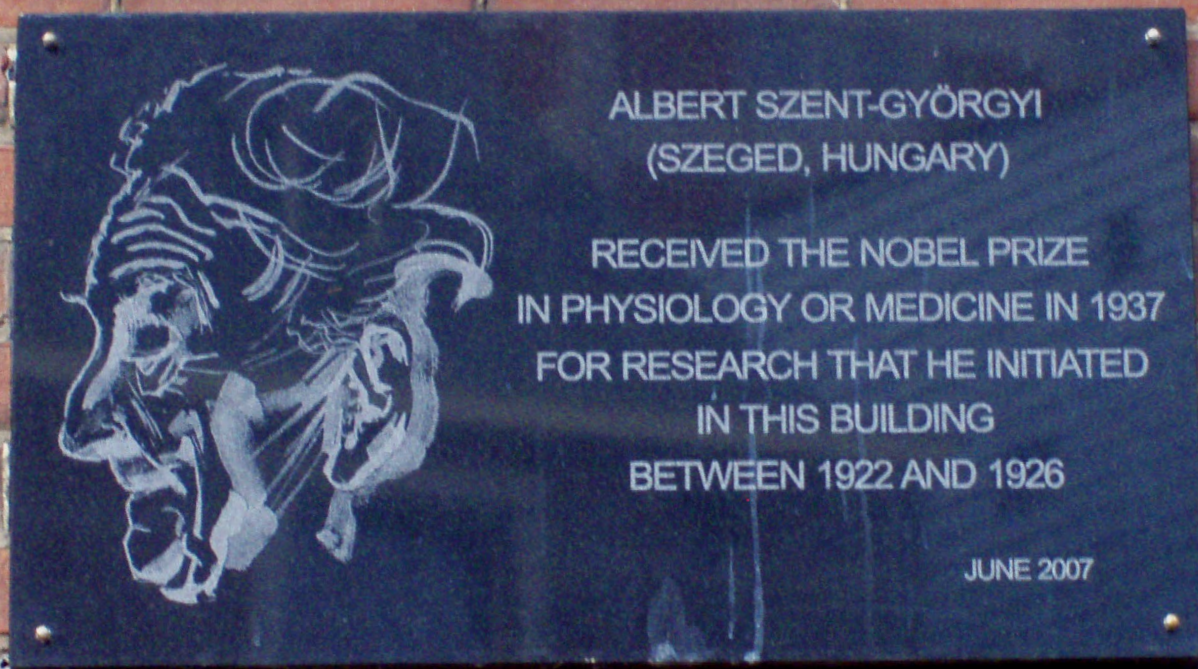
WHAT IS CELLULAR SENESCENCE?

Senescence is a form of aging that limits the capacity of cells to divide. It is normal for cells to stop dividing after they undergo a certain number of divisions, especially when telomeres – the ends of our chromosomes – shorten past a particular point. This is usually a signal to the cell that it risks incurring permanent damage if it undergoes another replication cycle. Senescence is a way for the cell to remain alive and contribute to tissue functions without dividing.

It is also extremely important for cells that have undergone particular types of stress, especially DNA damage or oncogene activation, to limit their ability to replicate – cells laden with damage

could lead to the development of cancer. Although cells would normally initiate an orderly process of programmed cell death called apoptosis, i.e., a systematic removal of the troubled cell, apoptosis is not always a viable option. Thus, some cells can remain in a senescent state for a prolonged period.

Senescence can also be part of a programmed series of events. For example, senescence helps form certain structures in the body in a developing embryo. It also may be an important process in wound healing. At this time, it is not entirely clear how and when senescence is preferred to apoptosis, but researchers in this field are currently examining these questions.



IGNOSE, GODNOSE, HEXURONIC ACID, ASCORBIC ACID...VITAMIN C!

By Jan Frederik Stevens, Ph.D.

In 1995, I graduated from the University of Groningen, the Netherlands. I have since visited my alma mater a couple of times. During my visit in 2010, I noticed a plaque on the east wall of the old physiology building where I took classes in applied physics and pharmacology (see picture).

Dated June 2007, the plaque draws attention to discoveries made by Dr. Albert Szent-Györgyi in that very building. While I stood there to take a picture of the plaque, I was greeted by Professor Ben Westerink who apparently recognized me and asked, "On a pilgrimage?"



Dr. Albert Szent-Györgyi, a Hungarian biochemist interested in cellular respiration, first isolated vitamin C in search for biological inhibitors of oxidation. He won the Nobel Prize in Physiology or Medicine in 1937.

You see, one of the natural substances that was discovered in that building ultimately turned out to be vitamin C.

Since that plaque was not in that facility until recently, it left me wondering why it took so long for the University to recognize Dr. Szent-Györgyi's early work. Although his studies in this building (1922-1926) resulted in six impactful papers published in *Biochemische Zeitschrift*, few professors at the University thought much of his work at the time. One professor was of the opinion that Dr. Szent-Györgyi's paper on the respiration of plants 'should be thrown in the wastepaper basket' (J.J. Beintema, *Journal of the History of Biology*, 2008, volume 41).

The compound Szent-Györgyi isolated inhibited biological oxidations and was abundantly present in adrenal glands. Disappointed that the substance from adrenal extracts did not rescue adrenalectomized cats, Dr. Szent-Györgyi left Groningen to work on the chemical characterization of the compound at the University of Cambridge. Although he

thought he had discovered an essential adrenal hormone, he actually had isolated a carbohydrate.

Without knowing the exact structure of the substance, Dr. Szent-Györgyi called it 'ignose' – derived from Latin '*ignorare*' meaning 'to not know' and the suffix '*ose*' to indicate it was a sugar-like compound. When he went to publish his results, the editors of the *Biochemical Journal* asked him to rename the compound. He then suggested 'Godnose' (only God knows) as a name for the molecule. This name was also rejected, and the editors and Dr. Szent-Györgyi finally agreed on the name 'hexuronic acid.' When hexuronic acid was discovered to prevent scurvy, it was later renamed 'ascorbic acid' to reflect these anti-scorbutic properties: in other words, it was vitamin C.

Dr. Albert Szent-Györgyi received the Nobel Prize in Physiology or Medicine in 1937 for his work in biological oxidation reactions, including the discovery of vitamin C. Other Nobel laureates from Groningen are Heike Kamerlingh Onnes (Physics, 1913), Fritz Zernike (Physics, 1953), and Ben Feringa (Chemistry, 2016).

METABOLIC MONITORING IN LABORATORY ANIMALS

By **Kate Shay, Ph.D.**

The purpose of metabolic monitoring is to get very precise information about metabolic activity in an individual.

Metabolic monitoring can take many forms, with a variety of methods used to measure metabolism. Ultimately, regardless of the technique used, the results give you information about the energy utilized by the body.

More accurate and detailed information comes from more constant monitoring. The most definitive information about metabolism comes from individuals in a metabolic ward, a controlled environment where the calorie intake and output is carefully monitored. However, for obvious reasons, most people do not want to be stuck in a hospital-like environment for days at a time. Indeed, the demands of these types of experiments are often quite impractical in humans; thus, we usually make use of laboratory animals.

The Linus Pauling Institute recently acquired a Promethion metabolic phenotyping system, used to monitor various aspects of metabolism in laboratory animals. In general, this system gives us a picture of energy use over time. For our purposes, it is especially useful to test how compounds of interest can influence metabolic rate. If researchers want to know whether lipoic acid can support weight loss, for example, the

various features of the Promethion system can tell us whether animal models fed that compound burn more calories.

The primary goal of using the Promethion system is accurate tracking of energy expenditure. The system has the capacity for real-time monitoring of exhaled gases

The Promethion system gives the Linus Pauling Institute a greater capacity to conduct high-quality metabolic research in laboratory animals.

– imagine a constant connection to a gas analyzer for everything you do, even when you sleep. In this case, however, continuous monitoring of the entire animal housing unit by an array of sensors does not interfere with daily activity. The animal is unaware of the monitoring, and behaves as it would normally.

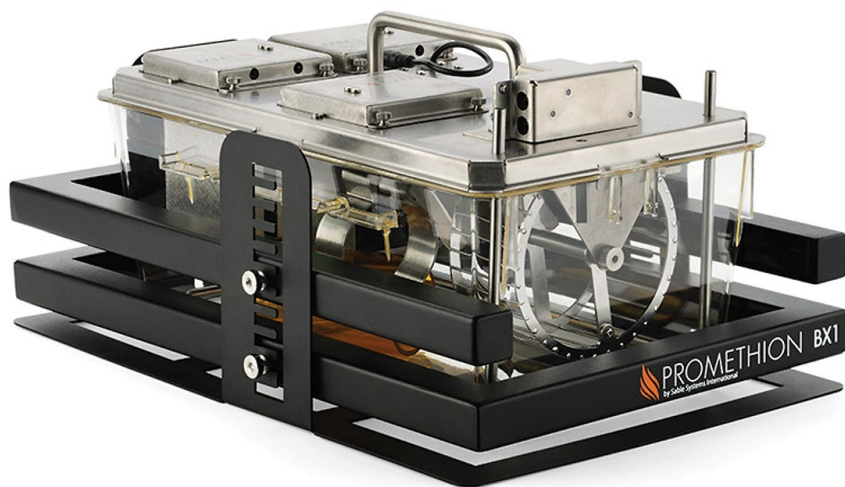
The system estimates energy expenditure by indirect calorimetry: a technique that calculates calories burned by oxygen consumption and carbon dioxide production, two gases that are indicators of metabolic activity. Because these gases are produced in different ratios when the body burns protein, carbohydrate, or fat, this

technique estimates what mixture of dietary fuels an animal is using to produce energy.

Physical activity also accounts for no small portion of the daily energy expenditure in animals. In the Promethion system, infrared sensors surrounding each cage monitor the movements of the animal throughout the day. Since all of the records of activity and respiration data are collected simultaneously, we can measure how animals expend energy during a resting period or when they are active. Because we also record body weight (fuel reserves) and food intake (calories consumed), this is a complete system for monitoring whole-body metabolism.

Animal monitoring studies can be short or long-term (up to several days), to allow the development of the best research design to address the hypothesis at hand. Since the Promethion system is so flexible, it provides few limitations on study design and allows researchers to ask the questions that interest them.

The Promethion system gives the Linus Pauling Institute a greater capacity to conduct high-quality metabolic research that will provide greater opportunities for federal funding. This certainly would not have been possible without backing from many supporting units at Oregon State University, and we appreciate the investment in the future of health research.



The Promethion High-Definition Multiplexed Respirometry System is produced by Sable Systems International. The unit consists of 10 individual metabolic cages for mice (pictured to the left) housed in a single system that allows multiple animals to be monitored continuously. The system is currently run by the Biological Models and Translational Research Core at the Linus Pauling Institute, and will support pre-clinical research at Oregon State University.



BARBARA MCVICAR

AFTER 21 YEARS OF SERVICE TO THE LINUS PAULING INSTITUTE, AND 28 YEARS EMPLOYED BY OREGON STATE UNIVERSITY, IT IS TIME TO SAY FAREWELL.



Dr. Balz Frei and Barbara McVicar, celebrating a successful Diet and Optimum Health conference in 2015

Barbara McVicar was hired by the Institute shortly after Dr. Donald Reed became the first interim director of the LPI. Over the last 21 years, she has primarily worked as executive support for Dr. Balz Frei, but now assists Dr. Fred Stevens. Barbara has been an outstanding member of our team from the beginning, so our goodbyes are now bittersweet as we wish her the best in her retirement years.

All of the faculty and staff agree that the LPI would not be the same place without Barbara. As Dr. Frei often said “She was the one who ran the Institute all these years... and I was given all the credit for it.” As this is the last newsletter that Barbara will contribute to, we asked her to write a few recollections of her time here at the LPI:

When the Linus Pauling Institute came to Corvallis from Palo Alto in 1996, I had been working in the College of Oceanography at Oregon State University. I was hired by the LPI shortly after the move. For a year or so, I was the lone person in the front office – yes, just me. I did everything: from hiring personnel, accounting, assisting with grant applications, and building the first LPI website.

It still surprises me to think how small we were back then. The Institute was only eight people at the time, including Stephen Lawson, Don Reed, and Ober Tyus (our first director of development). I was fortunate enough to have been involved in the interviewing and hiring process for the first permanent LPI director – it made a big difference for the Institute.

Balz Frei was our first choice for the job, and we felt so lucky that he accepted the position. Balz certainly jumped in with both feet and never looked back, and I went with him every step of the way. I loved working with Balz, and we made a great team. He was always so supportive and had faith in my abilities, and we trusted each other to get the job done.

Our team grew very quickly at that point. One of Balz’s first initiatives was getting new faculty hired for the LPI, and that included the ‘fab four’: David Williams, Maret Traber, Rod Dashwood, and Tory

Hagen. With their arrival and new people joining their labs, it was very busy – although the whole Institute could still all fit in one room, at least for the next few years.

My favorite aspect of my job is the variety – I really enjoy doing so many different things, whether it is helping plan events like the Diet and Optimum Health conference, arranging visits for donors, helping people by phone or email when they have questions, and even making copies! The same could be said for working with all the people here at the Institute. Everyone is different, and it makes the work more fun and interesting. Variety is certainly the spice of life.

As a non-scientist, I’m a bit of an outsider at LPI... more of a “regular person.” I’ve learned a lot about science over the years, so I love to help people as best I can when they call or email to ask questions. I think they feel like they can talk to me and get some information about the Institute in lay terms. Fortunately, the faculty are always available to answer the more technical questions!

The best part is when people call and tell me how grateful they are for the work everyone is doing at the Institute. We all really want to make a difference in people’s lives, so we try very hard to get the best information out to everyone.

After all these years, I still love doing my job at the Institute. I really like being the “go-to” person. After being at OSU for 28 years, I take great pleasure in helping people who ask me questions, knowing that I will likely be able to help them or at least steer them in the right direction. Everyone at the LPI has been great to work with over the years. We are all so committed to making LPI a great place to work and do research. It always seems like we are on the same page together.

I appreciate all the support I have received from everyone over the years. I will truly miss working here and being a part of LPI and OSU, and talking with all of our supporters. But, I am looking forward to retirement, playing with my grandkids, and traveling. Thank you... it’s been a great ride!



Thank You

For their years of dedicated service to the Linus Pauling Institute, we express our sincere gratitude and appreciation to Balz and Simone Frei. Under his leadership, Balz transformed the Institute into a world-class research program, recognized for research on the health benefits of micronutrients and other dietary compounds. As the head of the Healthy Youth Program at the LPI, Simone and her team brought the Institute's message touting the benefits of healthful eating and an active lifestyle.

All the faculty, staff, and students at the Institute wish the best to the Freis in their endeavors in the years to come.

Thank you again for your dedication.

Cand Freis

Zhou
Siva

Joy Hagen

Donald B. Fulp

Rong Wang *C. L. Miranda*

Victor Miki *Gerd Bobe*
Mat *Kim Myrson*

John P. Yu *Sandra Murgu* *David E. Williams*

Fritz Ambrust

Scott Leonard
Barbara

Judy Butler
Yuchen

Robert W. Dun
Robert V. Tanguay

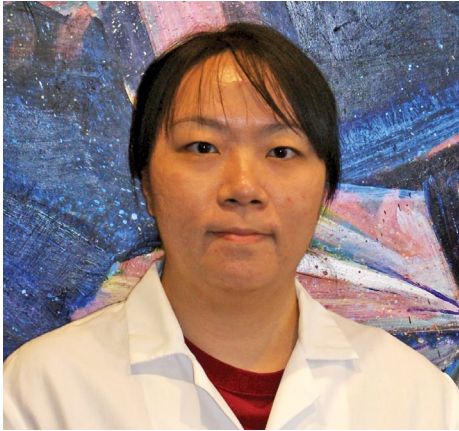
Agnieszka Indrko
Wojcik

Kate Peterson Gray
Emily Ho

Quinn King
Elizabeth K. Siddons

Richard M. ...
Joseph S. Dukeman

LPI STUDENTS



Yang Zhang

Ph.D. Student, Nutrition Program, College of Public Health and Human Sciences

After obtaining her bachelor's degree in food sciences and engineering in China, Yang came to the United States to study human nutrition at Utah State University. After obtaining her master's degree, she decided to pursue a Ph.D. at Oregon State University with Dr. Adrian Gombart, principal investigator at the Linus Pauling Institute.

Her project focuses on the combination of xanthohumol with vitamin D in immune health. She is currently testing 'nanofiber' bandages that contain both of these compounds to improve wound healing and reduce infections. These bandages can be placed at the site of injury, directing therapy where it is needed the most. Yang is also looking at how this combination of compounds may influence the gut microbiome.

Yang has the long-term goal of establishing her own lab in an interdisciplinary research area that incorporates "big data," biology, and medicine. Her hard work has paid off in three scholarship awards, and she is currently a Marion T. Tsefalas Graduate Fellowship awardee. This generous financial support has helped propel her research forward in her first two years at the LPI. Yang has earned travel awards from the College of Public Health and Human Sciences and a Young Investigator Award from our Diet and Optimum Health conference held in September.



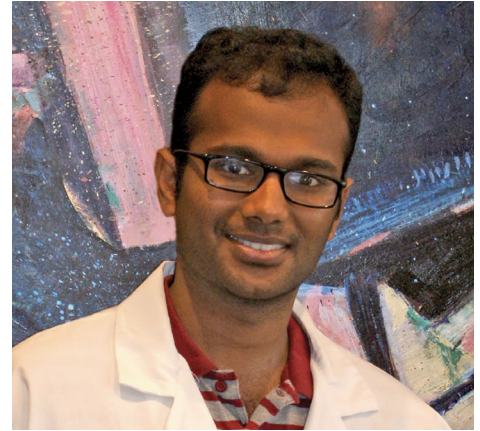
Lea Sophie Ullrich

Visiting Scholar, Institute of Pharmacy, University of Regensburg

Although she hails from Germany, Lea is no stranger to the United States and to Oregon. As an exchange student, she attended and graduated from a high school in Grants Pass, Oregon. After her acceptance into the pharmacy program at the University of Regensburg, she is hoping to be the first in her family to pursue a career in science.

Very interested in travel, Lea wanted to explore the various aspects of pharmaceutical research around the world. She recently returned to Oregon to work with Dr. Fred Stevens at the Linus Pauling Institute, in partial fulfillment of her rotation requirements of her undergraduate program. After her rotation here, she will complete the remaining requirements to become a licensed pharmacist in Germany. She is considering an application to come back to Oregon State University as a Ph.D. student.

For the past six months, Lea has taken part in multiple research projects using mass spectrometry techniques to monitor the metabolism of xanthohumol – a compound from hops. She has been pioneering new analysis techniques for detecting xanthohumol metabolites in biological samples, with the hope of developing new preservation techniques. This may eventually foster collaborations with the LPI around the world on xanthohumol research.



Bharath Sunchu

Ph.D. Student, Department of Biochemistry and Biophysics

Bharath grew up in Warangal, a city in South India. With his mother and father both being science teachers, science was a logical career choice. Completing his master's thesis examining the mechanisms of DNA replication in bacteria further strengthened his passion for scientific research.

An interest in human health and a background in pharmacy led Bharath to study the cellular biology underlying aging. Attracted to the idea that age-related disease could be prevented by treating the underlying causes of aging, Bharath is now working with Dr. Viviana Pérez. Using a comparative biology approach to study protein stability, Bharath has been working to understand why cells from long-lived species – like the naked mole rat – appear to keep their proteins intact and functional when under stress.

Figuring out how evolution has tackled the problem of misfolded proteins ultimately may help develop new therapies for age-related diseases, and Bharath is excited about the possibilities of taking this work into humans. Bharath is a Mark Sponenburgh-LPI Endowed Graduate Fellowship awardee, has received an Oregon Retired Educators Association's graduate student scholarship, and was the recipient of a travel award from the OSU graduate school. He is currently finishing his research for his Ph.D. dissertation.

DEVELOPMENTS

The Linus Pauling Institute will be welcoming Dr. Richard van Breemen as its new director in January. As he brings a wealth of scientific experience and administrative credentials to the Institute, we look forward to his arrival. Beyond his years of experience as the director of a botanical supplement research center, he has also led several NIH-funded clinical trials, been an author on scores of research articles on botanicals, and is a collaborator with countless partners throughout the world.

As we look forward, however, it seems appropriate to take a moment to look back at everything the Linus Pauling Institute has accomplished with our supporters.

When Linus Pauling first founded the Linus Pauling Institute of Science and Medicine, he was looking for a place to conduct research on the impact of nutrition on health, especially with his work on vitamin C. When he could not find support from other institutions, he turned to the public – and their support carried his research forward for the next 20 years.

Just before Linus Pauling's death, at a time when the Institute was looking for a new path forward in nutrition research, it found a home at Oregon State University (OSU). In 1996, the Institute made its way to Corvallis and within a year, Dr. Balz Frei took over the reins of leadership.

Dr. Frei ushered in a new era of change at the LPI, and the results were extraordinary.

Over the next 20 years, the new investigators and research programs at the Institute have brought in dozens of federal research grants and created opportunities for OSU students to participate in research. The LPI has advanced the pace and breadth of discovery, fostered the next generation of nutrition scientists, and seeded research facilities across the world with brilliant young minds – and none of it would have been possible without the generous support of our loyal donors.

I am sure that Dr. Pauling would be very proud to know that each one of these accomplishments, the scientists, and their work are now a part of his legacy.

The LPI continues to thrive under Dr. Stevens' deft leadership. Every day, our students, faculty, and staff are working to advance our understanding of the fundamental mechanisms of disease and the role that micronutrients and phytochemicals play in health.

I invite you to join Dr. van Breemen and the all the researchers at Linus Pauling Institute as we embark on the next era of scientific discovery.

Sincerely,

Amanto Marcotulli, J.D.

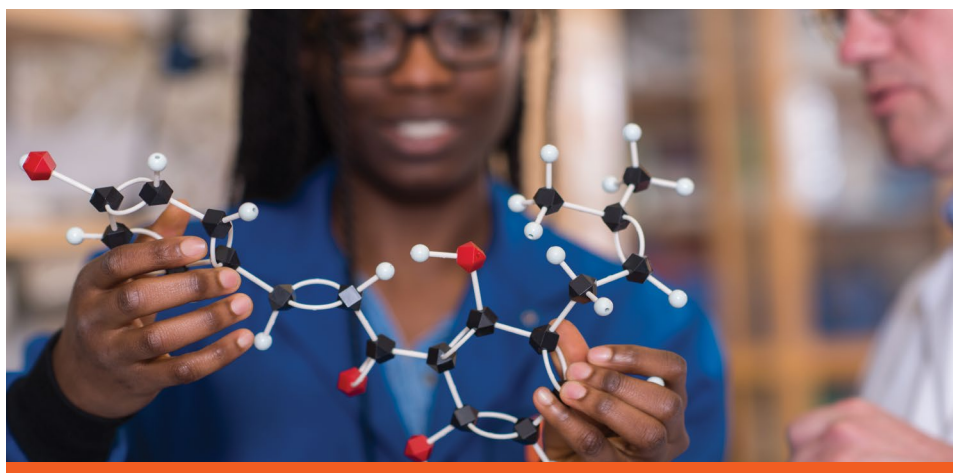
If you want to learn more about the many ways you can support the Institute, email Amanto.Marcotulli@osufoundation.org or call (503) 553-3400.



The new director of the Linus Pauling Institute, **Richard van Breemen, Ph.D.**

“Dr. Pauling would be very proud to know that each one of these accomplishments, the scientists, and their work are now a part of his legacy.”

— Amanto Marcotulli, J.D.



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LINUS PAULING INSTITUTE

Oregon State University
307 Linus Pauling Science Center
Corvallis, Oregon 97331

phone: 541-737-5075

fax: 541-737-5077

email: lpi@oregonstate.edu

website: lpi.oregonstate.edu



NOW IS THE TIME

In a climate where government funding for research is dwindling, your support for micronutrient research is more important than ever. To learn the many ways you can help support the LPI, please contact the OSU Foundation at (800) 354-7281 or go to osufoundation.org/GiveToLPI

Announcing the winner of the LPI Prize for Health Research for 2017. **LOOK INSIDE** ►