Profile of Mary Lou Guerinot

Jennifer Viegas, *Science Writer*

On the first Earth Day, April 22, 1970, Mary Lou Guerinot decided that she would major in biology in college in the hope of promoting environmental sustainability. As the 50th anniversary of Earth Day approaches, Guerinot, now a professor of biological sciences at Dartmouth College and a member of the National Academy of Sciences, is well on her way toward achieving that goal through her work on the molecular mechanisms of metal ion uptake and its regulation. Guerinot's work is laying the foundation for environmentally sustainable, nutrient-dense crops, as well as plant-based solutions for removal of toxic metals from soil. Her Inaugural Article (1) reports the identification of a transcription factor essential for plant growth under iron deficiency. The finding moves her team closer to understanding the iron homeostasis pathway in plants, holding promise for improving agricultural productivity and human health.

From Marine Microbiology to Plant Biology

Guerinot was raised in upstate New York, where she attended the Rochester-based Catholic all-girls St. Agnes High School. "Unlike the boys' Catholic high school nearby, it was basically science-light," she says. "We didn't have physics or calculus, and very few students went on to college to study science." She and a few other students urged their math teacher to let them study calculus on their own. The hard work on this subject and others paid off, and Guerinot was accepted at Cornell University's College of Agriculture and Life Sciences. She adhered to her decision to major in biology and earned a Bachelor of Science degree with distinction at Cornell in 1975. Four years later, Guerinot earned a doctorate in biology from Dalhousie University under the direction of David Patriquin, studying the sea urchin–lobster–kelp ecosystem.

Envisioning life as a marine microbiologist, Guerinot did a postdoctoral fellowship at the University of Maryland with Rita Colwell as her advisor. She worked on marine nitrogen fixation, the start of her lifelong interest in bacterial and plant iron metabolism.

When Guerinot's partner C. Robertson McClung went to graduate school at Michigan State University (MSU), Guerinot relocated with him and did a second postdoctoral stint with advisor Barry Chelm in the MSU-Department of Energy Plant Research Laboratory (PRL) from 1981 to 1985. Both choices proved to be fortuitous, as she is now married to McClung and has focused on plant research ever since. Guerinot says, "The PRL was the perfect place to make the transition to plant biology, with many luminaries on the faculty, such as Hans Kende, Charlie Arntzen, and Chris Somerville."

Mary Lou Guerinot. Image courtesy of Olga Zhaxybayeva (Dartmouth College, Hanover, NH).

Identification of Iron Transporter

Following the MSU postdoctoral fellowship, Guerinot was hired in 1985 as an assistant professor in the Dartmouth Department of Biological Sciences. In 1990 she went on sabbatical as a visiting assistant professor to the laboratory of Fred Ausubel, a molecular geneticist at Massachusetts General Hospital. Ausubel had recently begun studies on the model organism *Arabidopsis thaliana*. Inspired by the research, Guerinot worked with a library of *Arabidopsis* genes, which she sent to microbiologist David Eide of the University of Minnesota in 1993.

Eide was analyzing a yeast mutant defective in iron uptake. Using this mutant, they identified the gene *IRT1*, which could rescue the mutant by functional complementation. Eide and Guerinot collaborated on an article, which provided the first molecular insight into iron transport by plants (2). Guerinot says, "Indeed, *IRT1* was the first iron transporter to be cloned from plants."

Guerinot's group and others have since determined that *IRT1* is the founding member of the ZIP family of proteins found in all domains of life. She says, "Our studies on *IRT1* have contributed to the general knowledge of this family of transporters, members of which have been implicated in a number of important processes, including human breast cancer and virulence in the Leishmania parasite."

This is a Profile of a member of the National Academy of Sciences to accompany the member's Inaugural Article on page 24933 in issue 50 of volume 116.

First Woman Chair

In 1994 Guerinot was named the chair of Dartmouth's Department of Biological Sciences, making her the first woman to chair a science department at the college in its then 225-year history. After serving as associate professor from 1991 to 1997, she was named a full professor in 1997.

Mentoring others at Dartmouth, particularly women, is important to Guerinot. Over 100 undergraduate students have worked in her laboratory, with 38 completing honors theses under her direction. She has also trained 20 doctoral students and 23 postdoctoral fellows. For her efforts, Guerinot received Dartmouth's Graduate Mentoring Award in 2009 and the 2015 Dean of Faculty Award for Outstanding Mentoring and Advising.

Gene Discovery Concerning Iron Uptake Regulation

Guerinot served as associate dean of faculty for the sciences and as a vice-provost at Dartmouth, but decided to return full time to research and teaching in 2005. Her research projects following the identification of *IRT1* have resulted in numerous gene discoveries related to mineral uptake, long-distance transport, distribution, and deficiency signaling pathways.

For example, Guerinot and her colleagues isolated the *FRO2* gene, which helps plants to increase iron uptake under conditions of iron deficiency by reducing ferric iron to ferrous iron (3). They identified the gene *FIT1* as also being essential to plant iron deficiency response (4). The researchers additionally characterized the role of three closely related negative regulators of the iron-deficiency response (5). These genes could be used to biofortify crops for improved growth and nutrient content.

Development of Ionomics

In the mid-1990s Guerinot met David Salt, a plant geneticist now at the University of Nottingham who was then an assistant research professor at the Rutgers University Center for Agricultural Molecular Biology. Salt had conducted high-throughput screening, so in 2000 Guerinot invited him to collaborate with her and other colleagues on a project to quantify trace elements in *Arabidopsis*. The study involved genome-scale profiling of 18 elements in the shoots of 6,000 mutagenized *Arabidopsis* plants (6).

The article (6) launched the field of ionomics. Guerinot credits Salt with moving the field forward by making all of the ionomics data publicly available. Guerinot says, "The relatively high throughput and low cost of ionomic analysis means that it is a powerful approach to not only functionally characterize the genes and gene networks that directly control the ionome, but also to analyze the more extended gene networks that control developmental and physiological processes that affect the ionome indirectly." They have also used ionomics to develop signatures of different physiological states (7) and to examine natural variation in the ionome of both *A. thaliana* (8, 9) and rice (10), identifying novel alleles of numerous genes.

Contributions to Seed Biology

Guerinot was among the first plant biologists to use synchrotron X-ray fluorescence microprobes to study elemental distribution in plants. Her imaging study identified the vacuolar iron transporter *VIT1* as essential for proper iron storage in seeds (11). Vacuoles are internal membrane-bound compartments that function as reservoirs for ions and metabolites. She and her colleagues found that *VIT1* mediates iron sequestration into vacuoles and is highly expressed in developing seeds.

Another study using the same technology showed that the transporter *MTP8* determines the localization in seeds of not only iron, but also manganese (12). Uncovering these fundamental aspects of seed biology may aid the development of nutrient-rich seeds.

For her leadership and contributions to the field of plant mineral nutrition, Guerinot received the 2012 Dennis Robert Hoagland Award from the American Society of Plant Biologists (ASPB). Six years later, she received ASPB's Steven Hales Prize in recognition of her dedication as an educator, service to the plant biology community, and collaborative research projects.

Efforts to Ensure Food Safety

With funding from the National Institute of Environmental Health Sciences, Guerinot and colleagues are using high-throughput elemental analysis, genetics, and other tools to identify genes that regulate arsenic and cadmium uptake in *Arabidopsis* and rice. The project is part of the Dartmouth Toxic Metals Superfund Research Program, an interdisciplinary research center in which investigators work with communities, public health organizations, and state and federal agencies to apply research findings. Guerinot says, "Rice, a staple food for over half the world's population, represents a significant dietary source of arsenic and cadmium, both of which are in the top 10 most toxic elements on the ATSDR [Agency for Toxic Substances and Disease Registry] 2017 Substance Priority List" (https://www.atsdr.cdc.gov/SPL/#2017spl).

Through field trials conducted in Bangladesh, China, Arkansas, and Texas, Guerinot and her colleagues have already identified varieties of rice that tend to exhibit lower levels of arsenic (10). Genetic variation at the field sites was a determining factor for arsenic concentration, suggesting that breeding could yield cultivars with less grain arsenic.

Discovery of a Master Gene Regulator

With longtime collaborator Suna Kim and colleagues, Guerinot reports in her Inaugural Article (1) the identification of *URI* (Upstream Regulator of *IRT1*), which is essential for *Arabidopsis* growth under conditions of iron deficiency. The researchers characterize *URI*'s role in the network of genes responsible for integrating information about iron status and orchestrating a coordinated response. Guerinot says, "We are very close to having the whole pathway figured out. *URI* is a master regulator that is very high up the pathway; it controls almost all of the iron genes that we know about."

URI appears to control numerous other genes as well, such as those involved in circadian clocks. McClung, who is also a professor of biological sciences at Dartmouth, specializes in the study of biological clocks. Guerinot previously coauthored an article with him concerning the reciprocal interaction of the circadian clock with the iron homeostasis network in *Arabidopsis* (13). She is planning another collaboration with her husband to elucidate *URI*'s role in the circadian clock and how it may integrate with the iron pathway.

Earth Day Goal Within Reach

Guerinot is also looking forward to the 50th anniversary of Earth Day in 2020. She says, "Did I know 50 years ago that I would be working on one of the areas now deemed critical for a sustainable future? I thought I would end up working for the EPA, fighting polluters." The Earth Day initiative that she refers to is called "Foodprints for the Future," which addresses one of the largest contributors to climate change: The food system.

She explains that animal agriculture and food waste account for almost one-third of all greenhouse gas emissions. Plant-based food choices with climate solutions are therefore being sought. Guerinot says, "The vision is for low-impact, healthy, accessible, and affordable food for all and for the planet. My work does contribute in a very basic way to achieving this vision."

1 S. A. Kim, I. S. LaCroix, S. A. Gerber, M. L. Guerinot, The iron deficiency response in *Arabidopsis thaliana* requires the phosphorylated transcription factor URI. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 24933–24942 (2019).

2 D. Eide, M. Broderius, J. Fett, M. L. Guerinot, A novel iron-regulated metal transporter from plants identified by functional expression in yeast. *Proc. Natl. Acad. Sci. U.S.A.* **93**, 5624–5628 (1996).

3 N. J. Robinson, C. M. Procter, E. L. Connolly, M. L. Guerinot, A ferric-chelate reductase for iron uptake from soils. *Nature* **397**, 694–697 (1999).

4 E. P. Colangelo, M. L. Guerinot, The essential basic helix-loop-helix protein *FIT1* is required for the iron deficiency response. *Plant Cell* **16**, 3400–3412 (2004).

5 M. N. Hindt *et al.*, *BRUTUS* and its paralogs, *BTS LIKE1* and *BTS LIKE2*, encode important negative regulators of the iron deficiency response in *Arabidopsis thaliana*. *Metallomics* **9**, 876–890 (2017).

6 B. Lahner *et al.*, Genomic scale profiling of nutrient and trace elements in *Arabidopsis thaliana*. *Nat. Biotechnol.* **21**, 1215–1221 (2003).

7 I. R. Baxter *et al.*, The leaf ionome as a multivariable system to detect a plant's physiological status. *Proc. Natl. Acad. Sci. U.S.A.* **105**, 12081–12086 (2008).

8 I. Baxter *et al.*, Variation in molybdenum content across broadly distributed populations of *Arabidopsis thaliana* is controlled by a mitochondrial molybdenum transporter (*MOT1*). *PLoS Genet.* **4**, e1000004 (2008).

9 J. Morrissey *et al.*, The ferroportin metal efflux proteins function in iron and cobalt homeostasis in Arabidopsis. *Plant Cell* **21**, 3326–3338 (2009).

10 G. J. Norton *et al.*, Variation in grain arsenic assessed in a diverse panel of rice (*Oryza sativa*) grown in multiple sites. *New Phytol.* **193**, 650–664 (2012).

11 S. A. Kim *et al.*, Localization of iron in Arabidopsis seed requires the vacuolar membrane transporter *VIT1*. *Science* **314**, 1295–1298 (2006).

12 H. H. Chu *et al.*, The Arabidopsis MTP8 transporter determines the localization of manganese and iron in seeds. *Sci. Rep.* **7**, 11024 (2017).

13 S. Hong, S. A. Kim, M. L. Guerinot, C. R. McClung, Reciprocal interaction of the circadian clock with the iron homeostasis network in Arabidopsis. *Plant Physiol.* **161**, 893–903 (2013).