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MICROCYCLING:

Realizing the Potential of Lanthanide Metabolism

INTERVIEW WITH Dr. Norma Cecilia Martinez-Gomez

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Dr. Norma Cecilia Martinez-Gomez *is an Assistant Professor in the Plant and Microbial Biology department at UC Berkeley. The Martinez-Gomez lab specializes in methylotrophs and their utilization of a class of metals called lanthanides. Lanthanides, which were previously thought to be absent from biology, are found in cell phones, laptops, and many other commonly used electronic devices. Using methylotrophs, Martinez-Gomez hopes to develop more sustainable metal mining and recycling methods. In this interview, we discussed a recent paper from the Martinez-Gomez lab, which uncovered a novel chelator that binds to lanthanides.*

BSJ: Much of your research focuses on engineering bacteria to process and ultimately recycle commonly used metals. What first drew you to studying microbial recycling?

CMG: I have always been interested in harnessing microbes as platforms to solve environmental issues. In the beginning, the microbes that I worked with, known as methylotrophs, used one-carbon compounds and could be applied to reducing greenhouse gasses. As more research was poured into methylotrophy, the capacity to reduce one-carbon compounds, an important discovery was made simultaneously by two research groups: one from Gifu University in Japan and one collaborative group between Radboud University in the Netherlands and Max-Planck Institute for Medical Research in Germany. They discovered that microbes could utilize a whole class of metals called lanthanides. As a chemist, this was surprising because lanthanides are not the sort of metal that would have been thought to play a role in biology. This was surprising not only to me, but also to much of the global scientific community at large.

Lanthanides, also known as Rare Earth Elements, are a class of metals that form the bottom section of the periodic table. Lanthanides have unique properties, such as lanthanide contraction—the phenomenon in which poor shielding draws in electrons and gives the elements a smaller than expected size. It is hard to differentiate some of their aspects and even to separate them for individual study, but we do have them in pure form.

When you think about lanthanides and the chemical properties of these metals, it becomes clear why this finding was so significant. Due to their properties, lanthanides are used as superconductors, super magnets, and even sources of fluorescence, among other things. Their value extends to many important aspects of our lives, such as national defense.

When I began research, I already had the mindset of engineering bacteria to help us solve environmental issues, and the biology of lanthanide utilization seemed to be such an exciting avenue to study with regards to that. There are not yet metal mining processes that are environmentally friendly. But with microbes, we can definitely achieve sustainable metal mining and recycling practices.

In the past, we neither knew how efficient that process was going to be nor that our bacteria could accumulate lanthanides, but the knowledge that lanthanides were involved in the biology of methylotrophs opened doors for us. That is what drove me to think about methylotrophs, study how they utilize lanthanides, and develop methods to harness these bacteria and put more sustainable metal mining processes into practice.

BSJ: Part of your research focuses on a group of metals called Rare Earth Elements (REEs), or lanthanides (Ln), which is a term derived from the Greek word "lanthanein," meaning "to lie hidden." Is there any truth behind this name's meaning? Why are these elements grouped together?

CMG: Both on the chemical side and on the biological side, lanthanides were not looked at enough for a long time. I think, on the chemical side, it was because unlike other transition metals—such as iron—their capacity to donate electrons is not as interesting.

Historically, as electron donors, lanthanides are not very bioavailable; we find them fulfilling Lewis acid roles in nature. Lewis acids describe a specific definition of an acid in which the acid compound has a vacant orbital which can accept electrons from their respective lewis bases. Simply put, Lewis acids are substances that can accept electrons, while Lewis bases are substances that donate electrons. Lanthanides' lack of bioavailability skews how we see and study them. In biology, this caused them to be completely forgotten.

The term "Rare Earth Elements" is also misleading because it makes you think that they are rare. In reality, Rare Earth Elements are not rare in terms of abundance; in fact, in some sites they can be as abundant as elements known to be biologically useful, like copper or zinc. What can make them "rare" is their lack of bioavailability—in other words, how insoluble they are or how difficult it is for organism uptake. Because of their insolubility, we were not thinking about them, and nobody was adding lanthanides in their media. We have missed everything that many microbes, not just the ones that we are working with, probably do with them.

BSJ: In one study, you used a methylotrophic bacterium called Methylorubrum extorquens AM1 to study the ways in which it sequesters lanthanides. What makes this bacterium a good model organism?

CMG: Our microbe, Methylorubrum extorquens AM1, grows when the pH is seven. In that particular environment, the lanthanides are not going to be bioavailable. They are available in more extreme, highly acidic environments where the pH is one or two. The microbes that need to use them have to evolve mechanisms and systems to reach them in a neutral pH. Our microbes are awesome because they developed mechanisms where they produce novel chelators that bind the metals and bring them into the cell to allow for that metal to be used.

BSJ: Details of Ln uptake from nature are unknown, but it is suspected that a chelator could be involved. What exactly is a chelator?

CMG: I want to emphasize that we do not yet know all the different ways in which microbes can bring in lanthanide metals. What we are learning, at least for our microbes, is that they produce these small molecules, known as "chelators," that have moieties. Moieties are groups that can coordinate fairly well with the positive charge of the lanthanides. The chelators also have a structural component in which they are able to coordinate with the lanthanide. Once the lanthanide sticks to the chelator, it then can be recognized by specific transporters that bring it inside the cell. This type of coordination can involve different pathways. We have identified one of them, but we do not think that it is unique in its role. I think that there are likely other peptide-based or organic-based molecules, like

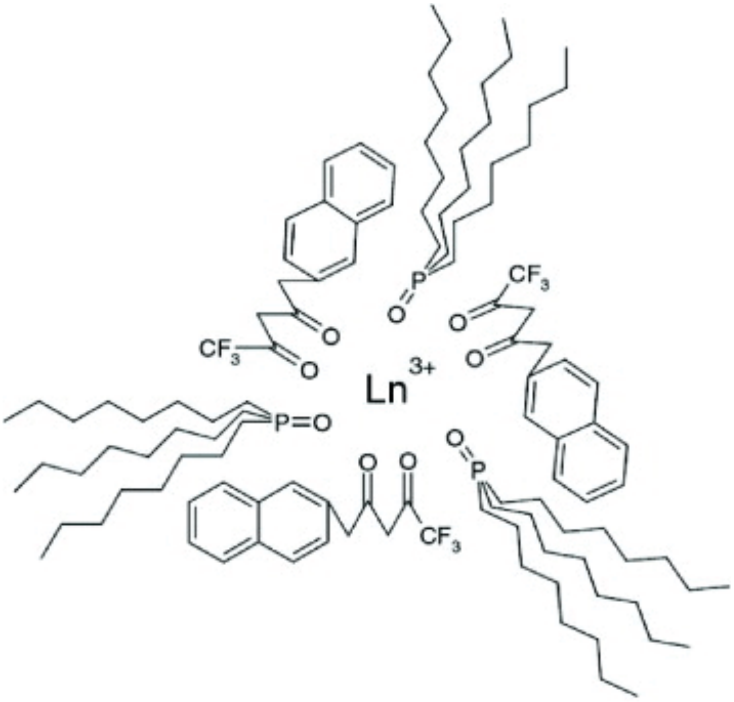

Figure 1: Chelators surrounding a Lanthanide (III) metal ion. A chelator is a type of chemical compound that binds tightly to metal ions. Though often used in medicine to remove toxic metals from the bloodstream, Dr. Martinez-Gomez's chelators act as a compound that will bind to lanthanide and produce a chelate compound in the process.

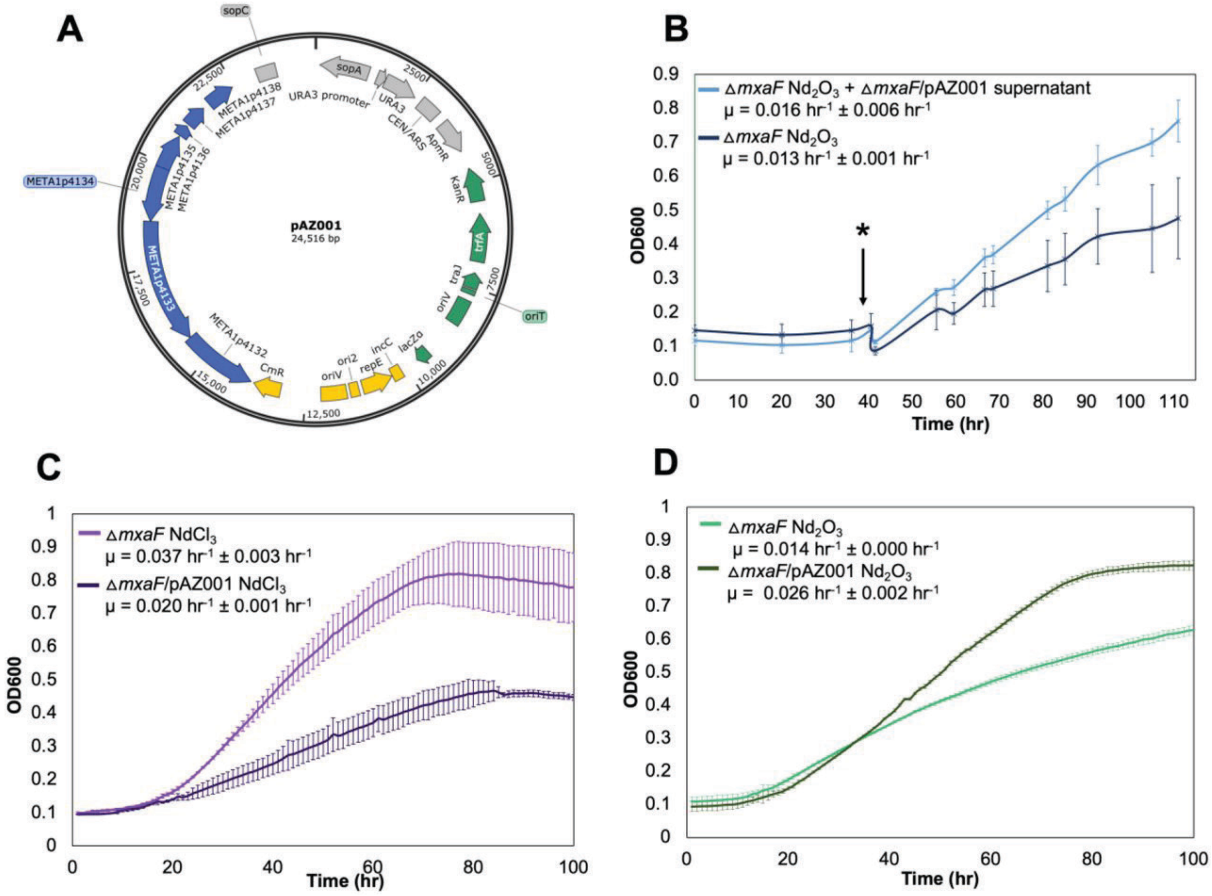

Figure 2: Effect of Different Conditions on Lanthanide-Dependent Growth. Four different conditions are applied to the chosen chelator; results are shown in the graphs above. Panel A diagrams the plasmid which contains the genes for the Lanthanide Chelation Cluster that produce the metal-chelating molecule. Panel B demonstrates that the inclusion of LCC increases chelation as opposed to a control that lacks it. Panel C shows how the presence of NdCl3, an Ln of high solubility, promotes slower growth of the culture compared to control. Panel D depicts how Nd2O3, an Ln of low solubility, promoted faster growth.

our chelators, that are secreted out of the microbe and coordinate with lanthanides, regardless of the environment in which the lanthanide is in.

BSJ: You have conducted experiments on the ability of methylotrophs to grow in environments of both low and high Ln solubility. Why was it necessary to experiment in both environments?

CMG: Until now, we had done all our experiments using a very soluble, bioavailable form of lanthanides. My group is studying how our bacteria will respond to an environment where lanthanides are ready to be used, as opposed to trapped within various products. Through this, we discovered crucial components for the transport and the use of lanthanides and even discovered storage of lanthanides in cells. We were not, however, able to understand what the microbe had to secrete to be able to grab the metals.

We had an "aha" moment and decided we needed to switch to less bioavailable sources. We switched to an oxide form—a much less bioavailable form of a lanthanide—and sure enough, we were able to identify some really interesting pathways that we had not seen before. We discovered pathways not just for chelation but also for regulatory mechanisms—even ones that may be coordinated with the production of other electron donors or electron active molecules. We are very excited about those findings, which have helped us translate our work to complex sources like ores and electronic waste. We can use what we are learning in the lab to engineer bacteria by applying this idea of recovery where the lanthanide is not bioavailable.

BSJ: REEs (Rare Earth Elements) are used to manufacture cell phones, laptops, computer hard drives, and even MRI machines. Given the many ways that methylotrophs can be used to recycle these essential elements, do you see microbial recycling becoming a commonly used process in the future?

CMG: We are a little far away from that still, but I definitely see it becoming a reality in the near future. My lab, as well as other groups, are working very hard to make this type of platform profitable. You need a certain amount of profit in order for the industries to say, "Oh, this is the way to go." I do think that we will get there. It will take us a couple of years, but once there is an investment, eventually microbial recycling will become a continuous, efficient, environmentally friendly process.

BSJ: Are there other materials that methylotrophs can recycle outside of REEs?

CMG: Our lab works with methylotrophs and methanotrophs, which are methanol and methane utilizers, respectively. The methanotrophs, which are cousins of the methanol utilizers I use currently, may be able to utilize different types of metals (for example, copper). In terms of methylotrophs, I am not sure if they could be used for the recycling of other metals, though it is possible. There are other ways in which we can make this platform industrially interesting. The type of methylotrophs that we use express a pathway called the "ethylmalonyl-CoA pathway." This pathway is known as the treasure trove for producing precursors of very interesting products, such as bioplastics, biofuels, and antibiotics. If we are thinking about using literal trash, such as electronic waste, we would want to then provide a source, which could come from organic matter, such as the lignin from dying plants, or volatiles, such as methanol, to start the degradation process. In addition to reducing electronic waste, there is a biofuel by-product. Recovering electronic waste metal and producing a biofuel in the process generates a circular economy that is demanded in our battery-dependent world.

BSJ: In your research, you mention how the structure of the lanthanophore could open the capabilities of binding to an Ln. In what ways do you see this new discovery expanding our current technology in regards to mining and separation of Ln?

CMG: The mining right now involves things like electronic waste and ores, but we are also beginning to think about even less obtainable materials. If we begin to understand how these molecules work, we can begin to think about how they apply to different industries. For example, we could start thinking about medical applications. Gadolinium is a metal lanthanide that is highly used as a contrasting agent in MRIs right now. But recently, there was a paper published saying how the accumulation of gadolinium in the human body can be toxic for patients that have to undergo MRIs constantly. The harmful effects continue even after the procedure is over. The gadolinium must exit the body after the procedure and humans will dispose of the contrasting agent via urine, leading to contaminated water. The free gadolinium then becomes a problem for even our crops as the same contaminated water travels farther and farther from its source. The identification of these lanthanophore molecules is going to help us clean the waters, starting from cleaning it at its source—the medical waste. We are also actively working on developing new contrasting agents in our lab.

BSJ: We read that your lab hosts workshops for seventh through ninth graders as well as a "Methylothon" to engage high school students in your research. Could you tell us about your motivations for hosting these events?

CMG: I started doing research when I was very young, around eleven or twelve years old. Scientists opened the doors of their labs to me and put me to work doing very simple tasks. The passion for science that I still have today started in that lab and the experience defined my junior years. Ever since my lab opened I have been extremely committed to having activities where we can invite young people to learn about research. The way I want to engage them is not how I first started out. When I was young, I was told, "You are going to plant a seed." I want them to actually run real experiments that may or may not work. And that's okay; sometimes experiments do not work, but the important part is to always have a hypothesis in mind. The Methylothon was initially an idea of a laboratory workshop run in high schools and was online due to COVID. We essentially show a high school teacher how to run the lessons and provide the material for them so that they can run these complex experiments from their own high school. Now that COVID restrictions have ended, we can not only go and help them in person, but also continue to conduct the program online in Canada as well as in other parts of the nation. It is really cool how we can have that accessibility.

Essentially, we aim to allow students to delve into complex experiments where they learn how to isolate and identify microbes. Within a mere high school setup, students learn to make their own scientific decisions while also discovering and experimenting with lanthanide's impact on plant growth. For our summer programs we run here at Berkeley, high schoolers work with us on an activity in the lab for two weeks. One year, we investigated plant microbe interactions. Another year, we did biomining; they collected electronic waste and at the end of the two weeks, they had their polonium isolated, but most importantly, they learned the whole experimental process: How do we run pipelines and how do we think about optimizing those pipelines? This is the goal of this program: to get these high schoolers in the lab and give them the ability to envision themselves in a future with science.

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