QnAs with Sang Yup Lee

Beth Azar, *Science Writer*

Sang Yup Lee tries to solve worldwide problems with some of Earth's tiniest inhabitants: microorganisms. Lee, a systems metabolic engineer and dean and distinguished professor in the department of chemical and biomolecular engineering at the Korea Advanced Institute of Science and Technology, harnesses biotechnology to create microorganisms that perform desired tasks. Those tasks include producing useful compounds, such as biofuels, chemicals, polymers, and medicinal compounds, as well as degrading toxic chemicals. His group has developed microorganisms that can mass-produce gasoline, plastics, and spider silk protein stronger than steel. He has pioneered technologies to efficiently and inexpensively create such microfactories. Lee, elected as a foreign associate of the National Academy of Sciences in 2017, recently spoke with PNAS about his career and the creation of a biosensor that may help produce natural compounds important for preventive medicine.

PNAS: How did you enter this field, and what motivates your work?

Lee: I graduated from the department of chemical engineering, which focuses on making low-value raw materials into high-value materials. Back then, much of the work focused on the petrochemical process. But thanks to advances in biology and biotechnology, we were able to apply the approaches and strategies of chemical engineering to create something very powerful. So chemical engineering expertise has been successfully used to establish a lot of different biotechnology processes for the production, for example, of recombinant proteins, therapeutic proteins, small-molecule drugs, polymers, and the like. Those are the things I have been working on.

Sang Yup Lee. Image courtesy of Sang Yup Lee.

I am motivated by big problems, the world's pending issues, like climate change, sustainable production and consumption, the aging society, and food shortages as population increases. I, of course, cannot solve all these problems, but at least I can address some of them. In the case of climate change, we're looking to replace fossil fuels and petrochemicals with sustainable, renewable raw materials. What we use are ethically sound microorganisms. We perform metabolic engineering to develop many novel and great processes for the production of a variety of chemicals and materials that used to be produced by the petrochemical industry.

PNAS: What are the real-world applications of your findings?

Lee: Although the work I've done on biofuels and materials gets a lot of attention, I'm most proud of the work we have done to develop various technologies to make these systems work. One great example uses synthetic small RNAs as a tool to knock out genes of interest to create multiple strains of microorganisms in a high-throughput manner. That technique has been widely recognized as a great tool, and many people use it to develop strains for research and development. Using traditional techniques, if you try to knock out 10 genes in many different microorganisms, it will take many years. Using this technique, it only takes a week.

In terms of developing strains to produce useful chemicals, such as fuels, we are working with a Korean company to commercialize biobutanal, a 4-carbon alcohol. With the company's support, we focused on microbial strain development. In addition they developed a very nice bioprocess. They are almost finished with the plant to commercialize it by the end of this year.

PNAS: In your Inaugural Article (1) you report a biosensor. Can you explain its mode of action and significance?

Lee: The Inaugural Article (1) stems from part of our work that focuses on producing natural compounds. The goal is to be able to produce natural compounds from plants and other resources that can prevent disease and help people stay healthy. Many of the natural compounds of interest come from plants. However, in most cases, the metabolic pathways to produce these compounds are not present in microorganisms. So we

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have to reengineer the microorganisms using metabolic engineering. Because metabolic engineering takes a lot of time and effort we wanted to be able to monitor the level of intermediate metabolites toward the production of desired natural compounds.

In the Inaugural Article (1) we focus on an intermediate metabolite called malonyl-CoA, which is important for the production of diverse functional compounds. We wanted to develop a biosensor to identify which engineered strain gives the most malonyl-CoA. We used a sensor that turns red when a strain makes lots of malonyl-CoA. Once we know which strain is the best, we can use that strain to introduce downstream pathways that convert malonyl-CoA to valuable compounds. We used the sensor to engineer *Escherichia coli* that produced four important natural compounds: two polyketide compounds, 6-methylsalicylic acid (antibacterial and antifungal) and aloesone (antiinflammatory), and two phenylpropanoid compounds, resveratrol (found in red wine and associated with antioxidant, antiaging, and anticancer properties), and naringenin (found in grapefruit and associated with anti-Alzheimer's disease and anticancer properties).

PNAS: How do you see this finding advancing the field?

Lee: Malonyl-CoA is not just an intermediate for natural compounds but many other chemicals, and the sensor can be used to produce anything that uses malonyl-CoA as a precursor. We are not the first group to develop a malonyl-CoA biosensor, but previous biosensors required multiple steps to detection. Our model is one-step colorimetric detection that gives you a much more linear relationship between the level of malonyl-CoA and the color. I think we can use the same technique to create biosensors for other precursors.

PNAS: What else are you working on?

Lee: We have used artificial intelligence to decipher drug–drug interactions and drug–food interactions. There are more than 2,000 approved drugs in the world, and hundreds of thousands of people die because of adverse effects of drugs per year, mainly because of drug–drug/metabolic interactions. We're missing a lot of drug–drug interaction possibilities. We used deep learning to examine the 192,000 known interactions and were able to identify 487,000 new potential previously unknown adverse drug–drug interactions. We're hoping pharmacists will pay attention, and these findings can be aligned to our healthcare system. We also identified interactions between food and drugs that we hope can be used to make people healthier.

1 Yang D, et al. (2018) Repurposing type III polyketide synthase as a malonyl-CoA biosensor for metabolic engineering in bacteria. *Proc Natl Acad Sci USA* 115:9835–9844.