

IB Interviews

A Conversation with Sang Yup Lee

Sang Yup Lee

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INDUSTRIAL BIOTECHNOLOGY: *Dr. Lee, congratulations on receiving the 2018 George Washington Carver Award for Innovation in Industrial Biotechnology and Agriculture. You are a pioneer in systems metabolic engineering, having leveraged the technology to develop microbial bioprocesses for the sustainable and environmentally-friendly production of chemicals, fuels, and materials from non-food renewable biomass. You are also one of just 13 people in the world elected as Foreign Associate of both National Academy of Engineering USA and National Academy of Sciences USA. Can you maybe share with the readers a little bit about how your career unfolded and what led you to KAIST?*

SANG YUP LEE: I graduated Seoul National University with a bachelor's degree in Chemical Engineering, and then one of my former advisors suggested I go to US for studying process design for chemical plants. He actually recommended a university, too—Northwestern. So I went there, and then, to make a long story short, I ended up majoring in biochemical engineering, which attracted me even though I didn't really know what that discipline meant at the time. After my PhD, I went back to Korea and became assistant professor at KAIST after a couple of years.

I've been at KAIST ever since! During this entire period of professorship, I had the privilege of having had great, great students, really bright students, probably the best in Korea, and maybe in the world. And we were able to perform research that's quite unique. For example, challenging the idea that certain chemicals and materials that could not be made through bio-based route. But we were able to design new enzymes, new pathways, and even optimize the whole cell as a biofactory for the production for all these chemicals and materials. There are generally two objectives when we perform research. First, achieve the highest titer, yield and productivity, suitable for commercialization. The other is to create entirely new, first-in-the-world routes to chemicals and materials through a bio-based route that may not be economically feasible at the moment, but maybe in 100 years when we run out of fossil oil or have no reason or no way to use such fossil resources, then there is a recorded procedure based on what we developed. So we only aim to have these two categories of projects. We have been producing a lot of chemicals and materials actually and many fortunately for the first time. Some of these processes have been translated into companies.

IB: *So is it the students forming these spinoff companies and you're in an advisory role?*

LEE: KAIST is the premier science and technology university in Korea, and my students usually have 3 different career paths: become a professor like myself at different universities, work at government research institutes, or work at a company or found a company. It is interesting to see that their job selection has been done quite equally—one third each. That balance recently has shifted slightly towards professorship, so there are more professors in this pool of my former students, but overall it's one-third each. Those who have become professors, I encourage them to expand from what they have been doing during their PhD because they want to build their own field of expertise. They're all doing quite well. And those who are working at companies or founded a company are also doing well. Many of them are playing important roles at big and small companies. I think they deserve the great recognitions they are receiving at companies and universities now because they worked very hard with creative minds during their studies at KAIST. So I'm very happy to be a professor seeing all my former students become successful!

IB: *Can you maybe talk a little about your innovation philosophy?*

LEE: Let me talk a little vaguely at first. Obviously, any innovation should be made so that it will be good for human beings and good for the planet. That's the mandatory objective that you can never violate. But if you go down to practical part, the approach we choose, we follow a certain path of thinking. First, we always define a good problem. Then, we generate an idea. For example, we might ask why terephthalic acid is always made through petrochemical route, and why is it so difficult to make it through bio-based route? Why are people looking at furan dicarboxylic acid or derivatives instead? So we study first, and then we look at the patents. If there's a patent, we avoid it. That's someone else's idea, and there's tons of other things we can do. In this particular case, there's no patent. So we fine tune the design and then start building the microbial cell factory. We could not yet report a complete cell factory that produces terephthalic acid from glucose, we reported first ever microorganism that can convert para-xylene (PX) to terephthalic acid by whole-cell bioconversion. Here, of course, PX is produced from biomass through chemical means, so entire value chain is more environmentally friendly. So, we choose projects like that. And as I mentioned, we try to achieve one of the two objectives if

possible—either best in the world or first in the world. In the first-in-the-world case, obviously we choose very difficult products to produce to demonstrate that it can be done. But for the best-in-the-world projects, we work closely with companies; either it is company-sponsored research, then of course they can immediately go back to demo-plant scale fermentation to produce in large amounts, or even go for commercialization. Or if no one is interested but we believe that it is important then we consider founding a company and try to commercialize it.

IB: *Can you describe how industrial biotechnology has evolved over your career and where you see it increasingly having an impact in the future?*

LEE: Industrial biotechnology is rapidly advancing due to multiple factors. First, increasing environmental pressure and equally increasing awareness on the importance of sustainability by the public and opinion leaders and decision makers. For the same reason, there are also increasing-levels of regulations on products derived from fossil oil such as one-time use plastics. More and more such regulatory actions and rules will appear towards protecting our environment. So we'll see the increasing roles of industrial biotechnology in addressing these problems.

It is also important to mention the rapid advances in technologies themselves. Genome sequencing, which is now essential for optimizing the microbial cell factory, cost me tons of money when I first reported this genome sequence of *Mannheimia succiniciproducens*, a small genome bacterium from the rumen of Korean cow. It cost us more than \$1 million and one and a half years of very hard work by many people. Now? I just give it to the company, 18 hours later, a full sequence comes in and cost is \$10,000 dollars for the very good sequence quality. This is just one example. People often talk about CRISPR, but for many bacteria CRISPR is not that useful, frankly speaking. We have a lot of different tools we can use. But for mammalian cells and plant cells, I think CRISPR and related technologies are quite good in more cases. In silico computational tools have rapidly advanced to better design microbial cell factories as well.

So these advances in technologies are rapidly changing how we build microbial cell factories and consequently the whole bioprocess to be implemented more rapidly. During the initial industrial biotech era, it cost so much money that people hesitated to go into some difficult products. But now, you can develop many different microbial cell factories and scan for the best ones more rapidly. So that means we can now develop industrially competitive strains with less time, effort, and money, especially compared with the previous decade.

Industrial biotechnology will not only play a role in the production of chemicals, materials, and fuels, but also nutritional compounds in increasing the beneficial parts of the food we're taking, and even natural functional compounds to be used in cosmetics. It's impacting all industrial sectors.

And I haven't even mention yet the possibility of using industrial biotechnology to produce inorganic compounds. Everything we've talked about so far is organic – organic chemicals and materials. Recently we scanned through the periodic table, using microorganisms and reengineered heavy metal detoxification mechanism to make metal nanomaterials out

of metal ion solutions. These include quantum dots, nanomagnets and beautiful energy storage materials, etc. So now we are even moving into producing inorganic materials using biotechnology.

IB: *So you see molecular electronics at some point?*

LEE: Absolutely. We can actually use the self-proliferating inorganic cell factory. Industrial biotechnology will contribute to developing organic-inorganic hybrid materials as well.

IB: *Can you discuss where you see policy playing a role? What works and what doesn't in your opinion?*

LEE: So first of all, I think there is still a lingering impact of GMO issues when we talk about genetically engineering organisms. Obviously metabolic engineering involves tons of genetic engineering. One good thing about industrial biotechnology employing developed microbes for fermentation is that it is always used in the closed tank environment rather than field trials like GMO corn, etc. So public opinion is much more favorable regarding these engineered bugs, cultured and contained in the tank. After fermentation they are all killed and not released into the environment. That's why we have been using a lot of food ingredients made by fermentation over many, many years. So I think that part is okay. However, policy still needs to be defined because there have been so many emerging technologies of rapid advances.

I mean, even though it's not my area of research, what if, you know, someone tried to fix the genetic disease of human using CRISPR and related engineering technology? There will be many ethical debates and thus regulations should be in place. So a lot of things can certainly happen due to the emergence of new technologies. Now we are using artificial intelligence and big data to more rapidly make microbial cell factories. So far, I do not see any problems with that approach. But who knows? I mean, when these new, emerging technologies come into play, there may be some unexpected outcomes. We should be always careful to follow the general rules for humanity so we don't harm people and we don't harm the planet. As long as we keep that principle very solidly, I think the use of all these different emerging technologies will be much beneficial. Proper regulation is needed, but probably we need soft regulations rather than hard regulations. Also, it is always important to communicate with the public and all the stakeholders based on scientific evidences.

IB: *What advice do you have for students just beginning to enter this field?*

LEE: Be brave. And I think young people, one of the major assets they have is they can do anything they want. They can fail and still can restart a new thing. It will be of course good to fail quickly and cheaply though (smile). Always, however, do something good for the future. And always have very solid background on one sub-field of technologies. Don't forget to have a broad knowledge around you and the world – that is, to become for example, a T-shaped knowledge person. We are now moving into the era of the fourth industrial revolution where everything is

more speedy, and technologies have much broader impact—a systems impact. So you have to be aware of a lot of different things. Education system should also change completely.

At KAIST, for example, we are running this program called Education 4.0. In this case, when you go to classroom, professors can do anything they want except for one thing—lecturing. So what you have is, not only just book and course-type online education system, but students will be given topics and recommended readings and videos and study at home and any-

where they want to get the knowledge. And then when they come to school, they discuss, debate, question each other and professor, and perform team works and team projects. This kind of education will still evolve with time and will change the way students are thinking and working, and will be increasingly beneficial and important in the future.

So again, they should be brave in thinking. Be creative, and of course work hard. Not all work and no play, though! Try to focus and then try to make their dreams a reality.

Editor's Note: The following text is excerpted from remarks delivered by Dr. Sang Yup Lee on receiving The George Washington Carver Award for Innovation in Industrial Biotechnology and Agriculture from the Biotechnology Innovation Organization (BIO) at the BIO World Congress, July 28, 2018, in Philadelphia, Pennsylvania.

It is my great pleasure to be here. First of all, I would like to thank BIO, the state of Iowa, the Iowa Biotech association, and of course the Carver award selection committee for giving me this award. I want to also thank Intrexon for sponsoring this award ceremony.

I am very pleased to accept this award on behalf of the family members of my laboratory at KAIST—including my former and present students and researchers. Since the establishment of my lab at KAIST about 25 years ago, we have been working on metabolic engineering of many different bacteria for the production of various chemicals, fuels, and materials. Being an academic laboratory, obviously, we wanted to establish some platform technologies for the development of very powerful, very efficient biofactories. And using those tools, we found that development of industrially competitive microorganisms can actually cost a lot of money and effort. Developing a typical industrial strain can require several hundreds of person-year effort with an injection of multi-tens of millions of dollars. As an academic, I cannot afford it. Can we develop something better? So we developed a number of tools that we collectively put together and called it systems metabolic engineering, which simply can be explained as integration of metabolic engineering with all the strategies and tools of systems biology, synthetic biology, and even evolutionary engineering—so that you can more efficiently develop

high-performance strains for the production of products of interest.

One example is the development of processes and strains for the production of various polymers, including unnatural polymers like PET [polyethylene terephthalate]. Obviously nature did not give us the enzymes and pathways to manufacture them. So we had to use protein engineering tools first to make enzymes that can do that job, put them into a host strain, and then perform systems metabolic engineering for efficient production.

And obviously I'm not going to talk about all these developments, but over the years, my group members worked very hard with creative ideas for the production of various chemicals and materials. Still, the achievements our group made were very small. However, if we add up all the achievements you have made and you are making, I can clearly say that we industrial biotechnologists are changing the world by providing sustainable chemicals, materials, and energy and also by providing better food, nutrition, and healthcare products. So we are indeed "DOers" who can make changes to make better world. And we can make better future for our children. Let me finish by quoting Mahatma Gandhi, who said, "Earth provides enough to satisfy every man's needs, but not every man's greed."

I think we should remember this phrase and continue to act to achieve this goal. With that I want to thank you all for this highest honor.