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PIONEER SCIENTIST INTERVIEW

Will genome editing technology push life science into a second outbreak?

Current base editors (BEs) catalyze only base transitions (C to T and A to G) and cannot produce base transversions. On 20 July 2020, researchers from Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences published a paper "**Glycosylase base editors enable C-to-A and C-to-G base changes**" on *Nature Biotechnology*, presenting a new type of base editors that cause C-to-A transversions in *Escherichia coli* and C-to-G transversions in mammalian cells. In this interview, we talk with **Dr. Changhao Bi**, corresponding author of this paper about the future insights of synthetic biology and genome editing.

This interview has been condensed and edited for clarity.

Q1: Hello, Dr. Bi. Thanks for accepting this interview. As we know, you completed your postdoctoral research at the University of Delaware and the Joint BioEnergy Institute (JBEI), Lawrence Berkeley National Laboratory. Your research mainly focuses on synthetic biology and genome editing. How do you think about the application prospects of synthetic biology?

Dr. Bi: Synthetic biology is an emerging research field that uses engineering concepts to transform and optimize existing life forms, or even to create artificial life from scratch. **At present, the application of synthetic biology mainly involves the modification of microorganisms to produce products.**

For example, DuPont modified the metabolic pathway of *Escherichia coli* to produce 1, 3-propanediol. Dr. Xueli Zhang, a researcher at our research group, successfully synthesized alanine by modification of *Escherichia coli*. The production of alanine in *E. coli* was originally low, but through synthetic biology techniques, the metabolic pathway was modified to produce L-type alanine with high optical purity efficiently. We have transferred the patent to Anhui Huaheng Biotech. As the synthesis cost is much lower compared with traditional chemical method, this company occupied 70% market share in the global alanine market and their market value has reached more than 3 billion RMB since it went public. This is a very typical application of synthetic biotechnology. Many people now claim that technologies such as CAR-T are also part of synthetic biology, which is somewhat controversial. In general, the application prospect of synthetic biology is good.

Q2: The traditional base editors catalyze only base conversion between pyrimidines and purines, while the new glycosylase base editor created by your team has high specificity and can catalyze any base change. What do you think are the key points and difficulties in achieving such accurate editing?

Dr. Bi: At present, our GBE editor can not achieve arbitrary base editing in one step. But it can achieve arbitrary base editing in *E. coli* through multiple steps using ABE and CBE together. It's still under research and has only a few practical applications. The most important role is to realize the specific editing of C-G and G-C in mammalian cells, which is the main innovation and significance.

The key point of using the GBEs is that we must pay attention to the sequence restriction to achieve high editing efficiency at the target site. In a word, it has a high requirement for the sequence.

There is no difficulty in editing mammalian cells, especially in the cells with high conversion rates, Hela, 293 cells, liposome etc. With vectors and lentivirus, it can be used to build mouse models.

Q3: Many natural products have health care functions and great economic value. We noticed that your team has been conducting some studies in this area, such as the synthesis of crocin using *E. coli*, which is also a practical application of synthetic biology. How will the new glycosylase base editors affect this research?

Dr. Bi: Our original purpose of studying gene editing technology is to engineer and construct microbes like *E. coli* and yeast cells more efficiently. New techniques have been developed and applied to the microbes after the advent of gene editing technology.

With the development of synthetic biology, it is now possible to synthesize high-value products by modifying microorganisms. The crocin produced by our team is one of the examples, but the yield is still relatively low and needs further optimization.

Q4: The 2020 Nobel Prize in Chemistry has been awarded jointly to Emmanuelle Charpentier and Jennifer A. Doudna "for the development of a method for genome editing". What does that mean for researchers and related industries engaged in genome editing research?

Dr. Bi: It is a great encouragement for the researchers studying gene-editing technologies. It proved the importance of genome editing and great potential that we can look forward to.

Meanwhile, the Nobel Prize is also a great encouragement to female researchers. Last year, our institute invited Frances H. Arnold, the 2018 Nobel Prize winner in chemistry, to give a talk. She was regarded as an idol by female researchers and students in our institute. The 2020 Nobel Prize in Chemistry awarded jointly to Emmanuelle Charpentier and Jennifer A. Doudna demonstrates that women “hold up half the sky” in the life sciences field. In our group, female researchers and students also make up half of the sky, which I think is a good phenomenon.

I don’t think the Nobel Prize will have a great impact on related industries. Maybe it will attract more investors to pay more attention to whether our work is likely to be transformed and play a role of draining traffic. However, the Nobel Laureates are generally engaged in primary scientific research, and tend to be less closely associated with the industry.

Q5: What do you think about the prospects for the future of synthetic biology and genome editing technology?

Dr. Bi: Synthetic biology and genome editing are revolutionary technologies. I hope that the development of these technologies will make life science research easier and more convenient, and more and more laboratories can use these technologies. I also hope that these technologies can push life sciences into the second outbreak. It is worth mentioning that there was no such technology before, when the first generation of gene editing technology- ZFN and TALENs appeared, only very professional laboratories could perform gene editing work, because of the high requirements to experiments and the need of huge synthesis work. CRISPR technology has brought a series of revolutions, enables many laboratories to do corresponding experiments. It will revolutionize biology and medicine and lead to many major achievements. Maybe that’s why it can win the Nobel Prize in chemistry. As far as we know, almost all human genetic diseases are caused by DNA mutations, and even some cancers have been found to be related with gene mutations. Gene editing or base editing can correct the gene mutations to treat the disease fundamentally, which is totally possible in the future.

Q6: At the end of the interview, do you have any advice or expectations for young researchers working on synthetic biology and genome editing?

Dr. Bi: For young scholars, **the first thing is to insist on innovation**. We need to persist in innovation, do things beyond the imagination of others, dare to try and take risks. It’s worth doing what is innovative, even if it failed.

Secondly, “History should be read with reservation”. I found that many researchers read a lot of papers, but couldn’t develop their own creative thinking and just do follow-up researches. It's fine anyway, but creative thinking should also be developed in the process. Once you have some ideas, read more papers to evaluate whether they are feasibility.

At last, you should focus on the important things. There are all kinds of research in the scientific community, but we must stick to the most important things right now, and do scientific research in our field related with these most important things. For example, the COVID-19 is the most important issue at the moment. With so many years of scientific development, we have no way to overcome this epidemic yet. The structure of this virus is simple, but we have not been able to contain it, which is a failure of scientific researchers. The ways we develop vaccines, such as attenuated vaccines were developed more than a hundred years old. Therefore, I suggest that our young researchers see the big picture and do what they can for these most important things.