ALLEN HO

Q&A: Tim Lu
Cocktail maker

Tim Lu's synthetic-biology research at Massachusetts Institute of Technology in Cambridge combines biological engineering with electronics and computer science to create bacteria that make structural proteins containing tiny semi-conductors called quantum dots. He explains how genome-editing techniques are furthering his research and their role in treating disease.

How do you use genome editing in synthetic biology?
Put simply, new editing technologies allow us to make genetic edits very efficiently. One of synthetic biology's main focuses is to reprogram DNA to achieve new functions inside living cells. Modifying DNA used to be quite a labour-intensive process, but that has changed. We spend a lot of our time iterating our designs and improving them, so the faster we can turn the crank, the faster we can converge on something that actually works. The range of cells that we can modify has also greatly expanded with new genome-editing tools to encompass animal, plant and bacterial cells, increasing the scope of applications.

Does your research have clinical applications?
Yes. The goal is to endow cells with basic computing ability. By making cells that can sense their environments and take decisions based on the signals they detect, we hope to create new diagnostics and therapies. These days you go to the doctor, get a diagnosis, and then pop a pill with no control over it after you swallow. But what if something you swallow could sense disease indicators and respond with treatment before you became sick?

That sounds amazing. But how exactly would these disease-sensing pills work?
The idea is to edit organisms to turn them into sensors that record what goes on inside the complex environment of the gut. In other words, to create bacteria that can tell whether there are signals of disease such as inflammation. If you ate these bacteria, they could then be recovered from your faeces to provide information about what happened as they transited through you. Bacteria could be engineered to not only sense their environment, but also to produce some sort of therapeutic molecule, so that they could deliver a drug only where it is needed.

Do you foresee genetically edited bacteria becoming part of the human microbiota?
Their first role is more likely to help us to better understand how this community of organisms contribute to health and disease. Microbiome studies are primarily just surveys. Researchers take faecal samples, sequence the bacteria in the sample, and see what species are there. From that they derive some interesting hypotheses that link certain bacteria to particular diseases. But missing from these studies is a functional understanding of what the microbes are actually doing. What if a microbe is only 0.5% of the gut microbiome, but has some really important function?

In my lab, we have done a lot of work on targeted antimicrobials. For example, we engineer bacteria-invading viruses called bacteriophages as ways of killing very specific bacteria or delivering genetic information into them. If you were to knock out one species at a time from a microbiome, and saw what effect that had on a host, you would get a much better understanding of what each member of the host's bacterial community does.

Do you think bacteriophages will be widely used as therapeutics in the future?
There has been a lot of interest in alternative antimicrobials because antibiotic resistance is such a big problem. Phages have a part to play in the solution, but there are regulatory issues. In some Eastern European countries you can buy phage products over the counter, even though a lot of what is available has not been subjected to rigorous clinical trials.

You often need a cocktail of different types of phages to properly target a bacterial species. If you were to approach that by taming wild phages, you would often find very different families that have differently organized genomes in your cocktail. The key regulatory issue is that you need to make sure that each phage in a therapy is consistent within clear boundaries of biological variation because they all have quite different safety profiles. We have been using synthetic biology techniques to create more uniform phage cocktails. These phages would work like antibodies — they have a common scaffold that can be reconfigured to target different bacteria.

Do you have any concerns about these new genome-editing technologies?
There is an emerging movement in which people are setting up shops in their garages. Community labs are being set up that allow anyone to come in and be trained. Previously, you had to be an expert in making zinc-finger vectors to edit DNA, but now — because CRISPR–Cas systems are so easy to use — anyone with molecular biology training can do it. On the one hand it is an exciting time for the field because this movement is going to bring in a lot of new ideas and talent. But on the other, it is also going to create new regulatory questions. The democratization of biological engineering is inevitable. Now we have to size up the risks and benefits so we can harness what is going to come of it. ■

INTERVIEW BY WILL TAUXE

This interview has been edited for length and clarity.