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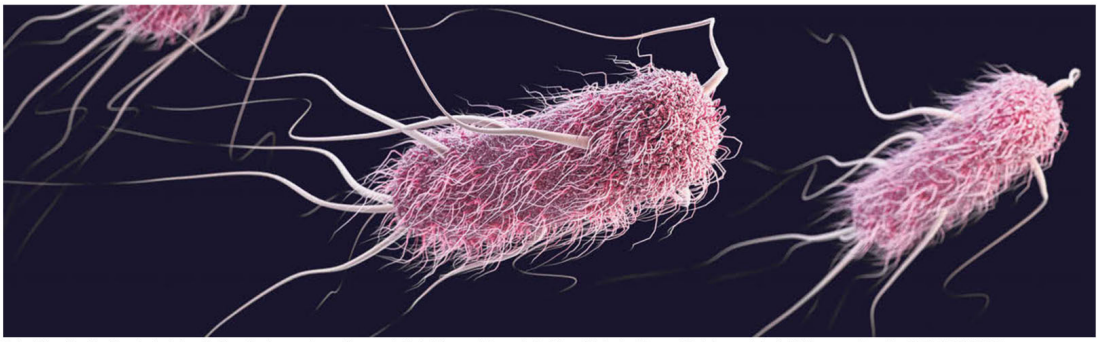

Escherichia coli, or E. coli, are bacteria found in the gut and commonly used in research. Bacterial research is amazingly rich – which is why it has contributed so much to all of biology, says the writer. PHOTO: ALISSA ECKERT

ScienceTalk

Genetic scissors from bacteria, a tool to slice and dice code of life

It can make precise changes to DNA, and has potential to cure diseases

Swaine Chen

French microbiologist Emmanuelle Charpentier (far left) and US professor Jennifer Doudna at a painting exhibition by children about the genome in Oviedo, Spain, in 2015. Last week, they won the 2020 Nobel Prize in Chemistry for discovering one of gene technology's sharpest tools: the CRISPR/Cas9 genetic scissors that can be used to change the DNA of animals, plants and micro-organisms with extremely high precision. PHOTO: REUTERS

"When will YOU win a Nobel Prize?"

Scientists receive regular reminders of how important this prize is in their relatives' (and the public's) mind. For many, the Nobel Prize is their idea of science.

Indeed these are the most famous awards in medicine, chemistry and physics.

Scientists also pay attention to the Nobel Prizes because we love science.

It's only natural to chat and debate about the most significant recent discovery in our fields. This requires broad perspective and context.

With only one prize each year, how can a breakthrough in cancer therapy be compared with or ranked against a fundamental discovery about infections?

This must be particularly stressful for the group that meets regularly in Sweden to decide who is to win the most coveted prize in science.

Last week, the 2020 Nobel Prizes were announced for the discovery of the hepatitis C virus (physiology or medicine), advancing our understanding of black holes (physics), and a technology for editing genomes (chemistry).

As a scientist studying the genomes or genetic make-up of bacteria, I want to provide a broader perspective on the latter to give some insight into where we might fruitfully invest in more research.

Dr Emmanuelle Charpentier and Dr Jennifer Doudna discovered one of gene technology's sharpest tools: the CRISPR/Cas9 genetic scissors.

Using these, researchers can change the DNA of animals, plants and micro-organisms with extremely high precision, read the statement by the Royal Swedish Academy of Sciences, in explaining the decision to award them the prize.

"This technology has had a revolutionary impact on the life sciences, is contributing to new cancer therapies and may make the dream of curing inherited diseases come true," it said.

The two women used a system called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) to edit a genome.

A genome is the entire set of DNA in an organism.

You may remember from school that your body is made up of individual cells; each cell has a nucleus, and inside the nucleus is DNA – the "instruction set for life". Your DNA is unique – these differences make you unique, specifying the colour of your eyes and your general height and weight, among many other traits.

Certain differences can influence your susceptibility to diseases such as diabetes, cancer or Alzheimer's.

Interestingly, we know that DNA differences do influence risk for these diseases, but we often don't know exactly what DNA changes are responsible, much less how this takes place.

But for some diseases, such as sickle cell anaemia, Duchenne muscular dystrophy or cystic fibrosis, we know exactly what DNA changes cause the disease.

If we could "edit" these specific changes, we would completely cure the disease.

Genome editing means making precise changes to the DNA of an organism, and it therefore has the potential to cure – not just treat – any disease caused by DNA differences.

Genome editing, therefore, has a huge range of applications.

The CRISPR system is a set of molecules that was originally discovered in bacteria.

Why did it win the Nobel prize? One key feature of CRISPR is that it is programmable and general.

There have been other technologies in the past that could be used to edit genomes, but CRISPR made it dramatically easier because it was the first technology that could be easily changed to target the sickle cell DNA mutation in one experiment, and then the cystic fibrosis mutation, with just a minor change, in the next experiment.

This programmability made it applicable to any genome edit we could ever want to make.

But though important, programmability was not quite enough.

What made CRISPR a front runner in Nobel Prize discussions in cafes across the world (or, more precisely, cafes across the street from research labs across the world) was that it was also a relatively small, independently functioning protein machine.

In other words, we could take just the CRISPR components, and they would work the same way in nearly any cell type – a heart cell, nerve cell, immune cell or even an insect cell, yeast cell or bacterial cell.

The system requires only a few components, then it performs its function in nearly any cell we put it in – it's a self-sufficient, all-in-one module.

Interestingly, the CRISPR system was extracted from bacteria, where it was used as a sort of immune system. In bacteria, the CRISPR system seems to have evolved to be self-contained, so that it could be transferred to other bacteria and still function properly.

These two features – programmability and modularity – are two advantages that CRISPR improved on, compared with other genome editing technologies.

This is why it has had such a broad impact on biology, and researchers are using CRISPR in nearly every imaginable cell type, to make better plants for farming, customised bacteria for biotechnology, modified mosquitoes for vector-borne diseases and fundamental research to find the DNA changes we'll later want to edit, to cure diseases.

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Looking more broadly, we have seen these key features in other Nobel Prize-winning technologies.

There is a very strong parallel with restriction enzymes (another DNA-cutting system), the discovery of which garnered a Nobel Prize in 1978.

A revolution in biology has been already wrought by restriction enzymes, and scientists expect CRISPR will herald another biological revolution of similar scale.

The use of restriction enzymes allowed for recombinant DNA engineering and molecular cloning.

In fact, nearly all of molecular biology was advanced by the clever application of restriction enzymes.

Like CRISPR, restriction enzymes come from bacteria. They can also be transferred between different bacteria and still function – they have the property of self-contained modularity.

In fact, many of the foundational technologies that support modern biology are derived from bacteria.

Many are modular – this seems to be something that evolution particularly selects for in bacteria, perhaps because they can easily transfer DNA among themselves.

Modularity, in turn, makes these bacterial systems highly efficient and easily extracted, so that we can use them for our own purposes in test tubes and in other cells – whether bacterial, plant or human.

Other examples of bacterial-related Nobel Prizes are: streptomycin as a treatment for tuberculosis (1953); transfer of DNA between bacteria (1958); the protein that copies DNA (a polymerase) (1959); the details of how cells respond to changing conditions (1965); application of DNA polymerases in polymerase chain reaction (1993); and bacterial phages for directed evolution (2018).

Bacteria are an enormously diverse group of organisms; what we call a single species of bacteria has individuals that are more different than humans are from chimpanzees.

Therefore, bacterial research is amazingly rich – which is why it has contributed so much to all of biology, a tiny fraction of which is recognised by Nobel Prizes.

The diversity of bacteria means that, for nearly any process or function we might need – be it copying DNA or editing the genome – there is likely some bacteria that has highly optimised that process.

Bacteria are, in fact, the Olympic athletes of any biological process.

The fact that many bacteria can exchange DNA also means that many of their molecular machines are self-contained and modular, and we can reasonably expect them to still work when isolated or transplanted, allowing us to repurpose them for our own ends.

In Singapore, there is a strong community of people working on bacteria and their molecular systems.

Some are working downstream on optimisation and application of CRISPR.

Others, like my lab, are doing more foundational work, the discovery science that comes before these prizes: understanding the process of DNA transfer, characterising the diversity of bacteria and delving into the details of how these bacterial machines work.

There is also a community of bacteriologists (called the Bacterial Ultra Group, or BUG) looking directly at the details for how bacteria cause disease, the direct interaction interface between bacteria and humans.

Bacteria are endlessly fascinating, and we have much more to learn from them.

More Nobel Prize-worthy discoveries and technologies are certainly lying in wait for us within these diverse organisms.

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About the writer

Dr Swaine Chen is an associate professor of medicine in the Infectious Diseases Programme at the Yong Loo Lin School of Medicine at the National University of Singapore, and a group leader in bacterial genomics at the Genome Institute of Singapore, Agency for Science, Technology and Research.

His research uses genome sequencing and genome manipulation to understand bacterial diversity and how bacteria cause infections in humans, such as the yusheng-associated outbreak of Group B Streptococcus infections in Singapore in 2015.

The overall aim of his research is to enable faster detection and more effective treatment of bacterial diseases.

In 2012, he was one of the co-founders of the Bacterial Ultra Group (BUG), an active research community in Singapore that studies the mechanisms and spread of antibiotic resistance and details of the strategies that bacteria use to infect humans.

You can find out more about BUG and Dr Chen's research on Twitter (@swaine_chen) or at https://swainechen.github.io

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