Synthetic biology

On a quest for new superbug antibiotics

Samantha Boh

Singapore researchers are offering new hope in combating superbugs – bacteria that are resistant to existing antibiotics.

They have found a way to cut and stitch together parts of the DNA of four naturally existing bacteria, to create 12 potential anti-superbug antibiotics, which could be ready for animal trials in two years' time.

Their work also offers a faster and cheaper option for the creation of new antibiotics.

But developing antibiotics to tame superbugs is the more important goal of the researchers at the National University of Singapore's (NUS) Department of Biological Sciences, said Assistant Professor Kim Chu Young, the lead scientist in the study.

To do that, they need to create three artificial DNA that can be mixed and matched in various ways, and then re-inserted into E. coli bacteria. Each bacterium will have a differently combined DNA, and will produce a different drug that has the potential to kill superbugs.

The NUS team has so far successfully created one of the artificial DNA. It is the most complicated of the three, said Prof Kim.

As for the prospect of the synthetic biology research helping to create antibiotics faster and more cheaply, he said it would not replace the current methods.

"Instead of two bullets, we now have three... which increases our overall chances of dealing with the problem (of superbugs)," he said.

New antibiotics are traditionally sourced from nature, including soil, or created in the laboratory by using chemistry to modify existing antibiotic drugs.

But finding antibiotics from soil has become tougher as countries grow more protective of their resources, hindering research on soil across borders. On the other hand, complex modifications of existing antibiotics could take many years, owing to the large number of chemical reactions that need to be worked out, said Prof Kim, who is a principal investigator for the NUS Synthetic Biology for Clinical and Technological Innovation programme.

He and his team of scientists are optimistic that with synthetic biology, a larger pool of 10 naturally existing bacteria can be modified to develop up to 5,000 new bacteria-fighting drug candidates.

With such a huge number of compounds, he is optimistic that "at least one or two drug molecules can be antibiotics".

He added: "It is not a scientific argument, but when you are dealing with such large numbers, you are more likely to find something rather than not find anything."

samboh@sph.com.sg

Assistant Professor Kim Chu Young said synthetic biology research helps create antibiotics faster and more cheaply. ST PHOTO: CHEW SENG KIM

Protein crystals used to determine the atomic structure of enzymes. These enzymes are used by soil bacteria in the process of synthesising natural antibiotics. PHOTO: KIM CHU YOUNG

NUS sets sights on synthetic biology

A new $25 million research programme at the National University of Singapore (NUS) has the potential to one day overcome the scourge that strikes the Republic regularly – dengue.

The study of synthetic biology has seen researchers abroad re-engineer the genome of the Aedes mosquito so that its offspring die before reaching adulthood.

But the NUS researchers have other ideas in mind, Associate Professor Yew Wen Shan of the Department of Biochemistry at the Yong Loo Lin School of Medicine told The Straits Times.

The more immediate focus of the NUS Synthetic Biology for Clinical and Technological Innovation – or SynCTI – is to study how to create antibiotics that can resist superbugs, and synthetic yeast whose characteristics can be altered by choice, among other things.

Synthetic biology research was made famous by bioscientist Craig Venter in 2003 when he successfully mapped the entire human genome, an achievement that could lead to medicine customised to an individual's unique genetic make-up.

Essentially, such research aims to construct biological components and systems that do not exist in the natural world, or modify existing biological systems. This could mean developing microbes that produce existing drugs, or re-engineering mosquitoes that will reduce the population of these dengue-causing insects.

The NUS SynCTI programme brings together the disciplines of engineering, medicine and science and Prof Yew, one of its principal investigators, said it is also "in the business of training the next generation of synthetic biologists".

NUS undergraduates right up to PhD students can do modules in the programme, which also offers attachments to polytechnic students.

SynCTI also partners the University of California, Berkeley, and Imperial College London, both of which will set up laboratories in the NUS Centre for Life Sciences, where the programme houses its seven local laboratories run by NUS faculty.

With most of its funds coming from the NUS, topped up by contributions from the National Research Foundation, Education Ministry and other government agencies and industry partners, SynCTI aims to take on "societal grand challenges", said Prof Yew. One example would be to target obesity, which is often due to abnormal micro-organism behaviour in the body. It is looking at a more creative solution than just a new pill.

"We could go as far as to restore normalcy by engineering a smart bug to reprogram the microbes residing in the body," he said.

Samantha Boh

ScienceTalk

Engineering artificial life in the lab

Scientists hope to use synthetic biology to find cures, create food and sustain resources

Yew Wen Shan and Matthew Chang

The current buzz in science and engineering is over synthetic biology.

There are many definitions of this "new kid on the block", and by most accounts they describe a meeting of the engineering sciences with the biological (biomedical) sciences.

This is an emerging area of research that can be described broadly as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems.

All living things have a genome which dictates what they look like and what they do. Humans have been altering the genetic code of plants and animals for thousands of years by selectively breeding those with desirable traits.

But as scientists learnt more about how to read and manipulate this code, they took genetic information associated with useful features from one organism and added it into others. Such genetic engineering has allowed researchers to develop new breeds of plants and animals faster.

More recent advances, however, have allowed scientists to make new sequences of DNA from scratch. By combining these advances with the principles of modern engineering, scientists can now use computers and laboratory chemicals to design organisms that do new things, such as producing biofuels or creating drugs.

Our understanding of biology and our command of engineering tools and standards have led us to this new frontier. In essence, synthetic biology is the purposeful design and engineering of biology to solve challenges confronting our world.

For more than two decades, biologists and engineers have been trying to make sense of each other's worlds: Understanding life has kept biologists busy, and bringing comfort and convenience to life has kept engineers hard at work.

But the quantum leap – in demonstrating this knowledge of life by engineering it – has been elusive to both sides until recently.

With the arrival of breakthrough technologies that allowed rapid sequencing of genomes and the synthesis of entire genes – even a whole microbe or chromosomes of yeast – humanity has finally obtained the means to engineer life.

Fast off the starting block, synthetic biology has already shown its potential in revolutionising many sectors of civilisation.

In areas as varied as energy, healthcare and the environment, this new discipline has achieved impressive and astounding results that were not previously possible.

For instance, Professor Jay Keasling, a synthetic biologist from the United States, has developed microbes that produce drugs, such as artemisinin, an anti-malaria drug that was first extracted from the herb sweet wormwood by the Chinese more than 2,000 years ago.

It can now be produced by drug company Sanofi using synthetic biology methods, and made more affordable to patients around the world.

Professor Craig Venter, a biochemist responsible for sequencing the human genome, has created the first microbe with an artificial, synthetic genome.

The US Defence Advanced Research Projects Agency, which enabled the birth of many breakthrough innovations such as the Internet, the Global Positioning System and self-driving cars, is attempting to develop a new type of biological manufacturing platform that makes it possible to rapidly design and engineer a range of synthetic organisms.

Others, like the company Oxitec, have employed synthetic biology methods in an effort to eradicate dengue fever by releasing – albeit with some controversy – engineered male *Aedes aegypti* mosquitoes into the wild to bring down entire populations of the dengue virus-carrying mosquitoes.

This involves genetically engineering the male of the mosquito species which carries the dengue virus, but loading a self-limiting gene, which means their offspring would die before reaching adulthood, thus controlling the population.

The astonishing potential of synthetic biology to change the way we live could also have serious ethical and cultural impact on our society.

Would the creation of synthetic organisms be publicly and ethically acceptable? Does our society possess adequate regulatory and legal policies for the safe release of synthetic organisms into the environment?

Since the birth of synthetic biology, the global community has been working relentlessly with the public, social scientists and regulatory experts to ensure that the field offers ethical and beneficial solutions to our civil society.

Some concerns pertain to risks and benefits. Synthetic organisms raise questions about public health, environmental contamination, and even deliberate misuse. Other worries are about risks and benefits, and the very idea of creating synthetic organisms.

In Singapore, the Government has indicated its desire to position the nation as a biological design hub. Recognising that synthetic biology can bring many benefits to the world that cannot be provided by nature, the National Research Foundation, with the Economic Development Board, has created a fertile landscape for synthetic biology to take root.

Their efforts are focused on local talent development in the foundational disciplines of synthetic biology, such as biochemical, metabolic, microbial and genome engineering, and molecular, structural and systems biology.

Like its counterparts in other countries such as the United States and Britain, where significant investments have been made in synthetic biology, Singapore is attracted by the massive global market estimated to be more than US$10 billion (S$14.2 billion) next year.

A little over three years ago, the National University of Singapore (NUS) launched the Synthetic Biology Initiative to bring together teams of doctors, scientists and engineers. Working together, this group of synthetic biologists came up with ways to improve the quality of life of patients seeking medical treatment in Singapore.

The challenges include designing and testing novel therapies to treat cancer, metabolic diseases such as diabetes and obesity, infectious diseases, cardiovascular diseases, and diseases associated with ageing, like Parkinson's.

The group is also setting its sights on using synthetic biology to provide personalised and precision healthcare, which is about finding and giving the right treatment to the right patient.

The initiative has since expanded into the new NUS Synthetic Biology for Clinical and Technological Innovation (SynCTI), which was launched officially on Wednesday.

SynCTI biologists and engineers will continue to work with their counterparts in local and global research institutes to create impactful technologies that will positively change a number of industries.

As synthetic biology germinates into a tree of hope for humanity, SynCTI, along with the other global centres and institutions, will continue to engage all sections of civil society, including social scientists and lawmakers, to ensure a stewardship of this new science that is guided by ethics.

If the efforts succeed, gone will be the days of humanity robbing the earth of its wonders and riches.

Instead of getting vanilla from vanilla beans, for instance, one could produce a sustainable version of this favourite flavour from engineered yeast.

Other environmentally sustainable solutions to pressing societal challenges include using microbes to recycle and recover metals like gold from discarded electronics, and re-engineering yeast to make better bread (even designer wine!).

Given the challenges confronting humanity, it is important to balance our needs with an understanding and respect of the world we live in.

But regardless of the debates, it is clear that synthetic biology is the new way to address old, pressing problems of society.

As we move forward together, societal engagement will become an increasingly important way to do so responsibly.

Assoc Prof Yew Wen Shan (far left) and Assoc Prof Matthew Chang. ST PHOTO: CHEW SENG KIM

Leading research initiatives at SynCTI

Associate Professor Matthew Chang, 40, is a synthetic biologist at the National University of Singapore (NUS).

He heads the NUS Synthetic Biology for Clinical and Technological Innovation (SynCTI) as programme leader, and teaches in the Department of Biochemistry at the NUS Yong Loo Lin School of Medicine.

Prof Chang obtained his doctorate at the University of Maryland in the United States. His research focuses on studying engineering biology, and developing a pioneering approach in reprogramming cells for clinical and industrial applications.

Prof Chang has published numerous studies in international journals and registered patents, based on his research in synthetic biology. His scientific contributions have been recognised with international honours and awards, and featured worldwide in the public media.

He is a strong advocate of promoting interdisciplinary science that marries engineering, biological, medical and social sciences through primary, secondary and tertiary education, and public science outreach.

Associate Professor Yew Wen Shan, 41, is a synthetic enzymologist at NUS.

He works at SynCTI, in the Department of Biochemistry at NUS Yong Loo Lin School of Medicine, and is a supervisor of the NUS Graduate School for Integrative Sciences and Engineering.

Prof Yew obtained his doctorate at the University of Illinois, at Urbana-Champaign in the US. He graduated with first-class honours in biochemistry from NUS, and was a Herbert E. Carter Fellow at the University of Illinois, and an A*Star International Fellow.

A recipient of the NUS Annual Teaching Excellence Award and the NUS Medical Faculty Teaching Excellence Award, he is passionate about training the next generation of doctors, scientists and engineers, and encouraging them to work together for the betterment of humanity.

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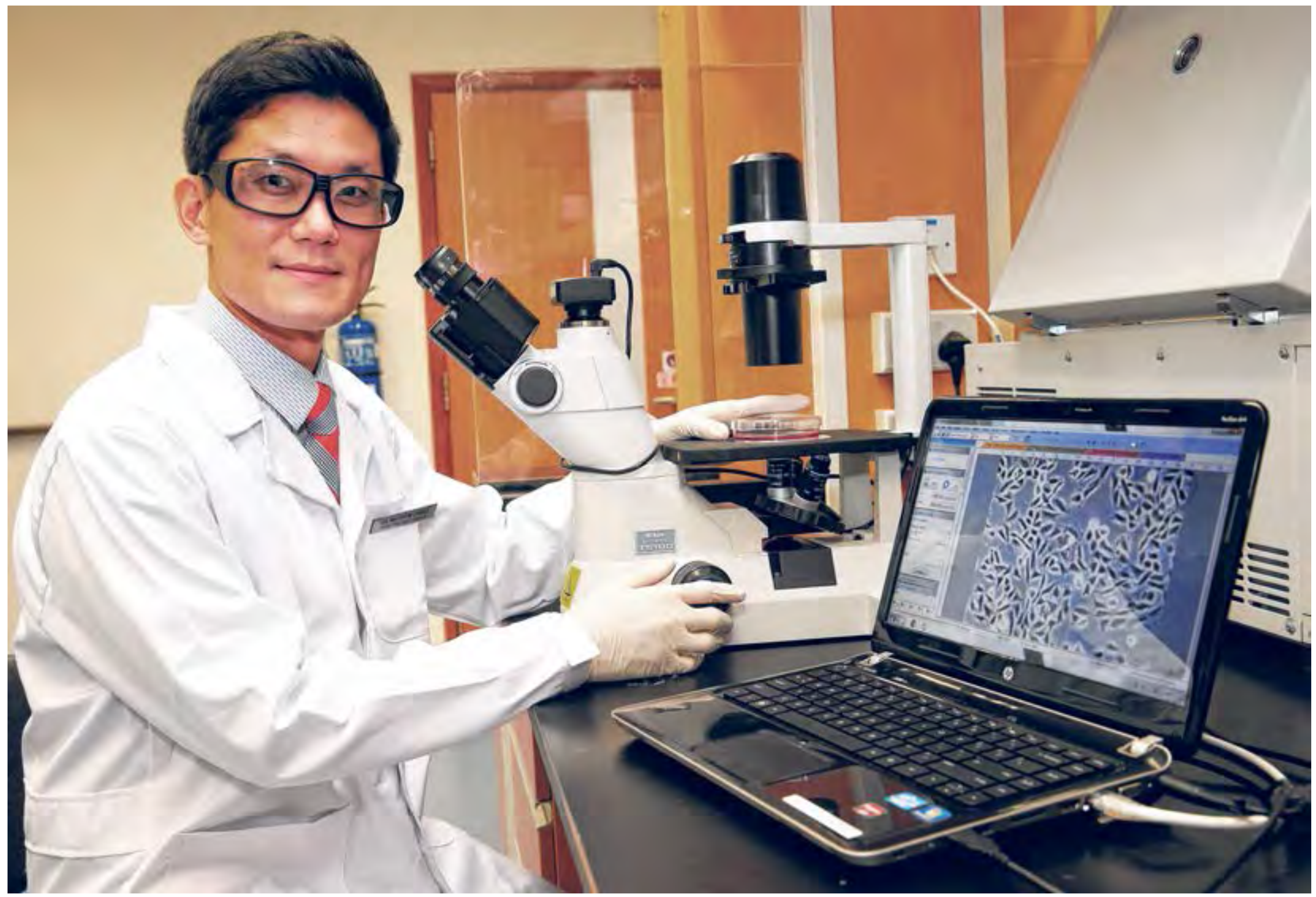
SCIENCE

Synthetic biology

Cooking up new ways to create food and medicines



Associate Professor Matthew Chang is leading an NUS team which will be creating a synthetic version of a chromosome found in yeast. ST PHOTO: CHEW SENG KIM

The emerging field of synthetic biology has opened up exciting opportunities for harnessing new biological systems. Samantha Boh looks at the scientists creating artificial life forms here.

Imagine Singapore becoming a wine-making country because climate no longer matters or mums baking chocolate-flavoured bread without having to use cocoa.

The search for the secret to producing such food and drinks, and more, is now under way internationally and researchers from the National University of Singapore (NUS) are part of the exploration team called the International Synthetic Yeast Genome Consortium.

The prize discovery is to come up with synthetic yeast whose characteristics can be modified at will.

It begins with creating the synthetic version of each and every one of the 16 chromosomes found in the garden-variety baker's yeast sold in supermarkets.

The consortium of scientists from various institutions, including the universities of Edinburgh in Scotland, Johns Hopkins in the US and Tianjin in China, have each been given a chromosome to create.

The NUS team is designing chromosome 15 and it is led by Associate Professor Matthew Chang, who heads the NUS Synthetic Biology for Clinical and Technological Innovation programme.

When all the 16 synthetic chromosomes are constructed, they will be incorporated into a living yeast cell, by replacing the original chromosomes residing in it. In doing so, an entirely new yeast strain is created.

The consortium hopes to get the synthetic genome done by 2017. When completed successfully, it will be the first time scientists have built the whole genome of a eukaryotic organism – an organism whose cells contain a nucleus, like plant, animal and human cells.

This could lead to the development of plants that can withstand climate change or are resistant to pathogens, said Prof Chang.

But that is far on the horizon.

Meanwhile, a team from Johns Hopkins and New York universities successfully modified a chromosome from scratch last year. The process involves reducing the genome size by removing non-essential features and adding new genetic components. "The whole premise is to reduce the size of the chromosomes to bare necessities and introduce choice elements which will allow design engineering and evolution of the genome," said Prof Chang, from NUS' Department of Biochemistry, Yong Loo Lin School of Medicine.

Yeast could potentially be modified to produce antibiotics or other drug precursors, he added.

He is also leading a team to create anti-cancer compounds by reprogramming a particular type of probiotic cell, where the cells convert a compound common in cruciferous plants like broccoli, into anti-cancer compounds. Animal tests show they killed most of the cancer cells, and there are plans for more tests.

He said the research targets cancer patients in remission. Humans "consume a lot of vegetables, so if we can supply the reprogrammed therapeutic cells, like in the form of a drink, we think the cancer can be managed to a certain extent".

samboh@sph.com.sg

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