SPOTLIGHT ON IMMUNOLOGY

Synthetic biology: a science to 'fuel, heal and feed'

Synthetic biology is rapidly changing the way vaccines are being designed, tested and produced.

"It never has to be shipped anywhere. We can synthesize right there and then. This whole process could save months."

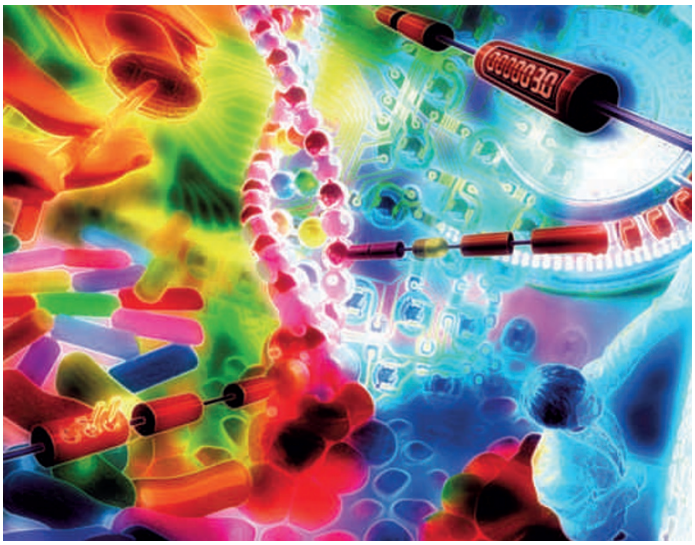
Philip Dormitzer, head of US research at Novartis Vaccines and Diagnostics

AS OF 28 February 2014, there had been a total of 375 laboratory-confirmed cases of humans infected by influenza virus H7N9, including 115 deaths that have been reported to the World Health Organization (WHO). This virus first emerged in March 2013, but numbers decreased during the winter. It is now back in earnest.

This time, the world is more prepared. After recognizing the initial outbreak, the Chinese Centre for Disease Control characterized the H7N9 strain and posted the virus sequences on the internet on 31 March 2013. By 6 April, less than a week later, Novartis and Craig Venter's company Synthetic Genomics Vaccines Incorporated (SGVI), had teamed up to create several potential vaccine viruses. By mid-June, manufacturing scale production of a vaccine candidate for clinical testing started, and on 14 November of the same year Novartis announced interim clinical trial results. In December, the vaccine was provided to the US government pre-pandemic stockpile. "This was the first time all of this had been accomplished before a second wave of an animal-origin flu outbreak in humans hit," says Philip Dormitzer, head of US research at Novartis Vaccines and Diagnostics.

Historically, vaccine manufacturing companies would learn of a potential pandemic, but would have to wait to receive a sample from the WHO before they could begin working on a potential vaccine. This can be a slow and arduous process, often leading to vaccines being produced long after the first peak of the virus' damage is done.

The ultimate goal of almost every immunologist is to create a vaccine that can be produced and delivered to patients before they are infected. Jose-Carlos Gutierrez-Ramos, head of BioTherapeutics research & development at Pfizer, predicts synthetic biology will reach this goal. "If we can cut the vaccine development time by half, or even two-thirds and get the drugs to patients faster, saving lives, then that's a good thing."



An engineering perspective

The European Commission defines synthetic biology as "the engineering of biology: the synthesis of complex, biologically based (or inspired) systems which display functions that do not exist in nature." This engineering perspective can be used to understand biology in terms of components and modules that can be assembled and disassembled. The components can be anything from a protein to a peptide, a piece of DNA or an entire bacterial cell.

In the past, some vaccines have been created using heated activation, where a patient is exposed to a weakened or dead version of the virus they are being immunised against. Ceri Lyn-Adams, strategy and policy manager for genomics, data and technologies at the Biotechnology and Biological Sciences Research Council (BBSRC), says that this is changing with the new technologies that synthetic biology has to offer. "Now we can engineer the vaccine, so that the genes that make the virus infectious or able to replicate aren't there. So you get the immune response, but no complications."

Building a synthetic virus

Professor Polly Roy from the London School of Hygiene and Tropical Medicine (LSHTM) has been studying the Bluetongue Virus (BTV), an insect-transferred virus in ruminants, for more than 25 years. "I have utilised multiple techniques and approaches including molecular biology, physical and biochemical techniques, cell biology and immunology to understand BTV down to the most precise details. This meant that I knew exactly how to make it synthetically."

And this is what she has done. In 2011, Roy and her team were the first to create a synthetic virus in a test tube, outside the cell. It was by understanding the exact workings of the BTV that the team could create the virus, "starting from the fundamental insides, and working their way out."

It was a pioneering achievement for the LSHTM team, says Roy. In the future, her team hopes to answer the fundamental questions of the BTV genetic sequence in

Timeline for UK funding of synthetic biology

Since 2007, British governments have taken a keen interest in the potential of synthetic biology and have promoted the UK as a hotspot for research in the field.

2010: The BBSRC published their Synthetic Biology Dialogue document, outlining the stakeholders' and public perception of the research.

2011: The EPSRC and European Research Council combined forces to create the Responsible Innovation Framework, a scoping study to find out how responsible innovation could continue.

2012: The Technology Strategy board commissioned a Synthetic Biology Road Map for the UK, to highlight a direction for synthetic biology research. Its goals were to establish a cohort of multi-disciplinary research centres, to build a community of researchers, to invest and accelerate the technology to market and assume a leading role in the global research community.

In November, George Osborne, the UK chancellor, spoke at the Royal Society about the "eight great technologies" to receive extra backing from the UK government. The Research Councils UK received a grant of £50million to invest in synthetic biology research.

2013: Imperial College London hosted the BioBricks Foundation SB6.0, at which David Willetts, the Minister of State for Universities and Science, said that synthetic biology could "fuel us, heal us and feed us."

2014: At SynBioBeta in early April, Willets announced that the BBSRC will receive £10million to invest in synthetic biology to establish 5 new centres for DNA synthesis across the UK and a further £2million for equipment and training. This is from the initial £50million allocation from 2012.

order to produce vaccines more efficiently. "If we can do this, we can potentially transfer our knowledge to other viruses."

Once you understand the structure of a virus, the next challenge is to completely and reliably reproduce it in a short space of time.

Improving the production line

Pfizer has started working with Massachusetts Institute of Technology (MIT) to improve biologic production in cells. "The beauty of collaborations like this one is we can bring the latest academic advances to real-world problems," says Gutierrez-Ramos.

At the moment, scientists compensate for anything that goes wrong in a cell – they remove the superfluous parts; they edit and change. "We want to be able to produce something where this human interference isn't necessary," says Gutierrez-Ramos. "We want to make a system where the unpredictable becomes predictable."

Gutierrez-Ramos and his team are hoping to improve the Chinese hamster ovary (CHO) cells, the most commonly used mammalian hosts and "work-horses of the industry", so that they can produce viruses and vaccines in a more reliable way.

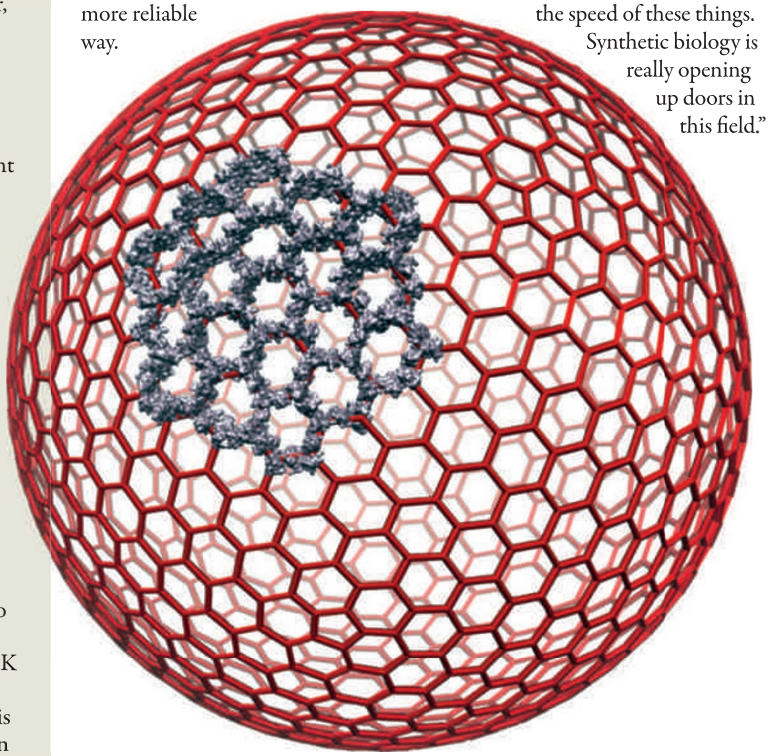
"We believe the concepts of synthetic biology allow us to do this. It allows us to put all the components in the right place and make something optimal for biologic production."

Time is of the essence

Big-pharma leaders like Novartis and SGVI have come together to develop new synthetic biology techniques in vaccine production, and have already shown that they can reduce the time taken from 126 days (H1N1 in 2009) to only 6 for producing a high-yielding virus strain that can be used to make vaccines in manufacturers' laboratories.

For self-amplifying messenger RNA, or SAM® vaccines, the vaccine itself is synthesized. "It looks like the virus to the immune system, but doesn't come with the genes that can allow spread from cell to cell, so you could get the increased potency of a viral vector vaccine with less risk," says Dormitzer.

Novartis and SGVI prototyped this technology during the 2013 H7N9 outbreak in China, and created a vaccine candidate that was immunogenic in mice only eight days after downloading the sequence from the internet. "It's not been used in humans yet," says Dormitzer. "But it raises the possibility that there can be even more dramatic accelerations in the speed of these things. Synthetic biology is really opening up doors in this field."



DEK WOOLFSON

A completely synthetic protein cage, engineered by Dek Woolfson, of Bristol University, that could be used for vaccine delivery.

Vaccine delivery

In January 2014 the BBSRC and Engineering and Physical Sciences Research Council (EPSRC) jointly announced that they would provide £13.6million for a new synthetic biology research centre at Bristol University. BrisSynBio will be headed by Dek Woolfson, professor of chemistry and biochemistry at the university. His interests in synthetic biology and vaccines are focussed on the delivery to patients. "We're looking for a vehicle that can be completely synthetic," says Woolfson.

Two years ago, Woolfson and his team created purely synthetic virus-like cages by combining two different types of protein. "You can encourage these proteins to come together and build up a honeycomb protein array, with many millions of peptides and proteins. These are dynamic and fold over, forming self-assembled cages. These are cage-like particles that don't look massively different (from an electron microscopy point of view) to a virus," says Woolfson.

The next step is to take this vehicle and determine its potential. He is hoping to do a proof of principle study to see if they are able to go all the way from the naked cages with nothing in or on them, and then use them as delivery vehicles. "We hope to start peppering the outsides with immunogenic peptides, or even whole immunogenic proteins and see what the response is."

The human population has seen many pandemics over the years, including the corona virus behind Severe Acute Respiratory Syndrome in 2003 and H1N1 influenza in 2009. Viruses like these had scientists, governments and public health officials scrambling to find a vaccine that will halt the virus in its tracks. But the future is looking brighter.

"At some point in the future you will just be able to swab someone's nose, sequence on the spot and post the sequence on the internet. Manufacturers can then download the sequence and make a version of the virus for vaccine manufacture," says Dormitzer. "It never has to adapt to eggs, it never has to be shipped anywhere. We can synthesize right there and then. This whole process could save months." ■

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VIB Group Leader in Autoimmunity

In the framework of a recent partnership with the **Hasselt University (UHasselt)**, VIB is seeking an outstanding early stage independent principal investigator to start a new research group in the field of autoimmunity. The new principal investigator will be appointed as VIB group leader and as associate professor at UHasselt. The PI will receive a 1,6 Million Euro VIB grant covering a first 4 year period that is renewable on a competitive basis.

The new group will be integrated in the Biomedical Research Institute (BIOMED) of UHasselt that has a longstanding reputation in multiple sclerosis and rheumatoid arthritis research. BIOMED offers a highly interactive and well-equipped environment in which basic and translational research is organized in the field of immunology, neuroscience and cardiology. BIOMED heavily invests in academia-clinic and academia-industry interactions for valorization of scientific findings. BIOMED employs approximately 130 people of which more than 80 are Ph.D. students and postdoctoral researchers. More information: **www.biomed.uhasselt.be**. The new group will be part of this community and will have access to all VIB programs and facilities.

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