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"I believe this is the beginning of a new era in cancer treatment. I believe cancer immunotherapy will be the Number One choice in the future."

TASUKU HONJO

PHOTO JENNY ÖHMAN

THE NOBEL PRIZE 2018

01. CHEMISTRY

The Nobel Laureates in Chemistry 2018, *Francis H. Arnold* (1/2), *George Smith* (1/4) and *Sir Gregory Winter* (1/4) employed genetic change and selection – the same principles as evolution – to create molecules for the common good.

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02. MEDICINE

The 2018 Nobel Prize in Physiology or Medicine was awarded to *James P. Allison* and *Tasuku Honjo* for their pioneering work in cancer immunotherapy. Immune checkpoint therapy has fundamentally changed the outcome for certain patient groups with advanced cancer.

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03. PHYSICS

The Nobel Prize in Physics 2018 was awarded to *Arthur Ashkin* (1/2), *Gérard Mourou* (1/4) *and Donna Strickland* (1/4) "for groundbreaking inventions in the field of laser physics," providing us with optical tweezers and corrective eye surgeries.

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IN FOCUS

THE POWER OF EVOLUTION

NOBEL DISCOVERIES

NOBEL LAUREATES IN CHEMISTRY EMPLOYED GENETIC CHANGE AND SELECTION – THE SAME PRINCIPLES AS EVOLUTION – TO CREATE MOLECULES FOR THE COMMON GOOD.

TEXT BY **MALIN OTMANI** CONSULTANT EDITOR **KARYN MCGETTIGAN**

ENZYME EVOLUTION

01. RANDOM MUTATIONS ARE INTRODUCED IN THE GENE FOR THE ENZYME THAT WILL BE CHANGED.

02. THE GENES ARE INSERTED IN BACTERIA, WHICH USE THEM AS TEMPLETES AND PRODUCE RANDOMLY MUTATED ENZYMES.

03. THE CHANGED ENZYMES ARE TESTED. THOSE THAT ARE MOST EFFICIENT AT CATALYSING THE DESIRED CHEMICAL REACTION ARE SELECTED.

04. NEW RANDOM MUTATIONS ARE INTRODUCED IN THE GENES FOR THE SELECTED ENZYMES. THE CYCLE BEGINS AGAIN.

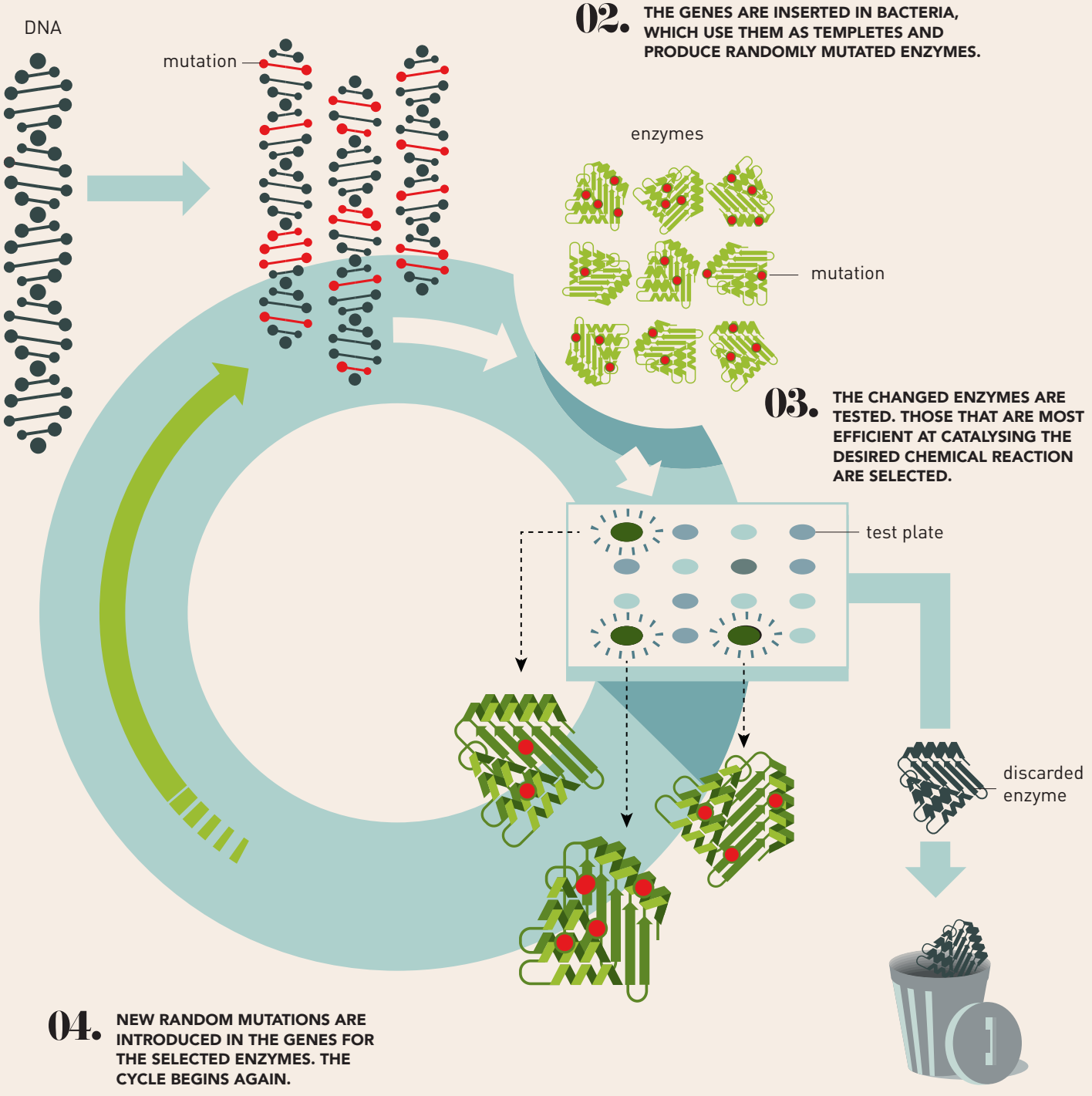
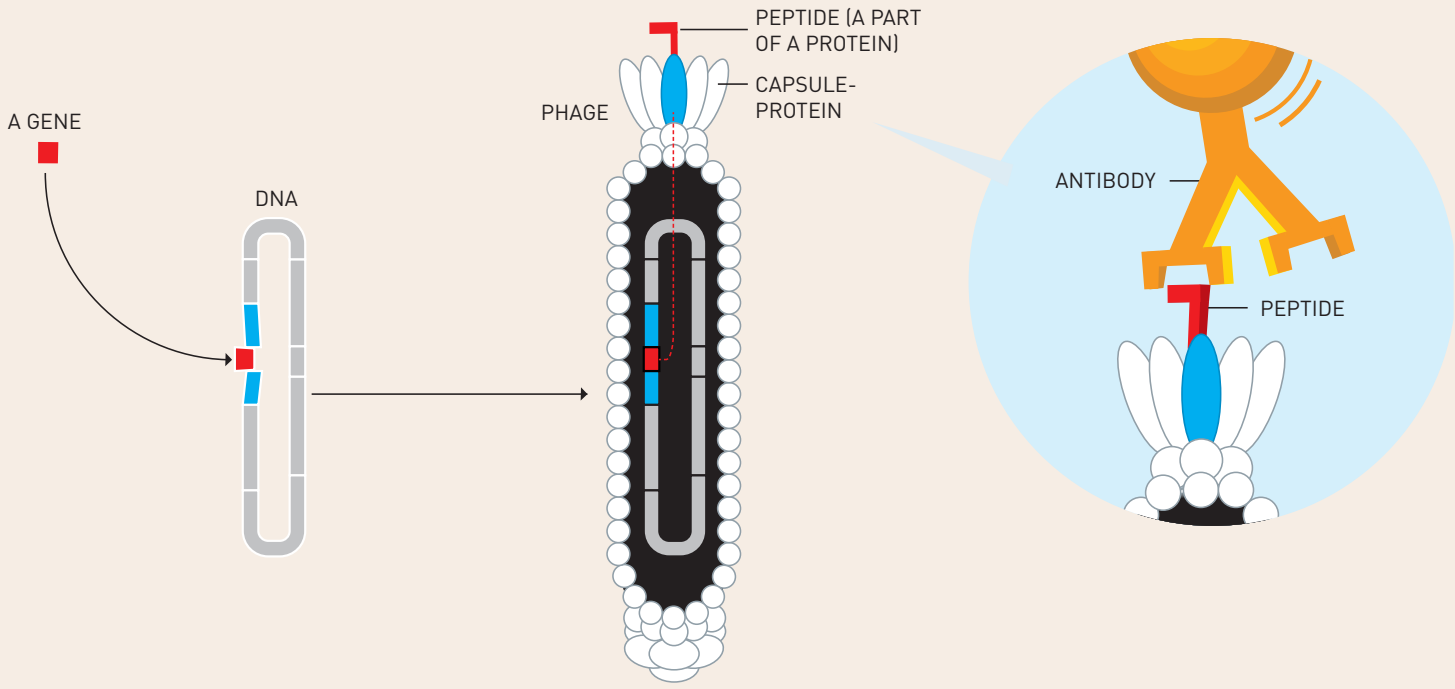


ILLUSTRATION JOHAN JARNESTAD/THE ROYAL SWEDISH ACADEMY OF SCIENCES

PHAGE DISPLAY



01.

Smith introduced a gene into the gene for a protein in the phage's capsule. The phage DNA was then inserted into bacteria that produced phages.

02.

The peptide produced from the introduced gene ended up as part of the capsule protein on the surface of the phage.

03.

Smith was able to fish out the phage using an antibody designed to attach to the peptide. As a bonus, he got the gene for the peptide.

"This Nobel Prize has opened up entirely new ways of producing biological pharmaceuticals. The importance for society and patients can hardly be overestimated; the entire industry of antibody-based pharmaceuticals had a turnover of more than $50-60 billion in 2018."

ILLUSTRATION **JOHAN JARNESTAD/THE ROYAL SWEDISH ACADEMY OF SCIENCES**

PHOTO **APELÖGA**

THE CHEMISTRY LAUREATES' groundbreaking work harnesses the process of evolution for the generation of novel biological compounds. Enzymes produced through directed evolution are used to manufacture everything from biofuels to pharmaceuticals, and antibodies evolved using phage display can combat autoimmune diseases and in some cases cure metastatic cancer.

Directed evolution of enzymes

Half of the Prize was awarded to *Frances H. Arnold*, who is a chemical engineer at the California Institute of Technology in Pasadena. Arnold carried out pioneering work in the 1990s on the directed evolution of enzymes: proteins that catalyze chemical reaction. She developed methods for inducing mutations in enzyme-producing bacteria and then screening and selecting the bacteria to speed up and direct enzyme evolution.

"Nowadays, her methods are routinely used in the chemical industry, for example in the manufacturing of chemical substances, such as pharmaceuticals, and in the manufacturing of renewable fuels for a greener transportation sector," says *Claes Gustafsson*, Professor of Medical Biochemistry at the University of Gothenburg and Chairman of the Nobel Committee for Chemistry 2018. "I am very impressed by Arnold's ability to develop new enzymes that catalyze reactions that are not catalyzed by naturally occurring enzymes, such as carbon-silicon bonds. I many cases, the enzymes that Arnold has developed offer a more effective and environmentally friendly alternative to the current metallic catalyzed reactions."

Copying nature's design process

Following the Nobel announcement, Arnold explained to *Adam Smith* of Nobel Media that what she actually does is "copies nature's design process":

"All this tremendous beauty and complexity of the biological world all comes about through this one simple, beautiful design algorithm, and what I do is use that algorithm to build new biological things. And to me it's not … it's obvious, it's totally obvious that this is the way it should be done."

In her Nobel lecture entitled "Bringing new chemistry to life", she described how her discovery is a versatile tool to make this planet a better place. She further emphasized in her speech at the Nobel Banquet that it is all too easy to apply the evolution incorrectly: both in practice and in theory. Therefore, we must use the term wisely.

Simple evolution in a petri dish

George Smith, currently Professor Emeritus at the University of Missouri, is someone who has used the term well. Smith shares the other half of the Chemistry Prize with *Sir Gregory Winter*. In 1985 Smith developed a method where a bacteriophage – that is to say, a virus that infects bacteria – is used to evolve new proteins. He coined his method phage display, which can be used to quickly select new binding proteins.

Gregory Winter, currently Researcher Emeritus at MRC Laboratory of Molecular Biology in the U.K., used phage display for directed evolution of antibodies. His goal was to produce new pharmaceuticals. *Adalimumab* (Humira) was the first produced with this method. Approved by the FDA in 2002, it has become a blockbuster drug used to treat illnesses such as rheumatoid arthritis and inflammatory bowel disease.


Claes Gustafsson

PHOTO JOHAN WINGBORG

"We are probably only at the beginning of this development because many new therapeutic antibodies, produced through phage display or other techniques, are currently in different stages of clinical trials."

CLAES GUSTAFSSON

Since then, phage display has become a powerful tool in drug discovery; it has been used to produce antibodies that may help to cure metastatic cancer, counteract toxins, and treat autoimmune diseases.

"This Nobel Prize has opened up entirely new ways of producing biological pharmaceuticals. The importance for society and patients can hardly be overestimated; the entire industry of antibody-based pharmaceuticals had a turnover of more than $50–60 billion in 2018," says Professor *Carl Borrebaeck* of the Department of Immunotechnology at Lund University and one of the world's leading researchers in the field of antibody design.

Only in its infancy

The Nobel Prize in Chemistry has also indicated new possibilities within antibody-based immunotherapy, which now has evolved to the field of immuno-oncology where the aim is to kick-start the body's own immune defense to eliminate tumors.

"Although there are pharmaceuticals on the market, this therapy is only in its infancy, which means that over the next few years there will be a revolution on how we look upon cancer therapy," says Borrebaeck.

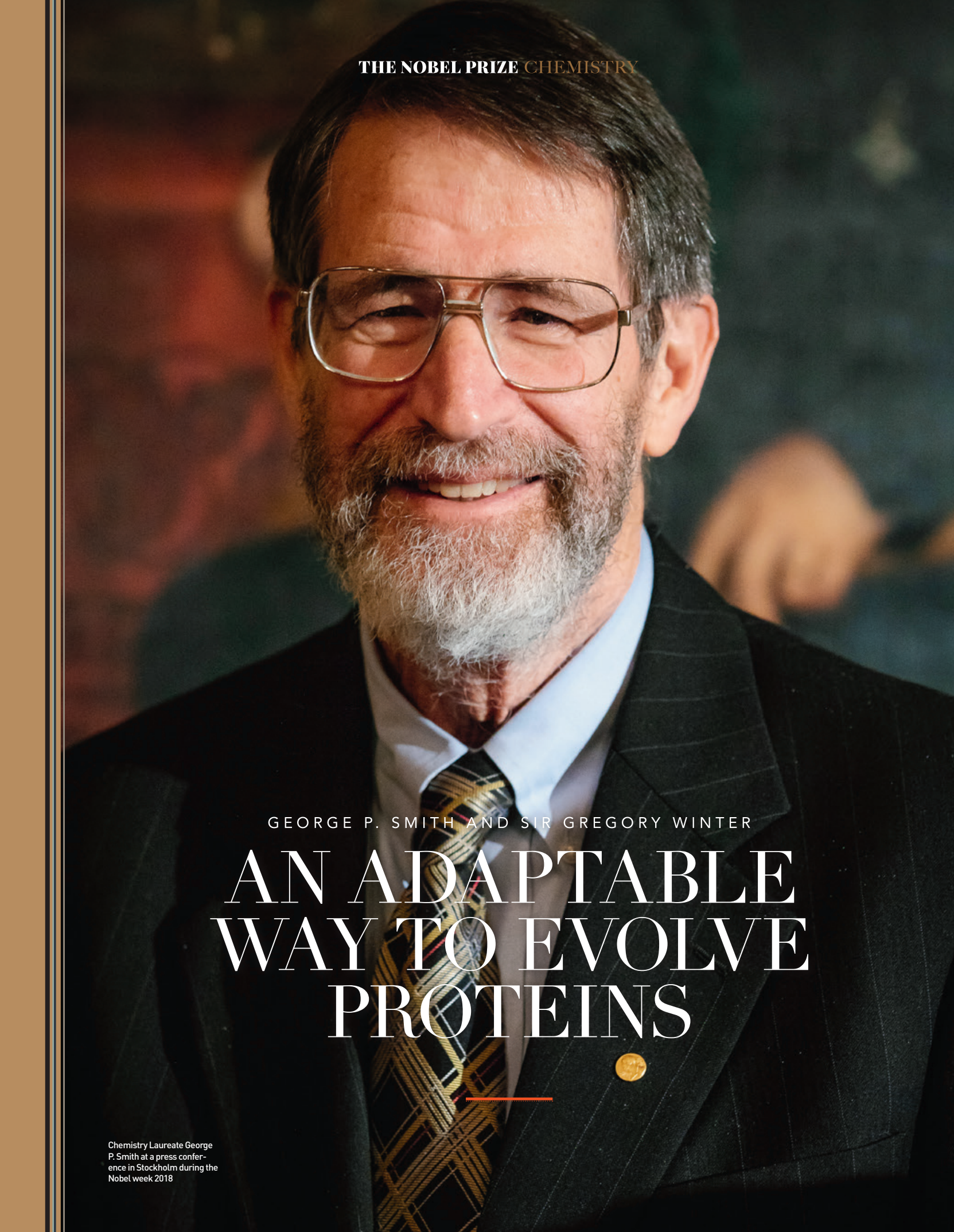
"We are probably only at the beginning of this development because many new therapeutic antibodies, produced through phage display or other techniques, are currently in different stages of clinical trials," adds Gustafsson.

The Laureates have now laid the foundation and have developed techniques that, in one way or the other are used by the majority of biopharma companies that develop biological drugs. *Göran Forsberg*, CEO of the Swedish company Cantargia, which specializes in antibody-based cancer treatments, agrees: "These technologies have been a part of our toolbox and will continue to be important in the future to further develop and broaden our project portfolio. Their contribution today is a pillar for the development of biopharmaceuticals."

Nordic strength

Carl Borrebaeck founded the Swedish company Alligator Biosciences in 2001, which is currently developing antibody-based pharmaceuticals for cancer treatment. The corporation has probably been the most successful in this field in all of Nordic Europe. In 2017, Johnson & Johnson licensed the company's immune-oncology agonistic CD40 antibody for more than $700 million.

The company started a clinical phase I study in December with ATOR-1015: a drug candidate developed for tumor-directed immunotherapy. The phase I study is a first-in-human dose-escalation study of up to 53 patients with advanced solid tumor disease at five different clinics across Sweden and Denmark. The primary aim will be to investigate the safety and tolerability of the drug and to identify the recommended dose for subsequent Phase II studies. NLS



GEORGE P. SMITH AND SIR GREGORY WINTER

AN ADAPTABLE WAY TO EVOLVE PROTEINS

Chemistry Laureate George P. Smith at a press conference in Stockholm during the Nobel week 2018

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Chemistry Laureate Sir Gregory Winter at the 2018 Nobel Prize Award Ceremony in Stockholm

PHAGE DISPLAY IS USED TO DISCOVER ANTIBODY THERAPIES INCLUDING HUMIRA FOR RHEUMATOID ARTHRITIS, PORTRAZZA FOR CANCER, AND BENLYSTA FOR LUPUS.

TEXT *by* **CHRIS TACHIBANA** PHOTO *by* **JENNY ÖHMAN**

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Chemistry Laureate George P. Smith at the 2018 Nobel Prize Award Ceremony in Stockholm

"IDEAS ARE NOT YOUR PROPERTY. THEY INFECT YOU FROM OTHER PEOPLE LIKE VIRUSES. THEY RECOMBINE IN YOUR BODY WITH OTHER IDEAS AND COME OUT AND INFECT OTHER PEOPLE. THAT'S HOW SCIENCE – AND CULTURE – FLOURISH."

THE 2018 CHEMISTRY NOBEL PRIZE honors three scientists for evolving, screening, and optimizing proteins: *George P. Smith*, Curators' Distinguished Professor Emeritus of Biological Sciences, University of Missouri, and *Sir Gregory Winter*, Master of Trinity College, University of Cambridge, UK, were awarded half the prize, with half to *Frances Arnold*, California Institute of Technology.

Phage display

The theme of this year's award is directed evolution, exemplified by the phage-display method that Smith developed and Winter extended. To use the method, researchers put a library of DNA sequences into bacteriophages – viruses that infect bacteria. As the phages replicate, they express the sequences as peptide amino acid chains on their surface. Selecting phages with a trait such as binding to an compound yields the DNA that confers that property. Mutagenesis and more selection optimizes the product.

Academia to pharma

Smith says that not patenting phage display was critical to its spread as a research and development tool. "I could talk about it and give samples to anyone in industry or academia," he says. "I doubt I'd have received a Nobel Prize if I'd been pursuing intellectual property protection instead."

He understands the reasons for patents but warns they can restrict creativity. "Ideas are not your property," he says. "They infect you from other people like viruses. They recombine in your body with other ideas and come out and infect other people. That's how science – and culture – flourish."

Winter moved phage display beyond small peptides. "We wondered about using this powerful technique to look at folded proteins, in particular to screen our repertoire of antibodies," he says, "and it proved to be a great technology."

Phage-display methods are now standard for developing antibody therapy, thanks in part to Winter's work as a founder of Cambridge Antibody Technology, developer of *adalimumab* (Humira).

An education initiative

Both Smith and Winter have moved on from the lab. The day of the Nobel Prize news, Smith visited an undergraduate genetics class, reflecting his work before he retired in 2015.

"The last six years of my time at university," he says, "my major focus was an education initiative." Funded by the US National Science Foundation, the project increased student diversity and use of mathematics in science, which Smith says was an integral part of his own research.

Smith was "a fabulous collaborator and one of most engaged people in the project," says Rainer Glaser, now Chemistry Department chair at Missouri University of Science and Technology. He worked with Smith on the initiative and says, "He was committed to increasing quantitative methods in science and especially to helping underprivileged students join the program." Smith developed a microbial evolution lab class that pushes students to do rigorous experiments and quantitative analysis.

This type of lab is usually for upper-level classes, Glaser says, "But George has high standards and developed it for first-year students."

After "a brief period of having to un-retire" for Nobel Prize activities, Smith will write papers from the education initiative. He'll return to community activities and progressive politics that have always been been a priority for him and his wife Margie Sable.

An advisor

Winter's current scientific work is advising investment and life science companies. He cofounded Bicycle Therapeutics, which chemically crosslinks phage-displayed peptides to increase their stability and binding.

Daniel Barton, Director of Business Development for Bio-sceptre, a cancer therapy company where Winter is on the Scientific Advisory board, says Winter advances both science and business, with "intellectual rigor and commercial experience." Biosceptre's drug target presents a new challenge to the antibody discovery and engineering technology that Winter helped pioneer, and he has great energy and enthusiasm for that type of work, Barton says. "He is a scientist to his core and remains curious and fascinated by the problems of biology."

Winter advises entrepreneurs to think about their commercialization goals and identify if industry partnerships, licensing agreements, or a startup is the best way to achieve them.

"Is the goal to get resources for the lab, validation of techniques developed in the lab, or doing public good?" Earning money is also a motivator, he says, "although I tend to think if you get the other things right, that will take care of itself."

MANAGING DRUG DEVELOPMENT requires different skills than leading a research group, Winter says, so get help from experienced advisors. That said, reflecting on his first startup, he recalls that funds were scarce because using antibody repertoires and phage display to make human antibodies "seemed pretty harebrained." He adds, "Sometimes you have to just learn drug development on the job and get on with it yourself. In startups, you have to do a lot of that." NLS