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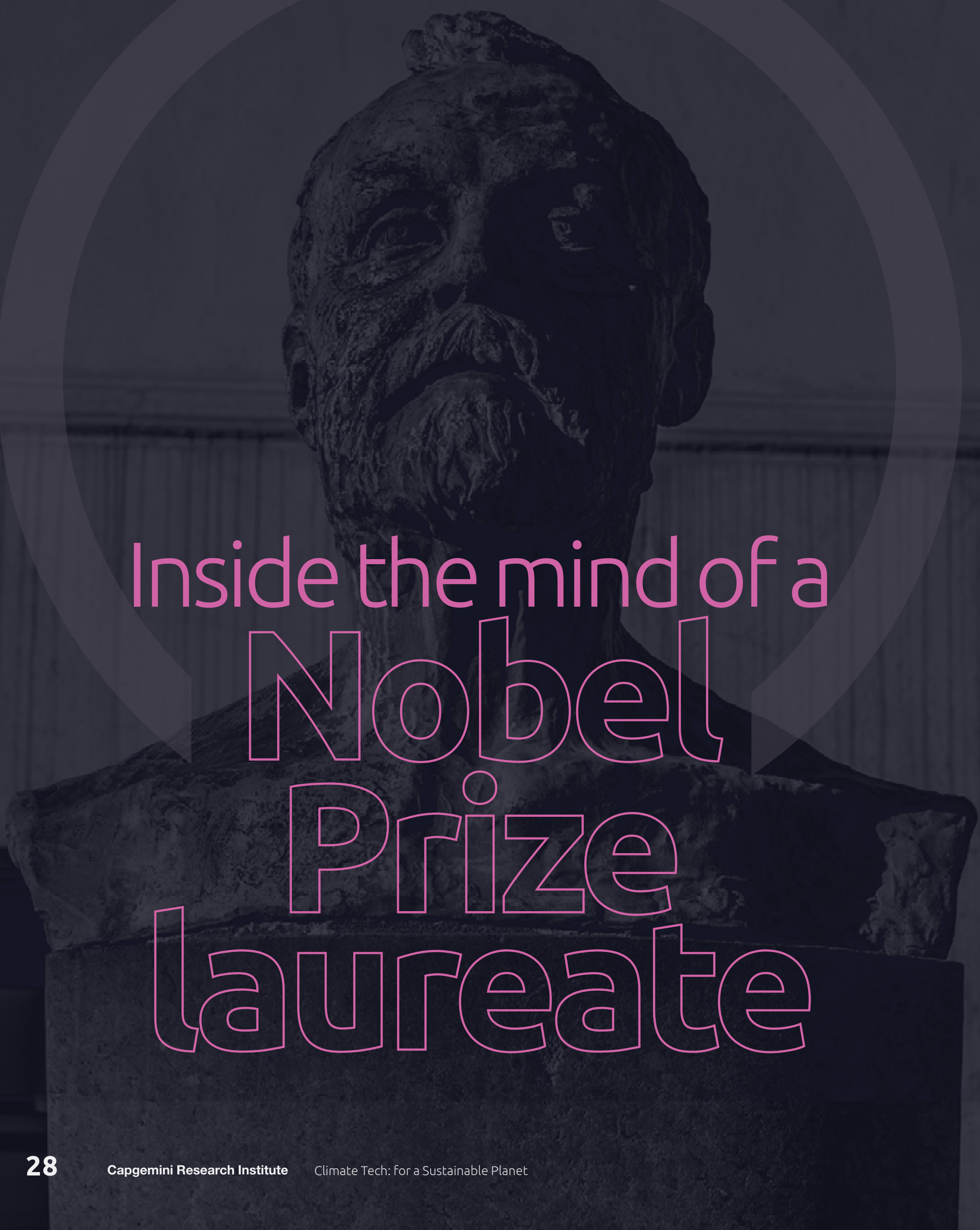
Conversations FOR TOMORROW



Inside the mind of a Nobel Prize laureate

DR. FRANCES ARNOLD

Nobel Prize winner in
Chemistry in 2018 for
Directed Evolution
California Institute of Technology

GIVING EVOLUTION A SHOT IN THE ARM

Dr. Frances Arnold

Dr. Frances Arnold is the Linus Pauling Professor of Chemical Engineering, Bioengineering and Biochemistry at the California Institute of Technology (Caltech). Dr. Arnold received the Nobel Prize in Chemistry (2018) for pioneering directed enzyme evolution and has subsequently created enzymes for use in alternative energy, chemicals, and medicine. She is co-chair of the President's Council of Advisors on Science and Technology (PCAST). She has been elected to all three US National Academies of Science, Medicine, and Engineering, and is also a director on the boards of prominent companies such as Alphabet and Illumina. The Capgemini Research Institute spoke to Dr. Arnold to understand how directed evolution, coupled with the resilience found in nature, can help create a sustainable world.

What got you interested in science?

I had all sorts of jobs when I was young, from taxi-driving to cocktail waitressing; but these were to pay the rent. Math and science were what made sense to me from an early age. I idolized my father, a nuclear physicist. I obtained a BSc in Mechanical and Aerospace Engineering and worked for a while in the nuclear industry and in solar energy, but my real love turned out to be something I did not even know could be possible until I went to graduate school at age 25: engineering the biological world.

WHAT IS DIRECTED EVOLUTION?

You won a Nobel Prize for your pioneering work on the directed evolution of enzymes. Can you help us understand what that is and how it can help society?

Enzymes are the catalysts responsible for all the wonderful chemistry of the biological world. We would like to use them in human applications, but they are not ideal for this. So, in the 1980s, I started to engineer amino-acid sequences for enzymes that would perform in human applications. Back then, no one knew which sequence would be required to encode a desired function – enzymes are complicated. However, evolution can show us how to encode enzymes more effectively. The simple process of mutation and natural selection that has given rise to the rich diversity of the biological world can be harnessed by chemists. Using newly developed tools in the fields of molecular biology and high-throughput screening, I developed ways to practice “evolution by artificial selection” for enzymes.

"I developed ways to practice 'evolution by artificial selection' for enzymes."

In other words, this is a simple optimization strategy for making random mutations at a low level and screening to find the mutations that can be most beneficial to us. Through various iterations, we find the best-performing steps. Nature is solving all sorts of problems that we throw at her – how to degrade plastic bottles, how to degrade pesticides, herbicides, and antibiotics. She creates new enzymes in response to these problems all the time, in real time. With directed evolution, we can do the same – create new enzymes in response to new problems.

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ENZYMES FOR A GREENER PLANET

Much of your research focuses on sustainability. What about this area of study excites you most?

What excites me most right now is expanding the chemistry of the biological world to compete with human chemists. Making and breaking bonds. All my projects are about sustainability or bioremediation – making things in a cleaner fashion or breaking them down again. I love working with enzymes. Nature has developed a vast array of enzymes that do incredible chemistry, but there's a lot that hasn't been explored yet.

We could have better processes by getting enzymes to do chemistry that would, for instance, dramatically reduce the cost of manufacturing pharmaceuticals by replacing 10 chemical steps with one or two enzymes. One particular example I am proud of is how Merck [a multinational science and technology company] developed an enzyme using directed evolution to make the drug Januvia, which is used to treat diabetes. The initial, unrefined process used toxic metals, with a lot of waste products. Merck has managed to reduce the waste to around one-hundredth of initial levels and remove toxic-metal catalysts from their process, just using enzymes to synthesize the pharmaceuticals.

I am also excited about reducing the cost and time necessary to develop these enzymes and the processes they are used in. I am working to incorporate machine learning [ML] and artificial intelligence [AI] into this evolutionary optimization. It promises to allow us to develop biological solutions much faster than in the past.

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How can bioengineering help the planet?

Everything that nature does is efficient. It's this highly evolved system that makes and breaks chemical bonds, creating chemicals and materials of magnificent functionality – but that won't persist forever. I think that biological chemistry, with its very high selectivity and power efficiency, can broaden our thinking around fabrication and recycling. Not only can we help break down everything we use in our daily lives into recyclable elements, we can also help create new products entirely, things which are not possible using traditional chemistry. Biological chemistry can have a beneficial effect on any application of conventional chemistry, and we should use it to find efficiencies. Life today is the product of 4 billion years of evolution, not of engineers in a laboratory. Nature has a lot to teach us.

You have co-founded three companies in the sustainable chemistry and renewable energy fields. Can you briefly describe them?

We founded Gevo [Green Evolution] in 2004 to make fuels from renewable resources. The concept was to engineer enzymes in yeast to make isobutanol, a precursor to jet fuel, instead of ethanol. Today, Gevo is one of the leaders in the development of renewable aviation fuel.

"Everything that nature does is efficient."

The second company, Provivi, was founded in 2014 to replace toxic pesticides. We developed processes to make non-toxic pheromones, chemicals that serve as signaling mechanisms, which, when sprayed in the field, confuse the mating instinct of insects. Our focus is to create a new foundation for safer, affordable, and sustainable crop protection.

The third company, Aralez Bio, was formed more recently, in 2019. It uses enzymes to make pharmaceutical intermediates.[1] They can make hundreds of new amino acids and other chemical building blocks, while cutting waste, energy consumption, and costs.

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1 Chemical compounds widely used in bulk pharmaceutical manufacturing and also in research.

USING AI TO CREATE NEW PROTEINS

How is new technology helping your research in bringing enzymes faster to market?

Evolution is a process. It's turning the crank of mutation and artificial selection. We can harness the power of evolution by automating and empowering it, using AI and ML. I have been publishing on this for 10 years. But even more exciting is that some of these generative AI capabilities are being used to invent proteins from scratch. Enzymes are more complicated, but I predict it will be possible to invent them, too, in the future. This is the convergence of experimental capabilities, understanding the features that really make up a successful protein and then harnessing the new methodologies made available through generative AI. I predict that, in the next few years, AI is going to be a powerful force – one capable of recoding life.

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How can generative AI help in creating new proteins?

I am on the board of Generate Biomedicines, a biotech startup which uses AI to generate therapeutic proteins that could be used to cure diseases. Machine learning algorithms can generate novel sequences for proteins that have never been seen in nature. These algorithms analyze hundreds of millions of known proteins, looking for statistical patterns linking amino acid sequence, structure, and function. Using these learned statistical patterns, the company generates custom protein therapeutics – from short peptides to complex antibodies, enzymes, gene therapies, and yet-to-be-described protein compositions.

MY ADVICE TO YOUNG WOMEN: BE FEARLESS

What is your advice to young women who want to enter the field of science?

Try different things. I tried many fields of science before I found what I love to do. If you're going to change the world, you've got to be fearless. Don't feel that you have to stick with something just because you said you were going to do it. If you don't like it, do something else.

THE IMPORTANCE OF THE INTERFACE BETWEEN SCIENCE AND PEOPLE

To what degree is finding the path to a sustainable world dependent on innovation from science/new technologies as opposed to behavioral changes?

It has to be both. What we have learned during the pandemic is, you can have all the science and technology you want, but if people won't be vaccinated, it doesn't do any good at all. We can offer scientific solutions, good or bad, but if people don't want them and don't accept the necessary behavioral changes, it's not going to happen. So, this interface between science and people is vitally important.

If you had a magic wand, in our transition to a sustainable world, what would you change right now?

I would love to see respect for biodiversity. I would love to see respect for the natural world that we rely on, but that we treat so badly. I would love to see the natural world being accounted for as an invaluable asset on which our very existence depends.

I WOULD LOVE TO SEE RESPECT FOR BIODIVERSITY

Dr. Frances Arnold,
Linus Pauling Professor of Chemical Engineering, Bioengineering and Biochemistry
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"We can offer scientific solutions, good or bad, but if people don't want them and don't accept the necessary behavioral changes, it's not going to happen."

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