Interview with the winner of the 2016 Millennium Technology Prize

Frances Arnold promotes the green revolution and wants to offer a strong role model for women in engineering.

On Tuesday, 24 May 2016, Technology Academy Finland (TAF) awarded the one-million-euro Millennium Technology Prize to American biochemist Frances Arnold. Arnold's pioneering innovation, directed evolution, mimics natural selection in the laboratory, enabling the production of new types of proteins that offer benefits for many sectors of the industry – and is often less expensive, more efficient and greener that earlier methods.

Towards the green revolution

1) Now each day your methods are used by hundreds of labs around the world to make life-saving drugs and everyday products. Which are you most proud of and which do you think have had the biggest impacts?

Enzymes optimized by directed evolution are being used to make nutritional products for humans and animals, fuel from biomass, and to test new drugs for toxicity. They are being used directly to treat human disease. Engineered enzymes are used in everything from DNA sequencing to glucose sensors for diabetes, laundry detergents, and food processing.

The wonderful thing about directed evolution is that it is both simple and general. Because the technology is accessible, it can be implemented in any laboratory. Many clever people all over the world have taken this technology and done all manner of brilliant things with it, things I would never have thought of.

I am working now on an interesting problem where we are trying to replace toxic pesticides with non-toxic insect pheromones. Pesticides get into our food, streams and rivers and cause all manner of harm. Imagine spraying a little bit of perfume in a field to confuse the insect pests so that they can't mate. If they can't mate they are not going to damage your crops. Wouldn't it be wonderful to do that instead of dumping highly toxic pesticides? Our hope is to make these complicated insect perfumes quite cheaply using enzymes.

2) What are your predictions for how these applications will create the kind of products, results and benefits we will see over the next few years?

I think in the next few years we will see many fine chemical products being made using biocatalysts, either enzymes or microbes that have enzymes in them. In the next few years we will see new drugs, agricultural chemicals, and many products that we use in our daily lives

being made cleanly and efficiently using biology. Directed evolution can improve the performance of the biological process and allow it to deliver products at competitive prices.

And I think we will have products that we can't even imagine now. My lab recently showed that we can make enzymes catalyse reactions never before known in nature, reactions that can make bonds, for example between carbon and silicon, that nature has never made. This opens up possibilities for expanding biosynthesis into whole new classes of materials that we could not previously imagine making. Inventive people will see possibilities for using biology to make whole new classes molecules, materials, products and processes.

3) So we could be on the brink of seeing a real green revolution in terms of products we only thought could be manufactured using fossil fuels, chemicals and lots of materials, being replaced for good?

The green revolution in chemistry is already happening—many researchers and companies are working hard on replacing fossil fuel feedstocks with renewable resources for producing fuels and chemicals we need. What has slowed down the green revolution is not technology development, it's been the low price of oil and our unwillingness to come to terms with the costs of doing business as usual. Plummeting oil prices remove much of the short-term economic driving force for implementing alternative technologies and also for funding further research and development. More far-sighted people and industries keep developing the technology, however, and will reap large benefits when the price of oil shoots back up. Oil is more plentiful than we thought a few years ago, but that is no excuse for the way we waste it. Good renewable and sustainable technologies will help extend this remarkable resource for future generations.

Innovation's technology is revolutionary

4) You've said "Directed evolution allows me to re-write the code of life" which is a big claim with implications on a grand scale. Could you expand on that idea for us a little and tell us about some of the developments that have been happening in that field recently?

Yes, we can rewrite the code of life, and in fact humans have been doing that long before I started. Everything from corn to carrier pigeons, lab rats, racehorses, we've been modifying the biological world through artificial selection, breeding poodles, hairless cats, and myriad other biological things that you would probably not find in the natural world if humans weren't there to select them. In the past, however, we've not had much control over that process. We could choose who would go on to parent the next generation based on the traits we desired.

Directed evolution is a new version of breeding that takes advantage of the huge advances that have been made in molecular biology in the last 30-40 years. These advances allow us to 'evolve' or breed not a whole organism but the gene that encodes a particular function, a

particular protein, to have features we want. We can make many copies of a specific gene with random mutations in it, use recombinant DNA technology to make the protein products of those mutated genes, and then we can rapidly search through them and choose which one or ones become the parent to the next generation. I don't have the same constraints that the farmer or the dog breeder had in the past—I can choose genes from 3 or 33 parents, recombine genes from different species, and I can control the rate and nature of the mutations. And I can select from their protein products those with features I like—say an enzyme that catalyzes a new reaction to make a useful chemical or one that could be used to cure a disease or one that does a better job at taking stains off clothes. I can use these methods of 'directed evolution' to create versions of proteins with properties that are pleasing to humans. This way we can circumvent our near-complete ignorance of how DNA sequence encodes a specific function—which we don't understand at the level of detail needed to make something useful.

The field is expanding rapidly as we explore and demonstrate new opportunities for using biology, for example bacteria, to cure disease, monitor and degrade pollutants, or replace toxic pesticides. People are finding new applications for proteins and enzymes as we learn how to use evolution to create new ones.

5) Is directed evolution same thing as gene manipulation?

It's not the same thing as gene manipulation as most people understand it (e.g. modifying crop herbicide resistance by inserting a new gene into the plant), although some might find the difference rather subtle. Directed evolution is instead a way to make a new and better protein, encoded by a new and better gene. The improved protein could be expressed from the new gene in an engineered food, and some companies are probably using directed evolution for that.

My work has focused on directed evolution of single genes to obtain the protein products of those genes, where the protein is what people use. The final products used by people no longer contain any DNA. I am interested in ways to make the proteins – usually enzymes – which are used for myriad purposes (laundry detergents and other consumer products, sensors in diagnostics, catalysts for making drugs, etc.).

6) Was there one "Eureka!" moment that led you to directed evolution, or was it a gradual process of discovery for you?

My breakthrough moment came in the early 1990s when I decided to try thousands of experiments at once, because our single experiments never succeeded. With my small team I made thousands of mutations, all over the protein, and looked to see which ones made it better. We accumulated improvements over several generations to get to the desired function. I then saw you could indeed change a protein and make it better for things we want it to do.

The real breakthrough for me was recognizing that the changes that made an enzyme better were impossible to predict. By sequencing the DNA that encoded my newly improved protein, I could see where the beneficial mutations appeared. They were often far from the active site of

the enzyme, and far from where any so-called 'rational' designer would have chosen to make changes. At that point I realized that not even the smartest person on the planet could explain the results of my mutations, much less predict them. I became extremely respectful of the evolutionary process, the blind algorithm of mutation and selection that has given rise to the most functional and beautiful engineered objects in the world. I knew I could use evolution to make new ones that no one else could make.

My technology colleagues, especially those in industry, were thrilled. For the first time they could see a general and reliable way to make better enzymes and match enzymes to their processes rather than vice versa. Directed evolution was rapidly adopted and further developed in industrial laboratories, with many successes.

Role model for women in technology

7) This is the first time TAF has awarded the Millennium Technology Prize to a woman (and in fact in 2011 you were the first woman ever to be awarded the Charles Stark Draper Prize for engineering, also the first woman to be elected to all three of the US National Academies – science, engineering, medicine), so what do you think about the opportunities for women in science and technology today, compared to when you were starting out?

I think my timing was very, very lucky and I'm very grateful for the pioneering work done by the few, strong women who entered these fields before I did. They had a rough time – getting jobs, being taken seriously by their colleagues, getting attention in a positive way. My timing was good, however, because when I received my degrees, engineering departments were just realizing that leaving half the population out of science and technology was a huge waste of brainpower. They wanted mentors, teachers, professors, researchers who could inspire young women to choose science and engineering careers. There I was with a PhD in chemical engineering, many job openings, and very few women who could fill them. Today there are many more women in science and engineering, but still not enough. I think the opportunities remain good!

8) Are there still barriers facing women in science and technology? Do we still have a long way to go yet before we reach ideal "gender parity" in these fields?

I believe that some women still face external barriers, but other barriers are more self-imposed: lack of confidence or desire to compete, misunderstanding of what science and technology can contribute to society. Science is not for everyone; it takes a lot of time and devotion to become really good, the same is true for engineering. You have to love it. What I see is that the most talented women have many opportunities. Whether they choose to pursue science or

engineering depends on how they feel about their whole life experience, perhaps more so than men. Opportunities today are excellent, but there are challenges to having a family and competing at the highest levels that women often feel more acutely.

9) Your winning awards like this helps cement your position as a role model for young women entering these disciplines. Do you see it as one of the benefits of winning prizes like this?

I certainly hope that young women can see themselves in my position someday. Serving on various prize selection committees myself, I know it's not all about the person who receives the prize. While it's very nice to get a prize, the benefits should go well beyond the person. We give each other prizes to highlight specific problems, to draw attention to particular fields, and to inspire others to use their talents in a positive way. I hope that my getting this prize will highlight the fact that yes, women can do this, they can do it well, and that they can make a contribution to the world and be recognized for it. I hope that women will see that one can have a rewarding career in science and technology.