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Special report
Groundbreaking discoveries of the past and the future

Eccentric, intellectual maverick, surfer – **Kary Mullis** has been given lots of names. The man who has been described in the press as possessing a "creative nonconformity that verges on the lunatic" may not be your typical scientist; he sure is a Nobel Prize winner. Let us therefore concentrate on his winning invention of the polymerase chain reaction and his current efforts: developing a chemical tool that could be used like an antibiotic for the flu.

By Julia Puppe

It is true, on the day Kary Mullis won the 1993 Nobel Prize for Chemistry, he went surfing. This has nothing to do with his groundbreaking discovery of the polymerase chain reaction (PCR). However, it has earned Mullis the reputation of not being your typical scientist, which, Mullis admits, is probably true – not because he likes surfing, but in comparison to the typical scientist of the 21st century. "They are generally extremely specialized, and they are much more businesslike than I am. If you, on the other hand, take the typical scientist of the 17th century, I fit the bill perfectly", Mullis laughs, and adds: "That's where the real rules of scientific discipline were established, people like Isaac Newton and the Royal Society."
Mullis sees science in a way people in the 17th or 18th century saw it, which, he explains, is not broken up into hundreds of little subspecialties. "I see things like physics, magnetism, gravity, chemistry, and also history as all being linked." This could be called a holistic approach to science, but Mullis shakes his head. "That sounds hokey. And Newton would have said no, that's just what science is."

How can you disagree with someone whose invention was awarded with the Nobel Prize? Yet, Mullis remarks, getting behind the concept of PCR was surprisingly simple once he had got over "that one little hump in there." It was the vision of an organic chemist rather than that of a molecular biologist that helped him. "When I thought of DNA, I thought of it in the most detailed way that I reasonably could. In my mind, I drew it as though it were an organic chemical. I noticed that when the molecular biologists made diagrams of DNA molecules, they always drew them as straight lines. But they really are little twisted structures that would better be drawn as two parallel lines, bearing in mind that they are actually antiparallel with

complementary sequences. If you can see it that way then PCR is almost tautological."

The invention of PCR replaced the tedious manual preparation of standard DNA samples in many laboratories all over the world – a "repetitive" and plain "boring" process, according to Mullis. "Beginning with a single molecule of DNA, the PCR can generate 100 billion similar molecules in an afternoon. The reaction requires no more than a test tube, a few simple reagents and a source of heat. The DNA may come from a hospital tissue specimen, from a single human hair, from a drop of dried blood at the scene of a crime, from the tissues of a mummified brain or from a 40,000-year-old wooly mammoth frozen in a glacier," says Mullis. Still it took some time for people to see just how important PCR would turn out to be.

In fact, Mullis' invention met a lot of resistance at first – not surprisingly, he believes. "If you were a trained molecular biologist and someone from the chemistry department came over and said: 'What you do in six months we can do in 12 hours', wouldn't you laugh at that? Most of the molecular biologists didn't particularly care for chemistry. So they resisted it for a little while." Mullis didn't think of it as a problem because he knew that the skeptics would slowly come across. And they did. "Some of the people who have published books on PCR methodology were the very same people who walked out of my first lecture about it," says Mullis, not even trying to suppress a smile.

Learning a new language

Mullis likes a challenge. The harder it is for him to understand a phenomenon immediately, the more interesting it is. "You look at something and ask yourself: 'Why is this that way?' In order to figure that out you need to read everything other scientists have said about it. This requires you to learn a whole new language." Over the last 10 years, Mullis got interested in immunology and learned the language immunologists speak. "I had an idea about how to tackle infectious diseases. When a new pathogen enters your body, the reaction is a new immune response. However, it can take a month before your immune system is really up and running. During that process a fast pathogen can wipe you out. So I thought: 'Why not use an old immune response, just refit it?'. But in order to even start to do something about it, I had to learn the language of immunology."

Mullis' language skills developed and so did his idea. This led to the formation of his latest venture, Altermune LLC, and his most recent patent application, which covers an approach for instantly mobilizing the immune system to neutralize invading pathogens and toxins. "We are altering the target of an immune response by using specific synthetic chemical linkers that divert an immune response from its nominal target to something completely different, which you would right now like to be temporarily immune to," explains Mullis and gives an example: "Let's say you just got exposed to a new strain of the flu. You're already immune to alpha-1,3-galactosyl-galactose bonds. All humans are. Why not divert a fraction of those antibodies to the influenza strain you just picked up? A chemical linker synthesized with an alpha-1,3-gal-gal bond on one end and a DNA aptamer devised to bind specifically to the strain of influenza you have on the other end, will link anti-alpha-Gal antibodies to the influenza virus and presto, you have fooled your immune system into attacking the new virus."

Sounds simple enough, but developing this chemical linker is not. “Doing this is a lot harder than I envisioned it when I first thought about it. There are a lot of people involved unlike PCR, where I could do it myself,” sighs Mullis. With his team of organic chemists, influenza and poultry specialists and immunologists, he is currently testing the Altermune method in chickens against a strain of flu called H3M2. Most humans are already immune to this typical laboratory strain, but Mullis’ vision includes H5M1, which is likely to prove disastrous. ”The flu has been living with humans for a long time. And it looks like about every once or twice every century, there is an epidemic. If there is going to be a worldwide epidemic of H5M1, it’s just a matter of time – and this time is likely to be worse than last time,” is Mullis’ grim prediction.

A chemical tool

Unfortunately, the bad news does not end there; there is also staphylococcus aureus to be worried about. “We have been killing it with antibiotics since the early 20th century but strains of it have become resistant. More and more organisms will become resistant to antibiotics, so we need new ones. In a way, our Altermune linkers are an antibiotic, they act like one,” says Mullis and points out that humans would not develop a new immunity. “You would use an old one. That’s really important from the point of view of immunology. Every time you make a brand new immune response, there is some little minor damage done to your body. You are going to kill cells even though they are completely innocent. If you use an immune response that you already have, this makes sense to me.” However, it would take the body some time to bridge an acquired immunity with a new pathogen, during which time the body might start an immunity response. “You may end being immune to the pathogen as a mop up process, so that next time the disease comes along, you will already have the memory cells of an immune response,” hopes Mullis.

Unlike Penicillin, the Altermune antibiotic is human generated, it is a chemical tool. Developing resistance against it will be harder for strains of bacteria than it has been in the case of Penicillin, named after the mould Penicillium notatum, which was found in fungi. Resistant strains of bacteria already existed when Penicillin was discovered by Alexander Fleming in 1929 because fungi have long made use of the antibacterial effect. “Nothing in nature is similar to the Altermune linkers. It will be hard for bacteria and the flu to deal with them. It really has great potential but it’s going slow. We are not part of a huge drug company,” says Mullis and admits that although he does not like the word he is, in fact, a bit of a maverick: “I like to have my fingers in all the little pieces I am working on. I know I need help from all kinds of specialties but I don’t want to go to meetings every week for three hours and talk it all over. If you are really good at doing something, large organizations just keep promoting you up to where you have nothing more to do with your original project. I’m trying to keep Altermune a small operation although we are now realizing that more people need to be involved.”

Of mice and chickens

Mullis is now actively seeking more professionals to take on the Altermune project. “As I learn more, I see that there are better ways to do it. You don’t have to go to some big cumbersome machine, because they’ll say: ‘Write it all up, we’ll meet and talk about it in a month or two’. That is very frustrating for me. I like to be able to

decide on my own schedule and take advice from everybody who works for me. But as of right now, that's just been changed," Mullis says with a wink.

Mullis is anticipating the first *in vivo* experiments to yield results this summer. This will tell him how sensitive H3M2 is in chickens. Then the Altermune linkers will be tested in mice against a different strain of influenza. "The chemically defined molecules we are making are the same. But there is a big difference between chickens and mice. The strain of influenza that works well in mice and attacks people doesn't attack chickens." Another problem is that the mice Mullis needs for his experiment will have to be bred first, which will take up to three months. "That's how biology is," says Mullis and shrugs his shoulder. "It's a complicated process. Hopefully, by summer, we will have an Altermune linker prepared that would not only be effective against the laboratory stream but against H5M1. Chickens have the same immunity against the alpha-Gal epitope as humans do, so if we develop something that works in chickens, like H5M1, it will probably work in humans."

If there is an emergency, Mullis thinks it is possible that the FDA might use his invention without it being tested in humans. "If there are people dying they will have to give it a shot. But I don't know what would actually happen. Whether or not it will ever be used in my life I don't know. But you have to start somewhere and the flu is not going to go away." Luckily, Mullis says, major scientific advances in the field of immunology are being made because of more biological fields becoming more and more chemically sophisticated. "Biology has been chemicalized. Biologists who don't understand chemistry are becoming fewer and fewer as they age and the younger population of biologist who know their chemistry are starting to become old enough to become professors. It's an exciting time for the biological scientist and for medicine."

BOXOUT 1

"Every November when I was young, my mother would give my brothers and me a pile of catalogues and let us pick what we wanted for Christmas. It was in one of those catalogues that I found a Gilbert Chemistry Set. Something about tubes filled with things with exotic names intrigued me. My objective with that set was to figure out what things I might put together to cause an explosion."
From: "Dancing Naked in the Mind Field", 1998

BOXOUT 2

"I discovered that whatever chemicals might be missing from the set could be bought at the local drugstore. In the 1950s in Columbia, South Carolina, it was considered okay for kids to play with weird things. We could go down to the hardware store and buy 100 feet of dynamite fuse, and the clerk would just smile and say, 'What are you kids going to do? Blow up the bank?'"
From: "Dancing Naked in the Mind Field", 1998

BOXOUT 3

“We were fortunate to have the Russians as our childhood enemies. We practiced hiding under our desks in case they had the temerity to drop a nuclear weapon on Columbia, South Carolina, during school hours. In 1957 the Russians launched the space race by putting Sputnik I into orbit around Earth. It was only twenty-three inches in diameter, but it revolutionized the American educational system. The government poured millions of dollars into science education. It was a fortuitous time to be young and in love with science.”
From: “Dancing Naked in the Mind Field”, 1998

PULL QUOTE
Kary Mullis: “Some of the people who have published books on PCR methodology were the very same people who walked out of my first lecture about it.”