AN INTERVIEW WITH...

Mario Capecchi

The prestigious March of Dimes Research Prize in Developmental Biology was awarded last month to Professor Mario Capecchi and Professor Oliver Smithies for independently developing gene targeting. Last month, we published an interview with and an essay by Oliver Smithies. This month, we celebrate the other winner — Mario Capecchi. In his essay, Mario describes his vision to harness the potential of homologous recombination in order to alter endogenous DNA sequence and how this now ubiquitous technology has a key role in functional genomic analysis.
Below is an excerpt from a conversation that Magdalena Skipper had with Professor Capecchi, in which she asked him about his scientific past and future, and what it was like to meet Elvis Presley.

Originally you trained in chemistry and physics. Why the transition to biology, especially at a time when many exciting discoveries were made in physics?
I enjoyed physics a lot. The one thing I wasn't looking forward to was that, at the time, a lot of people who worked in physics were involved in very large projects, involving accelerators and so on. [This work] required large teams and I was looking forward to doing something more individualistic…. The other factor was that I went to a college where you worked and studied. One of my jobs was at MIT, and there I got involved in molecular biology. There were actually quite a few people in physics who transferred to molecular biology — Cyrus Leventhal and Alex Rich… (I was working in Alex Rich's lab) — and I think that showed me that there were new things that people were now doing that involved more individual participation and contributions.

But biology is now driven by large projects, which then you tried to avoid….
Now biology is getting very large, that is true. What I like to do is try to work in areas that other people aren't working [in]. So I still have that same attitude. The other thing we have been doing, fairly purposefully, is that every 7–10 years we have gone into a new area. It stimulates you to think about new things….

What are your future goals?
Here is one thing we are thinking about now. Evolution has been doing experiments for millions of years … Can we now take advantage of our differences and are they going to be as informative as that which makes us similar? We have chosen to compare mice and bats. The question is, could we actually use the mouse as a surrogate for looking at bat functions on a genome-wide basis? We would then be able to study all the aspects that make bats different from mice, but in a system that is compatible with molecular biology and molecular genetics. For example, a mouse lives [for] 2 years and a bat lives [for] 30. Why is that? And what are the genes involved in this process? Obviously, bats can fly and mice can't and that's a very complex difference — not only do you have to have the structures that enable flight, but also the neural circuitry to be able to do that. Echolocation. Bats are much better at regeneration than mice….

Is there anything or anyone that has particularly inspired you in your career?
Jim Watson has certainly been the most influential person in my scientific carrier. One, he gave us an enormous amount of freedom and encouragement. For example, he was one of the few people that ran a lab in which he wasn't the major author of each paper — if you did the work, then he gave you the credit and you published it, obviously he critiqued it thoroughly.

He was also extremely enthusiastic, as well as optimistic, [about] what could be accomplished. At that time, at the beginning of molecular biology, the feeling was that you could approach any problem, no matter how complex; it was naive because we just didn't know how complicated things really were. On the other hand, we still had the feeling that if we simply applied molecular biology we could get an answer to any question that would pop into our minds. In a sense that's still true. The only thing I worry about is not what the scientist is doing but whether society is willing to continually support their efforts and be realistic as to what accomplishments they can expect in the short term. Now people are worried that scientists create problems, and I think we do create problems, but I also think we are the only ones that are going to create solutions to those problems. In the long term, the accomplishments are going to be astronomical, even unfathomable at this point, but we have to be in it for the long haul. It's not going to be tomorrow, it's going to happen in 20-year periods.

Is there, in your opinion, a new technology, yet to be developed, that would revolutionize biology the way gene targeting did?
I think what we will see enormous changes in is our imaging methodology. If we could enhance imaging of whole animals to cellular resolution, but then use essentially molecular probes to be able to visualize these process. The other [problem] is the speed of imaging — talking and thinking happen in almost milliseconds, whereas when you are using MRI you [take] minutes to capture images, so we are at vastly different time scales. The capture technology is going to have to improve enormously. We are not making enormous headway in determining how we think, how information is stored, how we retrieve it, how we put images and patterns together. We have no idea, simply because we do not have the technology to address these questions.

Among your many awards is one rather unusual one — America's Ten Outstanding Young Men Award, which you shared in 1971 with nine others, among them Elvis Presley.…
It was very amusing, and the collection of people was quite startling: there was Nixon's press secretary Ron Ziegler, for example…. Most of the people had made enormous amounts of money at an early stage in their life. There were only two scientists, the other one was George Todaro — he's accredited with first thinking about oncogenes. …Presley was a big factor … he always had an entourage … that was quite startling. He actually took us all to Graceland … it was quite something.