A conversation with Cathie Martin, Norwich UK

"We Can Really Do a Lot in Plants"

Cathie Martin from the John Innes Centre in Norwich UK, talks about how desirable traits can be conferred to plants by genetic modification and why she still hasn't tasted 'her' purple tomatoes.

Lab Times: One of the latest creations of your lab at the John Innes Centre in Norwich were genetically modified purple tomatoes. Why purple tomatoes?

Martin: The tomatoes got their colour from the production of very large amounts of anthocyanins, which are pigments present in many fruits and berries. They are also antioxidants and therefore supposed to be very healthy. And that is what we tried to prove by feeding them to mice and seeing what impact they had on their health.

Did they have an impact?

Martin: Yes. Our tests on mice bred to be susceptible to cancer showed that animals, whose diets were supplemented with the purple tomatoes, had a significantly longer lifespan compared to those that received only normal red tomatoes. We can now say that anthocyanins are very good, at least for mice, but most likely also for humans and you should try and eat large amounts of them.

How did you manage to get the anthocyanins into the tomatoes?

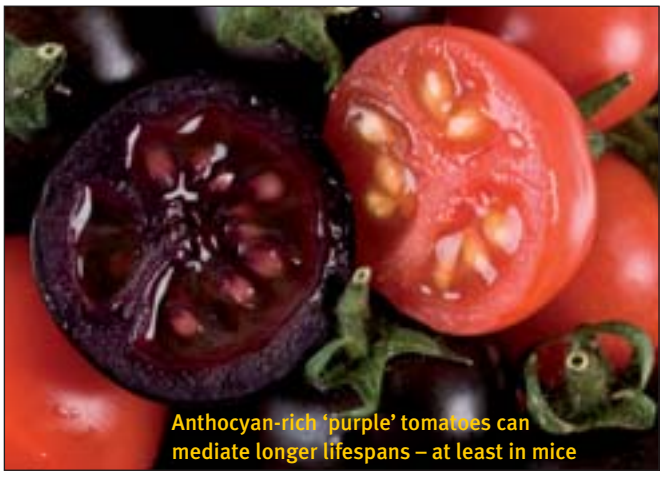
Martin: The engineering is very simple as plant molecular biology is quite far advanced. People think of it as an old-fashioned tool, lagging far behind the medical sciences. But we can really do a lot in plants. So, all we did was to turn on a metabolic pathway in the tomatoes that is already present in the plants by incorporating genes from the snapdragon flower. The metabolic pathway already exists in the leaves of the tomato. If you grow tomato-plants and you don't water them, they go purple. This is something completely normal. It is just not made in the fruit.

Why can't it be crossed in naturally?

Martin: There is no genetic variation available, even within in the wider species. There are relatives of tomatoes that *do* make anthocyanins in the fruit, for example, aubergines. But you can't cross them with tomatoes. So, we had to do it via metabolic engineering. In other fruits this could be done by conventional breeding because with anthocyanins there are usually varieties. Just think of blood-oranges: they produce a lot of them.

They are healthier than normal oranges?

Martin: Yes. We were funded by the European Union to do a project which clearly shows that blood-oranges are really good to prevent obesity by stopping white fat cells developing and so on. The problem is that the ability to produce blood-oranges compared to regular oranges is very limited because it has specific climatic requirements in terms of growing the oranges. For instance, they need cold temperatures during the night.



Anthocyan-rich 'purple' tomatoes can mediate longer lifespans – at least in mice

So you can't grow blood-oranges instead of normal oranges?

Martin: Exactly. But in terms of healthy food, it would be great to grow blood-oranges, for example, also in Florida.

So what can be done?

Martin: It is very difficult to breed oranges because you are dealing with trees. But you could produce markers, which will allow you to select for particular mutations. Hence, we have a marker for the blood-orange trait. But getting one producing anthocyanins under warm growth conditions would be almost impossible. So, the genetic modification would be the way to go. Generally speaking, genetic modification is always increasing the potential of whether a variation is available to you. In tomatoes there are no natural varieties that make as much anthocyanins as we can make using GMO. In oranges we have the natural variation but there is a problem with the environmental limitation. However, we could change that and it would be quite easy to do.

> *"The engineering is very simple as plant molecular biology is quite far advanced."*

When will your tomatoes be made available in supermarkets?

Martin: We don't know. One of the problems is that it has become very expensive to get a regulatory approval for a new trait. Even in the US, it would now cost around 30 million dollars. That means that the added value has to be 30 million dollars worth at least. And it is hard to see any consumer trait such as the extra amount of anthocyanins that could be worth 30 million dollars.

Is that the only reason?

Martin: Well, there are quite a few problems. One of the biggest is that all the big players in genetic modification are agro-industries. Monsanto is interested in produc-

er-traits to sell their products to the farmers. The added value that you get from herbicide resistance of soy-beans is, of course, much higher than from a tomato with extra anthocyanins. And then there are the GMO-regulations, which are a kind of self-fulfilling mechanism. They favour multi-national companies such as Monsanto. And Monsanto is happy with those sort of regulations because it gives them a kind of monopoly.

Do you see a chance that things could change? It seems that the resistance against GMOs in Europe is quite stable, isn't it?

Martin: I think there is a change going to come and it will be triggered by financial pressures in the animal feed sector. It is true that we have zero tolerance of genetically modified soy but that means that every country in Europe that is not importing GM soy has to pay a premium. In Ireland this premium is ten million dollars extra annually just for buying GM-free soy. It seems that they don't want to afford this much longer. So, when you get around this zero tolerance for GMO, everything will come more easily.

But isn't it a shame that this change might occur on economic grounds?

Martin: You are right. And I think that there should be many more people going out and saying this is the potential of GMOs. As a research-tool GM is perfectly okay. We have worked with it in plant-genetics for 25 years and the produced plants are not dangerous. They behave just like regular plants. It is incumbent on people who do fundamental research with GMOs to be able to stand up and show their big advantages.

So where do you see those advantages in your specific field of research?

Martin: I started to be interested in the possibilities of metabolic engineering about ten years ago. It became clear through talking to people from the medical field that there was a big interest in research on the impact of food on health. So I tried to develop systems, whereby one could ask in a scientific way, what kind of contribution particular compounds could have and how they could promote health. That involved making foods that have those compounds.

But do we really need this healthy food produced with GMOs?

Martin: There is a huge problem with chronic diseases, which are increasing – that is cancer, cardio-vascular diseases, obesity and so on. And there are major socio-behavioural risk factors associated with chronic diseases. The biggest one of these factors for the future is unhealthy eating because smoking and physical inactivity are going down. The problem is our diet. By reintroducing healthy compounds into the food that people do eat, we hope to reverse these effects.

> ***"With the tomato work, for example, we showed that you can use it as a production system for other chemicals."***

But what is wrong with the food that people eat nowadays?

Martin: The human genome evolved in a particular environment one to two million years ago. From the dietary point of view that was the environment of the hunter-gatherer. So they had very low fat, high protein but also high vegetable diet with fruits. Ten thousand years ago people started cultivating. The first cereals were produced and that allowed civilisations to develop. But the production of cereals meant something that is completely artificial in terms of a very high starch diet. Ten thousand years is nothing in terms of evolution, so the human genome evolved to have a low fat, low starch and high protein diet. And now our diet is completely different. I am very keen on the idea of food providing healthy ingredients instead of taking pills. That also means that the boundaries between pharmaceuticals and food become blurred.

What other major research areas exist at your institute?

Martin: One of the most advanced research areas is engineering late blight resistance in potato. Disease resistance in crops is comparatively easy to manage: you bring in a resistance gene that is present in a closely related species and with a breeding programme you can fix that gene. Potato breeding is really very difficult because they don't have seeds and, therefore, it takes much longer. We try to couple that with nutrition enhancement, so that we have the late blight resistance combined with a consumer trait to get a pull from the consumer and a push from the producer.

That sounds like very applied research, although the John Innes Centre is supposed to do basic science, isn't it?

Martin: Ten years ago we were doing very fundamental research. But that has changed a lot. Nowadays, my colleagues are much more interested in thinking about how to apply their work. I also want my work to be relevant to my friends. Still one of the best things you can do if you are grounded in fundamental science is to prove the principle. With the tomato work, for example, we showed that you can use it as a production system for other chemicals.

What other things besides anthocyanins do you want to produce?

Martin: Resveratrol, for example, would be interesting; it is one of the active ingredients in red wine. A company that makes resveratrol pills was recently sold to *GlaxoSmithKline* for 750 million dollars. So, you could use tomatoes as a system to produce resveratrol. Or take Tamiflu. The major bottleneck in the production is the availability of shikimic acid, which cannot be synthesised economically and is only effectively isolated from Chinese star anise, an ancient cooking spice. Roche, which owns the rights to Tamiflu, has to pay a premium to the Chinese for the star anise. So, one could try to produce shikimic acid in tomatoes.

Apropos spices: How do your tomatoes taste?

Martin: I am not supposed to confess that I have eaten them. So I can't make any special claims. But by all analytical techniques available it seems that they don't taste any different to normal tomatoes.

Why don't you know how it tastes?

Martin: The regulatory authority said that tomato seeds go right through you and this is an inadvertent environmental release. Now we are trying to get official permission to do human studies with a soup made from these tomatoes. But we first have to make sure that the seeds are really and completely destroyed by a special treatment.

INTERVIEW: KLAUS TASCHWER

Cathie Martin is a group leader at the John Innes Centre, Norwich, UK, the leading Research Institute in Plant Sciences in Europe. Her interests span the entire spectrum of plant biology and in biological questions from the fundamental right to the applied ends of plant science. She is also Editor-in-Chief of *Plant Cell*, the highest ranking international journal for plant research.