Mark Febbraio: "It will never be possible to get all the benefits of exercise in one pill"

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Mark Febbraio is principal investigator of the National Health and Medical Research Council and Head of the Cellular and Molecular Metabolism Laboratory within the Drug Discovery Program at Monash Institute of Pharmaceutical Sciences, Monash University, Australia

Mark Febbraio's team focuses on identifying genes, proteins and pathways that are important in metabolic diseases and in certain types of cancer related with obesity, in order to develop therapies that activate or block the pathway of interest. Currently some candidate drugs are already being researched.

Mark Febbraio is also CSO of N-Gene Research Laboratories Inc, a bio-technology company based in the United States, and founder and CSO of the company Kinomedica. His research focuses on understanding the mechanisms associated with exercise, obesity, type 2 diabetes and cancer, and he aims to develop novel drugs to treat lifestyle-related diseases. He is author of over 260 papers and has won both national and international awards. Before devoting himself full-time to research, Mark Febbraio was a professional athlete and winner of several triathlons.

- ***What led a professional athlete to devote himself to research?***

I was a professional athlete and spent many years competing in triathlons all over the world. Based on my own experience, I have always been fascinated by performance and human resistance. I completed my doctorate at the University of Victoria (Australia) on how extreme environmental temperatures can affect muscular metabolism during exercise.

- ***Is your research about reproducing the effects of exercise on the human body?***

My investigations focus on the benefits that exercise has for health, particularly in the case of diseases like diabetes, cardiovascular diseases, and some types of cancer. The idea is to develop drugs that in some way imitate exercise. We are working with a drug that is a peptide very similar to interleukin 6, because many years ago we discovered that during exercise, the muscle releases IL-6, which improves metabolic health.

We have developed a drug, but there are some aspects of interleukin 6 that are also prejudicial for our health since IL-6 can be pro-inflammatory under certain circumstances. In this case, we have modified the molecule so that it only has the benefits and to eliminate the negative qualities. The results were published in *Nature.*

We hope to undertake clinical trials with this drug. We have already passed on to the phase of non-human primates. The problem that may arise is that the molecule could be immunogenic; we don't know, but now we are working with a company that develops artificial intelligence models to ensure that there is no immunogenicity in the molecule. Then we will be able to move on to phase 1 trials.

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- ***You know that if it works, you'll be a millionaire?***

Yes, I know. We have created a company set up by a venture capital fund from New York to try and market the drug and, if we are lucky, sell it to a large pharmaceutical company. That is the aim.

- ***Aren't you worried that people will become lazy with a pill that imitates the beneficial effects of doing exercise?***

No. It will never be possible to get all the benefits of exercise from just a pill. It won't happen; exercise is a great antidepressant, it is good for your bones, for your mental and physical health… You can't get all of that from a pill.

But many people opt not to do exercise and get ill, so what we are trying to do is develop drugs that help people who are overweight, sedentary, etc.

In my opinion, society needs to be educated and one of the things I think we must do in the future is to be careful about how cities are planned, because if we look at a city like, for instance, Copenhagen -where it is very difficult to drive and there are lots of cycle lanes- people do exercise and there is very little obesity. But if we leave the city and go to other areas of Denmark where this type of infrastructure doesn't exist, we see obesity. So I believe this is one of the things that we have to do to develop.

But the other thing we need to tackle is how we can modify behaviour so that lifestyle-related diseases are reduced to a minimum; because right now these diseases are on the increase and obesity has not stabilised, it is still growing. We know that obesity is related with 60% of cancers so it is not only about cardiovascular diseases or dementia. It is about all diseases that are not transmissible.

- ***How can we tackle this pandemic?***

One of the things that we haven't been able to do is design a pharmacological intervention that suppresses appetite or hunger. This is a great challenge for science because the area of the brain, the hypothalamus, which regulates hunger, is also the same area of the brain that regulates mood. In the past, drugs that were aimed at the brain receptors that modify hunger and the need to eat had negative side effects, such as psychosis and depression. So, it is a great challenge for scientists to develop a drug that can regulate hunger.

What we are trying to do now is develop a drug that slightly increases energy expenditure. For instance, drugs directed at brown fat could become very important in the future because the metabolism of a person could slightly increase and, although they eat the same amount of food, lose weight.

The other challenges, apart from scientific ones, are in having good public health messages so that people try to eat more healthily and do exercise. Because we know that it is people with a lower socioeconomic or educational level who are most at risk of obesity.

But that's not the only problem, the problem we have is that there are people from minority groups who are under-represented in western societies, and they are affected by all of the problems. The majority of these people have changed their lifestyles, including their food intake.

- ***In this context, what is the responsibility of the food industry?***

The food industry is always going to try to exploit society because they are private organisations with shareholders who demand profits. But if you think about the role of governments, we see that a lot of work can be done to reduce the consumption of sugar in the population. Countries like Australia have forbidden some additives such as high-fructose corn syrup. But others, like the USA, have not. Why? You only have to look and see how powerful the maize industry is in that country. Governments have the responsibility to protect their citizens.

We are finding out things about sugar; we knew that it was bad for diabetes or obesity, but now we have seen that it is related with cancer. So, the responsibility of the food industry and governments is to educate people about what to eat and how to ensure that fresh fruit and vegetables are accessible and not a luxury.

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cancer. The responsibility of the food industry and governments is to educate people about what to eat and ensure that fresh fruit and vegetables are accessible and not a luxury

- ***Does it make any sense that it is more expensive to buy fresh produce than the processed foods of large fast food chains?***

In some countries, inflation means that many people cannot access fresh foods. Scenarios like the war in Ukraine are making products more expensive. In Australia, for instance, we have another problem: before the pandemic, many people came to work on farms, but now not so many visas are granted, which has meant that the prices of these foods have increased. And that means that you have to pay more for the same, which has caused higher inflation.

- ***Mark Febbraio presented the seminar "Role of gp130 receptor activation in metabolic disease, cancer and atherosclerosis," at the invitation of Dr. Guadalupe Sabio and Dr. M. Ángeles Moro.***