Edward Pearce: "Prevention is always more economical than treating a heart attack or a heart transplant"

21/12/2023

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Edward J. Pearce is an expert in immunobiology, who investigates the role of cellular metabolism in immune cell function and fate during infection and cancer in order to identify ways to inhibit or promote metabolic pathways to modulate immune responses. Dr. Pearce's long-term goal for his work is the modulation of metabolic processes to develop new therapies. Dr. Pearce joined Johns Hopkins University as a Bloomberg Distinguished Professor in 2020 from the Max Planck Institute of Immunobiology and Epigenetics.

Gene therapy in cardiovascular disease, when and how?

One of the main problems in the use of gene therapy in clinical practice is the rush there was to apply it, particularly in the 1990s. This meant that it was used before we had full knowledge of this disruptive treatment, and it caused the death of some patients. This affected the use of the therapy and meant no work was done on it for many years

When things are done in a hurry, the outcomes are not what you expect, and the possible risks are not properly considered.

We only recently understood how to administer viral vector therapy more safely, which had been a challenge, particularly in the field of cardiovascular gene therapy as we could not make a large enough amount of the modified genes or proteins reach the heart to obtain the desired effect. This is something we have recently been able to resolve, for the time being, in mice. This was a bottleneck that, once solved, allows us to continue progressing.

- ***And now, what's the next step?***

The technique's safety. We have to be sure that we administer not only the necessary, sufficient amount of protein to treat the heart or liver lesion, but also enough of the virus used as the vehicle to administer the gene therapy. That means we need to use the right amount of virus to avoid triggering an immune response that is more harmful than beneficial. Too much virus can trigger an unnecessary response that is prejudicial for the patient. It is a bit like what happens in transplants; you have to inactivate the immune system a specific amount, not too much not too little. In that way, we avoid the immune system itself triggering a response and attack on the virus used as the vehicle.

- ***Are you convinced that gene therapy will play an essential role in heart treatment?***

Conceptually, the idea that gene therapy could be the solution for cardiac anomalies makes a lot of sense and should be proactively studied. I don't think that gene therapy will be the solution for all patients with genetic cardiovascular diseases. To do so, in addition to this treatment, research is needed on other therapeutic alternatives for patients with cardiovascular diseases that are not of genetic origin. We have already started to see results in diseases like amyloidosis and hypertrophic cardiomyopathy.

Something that sounds like science fiction is what some pharmaceutical companies are researching. It's a gene therapy for the liver so that a person can never develop hypercholesterolemia; so you could eat whatever you want without the risk of having high cholesterol. It would be a kind of immunisation against heart disease. That means we would modify the genes in the liver using gene therapy so that our cholesterol would be like that of a vegetarian. Like I say, it sounds like science

fiction, but we already have the tools to alter genes in a mouse model.

So, one of the questions that particularly worries me is who will have access to these therapies. These are clearly very expensive treatments, a million dollars per patient, so I think they will only be accessible for a very small group of people and people who really need the treatment wouldn't be able to afford it. This is a serious problem that requires careful consideration.

These are very expensive treatments, but the costs of lifelong hospital and chronic care for patients with heart failure seem much more expensive. If costs were slightly lower, these might be cost-effective therapies.

Of course. Prevention is always more economical than treating a heart attack or than a heart transplant. It would make particular sense to use gene therapy for people with a higher risk of cardiovascular disease, but not for the majority of the population.

- ***You have been head of heart transplants at La Jolla for some years. Animal organs for transplants in humans?***

The case of the patient who received a pig's heart that had **been genetically modified to be more similar to a human heart**, who unfortunately died, was because there was no other option. In my opinion, the concept of xenotransplantation and its ramifications is something that is beyond me, because I imagine farms of animals, for instance pigs, destined to generate organs for transplants… I find it difficult to imagine.

I see it as more feasible for kidney transplants. In the case of the heart, we have to refine gene therapy to modify the genes of the pig's heart and minimise possible risks. Again, it sounds like science fiction, but really it isn't.

- ***Thirty years ago, nobody would have imagined that mobile phones would mean in our lives…***

That's right. I always remember that my father went to school on a horse. It's the same thing that happened in biology, where changes have occurred in areas like cancer, or immunotherapy that we would never have imagined. Like I said, the biggest challenge for me is that there should not be a gap in access to these new technologies. At the same time, we have seen the great potential of artificial intelligence in areas, for instance, like early identification of patients. In gene therapy, AI can be very useful, for instance, to discover why, in the case of two siblings who have the same gene defect, only one develops the disease.

If you love what you do, there's no sacrifice

- ***And the risks of AI?***

Recently, my centre did a study in which a patient contacted the doctor to make a complaint but didn't know whether the person they were speaking to was a human doctor or AI. And, surprisingly, when the results of this small study were analysed, it was found that patients were more satisfied

with the AI responses, which they perceived as being more sympathetic and a better listener. I find this really surprising because I would never have believed AI to be more sympathetic and understanding than a person.
And if we talk about possible risks, AI is the same as many other technologies; it depends on how they are used. For instance, insurance companies can use the information to decide whether to insure you or not: that's a bit scary!

- ***Why science?***

I studied literature at university. **One day, speaking to one of my cousins who is a physician**, I realised that the great stories are in medicine. Patients share their vulnerability with you, their fears, their lives... There are many writers who are physicians. So, I went back to university to study medicine. And thanks to that I was able to work with Dr. Valentín Fuster in New York. For me, that was transformative. At the start of my fellowship in New York, when I still wasn't sure if I wanted a career in research or in cardiology, Dr. Fuster showed me the satisfaction that comes from innovation and research. He's always thinking about the future, he never stops. I remember, right at the beginning of my training, I would spend more than 17 hours in the laboratory working on a project for a grant, even weekends and some days sleeping in the hospital. Many people wondered why I did that; it was a sacrifice... but for me it wasn't. Quite the contrary; it was pure pleasure and satisfaction. If you love what you do, it's no sacrifice. I can say that Dr. Fuster taught me the joy of research. For me, he's been a great influence on my life.

- ***Edward J. Pearce gave the seminar "Key events in plasmacytoid dendritic cell activation" at the invitation of David Sancho.***

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