Expert interview with Joe Miletich, MD, PhD, Senior Vice President of Research Sciences at Merck Research Laboratories.

Joe Miletich is an expert drug developer whose personal life and career have intersected with HPV. His older sister died of cervical cancer when he was a first year medical student. Twenty-five years later, following a career at Washington University in St. Louis, he joined Merck, a world leading company in vaccine development, and witnessed the development and commercialization of the first HPV vaccine, a vaccine that is used by millions of people over the world and can prevent the type of cancer that killed his own sister more than four and a half decades ago. Here he helps us understand the challenges behind the development of a vaccine that can prevent cancer and how important it is to improve the biological knowledge of human diseases to develop better medicines. He talks about the necessary long-term commitment to conduct thorough and long studies that will ensure a preventative vaccine is safe, tolerable and provide lasting immunity to protect vaccinated people against HPV infections and their consequences. *This article reports Dr. Miletich's personal views as an individual and cannot be attributed to Merck.*

1- Tell me about your career?

I am an MD-PhD and trained at Washington University in St Louis. After residency at UCSF, I worked as a professor of Internal Medicine and Pathology at Washington University for 18 years. I conducted basic research, saw patients and for the last half of my time there, I also directed the clinical diagnostic laboratories for the medical center.

Late in 1998, I decided to go to Merck because I was a bit dissatisfied with the unconscious bias in many academic research reports. I hoped to find more satisfaction bringing therapeutics to market because they must actually be proven to work. It was a chance to broaden my horizons and a very important time to me. I subsequently decided in 2002 to move to Amgen. It was a relatively small company at the time and I was given the terrific opportunity to set up and be responsible for all the discovery research, preclinical development and early clinical studies- where we test if the candidate medicine we invented is safe, tolerated, and has enough biological impact to pursue registrational clinical studies. Then in 2014, I left Amgen when the company took a different direction. I thought I might retire because I was in my 60s by then. But a very long-term friend and colleague asked me to return to Merck to reinvigorate its discovery, preclinical and early development and translational medicine efforts. That is what I have been doing for the last 5 and half years!

I got involved in the development of the HPV vaccine because in my first job at Merck I was responsible for toxicology. We were making sure that the vaccine was safe and well tolerated. When I left Merck in 2002, the clinical trials were started and by 2006 there was enough evidence for the vaccine to be approved. At the time, Gardasil was for 4 HPV types. Then, in 2014, the company received approval for Gardasil 9 that covers 9 HPV types and increases protection.

2- How has your personal experience affected your career choice?

In my last year as an undergraduate, my sister, who was 9 years older than me, was diagnosed with cervical cancer. At the time I didn't understand what it was and I didn't know much about cancer or its treatments. My sister was bright and well educated; she was the chief medical technician in a hospital. I assumed she would get excellent care. Not many treatments were available then; there were radioactive implants to preserve reproductive capacity or surgery. She chose the implants because she wanted to have children. I was not worried because I thought there would be a good outcome and went back to school. I started the MD-PhD program in St Louis. During that summer, my sister visited me a couple of times.

She helped me find an apartment and with various other things; she was always a very considerate older sibling and available to me. But late in the year it became clear she was going to die. It was so rapid! The radioactive implants had not worked and the cancer had metastasized widely to her bones and elsewhere. I spent our 3 week vacation taking care of her at home and then returned to school for mid-terms. Shortly after I got back to school I received a phone call that she was back in the hospital. I returned home and it was clear she was going to die soon. When I walked into her hospital room, she sent everyone away, the doctors, etc., and said: "You can all go away now, my brother's here and he can fix everything, I will be fine." That haunted me for many years. What I think she really meant was that she was going to die and it was OK since I was there, but those words have stayed with me ever since. Her death had a devastating effect on my life and on my family. I've thought about it frequently and realize that there are thousands of people and families ravaged by cancer in every corner of the world. I can't really say it was my singular driving force - that I chose my career because of that event - but it gave me an intense connection.

3. Where did the idea to make an HPV vaccine come from?

In the early 80s, there was an idea that HPV might cause some cancers. At this time, we did not understand much about what caused any cancers and the idea that a viral infection might be a cause initiated a vigorous debate. However epidemiologists showed that it was possible to recover HPV types 16 and 18 from early dysplasia and from malignant tumors. Evidence started to be overwhelming that it may be true. I vividly remember many discussions in our department at the time about incorporating tests for evidence of viral infection into screening programs for cervical cancer. Who should get the credit? The world has recognized the German virologist, Harald zur Hausen as the champion for the discovery of a link between HPV and cervical cancer. It was a milestone to recognize what causes these cancers but what do we do about it? The Australians, Ian Frazer and Jian Zhou made the next bigger step with the remarkable observation that a virus-like particle could be assembled from a single protein expressed late in the life cycle of the HPV, the L1 protein. Those observations in turn made it possible to make the vaccine. A lot of work was done in the early 90s to find the right conditions under which the particles form.

4. How did Merck get involved in the development of the HPV vaccine?

Somewhere in the mid-90s, the vaccine group at Merck started working on the HPV vaccine. I was not at Merck at the time, I was still at Washington University.

Merck has a very long history of making vaccines. So there was a commitment and heritage at Merck for wanting to make the HPV vaccine. Not all companies would embrace it because *to make a vaccine with the intent to give it to millions of people requires long studies to ensure that the vaccine is extremely safe and very effective*. *To actually prove that a vaccine works is very difficult because the things we are most worried about do not happen to everyone who is infected, but when they do it can be horrific*. Take HPV for example, almost everyone gets infected with different types of HPV strains during their lifetime. For most people it does not have any consequences. For those it does, the consequences can be catastrophic. So a very large number of people must be vaccinated and watched for an extended period of time to determine that the vaccine is safe and to detect possible side-effects. We also needed to figure out how long the protection lasts, if there is a necessity for revaccination with some periodicity. Development of a vaccine is a very long term commitment.

5. What were some of the challenges associated with developing Gardasil?

Many people are misinformed about vaccines. Because of the large number of people vaccinated, a subset will have adverse events or diseases that happen to coincide with the time they had the vaccine. Even if there is no evidence for a direct link, some people will blame it on the vaccine. It is an association and not causation.

There was also a lot of resistance to overcome because the cancers we are talking about are caused by strains of papillomavirus that are transmiited during sexual activity. There was a lot of pressure suggesting that instead of benefiting mankind, the vaccine would enable bad behaviors. But that was never the motive. As we know from epidemiology, 1 in 20 cancers worldwide are caused by HPV. Absolutely wonderful people, huge actual or potential contributors to society, are afflicted by these cancers and either their life or the quality of their life is severely limited. We are just trying to change that.

So there were struggles and there were frequent conversations on how to deal with the challenges and how to best engage with partners, official agencies and advocacy groups to help get the messages through. Of course, nothing has helped more than the evidence showing that after a decade of use the vaccine had a dramatic impact on the numbers of cancers and the immunity that it induces is long lasting.

Our biggest challenge now is the increased demand for vaccine. With the epidemiology showing the vaccine prevents these cancers and that the immunity is long lived, suddenly the world wants 10x more Gardasil than it wanted before, and that is a manufacturing challenge. It's not so easy to go from manufacturing tens of millions of doses a year to hundreds of millions of doses a year in a short time.

What about using single dose vaccination? This is a very complicated problem. A large fraction of people can get demonstrable protection from a single dose, and a larger fraction still from 2 doses. It depends on the age at which people are vaccinated. But the studies we have done were based on 2 or 3 doses, which was what we could do at the time. This is why the 2 and 3 dose schedules are approved in most places. This issue puts us, as a company, in a really tough spot because we don't think it's acceptable to say people should go to a reduced number of doses. We don't know which individuals the one dose schedule will work for or for how long. *I put myself in the position of one of the individuals who's getting the vaccine, not knowing how well or for how long I would be protected*.

So we are doing everything we can to increase production as soon as possible. We are also looking to see if we can change the vaccine to be more efficient as a single dose vaccine. But if you think back on everything I said, gaining the evidence through clinical trials that one dose works for most people and for an extended time, is going to take a while. This is a position that companies find themselves in from time to time and it is uncomfortable. Some might argue that we are taking this position because we want to maximize profit but it is not really true. We do worry about making assumptions; we believe it is better to act based on what we know for sure and on what is in the best interest of each individual who gets the vaccine. We are working on it. It takes time.

6. Many of our readers will be at high risk for the development of inherited cancers (HBOC, Li Fraumeni, Lynch Syndrome etc.). They will want to know how the cancer prevention drug development field may evolve. Are more preventive vaccines and drugs likely to be developed for this in the future?

That is ultimately what we want to do most of all. It is much more desirable to prevent diseases than to try to deal with them when they are established. I can genuinely say that in the companies I have worked at, there is no fear that we would go out of business if we were to

make preventatives. It is just harder to develop effective preventative medicines, and it takes a longer period of time and many more people to actually prove they work and are safe.

I have hope that it will become easier. Just think about the logistics. Before, to be enlisted in clinical trials, people had to come in into specialized centers. Now, with new technologies, much of the work can be done remotely. A larger number of people are becoming more knowledgeable; it is going to be easier to obtain true informed consent to participate. So I am optimistic, but that does not make the challenges associated with prevention go away immediately. We will have to work through them over time.

Then it comes down to the fundamental biology of the diseases and how much of that we understand. There are not that many cases where we truly understand the biological modulation we need to achieve to prevent diseases. We don't have a whole lot of examples like HPV just yet. But over time, I am hoping we will have more. Nothing happens quite as fast as I wish it could. But it is certainly not going to happen at all if we do not keep working at it. We should keep moving forward at the fastest pace we can.

7- Could you tell me what the cost for the development of the HPV vaccine was?

It is difficult to estimate because so many people have worked on it. And many individuals contribute to more than one project with their expertise. The capital cost of it over years is well over a billion dollars and then there are the additional costs of the actual production, testing, packaging and and distribution. It has been considerable, and for those who worry about how fast to get return on your money, vaccines and preventatives are not the greatest business because it can take decades. On the other hand, if the vaccine or preventative is quite impactful, people will use it for a long time. They do not draw as much competition as other medicines because they take a long time to test and develop and to replicate all of the evidence. *So vaccines tend to endure longer in the market place than other therapeutics but you have to be a company that intends to be a long term player* rather than worry about a return on investment in the next 5-7 years. A company like Merck also has a large portfolio of products and has medicines like Keytruda that do generate revenue in a shorter time period, to help balance things out.

George Merck's philosophy was to focus on where we can do good for people and the profits will follow as long as we don't lose that focus on good. You can either believe that or not; it's not just something you can say conveniently when it works. You have to believe it when things are not working, too. And honestly you need a bit of good fortune as well. *Without a deep enough understanding about human disease biology, which we still don't have, it is difficult to put together a low- risk businees strategy that has a high probability of financial and medical success*. You simply have to be confident that if you try hard and explore enough things in earnest, that something will turn up, and that it will turn up in time. And that is not easy in our world today where people are interested in how fast they will get a return on investment.

8- Looking back over time, your work and the work of your colleagues fixed quite a few people, didn't it?

I do take some satisfaction in that. Going back to one of your earlier questions, I did not set up my life to try to fix a problem about cancers that were caused by HPV. By the good fortune of opportunities that I had, I have been able to intersect with that very well and I've added to that effort where I could. It does mean a lot to be able to look back and say I did have some contributory role. I also can't help but wonder what it would be like if it could have been done decades earlier and my sister was still alive. And mostly I think about what it will mean when no other young women and young men will ever

again have to have to go through what she suffered.