CONVERSATIONS WITH MIKE MILKEN

Michael Hofman

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Mike Milken: Michael, thank you for joining me today.

Michael Hofman: Thank you, Mike. It's a real great pleasure and a great honor.

We are a very small world, with every single country affected by COVID-19 and this crisis. There's a lot of collateral damage that's occurred: research centers being shut down, patients with cancer, heart attacks and strokes not going in for treatment out of fear. You are a professor of biology specializing in nuclear medicine at the Peter MacCallum Cancer Center in Melbourne. For those that don't know, what is nuclear medicine and what are its applications?

Nuclear medicine is a unique specialty of medicine where we use radioactive substances, both for imaging but also for treatment. Everyone out there knows what a CT scanner and an MRI scanner is, but perhaps many people don't know what a PET scanner is,

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This interview has been lightly edited for clarity and readability.

which is the technology that we use. We can only image living things; we inject a radioactive substance that tracks some physiologic process in the body.

The most common substance we use for our PET scanning is a radioactive sugar. We inject it into a vein intravenously, travels around the body, and gets taken up by tissue that's using glucose, and that's very good for cancer imaging because cancers are using sugar to grow. So they light up very brightly on the scan and it allows us not only to see where they are on a whole-body level, but also characterize the aggressiveness of the tumor. We can inject any number of radioactive substances to track different processes. In the last five to six years, the compound I've been researching is PSMA, or prostate specific membrane antigen, which is one expressed in prostate cancer very specifically. So it's a game changer and allows us to visualize prostate cancer in a way that's never been seen before. That's the imaging side.

> ***"Chemistry has advanced enormously in the last decade or two. We now have the ability to target a variety of different tumors with different radioactive substances to increase the array of cancers and also other diseases that we're able to both image and treat."***

And then we can do a neat trick by just changing the type of radioactive substance from an imaging substance. They emit gamma rays that pass out of the body. The PET scanner detects it, but we can change to a beta or an alpha meter. These are therapeutic radioactive substances. They travel very short distances, but really result in cell death. So we use this to treat a variety of different cancers, and it's a really effective form because it's very personalized. We get the radiation to the sites of tumors whilst not affecting the rest of the body. So it's a unique way where we can both image and treat using the same processes.

Growing up, I don't suppose you dreamed of becoming a nuclear medicine investigator. How did you find your way into this research?

My parents were an early adopter of personalized computers in the home. So when I was in grade two, I think in back in 1982, my parents bought a Tandy TRS 80 with four kilobytes of RAM. I learned to program in BASIC, I think around the age of eight and that fascination and sort of self-education with information technology really continued to my twenties when I was in medical school. At that time, I was making web pages, but this was in the early days of the internet when the average person on the street had no idea what the internet was. I trained in internal medicine initially and then happened to be in a hospital that had a large nuclear medicine department. And it really got my attention because I thought, 'here is somewhere where I can combine my skills in information

technology and IT with medicine,' and that's something I was looking for. So I drifted towards that and it's been a great journey. I go to work most days and think I have one of the best jobs on the planet.

Now you had this love for programming, a love of technology. How did that translate into medicine? Not everyone who is a programmer wakes up one day and says, 'you know, I want to go into internal medicine.'

"All four of my grandparents survived [the Holocaust]. As I look at my family tree, actually about 90 percent of that generation was annihilated. So to some extent, it's a little bit of a miracle that I'm here today. My grandparents were really lacking the basic things of life, such as shelter, food, education, friendships, freedom. I think medicine encompasses some of those basic elements of life, which probably brought me towards medicine."

It's hard to pinpoint exactly what it was, but it probably relates to perhaps family heritage. All four of my grandparents lived in small towns in Poland, and then their lives were really ripped apart when they were in their adolescent years. Rather than going to school and being educated, they were actually shipped off to concentration camps where they lived in really appalling conditions. Most of their parents, brothers and sisters actually were murdered in the Holocaust. But all four of my grandparents survived. As I look at my family tree, actually about 90 percent of that generation were annihilated in the Holocaust. So to some extent, it's a little bit of a miracle that I'm here today, but all four of my grandparents survived. They ended up in displacement camps in Germany after World War II ended, and they went to various parts of the world really as refugees, wherever they could escape to.

At the age of 15, my grandparents were really lacking the basic things of life, such as shelter, food, education, friendships, freedom, and I think medicine encompasses some of those basic elements of life when you want to give back. So some of those elements probably brought me towards medicine. I think I was also just fascinated by the science, looking at biology. It looked like a really interesting career to study. I had the freedom and the ability to do that. The rest is history.

One side of my family also died in the Holocaust and was from Poland also. And so it's interesting when we think of the immigrants, their lives, their children, their grandchildren. How have your children reacted to the coronavirus pandemic? How have they adjusted?

I have three children aged nine, 13 and 15, and they've adjusted pretty quickly. Children are amazing; they adapt probably much faster than most adults. So, their school was closed for periods of time, but it was only closed physically, because they continued online education using Zoom and other electronic platforms. It was quite remarkable to watch the way classes transformed from a physical presence to using Zoom where they could see all 30 people in the class and interact with them. So they start their mornings quite differently. Instead of hopping on the school bus, they can sleep in a little bit longer, which they absolutely love, and they can have breakfast and then they go back to their bedrooms and they sit on their computers and interact with their classmates, with their teachers, and they do a whole day of school electronically. And it's quite remarkable. I think their learning has not been impacted as much as you would think, but I think it is having implications for socialization, perhaps mental health, how they're exercising they're not running around in the school playground at lunchtime, they're still within the confines of the house. So, I think that's having some adverse consequences. I don't think it's a sustainable way for the future, so I do look forward to the vaccines coming and returning back to normal life and going back to the school yard.

> *"Once you have a whole body PET scan, there's not a lot of value often in doing a physical examination or taking out your stethoscope because the information on that scan tells you everything you need to know. The classic medicine history examination is giving way to a whole new form of medicine where we are using a variety of different technologies."*

But I think the rapid transformation of education and also in health care is here to stay in a very positive way. There's been a dramatic change very quickly. Otherwise it would have taken a decade for some of these changes to occur. They occurred in days rather than decades. I think we'll see a lot of positive things coming from that for the future.

When I think of when people think of nuclear or radiation, they generally think of external beam radiation. I had external beam radiation in the late 1993 period; it was new at the time. I was one of the first persons to take hormone treatment first, then radiation; that study had not been done. But it was new, and in terms of conformal radiation where instead of shooting from your front in the back, they would shoot all around your body and lessen the amount of radiation that came in from any one angle and potentially cause less damage to your other organs. So when people think of radiation and nuclear, they think of this occurring outside the body, really not inside the body.

And as you described the two areas, one imaging is occurring by putting something inside your body. So we can image it; putting nuclear material inside your body so we can in fact kill tissue. And when you say travel a short distance, let's talk about that, because I think most of our listeners or viewers would say they thought it was external beam radiation. They were in a CAT scan and they were in something, an MRI; they were in an x-ray machine, they were in something that was external to the body, not necessarily internal.

This concept is one of theranostics, which is the field that I'm in and that's a word. The thera is therapeutic; the nostics is diagnostic. So it's really a combination of the two. And as you say, external beam radiation, I think it's fair to say has resulted in your living many, many more years than you thought you would have. I think it's in the public domain the doctor said you had 18 months to live a very long time ago. And external beam radiation has changed that around. Radiation will damage the DNA, and it will damage the DNA of tumors that are rapidly multiplying much more than normal tissues. So that results in a death to cancer cells in particular. But the problem with external beam radiation is one, the radiation passes through all your normal tissues to get to the tumor, and that can result in a lot of side effects. But also the radiation oncologist needs to decide where to put those external beam rays and they may miss some of your tumors because they do that on the basis of looking at a CT or MRI scan, or just on knowledge of where tumors spread, and they'll define an area to irradiate. But your tumors may be outside that area. So, the wonderful thing about the theranostic approach is that we inject a biologic compound intravenously into a vein. It travels around the body and binds to a specific receptor – in the case of prostate cancer, PSMA, on the cell surface of these cancers. It's taken up by the tumors wherever they are in the body. We don't need to program where to deliver the radiation; it travels around and finds the tumor tissues wherever they are. That can be in lymph nodes, bones, liver or any tissue. The radioactive compounds we use travel only, let's say, 0.2 of a millimeter in the case of Lutetium-177, which is the main radioactive compound we're using for treatment at the moment. So that's quite remarkable; a 0.2 millimeter path length means that we're getting extremely high doses of radiation to tumors and very little damage to normal tissue.

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It's quite a remarkable way to treat tumors, but we should reflect that like most things, this is actually not a new technology. It's been around for a very long time. In fact, it may

represent the first targeted treatment in modern oncology. A doctor by the name of Saul Hertz, who was a thyroid specialist back in the 1930s became aware that radioactive iodine could be used to treat thyroid cancer. So iodine is a mineral that's in a normal diet that we eat. It's very high in seafood. And it so happens that the thyroid gland is the only organ in the body that uses this mineral. It uses iodine to make thyroid hormone, which is one of our essential hormones. And he asked the question, 'what if I used a radioactive iodine, would I be able to image and treat men or women with a thyroid cancer?'

And radioactive iodine was one of the first compounds that could be made in cyclotrons or linear accelerators and psych and nuclear reactors. He got hold of very low doses of radioactive iodine and put them in people, and he was one of the first to cure men and women with metastatic thyroid cancer that had spread to various organs by using this concept. What's changed in recent times is chemistry has advanced enormously in the last decade or two. So we now have the ability to target a variety of different tumors with different radioactive substances to increase the array of cancers and also other diseases that we're able to both image and treat with this type of technology.

So Michael, for the lay listeners, when you say 0.2 millimeters, are we talking about the width of a hair?

Two millimeters is 0.07 of an inch. So a 0.2 of a millimeter is 0.0007 of an inch. So, people get an idea of what that is. It's a really short distance. So, this is real precision medicine.

The PET scan allows you to identify wherever the cancer is in your body. How many different forms of cancer do you think you see applications for? Can you use this to identify blood cancer?

When I started nuclear medicine training, I think there two PET scanners in the whole of Australia, this was a very boutique technology that was not widely available. This is a technology that is now widely available and there would be well over a hundred PET scanners in Australia today. Most patients that are diagnosed with cancer nowadays, whatever type it is will often come to have a PET scan because it is the most accurate way to stage the disease and know how far it has spread. In order to make rational and sensible decisions about how to treat your cancer, whether you should take a surgical approach or whether you need a more systemic therapy, you really need to know the state of play and a PET scanner does that.

When most people use the word precision medicine, they're not talking about PET scanning or imaging or theranostics; they're talking about genetics or gene sequencing. Back in the 1990s, the Human Genome Project was started and it took a little over 10 years for a collaborative network of researchers around the globe to really sequence the

3.2 billion base pairs in the human DNA because the technology to do that was really slow. Nowadays with newer technology, next generation sequencing, that can be done very rapidly. So, it's not uncommon nowadays for an oncologist to take a biopsy and sequence the entire DNA of your individual tumor. That's what most people think of when they hear precision medicine. But the problem with that approach is that if you were to biopsy 10 different sites of tumor in your body, presuming that your tumor has spread to different sites and you sequence it, you would find an array of different abnormalities and mutations at different sites.

So just due to sort of Darwinian evolution, as your tumor spreads and evolves in different organs that it spreads to, the genetics of that tumor changes. So when you do a biopsy and sequence the tumor at one site, it's not reflective of what's happening at all the other sites. And one of the advantages f PET scanning is that we image the whole body. And we can often see that the level of sugar metabolism or the level of PSMA expression in prostate cancer differs at varying sites in the body. And we can visualize that and quantify it on the PET scanner. It really allows us to see what's happening on a whole-body level and that complements what the genetic sequencing can do at individual sites. So by combining all these different technologies, we can get the best idea of the state of play of cancer within an individual.

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Let's talk about your job. It sounds like as you describe it three parts: one part is actually seen in interacting with patients and treating patients; the other part is imaging; and then the other part is deploying nuclear technology to deal with cancer. Many researchers don't really interact with the patient as much. The patient part, that third of your day and your activity, how has it helped you in the other two?

It helps enormously because it puts everything into perspective. It allows you to really understand and provide purpose for what you're doing, the ability to improve the lives of women and men who are presenting often with pain and poor quality of life, and use these treatments to improve their quality of life and extend duration of life is really humbling. I think also for the patients, showing them their PET scans as an integral part of what I do, and often oncologists are not showing patients their imaging. Patients actually love to see their imaging. Sometimes it can be a little bit distressing to see how far the cancer has spread, but the patients still want to have that knowledge. And it's also good to reflect in these COVID-19 times how there's been a rapid transition away from the standard of care medicine, which has been go to the doctor, they take a history, they perform an examination, and then the doctor tells you what to do. I think that's changing very quickly. We're now doing tele-health consultation using Zoom, and

because we can't examine the patient, we can't touch them because they're not in the room, we'll also employ other technologies such as these whole-body scans. Once you have a whole body PET scan, there's not a lot of value often in doing a physical examination or taking out your stethoscope because the information on that scan tells you everything you need to know. The classic medicine history examination is giving way to a whole new form of medicine where we are using a variety of different technologies, not only scanning, but also smart watches to monitor various vital signs instead of physically taking your pulse. You can just look at your smartwatch or do an ECG in the same way, and we're getting a whole new set of data in which to make our decisions and decide what is the best treatment for the patient in front of us.

"I think it's going to become more mainstream where the doctor acts as an advisor. We share all the data that we're accumulating with the patient, we advise of the pros and cons, and then the patients go off and do their own research and come back with ideas as well. And we become part of a team working on the shared goal of achieving the best outcome.""

I think as patients are also becoming more educated, they want to be part of this decision making. So rather than the doctor making the decision on behalf of the patient, we're increasingly entering an era – we already have, but I think it's going to become more mainstream – where the doctor acts as an advisor as part of the patient team. And we share all the data that we're accumulating with the patient, we advise of the pros and cons, and then the patients go off and do their own research as you did and come back with ideas as well. And we becomes part of a team working on the shared goal of achieving the best outcome.

The coronavirus – it's had a major effect in medical centers, medical research, medical care throughout the world, with many research facilities shut down where labs and people interacting with one another. If I had walked in to Peter Mac in February through August this year, take us through your teams, other teams, treating patients what's occurred?

Peter Mac is a great facility because it's half hospital and half research facility. And the elements of that have changed. On the research facility side, because there's been a mandate that if you can work from home you must work from home, there are fewer researchers in the building; many of those researchers are at home doing their research. There are still some coming in to do a central research.

And some research has been diverted towards COVID-19 research. That research is certainly going on, but it's fair to say that there are a lot fewer researchers physically in the building to date. On the doctor side of things, I think the wards are still busy. Cancer

has not stopped because of COVID-19. The number of people presenting to their doctors has decreased, which is unfortunate because people are presenting perhaps with later-stage disease because they ignored their pain, hoped it would go away. They're nervous to go to their family doctor because they didn't want to catch coronavirus as they went into those medical facilities. Nevertheless, our hospitals are still full and busy. Our PET scan volume has dropped maybe 10 percent, 15 percent, which is not a lot. And, so we're still very busy, but it's fair to say that the environment is very different.

Peter Mac has been designated as a COVID-19-free hospital. Royal Melbourne across the road is dealing with all the COVID-19 cases. But the effect of COVID-19 is really palpable in Melbourne at the moment, wherein what the government calls stage-four restrictions. We did very well initially. We got the numbers down very quickly; we had less than 10 cases diagnosed per day for a long period of time. But as the government eased those restrictions, the numbers increased quite sharply around six weeks ago, to the point where we had more than a thousand cases a day on a single day diagnosed. So we went back into restrictions to decrease the number of deaths happening from coronavirus, which I think is the really the appropriate action for government to take since life is so important. We're still dealing with the consequences of that and the flow on effects that I think are going to remain with us for several years.

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We did a research study many years ago, and we discovered in lung cancer, that it was quite often that you didn't get all the lung cancer. The promise of the PET scan is being able to get it where it is. And the other promise is understanding that the mutations might be different depending where they are in their body, not homogeneous from that side. Once we combine the quality of imaging and the targeted, what we would call real precision medicine. How soon what you're doing, and as a leader in the world where we see it throughout the world?

PET scanning and theranostics is exponentially increasing at the moment; it is one of the fastest-growing areas in medicine. Some of my peers in areas such as anesthetics where things have not really changed very much in the last 10 to 20 years, but in nuclear medicine the stuff I did only 20 years ago is not being done anymore. It's all been transformed. Every two or three years we have a new radioactive tracer to play with

both for imaging and therapy. So it's growing very rapidly at the moment for a variety of cancers, most recently prostate cancer, but it really does have a role in pretty much any cancer type we can think of. So I think we do need to invest in the next generation of nuclear medicine specialists. At the moment, you can become a nuclear medicine specialist in Australia either through internal medicine or radiology background. And it's a real team effort. I work with nuclear medicine technologists that are doing the scans; engineers who are operating the machinery; chemists who are actually making these radiopharmaceuticals within hospital radiopharmacies; physicists who are using the cyclotrons. We actually have a cyclotron in the basement of our hospital that can make radioactive substances. And then add to the nuclear reactor. There is one near Sydney in Lucas Heights that makes our Lutetium-177. So there is this massive array of specialization that's needed in order to do what I do. It's not a single-person exercise. And so I think we need more investment in nuclear medicine in order to advance it further. There is not enough investment happening.

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I think the Prostate Cancer Foundation has, in my little domain of nuclear medicine and prostate cancer, allowed it to flourish enormously because you've picked up on this actually very early on when PSMA was developed almost 20 years ago, to more recently where it's taken off in the nuclear medicine domain. Your foundation through the leadership of people like Jonathan Simons and Howard Soule have identified this as an area for prime investment, and have really poured money into centers like ours that has enabled us to do the research and treat the patients. You've been very active participants, not only by providing money, but also by linking researchers together. So one of the things the PCF leadership has been great at doing is linking me to other researchers around the globe that are into this domain to really progress what we can call team science. So that really enables us to proceed with quite a rapid pace and urgency. But we can always do better, so no doubt nuclear medicine is an area that it's rife for further investment.

Michael, I want to thank you for joining us today. I also want to thank you for the career path that you've followed. Obviously, as you know, we fund in more than 20 countries more than 200 academic centers, and it didn't take us very long to find this exceptional program that can change the world for cancer patients. We'll be following your research

very closely and hope that eventually your discoveries and the way of treating patients can be found throughout the world.

And I'd like to thank you, Mike, not only for the invitation to speak to you, but also for establishing the Prostate Cancer Foundation, which has really led the world in prostate cancer research. And you do it in such an active way rather than a passive way, and the global outreach and the rapid pace and urgency with which you do that is really very remarkable. So thank you on behalf of myself, but also all the prostate cancer patients and researchers globally.
