Interview with

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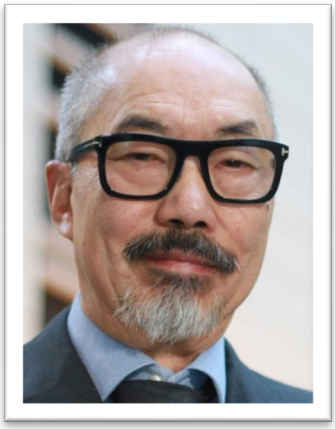
2023 CCRA Awardee for Outstanding Achievements in Cancer Research



How have your research accomplishments in cancer biology and immunology changed our understanding of cancer?

It is very difficult for me to address that in one broad stroke. There are thousands of cancer researchers all working together to try to understand how cancer comes about, how we can treat it, and how we can prevent it. But in this context, I can say that, in the very early times, our laboratory was able to discover the T cell receptor, which is basically the sensor of the immune system distinguishing what is foreign, such as a virus, bacterium, or parasite, from the host. Of course, the immune system is there to protect us against these pathogens, but what is really striking is that, within the last 15 years or so, it has become obvious that the immune system can also recognize cancer cells. So back in 1984, our laboratory's identification of the human TCR sensor (together with Mark Davis' identification of the mouse TCR) was really a fundamental discovery. It created the opportunity for tens of thousands of immunologists to study how immune cells make distinctions and how we can change the way we try to prevent and treat cancers.

I would also like to add that, back in 1995, a postdoctoral fellow in our lab named Paul Waterhouse showed that a molecule called CTLA-4 functioned as a "brake" on the immune system, particularly for T cells. When he knocked out this brake (or "immune checkpoint") in mice, the animal's immune cells started to rage and attack numerous tissues in the body. Jim Allison, at that time a professor in Berkeley, took advantage of that result and produced an antibody to block CTLA-4, allowing the anti-tumour immune response to continue. He thereby demonstrated that cancer patients treated with this antibody were able to sustain a more intense and prolonged immune response against their malignant cells. Together with the findings of Professor Tasuku Honjo on a similar braking molecule called PD-1, the fourth pillar of cancer treatment—immunotherapy in the form of immune checkpoint blockade—was created.

So, in answer to your original question, I would say that these two discoveries, the cloning of the TCR and the identification of CTLA-4 as the first immune checkpoint molecule, have been our most significant contributions to basic cancer research. From this firm base, the many trainees who have passed through my lab over the past almost 40 years have developed myriad novel ideas about the various genes involved in cancer development. Some of these hypotheses have even shown promise as new treatment opportunities, and are under examination accordingly.

What major advances do you foresee in the next decade and how will these improve the lives of cancer patients?

In answer to a question like this, I like to cite a quote from Confucius: “We all have two lives. The second one begins when we realize we only have one”. That very profound statement means a lot to both cancer survivors and cancer researchers. If I could twist this quote just a little bit, I would say that: “All medical scientists have two lives. The second one begins when they realize that immunology is the orchestra for most of life's symphonies”. I say this because I believe that continued learning about how our immune system prevents or combats cancer development will provide us with insights that we can use to attack malignancies, many of which remain untreatable today even with immune checkpoint blockade. I think that by knowing how we can combine certain immune interventions with standard drugs or other anti-cancer approaches we can definitely improve future cancer treatments in a concrete way.

What sustains you to continue your research program with such vigor and drive?

I cannot answer your question precisely, but I can tell you that I'm more excited about science today than I've ever have been, mainly because of the 150 trainees that have passed through my lab. Many of these talented individuals have become deans of medical schools, chairs of research departments, and directors of institutes. They have not only advanced the science of fighting cancer with their own dramatic discoveries but have also created many opportunities for others to do so. I am proud to have participated in building up all this combined experience and expertise over the years. I want to continue to do so and provide whatever insights I can to help push the field forward and finally conquer cancer.

To accomplish this task, we will all have to be open to new ideas. For example, together with Kevin Tracey, a neurosurgeon from New York, our lab has recently shown that our brain actually “talks” to the immune system and plays a role in steering our immune cells to attack cancer cells. A paper from our group on this work has recently been accepted for publication in *Nature Cancer.* These new insights will add a fresh dimension to the already vast body of knowledge and the collection of tools that we cancer researchers have amassed over the years to continue the fight.

What words of wisdom do you have for the next generation of cancer researchers who are hoping for a similarly long and successful research career?

I think success in research boils down to two simple things. To illustrate the first, I would like to quote an African proverb, which says, “If you want to go fast, go alone. If you want to go far, go together”. If the medical world is to truly understand cancer, we have to work as a team with as many collaborators as we can find. Only in this way will we dissect the many different aspects of this disease and be able to devise technologies to defeat it. For the second word of wisdom, I would like to quote an author by the name of Simon Sinek, who said, “Always start with Why”. Many organizations know what to do, and some may know how to do it, but very few ask why. For both young and old scientists, we must realize that we are not here to do just what can be done easily, or to do just the things we already know how to do. The most important issue to keep in mind is the “why” because so much of cancer is still unknown and the connections between concepts are still black boxes. A key question is: Why is the immune system able to achieve such great immunosurveillance for some cancers but not others, and at some times but

not others? And a query stemming from this observation: “Why is immune checkpoint blockade fantastic at treating certain cancers but not others?” Only by digging down and repeatedly finding the answers to “why” will we achieve the results that will propel the science forward.

What do you hope your legacy will be in terms of the cancer research immunology arena?

I do not make a point of thinking about my legacy. Indeed, I am very happy to fade into the sunset. That being said, I would say, as I mentioned earlier, that I am happy to have contributed to the education of the over 150 people who have trained in our laboratory. Many have become prominent and successful scientists and clinicians, and they continue to contribute to knowledge in basic science, translational science, and clinical science. Another quote from an Indian proverb comes to mind: “The flowers of all the tomorrows are in the seeds of today.” I like to think of my trainees as those seeds, who will set up their own labs and continue to spread flowers in the form of useful research discoveries. To think of it another way, it is those people who will be steering the next great ships, sailing in all directions, with a unified mission: to achieve a better understanding of cancer, how it evolves, and how we can stop it, and when we cannot stop it, how we can treat it.