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Q&A

# From the T-cell receptor to cancer therapy: an interview with Tak W. Mak

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This interview is part of a series of articles to mark the 25th anniversary of the launching of *Cell Death and Differentiation*.

**Fig. 1** Tak Wah Mak

Tak W. Mak, Fig. 1, was one of the first scientists to work on apoptotic mechanisms, initially from an immunological perspective. This interest sprang from his early work, which was dedicated to understanding mechanisms of T-cell recognition and development. Indeed, his laboratory was the first to clone the gene encoding the beta chain of the human T-cell receptor (TCR) and among the first to define the function of the immune checkpoint regulator CTLA-4. For his discoveries, Dr. Mak has been elected a Fellow of the Royal Society of London and a Foreign Member of the National Academy of Sciences (USA). He has also won many international prizes as well as received a dozen Honorary Doctoral degrees, including from the Karolinska Institute as well as from the Universities of Zurich, Göttingen, Hong Kong and Rome (Tor Vergata). His latest work ranges from defining novel connections between the nervous system and immune cells to exploiting properties unique to cancer cells in such a way as to kill them. Cell Death and Differentiation wondered: what in Dr Mak's early work triggered his scientific interest in the fields of cell death and differentiation, and how did his efforts in these areas lead to his current success in the field of cancer therapy? CDD interviewed Dr Mak to ask these questions and shares his answers below.

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SPRINGER NATURE
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**CDD: What was your scientific interest before working on cell death?**

My initial venture into science was as a virologist. My first scientific training was with Roland Rueckert at the University of Wisconsin in Madison, where I investigated structural aspects of picornavirus capsid proteins. I then moved to the Ontario Cancer Institute (OCI) in Toronto to study under Ernest McCulloch and James Till, who defined hematopoietic stem cells in 1961 [1]. I became immersed in hematopoiesis and retroviruses, and strove to understand the genetic basis of how retroviruses induce malignant transformation. Eventually I established my own laboratory within the OCI and collaborated with Alan Bernstein to investigate Friend spleen focus-forming virus (SFFV) and the differentiation of Friend cells. It was then that I first exploited the technique of molecular subtraction, using it to isolate transformation-specific sequences of SFFV [2]. To further my studies of retroviruses and learn more about molecular biology, I returned to Wisconsin to join Howard Temin's lab. I partnered with Irvin Chen to clone and sequence the reticuloendotheliosis virus strain-T, thereby identifying a viral homologue of c-rel [3]. David Baltimore later showed that c-rel was a member of the family of genes encoding the NFκB transcription factors [4]. After returning to Toronto from Wisconsin, my laboratory became more molecularly oriented. In addition to cloning and sequencing the SFFV virus [5], my team began to investigate T-cell development and differentiation.

In 1982, Yasuke Yanagi (a postdoctoral fellow from Japan) joined my laboratory and we began to apply differential display and molecular subtraction techniques to T and B cells in order to identify T-cell-specific cDNAs. Many of these cDNAs were subsequently shown to encode important genes like Lck and CD3, among others. One clone that immediately caught our attention was YT35, a T-cell-specific cDNA that encoded a protein, which exhibited extensive homology to the immunoglobulin light chain and contained identifiable V, J, and C regions. We concluded that YT35 encoded part of the human TCR and demonstrated that it specified the TCR β chain. In March of 1984, the paper describing our discovery was published in Nature back-to-back with the report from Mark Davis' lab on the cloning of the parallel gene for the murine TCR [6, 7]. Our results were further supported by the finding that the gene from which the Y35 cDNA had been derived showed evidence of rearrangement in T-cell leukaemia and lymphoma cells [8–10]. My lab's work for much of the next decade was focussed on the molecular analysis of TCR genes as well as on deciphering mechanisms of T-cell recognition and development. This theme continues today in the contexts of autoimmune diseases and cancer.

**CDD: When did you first hear about apoptosis?**

By the end of the 1980s, I had become more and more interested in the study of T-cell biology and the physiology of the immune system. I first heard about apoptosis by reading a paper that had been published by Andrew Wyllie in Nature in 1980 [11]. I was especially intrigued by the unusually programmed nature by which dexamethasone induced cell death in thymocytes. The work of Robert Horvitz and Xiao-Dong Wang also stimulated my interest in this field [12–15]. At that particular time, I had been galvanised by the reports of Oliver Smithies and Mario Capecchi that homologous recombination could be induced in mammalian cells [16, 17] [for details, please see http://nobelprize.org/nobel_prizes/medicine/laureates/2007/adv.html]. These were very exciting discoveries because they meant that one could combine this technical approach with the pioneering work of Martin J. Evans in growing murine embryonic stem cells [18, 19] to design genetically modified mammals at will. In short, one could create a vast array of strains of 'knockout' mutant mice, each lacking a specific gene, to study the roles of these genes in mouse physiology. Naturally, my team jumped at the chance to establish knockout mouse technologies in our lab. With help from our colleagues Janet Rossant and Alex Joyner in Toronto, Fig. 2, we used these approaches to generate mutant mice lacking genes involved in T-cell activation and development. Some of these mutants led us right back to apoptosis.

**CDD: How did your work in immunology links to your work on apoptosis in those early years?**

By 1990, our team of Wai Ping Fung-Leung, Marco Schilman and Armin Rahemtulla was successful in generating mice lacking CD4 and CD8 [20–22]. This work was followed by the generation of the Lck and CD28 knockout mice by Thierry Molina, Drew Wakeham and Arda Shahinian [23, 24]. The initial interest in CD28 was instigated by Craig Thompson. Our interest in cell death crystallised in 1991 when Klaus Pfeffer joined our lab and decided to create a mouse lacking TNF receptor-1 (TNFR1) [25]. His study of this mutant demonstrated that TNFR1 was important in the NFκB and JNK signalling pathways that mediate cell survival. Dr Pfeffer's investigation also rekindled my interest in c-rel and inspired me to learn more about the diverse functions of the NFκB gene family. At about this time, the laboratories of David Goeddel, Vishva Dixit and Jürg Tschopp were busy cloning genes downstream of TNFR1 and Fas, while those of Xiao-Dong Wang and David Wallach and others were identifying mammalian genes involved in the apoptotic cascade. My group then created animal models designed to help us understand the details of the signal transduction pathways leading to cell death and survival to.

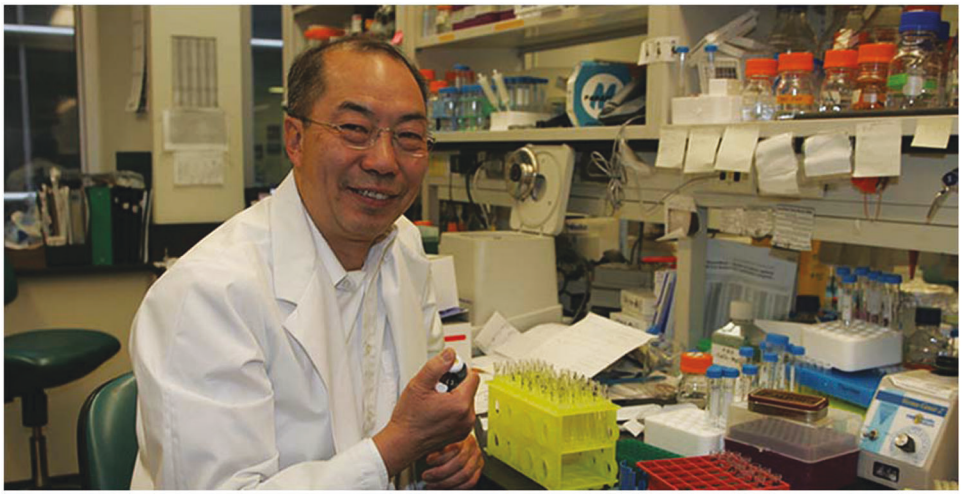

**Fig. 2** Dr Mak performing experiments at the Princess Margaret Cancer Centre in Toronto.

It was a stroke of luck that some of our work on immune cell development and activation overlapped with our studies on the control of cell death. Of significance, Paul Waterhouse in my lab together with Craig Thompson demonstrated that CTLA-4 is a negative regulator of T-cell activation [26], and Razq Hakem showed that the breast cancer gene Brca1 is related to functions of the master tumour suppressor p53 [27]. Atsushi Hirao in collaboration with Steve Elledge discovered that the activation of p53, which is induced by DNA damage is mediated by the checkpoint kinase Chk2 [28]. Jürgen Ruland identified Bcl-10 and MALT-1 as mediators of the signalling pathways leading from T- and B-cell antigen receptor engagement to NFκB [29, 30].

**CDD: Have there been any clinical implications of your immunology work?**

Shortly after the cloning of the TCR genes, we, our collaborators and others launched a series of studies to probe the clonality and lineage of lymphoid malignancies. Collectively, these data demonstrated the utility of TCR gene probes to assess the nature of the T-cell lineage as well as the clonality of the malignancies. Today, we and Naoto Hirano are on the threshold of using customized TCRs in therapies designed to suppress autoimmune diseases or enhance anti-viral immunity and immunotherapy.

Perhaps the most direct links from our immunology work to the clinic lie in the now-familiar concepts of CAR-T (chimeric antigen receptors-T cells) and immune checkpoint blockade. The cloning of the TCR genes served as the foundation for the creation of chimeric antigen receptors in T cells and their subsequent application to biological and clinical problems. The idea of a chimeric TCR was made a reality through the brilliant and determined efforts of Zelig Eshhar, Carl June, Michel Sadelain and others [31, 32]. CAR-T therapies are now approved for the treatment of several hematopoietic malignancies (https://www.cancer.gov/news-events/cancer-currents-blog/2018/tisagenlecleucel-fda-lymphoma). With respect to immune checkpoint blockade, after we showed that CTLA-4 was responsible for the reining-in of activated T cells, several other such regulators were discovered, including PD-1 and related molecules [33]. James Allison then demonstrated that treatment of a tumour-bearing mouse with anti-CTLA-4 antibody induced cancer shrinkage because inhibition of CTLA-4 allowed anti-tumour T cells to continue their attack on the tumour [34]. Anti-PD-1 antibodies are now the standard of care for several malignancies, including melanoma and lung, kidney and bladder cancers, among others. My own team is currently working on identifying agents that can combine with anti-PD-1 therapeutics to enhance their efficacy and combat the development of drug resistance. We are also collaborating with Naoto Hirano at our own institute and Mark Davis at Stanford University on strategies to design and produce customised TCRs directed against antigens expressed preferentially by tumours, especially in the case of non-hematopoietic cancers. Such agents will no doubt bring significant benefits to the clinic.

**CDD: How did your lab originally get into cancer research?**

Our group had shown that we could successfully use molecular analysis and knockout mouse technology to dissect the complex signalling pathways involved in immune cell differentiation, activation and death. We reasoned that the same approaches would yield much valuable information about the equally complex signalling pathways involved in tumorigenesis. After all, I was working in a cancer centre and so was naturally inclined to contribute to its ongoing research initiatives. We believed then, and still do today, that by understanding the molecular pathogenesis of this devastating disease, we can uncover knowledge that may lead to better

diagnoses and rationally targeted therapeutics. We therefore resolved to apply our expertise in generating genetically modified animals to creating mouse models of genes known to be involved in cancer, see Fig. 3.

Several aspects of our early work in this area pointed towards novel therapeutic targets for cancer treatment. For example, our report that the tumour suppressor gene PTEN is a phosphatase that opposes PI3K signalling [35] provided a rationale for targeting PI3K downstream effectors like Akt. Similarly, our findings that BCL-10 and MALT-1, which are encoded by genes involved in chromosomal translocations in MALT lymphomas, are activators of NFκB suggested that targeting elements in this pathway might be a useful therapeutic strategy [29, 30].

**CDD: Tell us about some of your current lines of cancer research.**

Most recently, my team has been focussed on finding innovative ways to kill cancer cells (while sparing normal cells) by exploiting properties unique to the former. A key such approach is to target the metabolic adaptations that tumour cells use to survive under conditions that would kill normal cells. Because these metabolic adaptations allow cancer cells to grow rapidly and avoid cell death, finding drugs that can block these metabolic reactions might kill these tumour cells or make them vulnerable to new types of anti-cancer treatment.

A prime example of this concept can be found in the relationship between isocitrate dehydrogenases (IDH) and cancer. IDH1 and IDH2 are enzymes whose functions are critical for normal metabolism. We, in collaboration with scientists inAgios Pharmaceuticals and others have identified several types of tumour cells, including those of acute myelogenous leukemia (AML), T-cell lymphomas (in collaboration with Philippe Gaulard), and some brain cancers, that contain mutations of IDH1/2, which allow them to produce the abnormal "oncometabolite" 2-HG [36]. We have developed mouse models bearing particular IDH mutations, alone and in combination with other tumorigenic alterations, to define the effects of 2-HG and determine why it causes malignant transformation. Current evidence indicates that 2-HG inhibits enzymes responsible for certain metabolic processes as well as enzymes involved in epigenetic modifications regulating gene expression [37]. Our original interpretation of our in vitro studies of IDH1-mutant AML was that mutated IDH1 proteins might be tumorigenic because the 2-HG they produce can inhibit the DNA demethylase TET2, triggering abnormal DNA methylation. However, our clinical colleagues then pointed out that IDH1 and TET2 mutations are mutually exclusive in AML. Moreover, IDH1-mutant AML and TET2-mutant AML differ markedly in their disease characteristics, for reasons that are a mystery. Another perplexing observation then arose in the context of angioimmunoblastic T-cell lymphoma (AITL), a cancer in which IDH2 mutation plays an important role. This malignancy features a complex microenvironment in which the transformed T cells comprise only a minority of the tumour cells. Unlike the case in AML, TET2 mutations are frequently found concurrently with IDH2 mutations in AITL tumour cells. We continue to investigate this dissimilarity.

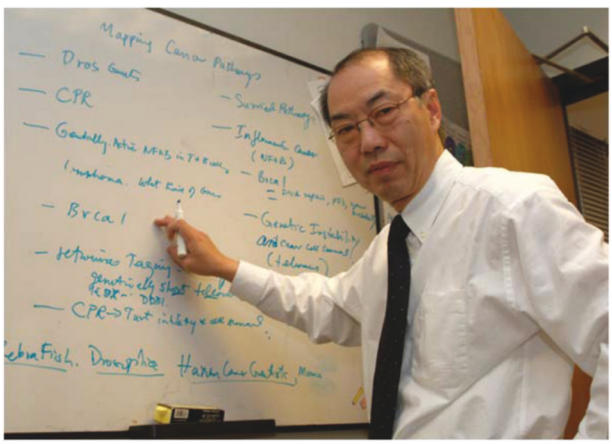


**Fig. 3** Mapping cancer pathways.

Returning to IDH1-mutant AML, we recently unravelled at least part of its mechanism when Satoshi Inoue in my lab discovered that loss of IDH1 function increases the sensitivity of normal hematopoietic cells to DNA damage and impairs HSC self-renewal [38]. Moreover, he found that the mutant IDH1 protein can downregulate the DNA damage sensor ATM by altering the methylation of its histones, and that this alteration is totally independent of TET2. The existence of this novel mechanism has been confirmed in samples from patients with IDH1-mutated AML [38].

Based on our collective work, Agios Pharmaceuticals Inc. has developed inhibitors that block the activity of mutant IDH1/2 enzymes and so prevent 2-HG accumulation. The use of these inhibitors thus reverses the metabolic and epigenetic changes imposed by 2-HG, allowing leukaemic cells to differentiate into 'mature' myeloid cells that are not malignant. Several of these inhibitors are now approved for the treatment of certain subsets of AML patients [39, 40]. We are gratified that our work has helped to bring concrete clinical benefits to those suffering from hematopoietic cell cancers.

**CDD: What is your feeling on the targeting of DNA damage repair pathways as an approach to cancer therapy?**

Exploiting DNA damage repair pathways as potential therapeutic targets for cancer treatment is a double-edged sword because an intact DNA repair machinery is essential

to minimise tumour development and preserve normal cells. On one hand, the inhibition of certain genes in these pathways, like p53 and ATM, can trigger particular cell division checkpoints and induce the apoptosis of cancer cells. On the other hand, interfering with DNA repair may compromise the survival of normal cells and allow mutational events to persist in cancer cells that could reduce genomic stability and promote tumour progression. That being said, I like to think of this strategy as 'fighting fire with fire', and past work has shown that this concept can indeed work. For example, Brca1-deficient breast and ovarian cancer cells have a defect in DNA repair but continue to survive because other DNA repair mechanisms, such as that mediated by PARP, can keep the malignant cells going. So, if one now applies a PARP inhibitor, the cancer cell cannot maintain what little genomic integrity it might have and is induced to undergo apoptosis. It is now an approved option to use PARP inhibitors to treat tumours in ovarian cancer patients with BRCA1/2 mutations [41, 42], Fig. 3.

Despite the above success, however, a major emerging concern is that tumours are heterogeneous with respect to their degree of genomic instability as well as their content of altered oncogenes and tumour suppressor genes. It is thus very difficult to predict the outcome of inhibiting a given target. Moreover, the multiple layers of feedback regulation that govern the functions of DNA repair genes remain a puzzle for the most part. The challenge is to identify key molecules that control cellular responses to DNA damage and whose targeting results in a good therapeutic index. Although such agents might be intrinsically mutagenic, they might still be of benefit to patients with advanced cancers. A current major thrust in my lab is to identify molecules that maintain the genomic stability of advanced cancer cells and so are culprits supporting malignancy. We then look for new classes of inhibitors that are capable of targeting these molecules and removing the insidious support, thereby killing the cancer cells.

**CDD: Can you give us some specific details on these new classes of inhibitors?**

Most advanced cancer cells exhibit aneuploidy, which is caused by genomic instability. The abnormal number of chromosomes in such cells impairs their ability to repair DNA damage and replicate DNA. An aneuploid non-transformed cell is usually doomed to rapid death, but clearly cancer cells manage to overcome the challenge and grow uncontrollably. Thus, a tumour cell must express one or more molecules that allow it to cope with its abnormalities and continue to divide. A tool that could preferentially kill cells exhibiting genomic instability and aneuploidy might therefore efficiently eliminate a tumour while sparing surrounding normal cells. We have carried out extensive molecular screening of aneuploid cells to find these coping molecules and have identified two kinases, PLK4 and TTK, which are essential for the maintenance of aneuploidy.

PLK4 is an atypical member of the Polo-like serine/threonine kinase family. PLK4 functions in DNA damage repair pathways but also regulates centriole duplication and so controls mitotic progression [43]. While normal cells contain only low amounts of PLK4, this kinase is overexpressed in aneuploid tumours, presumably to help them to live with their genomic instability [43]. Thus, targeting PLK4 should knock the support out from under aneuploid tumour cells while preserving normal cells. Based on this hypothesis, we used intensive high-throughput drug screening of aneuploid cancer cells plus medicinal chemistry to isolate a small-molecule chemical called CFI-400945, which is a very potent and specific inhibitor of PLK4 activity. This inhibitor has proven effective in killing cancer cells in breast cancer models in vitro and in vivo [43]. Phase II studies of CFI-400945 for the treatment of various types of aggressive cancers, including metastatic breast cancer, are currently under way. We are also engaged in identifying biomarkers for therapeutic response to CFI-400945 in order to pinpoint those patients most likely to benefit from this agent.

We've used a similar process to isolate an inhibitor of TTK, which is a dual-specificity kinase that participates in DNA damage signalling pathways but is also critical for maintaining the spindle assembly checkpoint during mitosis [44]. TTK is overexpressed in many aggressive solid tumours exhibiting aneuploidy or genomic instability [44]. Our inhibitor of TTK is a small-molecule chemical called CFI-2257. So far, CFI-2257 shows good anti-tumour activity with few toxicities and is proceeding to phase II clinical trials.

**CDD: What are your thoughts on oxidative stress as it relates to cancer?**

We became interested in oxidative stress through our work on Brca1/2. Precancerous cells generate excessive reactive oxygen species (ROS) that must be neutralised by anti-oxidant systems if these cells are to survive, proliferate and eventually transform. As a post-doc in my lab, Chiara Gorrini demonstrated that mouse mammary epithelial cells deficient for Brca1 produced high levels of ROS that reduced the survival of these cells. She then showed that Brca1 interacts with Nrf2, the master regulator of intracellular anti-oxidant signalling, to promote cell survival [45]. Indeed, NRF2 activation is known to promote tumorigenesis and increase the resistance of cancer cells to chemotherapeutic drugs [46]. NRF2 and NRF2-regulated anti-oxidant molecules may therefore represent novel anti-cancer targets. Dr Gorrini went on to potentially solve the mystery of why BRCA mutations, which occur in almost all types of tissues, lead so predominantly to breast and ovarian cancers.

She and her colleagues have identified an oestrogen-linked pathway involving NRF2 that supports the survival of Brca1-deficient cancer cells [47].

Other researchers in my lab, including Dirk Brenner and Isaac Harris, demonstrated that the reduced form of the anti-oxidant glutathione (GSH) is crucial for tumorigenesis. They examined Gclm-deficient mice, which cannot make GSH, and found that malignant transformation was decreased in these animals [48]. They then replicated these findings using BSO, a chemical inhibitor of GSH synthesis, and showed that when they combined BSO with auranofin, an inhibitor of the thioredoxin (TXN) anti-oxidant pathway, a synergistic increase in cancer cell death occurred both in vitro and in vivo. Because various GSH and TXN inhibitors are currently approved for use in treating human inflammatory disorders [49], our mouse work suggests that simultaneous blockage of the GSH and TXN pathways could be a valuable and easily implemented approach to treating cancer patients.

**CDD: Could this approach be applied to other types of disorders?**

Intriguingly, our work on oxidative stress and cancer has circled back to our interest in immunology. After leaving my lab, Dr Brenner established a group focussed on anti-oxidant functions in the context of T-cell responses. Together, we have shown that GSH regulates metabolic activity in T cells in a manner crucial for their effector functions. Upon activation, normal T cells undergo metabolic reprogramming that results in a switch to glycolysis and glutaminolysis for energy generation. GSH-deficient T cells start to activate normally but then cannot undergo the metabolic reprogramming needed to meet their increased biosynthetic and energy requirements. When we tried to induce autoimmune disease in our GSH-deficient mice, the mutant animals resisted the development of autoimmunity but also could not mount anti-viral responses [50]. This work shows that, perhaps surprisingly, GSH is vital for the metabolic reprogramming that has to occur in activated T cells in order for them to divide and mount their responses, be they directed against self-tissues or pathogens.

**CDD: Which of your recent findings have surprised you the most?**

I would have to say that I have been stunned by our demonstration that there is crosstalk between the brain and immune cells. Back in 2011, we joined forces with Kevin Tracey's group to investigate neural signalling and its influence on immune responses. To our astonishment, we discovered that stimulation of the vagus nerve could induce inflammatory T and B cells to produce the neurotransmitter acetylcholine (ACh) [51]. In 2019, Maureen Cox in my lab showed that this T-cell-derived ACh is vital for allowing the entry of these T cells into tissues under viral attack. She genetically engineered a mouse lacking the ability to produce ACh in T cells and observed that the immune cells of these animals could not control chronic viral infections [52]. Specifically, she showed that the enzyme choline acetyltransferase (ChAT), which catalyzes the rate-limiting step of ACh production, is vigorously induced in T cells during virus infection in an IL-21-dependent manner. Deletion of ChAT within the T-cell compartment reduces vasodilation in response to viral infection, blocking the access of anti-viral T cells to the infected tissues.

Dr Cox's work has provided us with the first genetic proof that immune cells need the brain chemical ACh to function. I think that this work provides an entirely new lens through which to look at numerous diseases, including cancer, viral infections and autoimmune conditions. With respect to cancers, a tumour is often surrounded by immune cells that can't break through its defenses, perhaps because the immune cells are not producing sufficient amounts of ACh. In this case, strategies to increase immune neurotransmitter production may be beneficial. The flip side is at play in autoimmune diseases such as rheumatoid arthritis or multiple sclerosis, where the autoimmune T cells attack self-tissues. In this case, a reduction in neurotransmitter signalling may quell the hordes of immune cells invading joints or the central nervous system. Our next research goal in this area is to identify and target the critical receptors that facilitate this crosstalk between immune cells and tissues under attack.

**CDD: Where do you see new challenges for your research?**

It has become very clear that, for the most part, no single agent treatment is going to cure cancer. Some drugs may induce remission but inevitably the malignancy develops resistance to the agent and returns in force. I believe that the only effective strategy will be to find combinations of approaches that differ in their fundamentals but complement each other in their effects such that a cancer cell has no way out and no time to evolve a way out, and so dies.

A case in point is immunotherapy, an approach that has changed cancer therapy forever and generated a paradigm shift in how anti-cancer drugs are discovered. The use of anti-PD-1 antibody to create an immune checkpoint blockade has been the most successful clinical application of this strategy but it still does not work for a significant proportion of treated patients [53, 54]. Even though some immune checkpoint therapies have produced some dramatic benefits, many tumours are refractory to these treatments, and many other patients develop resistance. We are working to identify agents that can combine with immune checkpoint blockade to kill these resistant cancer cells. Numerous clinical trials have been conducted or are under way to test

combinations of anti-PD-1 antibody with chemotherapy, radiation therapy, other checkpoint inhibitors or other types of cancer treatments. For our part, we are in the early stages of setting up a clinical trial to test our PLK4 inhibitor CFI-400945 in combination with an anti-PD-1 antibody for the treatment of aggressive breast cancers. We expect to do the same with our TTK inhibitor in the near future.

At the time of writing, there are over 2000 clinical trials under way examining various combinations of immune checkpoint therapies with other agents. Although enthusiasm still runs high, no dramatic advances have been observed thus far. These disappointing results indicate to me that the problem must be more complex than first thought. For one thing, most combinations on trial have been conceived based on animal models, while others feature only the addition of existing drugs. It is becoming clear that we have to move beyond the tumour itself and ramp up our understanding of the tumour microenvironment (TME). We already know that myeloid immune cells within the TME are important influencers of anti-tumour immune responses, but much more work is needed to dissect their various functions. Unfortunately, the myeloid component of the mouse TME is very different from that in humans, making this aspect of cancer biology difficult to model. Researchers are still keen to develop CAR-T approaches to attack cancer cells because this strategy appears to circumvent any suppression exerted by subverted immune cells in the TME. However, although certain leukaemias and lymphomas have been ameliorated using CAR-T therapy, success in treating solid tumours is still out of reach. The fundamental problem remains that it is difficult to identify antigenic targets specific to a given tumour. That being said, recent attempts to target cancer neoantigens and oncofetal proteins have shown some promise [55, 56].

It would be remiss of me not to mention what is looming as one of the most challenging immunological problems of our current times: the recurring waves of SARS-CoV-2 infection causing COVID-19. We are among the scores of laboratories diligently attempting to figure out how the body responds to this new virus, and how an effective vaccine can be produced. We are hopeful that our expertise in T cells may offer some novel approaches to inducing immunity that will help to protect the world's population from this scourge.

**CDD: Any final thoughts?**

In my opinion, we are witnessing one of the most exciting periods in the history of science. I feel lucky to have participated in the breakneck progress of the last four decades, and I am grateful to the thousands of my fellow scientists who have worked tirelessly to reveal the inner workings of normal and abnormal cells. With technical advances emerging every day, we can rapidly identify novel genes involved in various aspects of cellular processes and even manipulate them. We now need to better understand the heterogeneity of malignancies as well as the modes of operation of other polygenic disorders such as autoimmune diseases. A major future challenge will be to address the intricacy of the communication among gene products in various signal transduction pathways as well as the many levels of transcriptional and epigenetic control that exist. Teasing out these layers of complexity will eventually allow us to fully understand mammalian physiology and pathophysiology, both at the molecular level and the whole animal level. Only by achieving this goal will we able to devise truly effective approaches to treating human diseases.

As you have learned from this interview, my research streams seem destined to diverge, but then merge and bolster each other to bring me full circle to my scientific beginnings. In this way, my career has paralleled the evolution of CDD. The original focus of CDD over a quarter of a century ago was the fields of cell death and differentiation. Today, CDD still publishes reports in these fields, but also in many other research disciplines that seamlessly complement these topics, including neurobiology, immunology and cancer biology. It is this type of melding of research curiosities and efforts that will inexorably lead to satisfying answers to current and future scientific questions.

**CDD: What are your interests outside of scientific research? Do you have any hobbies? Favourite music, books, food?**

I have little time left outside of research. I am quite busy overseeing the science in my laboratory, attending meetings, sitting on various Scientific Advisory Boards, and chairing the Croucher Foundation, a charitable organisation based in Hong Kong that is devoted to supporting research and fellowships in science and engineering. I've also recently made the decision to spend more time in Hong Kong, living up to my billing as a Full Professor at Hong Kong University. You could say that I've undergone a form of 'natal homing' in my golden years. With all of these activities, there is not much chance for leisure. Nonetheless, I make efforts to visit my friends and my children and grandchildren when I can. I used to play some tennis and golf but now can only manage a few games of the latter per year. This, of course, means that I am not going to improve on what is already pretty bad golf to begin with!

My tastes in music, books and food are as varied as my interests in science. My favourite musical selections are classical (Mozart, Beethoven and Bach) but I also enjoy folk songs and some popular music. As for books, I have little time to read anything other than scientific journals. I have spearheaded the writing of a couple of books,

**Fig. 4** Aiming always high!

including a reference book in immunology entitled "The Immune Response" (2005) as well as an undergraduate version called the "Primer to The Immune Response" (2nd edition, 2014). I spend most of my remaining time reviewing manuscripts for journals and sitting on grant review panels.

As far as food is concerned, I eat mainly a Chinese diet and occasionally grab the time to cook some simple country-style Cantonese dishes. I also love Italian and Japanese cuisine, especially spaghetti vongole and sushi. There is no better way to unwind after a long and hectic day than by lingering over an exquisitely prepared meal served in delightful surroundings. And then I throw myself back into my science because there is no more exhilarating feeling than finding the answer to a perplexing research riddle, Fig. 4.

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## Compliance with ethical standards

**Conflict of interest** TWM is a co-founder of Agios Pharmaceuticals, Treadwell Therapeutics and Tcryption.



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