# Tak Wah Mak – Co-Director, Centre for Oncology and Immunology, InnoHK



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*At the Centre for Oncology and Immunology, a flagship of Hong Kong's Health@InnoHK initiative, science converges across disciplines and continents. Under the leadership of Professor Tak Wah Mak, the Centre is advancing a new understanding of how immune responses are shaped, not only by tumours, but by the nervous system itself. From pioneering research in liver regeneration to the evolving frontier of T-cell receptor therapies, the Centre for Oncology and Immunology is redefining the contours of immunotherapy.*

**What is the Centre for Oncology and Immunology, and how does it fit within the broader framework of InnoHK?**

The Centre for Oncology and Immunology (COI), established through a partnership between the Hong Kong government and the University of Hong Kong (HKU) under the Health@InnoHK initiative, is dedicated to advancing the scientific understanding of how the immune system can be harnessed to fight cancer. Since 2010, when the first immune checkpoint inhibitor was approved, immunotherapy has been recognised as the fourth pillar of cancer treatment. Therefore, COI seeks to build on this foundation through collaborative, cross-disciplinary research.

Structured as an international consortium, the centre brings together the leading institutions of the Princess Margaret Cancer Centre in Toronto, the Technical University of Munich, and HKU. This tri-

continental partnership fosters not only the exchange of scientific knowledge and collaborative discovery, but also the training of early-career researchers in Hong Kong, Germany, and Canada. Although the centre's formative years coincided with the disruptions of the COVID-19 pandemic, it has since established a dynamic and expanding research programme.

In addition to exploring strategies to modulate immune responses against cancer, COI has more recently begun investigating the emerging links between neural regulation and immunological control, with particular emphasis on liver cancer, leukaemia, and gastrointestinal malignancies.

**How were the Centre's research areas selected, and how does its international model shape scientific direction?**

The COI's research focus was initially shaped by the specialised expertise of its founding investigators. Professor Anskar Leung and Professor Steven Chan brought deep knowledge in leukaemia while Professor Carmen Wong contributed leadership in liver cancer, an area of interest due to the liver's regenerative biology, which shares parallels with cancer's uncontrolled proliferation. A focus on gastrointestinal cancers was driven by Professor Suet Yi Leung, a leading figure in colorectal and gastric pathology. While rooted in individual specialisms, the centre's international structure, which houses teams from Hong Kong, Germany, and Canada, has revealed shared mechanisms across tumour types to foster integrated research.

A notable example is Professor Alan Wong's work on multiplex CRISPR, developed during his training at the Massachusetts Institute of Technology. His technology, which enables simultaneous editing of multiple genes using variant Cas9 enzymes, has proved instrumental in understanding gene cooperation in complex malignancies like acute myeloid leukaemia. The centre's structure brings together such innovative molecular scientists with clinical and immunological leaders, including Professors Jürgen Ruland, Naoto Hirano, and Tracy McGaha, to form a cohesive network focused on immune-based cancer strategies.

Although immunotherapy has become a recognised pillar of oncology since the approval of anti-CTLA-4 therapy in 2010, its mechanisms and optimal combinations remain poorly understood. For instance, a PLK4 inhibitor developed with Professor Leung not only disrupted leukaemic cell division but unexpectedly triggered immune activation, likely through the cGAS–STING pathway. Despite over 2,000 trials exploring combination therapies, only two mechanistic pairings – CTLA-4 with PD-1 and PD-1 with LAG-3 – have demonstrated consistent efficacy, underscoring the need for deeper mechanistic insight to advance the field.

**How is the Centre contributing to a deeper understanding of immunotherapy's complexity, and what new strategies are emerging beyond CAR-T?**

The immune system's profound complexity and intricate tumour microenvironment continue to shape the course of cancer immunotherapy. This complexity, often underestimated, has contributed to a wave of poorly substantiated therapeutic approaches that failed to deliver the transformative impact many anticipated over the past fifteen years. However, CAR-T therapy emerged as a notable exception.

Operating independently of the tumour microenvironment, CAR-T cells act with precision and autonomy. Like special agents, they are capable of reaching specific targets regardless of context. While only two targets have received approval thus far, CAR-T has delivered impressive long-term remission rates in otherwise intractable haematologic cancers. We have seen 60 to 70 percent in relapsed or refractory B-cell acute lymphoblastic leukaemia and around 40 to 45 percent in diffuse large B-cell lymphoma. Given the absence of alternatives for these patient groups, such outcomes are particularly significant.

Yet, extending this success to solid tumours presents new challenges. The field is now revisiting TCR-based therapies, which engage peptide antigens presented on human leukocyte antigen (HLA) molecules, demanding both target specificity and HLA compatibility. This dual requirement limits patient eligibility and increases complexity, but progress is being made. Glycoprotein 100 (GP100) in uveal melanoma and MAGE-A4 in synovial sarcoma have recently become the first approved TCR, T cell receptor (TCR-T) therapies, suggesting a viable path forward. Central to this evolution is the identification of tumour-associated or viral-derived antigens that are shared across cancers. HPV, for instance, remains a prime target given its causal link to cervical, oropharyngeal, and anal cancers.

In parallel, Epstein-Barr virus has emerged as a key factor in ten percent of gastric cancers and most cases of nasopharyngeal carcinoma in Southeast Asia. Earlier assumptions that regional EBV variants explained this distribution have been replaced by growing evidence pointing to HLA-linked genetic susceptibility. In particular, the mutations HLA-A*02:07, HLA-B*46:01, and HLA-C*01:02 which are prevalent in Southern China yet rare in northern populations, suggest a deep evolutionary interplay between immune genetics and historical viral exposure.

As global life expectancy continues to increase, and with it the incidence of cancers rooted in immune and viral pathways, understanding and targeting these mechanisms becomes ever more

urgent. The future of immunotherapy, therefore, lies not in generalisation, but in precision, guided by immunogenetics, evolutionary virology, and shared antigenic targets across diverse tumour types.

**How is the Centre uncovering the neurological regulation of immune responses, and what new insights are emerging from this line of investigation?**

The relationship between the nervous and immune systems, while long speculated, has only recently begun to be understood in molecular and mechanistic terms. This line of inquiry, now being pursued by the COI, traces its origins to 19th-century physiological experiments by German researchers Jakob Henle and Rudolf Wagner, who observed that stimulating certain nerves connected to the spleen induced organ movement, hinting at a neurological role in immune modulation. For decades, the prevailing assumption was that parasympathetic, cholinergic fibres innervated immune organs such as the spleen. However, the absence of anatomical evidence for such fibres led to decades of uncertainty and halted further exploration.

More recent work, particularly by Dr Kevin Tracey in New York, has reshaped the field. It now appears that vagus nerve signals switch from cholinergic to adrenergic before reaching immune organs. Once there, these sympathetic fibres release norepinephrine, which in turn stimulates T and B lymphocytes to synthesise acetylcholine locally. This model offers a biologically elegant solution to a logistical challenge: acetylcholine has an exceptionally short half-life and cannot travel far. Rather than relying on widespread cholinergic innervation, the body delegates acetylcholine production to immune cells that can respond locally and precisely. Similar observations have been made in the liver. Studies, including those led by Dr Jonas Döring in Sweden, found no cholinergic innervation, but did confirm the presence of adrenergic nerves capable of triggering immune cell-derived acetylcholine release.

This decentralised model of neuroimmune interaction reveals an adaptive mechanism by which the nervous system modulates immune responses through cellular intermediaries. It not only resolves longstanding physiological inconsistencies but also opens new avenues for understanding how neural signals orchestrate immune function across different tissues and disease states.

**How has the discovery of immune-mediated neurotransmission reshaped our understanding of liver regeneration?**

Through its ongoing exploration of neuroimmune regulation, the COI has uncovered a fundamental mechanism underlying liver regeneration, an organ uniquely capable of restoring its original mass with precision. In a recent publication in *Immunity*, postdoctoral researcher Dr Nastaran Fazel Modarres reveals that acetylcholine, a classical neurotransmitter, must be produced by B lymphocytes to initiate this regenerative response. The study builds on the long-observed but poorly understood phenomenon whereby, following removal of 70 percent of liver mass, regeneration begins within minutes and halts exactly at the pre-injury volume, typically within seven days. While the contribution of Kupffer cells and their secretion of interleukin-6 to this process was previously known, what triggered their activity remained unclear.

This research demonstrates that norepinephrine – likely released from sympathetic nerve fibres – activates B cells, prompting them to secrete acetylcholine. This acetylcholine signal is, in turn, required to stimulate Kupffer cells to produce IL-6 and initiate hepatocyte proliferation. The pathway is not redundant: mice lacking acetylcholine production specifically in B cells failed to regenerate liver tissue and did not survive, whereas T-cell deficiency had no such consequence. These findings not only establish a critical role for B-cell-derived acetylcholine in liver regeneration but also introduce a broader conceptual framework, positioning immune cells as functional intermediaries of neural signals in tissue repair. In a system where acetylcholine’s half-life renders long-distance signalling biologically unfeasible, the decentralised relay via immune cells provides an elegant solution. This work opens new avenues for understanding regenerative control and may hold profound implications for the treatment of liver diseases, where repair mechanisms are often impaired.

**Where is the Centre’s neuroimmune research headed next, and how is it positioning these discoveries for therapeutic application?**

Building on a series of foundational breakthroughs, the COI is now focused on defining the receptor-mediated pathways that govern neuroimmune communication and exploring their translational potential. Among the principal targets are seventeen nicotinic and nine muscarinic acetylcholine receptors, alongside five adrenergic receptors, each contributing in distinct ways to the modulation of immune responses. Crucially, sympathetic nerve fibres – particularly those encircling the portal vasculature – appear to exert both gatekeeping and instructive roles, not only regulating access to the liver but also directing T and B lymphocytes to intervene before tumour cells can establish metastatic sites. The emerging view is that these nerves act as both sentinels and coordinators within the hepatic microenvironment.

This paradigm is reinforced by recent publications. A 2019 *Science* study from the group demonstrated that T cells require acetylcholine to dilate blood vessels and facilitate antiviral clearance. A 2023 *Nature Cancer* paper linked the absence of T cell-derived acetylcholine to more aggressive liver tumour growth. The Centre's forthcoming *Immunity* article extends these findings, showing that B cell-derived acetylcholine is indispensable for liver regeneration, its absence leads to regenerative failure and mortality. Collectively, these studies reposition neurotransmitter production as a central immune function with implications across infection, oncology, and tissue repair.

Attention now turns to understanding whether the nervous system also shapes metastatic destination. The liver's prominence as the first site of spread for pancreatic and colorectal cancers has traditionally been attributed to vascular anatomy. Yet the COI's researchers are exploring a more nuanced hypothesis: that sympathetic innervation may actively influence the fate of disseminated tumour cells. This question, at the intersection of neurobiology, oncology, and regenerative medicine, now defines the next chapter of investigation across the COI's teams in Toronto and Hong Kong.

**What experience does the Centre draw upon to advance translational science, and how is it bridging the gap from lab to clinic?**

My focus on translational science stems from a career that spans both academic research and commercial drug development. From 1993 to 2003, I served as Vice President of Research at Amgen during a period of significant transformation, following the success of erythropoietin and granulocyte colony-stimulating factor, two therapies that helped define the modern biotechnology era. I was recruited by Lawrence Souza, a key figure in Amgen's early history, and had the opportunity to help shape the company's research direction during its second wave of innovation.

After leaving Amgen, I co-founded several biotechnology companies – three of which went public – including Agios Pharmaceuticals, which developed four first-in-class therapies targeting AML, cholangiocarcinoma, glioma, and other indications. Agios also introduced the first targeted therapy for brain tumours and pioneered an activator of pyruvate kinase-R, now approved for treating paediatric anaemia.

More recently, my academic hospital in Toronto has launched two spin-offs: Treadwell Therapeutics, which has progressed three small-molecule candidates – two of which have received fast-track designation from FDA, with one currently under Type C review – and TCRyption, a

platform developing TCR-bases therapies designed for broader patient populations.

These experiences inform how we structure the COI's translational ambitions combining real-world regulatory and commercial insight with deep scientific discovery to move innovation forward.

**How can TCR therapies become more broadly applicable, and what innovations are needed to ensure their long-term viability?**

TCR-bases therapies have already demonstrated significant clinical promise, particularly in cancers that have long resisted conventional treatment. Although my foundation lies in basic science, close collaboration with clinicians has allowed the identification of outlier patient responses, isolation of the relevant TCRs, and evaluation of their potential for broader therapeutic application. This work contributed to the approval of a TCR-bases therapies for metastatic uveal melanoma – an especially aggressive cancer – targeting the GP100 antigen. Still, commercial viability remains constrained by narrow indications, high costs, and the logistical demands of personalised, cell-based manufacturing.

To address these challenges, emphasis is now placed on identifying tumour-associated targets that are conserved across multiple cancer types – pancreas, liver, colon, lung – so that a single TCR could benefit significantly larger patient populations and justify broader infrastructure investment. In parallel, regulatory flexibility and advances in clinical design are helping overcome biological limitations, particularly those linked to HLA restriction. Early trials using single TCRs, such as those targeting the E7 peptide in HPV-positive cancers, showed encouraging response rates, yet relapse was common due to tumour immune evasion, including the loss of β2-microglobulin or TAP1/TAP2. In response, FDA now permits the use of multiple TCRs, targeting both HLA class I and II molecules, a development that may reduce immune escape and prolong therapeutic effect.

As manufacturing technologies mature and costs continue to decline, the field is gradually evolving from bespoke, narrowly targeted interventions to more scalable, multi-indication platforms. By pairing biologically informed target selection with advances in logistics and accessibility, TCR-bases therapies may yet realise their full potential, not only as breakthroughs for rare and refractory cancers, but as durable, broadly applicable treatments across tumour types. I am a basic scientist in my mind, but a drug developer in my heart, and that perspective continues to guide how this therapeutic frontier is pursued.

**In your opinion, what should Hong Kong prioritise to foster a globally competitive biotech innovation landscape?**

To establish Hong Kong as a serious global contender in biotechnology, it is not enough to allocate funding alone. What is required is the cultivation of a culture that embraces risk, supports long-term innovation, and fosters scientific originality. In the earlier decades of biopharmaceutical development, pharmaceutical companies thrived by addressing well-defined unmet needs. But by the 1990s, the readily accessible targets had largely been exhausted, and innovation began shifting toward biotech. Companies like Amgen and Genentech – once considered bold outliers – proved that with scientific conviction and persistence, success was possible even with approaches the industry had dismissed. Therapies such as EPO, G-CSF, and trastuzumab went on to become multibillion-dollar products despite initial scepticism.

The current biotech environment, however, is facing headwinds. Venture capital has become increasingly cautious, with many investors either retreating or narrowing their focus to existing portfolios. As a result, early-stage companies are now expected to present near-pivotal clinical data – often supported by regulatory dialogue with FDA – before attracting meaningful funding or partnerships. This high threshold makes it more difficult for early innovation to progress, and risks leaving high-potential science stranded.

What is needed now in Hong Kong is a framework that connects academic science to translational pathways, encourages scientific risk-taking, and maintains strong links with global regulatory and investor ecosystems. Capital alone is not enough. Biotech has always progressed by challenging orthodoxy, tackling complexity, and advancing ideas that fall outside conventional lines. If that spirit is supported, the region has the potential not just to generate research, but to drive innovation with global therapeutic impact.

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