T Cells Revolutionizing Cancer Immunotherapy

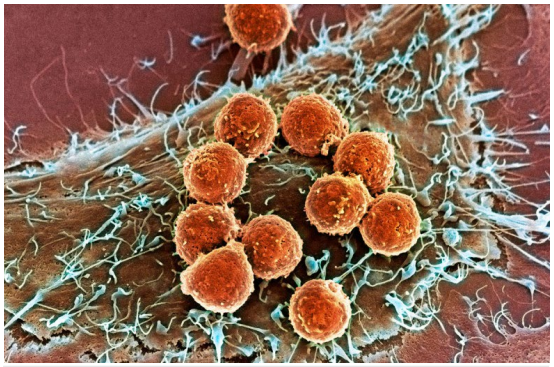
Interview with Kai Wucherpfennig, MD PhD, the new scientific consultant to Nextech Invest

Kai Wucherpfennig, MD PhD, is Professor of Microbiology and Immunology and Chair of the Department of Cancer Immunology and Virology at the Dana-Farber Cancer Institute, and Professor of Neurology at Harvard Medical School, and since 2015 exclusive scientific consultant of Nextech Invest.

Prof. Wucherpfennig's research focuses on the discovery of genes that control the activity of cytotoxic T cells in the tumor microenvironment drawing insights for the development of next-generation cancer immunotherapies. He has received a number of honors and awards, including his election as a Fellow in the American Society for the Advancement of Science, his election as a member of the Henry Kunkel Society at Rockefeller University, and his election as a member of the American Society for Clinical Investigation. He received his MD and PhD degrees from the University of Goettingen and completed post-doctoral work in immunology at Brigham & Women's Hospital, Harvard Medical School, and Harvard College. Prof. Wucherpfennig serves as an advisor to a number of immuno-oncology companies.

You started your scientific career in Germany and transitioned to the US East Cost? What attracted you to the US and particularly to Boston?

I obtained my medical training and doctoral degree at the University of Goettingen and spent the last year of medical school in the US, both in Chicago and in Boston. I was very intrigued with how medicine and science are integrated in the US, in particular in Boston. Most impressive to me were the high level of the science and the amazing pace of discovery. At the time, German medical schools had an 80:10:10 model for clinical work, teaching, and research. In Boston, faculty spent 80% of their time in the laboratory and only a fraction in the clinic. This enabled them to be at the cutting edge of their research field and this was, of course, where I wanted to be. I came back to Boston because I wanted to do the most exciting science I could envision.



A squad of white blood cells, T cells (orange) have spotted a cancer cell and docked on it in order to destroy it.

Credit: Memorial Sloan-Kettering Cancer Center

The Dana-Farber Cancer Institute has a long standing tradition in the field of immuno-oncology. What were the institute's contributions to the early development of the field and what role does it play now?

I joined Dana-Farber in 1995 because it had the strongest immunology program in Boston, in particular for human immunology. Immunology has been part of the fabric of the institute for many decades and there is a strong emphasis on discovery of immunological mechanisms relevant to cancer. Many key principles of immune function were discovered here and this long-term investment in immunology is now paying rich dividends. This includes key discoveries on the CTLA-4 and PD-1 pathways that have led to the FDA-approved immunotherapies. These immunotherapies enhance immune function against tumors by releasing the brake on a key immune cell population, namely T cells that can detect and kill tumor cells. An example is the antibody ipilimumab, which can induce durable responses lasting for many years in patients with metastatic melanoma. Many discoveries on this immunological pathway were made here, and a Dana-

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Research abstract

Kai W. Wucherpfennig, MD PhD

T cells play a central role in cancer immunotherapy. They have the ability to specifically detect and selectively destroy cancer cells following recognition of a tumor antigen. We work on the mechanisms that constrain the activity of cytotoxic T cells in the tumor microenvironment. We have identified a series of negative regulators of T cell function in tumors. Our work focuses on the molecular mechanisms by which these genes inhibit T cell function against tumors and the development of novel cancer immunotherapies based on these insights.

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Farber investigator led the pivotal phase 3 trial leading to approval of ipilimumab, now marketed as Yervoy by Bristol-Myers Squibb.

Could you describe the focus of your research at Dana-Farber and what its potential contribution to cancer drug development is?

The laboratory that I am heading at Dana-Farber studies how T cells detect and kill tumor cells. Yet, some tumors have the ability to trick the immune system and remain undetected by the T cells. We are particularly interested in the mechanisms that inhibit the function of these critical immune cells in human tumors. Targeting of these immunosuppressive molecules offers opportunities to enhance immune system function in tumors as we have seen with the approval of ipilimumab and more recently the PD-1 inhibitors nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda, Merck & Co).

Why are T cells so crucial in fighting cancer? What are some of the current approaches to use them in cancer therapy?

Tumor-specific T cells are at the center of the current revolution in cancer immunotherapy.

T cells recognize peptides on the surface of tumor cells (a peptide is a fragment of a protein). Each peptide has a unique sequence and T cells can read this sequence similar to a barcode. The key point is that tumors acquire many mutations that change the sequences of these peptides, meaning that the barcodes become distinct. T cells can recognize the mutant peptides and thereby precisely distinguish tumor cells from healthy cells. No other drug or therapeutic approach can achieve this level of specificity, and this specificity translates into improved efficacy and lower side effects compared to other approaches to cancer therapy. I believe that we will be able to use the inherent specificity of T cells for tumor cells to develop therapies that eradicate tumors without causing significant damage to healthy tissues. In contrast, chemotherapy indiscriminately kills all dividing cells which causes the well-known severe side effects associated with this therapy. What is exciting is that there are many ways to enhance the activity of such tumor-specific T cells. These include targeting of molecules that inhibit T cell function, vaccines that stimulate such T cells, and transfer of genetically engineered T cells into cancer patients. We have evidence from clinical trials that all of these approaches can work.

> *"Immunotherapy will become a central component of cancer therapy"*
>
> *- Kai W. Wucherpfennig, MD PhD*

If you were to name the scientific discovery that made an impact in T cell-based cancer drug development, what would that be?

We have developed a new approach to discover targets for cancer immunotherapy that improve the function of tumor-specific T cells. This approach utilizes new genetic libraries that allow many therapeutic targets to be evaluated at the same time. Importantly, this discovery process can be performed directly in tumors. This allows us to discover genes that impair T cell function in tumors. We are currently using this approach in my laboratory for systematic discovery of combination immunotherapies.

In your view, how will cancer therapy change in the next five to ten years?

Immunotherapy will become a central component of cancer therapy. In melanoma, an immunotherapy (PD-1 antibody) was already shown to have much higher activity than chemotherapy. As a consequence, immunotherapy is already a front-line therapy in melanoma. It is also apparent that many different approaches to immunotherapy are working in animal models and in patients. As a consequence, we are witnessing a very fast pace of discovery and translation of many discoveries into clinical trials. In the future, oncologists will have a wide repertoire of immunotherapy tools at their disposal. Surgery will continue to be an important part of cancer care, but immunotherapy will progressively replace chemotherapy. This means that patients will suffer fewer side effects and emerge healthier at the conclusion of treatment.

What do you consider as some of the biggest challenges in transforming cancer into a curable disease?

Many patients with cancer are already being cured if their tumor has not yet spread to other parts of the body (metastasized). Metastatic cancers continue to be far more challenging to treat because of the tremendous diversity in the biological pathways that drive tumor growth. Scientists used to think of a cancer as a clone of cells that are abnormal and that most cells in a tumor were very similar to each other. We are now discovering a tremendous diversity among the tumor cells in a given patient. This tremendous diversity means that some cells can be resistant to a therapy and grow out later as a treatment resistant tumor. Immunotherapy has the potential to treat such metastatic tumors because T cells typically recognize multiple mutant peptides. This means that immunotherapy is a combination therapy. Simultaneous targeting of multiple antigens makes it less likely that stray tumor cells remain following treatment.

Barack Obama and Joe Biden recently announced the launch of the Cancer Moonshot program. What impact do you envision that this program will have in advancing cancer therapy?

The scientific opportunities have never been greater, but funding by the National Institute of Health in the US has contracted significantly over the past ten years. This means that currently not all exciting ideas can be pursued because of lack of funding. The country needs to reaffirm its commitment to biomedical discovery so that we can develop the next generation of cancer therapies at a rapid pace.

Glossary

Melanoma – malignant tumor found predominantly in the skin that arises due to uncontrolled growth of pigment cells called melanocytes.

T cell – a type of white blood cell that plays an important function in the immune system to recognize and destroy virus-infected cells and cancer cells.

Immune checkpoints – *e.g.* PD-1, CTLA-4 – regulate the immune system's response. To remain undetected by the immune system many tumors turn down the immune response by interfering with T cell activity. Checkpoint inhibitors such as ipilimumab counteract this effect and make the tumors visible to the immune system.

For more information on Kai Wucherpfennig's research, visit his lab website **here**.