

Editorial

Leland W.K. Chung: a mentor of great compassion and vision-Preface of the special issue in memoriam and celebration of Leland W.K. Chung from special issue senior guest editor

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I first met Dr. Leland W.K. Chung (**Figure 1**) when I was a graduate student at the University of Colorado, Boulder in 1984. Leland and his wife, Dr. Haiyen Zhou, were friends of my thesis advisor, Dr. Noboru Sueoka, and Noboru's wife, Dr. Tamiko Kano-Sueoka. At that time, Leland was an associate professor at the School of Pharmacy, which was housed on the Boulder campus. I first learned about the role of stroma as a mediator of prostate growth from a lunchtime lecture that Leland gave to the Sueoka lab. Although I was in a PhD program with a major focus on developmental biology, Leland's lively presentation was a bracing moment in my early understanding of the importance of the reawakening of developmental pathways in mature organs as the basis of disease. Largely because of the impact of this talk on my thinking about biology, I decided to take up a postdoctoral position in Leland's new lab at the University of Texas M.D. Anderson Cancer Center in 1987, after completion of my doctoral studies. I was a member of Leland's lab for a little over three years, when I left for my first faculty position in Boston. Throughout my career, Leland remained my closest and most valued mentor, helping me along the way many times with his insight and generosity.

Leland W.K. Chung was a renowned basic and translational scientist in the prostate cancer field, widely considered a pre-eminent thought-leader in modeling and therapeutic targeting of prostate cancer metastasis, particularly to

bone. He was among the very first to propose, and subsequently demonstrate, that stromal-epithelial interactions are required for hormone-responsiveness of epithelial tissues in accessory sex organs, for prostate carcinoma growth, and for prostate cancer progression to lethal disease. This line of research, which continued throughout Leland's career, led to an improved understanding of mechanisms of hormone-sensitivity in the normal state, to insight into the origin of age-dependent prostate disease, and the manner in which the tumor microenvironment can be a major driver of malignant epithelial growth and carcinoma progression. This body of work is considered seminal in the history of cancer biology, and Leland is recognized as one of a very few pioneers in the study of the tumor microenvironment in solid tumor systems. For many years, the idea that the microenvironment played any significant role *at all* in cancer was considered heretical and a violation of the view that cancer cells were autonomous entities, growing and invading the interstitial spaces and suffering little impact from their external condition. Today it is firmly established that the tumor microenvironment is critical for cancer progression and metastasis, that profiling the microenvironment can provide prognostic information that profiling the actual tumor does not, and that innovative treatment strategies can be developed from studying microenvironment-cancer interactions and deploying those insights clinically. This acknowledgement of the



Figure 1. Leland W.K. Chung (left) and Michael R. Freeman (circa 2015). Photocredit Dr. Mary C. Farach-Carson.

importance of the work in this area is seen in activities sponsored by major cancer organizations, such as the AACR Innovator Award for Research in the Tumor Microenvironment, and the NCI-sponsored Tumor Microenvironment Network. There are only a handful of investigators who can be considered to have launched this line of research. Beyond Leland Chung, Gerald Cunha and Mina Bissel, this was a largely unpopulated research area for many years.

Leland is also considered one of the most creative developers of model systems to study mechanisms of disease progression in prostate cancer. These models include tissue recombination systems, the ARCaP M/E model, which is used to study epithelial-mesenchymal transition in advanced disease and androgen receptor reprogramming, and the C4-2/C-42B progression system, which is one of the most widely used in the field for modeling castration-resistance in the context of lineage plasticity. A number of novel concepts were es-

tablished using these models, including identifying the role of stromal androgen receptors in tumor promotion, and the concept that prostate cancer cells metastatic to bone can take on the properties of bone cells. This last concept, called “osteomimicry”, is now recognized as a fundamental property of carcinoma cells that migrate to and proliferate in the skeleton. Leland and his collaborators pioneered the concept of osteomimicry.

Aggressive prostate cancers typically demonstrate a strong tropism to bone, and it is metastasis, not clinically localized prostate cancer, which is the major contributor to death from the disease. Translational studies in this field have been hampered by a lack of model systems to study the mechanism of prostate cancer metastasis to bone, and of devising ways of therapeutically targeting metastatic tumors. Leland made significant strides in improving this scenario during his career. However, more recent research truly broke new ground in this area. He and his colleagues described a new model of cancer tropism involving the activity of the bone cytokine RANK-L. This line of research has a number of extremely novel elements, including (1) the demonstration that a single cytokine is capable of driving an indolent tumor cell to the bone and soft tissues; and (2) that tumor cells expressing RANK-L can act as powerful metastasis-initiating cells (“MICs”), in which non-metastatic cells are co-opted into tumor formation at metastatic sites. These results also apply to cells of non-prostatic origin. These findings demonstrated that the metastatic niche can be seeded by a very small number of cells, which can then recruit bystander tumor cells to form metastases. Although he primarily worked in model systems, Leland’s group assembled evidence that this metastasis-initiating mechanism operates in human cancer. Like many of Leland’s accomplishments, these discoveries require a rethinking of assumptions by workers in the field about how metastases, particularly to bone, occur. In concert with his work on metastasis, Leland led a NCI P01 program project grant focusing on prostate cancer bone metastasis for 16 years. This team of investigators was highly productive, with many innovative concepts, technologies, and clinical trials emerging from the studies conducted with funding from the P01 mechanism.

In memoriam, Leland W.K. Chung

Leland was a highly translational basic scientist, in the sense he was adept at taking insights from model systems and applying them to the human condition. His more recent work within the strong clinical environment at Cedars-Sinai resulted in studies meant to move laboratory discoveries in directions that will benefit patients. These include innovative methods to profile circulating tumor cells and to image metastases in vivo. One of his final papers, which is still in press, was the demonstration of a novel method of tumor targeting using a modified version of the ubiquitous cholesterol-lowering agent, simvastatin. This paper was accepted a few days before Leland passed away.

For those of us who were fortunate to have trained with Leland, and who have been commiserating about the loss of this towering personality in our lives, the theme that has emerged as his greatest impact on us personally has been as a role model for how one should engage with trainees and colleagues. Leland was unfailingly sparkling in demeanor,

seemingly always thrilled to see a student or colleague knock unannounced at his door, an endless source of optimism and determination, and a gentle spirit that powerfully conveyed affection and confidence in young investigators and their potential. Over many years, when Leland spoke to me of the future of my career, even in periods of self-doubt and failure, he never wavered in his conviction that I had only taken a few steps, and that the path ahead was bright and full of accomplishment. As Leland's trainees speak with each other about our own experiences with him, it turns out he appears to have had the same conversation with all of us. We will greatly miss this irreplaceable figure in our lives.

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