

Editorial

Targeting the Heterogeneous and Plastic Tumor Ecosystem in Prostate Cancer — A *CHP* Special Issue Dedicated to Dr. Leland W. Chung

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Human cancers represent a live ecosystem. Both primary tumors and disseminated diseases are comprised of malignant and benign cells in the tumor microenvironment or TME. Cancer cells, non-cancer cells, and non-cellular components (e.g., extracellular matrix or ECM, ECM rigidity or stiffness, interstitial fluid volume and pressure, inflammatory cytokines, oxygen tension, and nutrient availability) in the TME constantly interact to drive tumor evolution and progression. Both the cancer parenchyma and TME should be targeted holistically to achieve enduring therapeutic efficacy and hence long-lasting clinical benefits.

The concept that non-malignant cells and the environment (e.g., chronic inflammation) surrounding the tumor parenchyma may play a role in aiding tumor development and cancer progression was proposed by the pathologist Rudolf Virchow in the 1860s. However, it is the pioneering work by scientists including **Dr. Leland W.K. Chung** to experimentally demonstrate the essential and causal functions of stromal cells and stromal components in facilitating tumor growth and cancer metastasis. Dr. Chung, a scientific giant working primarily on prostate cancer, was among the first to evince the importance of tumor stroma in driving prostate cancer progression and bone metastasis. Please visit <https://ascopost.com/issues/august-25-2021/leland-chung-dies-at-80/> and [https://urologichistory.museum/the-scope-of-urology-newsletter/issue-6-summer-2021/leland-w.-chung-phd-\(1940-2021\)](https://urologichistory.museum/the-scope-of-urology-newsletter/issue-6-summer-2021/leland-w.-chung-phd-(1940-2021)) for an appreciation of Dr. Chung's scientific legacy.

Prostate cancer is a disease of aging; the incidence increases dramatically in men over 50–55 years old and prostate cancer is the most common non-cutaneous cancer in men in the U.S. and most other developed countries.

Currently, the mortality rate of prostate cancer is second to that of lung cancer. Most of the cancer-related deaths are caused by metastatic disease. One of the most exciting developments in modern medicine has been the step-by-step reconstruction of the disease in combination with molecular analysis of genetics, cell biology, and animal models. Dr. Chung is recognized as an early pioneer in establishing the importance of stromal-epithelial interactions by unveiling the key role of the androgen receptor in the stroma in driving prostate gland development. His later work in prostate cancer advanced the concept of a “vicious cycle” between prostate cancer and its microenvironment; he demonstrated the critical role of TME in driving progression to androgen independence and metastasis to bone. As an example, the C4-2/C4-2B model, developed by Dr. Chung, is among the most widely used in the field for modeling castration resistance in the context of clonal selection and understanding therapy-driven cellular plasticity. As another example, the metastatic prostate cancer patient-derived ARCaP cell model, developed by Dr. Chung, represents the full spectrum of cancer cell heterogeneity and was used to demonstrate the functional roles of epithelial-mesenchymal transition and androgen receptor reprogramming to promote prostate cancer progression.

Dr. Chung used many of the unique models developed in his lab to advocate for the novel concept of “osteomimicry”, which is now recognized as the manifestation of lineage-plastic properties of carcinoma cells that migrate to, and proliferate in, the skeleton. In addition, Dr. Chung’s group demonstrated critical roles for a variety of extracellular matrix, cytokine, and signaling factors to orchestrate tumor growth and metastasis. For example, they reported a new model of “cancer tropism” involving the bone cytokine RANK-L, which is capable of driving indolent prostate cancer cells to the bone and prostate cancer cells expressing RANK-L can act as powerful metastasis-initiating cells, which then attract low-metastatic cells to the bone metastatic sites.

In brief summary, Dr. Chung has made major scientific discoveries in understanding prostate cancer biology and demonstrating the indispensable roles of heterotypic cancer cell-stromal interactions in driving bone metastasis and for developing new imaging technologies for cancer diagnosis and new gene therapies to kill metastatic prostate cancer cells.

We dedicate this Special Issue of CHP to Dr. Chung in recognition of his scientific achievement and in celebration of his legacy.