

Pioneering the Discovery and Development of Novel Therapeutics to Prevent Metastasis



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A NEW PARADIGM IN CANCER TREATMENT

The field of cancer therapy is an area of intense investment that is driving drug discovery and development. This burgeoning area of research and development has yielded tremendous scientific advances. Thanks to the growing understanding of cancer biology we have seen considerable progress from chemotherapy, to pioneering drugs like Herceptin®, to PD-1 inhibitors and even genetically engineered immune cell therapies using chimeric antigen receptor (CAR) and T-cell receptor (TCR) technologies.

Despite these advances, cures remain elusive for most patients. Investigators have been exploring new paradigms in cancer treatment that may provide much needed, more effective solutions that save or prolong patients' lives.

Even with the development of novel therapies that have improved patient outcomes and can extend patient lives by months or years, the tragic reality is that a majority of patients, even many deemed

"cured", relapse with lethal distant metastasis. This reality motivates the research focus at HiberCell, where we are looking to complement progress in primary tumor and/or stage IV metastatic cancer treatment with therapeutics derived from our foundational understanding of disseminated tumor cell dormancy biology and its role in cancer metastasis.

DORMANCY, RELAPSE AND METASTASIS

Tumor cell dormancy refers to an adaptive response of a cancer cell, after it detaches from the primary tumor and disseminates throughout the body. These disseminated tumor cells (DTCs) enter a state of dormancy or "hibernation". In this dormant state, DTCs spend most of their time not dividing. DTCs survive like this via the activation of an adaptive survival pathway that facilitates cellular crosstalk between DTCs and host cells in the surrounding microenvironment.

DTCs live in the bones, lungs and other hospitable tissues of patients. Eventually, these dormant DTCs "awaken"

in response to specific cues from their surrounding microenvironment. Upon reawakening, these DTCs can trigger metastasis, even in the absence of the primary tumor that had been successfully treated months or years prior. This hibernation capacity of DTCs speaks to the temporal context of the biology we are targeting and is the root of our company name, HiberCell.

As we continue to define the innate features of DTCs, their requisite relationship within the niche that they occupy and further associate the endowed survival advantage(s) bestowed upon these cells, we hope to more thoroughly understand their impact on cancer metastasis in patient disease.

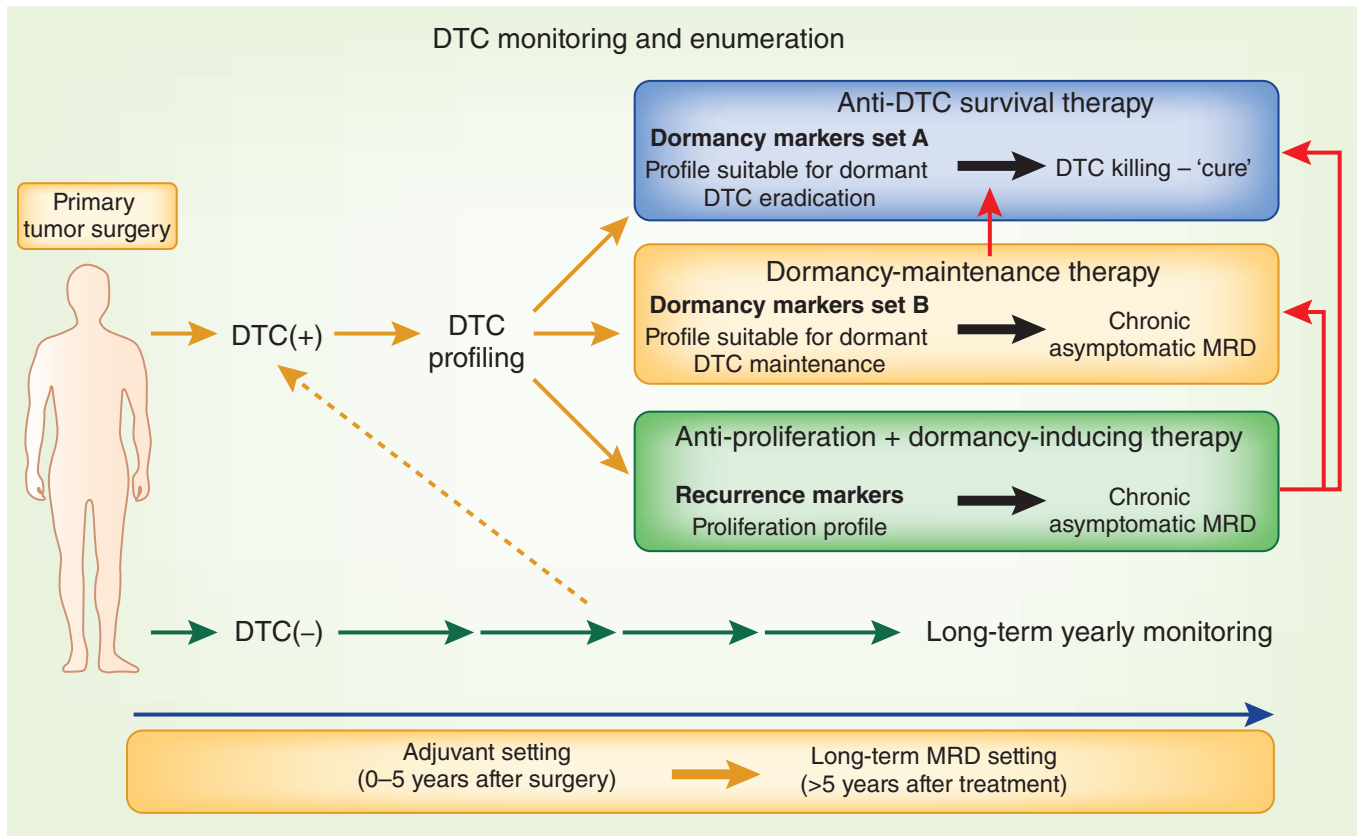
Importantly, in their dormant state, DTCs appear to be invisible to the immune surveillance system and as such can live for years in an asymptomatic state without detection. Given this unique adaptive phenotype they also evade standard of care chemotherapeutics, which largely target proliferative tumor cells in loco-regional or distant organ microenvironments.

Academic researchers have demonstrated that the presence of DTCs is highly predictive of an increased risk of metastasis¹. In fact, when DTCs are identified in cancers including breast, lung, prostate, colorectal, gastric and esophageal cancers, their presence has been correlated with reduced metastasis-free survival.

HiberCell's emergence as the leading tumor dormancy company is the culmination of progress on multiple fronts including a refined understanding of the foundational role DTCs play in systemic cancer biology. To accomplish this, we are pursuing the development and validation of novel tools that permit better detection, isolation as well as genomic annotation of key survival mechanisms that are activated within these dormant DTCs and contribute to their reawakening.

NEW THERAPEUTIC OPPORTUNITIES

Metastatic disease often emerges years or decades after successful surgery or adjuvant treatment. The ability to identify and eliminate DTCs,



Metastasis Awakening: Targeting dormant cancer.

UNDERSTANDING THE BIOLOGY OF DORMANT DTCs AND THEIR “ECOLOGICAL NICHES” WITHIN TARGET ORGAN TISSUES IS AN IMPORTANT ELEMENT OF OUR RESEARCH STRATEGY.

and more importantly dormant DTCs, represents a significant opportunity to prevent cancer relapse and metastasis. This strategy differs considerably from other cancer treatment paradigms that have focused on treating primary tumors and proliferative advanced metastatic lesions.

Dormant DTCs are metabolically active and establish a specific crosstalk with the surrounding tissue microenvironment to enable their survival and quiescence programs. Understanding the biology of dormant DTCs and their “ecological niches”

within target organ tissues is an important element of our research strategy.

Through the use of biomarkers, single DTC genetics and transcriptomics, we are defining the distinguishing characteristics of DTCs with a focus on clinically meaningful dormancy mechanisms and endpoints. When it comes to our therapeutic portfolio, we believe that targeting these signature mechanisms of survival and reawakening with a monotherapy or combination therapy will make it possible to extend disease-free and metastasis-free intervals while

improving patient outcomes through a reduction in metastatic recurrence rates.

HiberCell is passionately committed to accelerating this new paradigm in cancer treatment forward through research that involves modulating novel therapeutic pathways that we believe will build on, and combine with, current cancer treatments to provide meaningfully improved outcomes to cancer patients.

REFERENCES

1. Braun, S. *et al.* A pooled analysis of bone marrow micrometastasis in breast cancer. *N. Engl. J. Med.* **353**, 793-802 (2005).