

PREDICTING PATIENT RESPONSE TO CANCER TREATMENTS VIA MONITORING CULTURES OF CIRCULATING TUMOR CELLS

A collaborative study led by scientists from the Mechanobiology Institute (MBI), Singapore MIT Alliance for Research and Technology (SMART) - BioSystems and Micromechanics (BioSyM) and the National University Hospital at the National University of Singapore has led to the development of a novel technique for culturing circulating tumor cells (CTCs). This assay could be used for predicting cancer treatment outcome. Their work is published in *Oncotarget* on 6 May 2015 ¹.

Presence of Circulating Tumor Cells correspond to worsened disease status

Cancer is among the leading causes of death in Singapore today. More than a hundred types of cancers have been identified, each with distinct characteristics and treatment challenges. Cancer results when otherwise healthy cells divide uncontrollably as a result of genetic anomalies. This will produce a mass of abnormal cells called a tumor.

As the cancer develops, cells may escape from the tumor and into the surrounding blood vessels, alike seeds that leave a plant for dispersal. These cells, termed as CTCs, may eventually squeeze through the blood vessels and land at new sites to form new tumors. The process is known as metastasis, and is associated with poor patient prognosis and high mortality rates.

Enriching CTCs in blood - 'Compiling needles in the haystack'

However, most conventional methods used to isolate CTCs from whole blood lacked efficiency, owing to the low populations of CTCs in blood. Some procedures also exclusively select for sub-populations of CTCs, further leading to reduced CTC counts.

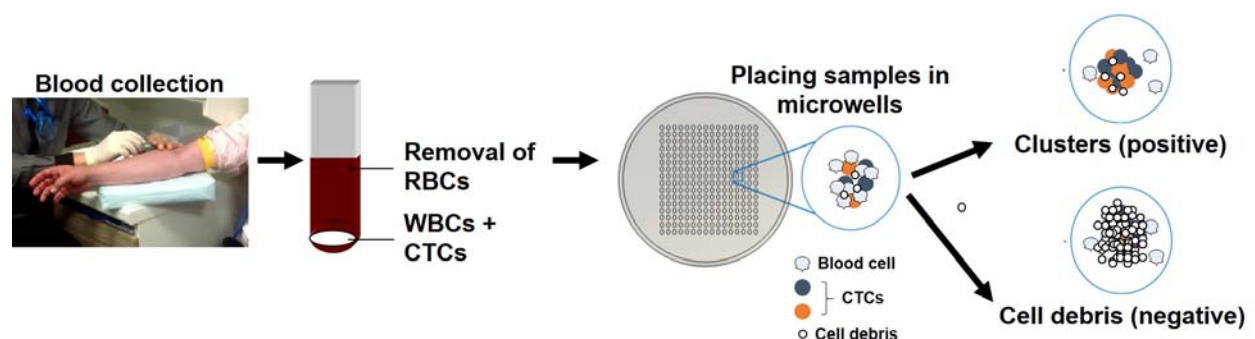
In an attempt to overcome these setbacks, MBI researchers have developed a novel methodology for efficiently culturing CTCs from whole blood. In this method, CO₂ lasers were first used to engrave microwell patterns on a petri dish. Whole blood samples from

patients with early or advanced stage breast cancers were first treated to have their red blood cells removed before being deposited into the patterned dishes. The geometry of the microwells, the non-adherent nature of the dishes, and the oxygen-deficient growth conditions were found to favor cancer cell growth. As the cancer-like cells grew, the other non-cancerous cells such as white blood cells do not proliferate or underwent cell death over time. The authors discovered that after two weeks, cell clusters consisting of cells with characteristics of CTCs were formed. Mechanistically, these cells had become increasingly invasive while their genetic profiles revealed cancer-causing alterations or mutations.

Ability to form CTC clusters correspond to patient survival period

The authors conducted tests over 220 clinical samples from both localized and metastatic cancers, and achieved over 60% success rate in culturing these CTCs. From these data, it was suggested that the development of cell clusters could be affected by the duration and nature of treatment undertaken by the patients. Cluster formation progressively declined with increase in treatment duration. As noted by the authors, this could be due to the patient's response to therapy.

The ability to capture and efficiently grow CTCs from a blood sample will provide researchers and clinicians valuable tools to investigate the best therapy options for the patient. Along with other benefits such as shorter culture durations, low quantities of sample needed and a minimally invasive procedure, this technique is well-poised to be an ideal tool for assessing the status of cancer as well as for predicting the efficacy of specific treatment regimes.



¹ Khoo, B. L. *et al.* Expansion of breast circulating cancer cells predicts response to anti-cancer therapy. *Oncotarget* (2015 (in press)).