Scientists at SMART Centre developed novel biochip for identification and enrichment of circulating tumour cells (CTCs)

(Details published in Scientific Reports (Nature Publishing Group))

Singapore scientists, lead by Prof Chwee Teck Lim (NUS) and Prof Jongyoon Han (MIT), members of Singapore-MIT Alliance for Research and Technology, in collaboration with National Cancer Centre Singapore (NCCS) and National University Hospital (NUH), developed a novel microfluidic biochip for the ultra-high throughput separation of circulating

tumor cells (CTCs), rare cancer cells found in blood of cancer patients, for cancer diagnosis and prognosis. The findings, to be published in *Scientific Reports* (Nature Publishing Group), are a huge step towards early cancer detection and treatment monitoring.

CTCs, cancer cells of solid tumor origin that are shed into the blood stream from tumors of patients, can lead to the metastatic spread and subsequent growth of tumour cells at distant sites within the body. Detection and characterization of CTCs from minimally invasive "liquid biopsy" provides critical insights into tumor biology and is critical for companion diagnostics and care. The isolation and recovery of these CTCs is very challenging, primarily due of their low abundance in peripheral blood and their physiological and morphological similarity to other hematologic cells.

"In this work, we introduced an ultra high-throughput microfluidic device for CTCs isolation from blood using inertial microfluidics to realize a single step label-free enrichment. This method uses the inherent Dean vortex flows present in curvilinear microchannels for focusing the CTCs near the microchannel inner wall while driving the smaller hematologic cells toward the microchannel outer wall, allowing an efficient separation at the outlet (see Fig. 1)," said Dr Majid Ebrahimi Warkiani, SMART postdoctoral associate who led the work along with other students and collaborators.

In collaboration with scientists and doctors from the NCCS and NUH, clinical validation of this device was carried out using blood samples collected from patients with advanced stage lung cancer with high purity and yield (n=20; 5-88 CTCs per mL). "The spiral biochip identifies and addresses key challenges of the next generation CTCs isolation assay including (i) high sensitivity – 100% detection rate; (ii) high throughput sample processing (3mL/hr); (iii) single step CTCs isolation and retrieval; and (iv) cancer prognosis via an antibody independent technique," Dr Majid added.

To the researchers in NUS, such work is just the beginning of a long journey into cancer research. The application of microfluidic systems for CTCs enrichment offers unparalleled opportunities to characterise cell molecular traits at the single-cell level. The team are currently working on advancements to their microfluidics platform and they envision that spiral microfluidics will be a versatile blood separation technique for enriching other cell populations from blood. The enhanced CTC enrichment method will permit extensive downstream characterization works, such as cancer heterogeneity studies, study of phenotypic stability of CTCs *in vitro*, mutational analysis, demonstrating CTC tumorigenicity

as well as comparison of CTC to cells from tumour biopsies. These are planned in collaboration with the NCCS, NUH and Genome Institute of Singapore (GIS).

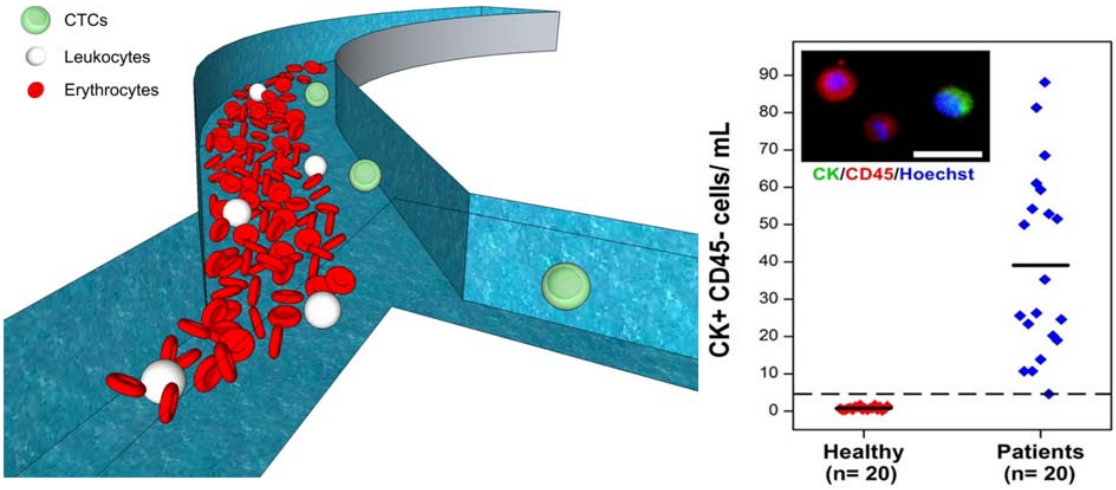

Figure 1. Schematic illustration of the separation principle for high-throughput CTCs isolation. CTCs enumeration plot for healthy donors (red) and lung cancer patients (blue).

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