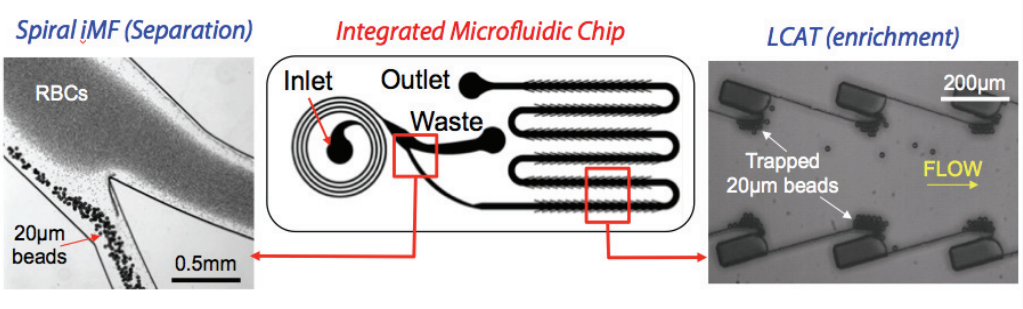
Center for Advanced Design and Manufacturing of Integrated Microfluidics (CADMIM)

University of California, Irvine, Abraham Lee, 949.824.8155, aplee@uci.edu
University of California, Irvine, Gisela Lin, 949.648.1487, gisela@uci.edu
University of Cincinnati, Ian Papautsky, 513.556.2347, ian.papautsky@uc.edu

Integrated Microfluidic Device for Isolation & Enrichment of Rare Cells

High fidelity sorting, isolation, and concentration of target cells is a critical step in many diagnostic and therapeutic applications. Selective isolation of rare cells from complex mixtures, however, remains a critical challenge that has not previously been fully addressed. For example, cancer tumor cells that travel through the bloodstream can evolve to become clinically relevant as they are often the first indicators of tumor spreading. The moving tumor cells have the potential to inform physicians and guide therapy in lieu of more invasive tissue biopsies.

A CADMIN research team has successfully combined two microfluidic components for the selective isolation and enrichment of rare cells from untreated liquid samples - an inertial microfluidic (iMF) component and a lateral cavity acoustic transducer (LCAT) component. Microfluidics use the physics of fluid flow on the microscale scale; in the present a device, fluid samples are directed through micro-sized channels with specific geometries that cause the various cells to separate into distinct streams due to their different sizes. This integrated device takes advantage of the precise cell sorting capability of the iMF component and the rapid purification capability of the LCAT component to achieve higher quality cell isolation from complex mixtures compared to standard methods.



20μm-diameter beads separate from whole blood due to inertial forces (RBC = red blood cells). 20μm-diameter beads get trapped in the microvortices of LCAT as they pass through the main flow channel.

This integrated microfluidic device has the potential to achieve improved target cell purity and allows users to analyze complex samples like whole blood or untreated water. The device is being fabricated using scalable production methods such that transfer to industry is more straightforward. So far, results demonstrate

the feasibility of the approach using model systems and indicate that the developed approach will also work with actual samples (such as whole blood).

The advantage of the developed microfluidic platform lies in its simplicity. The instant the untreated sample makes a single pass through the device, both target cell isolation and active enrichment are complete, resulting in an automatically prepared sample with higher target cell purity than is currently attainable. This leads to quicker, more reliable results without the need for binding assays, labelling, sample recirculation, or further post-processing. It is this active, integrated enrichment process immediately following highly selective cell isolation, all in one lab-on-a-chip, that sets this method apart from all the others.

This device has the potential to make significant impacts in front-end sample preparation workflows for cancer diagnosis by dramatically reducing the duration of the target circulating tumor cell identification and enumeration process and increasing the reliability of these measurements. An end product based could be a handheld device to isolate tumor cells from patient blood. These cells can then be used to tailor the therapy and/or monitor therapy response. Even broader impacts can be anticipated to be realized as the developed technology is applied to other blood-based diseases (malaria, hepatitis, etc.) as well as other business sectors where target cells are present in complex fluid mixtures (such in environmental monitoring, agriculture, consumer products, and forensics).

By using microfluidic technology, the resulting device becomes a miniature lab-on-a-chip amenable to mass production. Thus, this highly capable device will facilitate portable use - i.e., at the patient bedside (in the home or hospital) or anywhere point-of diagnosis is required (factory, beach, farm, crime scene, etc.)

> **Economic impact**: To date this work has not yet generated direct economic impact because the team has so far only completed the initial feasibility and proof-of-concept. However, we probably would have not been able to conduct this early phase basic research on our own, mainly because of lack of knowledge and experience with microfluidic chip development. Therefore, this work indirectly saved the equivalent of the R&D costs for this project because it was done at CADMIM rather than at our company.

In general, the global cancer diagnostics market is expected to reach roughly $13.1 Billion by 2020 with a compound annual growth rate (CAGR) of 12.9% from 2015 to 2020. Circulating tumor cells have emerged as the premier biomarker for cancer. Furthermore, since these cells travel through the bloodstream, the demand for liquid biopsies has grown tremendously. Highly invasive, costly, traditional tissue biopsies will only reveal genetic information (i.e., DNA) in one part of the tumor. However, tumor cells die routinely just like other cells and enter the bloodstream. Thus, blood contains DNA from all over the tumor, and acquiring measurements from blood is more informative and much less invasive compared to tissue.

As liquid biopsies become more sophisticated and capable of ultra-sensitive molecular readouts, their applicability to cancer diagnosis (as well as other diseases) is expected to rise dramatically. In fact, it is estimated that by 2029, the total annual market for liquid biopsies could be ~$12B in the U.S. alone. The integrated microfluidic device described here would feed directly into these markets.

For more information, contact Dr. Abraham Lee at the University of California, Irvine, aplee@uci.edu, Bio https://engineering.uci.edu/users/abraham-lee, 949.824.8155.