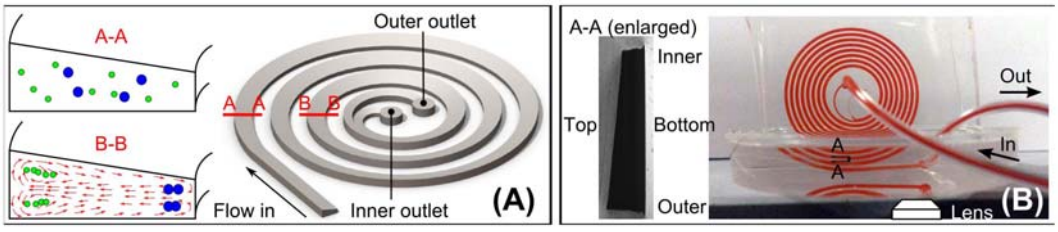
Innovative Technologies for Sorting Cells based on Their Physical Properties

Cell sorting, the process of separating cells of interest from a large number of samples, is a key step in advanced techniques for disease diagnosis. Existing methods, such as fluorescence-activated and magnetic-activated cell sorting (i.e., FACS and MACS, respectively) use antibodies as tags or labels to identify specific cells. Such labeling increases the complexity of the separation process and may alter the functionality of cells sorted.

Physical properties of cells often reflect their biological states, which have direct implication in disease diagnosis and treatment. Sorting cells based their physical properties not only avoids the complexity in conventional methods but also offers new capabilities in disease diagnosis. For instance, the deformability a cell is known to be an effective marker for differentiating certain types of cancerous cells from healthy ones, yet it cannot be identified by an antibody.

Collaboration in the **SMART BioSyM IRG** between **Dr. Jongyoon Han (MIT) and Dr. Peter C. Y. Chen (NUS)** has produced innovative technologies for label-free cell sorting. The research team in this collaboration has engineered microsystems that exploit the complex dynamics of micro-particles in confined flow and utilize real-time feedback control techniques to achieve effective sorting of cells based on their intrinsic physical properties, such as size and deformability.

For sorting cells by size, their investigation, which is reported in a paper to appear in ***Scientific Reports*** [1], revealed the complex fluid dynamics in a microfluidic channel with a specially designed and **patented trapezoidal** cross-sectional geometry [2]. In such a channel, particles are subject to two major forces, namely, the inertial lift force that tends to focus the particles to the inner wall of the channel, and the Dean drag force of the Dean flow (induced by the centrifugal effect of the fluid) that drags the particles along the Dean flow direction. In particular, due to the trapezoidal shape of the channel cross-section, the Dean flow forms two strong vortices at the outer side of the channel. While the relative large particles are focused at the inner side, these vortices can trap the relative small particles at the outer side, thus making high-resolution size-based separation possible. This is the first time the phenomenon of particle focusing was experimentally observed in 3D in a spiral microfluidic channel. This research not only significantly advances the field of microfluidics research but also suggests (for this novel device) a broad spectrum of potential applications, ranging from cancer diagnosis and therapy to stem cell engineering.

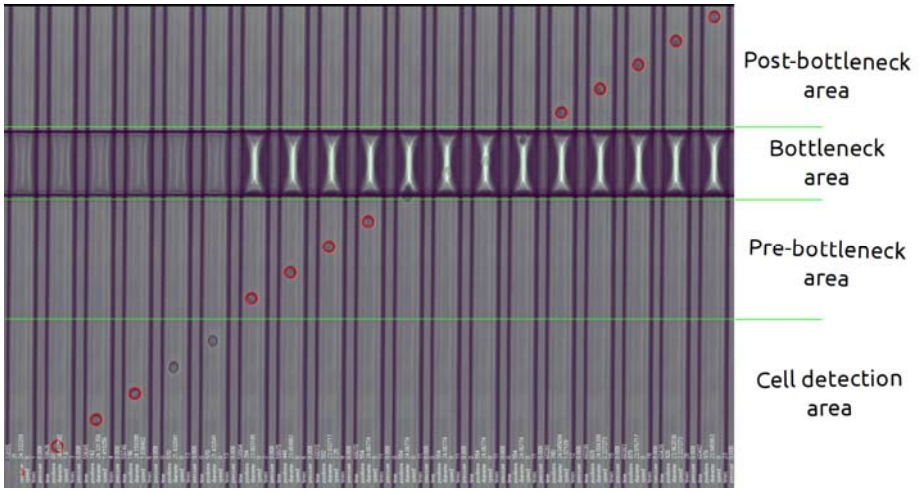


(A) Schematic of a trapezoidal cross-section spiral microchannel illustrating the principle of particle focusing and trapping within the Dean vortices.

(B) An actual spiral microfluidic device for side view focusing position measurement. The microfluidic channel is filled with red dye for visualization. Samples are flowed from center loops to outer loops for the measurement.

For sorting cells by deformability, the research team pioneered the technique of "active channel control" for differentiating cells (in a population with large size-variation) by their individual deformability, as is reported in a recent paper published in the ***Journal of Micromechanics and Microengineering*** [3]. They engineered a microfluidic system incorporated with feedback control to deal with large size-variation in primary clinical cell samples. This system consists of a flow channel to deliver cells through a bottleneck section whose height can be adjusted in real-time by air pressure applied in an adjacent control channel. By dynamically setting the height of this bottleneck section to be a fraction of the diameter of individual cells, the cells are forced to deform as they pass through the bottleneck section. An analytical model reveals that the passage time of a cell is indicative of its deformability, which was also validated by experiments using MCF-7 and MCF-10A cell lines.

These innovative technologies, together with the underlying intellectual properties, form an increasingly strong knowledge base for launching integrated solutions for label-free cell and particle sorting, with wide ranging potential applications in areas as diverse as disease diagnosis, stem cell engineering, and water filtration.



A record of frame stream (taken at 25 frames/s) shows a MCF-7 cell approaching and passing through the bottleneck section. When the cell (marked by a red circle) approaches the cell detection area (bottom left), its presence is detected and its diameter is estimated.[3]

References

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[3] G. Guan, P.C.Y. Chen, K.W. Peng, A.A. Bhagat, C.J. Ong, and J. Han, Real-time control of a microfluidic channel for size-independent deformability cytometry, *Journal of Micromechanics and Microengineering*, 22 105037, 2012.

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[5] G. Guan, A.A. Bhagat, L. Wu, Z. Li, C.J. Ong, P.C.Y. Chen, and J. Han, High resolution size based micro particle/cell separator with trapezoidal cross section Spiral microchannels, Proceedings of the 2012 International Conference on Miniaturized Systems for Chemistry and Life Sciences (MicroTAS 2012), 518-20, Okinawa, Japan, Oct. 2 - Nov. 1, 2012.