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Hydrodynamic blood cell separation using fishbone shaped microchannel for circulating tumor cells enrichment

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ABSTRACT

Cancer patients have a range of from 1 to 1000 circulating tumor cells (CTCs) with 5×10^9 erythrocytes in 1 ml volume of their peripheral blood. Due to this rarity of CTCs, a pre-process for the enrichment of CTCs in blood sample is required. For a fast and passive CTCs enrichment process, we developed a fishbone shape microchannel, which has geometry of 50 repeated 45° angled expansion and contraction channels. The enrichment process can be achieved from the differences between the dominant forces with respect to the diameter of each type of cell. For the feasibility test, we used three different sizes of microparticles of 2 μm, 6 μm, and 13 μm dia. to mimic platelet, erythrocytes, and leukocyte or human breast cancer cells, respectively. The results show that the smaller particles (2 μm or 6 μm dia.) laterally move to both side wall directions by dominant inertial lift force, whereas the larger particle (13 μm dia.) focused on the centerline of the channel by dominant momentum change-induced inertial force under appropriate fluid flow velocity. We also performed a cell separation experiment using MCF-7 and a human erythrocyte mixture. The recovery efficiency of MCF-7 is over 98% at the detection window with a high throughput (250 μl/min).

1. Introduction

The separation of circulating tumor cells (CTCs) from a cancer patient's peripheral blood has been a critical task in diagnosing tumor metastasis [1–4]. A cancer patient has between 1 and 1000 CTCs with 5×10^9 erythrocytes, 4×10^6 leukocytes, and 3×10^8 platelets in 1 ml volume of their peripheral blood [5]. Over the past few decades, many researchers have attempted to distinguish the CTCs from the peripheral blood sample using various methods such as hydrodynamic [5–9], magnetic [10], dielectrophoretic [11], or fluorescence [12] activated cell sorting system; however, this remains a considerable challenge because of the rarity of CTCs. To overcome the limitation due to the rarity, many researchers have attempted to develop a pre-separation process in which the erythrocytes, leukocytes or platelets are removed from the blood sample. Despite the recent success in manipulating microliter amounts of sample liquid in microscale channels [2,13], it is still limited in dealing with the cellular and fluid complexity of large volumes (milliliters) of whole blood samples which have a sufficient amount of blood to diagnose the tumor metastasis. Systems with cost-effective, label free, and high-throughput CTCs enrichment will have a significant impact on both research and clinical applications [7]. The passive separation methods have many advantages such as no external devices, simple structures, and simple operation procedures [1]. Recently, passive separation methods using inertial effects with parallel expansion-contraction reservoirs/microchannels or multi orifice structures have been developed for cell separation [1,14,15]. While different sized cells can be partially separated in these structures/microchannels, the problem remains of the need to enhance both separation efficiency and the throughput yield (~140 μl/min).

To overcome these limitations, we developed a fishbone shaped microchannel device with a geometry of 50 repeated, 45° angled expansion and contraction channels that can be facilitated for a fast enrichment process (≥250 μl/min) with high recovery efficiency (>98%) by the combination of momentum change-induced inertial

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force and the inertial lift force with respect to the diameter of cells. Three different sizes of microparticles were employed to mimic each size of blood cells such as the platelet, erythrocytes, and leukocyte or human breast cancer cells (MCF-7). Also, we successfully demonstrated fast enrichment with high recovery efficiency using a human breast cancer cell spiked in a human peripheral blood sample.

2. Theory

Under a micron sized fluid flow circumstance, dimensionless numbers are used to analyze the physical phenomena of fluid or particle behavior [15,16]. The degree of particle adjustment to the accelerating flow by the channel geometry can be predicted by the Stokes number (St), which is defined as,

$$\mathrm{St} = \frac{\tau_p}{\tau_f} = \frac{\rho_p d^2/18\mu}{D_h/U_m} = \frac{\beta}{18} Re_p \tag{1}$$

where τ_p is the relaxation time of the particle, τ_f is the characteristic time of the flow, D_h is the hydraulic diameter of the contraction channel, U_m is the maximum flow velocity in the microchannel, d is the particle diameter, μ is the viscosity of the fluid, ρ_p is the density of the particle, β is the kinetic dynamic fluid viscosity, and Re_p is the particle Reynolds number. The large St value implies that the particles tend to continuously move to the original direction instead of following the fluid streamline under a sudden fluid flow change by the channel geometry [16,17]. For the ratio between the inertial and viscous effects of fluid flow, the Reynolds number is a useful value to interpret the lateral particle motions. Normally, the inertial effect is ignorable in the microfluidic case, but the high fluid flow condition differs. The particle movement in the microfluidic case can be defined by the particle Reynolds number as follows,

$$Re_p = Re_c \frac{d^2}{D_h} = \frac{\rho_f U_m d^2}{\mu D_h} \tag{2}$$

where Re_c is the channel Reynolds number and ρ_f is the density of the fluid. The inertial effect on a suspended particle in liquid can be described by the particle Reynolds number. When $Re_p > 1$, at the beginning point of the expansion structure where the streamline changes, the particles in suspension tend to migrate toward to equilibrium positions where the point of force balance between the shear-gradient lift force (F_{LS}, $F_{LS} \propto f_l \rho_f U_m^2 d^3/D_h$) and the wall effect lift force (F_{LW}, $F_{LW} \propto f_l \rho_f U_m^2 d^6/D_h^4$) [7,18,19]. The f_l represents the dimensionless lift coefficient. The two forces which act bi-directionally on the particle are inertial lift forces that drive particles toward both side walls of the channel [1]. On the other hand, at the end point of the expansion structure (starting point of contraction structure), where the streamline changes rapidly, the additional force acts on particles due to the sudden fluid direction changes. The additional force is a momentum change-induced inertial force, which drives particles toward the center direction. The momentum of the particles is proportional to the diameter of particles with the fixed particle density, and the momentum change-induced inertial force acts more strongly on larger particles than on smaller particles. The momentum change of particles can be stronger with respect to the extreme fluid flow direction changes. The 45° slanted contraction structure in this study can induce more momentum changes to the each size of particles compared with rectangular shape of structure. The momentum change-induced inertial force (F_i) can be estimated by

$$F_i = ma \sim m\frac{\Delta v}{\Delta t} = \frac{\Delta (mv)}{\Delta t} \tag{3}$$

where U is the average fluid flow velocity, D_h is the channel dimension, d is the diameter of the sphere shape of the particle, and ρ_p is the particle density. The inertial force F_i can be transformed to

$$F_i \sim \frac{\rho_p \pi d^3 U^2}{6 D_h} \tag{4}$$

This force will be balanced by the Stokes drag force ($F_d = 3\pi\mu d U_s$) where U_s is the relative velocity between the particle and the fluid [16,17]. When $Re_p < 1$, the particle behavior tends to follow the fluid flow pattern with a slight inertial effect. The inertial lift force (F_L) and the momentum change-induced inertial force (F_i) act more weakly on small particles rather than on large particles. The inertial effect acting on a small particle is negligible. Consequentially, under appropriate fluid flow conditions, the large particle will migrate toward the centerline of the channel due to the domination of F_i, whereas the small particle will migrate to near both side walls by the influence of F_L (shear gradient lift force and wall effect lift force) rather than F_i, the smallest particle will migrate along with the flow pattern because of low Re_p with a little inertial effect, as shown Fig. 1(a).

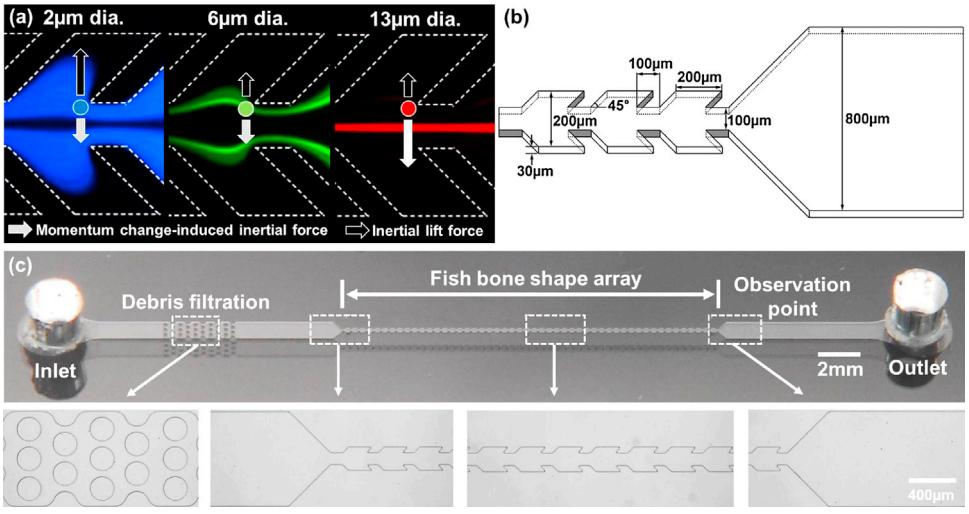

Fig. 1. (a) Particle trajectory differences based on size. (b) Schematic diagram of fishbone shaped microfluidic channel. (c) Optical image of fabricated fishbone shaped microfluidic channel. Inset images indicate debris filtration, entrance of fishbone shape microchannel, fishbone shape array, and observation point, from left to right.