Sensors & Actuators: B. Chemical 272 (2018) 324–330

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

Magnetic activated cell sorting (MACS) pipette tip for immunomagnetic bacteria separation

Sein Oh[a], Su Hyun Jung[b], Hyekyung Seo[a], Mun-Kyeong Min[b], Byeongyeon Kim[a], Young Ki Hahn[c], Joo H. Kang[b,*], Sungyoung Choi[a,*]

[a] Department of Biomedical Engineering, Kyung Hee University, 1732 Deogyeong-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-701, Republic of Korea
[b] Department of Biomedical Engineering, School of Life Sciences, Ulsan National Institute of Science and Technology (UNIST), UNIST-gil 50, Ulsan 44919, Republic of Korea
[c] Samsung Electronics, 4 Seocho-daero 74-gil, Seocho-gu, Seoul 06620, Republic of Korea

ARTICLE INFO

Keywords:
Magnetic activated cell sorting
Pipette tip
Immunomagnetic separation
Microfluidics
Bacteria separation

ABSTRACT

Magnetic activated cell sorting is a well-established technology to sort target cells from heterogeneous cell populations based on their specific surface receptors. However, conventional bulk separators rely on irregular and dense ferromagnetic matrices that can cause variances in separation purity and recovery. Recent microfluidic separators typically use narrow and two-dimensional laminar flows that can lead to low separation throughput. Here, we present a magnetizable micropipette tip incorporating a ferromagnetic matrix of nickel meshes that have regular and rectangular micropores. The functional pipette tip can be transiently magnetized by permanent magnets, thereby enabling the efficient capture and release of target cells by simple pipetting. We performed parametric studies to investigate optimal separation protocols such as the number of mesh layers and pipetting repetitions. We then applied the functional pipette tip for separation of bacterial cells from whole blood, confirming that the separation quality is sufficient for downstream cell culture and analysis. The magnetizable pipette tip provides high-throughput separation, processing 1 mL of blood within 7 min, and high-recovery separation, recovering ≈90.5% of the bacterial cells spiked into blood.

1. Introduction

Cell sorting based on surface markers is an effective tool to isolate target cells from complex background matrices that has been used extensively for biomedical applications ranging from in vitro diagnostics for rapid detection of pathogens [1,2] and diseased cells [3,4] to therapeutics [5,6] and tissue engineering [7,8]. However, simple, low-cost, and effective methodologies for isolating target cells from a vast background of blood cells and circulating macromolecules remain to be developed. Fluorescence-activated cell sorting (FACS) can provide high separation purity and recovery [9,10], but its use is often limited by the high cost of the equipment and difficulties in operation and maintenance. The serial separation nature of FACS also causes low throughput, especially when separating target cells from whole blood because of the overwhelming number of blood cells. Affinity chromatography, which is based on interactions between cell surface receptors and immobilized ligands [11–13], often shows variances in separation efficiency because it lacks an effective way to induce ligand-receptor interactions. Although microfluidic methods enable effective contact between cells and ligand-coated surfaces by incorporating surface ridges and disrupting laminar streamlines [14,15], the intrinsic dependence of ligand-receptor interactions on shear rate requires precise flow-rate control with external pumping equipment. In addition, the release of captured cells for downstream analysis requires another non-trivial process [16].

Magnetic-activated cell sorting (MACS) enables the parallel capture and release of a large number of target cells. In conventional MACS approaches, target cells are attached to antibody-functionalized magnetic particles and then captured inside a column packed with steel spheres or steelwool that generates a high degree of magnetic field gradient in the presence of permanent magnets [17]. A magnetizable separation column allows for high-gradient magnetic separation and simple target-cell recovery, but the irregular and dense ferromagnetic matrix can lead to complications, such as non-uniform magnetic forces and flow distribution, that affect separation performance. MACS has recently been implemented in microfluidic devices, offering advantages such as precise flow control, uniform magnetic fields, and high separation efficiency [5,18–25]. Microscale MACS separators typically

* Corresponding authors.
E-mail addresses: jookang@unist.ac.kr (J.H. Kang), s.choi@khu.ac.kr (S. Choi).

https://doi.org/10.1016/j.snb.2018.05.146
Received 26 February 2018; Received in revised form 25 May 2018; Accepted 25 May 2018
Available online 29 May 2018
0925-4005/

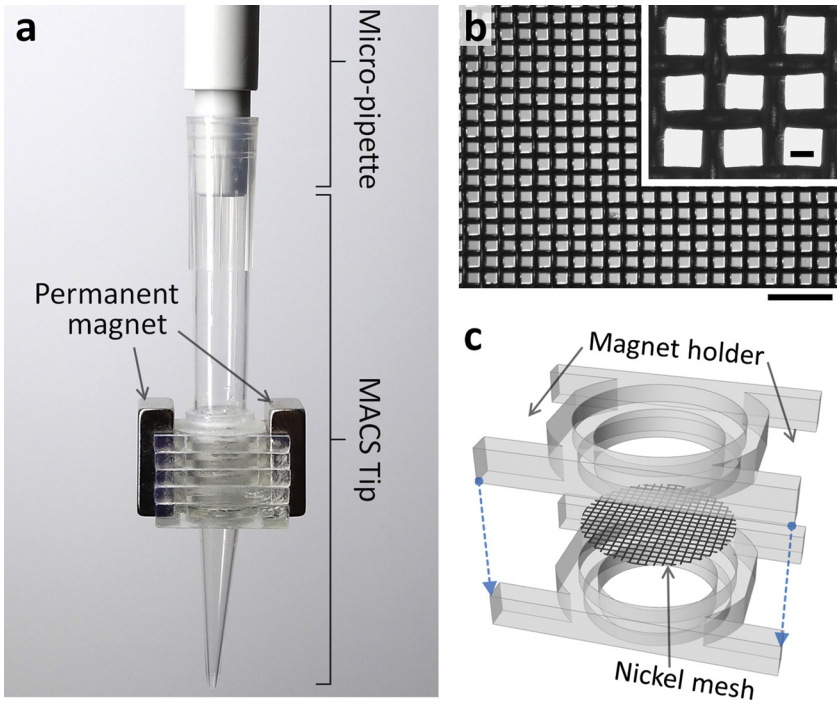

Fig. 1. MACS Tip for immunomagnetic separation. (a) Photograph showing the MACS Tip, which is composed of layers of nickel meshes that can be magnetized with permanent neodymium magnets. (b) Micrographs of the nickel mesh with rectangular pores of ≈168 μm × ≈156 μm. Scale bar, 1 mm. The inset is an enlarged view showing the woven structure of the nickel wires. Scale bar, 100 μm. (c) 3D-printing design for placing and fixing the nickel mesh and holding the magnets.

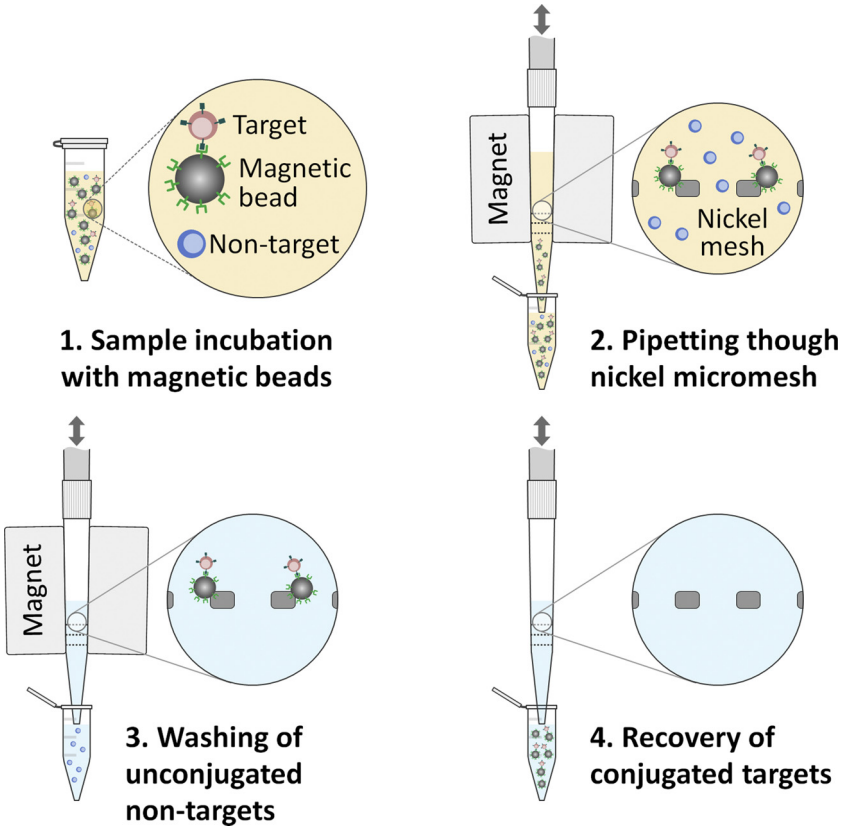

Fig. 2. MACS-Tip separation procedures: target-cell capture, washing, and release via simple pipetting.

use a horizontal magnetic field that enables continuous-flow separation by laterally dragging labelled cells [5,18–25]. However, the two-dimensional and planar nature of the separators typically results in low separation throughput. Although high-throughput methods have been developed based on three-dimensional magnetic structures [24,26,27], their fabrication involves photolithography patterning, silicon wafer etching and permalloy film deposition, which considerably increases fabrication complexity and cost. In addition, most microscale separators rely on bulky and expensive fluidic accessories such as syringe pumps that increases the difficulty of sample handling and the separation cost.

Here we present a magnetizable micropipette tip for MACS, called the *MACS Tip* that enables high-throughput and high-gradient magnetic separation via simple pipetting (Fig. 1). The MACS Tip is a 1-mL pipette tip with layers of nickel meshes having regular and rectangular