Rapid Bacteria Extraction from Whole Blood Using a Pneumatically-Regulated Nano-Sieve Device

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Life-threatening bloodstream infections (BSI), such as sepsis, mainly caused by the body's syndromic response to pathogen infection, are a major public health concern, leading to ~11 million deaths each year [1]. The diagnosis of sepsis is extremely challenging as the isolation of low concentration pathogens from bodily fluids such as blood is difficult, relying on time-consuming and complicated isolation processes. The rapid detection of infecting strains is critical for the effective treatment of BSI, aiming to save more lives. Here, we present a miniaturized nano-sieve device, regulated by a pneumatic-induced chamber, for the efficient separation of *Escherichia coli (E. coli)* from whole blood. The red blood cells (RBCs) in bacteria-spiked blood sample were firstly depleted with a solid phase immunoassay, thus obtaining plasma sample without losing the bacteria, as shown in **Fig. 1a.** The pneumatic-regulated nano-sieve (**Fig. 1b**) was used to capture, purify, and retrieve *E. coli* bacteria. During the capturing procedure, the pneumatic chamber under the positive pressure increases the pinning force of the nano-sieve channel, allowing bacteria capture at a high flow rate without leaking issues (**Fig. 1b-i**). With the negative pressure (**Fig. 1b-ii**), the fresh buffer are used to easily retrieve and purify the *E. coli* bacteria from the original sample (**Fig. 1a**). In **Fig. 1c**, the enriched bacteria show a strong fluorescent signal under the fluorescent microscope, suggesting that most of the bacteria are trapped by microbeads-patterned nano-sieve device. A trapping efficiency of 72.3% (± 3.2%) is achieved by comparing the bacteria concentration before (**Fig. 1d-i**) and after (**Fig. 1d-ii**) the capture procedure. This integrated and centrifuge-free bacteria isolation device establishes a useful platform, paving ways for multiplexing, labor-free, and efficient pathogen separation for the rapid and accurate bloodborne diseases detection, such as sepsis [2].

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[1] Rudd, K.E., Johnson, S.C., Agesa, K.M., Shackelford, K.A., Tsoi, D., Kievlan, D.R., Colombara, D.V., Ikuta, K.S., Kissoon, N., Finfer, S. and Fleischmann-Struzek, C., 2020. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet, 395(10219), pp.200-211.

[2] Kumar, S., Tripathy, S., Jyoti, A. and Singh, S.G., 2019. Recent advances in biosensors for diagnosis and detection of sepsis: A comprehensive review. *Biosensors and Bioelectronics*, *124*, pp.205-215.

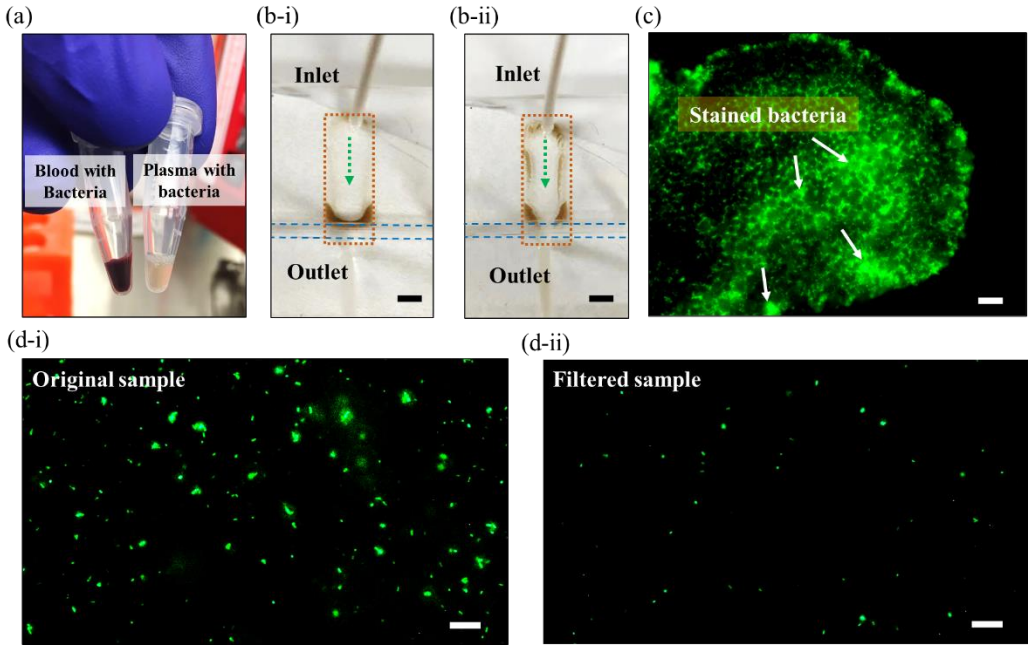

Figure 1*: (a) The comparison of the bacteria-spiked whole blood sample and the plasma sample after RBCs-depletion immunoassay. (b) The microbeads-patterned and pneumatic-regulated nano-sieve device under the positive pressure (b-i) and the negative pressure (b-ii). The blue dashed lines indicate the position of the pneumatic chamber. The brown dashed rectangle shows the nano-sieve channel. The green dashed arrows indicate the flow direction. Scale bar: 2 mm. (c) Stained bacteria (green) captured by microbeads. (d) The comparison of the concentration of stained bacteria before (d-i) and after (d-ii) the purification by the applied nano-sieve. The scale bars (figure 1c and 1d): 10 µm.*