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# Deterministic Lateral Displacement the sorting of Extracellular Vesicles from complex biological samples<sup>†</sup>

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**Abstract:** Extracellular Vesicles (EVs) are biological nanoparticles secreted by cells. Their role as biomarkers makes them increasingly attractive since they are accessible by liquid biopsy. However, their isolation method using ultracentrifugation (UC) is still not standardized. This paper reports on a microfluidic method for the isolation of EVs based on Deterministic Lateral Displacement (DLD) principle, a sorting technique composed of a pillar array. We improve our initial DLD device to develop a new method to sort EVs in a low-step process. DLD and UC sorted EVs are comparable in size and concentration according to Nanoparticle Tracking Analysis (NTA).

**Keywords:** extracellular vesicles ; DLD size sorting ; biomarkers

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## 1. Introduction

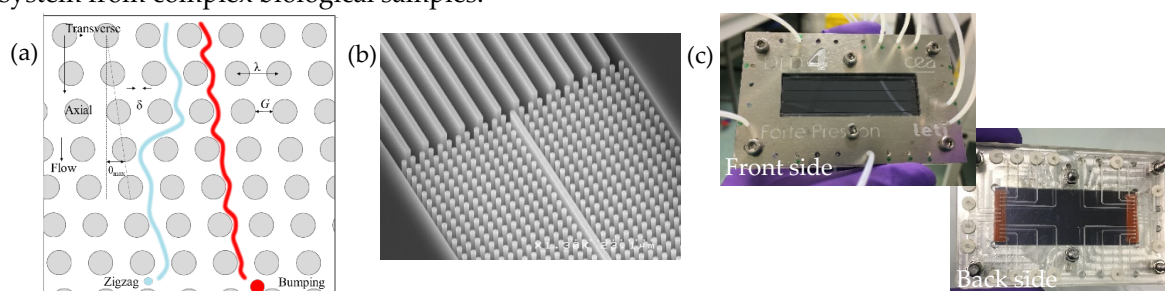
EVs are lipid nanoparticles secreted by cells for communication purpose that circulate in biological fluids such as blood. They cargo information through vesicle surface protein expression and mRNA transportation, thus reinforcing their role of biomarkers available by liquid biopsy. EV isolation is a technological challenge currently addressed using ultracentrifugation. However, since 2018, the International Society of Extracellular Vesicles (ISEV) has incited scientists to develop reproducible and standard methods for EV isolation [1] to overcome ultracentrifugation limitations. Improving our initial DLD size sorting device [2], in terms of DLD design, fabrication and fluidic packaging have allowed the sorting of submicronic biological particles, as EVs, as we reported here.

## 2. Materials and Methods

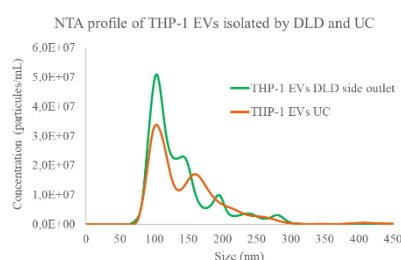
DLD device is composed of a silicon DLD chip fabricated using CEA silicon technologies integrated into a polymer-based fluidic cartridge, specifically equipped to withstand inlet pressures of several bars. THP-1 cell removal occurred by a low-speed centrifugation (300g, 10min) and supernatant is directly introduced in the DLD sorting device at a flow rate about 180 $\mu$ L/h. The analysis of partial distribution was performed using NTA (NS300, Malvern Panalytical) at 22°C.

## 3. Discussion

In this context, we report on a microfluidic approach based on DLD to isolate EVs from complex biological samples with good purity levels and recovery yields. This technique consists of a size sorting system using a slightly disoriented pillar array, which geometrical parameters define a cut-off diameter ( $D_c$ ). Particles smaller than  $D_c$  are not deviated by the pillar array on the contrary to larger particles, as illustrated on Figure 1 (a). The cut-off diameter of 345nm has been set to collect the entire EV population, distributed between 50 and 300nm. A Scanning Electron Microscopy (SEM) picture of the array and integrated fluidic system are shown in Figure 1 (b) and (c). EVs are isolated from cell-free THP-1 culture media. Supernatant, containing various components, is injected into the DLD device. Non-deviated samples (containing EVs) are analyzed by NTA. Ultracentrifugation-isolated and DLD-isolated EVs are then compared in terms of size and concentration, as shown in Figure 2, revealing that DLD isolation method is clearly comparable to ultracentrifugation. We show that DLD size sorting is an interesting way to offer a reproducible and standardized EV isolation system from complex biological samples.



**Figure 1.** (a) Scheme of DLD size sorting principle; (b) SEM picture of DLD silicon chip; (c) Pictures of DLD chip device composed of silicon chip and microfluidic cartridge.



**Figure 2.** Comparison of NTA profile size VS concentration of EVs isolated from THP-1 cells by conventional ultracentrifugation (green curve) and with our DLD microfluidic device (orange curve).

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**Conflicts of Interest:** The authors declare no conflict of interest.

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