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DETERMINISTIC LATERAL DISPLACEMENT FOR THE SORTING OF EXTRACELLULAR VESICLES FROM COMPLEX BIOLOGICAL SAMPLES

T3-359.f

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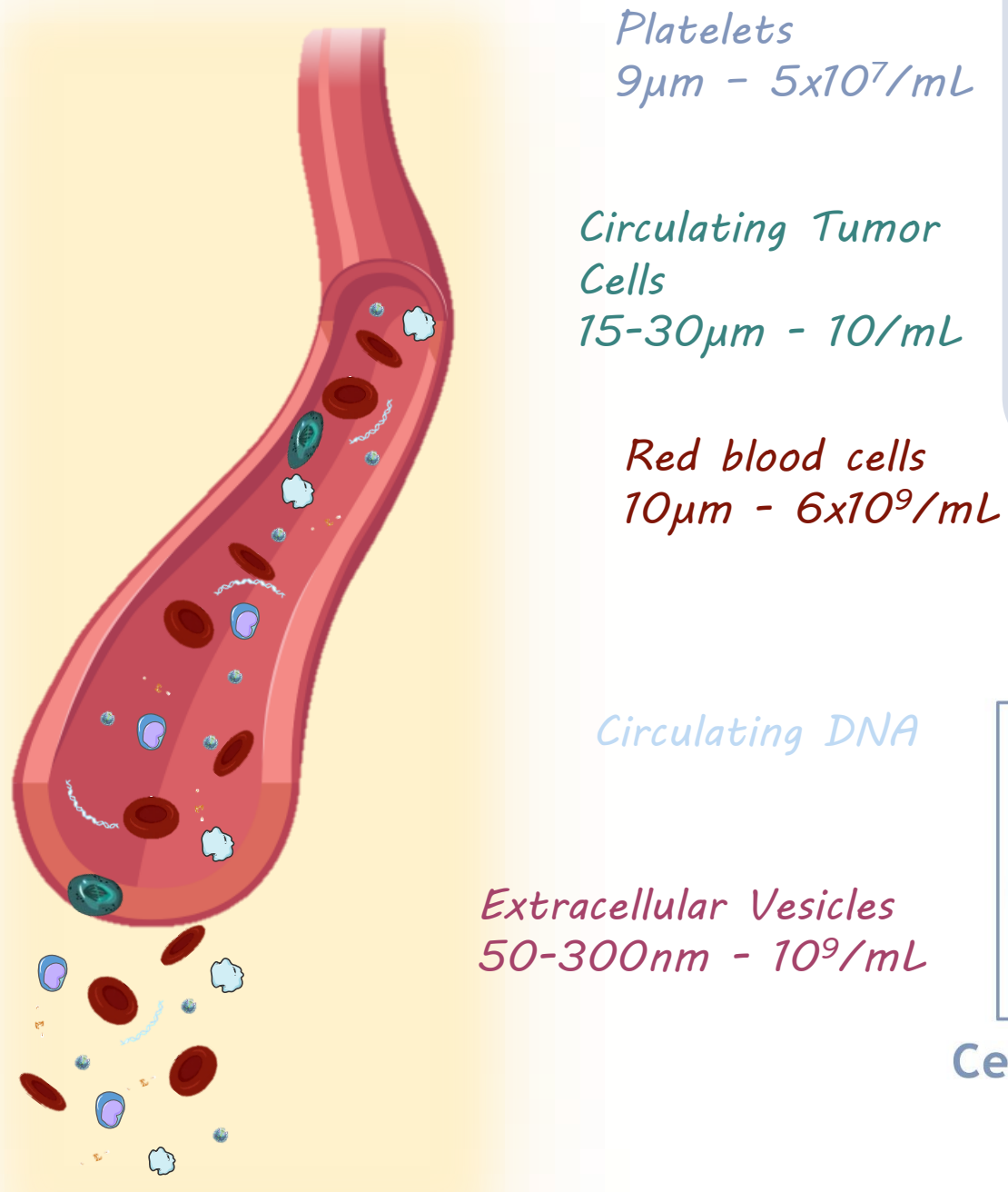
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CONTEXT

EVs in biofluids



EVs are lipid nanoparticles secreted by cells for communication purpose that circulate in biological fluids as blood. They convey information from a parental cell to another cell through surface proteins and their DNA/RNA content. Thus, they are considered as promising biomarkers in the field of liquid biopsy. EVs isolation is a technological challenge currently addressed using Ultracentrifugation (UC), but the International Society for Extracellular Vesicles deplore a lack of reproducible methods.

How can DLD replace UC for EVs isolation ?

Differential centrifugation:

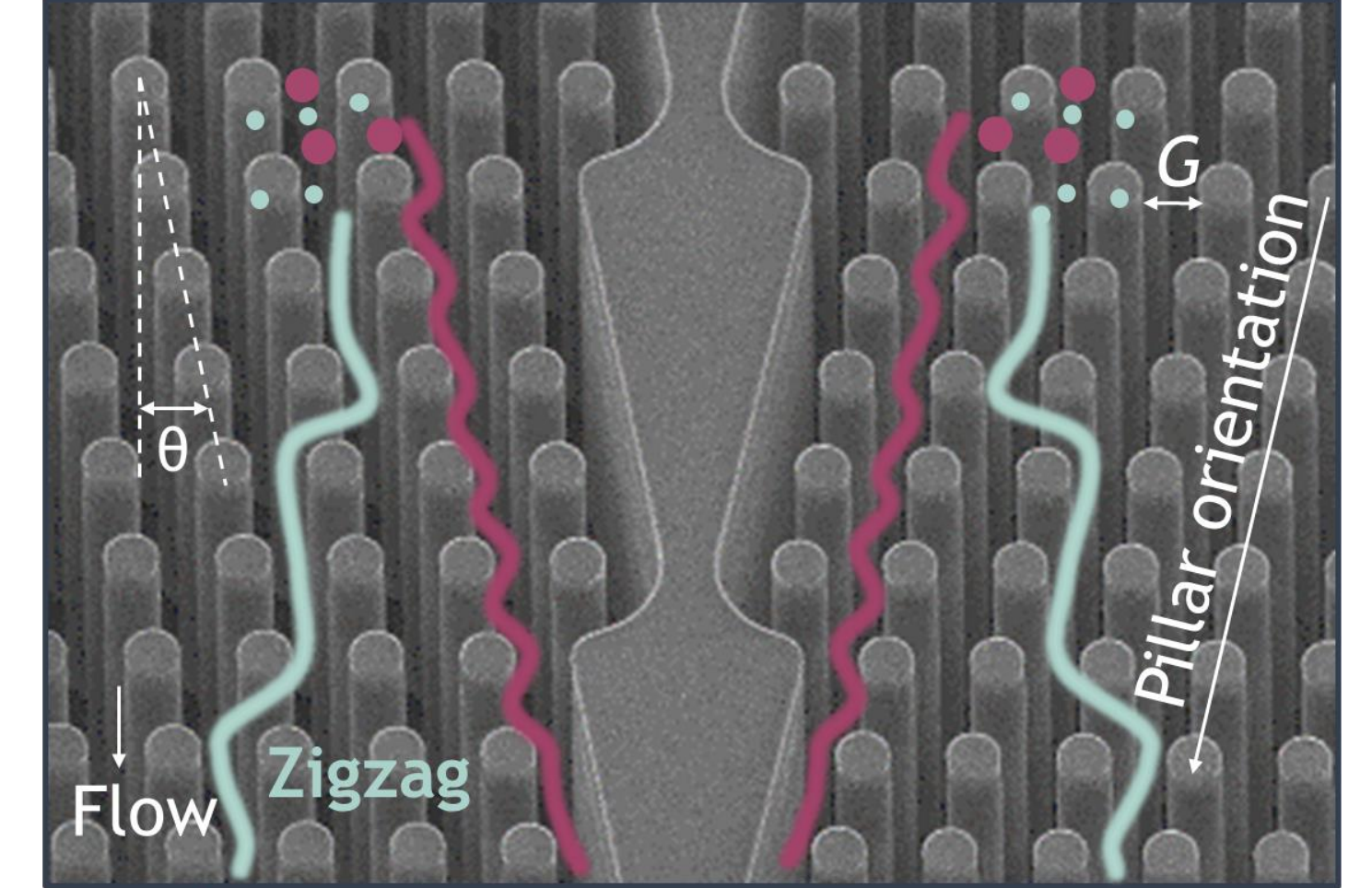


DLD:



Sorting principle

Applied to a mirrored DLD component:



Around a critical diameter:

$$D_c = 1,4G \tan \theta^{0,48}$$

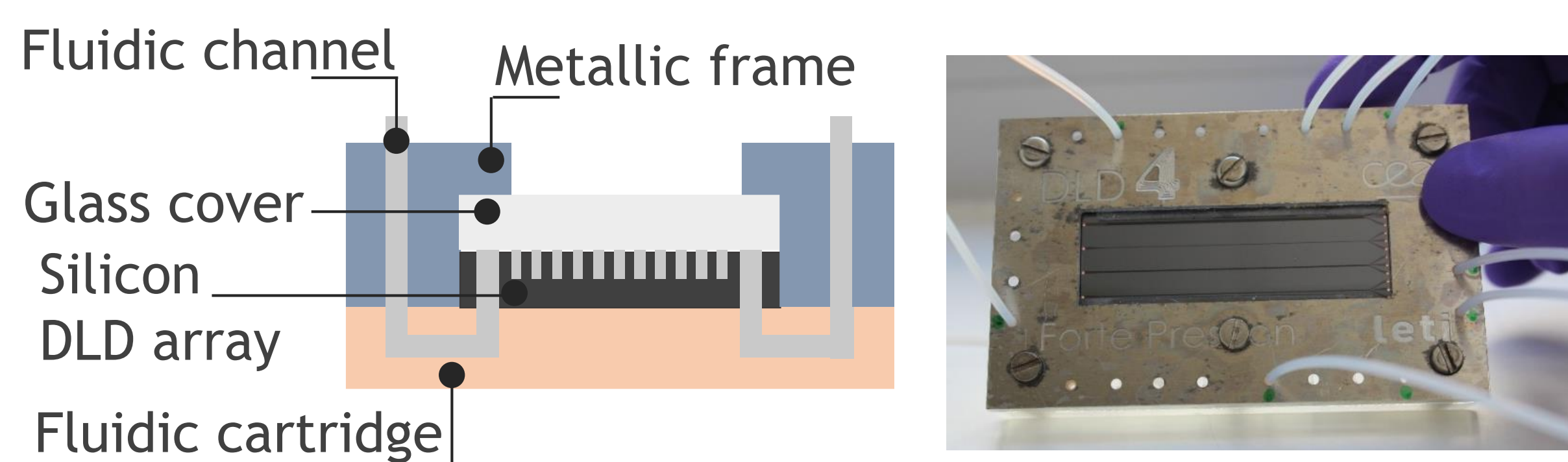
EXPERIMENTAL

Preparation of cell culture media before DLD separation

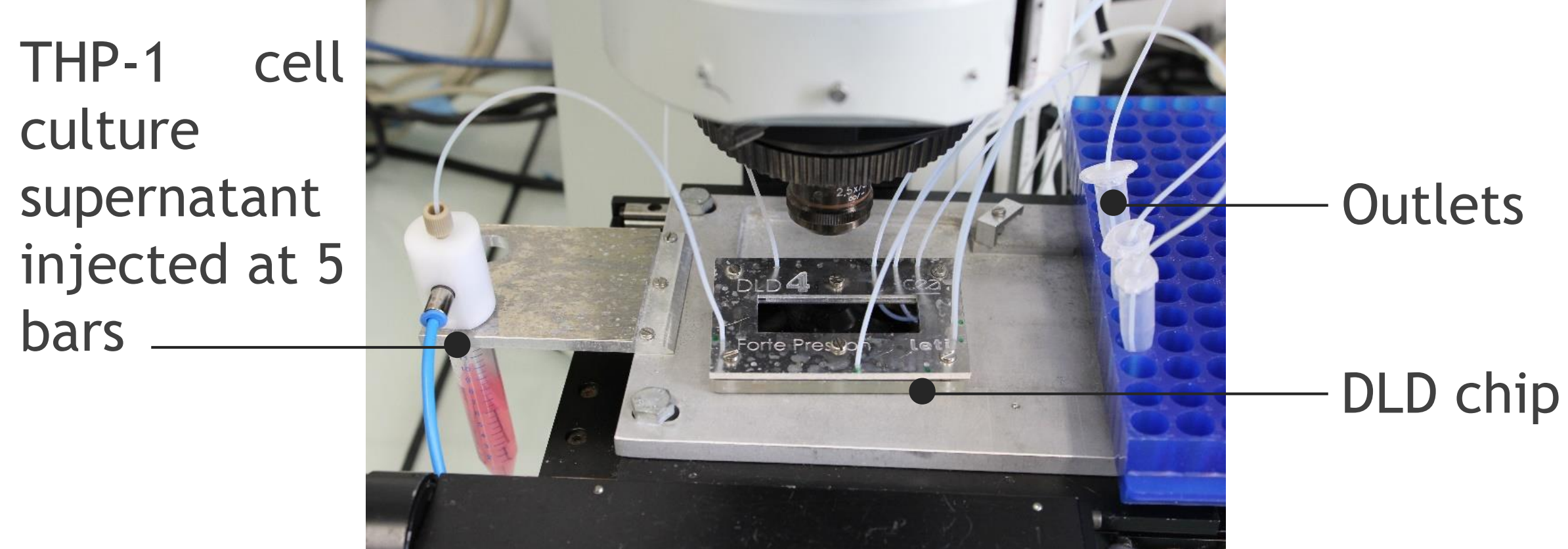


- THP-1 monocytes cultured in classical media at 37°C with 5% CO₂
- 48h before DLD separation, media is replaced by EV-free media

Fabrication of fluidic cartridge

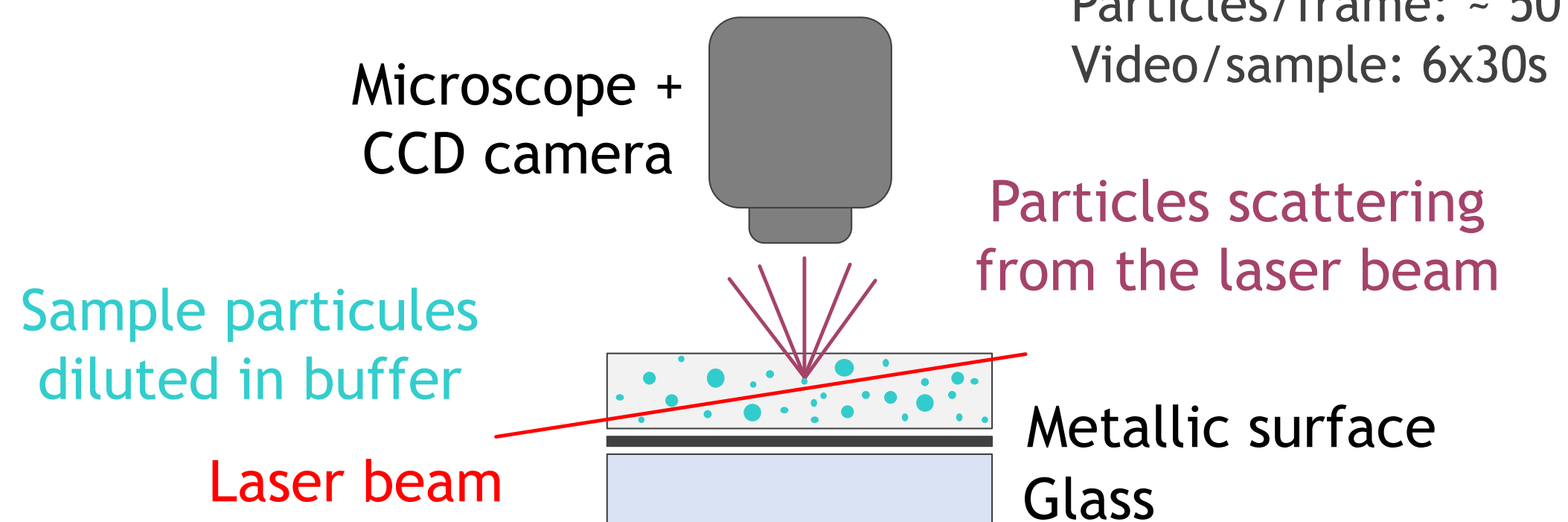


DLD separation



Size characterization of sorting sample

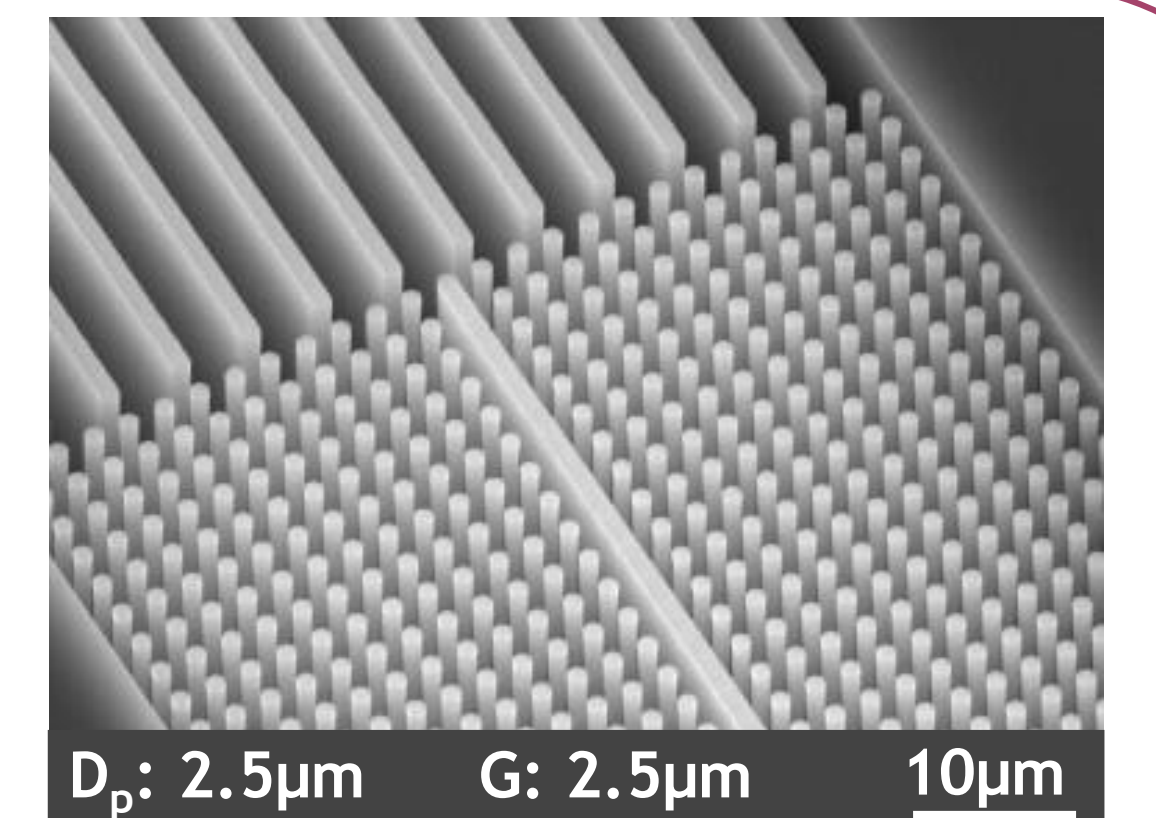
Nanoparticle Tracking Analysis:



RESULTS

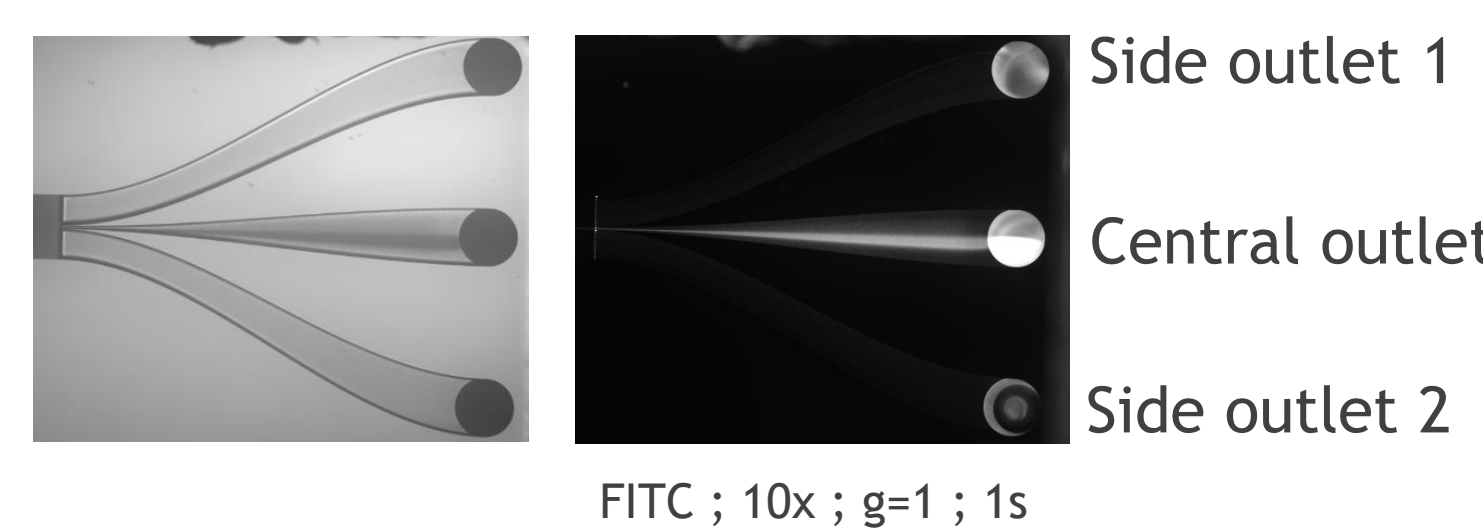
1- Silicon DLD array

- Hydraulic resistance optimization (3µL/min)
- Critical diameter: ~ 345nm according to Davis model
- Fabrication on 200mm wafers
- Pillars Aspect Ratio as high as 15 (2.5µm in diameter)



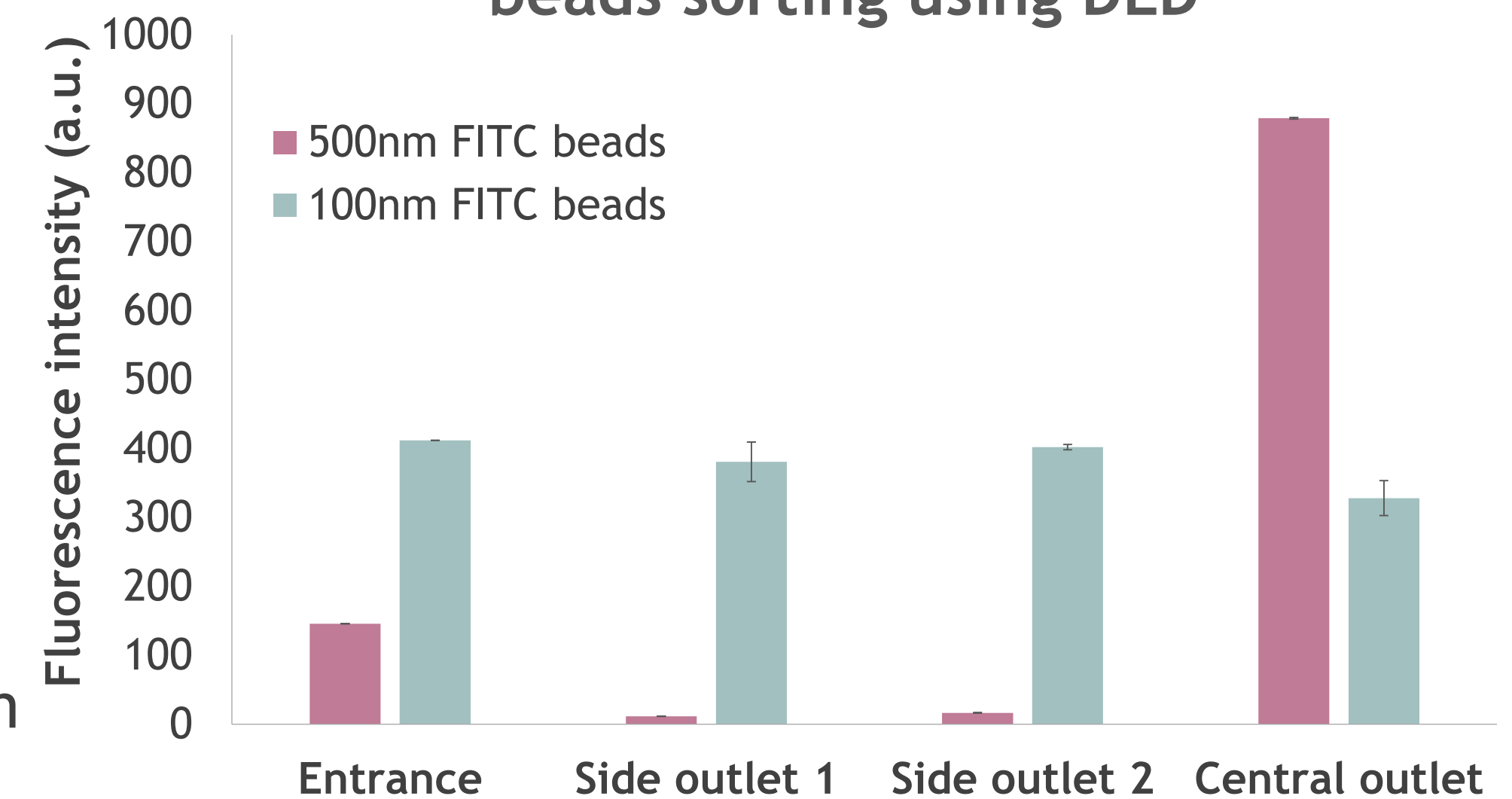
2- DLD size sorting validation using fluorescent beads

Fluorescence microscopy of 500nm beads along DLD outlets



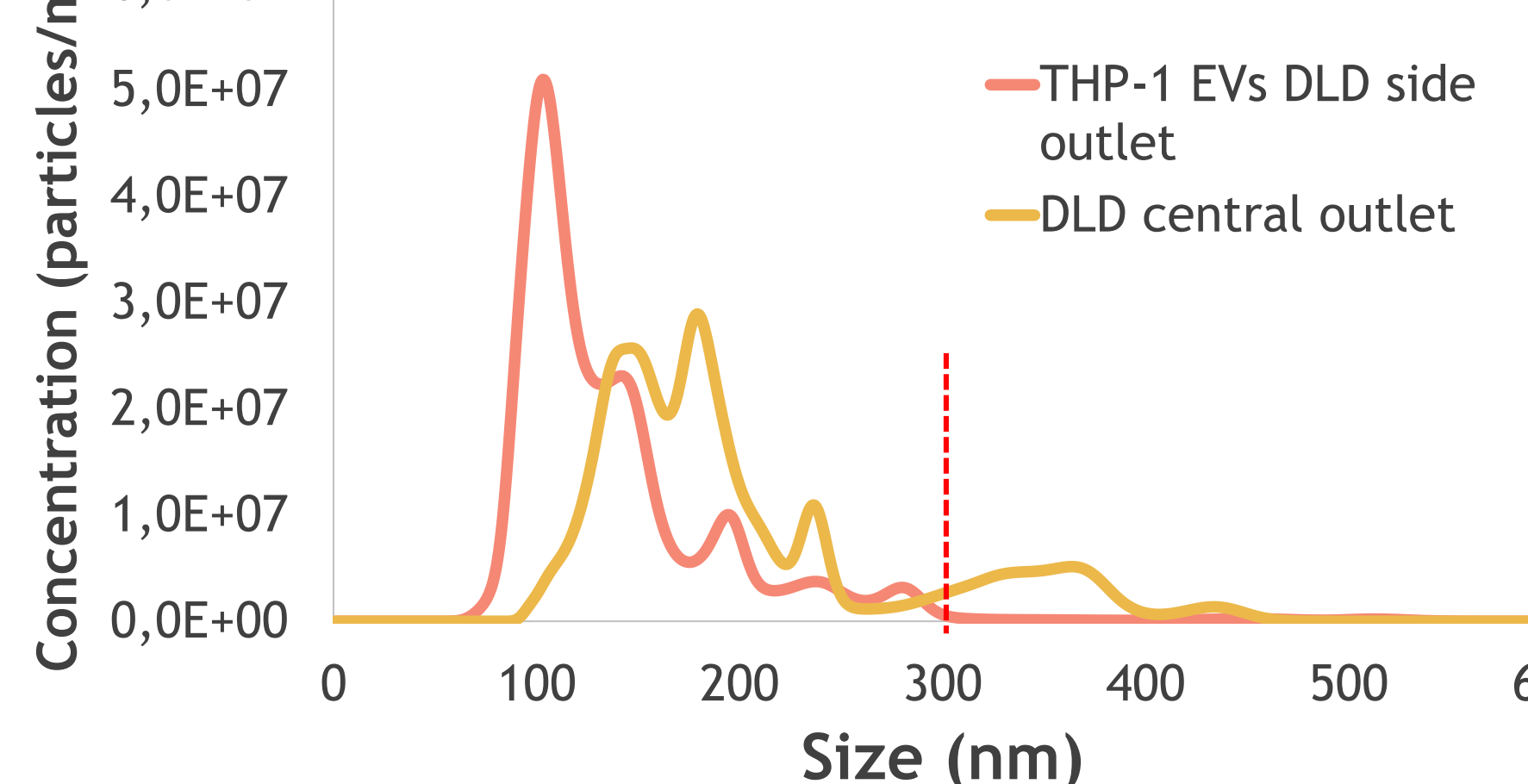
- Deviation of 500nm beads
- No deviation of 100nm beads
- Validation of critical diameter ~ 345nm

Fluorescence intensity related to beads sorting using DLD



3- Sorting EVs from cell culture media using DLD array

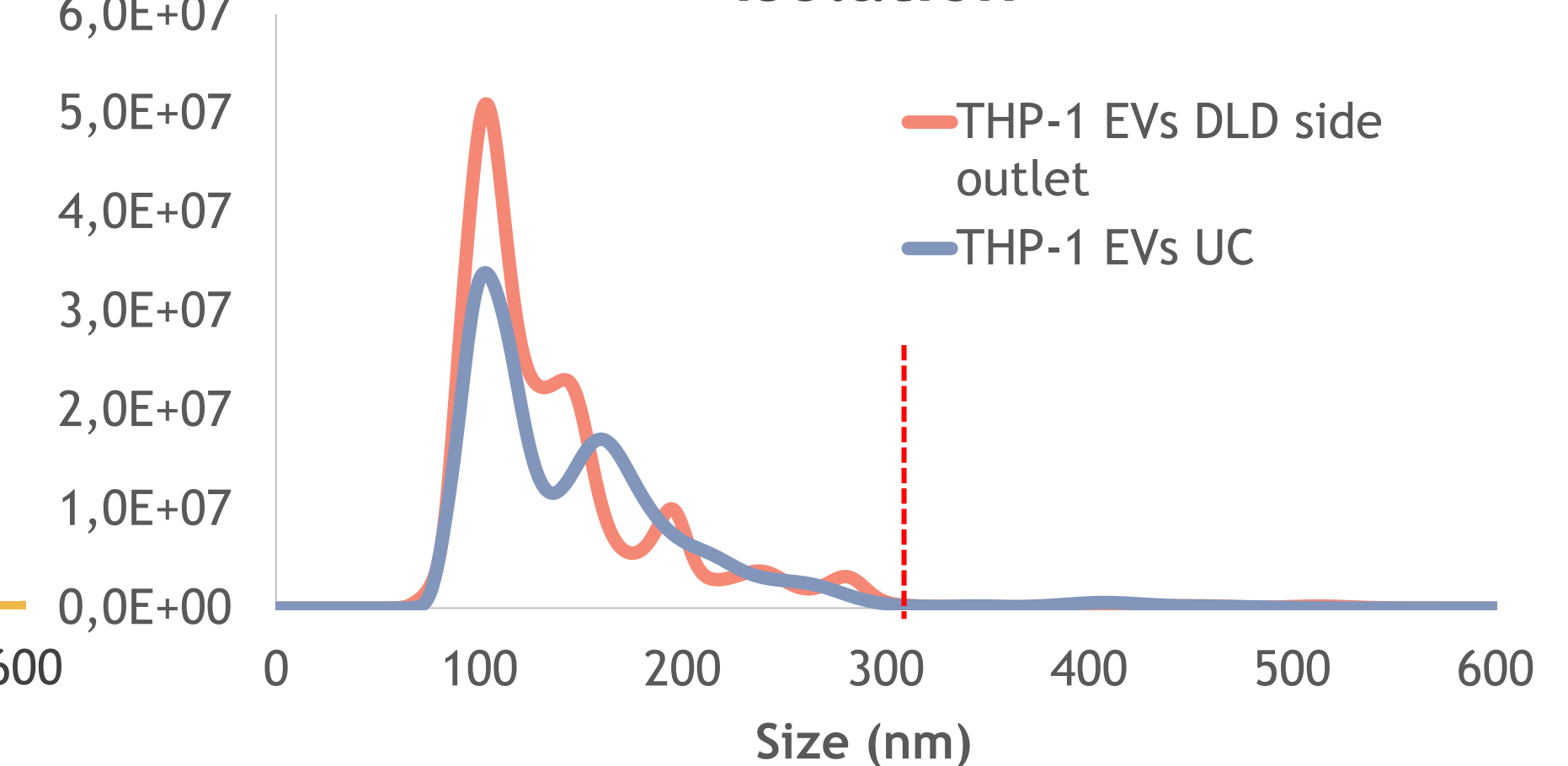
Size comparison of DLD outlets for THP-1 EVs isolation



- THP-1 EVs in side outlet of DLD
- Cell debris in central outlet

4- Comparison of sorting of EVs by DLD or by UC

EVs size comparison of DLD and UC isolation



- Similar size distribution trend for the main population subset compared with UC

Isolation process: ~ 10h ; 1.5mL collected ; [EVs] = 10⁸-10⁹/mL

CONCLUSIONS & MAIN OUTPUTS

- ✓ Original strategy enabling the **easy-to-operate** isolation of EVs
- ✓ Optimization of specific DLD **design and hydraulic resistance**
- ✓ **DLD Isolation of THP-1 EVs** from cell culture medium comparable to corresponding UC isolation
- ✓ Promising **non-destructive size-based microfluidic technique** for EVs isolation from complex biofluids