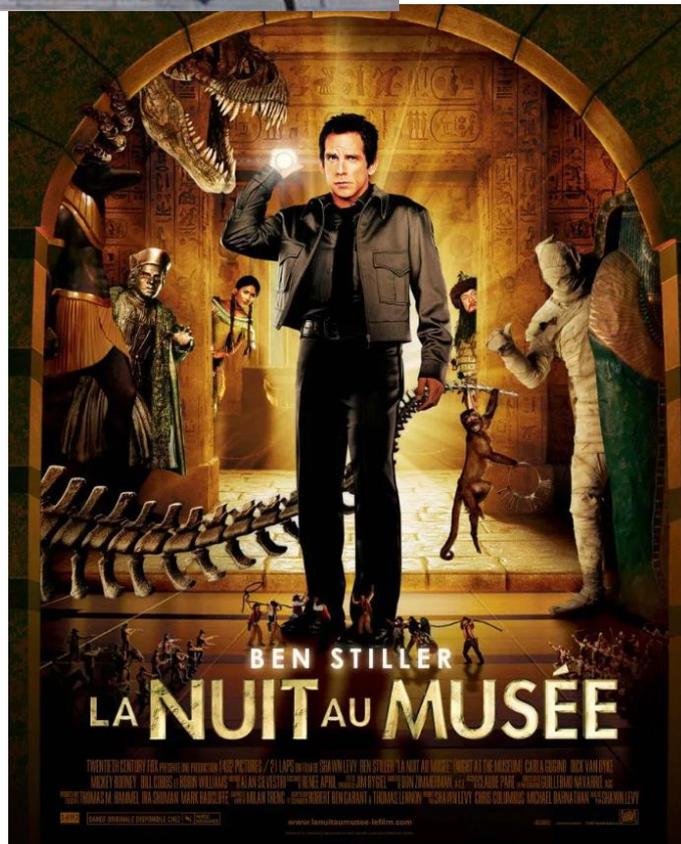
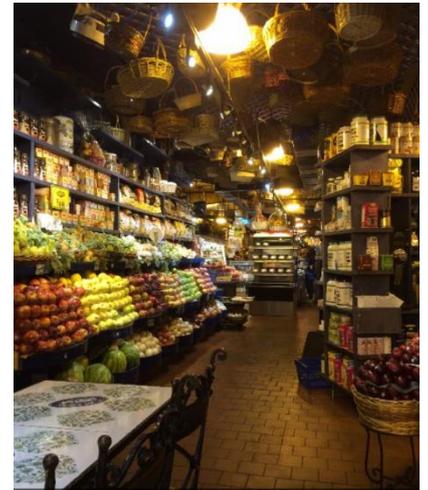


Jour 5 : jeudi 22 février 2024

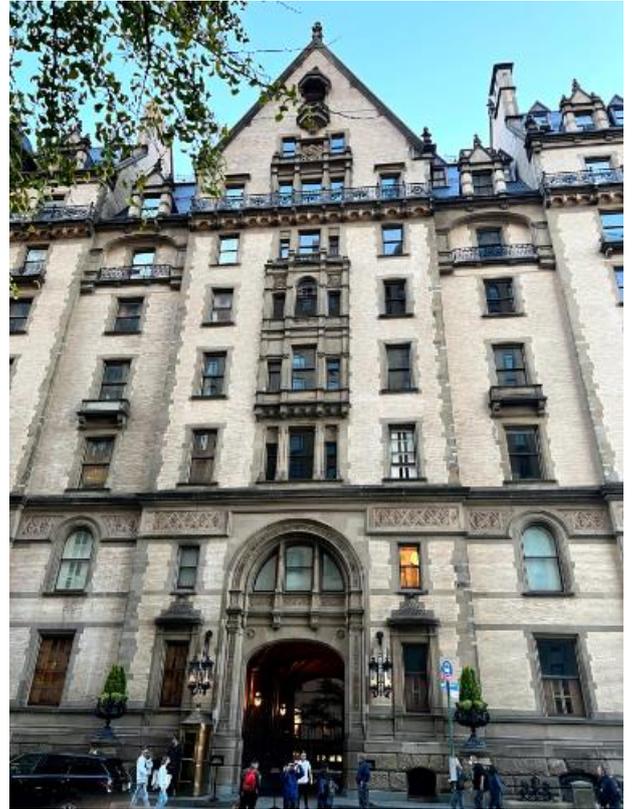
Ce matin, après avoir pris nos sandwiches et notre boisson au primeur (market) à côté de notre hôtel, nous sommes allés au musée Américain d'histoire naturelle, à cet endroit même où a été tourné « la nuit au musée » ....



Après avoir regardé un documentaire sur le « retour des baleines bleues », nous avons admiré les galeries, toutes aussi fantastiques les unes que les autres, en particulier, les dioramas des mammifères d'Afrique et d'Asie, le royaume sous-marin d'*Ocean Life* et l'exposition consacrée aux pierres précieuses et aux minéraux...

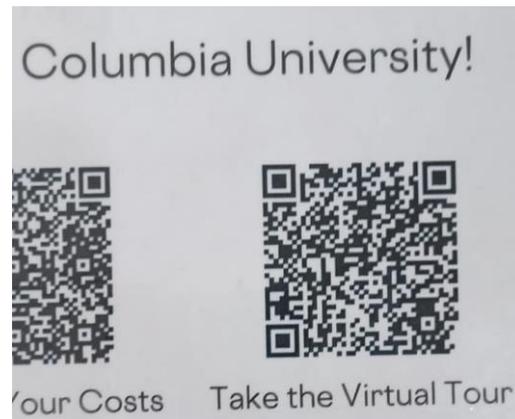
Jour 5 : jeudi 22 février 2024

Après un déjeuner dans Central Park, nous nous sommes dirigés dans la 72<sup>ème</sup> rue pour voir l'hôtel Dakota où John Lennon a été assassiné.



Puis nous avons pris le métro jusqu'à l'université Columbia

Prêt pour une visite virtuelle ?

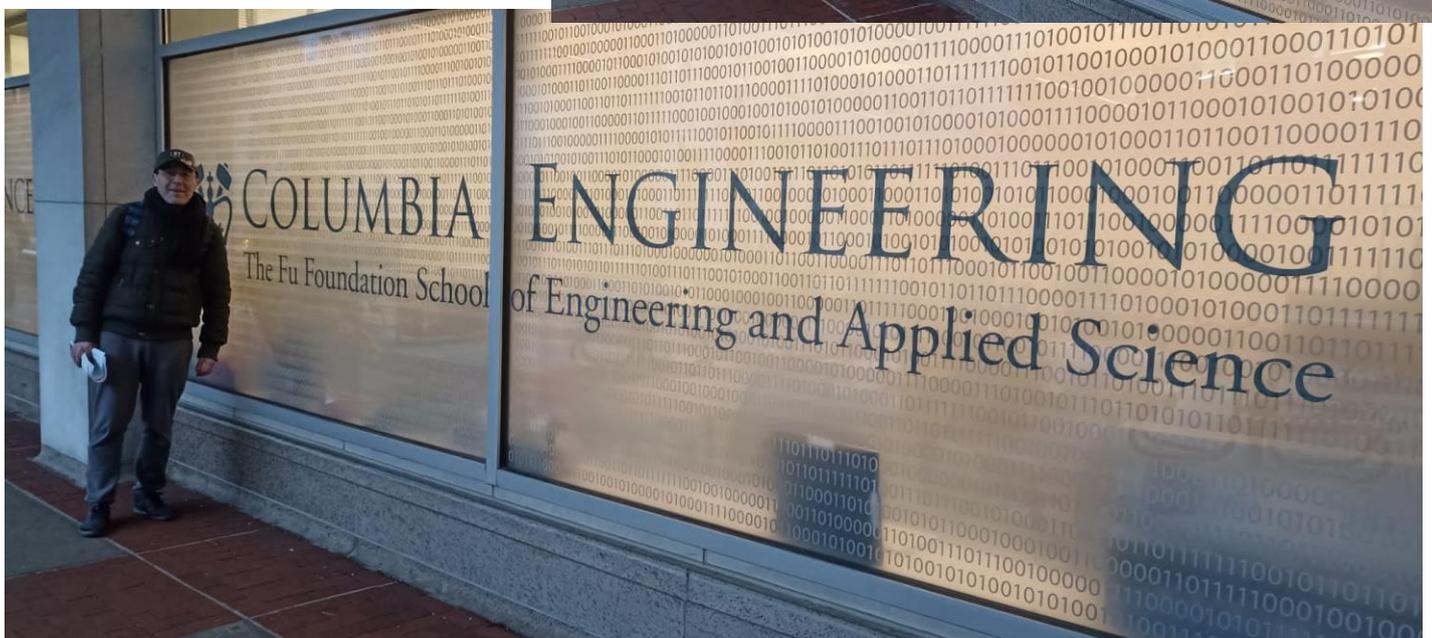
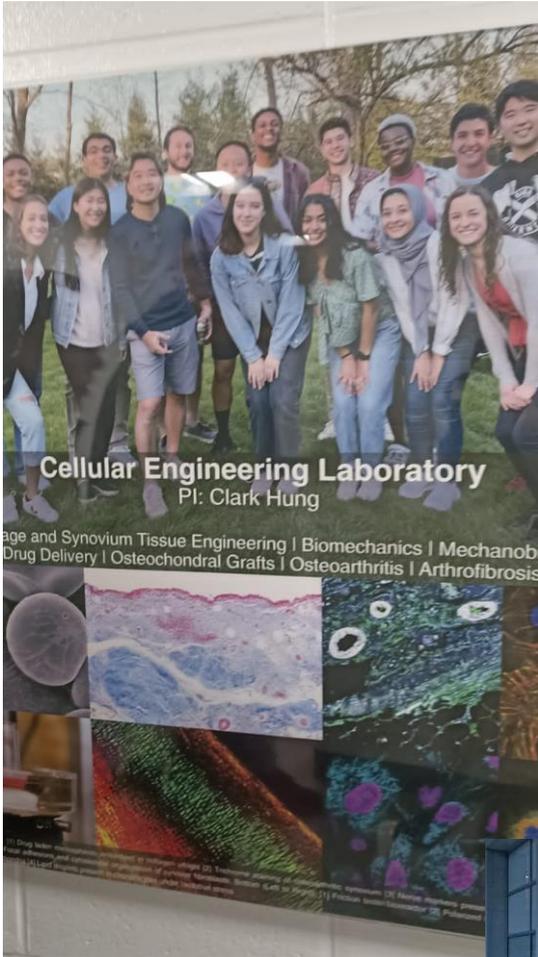


Devant la célèbre bibliothèque

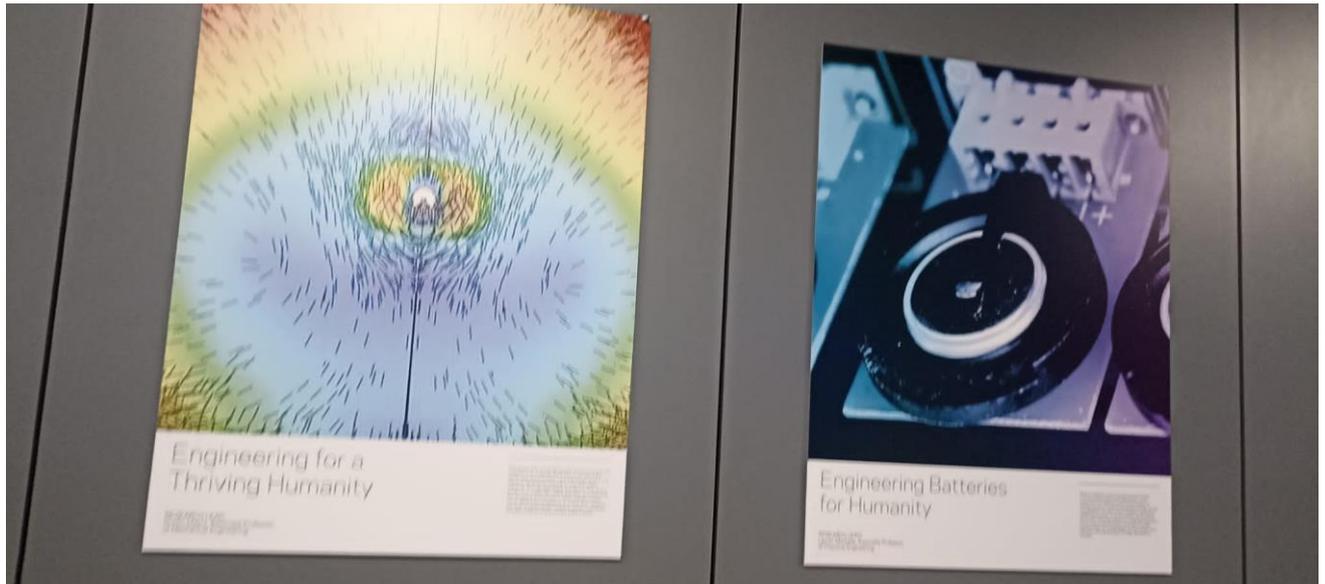


Jour 5 : jeudi 22 février 2024

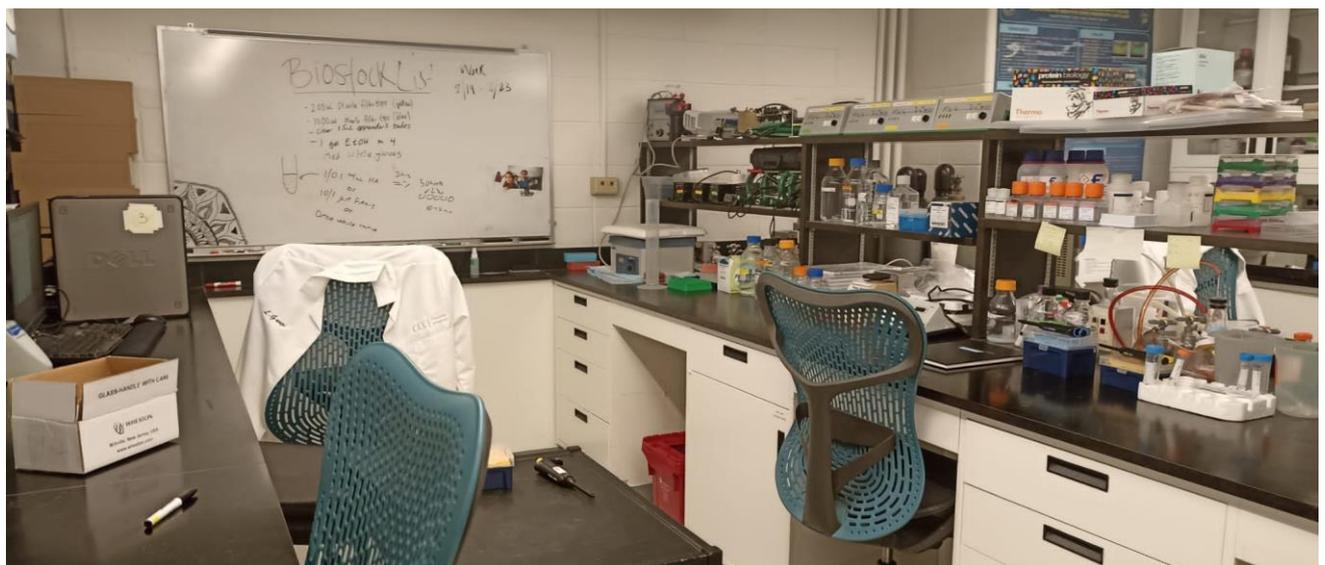
## Entrons dans les laboratoires de l'informatique et de l'ingénierie médicale



Jour 5 : jeudi 22 février 2024  
Quelques exemples de travaux :



Visite des laboratoires d'ingénierie médicale







# Focused Ultrasound-mediated Blood-Brain Barrier Opening Increases Extracellular Vesicle Concentration In Serum



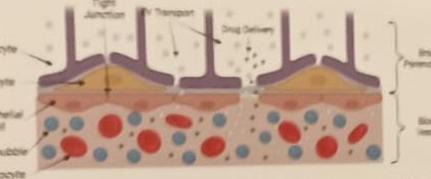
Iosif N. Tsitsos<sup>1</sup>, Alina R. Kline-Schoder<sup>1</sup>, Sua Bae<sup>1</sup>, Keyu Liu<sup>1</sup>, Antonios N. Poullopoulos<sup>1</sup>, Robin Ji<sup>1</sup>, Sergio Jimenez-Gambini<sup>1</sup>, Chris Dusefian<sup>1</sup>, Melody R. DiBenedetto<sup>1</sup>, Alec J. Batts<sup>1</sup>, Danae Kokkosal<sup>1</sup>, Akiva Mintz<sup>1</sup>, Lawrence S. Honig<sup>1</sup>, and Elio E. Konofagos<sup>1</sup>  
<sup>1</sup>Department of Biomedical Engineering, <sup>2</sup>Department of Radiation Oncology, <sup>3</sup>Department of Radiology, <sup>4</sup>Department of Neurology, Columbia University, New York, NY, USA

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## Introduction

### Focused Ultrasound-mediated Blood-Brain Barrier Opening

Focused Ultrasound (FUS), in combination with intravenously administered microbubbles (MB), induces safe and transient blood-brain barrier opening (BBBO) in mice [1], non-human primates [2], and humans [3]. FUS-BBBO has been studied both as a tool for enhanced drug delivery [4], and neuroimmunomodulation [5].



**Figure 1:** Schematic of the BBB after FUS-BBBO. Tight junctions are disrupted by microbubble activity under FUS, leading to increased drug delivery to the brain and enhanced EV transport to the bloodstream.

**Biomarker transport through the BBB**  
 FUS-BBBO enhances concentration of brain-specific biomarkers in blood [6]. Extracellular vesicles (EV) from brain cells may contain important disease and inflammation biomarkers [7].  
**Hypothesis:** FUS-BBBO increases concentration of brain cell-specific EVs in blood, allowing for enhanced, non-invasive biomarker detection.

## Objective

Assess the effect of FUS-BBBO on the concentration and content of EVs in the serum of healthy wild-type mice and Alzheimer's disease (AD) patients.

## Materials and Methods (Continued)

### FUS-BBBO in Alzheimer's disease patients

Parameter	Experimental condition
Transducer	Single-element, spherical, phased array, 1.5 MHz
Frequency	1.5 MHz
Peak Negative Pressure	200 psi
Pulse Length	10 ms
Pulse Repetition Frequency	2 Hz
Microbubbles	Definity (Lectustics)

**Figure 4:** Setup of clinical FUS-BBBO system [8].

## Results

### Serum EV concentration increases after FUS-BBBO in mice

**Figure 5:** Serum concentration of EVs increases 1 hour after FUS-BBBO in mice. The change in EV concentration for the FUS-BBBO group is significant with respect to both naive and sham groups [9]. Western blots for EV markers confirmed successful EV isolation [9].

### EV content is altered by FUS-BBBO in mice

**Figure 6:** Volcano plot of differentially expressed genes 1 hour after FUS-BBBO. Downregulated genes include *IL6*, a pro-inflammatory gene, and *Sox2*, a proliferation-associated gene. Upregulated genes include *Clcn11*, a tight-junction encoding gene.

**Proteomic analysis**  
 Comparison of inflammatory response-associated (lipopolysaccharide binding protein (LBP), and hemoglobin-associated proteins) hemoglobin alpha and beta.

### Preliminary results in AD patients

**Figure 7:** EV concentration in serum increases 1 hour after FUS-BBBO and decreases close to baseline levels 3 days after the procedure [9]. Comparison of serum neurological biomarker concentration in serum and isolated EVs 3 days after FUS-BBBO shows enhanced biomarker detection in EVs [9].

## Discussion and Conclusions

### A tool for improved brain liquid biopsy

Increased serum concentration of EVs following FUS-BBBO can be harnessed for non-invasive monitoring of brain-specific biomarkers through liquid biopsy.

### EVs reflect immunological response in the brain following FUS-BBBO

Increased expression of inflammatory genes in EVs after FUS-BBBO is consistent with previous findings of FUS-BBBO induced immune response [5].

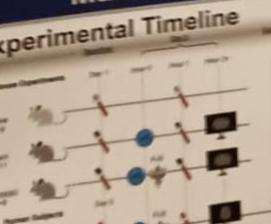
### Future work

Investigate the effect of FUS parameters on the concentration and content of EVs in serum.  
 Identify the cells of origin of EVs released following FUS-BBBO.

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## Materials and Methods

### Experimental Timeline



**Figure 2:** Experimental timeline for mice and AD patients. Baseline blood draws were collected the day before FUS for mice and immediately before FUS for AD patients. Blood was also drawn one hour post-FUS or sham procedure, and three days post-FUS procedure for patients. Contrast-enhanced MRI confirmed successful BBBO.

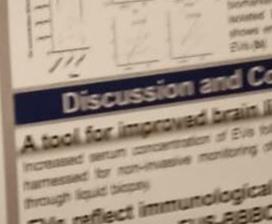
### FUS-BBBO experiments in mice

Parameter	Experimental condition
Transducer	Single-element, spherical, phased array, 1.5 MHz
Frequency	1.5 MHz
Peak Negative Pressure	200 psi
Pulse Length	10 ms
Pulse Repetition Frequency	2 Hz
Microbubbles	In-house synthesized DEPOCIN-PEG2000
Ultrasound Localization	0.4 T
MB Field Strength	Continuous (ultrasound) 200 mW/cm <sup>2</sup>
Acoustic Output	Non-invasive Training Protocol (Sonicare, Blue) reducing treatment time substantially
EV Analysis Methods	

**Figure 3:** Experimental setup of FUS-BBBO experiment. Mice were anesthetized using isoflurane and intubated. A 1.5 MHz FUS system was used for FUS. Blood samples were collected at 1 hour and 3 days post-FUS for both mouse and human samples.

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Jour 5 : jeudi 22 février 2024

En métro, nous retournons à notre hôtel pour récupérer les bagages.

Une boisson chaude réchauffe tout le monde.

Nous prenons la navette jusqu'à l'aéroport JFK.

Nous enregistrons nos billets puis nous passons les contrôles en douane.

Une heure de détente pour prendre une collation avant d'embarquer.

Nous décollons à 23h30.... Et nous atterrissons à Paris, le vendredi 23 février 2024, vers 12h20, heure locale.

Vers 15h00 nous prenons la navette de l'aéroport Charles de Gaulle à Amiens....

