

## Extracellular Vesicles in Brain Cancer Blood Testing

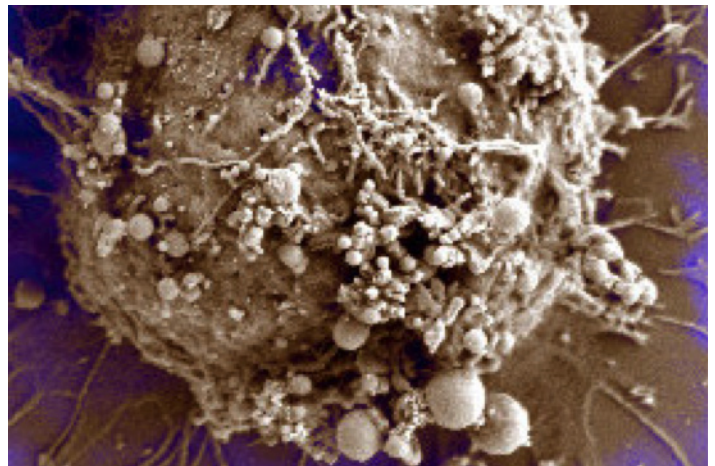
*Can a new screening for tiny cell particles help monitor the progress of brain cancers?*

Extracellular vesicles (EVs) are a diverse group of membranous structures that are shed from all cells of the body. They include exosomes, oncosomes, migrasomes and microvesicles, which play a role in cell-to-cell communication. Because cancer cells also shed these structures (Figure 1), and because they can be found in blood and other biological fluids, researchers are investigating whether they can capture cancer-related EVs as a noninvasive test for brain cancers at the time of diagnosis, through treatment and post-therapy.

Cancer cells can release up to 10,000 EVs per day. But since all cells release EVs, the question has remained how to isolate cancer-related EVs to retrieve the most information possible about a patient's cancer status. In a paper published in *Nature Communications* in January 2018, **Shannon Stott, PhD**, Assistant Professor at the Center for Engineering in Medicine at Massachusetts General Hospital Cancer Center, and colleagues describe a new technique using microfluidics and engineered nanosurfaces to capture EVs released from glioblastoma multiforme (GBM), the most common and aggressive form of brain cancer.<sup>1</sup> "As a mechanical engineer, this is an area where I decided I could contribute to the field—by developing a technology that would pull out just the tumor-specific EVs," says Dr. Stott, who is also a member of the BioMEMS Resource Center at Massachusetts General Hospital.

### MICROFLUIDIC CHIP TECHNOLOGY

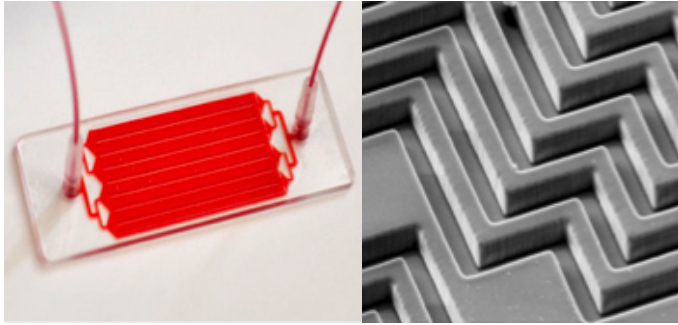
Since EVs are about 20,000 times smaller than a cell, the team needed to modify current techniques for moving bodily fluids through chip devices in order to capture accurate data at this scale. Stott's technology works by manipulating interactions between blood particles and the nanoparticles on the device surface. "By using microfluidics, we are able to have very precise control of how these vesicles move through our technology," says Dr. Stott, "ultimately enabling highly specific capture."



### Extracellular Vesicles Shed by Cancer Cells

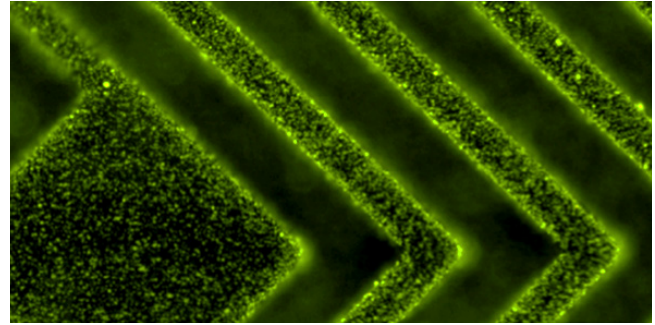
Figure 1: Electron micrograph of a tumor cell releasing extracellular vesicles.

By using a staggered herringbone pattern (Figure 2), the team was able to create chaos in the blood as it moved through the microfluidic chip. This resulting "chaotic flow" forms vortices in the fluid that increase the interactions between the vesicles and the engineered nanosurfaces of the device. In this proof-of-concept example, the <sup>EV</sup>HB-Chip device is lined with antibodies targeted against glioblastoma surface proteins. As the EVs from the glioblastoma cells flow through the chip they are captured by the antibodies on the surface of the device (Figure 3).



### Microfluidic Chip for EV Capture

Figure 2: Microfluidic chip (left) containing a herringbone-shaped engineered nanosurface (right).



### Microfluidic Chip Coated with EVs

Figure 3: Green dots are EVs from a GBM patient captured on a microfluidic chip.

## PROOF OF CONCEPT IN GLIOBLASTOMA

In their study, the team, including Dr. Xandra Breakefield and Dr. David Ting, identified tumor-related EVs from 13 GBM patients. Furthermore, six of the patients possessed the epidermal growth factor receptor variant III (EGFRvIII) mutation, which is specific to GBM tumors, and the device was able to detect this specific mutation in five of the patients. The researchers were also able to perform RNA sequencing on these vesicles and identify hundreds of tumor specific genes. “We could look at these genes and map them to subtypes of tumors in glioblastoma as well as see markers of progression, angiogenesis and molecules that might give an indication of the aggressiveness of the tumor,” says Dr. Stott.

Dr. Stott and her colleague, Dr. Brian Nahed at Massachusetts General Hospital, have initiated a larger GBM study with this technology with the intention of following patients from the day of diagnosis throughout the course of their treatment—with the goal of trying to understand the clinical relevancy of the information from EVs. More than 50 patients have enrolled in this study with some receiving EV analysis up to 30 different time points during treatment. “It is early, but we are seeing dynamic responses in biomarkers throughout the patients’ treatments,” says Stott. “We are working to look at the correlation with their treatment responses.”

Stott has focused on GBM initially because it is inherently difficult to source tissue from the brain, which is an obstacle to cancer screening. Early data suggests that EVs, in contrast to cancer cells or other, larger biomarkers of brain cancer, may be able to more readily pass the blood-brain barrier, which gives them the ability to convey important information in the blood about what’s going on there. “This technology is the next step for having a universal test for brain cancers,” says Dr. Stott, “and we hope that it can better match patients to the most appropriate clinical trial.”

While this first application is in GBM, the team is also investigating the technology’s potential with other cancers, pancreatic vesicles and neurodegenerative diseases.

<sup>1</sup> Reátegui E, Van der Vos K, Lai C, et al. Engineered nanointerfaces for microfluidic isolation and molecular profiling of tumor-specific extracellular vesicles. *Nat Commun.* 2018; 9(1):175.

# ADVANCES AT MASS GENERAL CANCER CENTER NOVEMBER 2018

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