**Docket #:** S17-343

# Exosome platform for tissue-specific drug delivery of mRNA or other therapeutic cargo

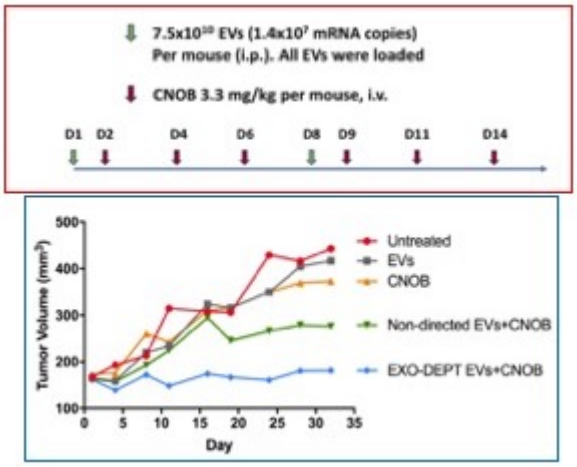
Researchers in Prof. A.C. Matin's laboratory have developed a versatile exosome (extracellular vesicle, "EV") drug delivery platform that can selectively target therapeutic agents to tumors or other tissues that overexpress extracellular receptors. This technology, called “EXO-DEPT” (exosome-directed enzyme prodrug therapy), directs therapeutic agents to the disease tissue while minimizing effects on healthy tissue by utilizing high-affinity ligands tethered to exosomes. This specificity allows higher concentrations of toxic drugs to be confined to a target/tumor site while preventing damage and severe side effects elsewhere. This may also decrease the risk drug resistance. EXO-DEPT was demonstrated by delivering functional exogenous mRNA to in HER2 positive breast cancer cells, thereby converting a harmless prodrug to a highly toxic drug that arrested tumor growth in mice. The basic system could also be adapted for a range of cargo molecules (e.g., siRNA, DNA, proteins or small molecule drugs) and receptor targets (e.g., PSMA, bombasin, folate, transferrin and sigma). Moreover, as exosomes can cross the blood brain barrier, this technology can treat metastasized cancer to the brain (often the case with breast and other cancers) as well as neurological diseases, such as Alzheinmer's.

**Stage of Research**

The inventors have demonstrated that the EXO-DEPT system with a high affinity anti-HER2 antibody can specifically deliver mRNA cargo to HER2 positive cells. Furthermore, they have shown that the functional mRNA delivered to the tumor cells converts a prodrug (CHOB) into a highly toxic drug (MCHB) which completely arrests tumor growth in a mouse model of HER2 positive breast cancer. This is the first demonstration of EV-mediated delivery of functional exogenous mRNA to tumors. The inventors continue to enhance the therapy and have a program to utilize the

platform in treating metastatic brain tumors.

**Figures:**




Description: Treatment of implanted orthotopic HER2 positive breast cancer in mice. Note that while controls show continued tumor growth, mice treated with EXO-DEPTs + the prodrug show complete arrest of tumor development.

# Applications

- **Drug/biomolecule delivery** - exosome delivery of therapeutic cargo to tissue that expresses a specific extracellular receptor, particularly for tumor-targeting in cancer

# Advantages

- **Tissue-specific, localized delivery** - by selectively targeting the drug and any toxic effects to specific cells, tumors or disease tissue, this drug delivery system could:
  - reduce severe side effects and prevent damage to healthy tissue, particularly for chemotherapy
  - increase concentration of drugs inside the targeted cells
  - avoid drug resistance
- **Versatile platform** - basic EXO-DEPT platform could be adapted for:
  - any condition where a disease tissue or tumor overexpresses an extracellular receptor

    - a range of therapeutic cargos, including mRNA, siRNA, DNA, proteins or small molecule drugs or prodrugs
    - activating a variety of prodrugs, including the prodrug CB1954 which has already been approved for clinical trials
- **Exogenous mRNA delivery** - “zipcode” technology promotes mRNA entry into exosomes
    - EXO-DEPT is the first example of functional exogenous mRNA delivered to cytoplasm via exosome
    - unlike DNA, mRNA can be directly translated without being transported to the nucleus and it does not have a risk of insertional mutagenesis
- **Crosses blood-brain barrier** - enabling drug delivery to metastatic brain tumors
- **Advantages of exosomes/extracellular vesicles:**
    - unlike other nanoparticles, exosomes are non-immunogenic because the lipid bilayer composition is similar to the body's own cells, especially when derived from mesenchymal stem cells or a patient's own dendritic cells
    - stable in vivo - can circulate for extended periods of time within the body while avoiding the endosomal pathway as well as degradation by macrophages and lysosomes
    - delivers cargo directly to cytoplasm

# Publications


- Alexis V. Forterre et al. Extracellular Vesicle-Mediated In Vitro Transcribed mRNA Delivery for Treatment of HER2+ Breast Cancer Xenografts in Mice by Prodrug CB1954 without General Toxicity *Molecular Cancer Therapeutics*, March 2020.
- Jing-Hung Wang et al. Anti-HER2 scFv-Directed Extracellular Vesicle-Mediated mRNA-Based Gene Delivery Inhibits Growth of HER2-Positive Human Breast Tumor Xenografts by Prodrug Activation *Molecular Cancer Therapeutics*, May 2018.
- Steven M. Jay,. "An EVolving approach to directed enzyme prodrug therapy for cancer", *Science Translational Medicine*, March 21, 2018.


# Patents

- Published Application: WO2019067464
- Published Application: 20210161817
- Issued: 11,517,530 (USA)

## Innovators

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