

## METHODS OF MAKING EXTRACELLULAR VESICLES AND OF REDUCING THEIR UPTAKE BY THE LIVER

### SUMMARY (1024-CHARACTER LIMIT)

Researchers at the National Cancer Institute (NCI) have developed scalable cGMP-compatible technologies to obtain highly purified engineered extracellular vesicles (EVs) for therapeutic delivery. The NCI invention 1) includes novel forms of the immunotherapeutic agent heterodimeric, interleukin-15 (hetIL-15) designed to therapeutically enhance EV and 2) provides methods of reducing liver uptake of EVs, thereby increasing delivery to target sites, such as tumors.

### NIH REFERENCE NUMBER

E-083-2016

### PRODUCT TYPE

- Therapeutics

### KEYWORDS

- Extracellular Vesicles
- EV
- Heterodimeric Interleukin-15
- hetIL-15
- Cancer
- Vaccine
- Drug Delivery
- Nanomedicine
- Personalized Medicine

### COLLABORATION OPPORTUNITY

This invention is available for licensing and co-development.

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### STATUS

Active

## DESCRIPTION OF TECHNOLOGY

Extracellular vesicles (EVs) are an emerging new class of nano-sized biological delivery systems involved in intercellular communication, immune responses, and tissue regeneration, that are increasingly being investigated for therapeutic potential. Since EVs are released by cells endogenously and naturally transfer genetic material and proteins, they offer a safer alternative for delivery of biologicals (e.g. RNAs, cytokines, monoclonal antibodies). In addition, EVs carry complex biological messages of the parental cell, and thus are being tested as safer alternatives to cell therapy (e.g. in lieu of mesenchymal stem cell therapy for heart tissue regeneration). Furthermore, in human clinical trials EVs have been used as cancer vaccines and for immunomodulation.

Significant opportunity for EV discovery and understanding remain. For the successful translational development of EVs there is a need for efficient, scalable processes for production, therapeutic enhancement, and purification. In addition to being scalable, these methods must retain the biological properties of EVs to avoid loss of their therapeutic activity. There are also opportunities to improve the use of EVs to treat disease. Administered EVs are rapidly cleared by the reticuloendothelial system (RES), especially by liver macrophages. The clearance of EVs by the RES decreases their delivery to desired target sites, including tumors. Consequently, there is a need for improved EVs, methods of producing EVs, and methods of improving delivery of EVs to a target site.

Researchers at the National Cancer Institute (NCI) have developed a method of scalable EV production and effective delivery, thereby representing a significant market opportunity. The NCI's technology provides a fully scalable procedure for production and purification of extracellular vesicles enriched for hetIL-15, a molecule in clinical trials for treatment of metastatic cancer. The technology includes a novel, bioactive, fully human form of the cytokine (hetIL-15/Lactadherin) capable of more efficiently coating the surface of EVs. The invention also includes methods for producing large amounts of these EVs in a bioreactor, and ways of efficiently obtaining highly purified EV preparations using cGMP-compatible tools (namely, tangential flow filtration and size-exclusion chromatography). Moreover, the invention includes methods of blocking the rapid clearance of administered EVs by liver macrophages, which enables enhanced accumulation of EVs carrying the therapeutic molecule, hetIL-15 to tumors. Implementation of the NCI's methods will allow interested commercial partners to proceed with large-scale production of EVs for therapeutic use. Additionally, commercial partners may expand on the scope of the invention, for example by developing more effective molecules for blocking liver uptake and using the hetIL-15/Lactadherin protein to coat EVs from primary human cells.

## POTENTIAL COMMERCIAL APPLICATIONS

- cGMP-compatible, large-scale purification of EVs from cultured primary cells and cell lines for pre-clinical and clinical development
- Development of therapeutic EVs enriched for bioactive hetIL-15, using EVs from primary human cells

or recombinant cell lines

- Development of novel molecules that block scavenger receptors, in order to modulate uptake of therapeutic EVs by liver macrophages and enhance targeted EV delivery

## COMPETITIVE ADVANTAGES

- 60 times higher EV yield per mL cell culture vs. conventional methods
- 55 times more loading of bioactive hetIL-15 on EVs
- 4-5 times less clearance of EV by liver macrophages, and a corresponding increased delivery of EVs to tumors

## INVENTOR(S)

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## DEVELOPMENT STAGE

- Pre-clinical (in vivo)

## PUBLICATIONS

Watson D et al. Efficient production and enhanced tumor delivery of engineered extracellular vesicles. [PMID 27522254]

## PATENT STATUS

- **U.S. Patent Filed:** U.S. Patent Application Number PCT/US2017/025550, Filed 31 Mar 2017

## RELATED TECHNOLOGIES

- E-141-2008
- E-054-2013

## THERAPEUTIC AREA

- Cancer/Neoplasm