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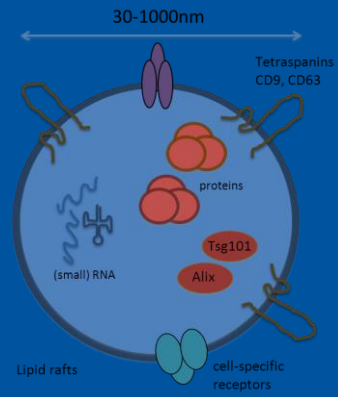

Extracellular vesicles for therapeutic RNA delivery

EIC-ERC Workshop on Gene and Cell Therapy, June 29th, 2021

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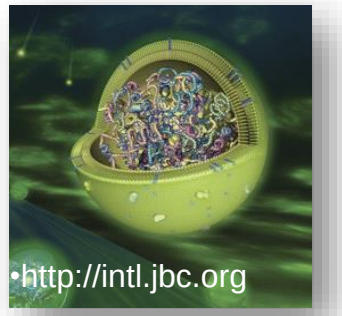
University Medical Center Utrecht

Extracellular vesicles

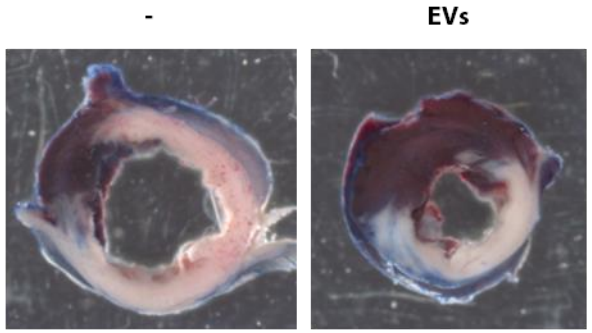
- EVs: membrane surrounded structures released by cells
- Natural carriers of biomolecules
- Constitutive release & after activation
- Capable of functionally transferring cargo to recipient cells

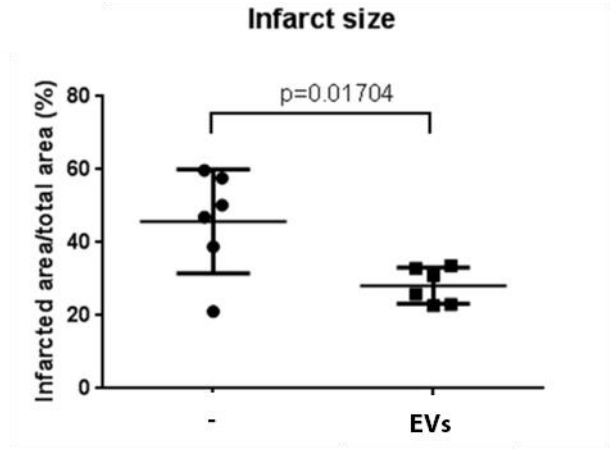


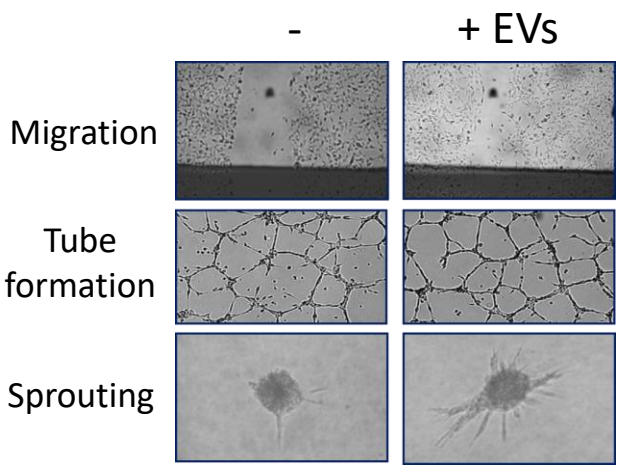
Extracellular vesicles for RNA delivery

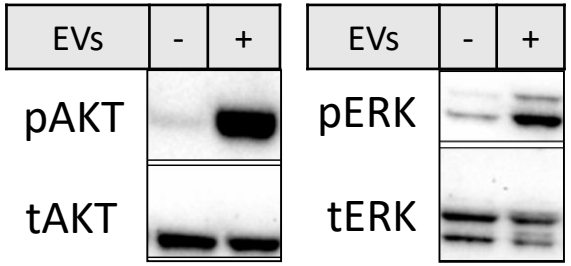
Potential advantages over synthetic systems:

- No/low immunogenicity
- Stable
- Utilize native mechanisms for targeting, uptake and intracellular trafficking
- Intrinsic therapeutic efficacy



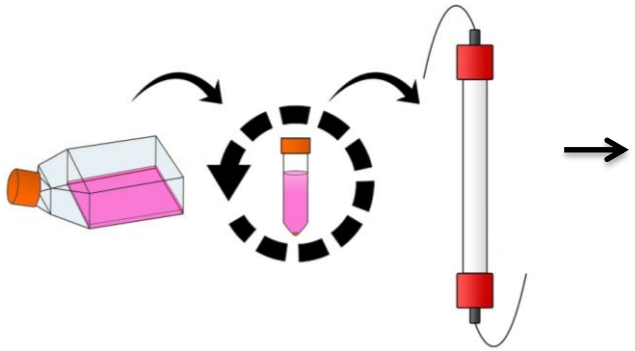


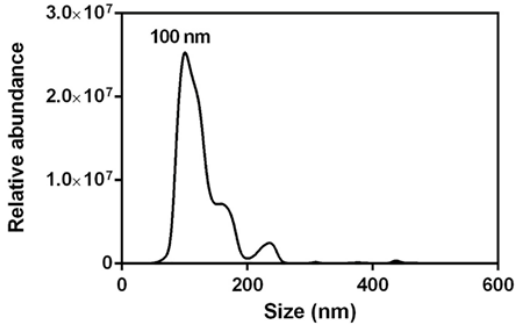


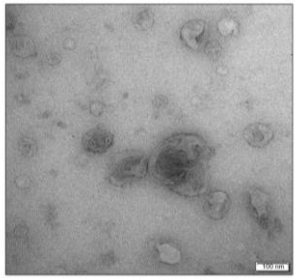


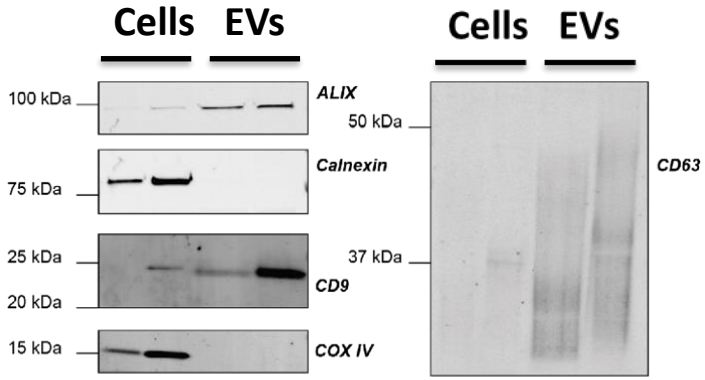
Vrijsen et al., Adv Healthc Mat, 2016;
Mol et al., Nanomedicine NBM, 2017;
Maring et al., J Cardiovasc Transl Res, 2019

EV loading & targeting

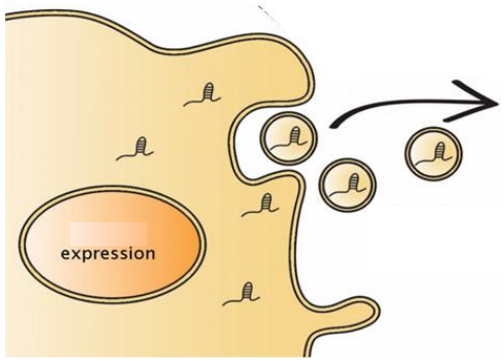






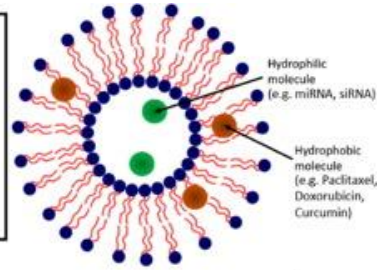


Loading



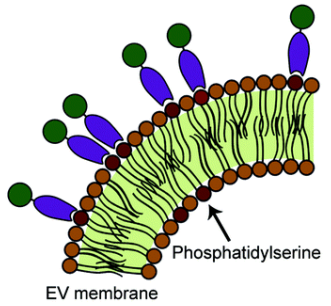
Active Loading:
Electroporation
Sonication
Detergents (e.g. saponin)
Freeze-thaw

Passive Loading:
Incubation (RT or 37°C)



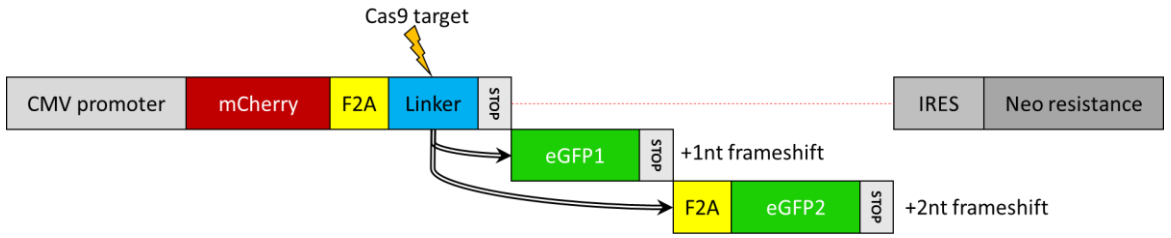
Parameters affecting loading efficiency and activity:
Size, concentration and polarity of cargo
Incubation time, loading protocol
Cargo aggregation (e.g. RNA loading using electroporation)
Denaturation/loss of therapeutic activity (e.g. freeze-thaw)
EV isolation method and estimation of starting material

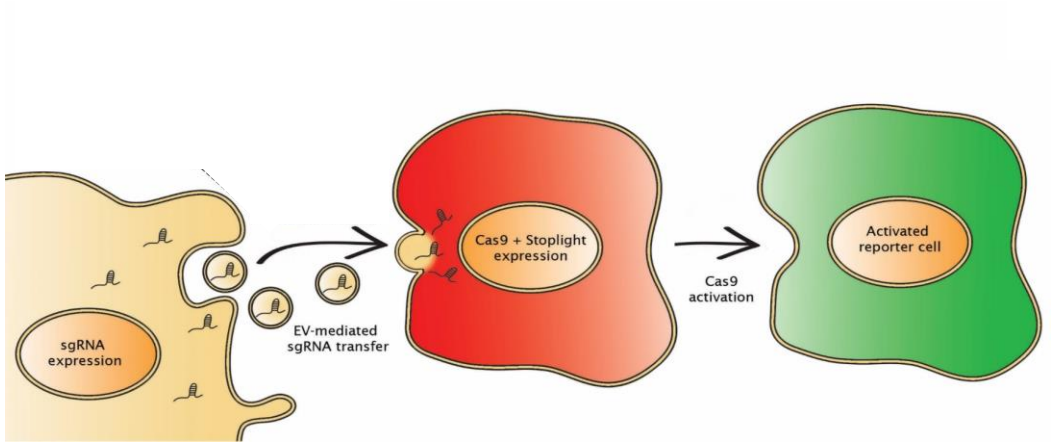
Targeting



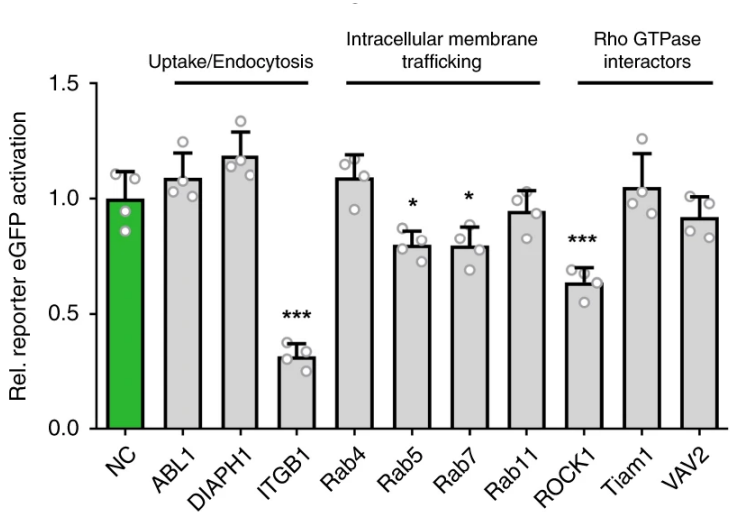
Kooijmans et al., J Extracell Vesicles, 2016;
O'Loughlin et al., Mol Ther, 2017;
Kooijmans et al., Nanoscale, 2018;
Rankin-Turner et al., Adv Drug Deliv Rev, 2021;

Mechanistic insight

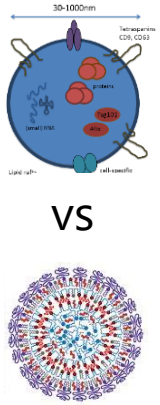


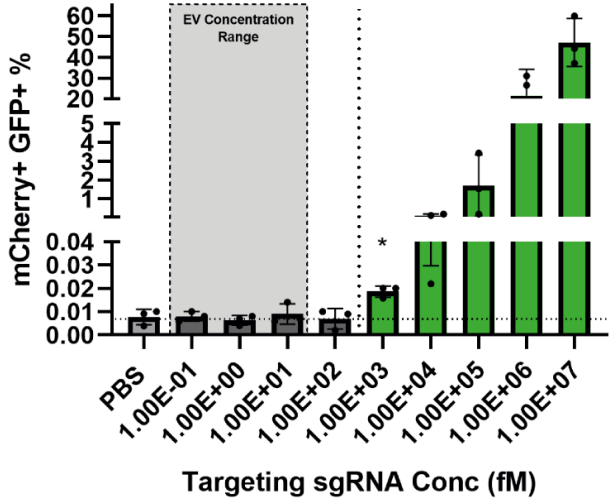


Molecular mechanisms



Efficiency

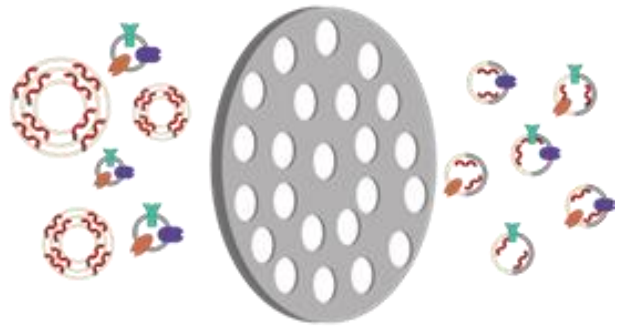




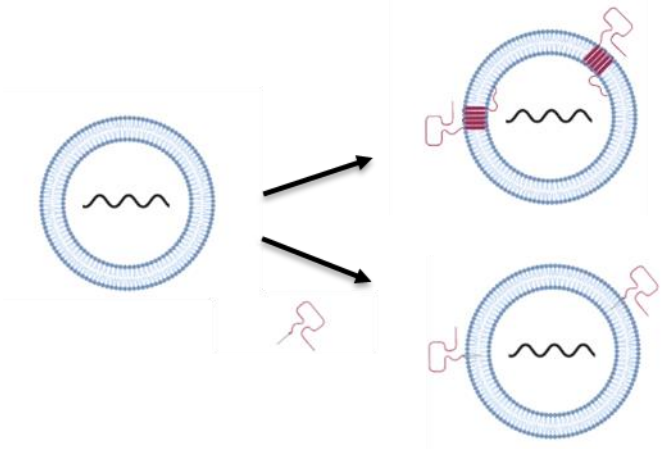
Costa Verdera et al., J Control Release, 2017;
De Jong et al., Nat Commun, 2020;
Murphy et al., Nano Lett, 2021;

EV hybrids & mimics

Hybrids



Mimics



Does incorporation of EV components improve delivery characteristics of synthetic nanocarriers?

Evers et al., submitted;

Acknowledgements

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