

# ReNeuron

## TARGETED DELIVERY OF THERAPEUTIC PAYLOADS USING STEM-CELL DERIVED EXOSOMES

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# Introduction



ReNeuron's seven proprietary cell lines and Conditional Immortalisation Technology.



Distinct Exosome Profiles influence cellular tropism.



Recent *in vivo* validation of CustomEX™ targeting capabilities.

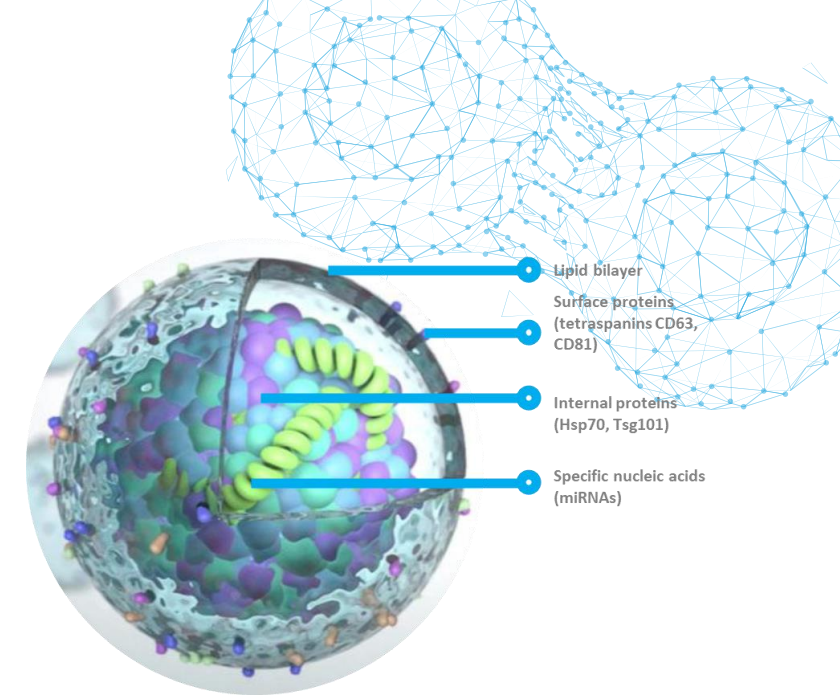


Confirmation of targeted delivery of a therapeutic payload *in vivo* using the CustomEX™ platform.

# Why stem cell exosomes?

## ⦿ Limitations around current delivery platforms

- **Safety** - Viral vectors have been plagued by side effect issues. Viral vectors and LNP's , both have immunogenic properties that are problematic
- **Efficiency of loading and delivery** - Limitations on the type, size of cargo and the efficient delivery of therapeutic dose (endosomal escape)
- **Tissue/cell targeting** - Lipid Nanoparticles & HEK derived exosomes have limited targeting abilities with delivery mainly to the liver.



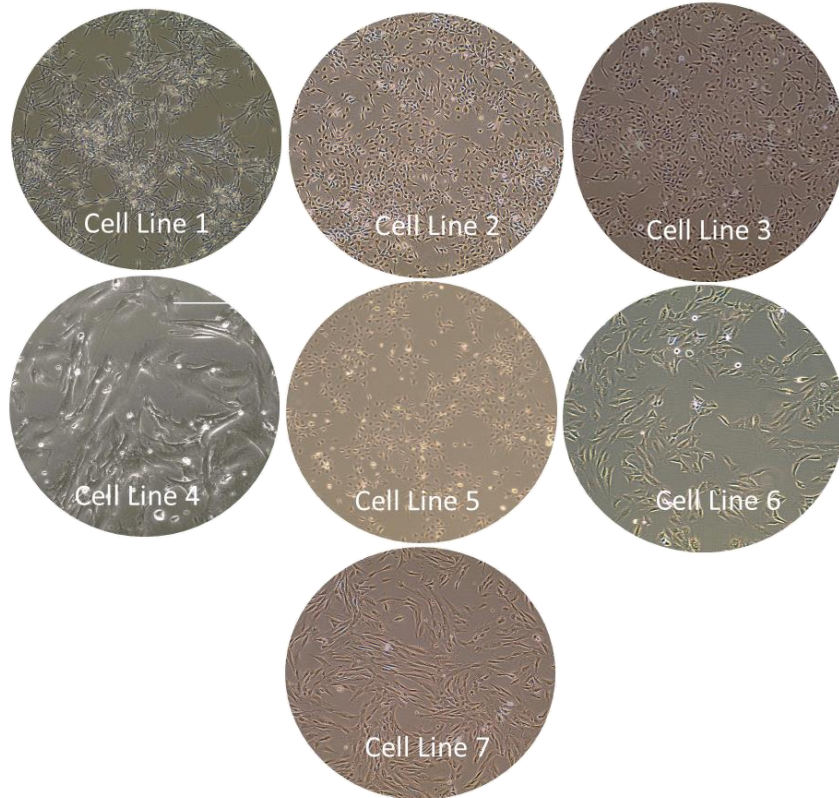
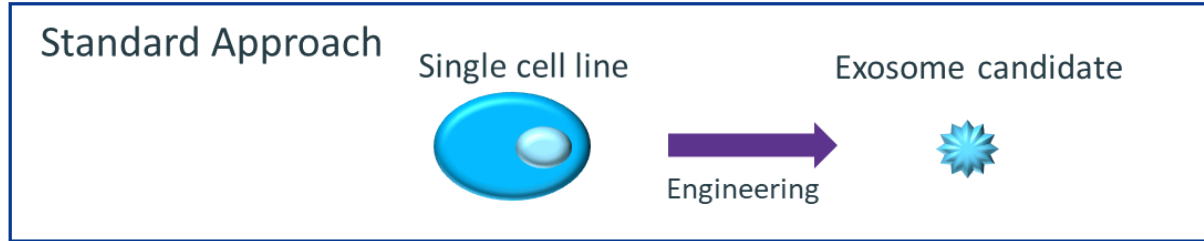
## ⦿ Stem cell exosomes - targeted delivery platform for complex drug modalities

- **Safety** - Naturally occurring nanoparticles released by all cells for the purpose of intercellular communication – non immunogenic
- **Efficiency of loading and delivery** - Proven ability to carry and deliver more than one bio-active cargo simultaneously including proteins and nucleic acids
- **Tissue/cell targeting** - Critically, they target recipient cells via specific surface proteins that are determined by their cell of origin

EXOSOME CELL SOURCE IS AN IMPORTANT CONSIDERATION FOR TARGETED DRUG DELIVERY



# CustomEX™ - A customisable, exosome platform optimised for specific targeting capabilities



## Competitors – Single cell line approach

- Single cell line, single outcome
- ‘One size fits all’

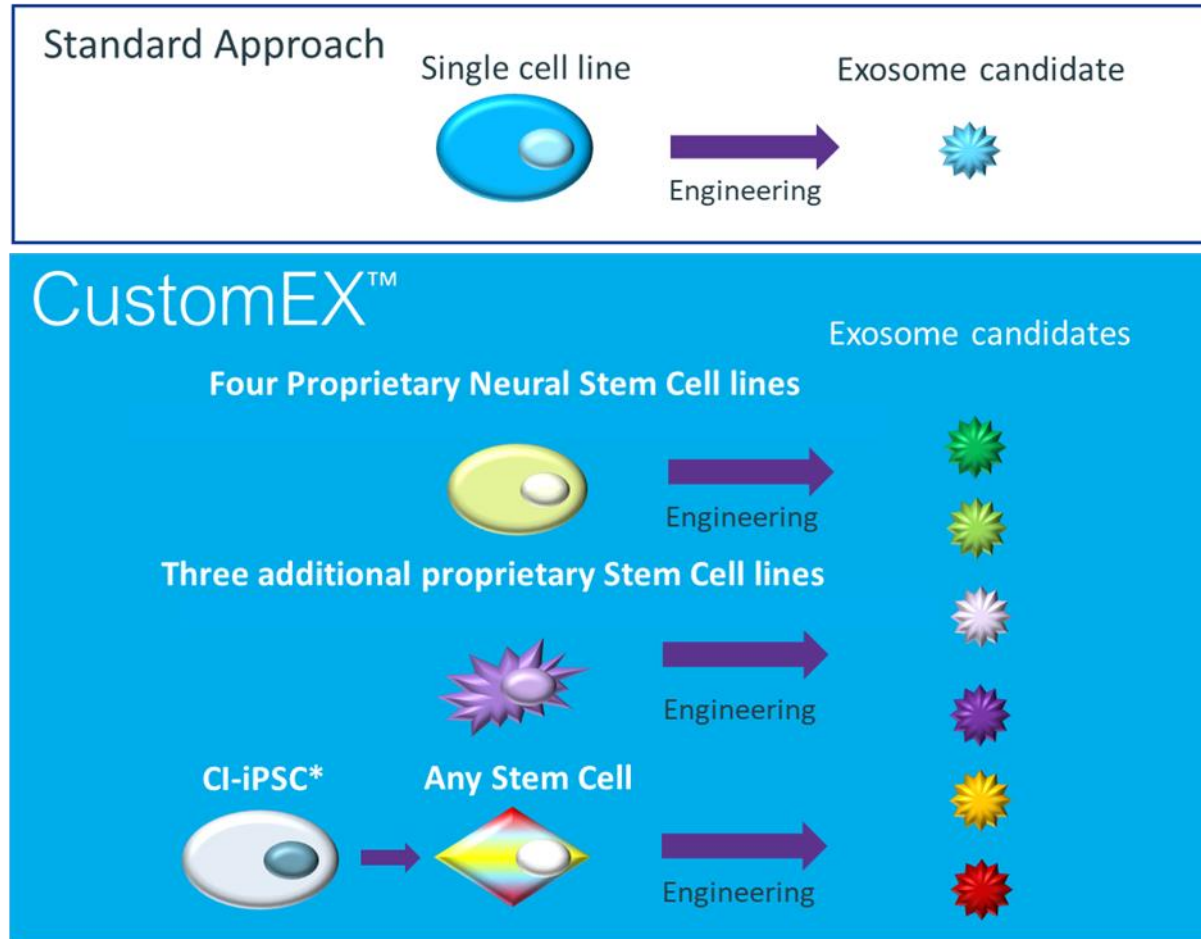
## ReNeuron – Portfolio of stem cell derived exosomes

- Exosomes have functional properties based on parent stem cell line
- Multiple conditionally immortalised exosome producer lines allows candidates to be chosen for their ability to target specific tissues and cell types

## ReNeuron – Know-how and IP

- 15+ years of experience in CLD and GMP manufacture of stem cells
- IP around conditional immortalization and production of stem-cell derived exosomes and loading
- 10+ years of clinical safety data for conditional immortalization technology

# CustomEX™ - A customisable, exosome platform optimised for specific targeting capabilities



CustomEX™ is a trade mark of ReNeuron Limited

\*CI-iPSC: Conditionally immortalised induced pluripotent stem cells

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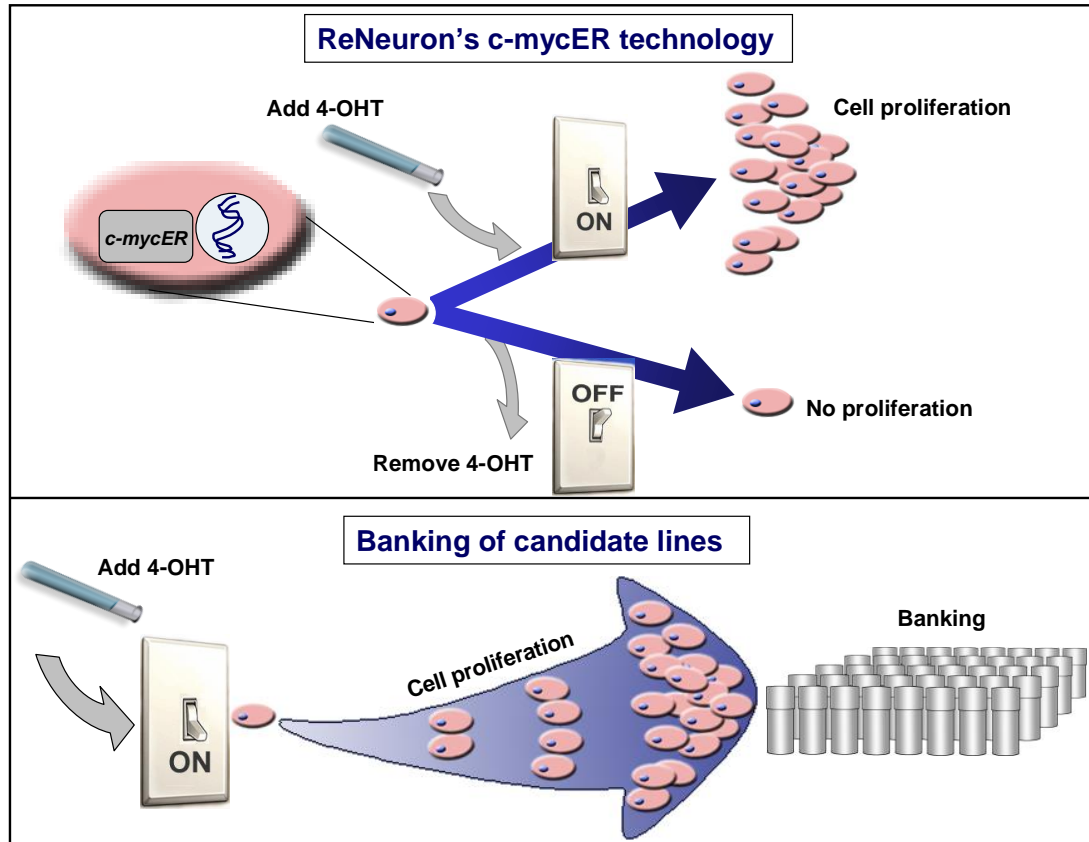
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# Conditional Immortalisation – The ReNeuron Advantage

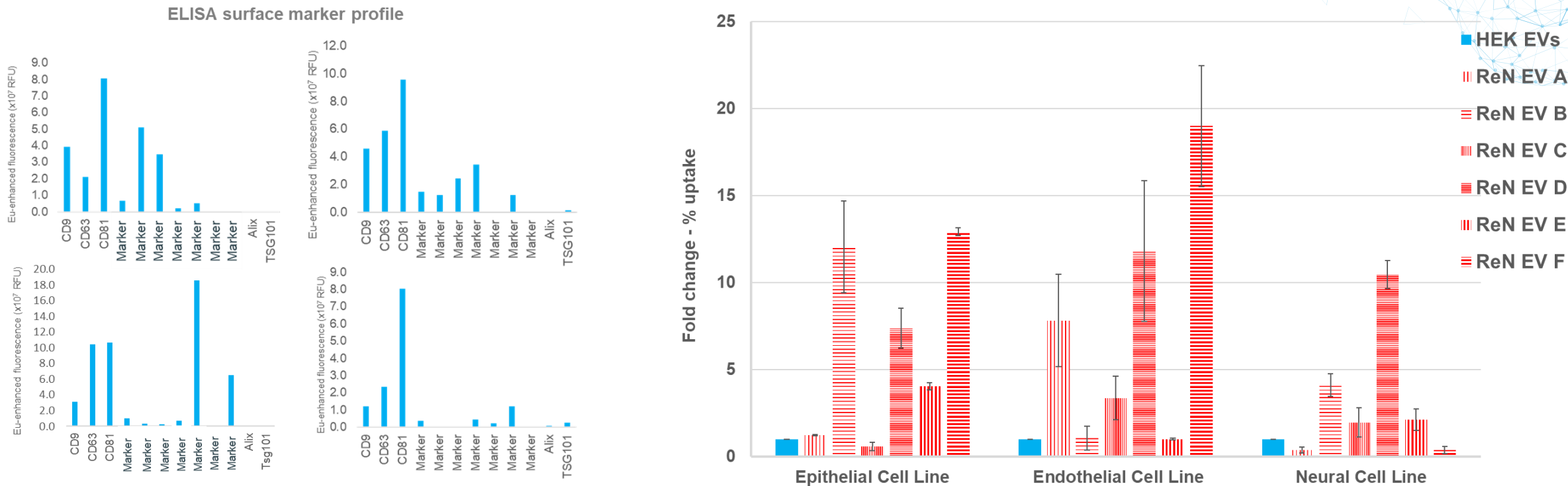


- Standard stem cell exosomes have significant barriers to their clinical translation
  - Heterogeneity
  - Scale
- Consistent and Scalable Exosome Production through Conditional Immortalisation of the producer cell line
  - Stable producer cell line - Consistent phenotype maintained over multiple passages
  - Fully qualified xeno-free GMP process – tightly controlled USP with strict release criteria
  - Scalability - produced to a commercially relevant scale in multi-tier tissue culture flasks
  - Stable exosome product at 4 °C, -80 °C
  - Safe: No c-MycER<sup>TAM</sup> within exosomes

CONDITIONAL IMMORTALISATION TO PRODUCE CONSISTENT EXOSOMES AT A CLINICALLY RELEVANT SCALE

# In vitro data highlighting exosome targeting is dependent on cell source

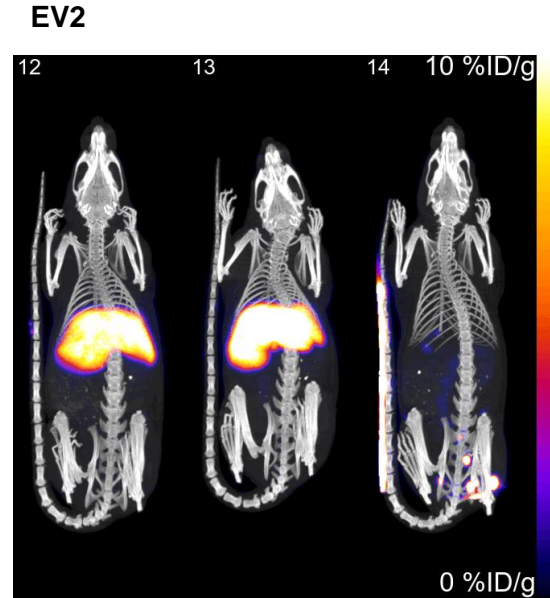
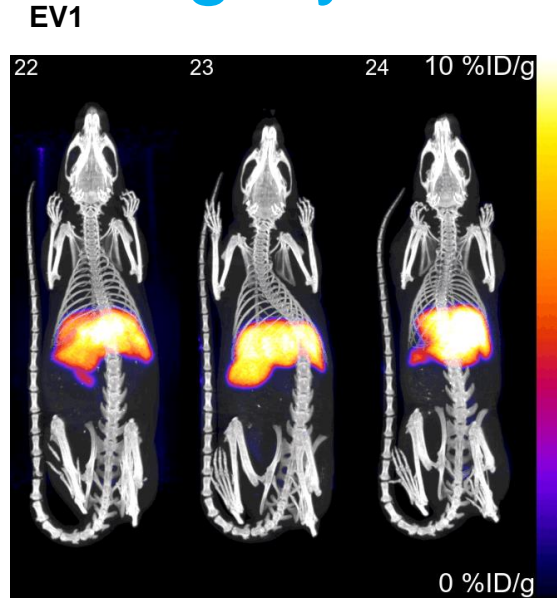
Exosome biology influences tropism and delivery of cargo – *selection of exosome type is an important consideration.*



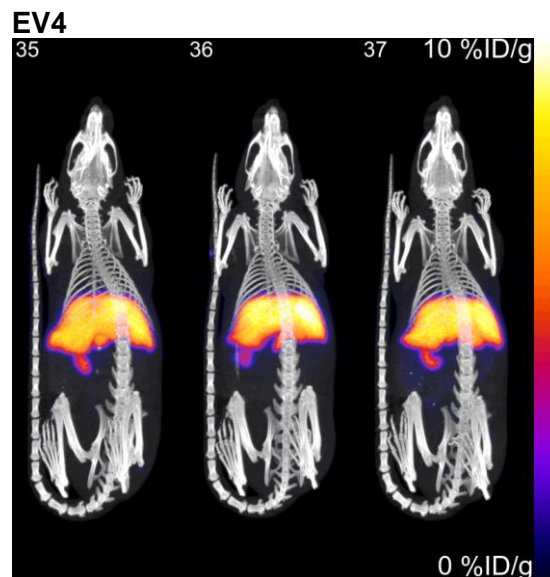
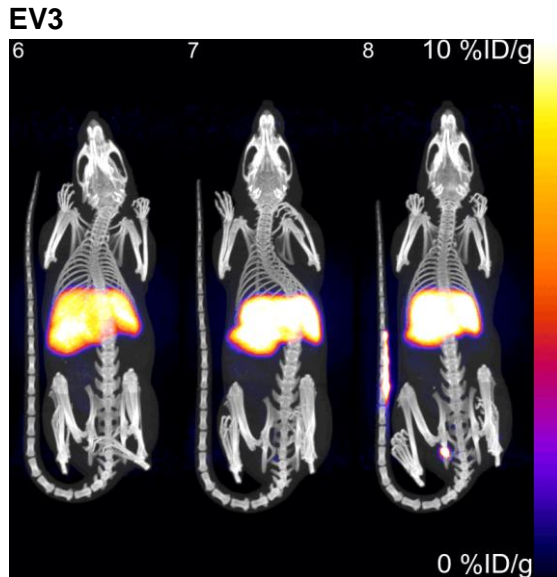
- Previous results indicated that the CustomEX™ products were distinct in their protein expression profiles and uptake profiles in a panel of cell lines suggesting that exosome biology influences tropism and therefore may result in better delivery of a therapeutic cargo.



# Main Tissue Distribution Similar Irrespective of Cell Source Following Systemic Administration

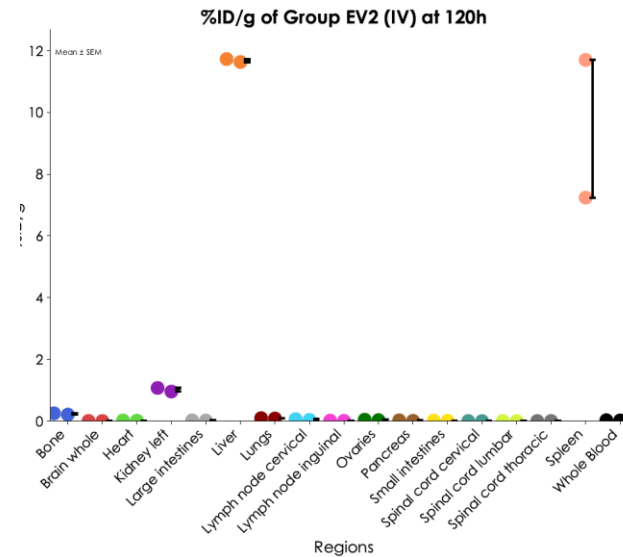
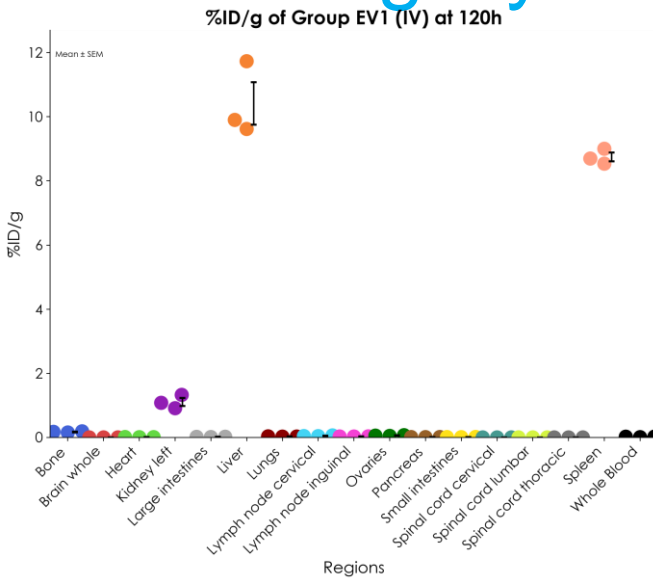


*\*Note 1 animal had a missed injection and was excluded from the analysis.*

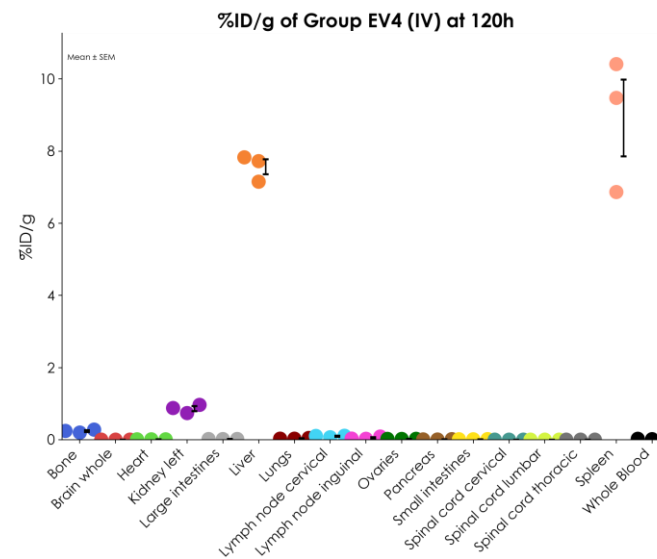
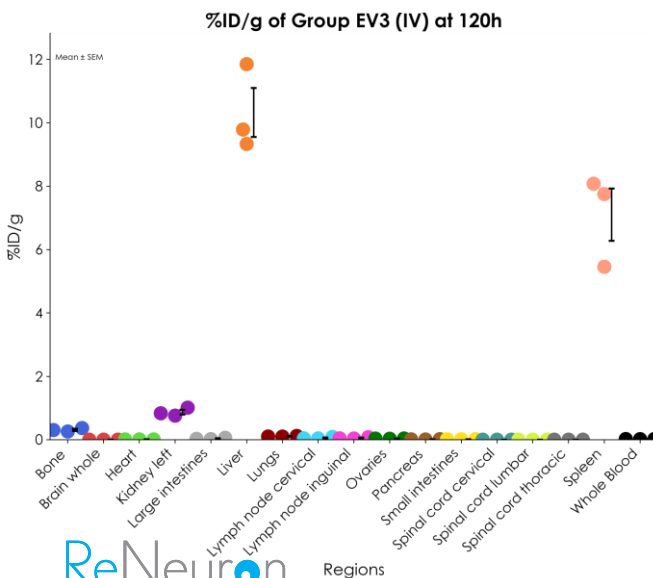


- **Zr-89 labelled exosomes mainly trafficked to the liver and spleen** (and to a lesser extent the kidney).
- This signal was retained up to 120h timepoint.
- Biodistribution to the liver, spleen and kidney was further confirmed at the experimental end point (120h) using gamma counting outputs of the selected tissues/organs.
- This also indicated that the **distribution follows the same pattern irrespective of exosome cell source**.
- This potentially indicates that no differences in biodistribution will be observed when carrying out a radioactive PET/CT study due to limits in resolution and due to the whole organ/tissue being quantified.

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# Confirmation in vivo that exosome targeting is dependent on cell source

## Immune targeting capabilities of CustomEX™ #3

### Small animal (rat) biodistribution study

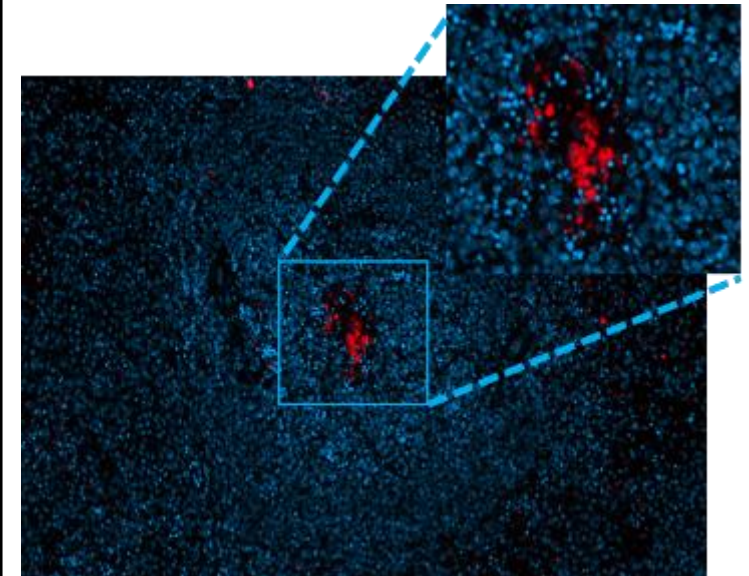
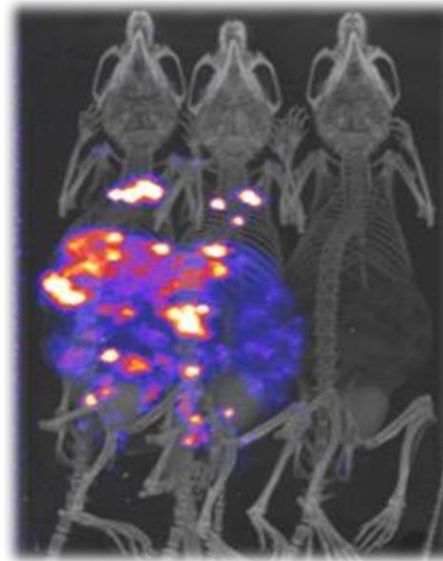
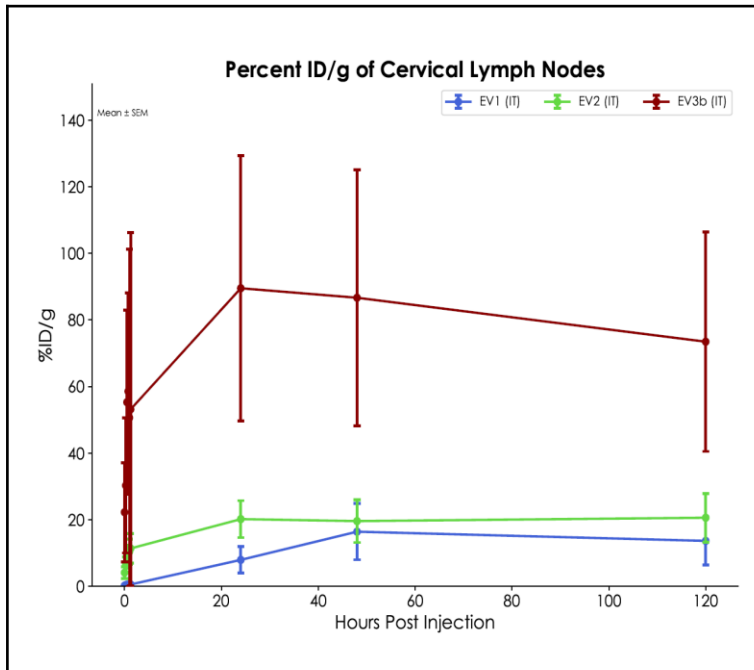
- IT administration of Zr<sup>89</sup> labelled exosomes
- Distinct function of CustomEX™ #3 to target the cervical lymph node

### Small animal (mouse) biodistribution study

- Similar lymph node targeting observed following IP administration

### Large animal (pig) spleen perfusion

- Systemic delivery of CustomEX™ #3
- Confirms immune cell targeting through accumulation of fluorescently labelled CustomEX™ #3 in the white pulp (germinal centre) of the spleen

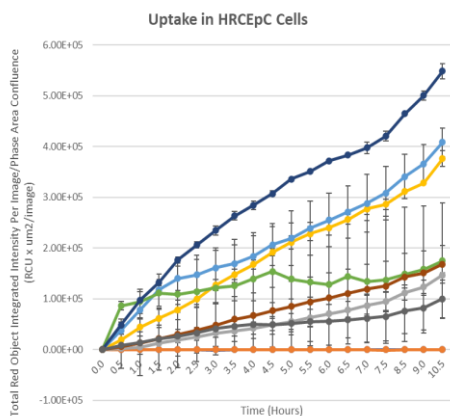
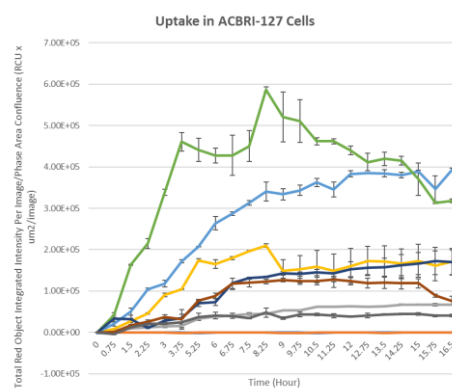
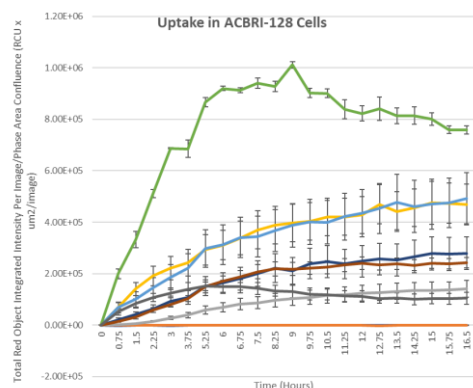




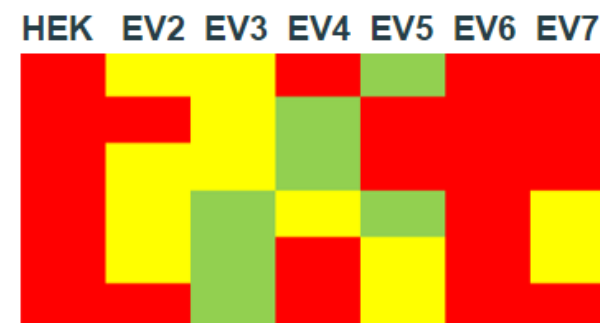
# Investigating cellular tropism – *in vitro* studies

- *In vitro*: Empirical screening of a panel of primary human cells suggested that there were specific CustomEX™ exosomes that could be used to enhance cellular tropism in target organs.
- Uptake data highlighted some key differences both when comparing CustomEX™ exosomes and HEK-derived exosomes at a cellular level *in vitro*.
- This difference is not necessarily reflected when quantifying whole tissues/organs.

## Kidney – primary cells:



Renal epithelial  
Renal mesangial  
Renal endothelial  
Hepatocytes  
Stellate  
Hepatic endothelial

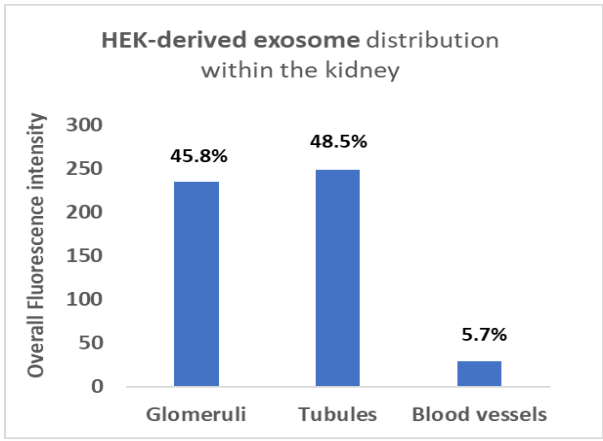
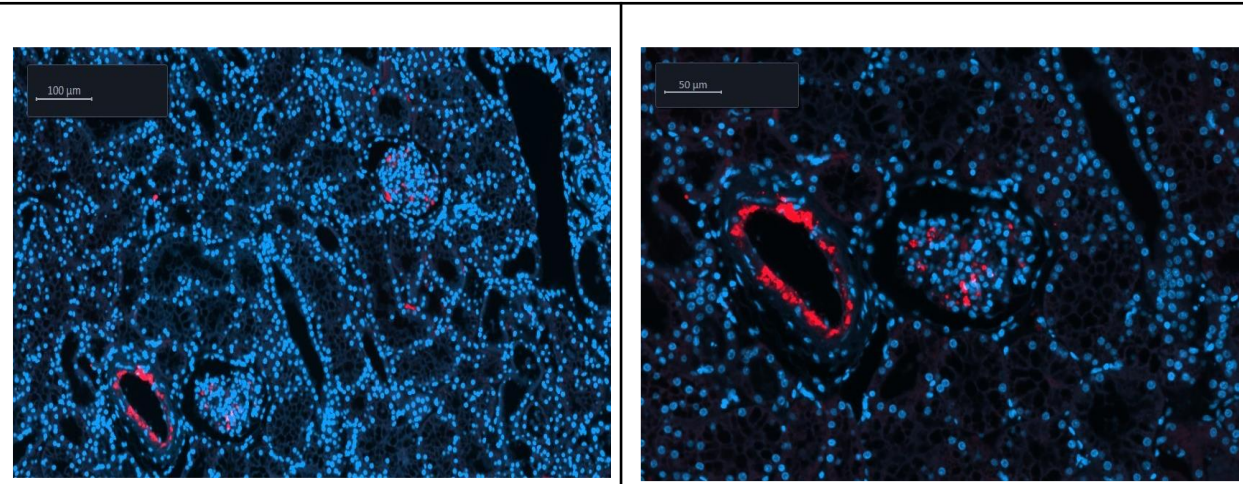


High Medium Low

# Confirmation that exosome tropism is at the cellular level

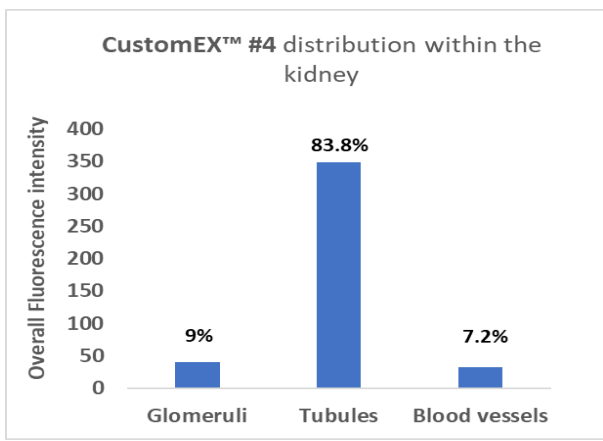
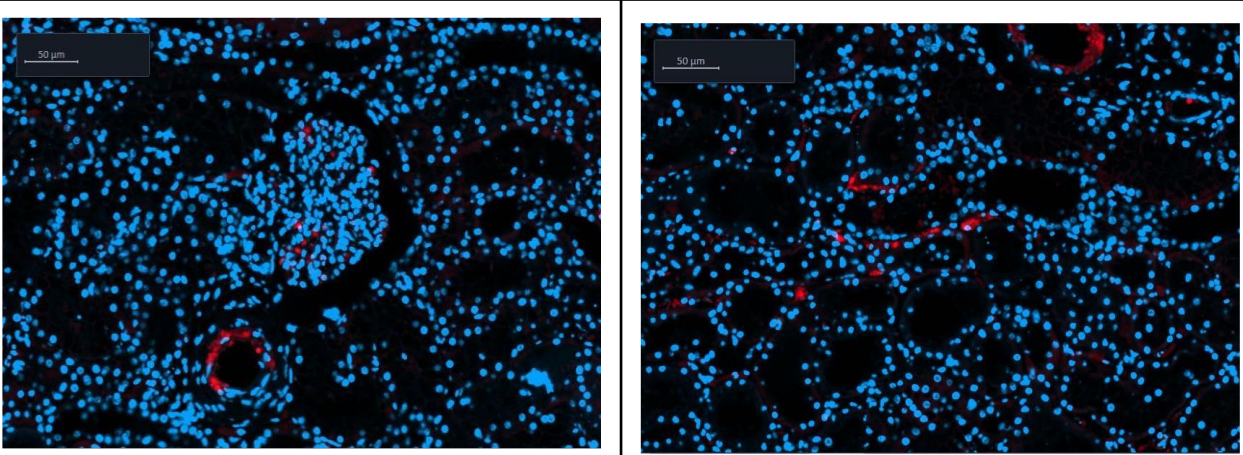
## Kidney tubule targeting capabilities of CustomEX™ #4

HEK-derived exosomes



Non-targeted delivery

CustomEX™ #4



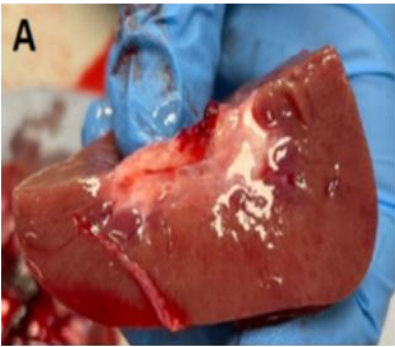

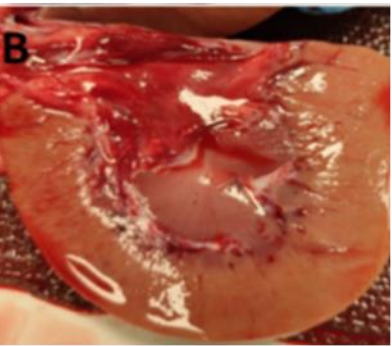
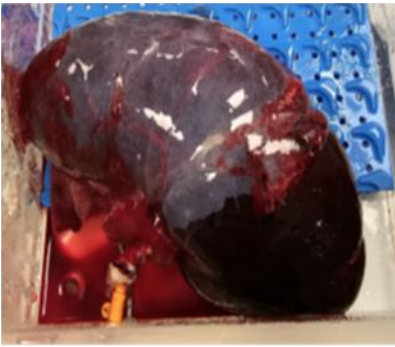


Tubule targeted delivery



# Confirmation of safety profile

Compared with an alternative drug delivery system

Control Kidney	Exosome exposure	Exosome exposure
		
Acute kidney injury*	AAV exposure*	Allogeneic blood transfusion*
		

- Exosome treated kidneys show **no evidence of inflammatory acute kidney injury or damage.**
- Confirmed by independent pathology report (Remuzzi score =0)
- Glucose, lactate, arterial pCO<sub>2</sub> remain stable throughout the procedure
- AAV treated kidney with evidence of necrosis throughout kidney
- Allogeneic blood transfusion without immunosuppression showing hypoperfusion and oedema

*\*Images of acute kidney injury, AAV exposure and allogeneic blood transfusion courtesy of Pebble Biotechnology Laboratories.*



# Confirming targeted delivery of a therapeutic payload *in vivo*

## Systemic lung targeting capabilities of CustomEX™ #3

### Vehicle control



### HEK-derived exosomes



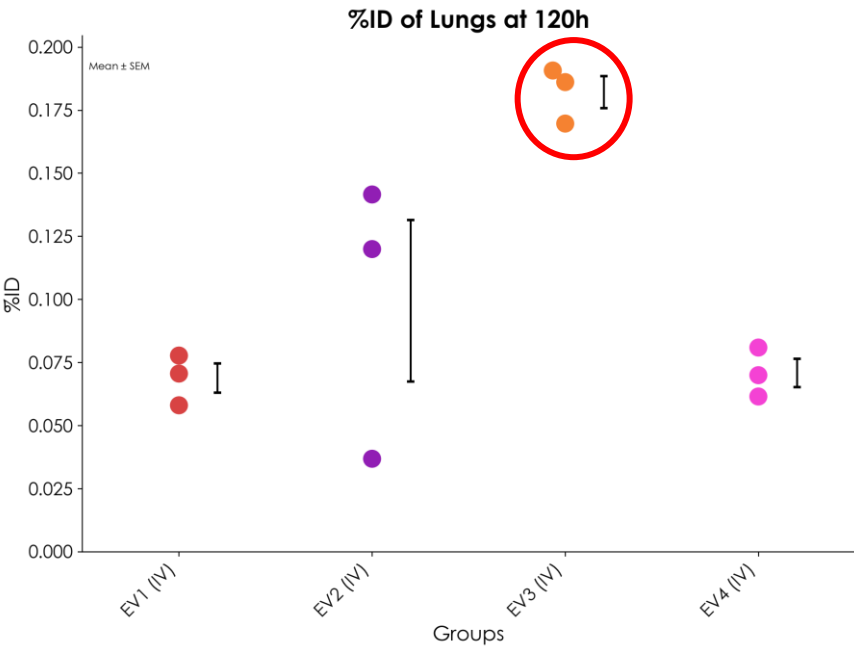
### CustomEX™ #2



### CustomEX™ #3



### CustomEX™ #4



- Fluorescent biodistribution (740nm) corroborates radio-labelling method and confirms lung targeting of CustomEX™ #3

# Confirming targeted delivery of a therapeutic payload *in vivo*

## Systemic lung targeting capabilities of CustomEX™ #3

### Vehicle control



### HEK-derived exosomes



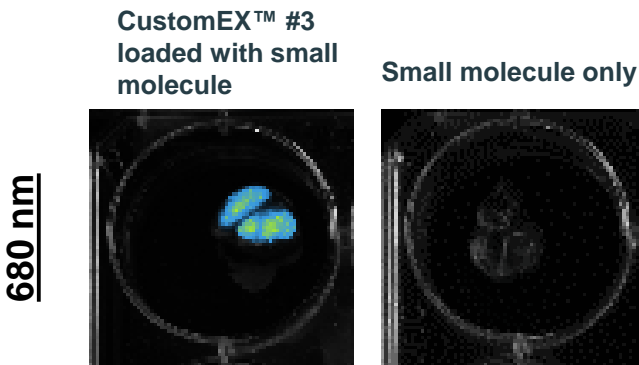
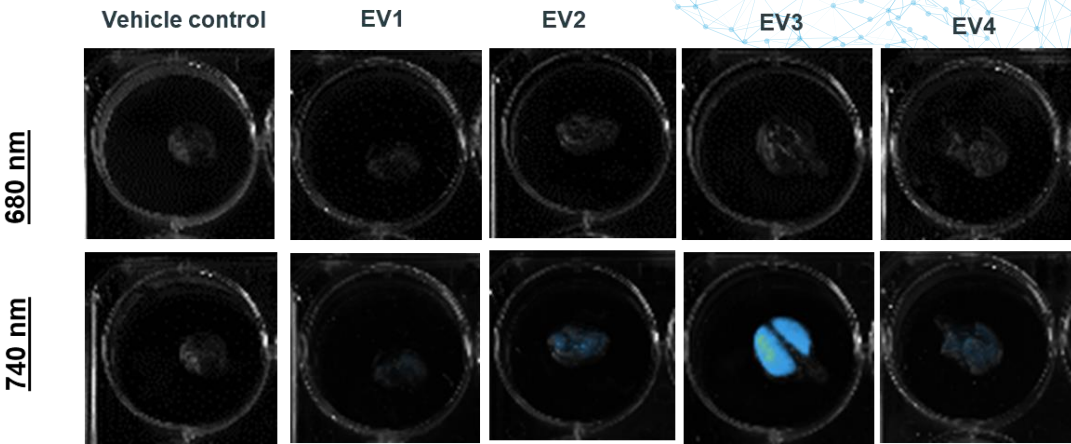
### CustomEX™ #2



### CustomEX™ #3



### CustomEX™ #4



- Loading with a fluorescently labelled small molecular weight therapeutic payload (680nm) does not alter targeting and is successfully delivered to the lung



# Summary



**Confirmation *in vivo* that exosome targeting is dependent upon cell source.**

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## **Examples:**

A specific CustomEX™ exosome targets the lymph nodes (immune system) greater than other exosome types.

A specific CustomEX™ exosome selectively targets the tubules within the kidney.

A specific CustomEX™ exosome targets the lung following systemic administration.

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**No sign of immune response or toxicity** with any of the exosome candidates - possible use of CustomEX™ for repeat administration unlike viral vectors.

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**Confirmation of targeted delivery of a therapeutic payload *in vivo*** using the CustomEX™ platform following systemic delivery

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Proven technology to **load proteins, nucleic acids and small molecular weight drugs.**

# Acknowledgments

## ReNeuron team:

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