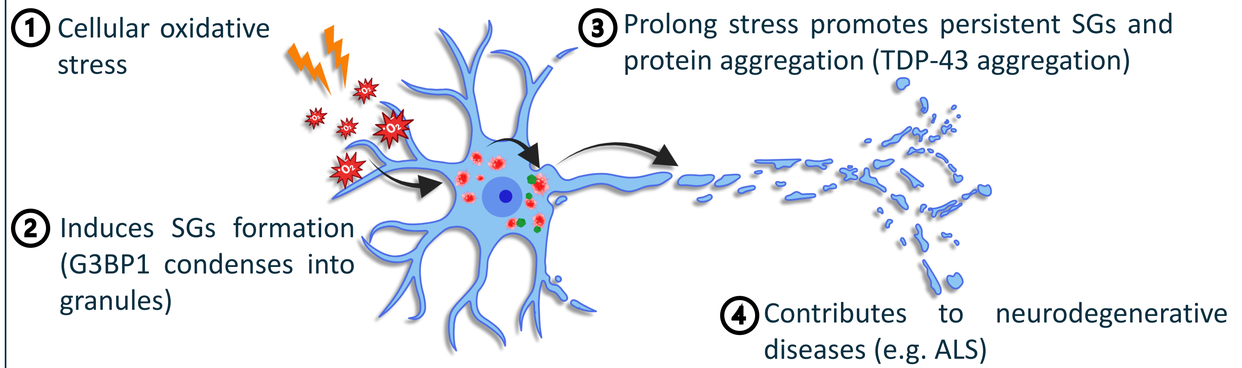
Extracellular Vesicles Regulate Stress Granule Dynamics and Distribute to the Brain Following Intranasal Delivery

Steven Tandiono[1], Meiling Yu[2], Revadee Liam-Or[2], Adam Walters[1], Khuloud Al-Jamal[1,2]

[1]King's College London, London, UK; [2]The University of Hong Kong, HKSAR, China

BACKGROUND

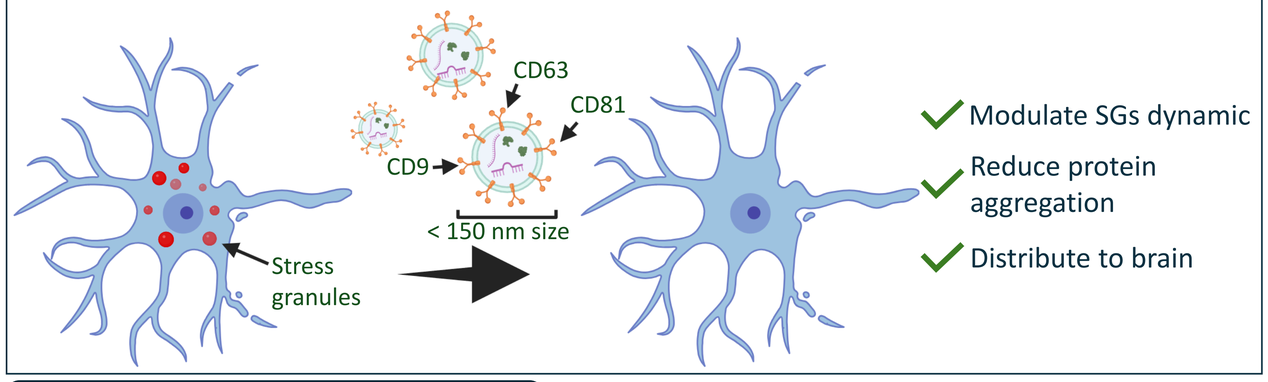
- **Stress granules** (SGs) are membraneless ribonucleoprotein assemblies that form in response to cellular stress to regulate mRNA translation and proteostasis
- SGs may seed **protein aggregation** such as **TDP-43** that are linked to neurodegenerative diseases including **ALS** (amyotrophic lateral sclerosis)



- **Mesenchymal stem cells** (MSCs) are known for their regenerative and tissue repair properties, with growing evidence suggesting that these therapeutic effects are mediated by their **extracellular vesicles** (EVs).
- By **modulating cellular stress responses**, MSC EVs may represent a promising **therapeutic strategy** for neurodegenerative diseases

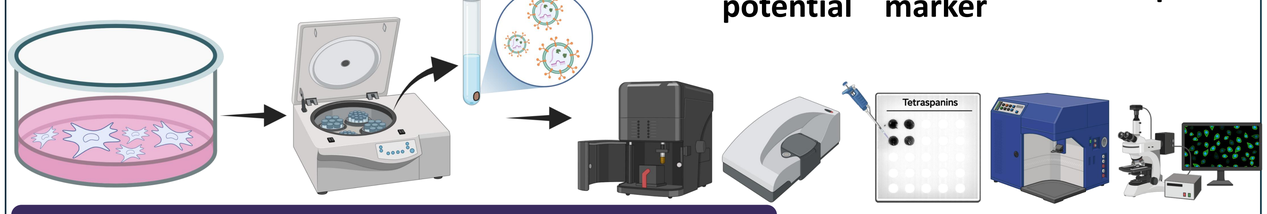
HYPOTHESIS / AIM

MSC-derived EVs regulate SGs dynamics *in vitro* and distribute to the brain following intranasal administration

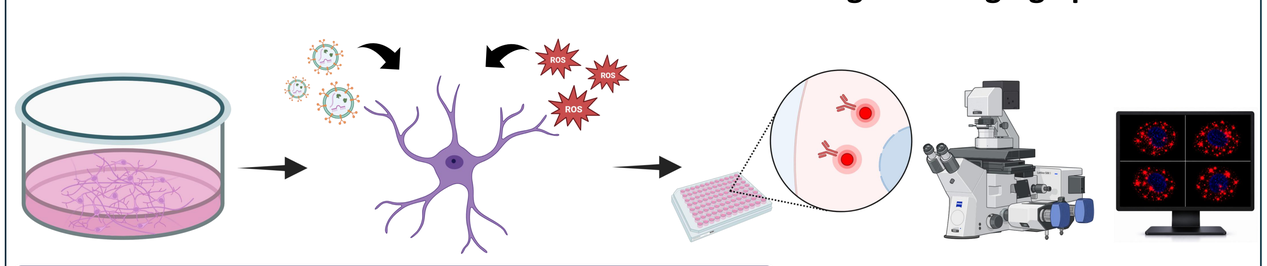


METHODS

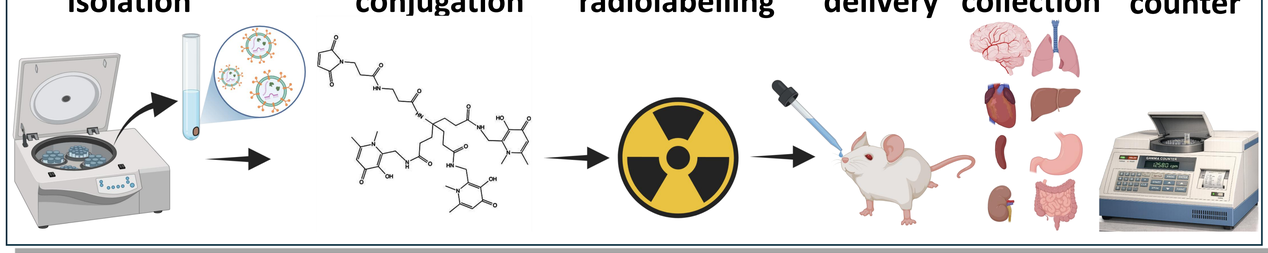
A. MSC EVs isolation and characterization



B. *In vitro* stress granule assay

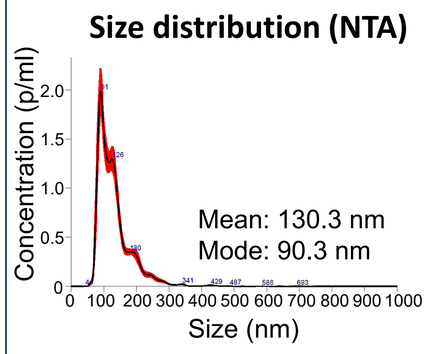


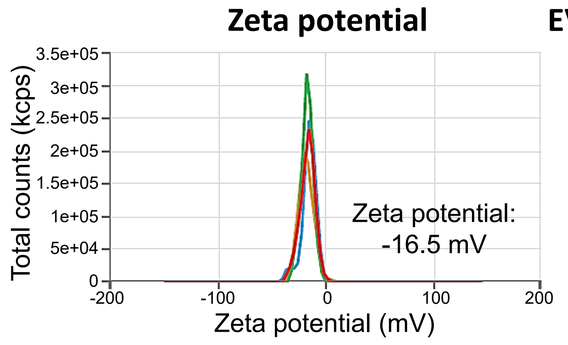
C. *In vivo* biodistribution

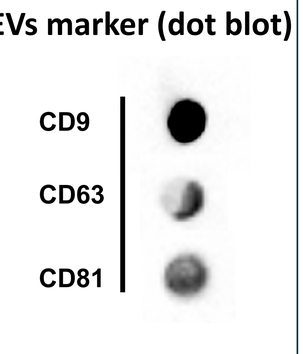


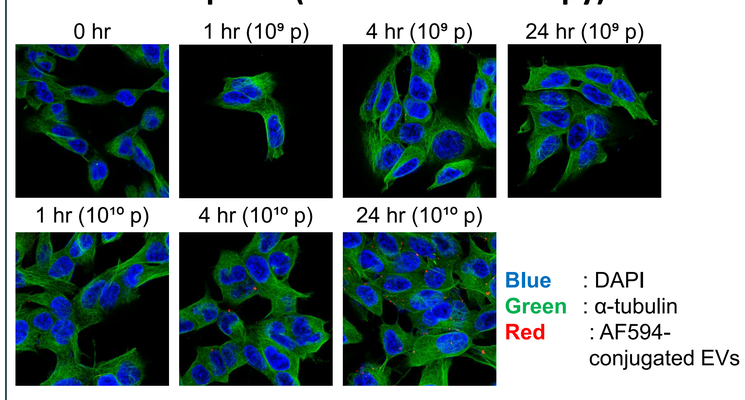
RESULTS

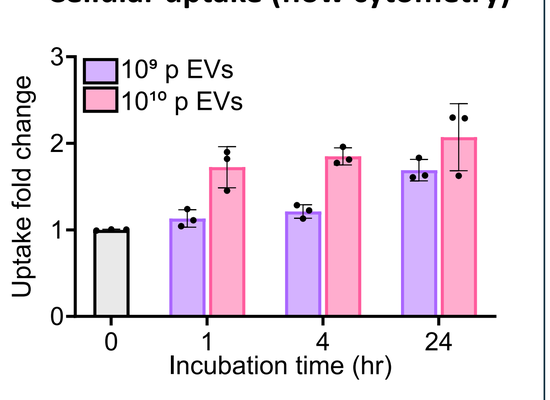
A. MSC EVs successfully isolated and internalized by SH-SY5Y cells



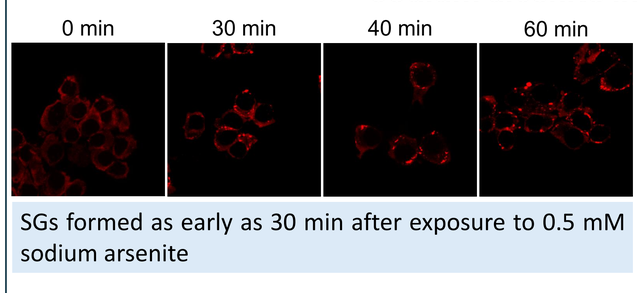




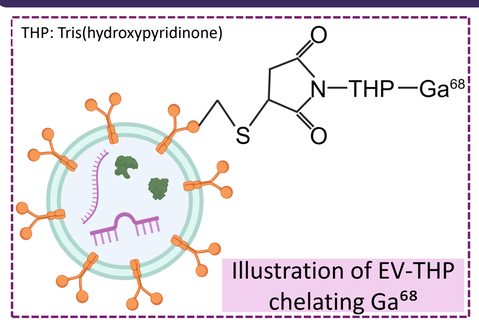


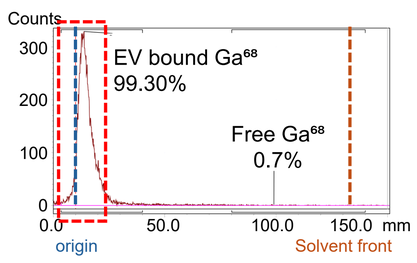


B. MSC EVs inhibit SGs formation *in vitro*

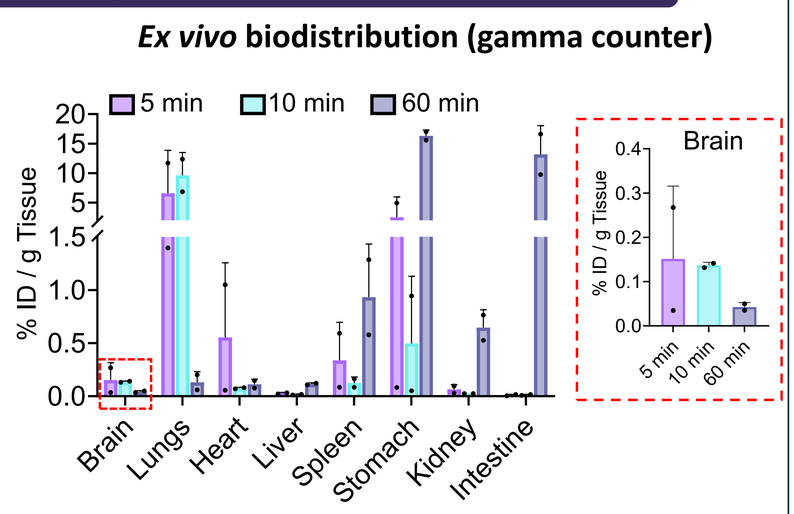


C. EVs distribute to brain following intranasal administration





Ga^{68} successfully chelated to THP-functionalized EVs surfaces, with no detectable free Ga^{68}



Key findings:
- ✓ EVs were successfully conjugated with THP for stable Ga68 radiolabelling
- ✓ EVs rapidly detected in the brain following intranasal administration

CONCLUSION

- MSC-derived EVs regulate SGs dynamics induced by oxidative stress
- Intranasal delivery enables EVs to rapidly reach the brain
- EVs hold therapeutic potential for neurodegenerative diseases

FUTURE DIRECTIONS

- Determine EVs cargo responsible for SGs modulation
- Evaluate impact on protein aggregation
- Assess impact on animal models of ALS/FTD

ACKNOWLEDGEMENTS

We thank the Indonesia Endowment Fund for Education (LPDP) for funding support, King's College London and all members of Al-Jamal and Walters research group for their support and assistance

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