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Circulating Biomarkers of Brain Dysfunction in Myotonic Dystrophy type 1 (DM1)

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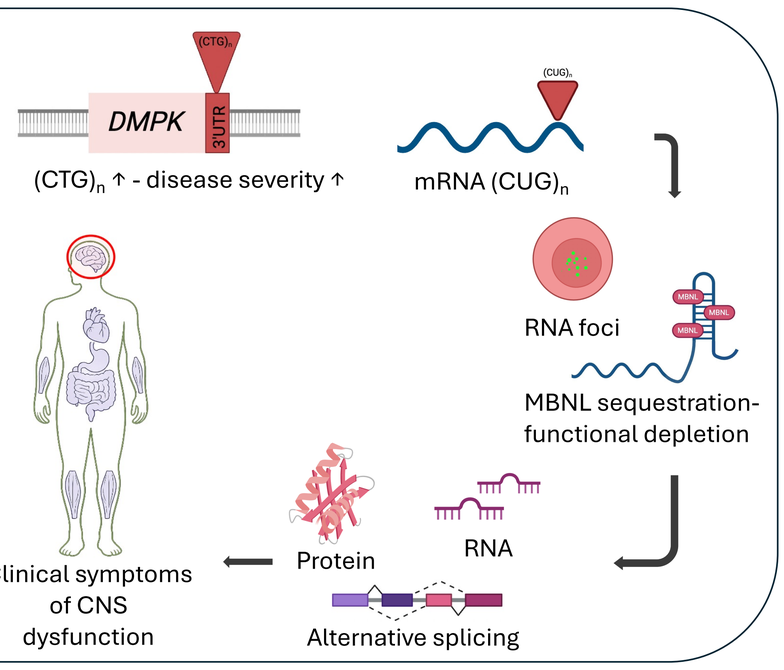
Introduction

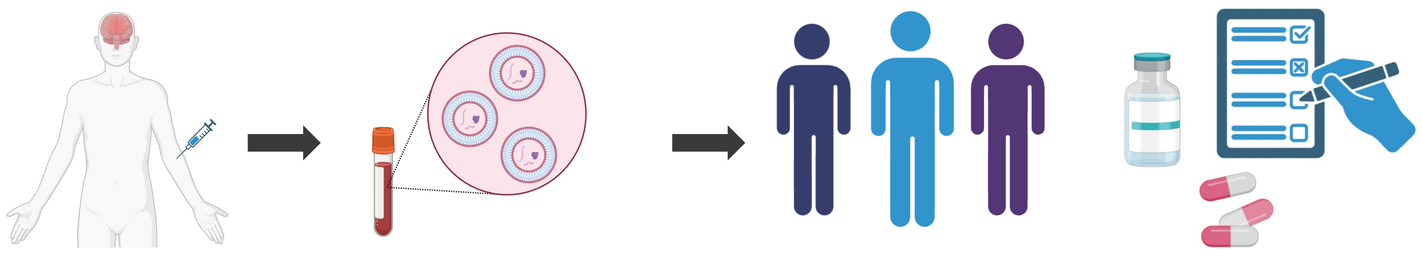
- Clinical symptoms of DM1 brain disorder include intellectual/learning disabilities, attention deficits, visuo-spatial deficits, dysexecutive syndrome, excessive daytime sleepiness, and fatigue. Overall, they are highly debilitating.
- DM1 is caused by non-coding $(CTG)_n$ repeat expansions in the 3' UTR of *DMPK*, whose $(CUG)_n$-containing transcripts form nuclear RNA foci that sequester splicing regulators (e.g. MBNL) and disrupt normal cellular splicing.
- Toxic RNA accumulation affects both neurons and glial cells in the brain. However, the full impact of different cell types in brain pathology, disease progression and therapeutic response, remains elusive.
- Existing DM1 brain biomarkers are inadequate. Neuroimaging (MRI, DTI) detects only slow, long-term changes. CSF biomarkers (tau, Aβ) require invasive sampling. Blood NfL, while promising for diagnosis, lacks cell-type specificity, shows limited longitudinal sensitivity, and correlates weakly with cognitive symptoms - highlighting the need for minimally invasive, mechanism-linked molecular biomarkers.
- As CNS-targeted therapies for DM1 advance toward clinical trials, the lack of objective, easily accessible molecular biomarkers of brain dysfunction has become a central bottleneck. Such biomarkers are essential for (a) early diagnosis, (b) rapid and quantitative assessment of cognitive dysfunction, (c) patient stratification in clinical trials, and (d) evaluation of therapeutic efficacy in the CNS.



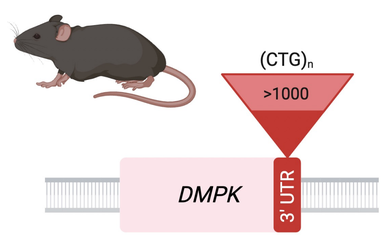
Research Objective

Extracellular vesicles (EV) are cell-derived membrane particles carrying proteins, lipids, and nucleic acids that mirror the physiological state of the parent cells. They can cross the Blood-Brain Barrier and preserve tissue- and cell type-specific molecular signatures, making them a valuable source for CNS readouts.

- ➢ The aim of the project is to uncover and validate EV-associated molecular biomarkers that reflect brain dysfunction in DM1.
- ➢ My specific goal is to discover minimally invasive cell type-specific biomarkers for patient stratification and therapeutic monitoring, to inform future clinical trials targeting the CNS.



DMSXL: Mouse Model of DM1

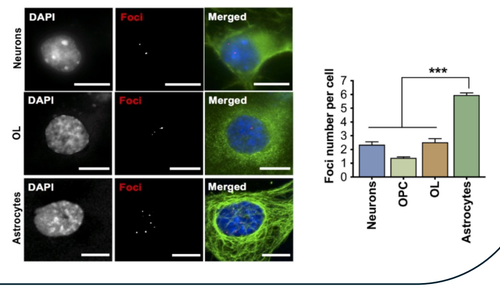


DMSXL transgenic mice

Key CNS phenotypes

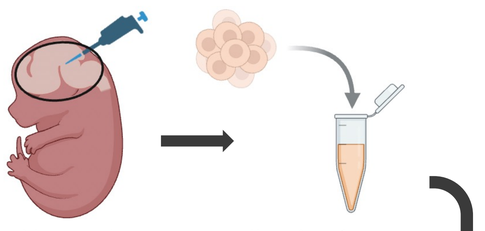
- Impaired spatial & recognition memory
- Impaired social cognition
- Impaired sensorimotor processing
- Emotional and anxiety-related behaviors
- Reduced goal-directed behavior
- Impaired LTP activation

➢ The CNS phenotypes of DMSXL mice are associated with RNA foci present in both neurons and glial cells

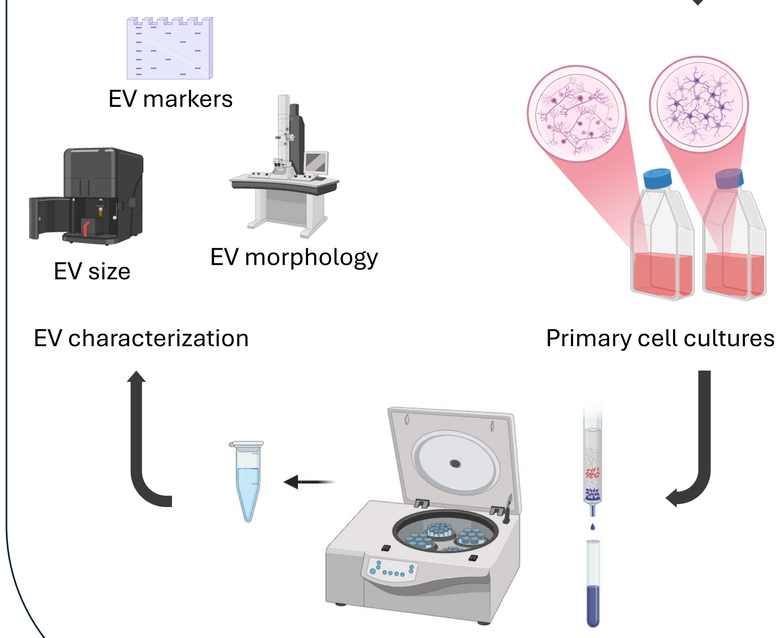


Work Plan and Methods

1. Isolation and Characterization of Neuron- and Astrocyte-derived EVs

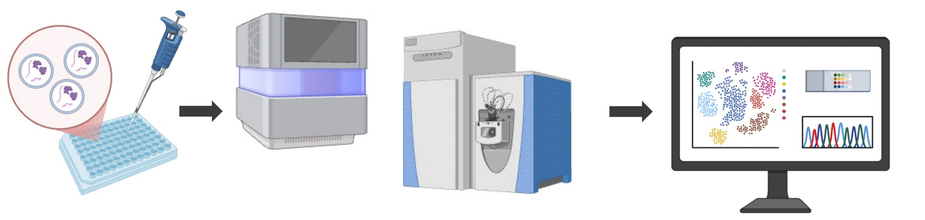


Neuron/astrocyte collection from DMSXL mice



2. Transcriptomic and Proteomic Analysis of EVs

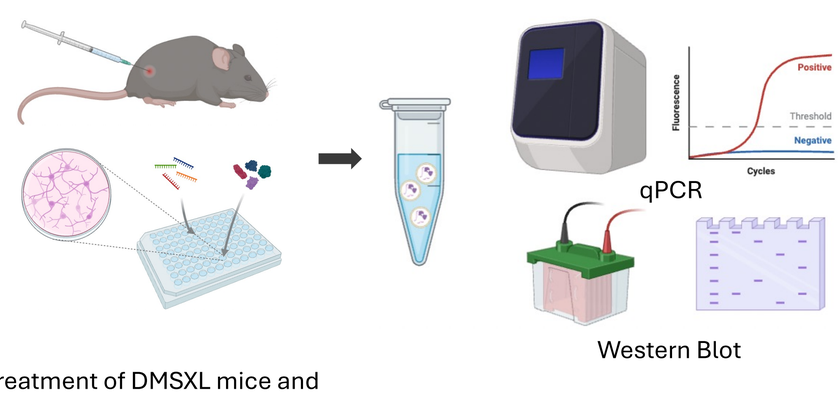
- Identification of differentially expressed mRNAs, miRNAs, and proteins
- Detection of dysregulated pathways in neuroglial communication



Transcriptomics/proteomics on EV cargo — Bioinformatic analysis of data

Partner: Ana Conesa (BioBam Bioinformatics-Valencia)

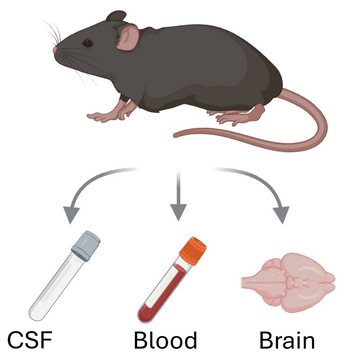
3. Evaluation of Biomarker Response to Therapeutic Intervention



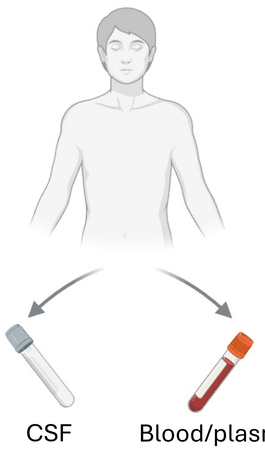
Treatment of DMSXL mice and primary neurons/astrocytes with ASOs and MBNL decoys

Quantification of EV-derived biomarkers

4. Biomarker Selection and Validation in Human and Mouse Biofluids

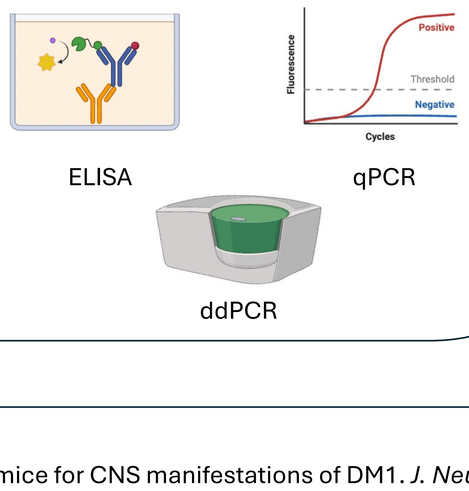


Validation of biomarkers in control vs DMSXL mice



Validation of biomarkers in healthy individuals and DM1 patients

Partner: Eric Wang (University of Florida)



Expected Outcomes

- Establish and optimize protocol for effective and reproducible CNS cell type-specific EV isolation from cell culture media and biofluids.
- Uncover biomarker panel of CNS dysfunction in DM1.
- Investigate transcriptomic and proteomic alterations.
- Validate identified biomarkers in human blood and CSF.

References

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