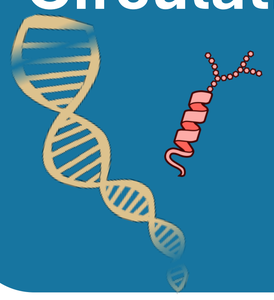
Circulating Biomarkers of Brain Dysfunction in Myotonic Dystrophy type 1 (DM1)

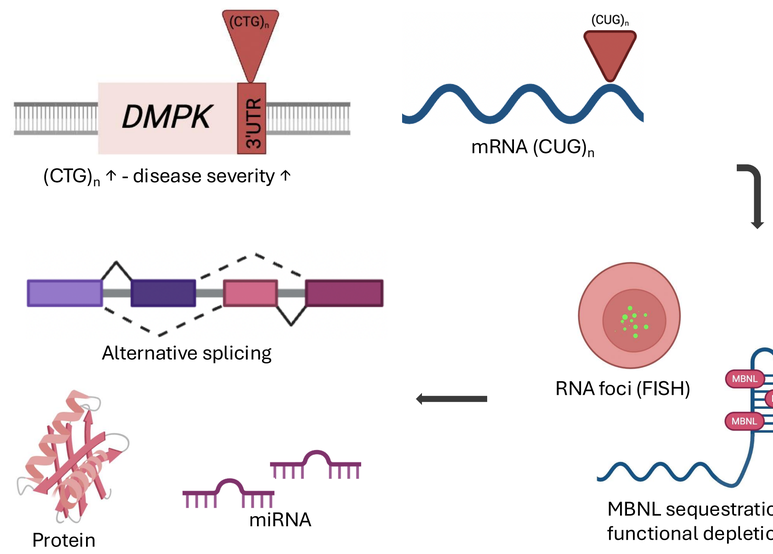


Panagiotis Strevinas[1,2], Fréderique Rau[1], Denis Furling[1], Geneviève-Gourdon[1], Mario Gomes-Pereira[1,3]
[2]panagiotis.strevinas@inserm.fr ; [3]mario.pereira@inserm.fr

[1] Sorbonne Université, Inserm, Centre de Recherche en Myologie, 75013 Paris, France

Introduction

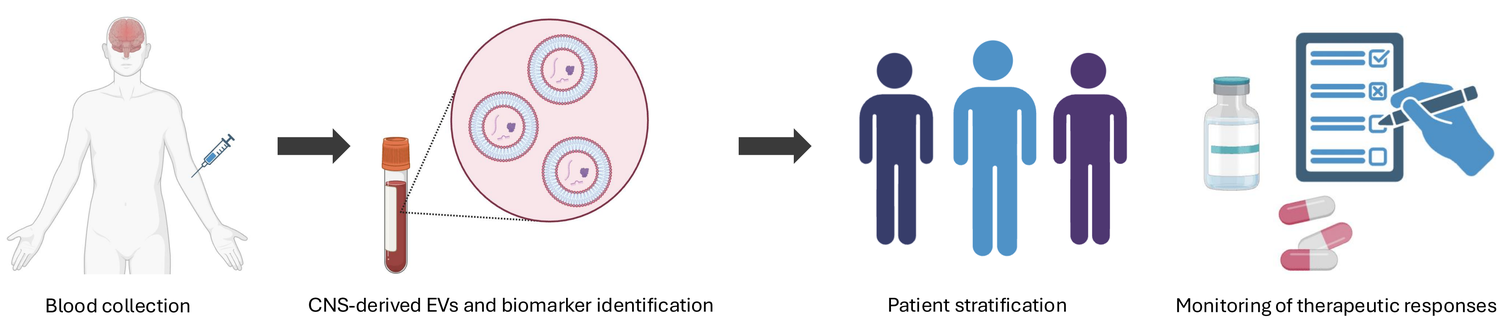
- Myotonic Dystrophy type 1 (DM1) is a rare neuromuscular disease that affects the muscles and the central nervous system (CNS), among many other tissues.
- Clinical symptoms of DM1 brain disorder include intellectual/learning disabilities, attention deficits, visuo-spatial deficits, dysexecutive syndrome, excessive daytime sleepiness, and fatigue. Overall, they are highly debilitating.
- DM1 pathology is caused by non-coding **$(CTG)_n$ repeat expansions** in the 3' UTR of the gene *DMPK*.
- The corresponding RNA transcripts with expanded $(CUG)_n$ repeats accumulate in the nucleus forming aggregates (**RNA foci**), and sequester splicing regulators (such as MBNL), altering the normal **splicing** program of the cell.
- Toxic RNA accumulation affect 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.
- Research on biomarkers of brain dysfunction in DM1 is scarce. Biomarkers are essential to enable **(a)** earlier and proper diagnosis, **(b)** monitoring of disease progression, and **(c)** assessment of therapeutic responses.



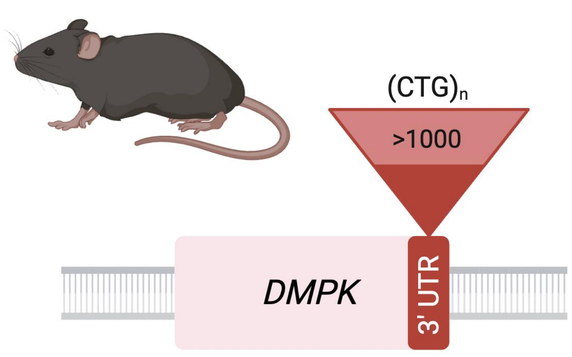
Research Objective

- 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 of CNS biomarkers.

➢ 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

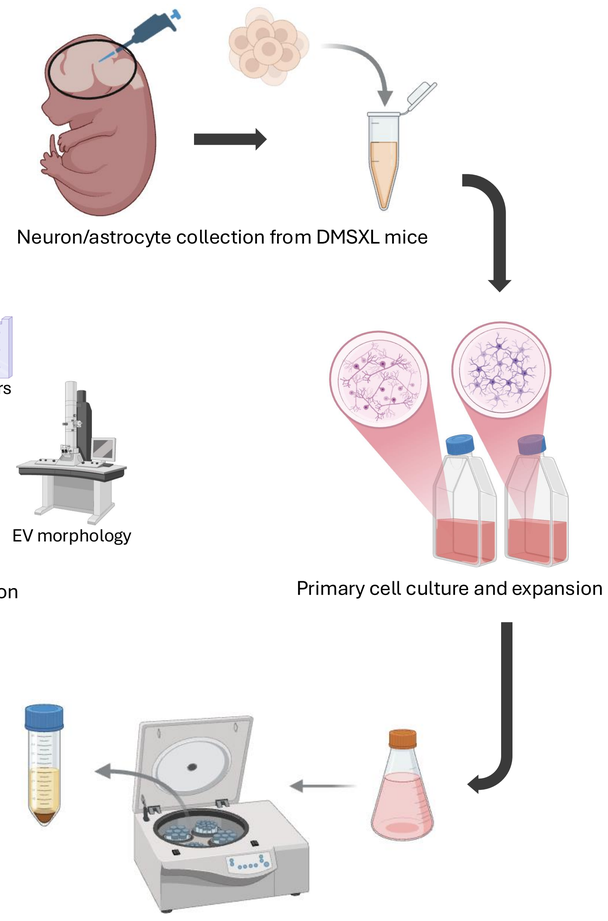


DMSXL mouse model characteristics

- High mortality
- RNA foci
- Splicing abnormalities
- Multisystem pathology: CNS, muscle, heart …

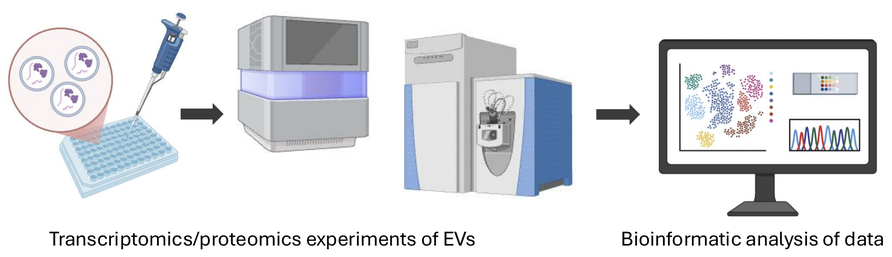
Research Aims and Methods

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

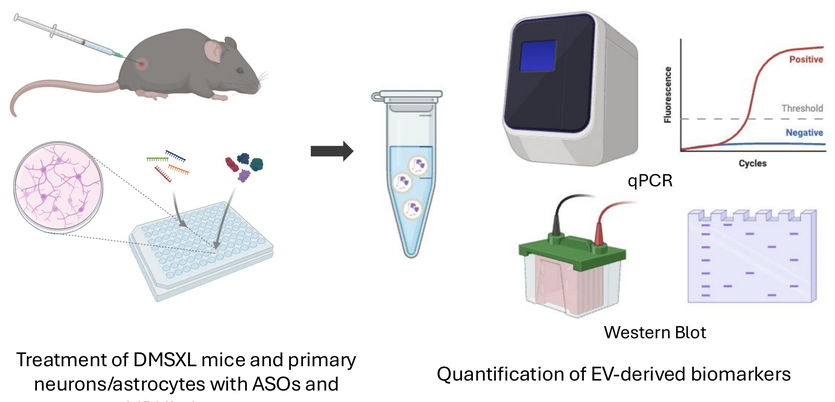


2. Transcriptomic and Proteomic Analysis of EVs

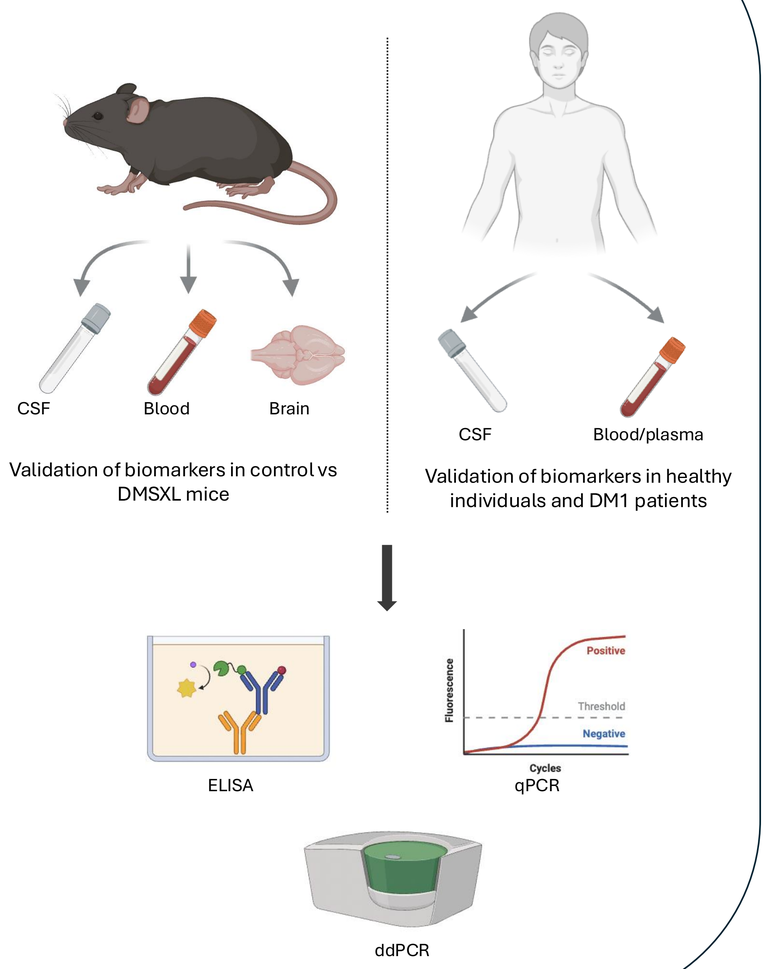
- Identification of differentially expressed mRNAs, miRNAs, and proteins
- Detection of dysregulated pathways in neuroglial communication



3. Evaluation of Biomarker Response to Therapeutic Intervention



4. Biomarker Selection and Validation in Human and Mouse Biofluids



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 (Secondment, Dr. Ana Conesa, Valencia, Spain).
- Validation of identified biomarkers in human blood and CSF (Secondment, Dr. Eric Wang, Florida, USA).

Perspectives

- Validation of biomarker panel using biofluid samples obtained from patients participating in clinical trials for DM1 therapeutics

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