Development of circulating muscle-specific biomarkers of Myotonic Dystrophy

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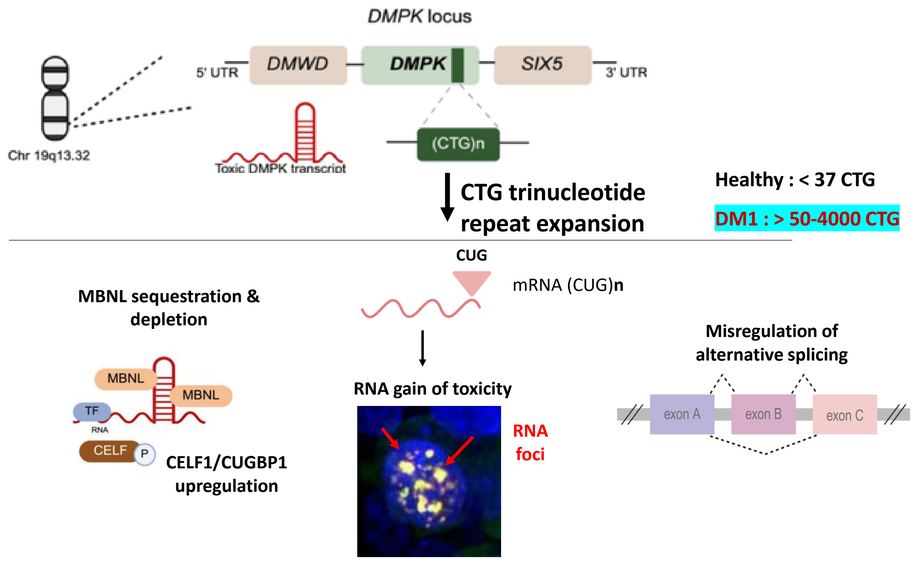
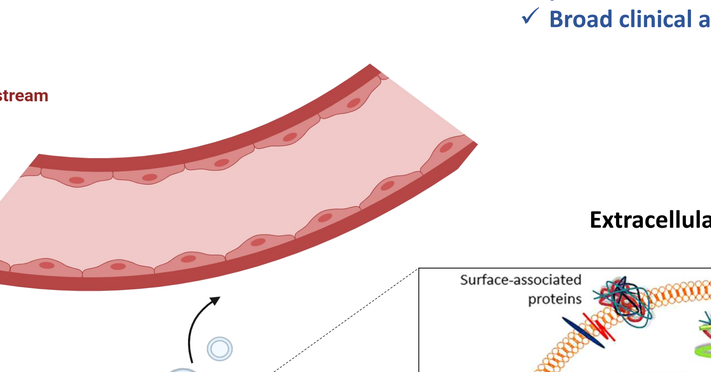
Background

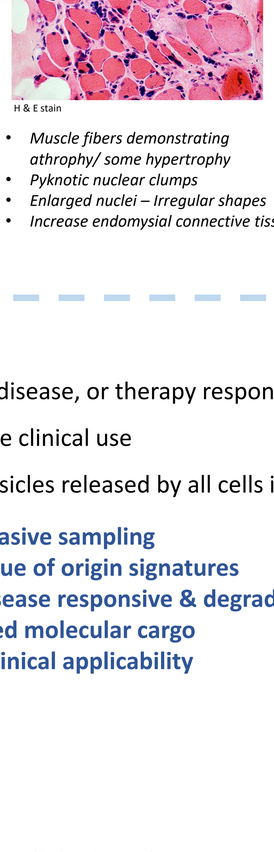
A. Myotonic Dystrophy type 1 (DM1) : **Molecular Pathogenesis**



B. DM1 **clinical** manifestations : DM1 is a **multisystemic** highly variable disease, primarily affecting the **muscles**



Representative DM1 muscle histology



- *Muscle fibers demonstrating athrophy/ some hypertrophy*
- *Pyknotic nuclear clumps*
- *Enlarged nuclei – Irregular shapes*
- *Increase endomysial connective tissue*

C. Circulating **Biomarkers –** Why **Evs ?**

- Biomarkers are measurable indicators of biological processes, disease, or therapy response
- ***NO*** circulating biomarkers in DM1 are fully validated for routine clinical use
- Extracellular vesicles (EVs) are nanoscale membrane-bound vesicles released by all cells in biofluids
- ***Advantages of EVs as a source of biomarkers:***

✓ **Non-invasive sampling**
✓ **Cell/tissue of origin signatures**
✓ **Rich, disease responsive & degradation-protected molecular cargo**
✓ **Broad clinical applicability**

Arandel et al., 2022, Szatmári et al., 2023, Kuntawala et al., 2025

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https://www.entry-dm.eu

Research Objectives

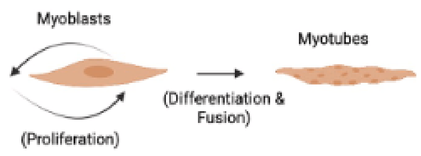
A) Identification of muscle-specific biomarkers carried by extracellular vesicles (EVs) in DM1 cell models

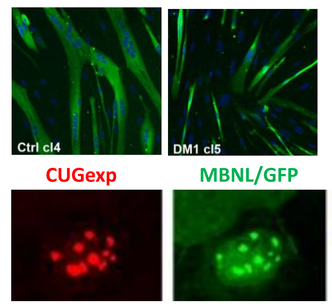
B) Validation of candidate biomarkers in DM patients

Workflow

1. EVs isolation & characterization from DM1 cells

➢ **Human immortalized DM1 cell model generated from** DM1 patient (*n=2600 CTG repeats*) muscle biopsy recapitulates DM1 muscle pathology

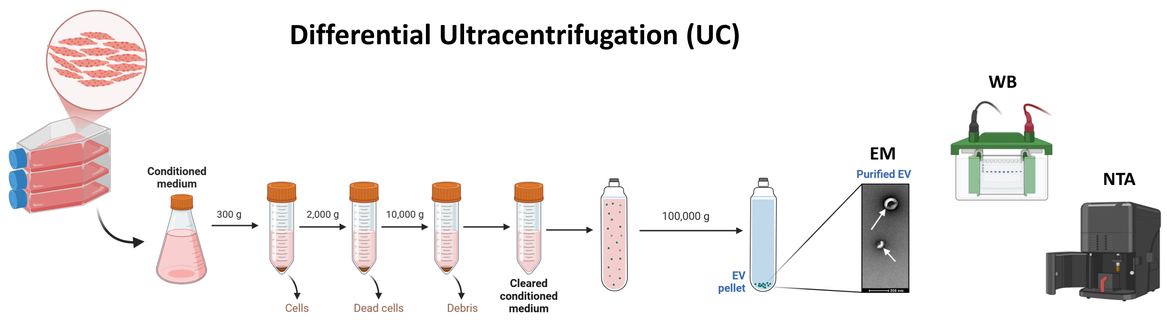




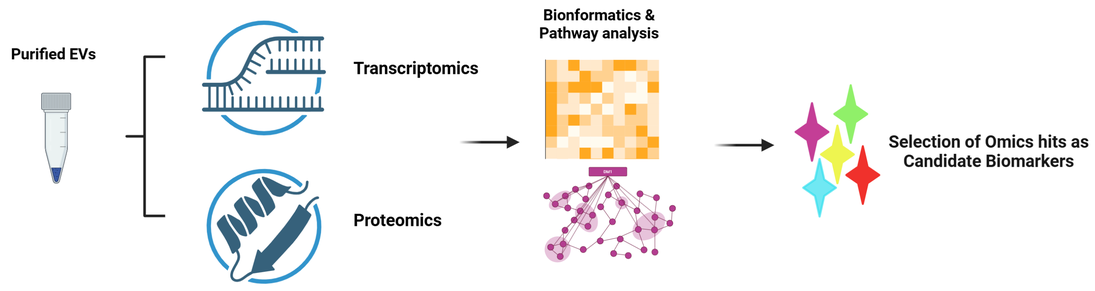
✓ **Reduced fusion index**
✓ **RNA foci colocalized with MBNL**
✓ **Mis-splicing** (BIN1, DMD, LDB3)

(Arandel et al., 2017, 2022)

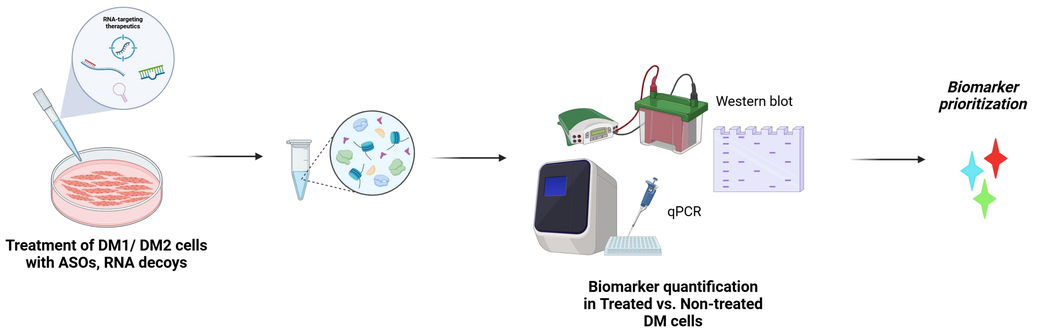
Differential Ultracentrifugation (UC)



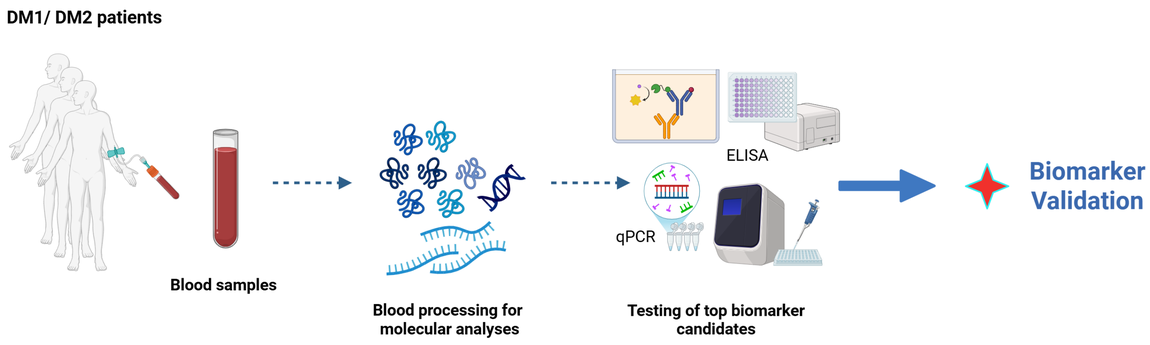
2. EV cargo analysis/ Identification of candidate biomarkers



3. Evaluation of Biomarker Response to Therapeutic Intervention



4. Biomarker validation in DM1 patient samples



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Expected Impact

Development of circulating biomarkers specific to DM muscle pathology and responsive to therapies targeting mutant RNA toxicity, applicable for upcoming clinical trials.
Such biomarkers could serve as valuable tools for monitoring disease progression and evaluating therapeutic efficacy in DM patients.