Muscle genetic diseases in the age of transcriptomics

Jean-Baptiste Dupont[1]*, Virginie Mournetas[2], Emmanuelle Massouridès[3], Jianjun Guo[4], Shelby Hamm[5], John T. Gray[6], Martin K. Childers[7], Robert W. Grange[5], Christian Pinset[3], and David L. Mack[8]

1: Translational Gene Therapy for Genetic Diseases - INSERM UMR 1089, Nantes, France
2: Translational Innovation in Medicine and Complexity - EHPP UMR 5525, La Tronche, France
3: CECS I-Stem - INSERM UMR 861, Corbeil-Essonnes, France
4: Clinical NGS Group, Thermo Fisher Scientific, South San Francisco, USA
5: Department of Human Nutrition, Food, and Exercise, Virginia Tech, Blacksburg, USA
6: Vertex Pharmaceuticals, Boston, USA
7: Asklepios Biopharmaceutical, Durham, USA
8: University of Washington, Department of Rehabilitation Medicine, Institute for Stem Cell and Regenerative Medicine, Seattle, WA, USA

**** Contact: jean-baptiste.dupont@univ-nantes.fr***

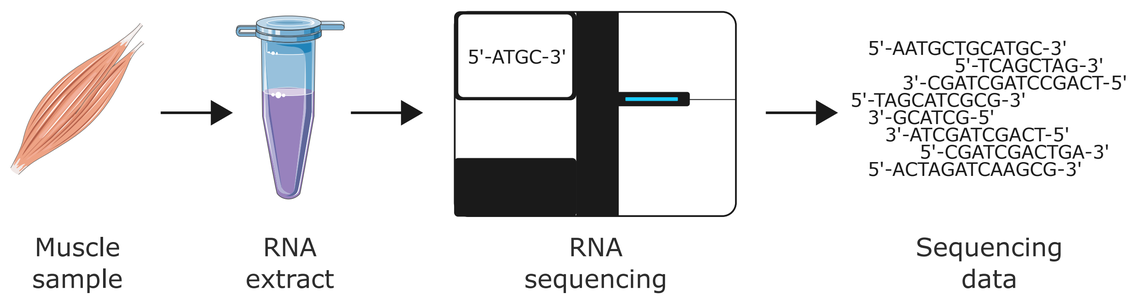
Clinical and scientific context

Inherited muscular disorders encompass many different conditions and affect hundreds of thousands of patients worldwide

First generation gene therapy has shown promises in recent clinical trials

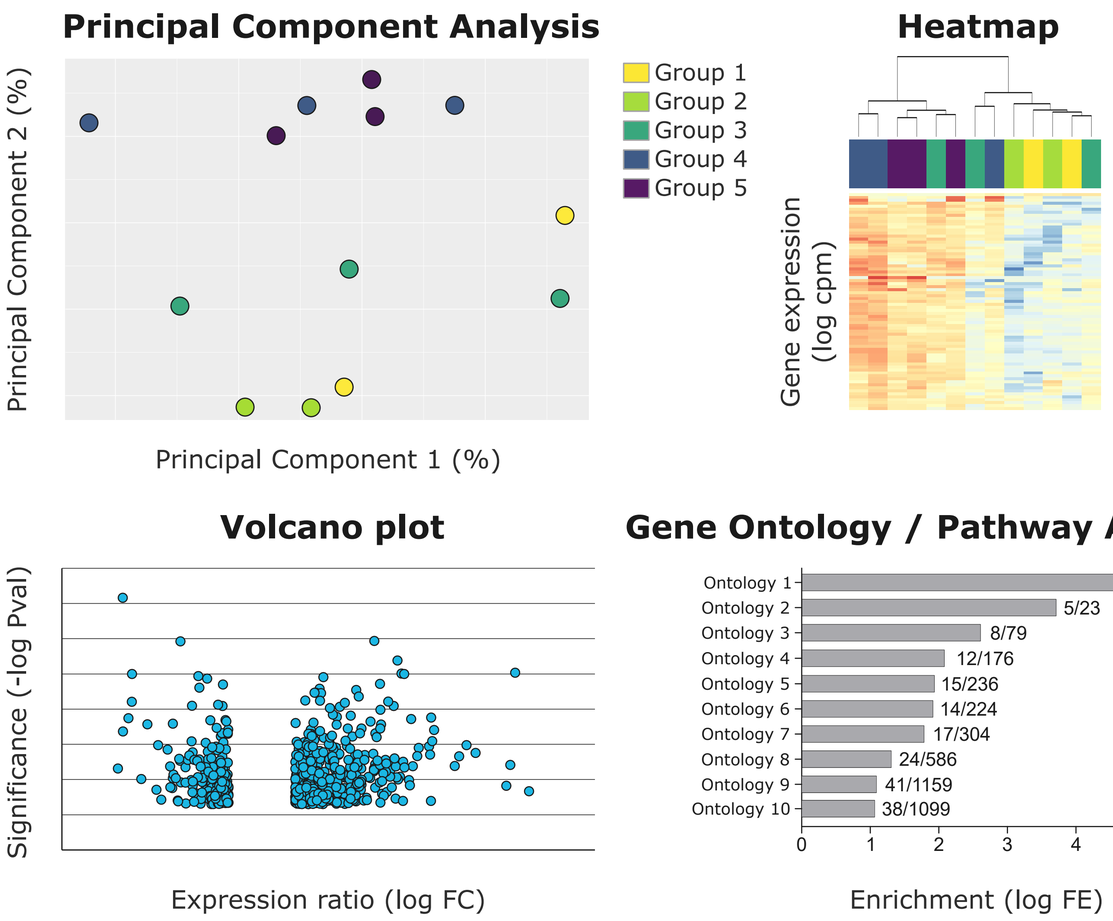
Remaining issues:
- **Overestimated efficacy / unanticipated toxicity**
- **Complex pathophysiology**
- **Lack of reliable biomarkers / alternative targets**

Current limits of transcriptomics

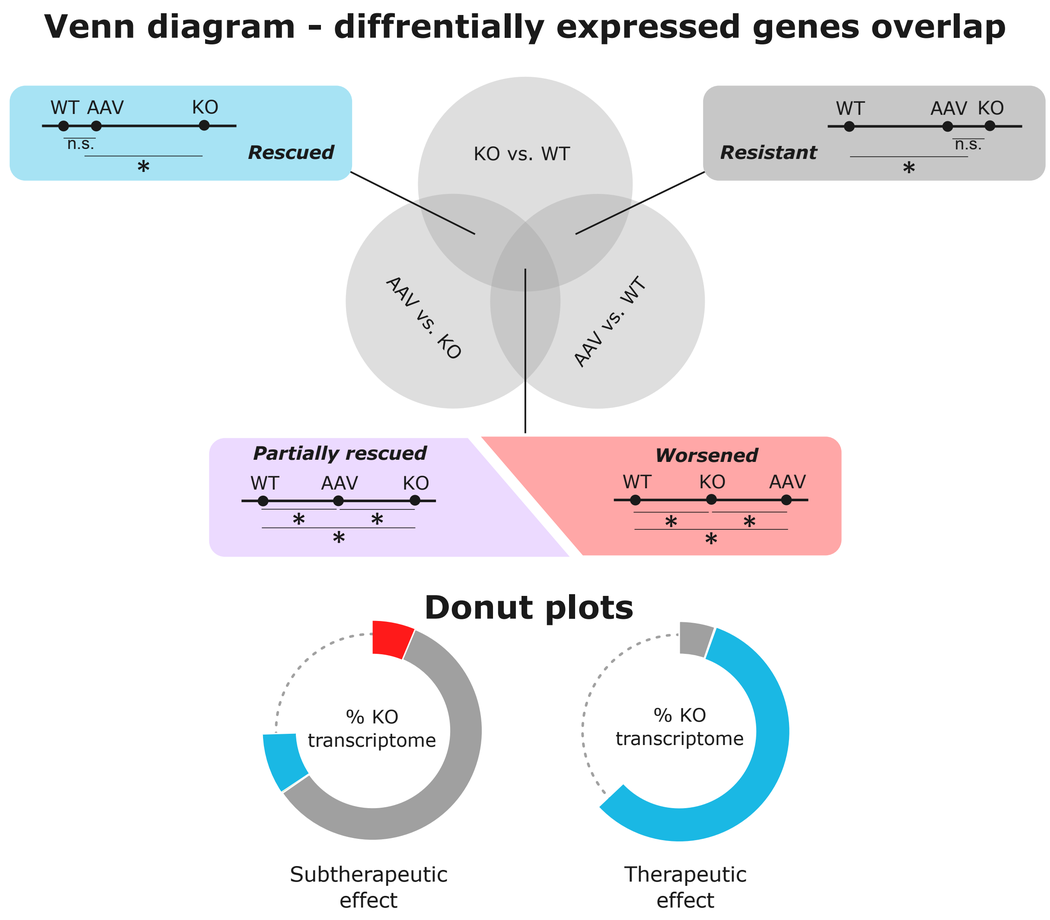


Remaining issues:
- **Expansive technology and complex data**
- **Analysis pipelines not standardized**

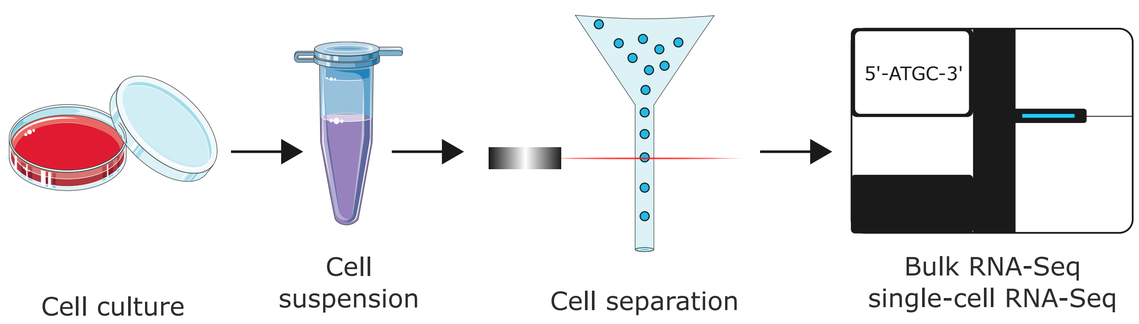
Basic transcriptome analysis



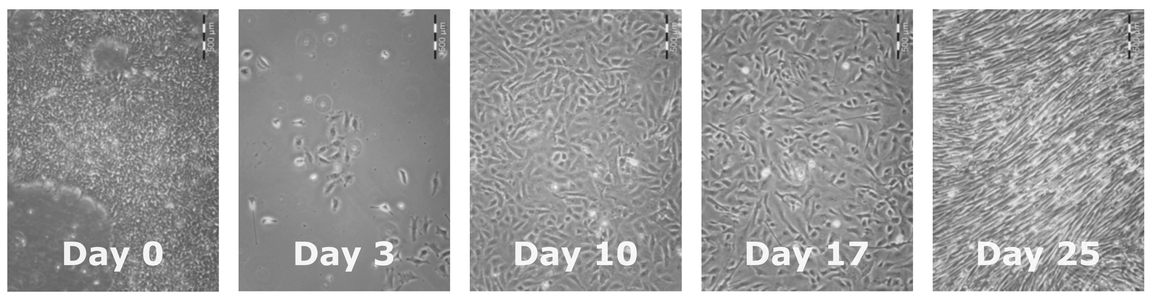
Transcriptome remodeling



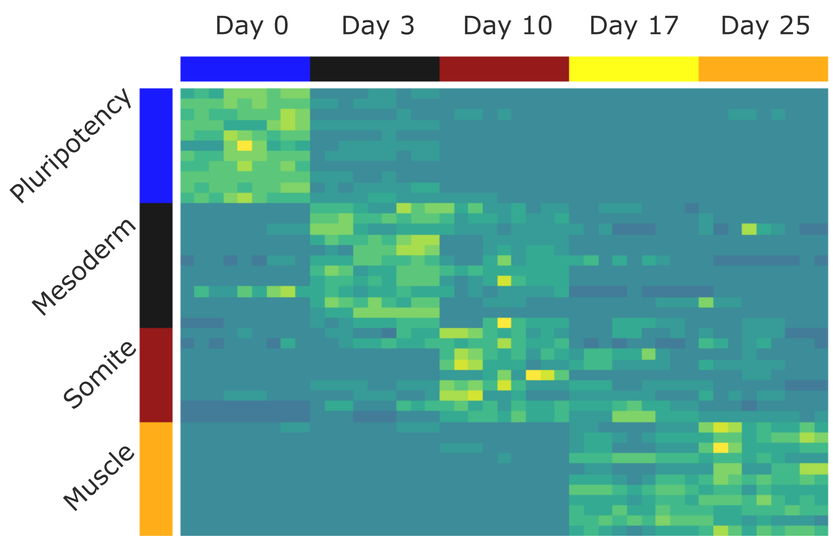
Transcriptome analysis in stem cells



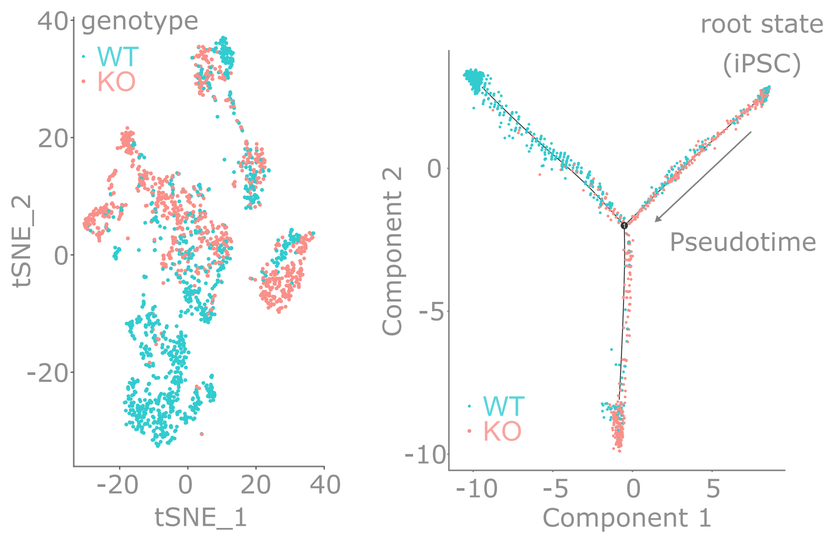
Differentiation of induced pluripotent stem cells (iPSCs) into the myogenic lineage



Bulk RNA-Seq



Single-cell RNA-Seq: clustering / developmental trajectory



Perspectives

Extension of single-cell / single-nucleus RNA-Seq to in vivo studies

Multi-omic analyses

Algorithms for biomarker discovery

iPSC-derived models for gene therapy optimization

Sources:
- Dupont J-B, Guo J, Renaud-Gabardos E, Poulard K, Latournerie V, Lawlor MW, et al. AAV-Mediated Gene Transfer Restores a Normal Muscle Transcriptome in a Canine Model of X-Linked Myotubular Myopathy. Mol Ther. 2020 Feb 5;28(2):382–93.
- Mournetas V, Massouridès E, Dupont J-B, Kornobis E, Polvèche H, Jarrige M, et al. .Myogenesis modelled by human pluripotent stem cells: a multi-omic study of Duchenne myopathy early onset. J Cachexia Sarcopenia Muscle. 2021 Feb 12(1): 209-232