Overall meeting summary

In recognition of the fact that recently approved drugs for muscle disease are most beneficial in preventing or slowing muscle loss but are unlikely to be as useful for those who have already lost significant muscle, the neuromuscular patient advocacy community is catalyzing efforts to rally clinicians, investigators, and therapy developers to align on promising strategies for regenerating muscles that have wasted away from disease.

On July 19, 2024, in Quebec, Canada, the **Muscular Dystrophy Association (MDA)** joined with partners in the advocacy field – **AFM Telethon, Cure Duchenne, Cure Rare Disease, FSHD Society, Jain Foundation, Muscular Dystrophy Australia, RYR-1 Foundation, SMA Foundation and Solve FSHD** -- to host an in-person summit on muscle regeneration. This first of its kind summit provided a focused opportunity for leading muscle biology experts to identify and discuss both current hurdles and new strategies that can benefit people struggling with advanced muscle weakness and degeneration. Pre-recorded videos providing patient perspectives on the potential life-altering impact of therapeutic muscle regeneration were shared with the summit participants to ensure that the needs of the patient community were at the forefront of discussions. Prior to the meeting, participants were asked to respond to a survey to evaluate areas of alignment and diverse views leading into the discussions. Survey responses were summarized and used to guide the plenary discussion and define the topics for the three breakout sessions. The meeting was facilitated by Wendy Selig of WSCollaborative.

Participants aligned around a shared definition for muscle regeneration for the purpose of the meeting: "***Therapeutic strategies to restore functioning muscle lost to neuromuscular conditions***". There was a consensus that enhancing regeneration or restoring it to near healthy levels can have a profound effect on the progression of muscle wasting diseases and patients' quality of life. Ideally, muscle regeneration strategies should aim to halt and/or reverse degenerative processes by accomplishing one or more of the following: removing fatty fibrotic tissue, enhancing satellite cell activity, generating new muscle fibers, increasing muscle fiber size and/or improving the force-generating capacity of muscles. Factors that may influence regenerative ability include primary/secondary causes of the disease-related degeneration for different muscular dystrophy subtypes and even different mutations within a single disease-causing gene. Defining functional outcomes and biomarkers to measure successful regeneration are vital to regulatory approval but are currently not well defined or sufficient to perform a comprehensive read-out of muscle regeneration.

Overall, meeting participants aligned around a common definition of therapeutic muscle regeneration, the need for better translation from animal models to humans, the need for a better understanding of the biology of muscle regeneration in humans, including the need for better availability of human samples, and the need for consistent biomarkers and outcome measures for therapies aimed at muscle regeneration. ***It was concluded that it would be helpful to evaluate these issues in the context of a more specific therapeutic approach for muscle regeneration in a smaller, focused workshop with a mix of research and clinical participants.***

Meeting Detail

Opinions on current progress of the field

Meeting participants conveyed mixed opinions when asked to characterize current progress of the muscle regeneration field. Positive opinions focused on progress in characterizing the muscle microenvironment and regenerative pool of satellite cells, using improved tools and quantification methods. Negative opinions conveyed a disappointment in the slow progress compared to other fields such as gene therapy and lack of innovative solutions to hurdles identified in previous decades. Contributing factors to a perceived lack of progress included the complex nature of muscle regeneration and multiple systemic factors that can influence the process, as well as patient-to-patient variability.

Current regeneration strategies

Current strategies explored by the field to achieve therapeutic muscle regeneration include strategies to influence the intrinsic environment: directing fate of fibroadipogenic progenitors (FAPs), inhibition of inflammation, targeting mitochondria, altering protein synthesis/degeneration, enhancing endogenous stem cell activity, modulation of pathways to control cell division of satellite cells; and extrinsic approaches: transplantation of progenitor cells, gene editing, synthetic biology to enhance the functionality of expanded progenitors and biomaterial approaches for tissue engineering. These approaches are at different stages of development, with some nearing clinical testing. Some are tailored towards individual diseases while others trend towards applicability across multiple diseases. There may be a need for strategy prioritization depending on the specific disease and state of the muscle microenvironment as a reflection of disease progression. Moving forward, a better understanding of patient heterogeneity and the role of genetic modifiers will help to stratify patients for different strategies and to design informative trials. The use of artificial intelligence (AI) on large genomic datasets with accompanying phenotype data from natural history studies may provide new insights to help power trials and guide the length of regeneration studies. Testing therapies in acute injury settings as an alternative to disease-induced muscle degeneration may accelerate clinical testing timelines for muscle regeneration therapies. Additional needs of the field include understanding differences in regeneration between animal models and human at different stages of development and disease progression.

Exploration of new strategies

Novel strategies towards muscle regeneration mentioned in pre-meeting survey responses were discussed. These include delivering cargo to quiescent muscle stem cells, ablation of existing mutation-carrying satellite cell populations prior to transplant with healthy progenitors, innate immune cellular therapy approaches, exploring how lizards are able to rebuild whole appendages, bioelectromechanical devices to stimulate and guide stem cell therapy, and targeting IGF-1 and TGF-beta signaling pathways in a tissue specific manner.

Challenges and barriers to progress

Prominent challenges and barriers to progress in the field can be put into three categories: issues that affect translatability, issues that affect scalability and gaps in knowledge of muscle cell biology. Understanding differences in the regenerative capacity between experimental models and humans is vital to addressing the translational gap in the field. Investigators expressed the desire to have access to more patient samples representative of different stages of disease with corresponding phenotypic data and suggested that advocacy groups could potentially facilitate biobanking efforts. Such samples could be used to establish relevant human biomarkers for regeneration, which will aid in conducting pharmacodynamic studies to define target engagement and its relationship to functional outcome measures for a given therapy. Additional gaps identified include insufficient knowledge of muscle stem cell biology and the muscle stem cell niche in normal and disease states, as well as of the signals in different cell populations that contribute to muscle regeneration. More specific concerns were raised around safety (immunogenicity, tumorigenicity), long-term satellite cell exhaustion and body-wide delivery as it relates to specific strategies. Investigators could not align on the necessity to correct the underlying genetic defect prior to application of muscle regenerative strategies. Finally, business agreements and tech transfer issues were identified as major bottlenecks that have delay progress in the field.

Break-out Group 1: Application of exogenous therapeutic progenitor cells (moderated by Dr. Sharon Hesterlee and Dr. Angela Lek from Muscular Dystrophy Association)

The application of exogenous stem cells as a therapeutic intervention was a primary focus of this group. While the potential benefits were recognized, there remains uncertainty about the overall translatability of this strategy. Various types of cells, their transplantation methods, and the management of the local environment were discussed. Key takeaways from the discussion included recommendations to:

- Conduct thorough baseline studies to understand the condition of untreated muscles at the molecular and tissue level
- Prioritize autosomal recessive, loss-of-function diseases for initial proof-of-concept studies
- Explore testing in non-ambulant patients, targeting muscle groups required to retain independence (e.g. muscles required to operate a power wheelchair)
- Identify the optimal cell source for transplant; recognizing that different properties for localized vs systemic delivery may be required
- Develop and optimize localized delivery methods for initial clinical trials to ensure targeted and measurable outcome for a specific muscle group
- Consideration of steroids and their potential to negatively impact targeting and engraftment
- Exploration of anti-fibrotics to prime the body for engraftment.
- Engage with patient advocacy groups to align research priorities with patient needs and expectations
- Promote understanding and benefits of localized regenerative strategies and the risk/benefit profile across patient community in order to attract investor interest in early-stage companies in the space

A structured, four-part research program for moving this work forward was recommended by the group, including: (1) Studying natural history and immunity related to stem cell therapy; (2) Focusing on manufacturing processes and scalability and identifying the best cell types for therapy; (3) Developing *in vivo* and *in vitro* models to refine procedures; and (4) Establishing clinical outcomes, immunosuppression strategies, disease readouts, and relevant biomarkers.

Break-out Group 2: Therapeutic modulation of endogenous cell populations and/or pathways (moderated by Lucienne Ronco from FSHD Society)

The need to target multiple aspects of disease-related muscle degeneration was addressed in this group.

Key takeaways from this group discussion include the following recommendations:

- Focus on a cocktail of molecules/therapeutics hitting multiple regenerative mechanisms simultaneously and on advancing a cooperative trial approach to test multiple possible combinations by leveraging cooperation among different companies. Such a cooperative system would incorporate consistent standards to measure responses, consistent biomarkers, and an agreement to perform to common standards.

- Multiparametric biomarkers will be required in these studies to measure the mechanism of action of this type of novel therapeutic, level of regeneration, and overall muscle health. Along these lines:

    - Work to replace biopsies with fine needle aspirate and smaller sample collection and/or biofluids
    - Define markers of active regeneration
    - Evaluate how well noninvasive imaging techniques like MRI or DEXA can be used to measure regeneration.
    - Use highly sensitive and specific methods (like quantitative MS and Soma logics Aptamer technology).

- Therapeutic mechanisms should be prioritized by commonality across multiple muscle dystrophies

- Understanding of exercise and how it might support other mechanisms to drive regeneration should be advanced. Exercise/stress challenges should be conducted in healthy volunteers to assess SC recruitment in a healthy environment. This will inform studies in dystrophy patients.

- Natural history data from patients at specific life stages and over time are essential. Functional/imaging/biomarker biosamples must be collected as part of these efforts. The resulting large data set should be analyzed by AI.

Break-out Group 3: Biology of regeneration (moderated by Jason White from Muscular Dystrophy Australia)

This group focused on the need to establish a baseline of regeneration kinetics and to translate mouse work to the human condition at a basic level. Key takeaways from this group discussion included to the following recommendations:

- Focus on comprehending the basic kinetics of muscle regeneration in humans. Use MRI and other imaging modalities to achieve resolution at the fiber and nuclear levels. Form a discussion group to explore these techniques further.

- Define the environment affecting muscle regeneration, taking into account disease specificity and variability within individual muscles. Understand the role of the muscle matrix, surrounding fluid, and soluble factors.

- Promote ongoing discussions among basic scientists, clinicians, imaging specialists and other technologists to align approaches and measures of successful regeneration.

- Advance patient registries and the collection of comprehensive genetic information and clinical progression data.

- Address ethical considerations relevant to collecting needed human biopsies and appropriate biological materials to advance this research.

- Compare multiple disease types to evaluate the regenerative process and identify common factors.

List of meeting participants

Participant	Affiliation
Abigail Mackey	University of Copenhagen
Albert Almada	University of Southern California
Alireza Shahin	Evolved Bio
Angela Lek	Muscular Dystrophy Association
April Pyle	University of California
Brad Olwin	University of Colorado, Boulder
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Christoph Lepper	Ohio State University College of Medicine
Doug Albrecht	Jain Foundation
Douglas Millay	Cincinnati Children's Hospital Medical Center
Emanuela Gussoni	Boston Children's Hospital
Evrim Atas	Muscular Dystrophy Association
Fabio Rossi	University of British Columbia
Faye Mourkioti	University of Pennsylvania
Feodor Price	Harvard University
François Lamy	AFM Telethon
Fred Relaix	INSERM
Jason White	Muscular Dystrophy Australia
Jean-François Briand	AFM Telethon
Karen Chen	SMA Foundation
Kelly Howell	SMA Foundation
Lawrence Hayward	University of Massachusetts Chan Medical School
Lorenzo Puri	Sanford Burnham Prebys
Lucienne Ronco	FSHD Society
Mahasweta Girgenrath	Entrada Therapeutics
Mary Lee Mackichan	Private Foundation
Michael Goldberg	RYR1 Foundation
Michael Kyba	University of Minnesota
Michael Rudnicki	University of Ottawa
Natasha Chang	McGill University
Penney Gilbert	University of Toronto
Peter Currie	Monash University
Peter Zammit	Kings College London
Po-Ting Liu	Cure Duchenne
Richard Horgan	Cure Rare Disease
Rita Perlingeiro	University of Minnesota
Rob Krauss	Mount Sinai School of Medicine

Robert Schneider	NYU Grossman School of Medicine
Ryan Mitchell	Satellos Bioscience
Saverio Tedesco	University College London
Sharon Hesterlee	Muscular Dystrophy Association
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