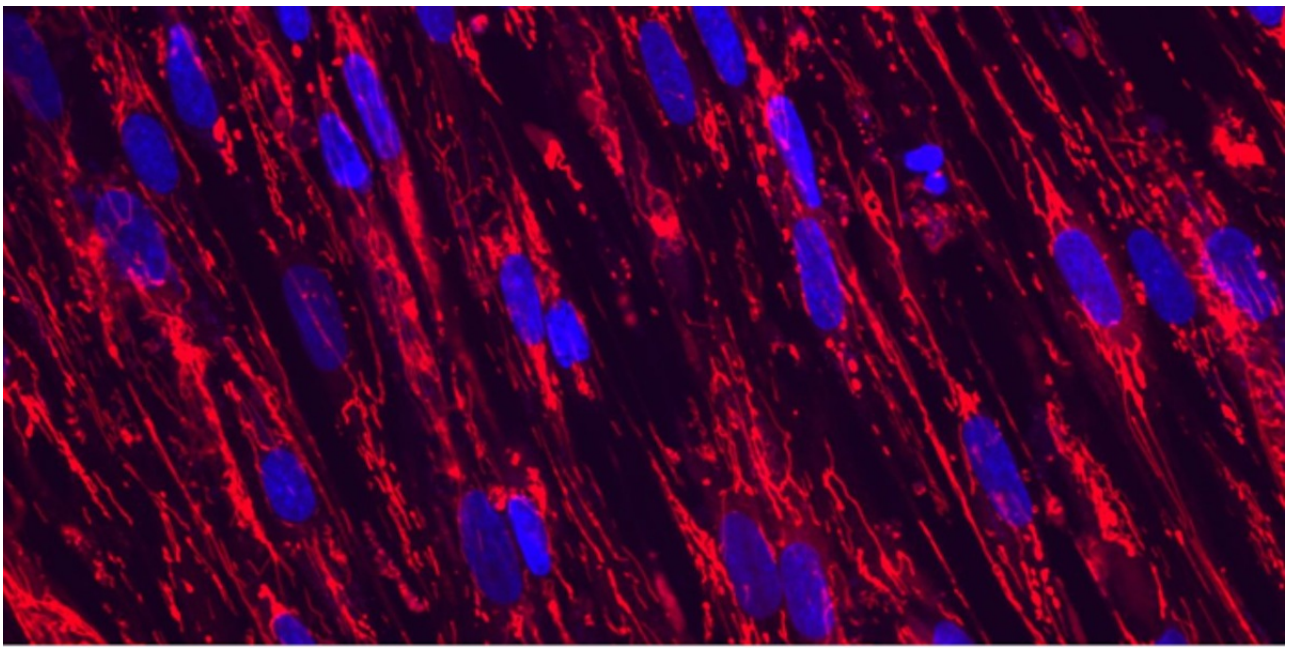
Diseases of Aging and Regenerative medicine (DARe) research at Novartis

Using human data to understand age-related diseases across organ systems and restore health

Age-related diseases, including neurodegenerative diseases and cardiovascular and metabolic diseases, account for a substantial and rising portion of the global health burden.

DARe scientists are committed to understanding and targeting the underlying molecular mechanisms that drive age-related diseases to develop regenerative pharmacological interventions for patients in indications of core interest to Novartis. We are committed to understanding age-related disease pathophysiology across organ systems by anchoring our approach to human data. By elucidating the underlying mechanisms and temporal aspects of aging in relation to disease, we strive to develop interventions that restore cell and tissue function.



The mitochondrial network in cultured human skeletal muscle cells, courtesy of Ryan Hahn

DARe is currently investigating three **fundamental processes** associated with **aging and age-related diseases** that have potential to deliver novel therapeutic approaches. These processes are intricately linked and play a crucial role in maintaining cellular health and function across organ systems.

- **Mitochondrial dysfunction**, a hallmark of aging, impairs ATP production and increases free radicals, causing biomolecular damage.
- **Declining DNA repair** mechanisms with age lead to genomic instability and cellular dysfunction, contributing to aging and diseases.
- **Extracellular Matrix (ECM) alterations** with age affect cellular activities and tissue structure, impacting organ function.

In addition to studying these prominent aging-relevant processes, DARe scientists are exploring the **modulation of cell fate and state** as a promising therapeutic strategy for the **regeneration of tissue and organ function**. Our strategy is based on human data and driven by our data science powered 'Regeneration Engine,' which learns from high-resolution datasets. We utilize phenotypic screening, bioengineering, and *in vitro* disease models, guided by the Regeneration Engine. This approach builds on research efforts around osteoarthritis and tendinopathy and has expanded to Alzheimer's Disease and Sjögren's Disease.

Exercise can counteract diseases associated with aging and we aim to delineate the molecular and cellular mechanisms underlying the benefits of physical activity. Our approach, anchored in human data, has a particular emphasis on the

hallmarks of aging, such as exercise-induced reversal of age-related mitochondrial dysfunction. Like exercise, body weight loss in the context of obesity has demonstrated health benefits across organ systems. To complement exploratory efforts on mitochondria, we are also looking at alternative approaches to increase **energy expenditure** in skeletal muscle for the treatment of age-related obesity.

> We have an exciting opportunity to reimagine the discovery of medicines for human diseases using the lens of aging and regenerative biology across organ systems.
>
> - **Michaela Kneissel**, Global Head of DARe for Biomedical Research at Novartis

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