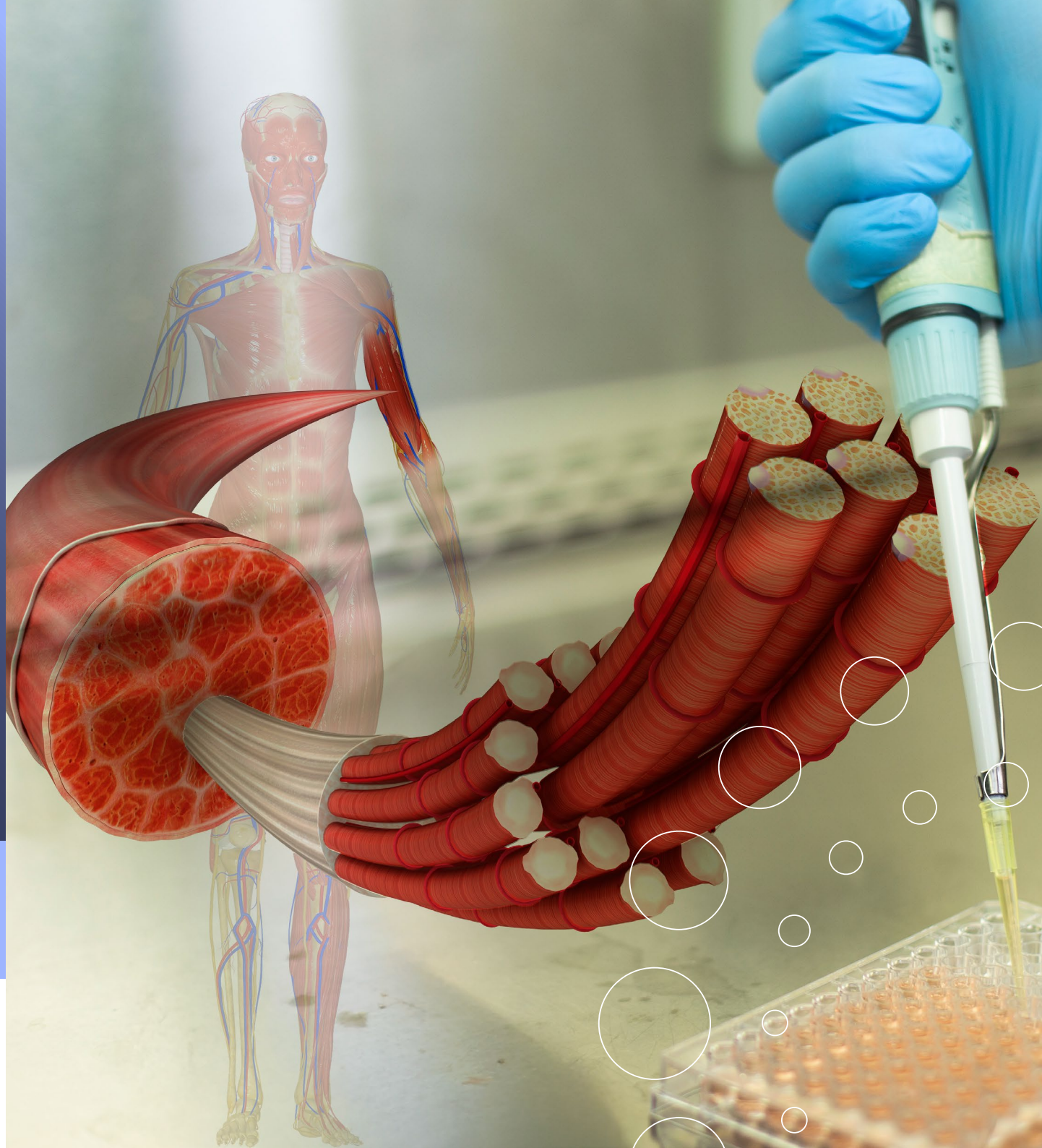
Creating Skeletal Muscle from Stem Cells

Dr Michael Hicks

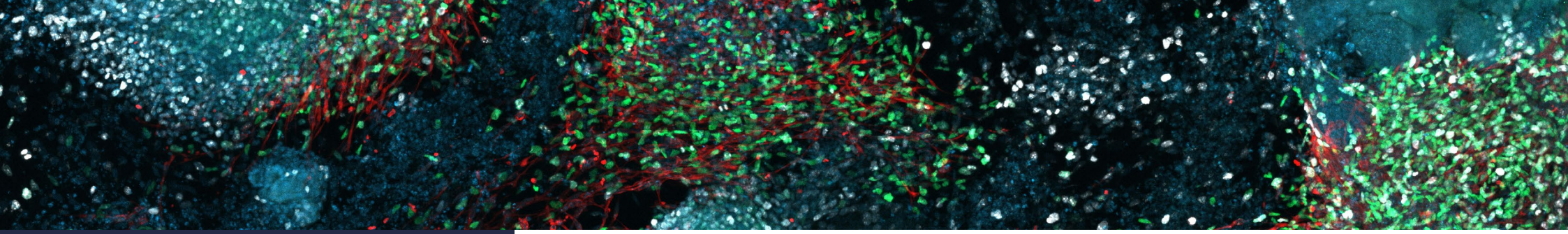
JANUARY 2025

doi.org/10.33548/SCIENTIA1160

MEDICAL & HEALTH SCIENCES



Scientia



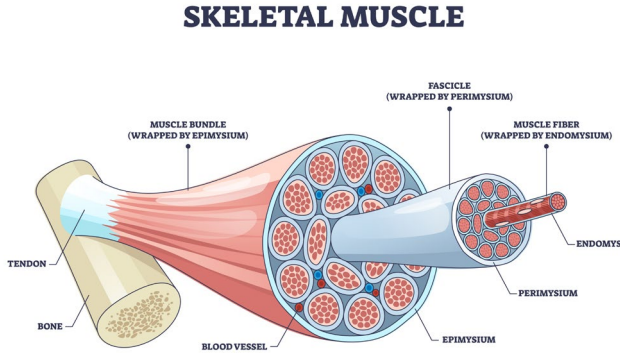
Creating Skeletal Muscle from Stem Cells

Recognising the precise steps involved in the differentiation process of stem cells into various cell types is crucial to regenerative medicine. Researchers face the specific challenge of how to fine-tune and optimise protocols for directing stem cells to differentiate into specific cell lineages. As such, the directed differentiation to skeletal muscles has not yet advanced to the clinical trials stage. Dr Michael Hicks from the School of Medicine at the University of California, Irvine, is working to change this with his extensive studies into the transition of stem cells into skeletal muscles.

Transplanting Stem Cells into Skeletal Muscles

Human pluripotent stem cells (hPSCs) have a remarkable ability to differentiate into any cell type in the body, including muscle cells, blood cells, and neurons. Unlike human embryonic stem cells, induced hiPSCs are derived from adults, often from individuals with specific genetic disorders, and offer a promising avenue for tailoring personalised regenerative medicine strategies for a multitude of diseases. For instance, the directed differentiation of hPSCs into pancreatic cells producing insulin is currently revolutionising the treatment landscape for Type 1 diabetes. Furthermore, hPSC-based therapies hold immense potential for addressing a surprising spectrum of debilitating conditions, ranging from neurodegenerative disorders like Parkinson's and Alzheimer's diseases to genetic ailments, as well as diverse diseases like arthritis and cardiac defects.

The process of transplanting stem cells into skeletal muscles is of particular interest in medical science. The ability of stem cells to self-renew could offer an alternative response to injuries and replace damaged muscles over a lifetime. However, so far, generating clinical-grade skeletal muscle cells from hPSCs has been challenging.

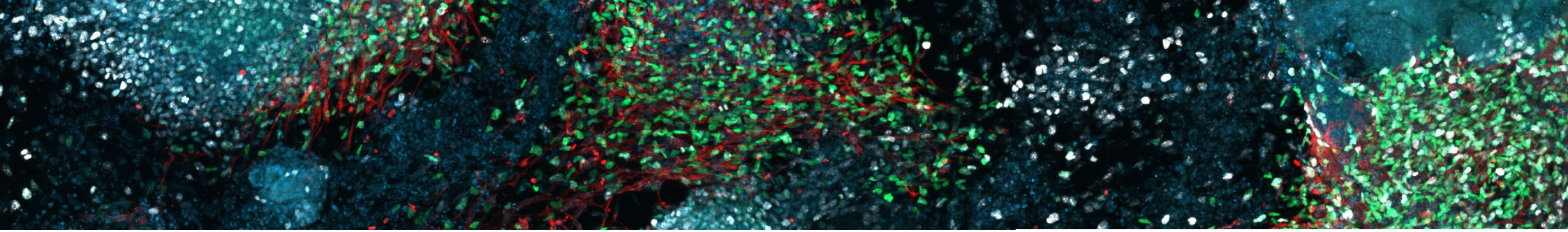


Obstacles and Gaps

Researchers have made progress in isolating hPSCs from patients and modifying them in the laboratory. However, challenges arise when reintroducing these modified cells into patients, where they must effectively replicate and regenerate. Dr Michael Hicks from the School of Medicine at the University of California, Irvine, is working to minimise the gaps in understanding the progenitors involved in early skeletal muscle formation, especially during initial myogenic commitment.

To form the skeletal muscle system, progenitors first divide to form paraxial mesoderm, which develops into blocks of tissue known as somites. These blocks of tissue then divide into the ventral sclerotome, giving rise to bone and cartilage, and the dorsal dermomyotome from which skeletal muscles arise. However, genetic variability, that is, differences in the sequences of genes between individuals, adds complications when attempting to do this in a dish since small differences between cells taken from different people can lead to inconsistent outcomes during this differentiation process.

< Skeletal muscle is composed of long, cylindrical cells called muscle fibers, which are multinucleated and striated due to the organized arrangement of myofilaments. These fibers are bundled together in fascicles, surrounded by connective tissue called perimysium. Each muscle fiber contains sarcomeres, the basic contractile units needed for voluntary movement. Skeletal muscles are also richly supplied with blood vessels and nerves, facilitating energy supply and motor control. It repairs through a coordinated regenerative response by muscle stem cells known as satellite cells.



Crucial transcription factors (proteins involved in converting or transcribing DNA into RNA that composes our genes) like Pax3, Pax7, Eya1, and Six1 play are involved in the process of muscle development. Still, their role and timing in hPSC differentiation remain unclear. Additional signalling mechanisms like the Wnt pathway and other secretions from neighbouring cells also play a part in directing muscle cell fates.

Dr Hicks emphasises that research development should focus on understanding in vitro myogenesis which focuses on the robust differentiation of hPSCs into pre-myogenic progenitors to identify optimal microenvironments for muscle development.

Identifying Early Differentiation Checkpoints

Dr Hicks recognised that studying prenatal muscle development might help address the gaps in understanding hPSC muscle differentiation. His team examined progenitor markers expressed in the developing limb at the seventh week of human embryos, leading to the identification of a SIX1+PAX3+ co-expressing myogenic population. Further investigation revealed that SIX1 expression could serve as a potential checkpoint to distinguish between hPSC differentiations that would later successfully mature into skeletal muscle progenitor cells.

The expression levels of SIX1 can be used to optimise protocols for directed differentiation of myogenic cells derived from hPSCs in clinical settings. By inducing robust expression of SIX1+PAX3+ precursors early in directed differentiations, the authors reported consistent derivation of muscle formation across all patient hiPSC lines tested. In the absence of SIX1, PAX3 expression was affected in cell lines, and muscle progenitors failed to emerge.

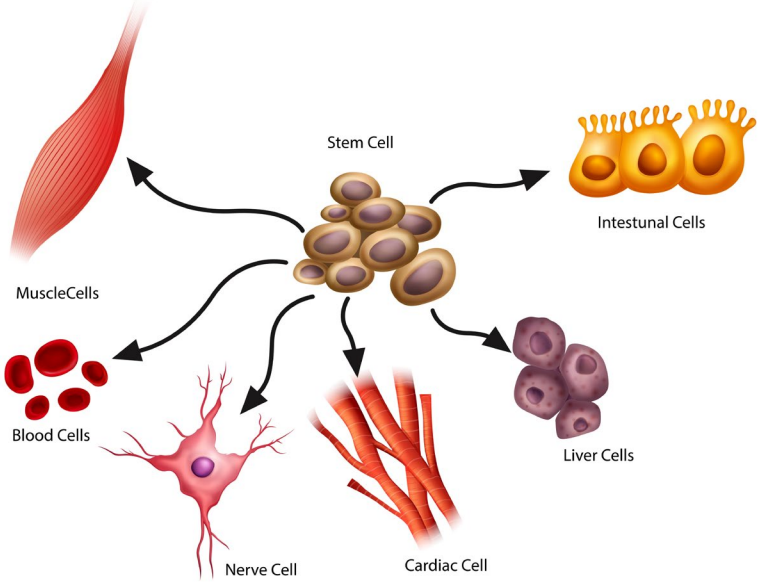
The researchers propose predicting the emergence of the SIX1+PAX3+ phenotype as an early indicator for improving subsequent myogenic differentiation.

Building on Ground-breaking Discoveries

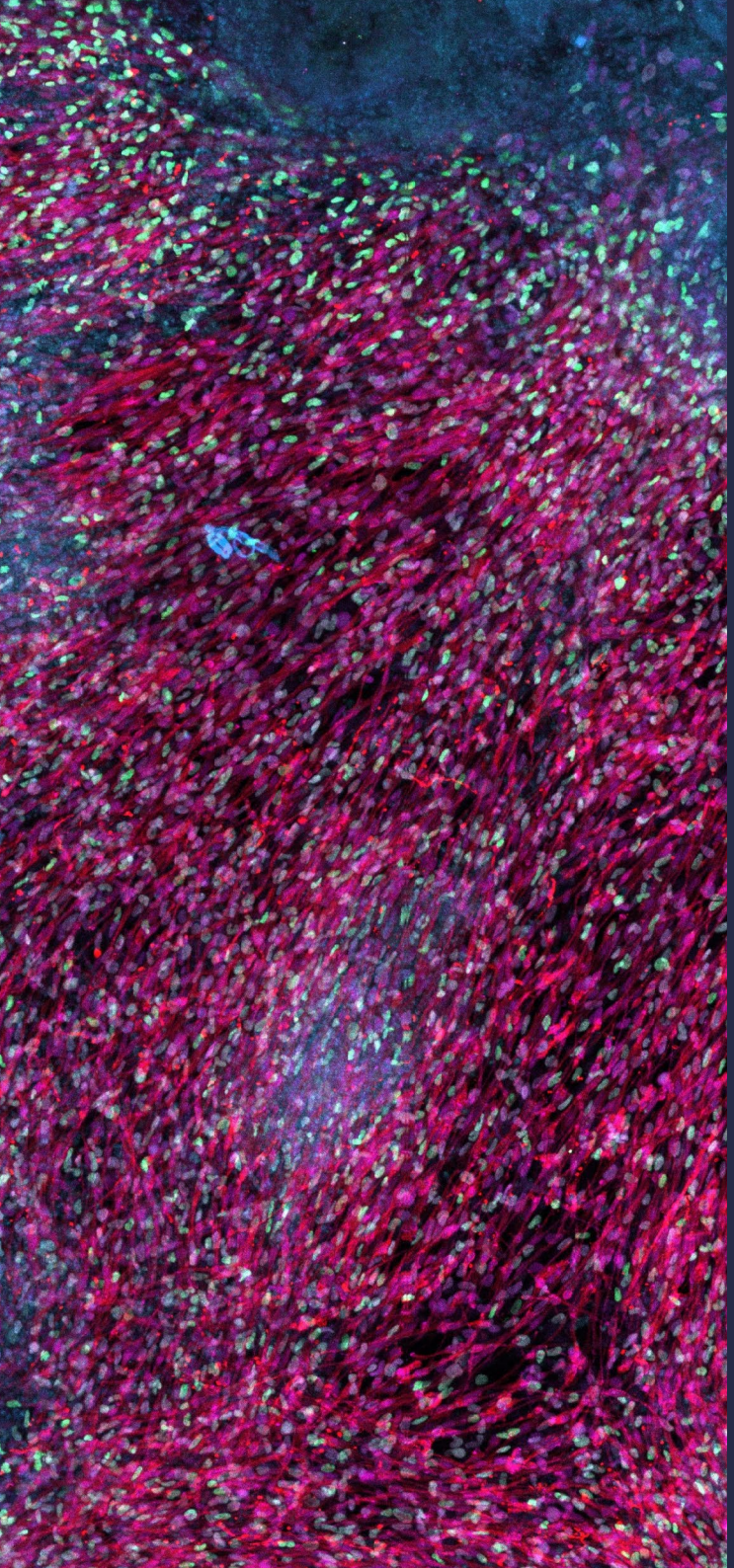
The ability to induce hPSCs derived from any individual and reprogramme them to an embryonic state in laboratory settings was a ground-breaking discovery by Drs Yamanaka and Gurdon, winners of the Nobel Prize in 2007. These reprogrammed cells hold the potential to be differentiated into various tissue types, offering immense potential for personalised medicine.

Achieving consistent differentiation of induced hPSCs is crucial for generating clinical-grade muscle cells, essential for effective cell therapy to replace damaged or dysfunctional muscle tissues. Dr Hicks' latest study presents a stepwise approach to optimise differentiation protocols for deriving skeletal muscle progenitor cells from various patient-specific hPSCs lines. The team identified a critical developmental checkpoint at an early stage of myogenic commitment that predicts successful differentiation and validated the emergence of myogenic-specific markers early in the protocol.

The next step in Dr Hick's research is to test and develop strategies to mature skeletal muscle progenitor cells into satellite cells like those found in adults. The idea is that these satellite cells can reside in the body's stem-cell niche and continuously self-renew damaged muscles. Such regenerative cell replacement therapy holds significant promise for personalised medicine across multiple medical specialities.



Human pluripotent stem cells are a type of stem cell capable of differentiating into almost any cell type in the body. Derived from early embryos or reprogrammed adult cells, they possess the unique ability to give rise to all three germ layers: ectoderm, mesoderm, and endoderm. This versatility makes them invaluable for research, regenerative medicine, and potential therapies for various diseases and injuries. Their ability to selfrenew indefinitely in culture also provides a powerful tool for studying development and disease mechanisms.



MEET THE RESEARCHER

Dr Michael Hicks
Department of Physiology and Biophysics, School of Medicine, University of California, Irvine, Irvine, CA, USA

Dr Michael Hicks is an Assistant Professor of Physiology and Biophysics at the University of California, Irvine (UCI). He also serves as associate director of the UCI Muscle Biology and Disease Research Center and contributes to the Sue and Bill Gross Stem Cell Research Center. His research focuses on skeletal muscle regeneration using adult muscle stem cells and human pluripotent stem cells. He completed his doctoral research at the University of Arizona, then undertook research at the University College London and the University of California, Los Angeles. His research group studies stem cell regeneration and the influence of diseased microenvironments on stem cell behaviour by employing emerging technologies. Dr Hicks holds two patents and has several notable publications, including papers in *Stem Cell Stem* and *Nature Cell Biology*.

CONTACT

mrhicks1@hs.uci.edu
https://hickslab.org/
https://twitter.com/mic_hicks/

KEY COLLABORATORS

Olga Jaime, School of Medicine, University of California, Irvine

Jessica Arias, School of Medicine, University of California, Irvine

Shreya Pavani, School of Medicine, University of California, Irvine

Professor April Pyle, Microbiology, Immunology, and Molecular Genetics, University of California, Los Angeles

FUNDING

National Institutes of Health

FURTHER READING

OG Jaime, J Arias, S Pavani, *et al.*, SIX1+PAX3+ identify a progenitor for myogenic lineage commitment from hPSCs, *Development*, 2023, 150(14), dev201509. DOI: https://doi.org/10.1242/dev.201509

< Skeletal Myogenesis from human pluripotent stem cells
Credit: Dr Michael Hicks