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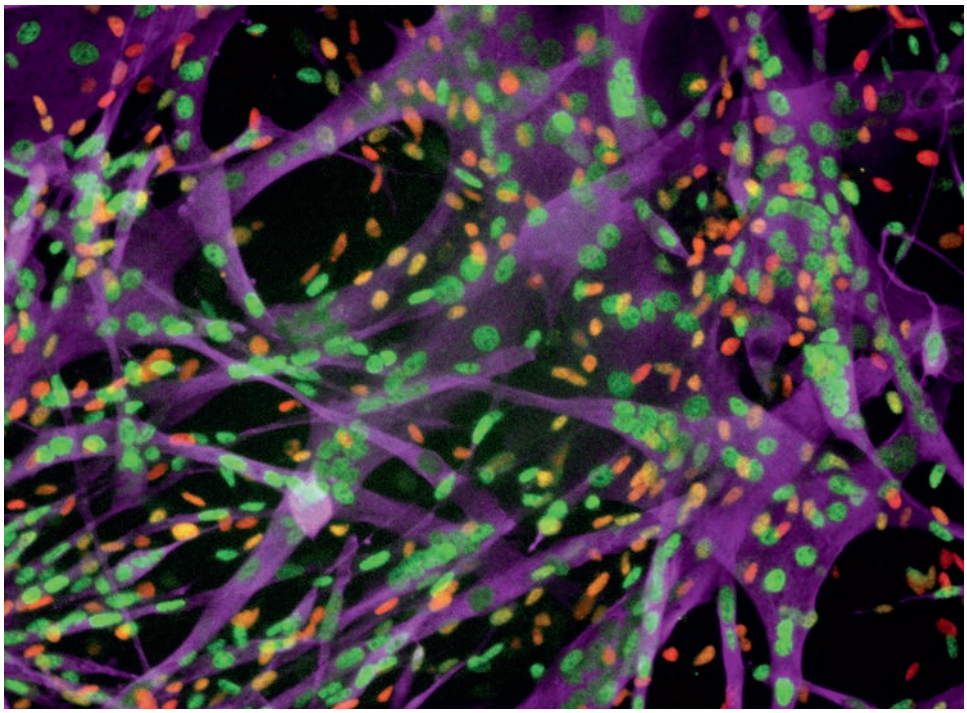
The Hochedlinger laboratory explores the molecular mechanisms underlying pluripotency, which is the ability to produce all mature cell types of the body. Previous groundbreaking discoveries have shown that adult cells can be reprogrammed into pluripotent stem cells by activating a handful of embryonic genes. The resultant cells, called induced pluripotent stem cells (iPSCs), have tremendous therapeutic potential; they can be derived from any patient's skin or blood cells. In the laboratory, iPSCs can be coaxed into many specialized cell types. Our lab has contributed to a better understanding of the process of cellular reprogramming, which allowed us to elucidate basic mechanisms that maintain cellular identity and prevent aberrant cell fate change. Our ultimate goal is to utilize these mechanistic insights for the development of new strategies to treat cancer and other complex diseases.

The Hochedlinger lab is studying the mechanisms underlying cell fate transitions by using transcription-factor-mediated conversion of somatic cells into induced pluripotent stem (iPSCs) as a tractable tool. iPSCs are typically derived by viral transduction of the embryonic transcription factors Oct4, Sox2, c-Myc and Klf4, which reset the differentiation state of an adult cell into that of a pluripotent cell. The underlying transcriptional and epigenetic changes remain largely elusive due to the low efficiency of reprogramming and the heterogeneity of cell cultures. Importantly, iPSCs have been derived from different species—including human patients—and therefore provide a unique platform to model degenerative disorders such as Alzheimer's disease, Parkinson's disease and diabetes. Moreover, iPSCs could be ultimately used in regenerative medicine to replace damaged cells and tissues with genetically matched cells.

We have identified biomarkers to track and prospectively isolate rare intermediate cell populations that are poised to become iPSCs, and we are currently using these populations to understand the transcriptional, epigenetic and proteomic changes in cells undergoing reprogramming. Additionally, our lab has conducted unbiased shRNA screens for barriers to reprogramming, uncovering new mechanisms that safeguard somatic cell identity. For example, we identified components of chromatin assembly (CAF-1), protein sumoylation (SUMO-2, UBC9) and alternative polyadenylation of RNA (NUDT21) as novel safeguard mechanisms and we are currently exploring the underlying mechanisms as well as their role in tissue homeostasis and cancer. More recently, we discovered that MAPK signaling is critical to preserve the epigenetic and genomic stability as well as full the developmental potential of mouse pluripotent stem cells. Mechanistically, we showed that MAPK signaling is critical to fine-tune global DNA methylation levels and maintain genomic imprinting. Importantly, we extended these observations to human cells, allowing us to provide more stable and thus safer embryonic stem cell and iPSC models.

We hypothesized that the manipulation of safeguard mechanisms we previously identified in the context of iPSC reprogramming might endow somatic cells



Induced myogenic progenitor cells (iMPCs) derived from fibroblasts. Immunostaining for markers of muscle stem cells (Pax7, red) and differentiated cells (MyoD, green; MyHC, purple)(see Bar-Nur et al., Stem Cell Reports 2018 May 8;10(5):1505-1521).

Image: Ori Bar-Nur, PhD

with increased plasticity and could facilitate the derivation of adult stem cell types that have been difficult to capture using conventional approaches. Indeed, we recently provided proof-of-principle evidence for this idea by showing that pharmacological inhibition of defined safeguard mechanisms, together with overexpression of the muscle-specific transcription factor MYOD, reprograms fibroblasts to muscle stem cell-like cells. The reprogrammed cells share key molecular and functional characteristics with *bona fide* muscle stem cells including dependence on PAX7, self-renewal, differentiation and the ability to engraft in the muscles from a dystrophic mouse model. Ongoing efforts include dissection of the underlying mechanisms and an attempt to recapitulate these findings in human cells.

Selected Publications:

Di Stefano B, Ueda M, Sabri S, Brumbaugh J, Huebner AJ, Sahakyan A, Clement K, Clowers KJ, Erickson AR, Shioda K, Gygi SP, Gu H, Shioda T, Meissner A, Takashima Y, Plath K, **Hochedlinger K**. Reduced MEK inhibition preserves genomic stability in naive human embryonic stem cells. *Nat Methods*. 2018 Aug 20.

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Bar-Nur O, Gerli MFM, Di Stefano B, Almada AE, Galvin A, Coffey A, Huebner AJ, Feige P, Verheul C, Cheung P, Payzin-Dogru D, Paisant S, Anselmo A, Sadreyev RI, Ott HC, Tajbakhsh S, Rudnicki MA, Wagers AJ, **Hochedlinger K**. Direct Reprogramming of Mouse Fibroblasts into Functional Skeletal Muscle Progenitors. *Stem Cell Reports*. 2018 May 8;10(5):1505-1521.

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