receptor (CALCR), which is a GPCR important for the maintenance of MuSCs, had decreased proliferation in the presence of collagen V. MuSCs depleted of CALCR failed to respond to incubation with collagen V, indicating that CALCR mediates the function of collagen V in maintaining quiescence and stemness. Moreover, CALCR specifically bound to collagen V, which activated intracellular signalling downstream of CALCR.

This work uncovers a self-sustaining signalling cascade initiated by Notch: the authors propose that Notch senses the homeostatic environment in which MuSCs reside and promotes the secretion of collagen V, which reinforces the properties of the stem cell niche that induce quiescence.

Kim Baumann

ORIGINAL ARTICLE Baghdadi, M. B. et al. Reciprocal signalling by Notch–Collagen V–CALCR retains muscle stem cells in their niche. *Nature* **557**, 714–718 (2018)
FURTHER READING Almada, A. E. & Wagers, A. J. Molecular circuitry of stem cell fate in skeletal muscle regeneration, ageing and disease. *Nat. Rev. Mol. Cell Biol.* **17**, 267–279 (2016) | Bray, S. J. Notch signalling in context. *Nat. Rev. Mol. Cell Biol.* **17**, 722–735 (2016)

> the pattern of chromatin modifications in immune cells could be used to predict their identity

Finally, EpiTOF analysis of immune cells from monozygotic and dizygotic twins revealed that non-heritable factors (e.g. environmental influences and/or somatic mutations) accounted for 70% of the variance in chromatin modification profiles. The heterogeneity in chromatin modification profiles between twins increased with age and approached the levels in paired non-related individuals, suggesting that it is mostly non-heritable factors that drive age-associated increased heterogeneity in chromatin modifications.

In summary, EpiTOF enabled the creation of an epigenetic atlas of 22 different immune cell types based on their chromatin modification profiles, and should be useful for dissecting epigenetic landscapes related to disease and ageing.

Grant Otto

ORIGINAL ARTICLE Cheung, P. et al. Single-cell chromatin modification profiling reveals increased epigenetic variations with aging. *Cell* https://doi.org/10.1016/j.cell.2018.03.079 (2018)

Journal club

THE BEGINNING OF TOTIPOTENCY

"For the discovery that mature cells can be reprogrammed to become pluripotent". Many of us may know the succinct summary of the Nobel Prize-winning discovery shared jointly by Sir John Gurdon and Shinya Yamanaka. Especially Gurdon's seminal papers are an inspiration for my research and provide examples of a standard of science that should hold true as much today as they did more than half a century ago.

This is what I learned from Gurdon's early papers:

1. Ask a clear question of fundamental importance. It was controversial at the time whether differentiated cells contain the same set of genes as the early totipotent embryo. Gurdon's experiments were driven by curiosity as to whether the nucleus of a differentiated cell could support development of other cell types.

2. Choose your experimental system wisely. Early nuclear transplantation experiments showed promise in reprogramming nuclei from blastula but not from later stage embryos of the frog *Rana pipiens* (Briggs et al., 1952). Eggs from this frog species were limited owing to seasonal egg laying. Instead, *Xenopus laevis* could be stimulated to lay eggs throughout the year and proved to have better developmental potential (Gurdon et al., 1958).

3. Overcome technical challenges. Extraction of the meiotic chromosomes from *X. laevis* eggs was difficult and could be overcome by UV irradiation to fragment DNA (Gurdon et al., 1958).

4. Use unambiguous markers for a 'clean' readout. To unequivocally demonstrate that the frog emerging from the somatic cell nuclear transfer (SCNT) experiments was derived from the nucleus of a differentiated donor cell, and not from the nucleus of the host egg, donor nuclei were derived from a natural mutant whose cells harboured one rather than two nucleoli (Gurdon et al., 1958).

5. Use a functional assay to assess the result. SCNT experiments demonstrated that nuclei from intestinal epithelial cells can give rise to fertile adult frogs (Gurdon et al., 1966). Therefore, a key conclusion was that differentiated nuclei retain genes necessary for generating all cell types, including functional gametes. Importantly, the work also implied that the egg cytoplasm can reprogramme differentiated nuclei back to a totipotent state.

Surprisingly, 60 years on, we are still largely in the dark about the mechanisms that enable reprogramming to a totipotent chromatin state. Epigenetic modifications likely contribute barriers to reprogramming (Hoermanseder et al., 2017). We also think that certain transcription factors — by serving as pioneer factors that enable opening of chromatin and facilitate embryonic genome activation — have important roles in overcoming these barriers to reprogramming. However, how chromatin is efficiently reprogrammed by potential pioneer factors only hours after fertilization and what signals and additional molecular factors mediate this transition to totipotency remain questions of fundamental importance.

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The author declares no competing interests.

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