TWO CLOCKS, ONE BODY: A NEW MAP OF MAMMALIAN AGEING

The serial cloning experiments discussed in two earlier posts have recently been joined by a new paper that reframes them. The new paper, published in Nature (1), offers a molecular map of mammalian ageing precise enough to show, in retrospect, exactly what those experiments were measuring — and what they were missing. The earlier posts now read as two chapters of a larger story.

The paper does something that had never been done at this scale: it integrates more than 11,000 transcriptomes from over 25 tissues across four mammalian species — mouse, rat, macaque, and human — to build a unified molecular portrait of ageing and mortality. The result is not a single clock but a modular architecture: 28 co-regulated gene expression modules, each tracking a different biological subsystem, from inflammation and interferon signalling to mitochondrial respiration and chromatin remodelling. The most striking finding is that the mortality-associated transcriptomic signature is conserved across species and cell types — and that it can be reversed. Reprogramming, cell immortalisation, heterochronic parabiosis, and early embryogenesis all attenuate or erase it. Epigenetic age, the paper makes clear, is a state, not a sentence.

This brings into sharp focus a distinction that two earlier papers from the Wakayama laboratory illuminate with unusual clarity. In 2013, that group reported serial recloning of mice through 25 generations using somatic cell nuclear transfer with trichostatin A (TSA) as an epigenetic reprogramming agent (2). Efficiency did not decline. Body weight, lifespan, and fertility remained normal. No accumulation of epigenetic abnormalities was detected. The conclusion — that serial cloning might continue indefinitely — was bold, but the data supported it. What the experiment had demonstrated, without framing it in those terms, was a repeated, successful reset of precisely the transcriptomic ageing signature that the Nature paper now maps so carefully: each round of nuclear transfer was, in effect, a rejuvenation of the epigenetic layer.

The sequel, published in Nature Communications in 2026 by the same group after twenty years of continued experiment (3), tells a different story. Cloning was continued through 58 generations before the lineage finally collapsed. And here the two levels diverge completely. Epigenetic reprogramming kept working: histone modification profiles in 51st-generation embryos were indistinguishable from those of first-generation clones. The transcriptomic clock was being reset at every cycle. But the DNA sequence itself — the hardware beneath the software — was silently accumulating damage that no reprogramming could touch. Whole-genome sequencing revealed approximately 3,700 single-nucleotide variants from generation 1 to 57, plus large structural variants including chromosome translocations and loss of an entire X chromosome. The cloned mice looked normal, lived normally, and died normally — until the mutational load crossed a threshold and the lineage simply ended.

The two levels, in other words, are genuinely parallel and genuinely non-intersecting. The epigenetic/transcriptomic level is malleable: it can be measured by molecular clocks, modulated by dietary or pharmacological interventions, and reset by

reprogramming. The mutational level is a ratchet: it accumulates with each cell division, leaves no trace in gene expression profiles, and cannot be erased by any known biological mechanism short of meiosis. When the near-final-generation cloned females were mated with normal males, a small fraction of embryos survived — rescued by meiotic recombination and fertilisation. The experiment thus provides, almost accidentally, a direct demonstration of why mammals reproduce sexually: not merely to generate variation, but to purge a mutational debt that clonal reproduction accumulates without limit.

The practical implication is sobering. The molecular clocks built in the Nature paper — transcriptomic, epigenomic, proteomic — measure the reversible layer with impressive precision. But they are blind to the other layer. An intervention that dramatically lowers your clock age while leaving somatic mutation burden untouched may be doing something real and valuable at one level, while the underlying genetic text continues to erode at the other. Both currencies of ageing are real. Neither is sufficient on its own. And the most honest reading of these three papers together is that we now have a clearer map of what can be reversed — and a much clearer view of what cannot.

1. https://doi.org/10.1038/s41586-026-10542-3
2. http://dx.doi.org/10.1016/j.stem.2013.01.005
3. https://doi.org/10.1038/s41467-026-69765-7