Time unlocks bovine fibroblast immortality to pave the way for cultivated beef

We demonstrate that bovine fibroblasts can undergo spontaneous immortalization after 500 days in culture, without genetic modification or p53 inactivation. These rare events provide a safe, stable and economically viable cell source that overcomes key barriers to cultivated beef production.

This is a summary of:
Pasitka, L. et al. Spontaneous immortalization of bovine fibroblasts following long-term expansion offers a non-transformed cell source for cultivated beef. *Nat. Food* https://doi.org/10.1038/s43016-025-01255-3 (2025).

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The problem

Beef production is among the most resource-intensive forms of agriculture, driving deforestation, reducing biodiversity and using more land and water than any other animal protein. Cultivated meat is positioned as a sustainable alternative, with the potential to dramatically cut land use and water consumption[1]. However, efforts are hampered by the limited lifespan of primary cells in culture. Historically, immortalization required genetic modification that disables tumour suppressors, such as p53, raising regulatory and consumer concerns[2]. Recently, we demonstrated that chicken fibroblasts undergo spontaneous immortalization without p53 inactivation and can be adapted to high-density suspension cultures[3]. However, cells from ruminants are especially resistant to immortalization[4], a phenomenon tied to Peto's paradox, where large animals evolve strong anti-cancer defences. This resistance has created a major bottleneck for cultivated beef, as no spontaneous immortalization has previously been demonstrated.

The discovery

We investigated whether bovine fibroblasts could overcome senescence without genetic engineering if maintained in long-term culture (Fig. 1a). More than 30 primary fibroblast isolates were established from Holstein and Simmental cattle breeds and continuously propagated for over 500 days, spanning more than 240 population doublings (Fig. 1b). Cells were monitored through senescence and recovery using transcriptomics, telomere length assays, mitochondrial function tests and genomic stability analyses. This design was chosen to characterize extremely rare immortalization events in real time, providing an opportunity to test whether large-animal cells could undergo spontaneous immortalization under extended culture.

Bovine fibroblasts entered classical senescence after 60 doublings, exhibiting hypertrophy, telomere shortening, γH2AX foci and a senescence-associated secretory phenotype. Remarkably, proliferating colonies emerged in both genetic backgrounds after 400 days of stagnation. These immortalized cells displayed telomere elongation, telomerase (TERT) activation, and restoration of mitochondrial function coordinated by PGC1α. Importantly, immortalization occurred independently of *TP53* mutation or inactivation, preserving DNA repair capacity and avoiding transformation-associated risks. Lines derived from both cattle breeds remained karyotypically stable and failed to form colonies in soft agar, underscoring the absence of transformation. Our study constitutes the first demonstration, to our knowledge, of spontaneous immortalization in cattle cells, overturning longstanding assumptions that such events were restricted to smaller animals[4].

Finally, an economic feasibility study of beef cultivation showed that when medium costs are reduced below US$1 per litre, total production costs dropped to US$7–10 per pound. Sensitivity analysis revealed that cell density is the single most important driver of cost, underscoring the importance of immortalized bovine fibroblasts that are capable of high-density suspension culture.

The interpretation

Although the production of cultivated chicken is steadily advancing, cultivated beef production represents the field's greatest technical and economic challenge. Our demonstration that bovine fibroblasts undergo spontaneous immortalization through p53-independent mechanisms in two independent genetic backgrounds (Holstein and Simmental) suggests an underlying biological mechanism rather than a random event. This pathway might be broadly conserved across mammals, offering potential for developing stable, non-transformed cell lines for multiple livestock species without genetic modification. The telomerase reactivation and PGC1α-mediated mitochondrial recovery pathway seems to be distinct from cancer-associated immortalization and could represent a possible pathway to escape senescence.

As we demonstrate spontaneous immortalization for only two cattle breeds, claims of generalizability are limited. We cannot definitively establish whether this mechanism exists across other mammals or cattle breeds. The low probability of immortalization and the extended timeframe required to isolate immortalized cells make this approach impractical for routine cell line development. Additionally, although our immortalized cell lines showed no tumorigenic potential in soft agar assays, a comprehensive safety assessment remains necessary. Furthermore, our economic projections are theoretical and depend on numerous assumptions about scaling, efficiency and market conditions, which remain unvalidated at commercial scale[5].

Future work will assess whether spontaneous immortalization extends to other mammals. We will dissect the molecular program enabling fibroblasts to bypass senescence. We will also test whether transdifferentiation of immortalized bovine fibroblasts into muscle and fat is possible, by adapting strategies that are already validated in chicken, to generate edible tissues (Fig. 1c).

Yaakov Nahmias
The Hebrew University of Jerusalem, Jerusalem, Israel.

EXPERT OPINION

"The authors have done a fantastic job of developing spontaneously immortalized bovine fibroblast cell lines to be used in the cultivated meat field. The cell lines were thoroughly characterized using transcriptomic and metabolic analyses. Most importantly, the economic potential of the bovine cell lines was carefully detailed." **Larry S.W. Loo, A*STAR Genome Institute of Singapore (GIS), Singapore, Singapore.**

FIGURE

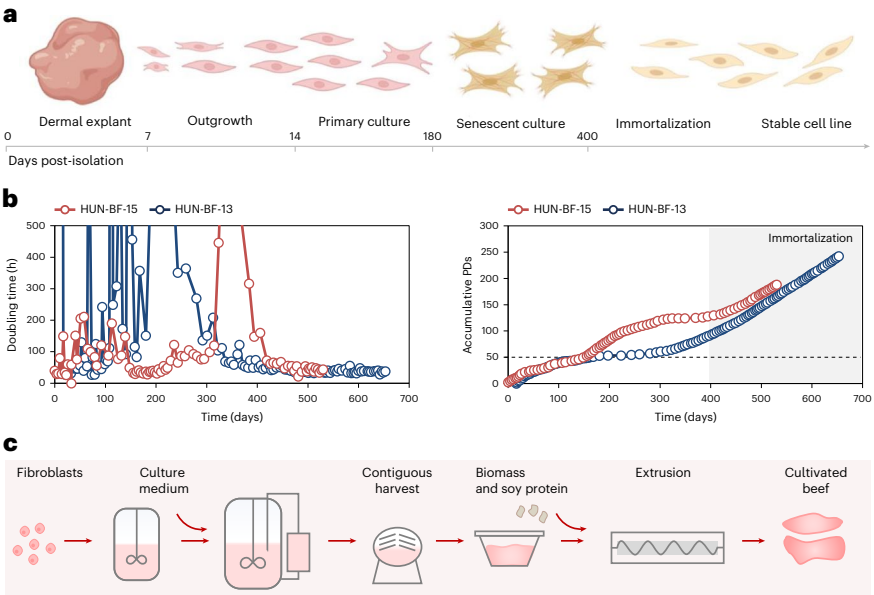

Fig. 1 | Immortalization and application of bovine dermal fibroblasts for cultivated beef production. **a**, Primary dermal fibroblasts were isolated from cattle and continuously cultured for 400 days, undergoing replicative senescence followed by spontaneous immortalization. **b**, Spontaneous immortalization of fibroblast lines from two cattle breeds, Holstein (HUN-BF-15) and Simmental (HUN-BF-13), with doubling time (left) and number of population doublings (PDs; right) depicted. **c**, Schematic overview of the bioprocess workflow for large-scale cultivated beef production using immortalized bovine fibroblasts as a cellular platform. Panel **a** created in BioRender. Cohen, M. (2026) https://BioRender.com/ghpuivq. © 2025, Pasitka, L. et al.

BEHIND THE PAPER

The road to technological revolutions often begins with healthy scepticism. As a chemical engineer, I viewed cost efficiency as the greatest hurdle for cultivated meat. We sought animal cells that could match Chinese hamster ovary (CHO) cells, the biomanufacturing benchmark. Fibroblasts stood out for their rapid expansion in inflammatory and nutrient stress conditions. Since Hayflick first described spontaneous immortalization in 1961, we have envisioned using this natural process to create stable, non-genetically modified cell sources.

Chicken fibroblasts were immortalized quickly, and to our surprise, floating cells remained intact, enabling single-cell suspension and validating the cost efficiency of continuous manufacturing. Extending this strategy to cattle proved far more difficult. Months stretched into years, and perseverance replaced certainty. After 400 silent days, proliferating colonies finally appeared as a true 'eureka' moment that overturned our long-held assumptions about bovine cell biology and revealed what persistence can pay off. **Y.N.**

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   This paper reports a techno-economic analysis showing that continuous manufacturing with animal-free medium can reach cost parity with traditional chicken production.

FROM THE EDITOR

"The paper by Pasitka et al. stood out to me because stable bovine cell lines are difficult to generate. Now, a cell line has been established without genetic modification, which is important for regulatory approval — and with the potential for cultivated beef to be produced at similar prices to beef from livestock." **Annisa Chand, Senior Editor, *Nature Food*.**