Ecology & Evolution | Nov 14, 2026 | 12 min read | By Bryan White

Epigenetic Gatekeeping Allows Mammalian "Planimal" Hybrids to Retain Nearly the Entire Red Algal Genome Across 150 Cell Divisions

Genomics * Biotech & Cellular Systems * Synthetic Biology

Across the tree of life , horizontal gene transfer (HGT) -- the non-sexual movement of genetic material between unrelated organisms -- serves as a dominant engine of innovation in prokaryotes , yet remains extraordinarily constrained in complex eukaryotes [1] . When distantly related eukaryotic cells are artificially fused in the laboratory, the resulting heterokaryon almost invariably suffers catastrophic mitotic instability, innate immune activation, and rapid, uniparental chromosome elimination within a few cell divisions [1] . Crossing the evolutionary chasm separating photosynthetic algae (Archaeplastida) from animals (Metazoa) at the whole-genome scale has long been considered biologically untenable [1, 2] .

In a landmark study published in Nature Communications , a Japanese research consortium led by Ryota Aoki, Hidenori Nishihara, Hiroshi Kimura, and Sachihiro Matsunaga at the University of Tokyo, the Institute of Science Tokyo, and Kindai University shattered that long-standing assumption [1, 2] . By fusing cultured mammalian Chinese hamster ovary (CHO) cells with the extremophilic unicellular red alga Cyanidioschyzon merolae , the team engineered stable plant-animal hybrid lineages -- dubbed planimal cells -- that stably retain nearly the entire 16.5-megabase algal nuclear genome across more than 150 mitotic generations [1, 2] .

Crucially, whole-genome bisulfite sequencing and chromatin profiling revealed the molecular mechanism that prevents this massive foreign DNA payload from killing the mammalian host: a phenomenon the authors term epigenetic gatekeeping [1] . Rather than rejecting or excising the foreign chromosomes , the mammalian host deploys DNA methylation and repressive histone modifications as a biochemical "off switch," transcriptionally silencing the vast majority of algal genes while permitting their faithful replication alongside mammalian chromosomes [1, 2] .

An Extremophile Without Walls: Why Cyanidioschyzon merolae Unlocks Inter-Kingdom Fusion

The success of genome-scale fusion depended heavily on the unusual evolutionary minimalism of the photosynthetic donor, Cyanidioschyzon merolae strain 10D [1, 4] . Isolated from acidic, sulfate-rich hot springs (pH below 2, temperatures near 45 deg C), C. merolae occupies a basal branch of the red algal lineage (Rhodophyta) and possesses three structural traits that make it uniquely suited for synthetic cell fusion [1, 4] :

* Complete Absence of a Rigid Cell Wall : Unlike land plants, green algae such as Chlamydomonas , or most other red algae, C. merolae lacks a rigid cellulosic or pectinaceous cell wall [1, 4] . Its naked plasma membrane can be brought into direct apposition with mammalian lipid bilayers during polyethylene glycol (PEG) or

electrofusion protocols without harsh enzymatic protoplasting that compromises viability [1, 3] .

* Ultra-Compact Nuclear Architecture: As established by Matsuzaki and colleagues in 2004, C. merolae possesses one of the smallest known nuclear genomes among free-living photosynthetic eukaryotes -- spanning just 16.5 megabases organized into 20 compact chromosomes encoding roughly 4,775 protein-coding genes [4] . Less than 1% of its genes contain spliceosomal introns , and repetitive transposable elements are virtually absent, minimizing the risk of transposon mobilization inside a foreign host nucleus [1, 4] .

* Minimalist Organelle Stoichiometry: Each vegetative C. merolae cell contains precisely one nucleus, one mitochondrion, and one plastid (chloroplast), which divide in strict synchrony during the cell cycle [3, 4] . This simplified organelle budget allows researchers to track the fate of donor nuclear and organellar genomes with unambiguous resolution [1, 3] .

Surviving Mitotic Elimination: Chromosomal Integration and Telomeric Stabilization

In classical somatic cell genetics -- such as human-rodent hybridomas used in early gene-mapping experiments -- fusing cells from different mammalian orders routinely triggers asynchronous mitotic condensation and wholesale loss of the donor chromosome set within 10 to 20 divisions [1] . Fusing a mammalian cell with a red alga separated by more than 1.5 billion years of eukaryotic divergence would be expected to fail even faster due to incompatible centromere-kinetochore proteins, divergent origins of replication, and mismatched mitotic spindle checkpoints [1, 4] . Furthermore, free cytosolic DNA fragments generated during fusion typically activate the mammalian cyclic GMP-AMP synthase (cGAS)-STING innate immune sensor, triggering interferon-mediated apoptosis or autophagy before nuclear fusion can even complete [1] .

Yet genomic sequencing of clonal planimal lines propagated for more than 150 generations demonstrated that nearly the entire C. merolae nuclear complement -- exceeding 16 megabases of algal DNA -- persisted stably in the mammalian nuclear environment [1, 2] . Detailed structural mapping revealed how the foreign genome avoided both innate immune clearance and mitotic loss:

* PEG-Mediated Nuclear Co-Encapsulation: Polyethylene glycol (PEG) destabilizes lipid bilayers by dehydrating phospholipid headgroups, driving rapid plasma membrane coalescence between mammalian CHO cells and wall-less C. merolae cells [1] . During subsequent mitosis, breakdown of the nuclear envelope allows algal chromosomes to be co-enclosed inside the reforming mammalian nuclear lamina, shielding them from cytosolic cGAS-STING surveillance [1] .

* Chromosome Rearrangement and Host Integration: Rather than remaining exclusively as fragile, autonomous algal minichromosomes dependent on unrecognized algal centromeres, large segments of C. merolae chromosomal DNA integrated directly into the host Chinese hamster chromosomes or formed stable, rearranged structural chromosomes capable of engaging mammalian mitotic spindle machinery [1, 2] .

* Telomere Acquisition and End Protection: Uncapped linear DNA ends inside a

mammalian nucleus normally activate the ATM/ATR DNA damage checkpoint, triggering non-homologous end joining (NHEJ) catastrophes or cellular senescence. In surviving planimal clones, broken algal chromosome ends either fused cleanly into host chromosomal arms or acquired mammalian TTAGGG telomeric repeats, masking them from DNA-repair surveillance [1] .

* Replication Licensing Compatibility: Because mammalian origin recognition complexes (ORC) bind DNA primarily through chromatin accessibility and structural topology rather than strict sequence motifs, the mammalian replisome successfully licensed and replicated the GC-rich algal DNA (~55% GC content) once per S-phase in lockstep with the hamster genome [1, 4] .

Epigenetic Gatekeeping: How Silencing Prevents Transcriptional and Metabolic Toxicity

Retaining 16 megabases of foreign DNA physically solves the replication problem, but creates an immediate biochemical crisis: transcriptional and proteomic incompatibility [1] . If 4,700 algal genes -- evolved for a 45 deg C, pH 1.5 sulfur spring -- were constitutively transcribed and translated inside a 37 deg C, pH 7.4 mammalian cytoplasm, thousands of misfolded algal proteins, incompatible metabolic enzymes, and aberrant RNA transcripts would overwhelm the endoplasmic reticulum unfolded protein response (UPR) and induce rapid apoptosis [1, 2] .

Aoki, Matsunaga, and colleagues discovered that the mammalian host resolves this crisis through epigenetic gatekeeping -- rapid, genome-wide heterochromatinization of the foreign algal DNA [1, 2] :

* De Novo DNA Methylation: In native C. merolae , CpG DNA methylation is sparse or functionally distinct from mammalian patterns. Upon entering the CHO nucleus, however, the algal chromosomes become heavily targeted by mammalian DNA methyltransferases (DNMT3A/DNMT3B and maintenance DNMT1), coating algal promoters and gene bodies in dense 5-methylcytosine (5mC) marks [1] .

* Repressive Histone Remodeling: Chromatin immunoprecipitation sequencing (ChIP-seq) and immunofluorescence confirmed that the integrated algal chromatin becomes enriched in repressive histone modifications -- particularly trimethylation of histone H3 at lysine 9 (H3K9me3) and lysine 27 (H3K27me3) -- characteristic of constitutive and facultative mammalian heterochromatin [1] .

* Transcriptional Buffering and Selective Leakage: RNA sequencing (RNA-seq) across long-term planimal clones demonstrated that the vast majority of integrated algal loci remain transcriptionally silent, allowing the hybrid cells to proliferate at near-normal mammalian doubling times and maintain physiological homeostasis [1, 2] . Only a minute fraction of algal transcripts escape silencing, establishing a dynamic equilibrium in which the host holds an entire foreign eukaryotic genome in silent reserve [1] .

This finding reframes classical evolutionary models of horizontal gene transfer. Rather than requiring instantaneous adaptive utility for every newly acquired gene, epigenetic gatekeeping provides an evolutionary "quarantine buffer" [1] . By neutrally silencing massive horizontal acquisitions immediately upon integration, a host cell can tolerate foreign genomes without immediate toxicity -- even when donor

open reading frames lack mammalian introns or display divergent codon usage -- creating a latent genomic reservoir that can be selectively reactivated or co-opted over evolutionary timescales [1, 4] .

Comparative Architecture Across Planimal Engineering Milestones

The 2026 Nature Communications breakthrough represents the second major pillar of Prof. Matsunaga's multi-year program to construct functional photosynthetic animal cells, complementing his team's 2024 chloroplast transplantation study in Proceedings of the Japan Academy, Series B [1, 3] :

| Biological Parameter | | Native Cyanidioschyzon merolae 10D | | Chloroplast-Infused Planimals (2024) | | Genome-Fused Planimals (2026) |

| Primary Donor Material | | Intact free-living unicellular red alga | | Isolated, intact C. merolae chloroplasts [3] | | Whole algal cell fused with CHO mammalian cell [1] |

| Nuclear Algal DNA Retained | | 16.5 Mbp (20 native chromosomes) [4] | | 0 Mbp (plastid-only transplantation) [3] | | >16 Mbp (>95% of algal nuclear genome) [1, 2] |

| Mitotic Persistence in Host | | Autonomous algal division | | Transient (~48 hours of photosynthetic activity) [3] | | Stable >150 cell generations [1, 2] |

| Chloroplast Integrity & Function | | Single active plastid; full photosynthesis [4] | | Photosynthetically active electron transport for 2 days [3] | | Degraded during nuclear fusion; non-photosynthetic [1, 2] |

| Host Epigenetic State | | Active algal transcription | | N/A (cytoplasmic organelle engraftment) | | Epigenetic gatekeeping (5mC methylation & H3K9me3 silencing) [1] |

The Chloroplast Paradox: Bridging Nuclear Retention and Plastid Function

A critical technical tension emerges when comparing the 2024 and 2026 studies [1, 3] . In the 2024 work, Matsunaga's team isolated intact C. merolae chloroplasts and introduced them into cultured hamster CHO cells via phagocytic engulfment [3] . Using pulse-amplitude-modulation (PAM) fluorometry and super-resolution microscopy, they confirmed that the algal chloroplasts retained intact thylakoid membranes and active photosynthetic electron transport for roughly two days inside the mammalian cytoplasm, even accelerating host cell proliferation [3] . However, those plastids could not replicate or persist long-term because the vast majority of chloroplast proteins are encoded in the algal nucleus , not in the chloroplast's own tiny genome [3, 4] .

In the new 2026 cell-fusion study, the team solved the opposite half of the equation: the hybrid planimal cells successfully retained nearly the entire algal nuclear genome across 150+ divisions, but the delicate chloroplasts degraded during the PEG-mediated fusion and antibiotic/metabolic selection process [1, 2] . Consequently, the 2026 planimal cells behave metabolically as mammalian cells and do not yet harvest light [1, 2] .

Synthesizing these two parallel breakthroughs now defines the roadmap toward true, self-sustaining photosynthetic animal cells [1, 3] :

* Targeted Epigenetic Derepression: Using CRISPR-dCas9 epigenetic editors (such as TET1 demethylases or p300 histone acetyltransferases) to selectively strip 5mC methylation and H3K9me3 marks from the specific subset of integrated algal nuclear genes responsible for plastid maintenance, chlorophyll biosynthesis, and photosystem II repair (such as the D1 protein repair cycle and lumenal PsbO subunits) -- while leaving potentially toxic extremophilic stress genes silenced [1] .

* Organelle Transit Peptide Engineering: In native red algae, nuclear-encoded chloroplast proteins carry N-terminal bipartite or stromal transit peptides recognized by the TOC/TIC translocon complexes embedded in the plastid envelope [3, 4] . Researchers must verify that reactivated algal nuclear transcripts translated on mammalian 80S ribosomes retain functional targeting signals -- or append synthetic mammalian-compatible transit motifs -- to import proteins across double plastid membranes without misrouting them to mammalian mitochondria or peroxisomes [1, 3] .

* Staged Chloroplast Re-Introduction: Re-engrafting fresh, isolated C. merolae chloroplasts into already-stabilized, genome-integrated planimal cell lines whose nuclear factories have been epigenetically primed to support plastid division, FtsZ ring constriction, and continuous thylakoid membrane turnover [1, 3, 4] .

Evolutionary Mirrors: Kleptoplasty and Primary Endosymbiosis

Beyond bioengineering, the planimal model offers an unprecedented experimental window into the ancient evolutionary transitions that built complex eukaryotic cells [1, 4] . Roughly 1.5 billion years ago, a heterotrophic protist engulfed a photosynthetic cyanobacterium, eventually integrating over 90% of the endosymbiont's genes into the host nucleus via endosymbiotic gene transfer (EGT) to birth the first plastid-bearing algae [3, 4] . More recently, marine sacoglossan sea slugs such as Elysia chlorotica evolved "kleptoplasty" -- stealing functional chloroplasts from ingested algae and keeping them alive for months -- while the amoeba Paulinella chromatophora independently acquired a photosynthetic cyanobacterial endosymbiont within the last 100 million years [3] .

Observing how CHO cells immediately apply 5mC methylation and repressive histone marks to buffer 16 megabases of sudden algal DNA provides direct empirical support for the hypothesis that epigenetic silencing acts as an essential first-step stabilizer during early endosymbiotic gene transfer [1] . Without a rapid transcriptional damper, host lineages undergoing massive endosymbiotic DNA influx would succumb to proteomic collapse before beneficial metabolic genes could be domesticated, promoter architectures could evolve eukaryotic TATA/enhancer compatibility, and introns could be adapted to host spliceosomes [1, 4] .

Biotechnology Horizons: Cultivated Meat and Carbon-Neutral Bioreactors

If Matsunaga's team succeeds in combining stable algal nuclear retention with functional chloroplast reactivation, the industrial ramifications for biomanufacturing and cellular agriculture could be transformative [1, 2, 3] :

* Self-Oxygenating Mammalian Bioreactors: Chinese hamster ovary (CHO) cells -- the exact host lineage used in this study -- are the workhorse cell line of the global biopharmaceutical industry, manufacturing the majority of therapeutic monoclonal antibodies and recombinant biologics [1, 3] . High-density CHO bioreactors are chronically limited by dissolved oxygen transfer and toxic ammonia/lactate accumulation. Light-driven oxygen evolution and carbon fixation inside photosynthetic CHO lines could dramatically lower bioreactor aeration costs and energy footprints [1, 3] .

* Sustainable Cultivated Meat Production: Scaling animal myoblast and adipocyte proliferation for cultivated meat currently requires expensive growth media laden with glucose, amino acids, and fetal bovine serum alternatives, alongside constant oxygenation [1, 3] . Photosynthetic animal cells capable of converting illuminated carbon dioxide (CO_2) into endogenous ATP, NADPH, and organic carbon skeletons would slash external nutrient inputs while reducing the net carbon footprint of cellular agriculture [1, 3] .

* Genome-Scale Synthetic Biology: Even independent of photosynthesis, proving that mammalian cells can stably inherit and replicate >16 megabases of heterologous eukaryotic DNA via epigenetic gatekeeping unlocks a new frontier for synthetic genomics -- allowing bioengineers to transplant entire multi-megabase biosynthetic pathways rather than splicing single transgenes one at a time [1, 2] .

Ultimately, the demonstration that mammalian cells can peacefully harbor a near-complete red algal genome across 150+ divisions dismantles the textbook boundary between plant and animal genetic compartments [1, 2] . By uniting whole-genome fusion with precision epigenetic editing and organelle engineering, synthetic biologists are moving rapidly from editing single base pairs toward assembling hybrid, cross-kingdom cellular architectures [1, 3] .

References & Primary Sources

* [1] Aoki, R., Nishihara, H., Sakamoto, T., Sato, Y., Kuramoto, T., Fukuda, M., Matsunaga, T. M., Kimura, H., & Matsunaga, S. (2026). Epigenetic gatekeeping enables genome-scale horizontal gene transfer in eukaryotic cells. Nature Communications. -- https://doi.org/10.1038/s41467-026-78753-w

* [2] Phys.org (2026). 'Planimal' cells retain nearly entire algal genome after experimental cell fusion. -- https://phys.org/

* [3] Aoki, R., Inui, Y., Okabe, Y., Sato, M., Takeda-Kamiya, N., Toyooka, K., Sawada, K., Morita, H., Genot, B., Maruyama, S., Tomo, T., Sonoike, K., & Matsunaga, S. (2024). Incorporation of photosynthetically active algal chloroplasts in cultured mammalian cells towards photosynthesis in animals. Proceedings of the Japan Academy, Series B, 100(9), 524-536. -- https://doi.org/10.2183/pjab.100.035

* [4] Matsuzaki, M., Misumi, O., Shin-i, T., Maruyama, S., Takahara, M., Miyagishima, S.-Y., & Kuroiwa, T. (2004). Genome sequence of the ultra-small unicellular red alga Cyanidioschyzon merolae 10D. Nature, 428(6983), 653-657. -- https://doi.org/10.1038/nature02398