

The First Cells We Never Saw

QTC-022 · From Quarks to Consciousness

The Universe, Life, and How We Found Out

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Article Abstract

No fossil preserves the first cell. By the time rocks offer persuasive biosignatures, life was already building communities. Laboratories approach the missing interval from the other direction: fatty-acid vesicles grow and divide, droplets concentrate catalysts, genetic polymers copy inside compartments, and synthetic cells integrate selected functions. None is the historical first cell. Each begins with materials, catalysts or operating conditions supplied by researchers, while genome-minimized organisms inherit an evolved parent. Even modern membranes preserve an unresolved lipid divide between bacteria and archaea. The evidence therefore supports cellularization as an extended integration of boundary, heredity, energy and reproduction, perhaps across exchanging populations. LUCA belongs later in that story: it is the common ancestor reconstructed from survivors, not the first life that ever existed.

In 60 Seconds

We never observed cellularization, and the rock record starts after its decisive work. Ancient stromatolites and hot-spring biosignatures indicate communities, not the first membrane enclosing the first hereditary chemistry. Experiments show that several pieces need not appear together. Fatty-acid vesicles self-assemble, admit some nutrients, grow and divide. Coacervate droplets concentrate RNA without membranes and can later acquire fatty-acid shells. Internal polymers or catalysts can make model protocells grow competitively. Yet every demonstration supplies part of the cycle, and no lineage has bootstrapped boundary synthesis, transport, energy, copying and division from bounded geochemical inputs. Modern membranes add another puzzle: bacteria and archaea use contrasting lipid chemistries, although engineered hybrid membranes can be viable. Minimal cells do not reveal the beginning either; they are reduced descendants supported by rich media and inherited machinery. The best reading is a transition across stages and populations. Universal common ancestry describes the survivors. It neither identifies the first cell nor says life began only once.

Why This Question Matters

A picture of one lucky vesicle becoming alive is memorable and probably misleading. Cellular life requires several causal loops to close at once: an inside must persist, supplies must cross, useful products must remain, information must be copied, and descendants must inherit enough organization to continue. Separating these functions lets experiments reveal genuine progress without turning every vesicle into life. It turns supplied parts into a precise research map. It also prevents

LUCA, minimal genomes and ancient biosignatures from answering a question they were never designed to answer: what the first cells were.

1. The Rocks Begin Too Late

The Question

If the earliest persuasive rocks already record reefs or hot-spring communities, then cellularization happened before the surviving story begins. A biosignature can establish an inhabited world while revealing almost nothing about the first boundary, genome or reproductive cycle.

The first cells left no labelled specimen. Earth continuously alters its oldest crust through burial, metamorphism, deformation and erosion. Soft microscopic organisms are poor candidates for preservation even in younger rocks, and early cells lacked the mineralized skeletons that later make fossils conspicuous. The record therefore begins with consequences: layered structures, carbon chemistry, mineral textures and environments whose best explanation may involve life. None supplies a portrait of the first successful compartment.

At the roughly 3.43-billion-year-old Strelley Pool Formation in Western Australia, Abigail Allwood and colleagues mapped a reef-scale assemblage of stromatolites with several morphologies and environmental associations.[1] The strength is not one suggestive bump. It is an organized sedimentary system extending over kilometres and interpreted as an established microbial ecology. That is also the limitation. A community capable of building persistent structures is already downstream of whatever joined heredity to cellular reproduction.

The approximately 3.48-billion-year-old Dresser Formation adds evidence from a terrestrial hydrothermal setting. Tara Djokic and colleagues reported hot-spring deposits containing textures and geochemical signals consistent with life in ponds or vents on land.[2] Such a site broadens the environments occupied by early organisms. It does not prove that life began at a hot spring, and it does not preserve a membrane. Habitat evidence answers where some life lived, not how cellular life first assembled.

Older claims become more fragile. Allen Nutman and colleagues interpreted conical structures in 3.7-billion-year-old Isua rocks as stromatolites.[3] Abigail Allwood's team later examined another exposure and argued that similar shapes were produced by deformation rather than microbial construction.[4] In the Nuvvuagittuq belt, Matthew Dodd and colleagues reported tubes and filaments in hydrothermal precipitates whose host rocks may be at least 3.77 billion years old.[5] Age, association and biogenicity remain debated. Suggestive form is not a time machine.

These disputes are not a failure of geology. They expose what ancient evidence can and cannot carry. Multiple, independent lines—sedimentology, chemistry, spatial context and morphology—make a claim stronger, while metamorphism removes decisive details. By the time evidence becomes persuasive, life already appears ecological. The earliest rocks can place cellular existence before a date. They cannot tell whether the first boundary was a fatty-acid vesicle, a mineral pore, a droplet or something no longer represented.

Where That Leaves Us

The geological record gives a one-sided bracket: cellular communities existed by the time persuasive structures survive, but their founding transition lies offstage. To investigate that interval, evidence

must be built as well as excavated. Laboratory compartments let each required function be isolated, supplied and tested, beginning with the deceptively simple act of making an inside.

2. A Boundary Is Not Yet a Cell

A boundary does two opposing jobs. It keeps a reaction network from dispersing, yet it must let food, waste and energy cross. Seal the interior perfectly and chemistry exhausts its supplies. Make the boundary freely permeable and useful products leak away while gradients vanish. Modern cells solve this with phospholipid bilayers, channels, pumps and enzymes. The first compartments could not assume that machinery; boundary and internal chemistry had to be mutually tolerable before either could become elaborate.

Fatty acids offer a simpler model. In water and within suitable concentration, pH and salt ranges, they assemble into bilayer vesicles. Martin Hanczyc, Shelly Fujikawa and Jack Szostak showed encapsulation, growth and division-like transformations in such compartments.[6] Ting Zhu and Szostak later linked membrane growth to filament formation and fission without a protein cytoskeleton.[9] These are significant physical capacities. A vesicle that pinches in two, however, has not necessarily copied a functional difference or produced descendants able to repeat the cycle.

Primitive permeability can be an advantage. Mark Sacerdote and Szostak measured sugar passage across model membranes and found that structure strongly affected rates, with ribose crossing faster than related pentoses in their conditions.[30] Sheref Mansy and colleagues then showed that activated nucleotides could enter fatty-acid vesicles and extend a genetic template inside.[8] No protein transporter was required. The price is leakage: a membrane permissive enough to feed chemistry may struggle to retain small products or a usable ion imbalance.

A boundary begins to matter evolutionarily when the inside changes the fate of the whole package. Irene Chen, Richard Roberts and Szostak encapsulated nucleic acids in fatty-acid vesicles. Osmotic stress made the loaded vesicles acquire membrane from relaxed competitors and grow.[7] Katarzyna Adamala and Szostak later used an encapsulated catalyst whose product promoted membrane growth.[11] Both experiments joined internal state to external success. Neither internal state was generated and inherited by a complete autonomous cycle.

The word protocell is therefore a functional label, not a historical identification. It may denote a vesicle that performs one cellular operation, a compartment integrating several, or a platform for testing coupling. The useful question is always what the researchers supplied: amphiphiles, templates, catalysts, activated substrates, mixing, temperature or division. Naming those inputs does not diminish the result. It reveals which causal loop remains open before a bounded chemical object can become an evolving cell.

Where That Leaves Us

A membrane can protect, feed and phenotype an interior without making a living lineage. The central distinction is reciprocal continuity: contents must help reproduce the boundary, and descendant boundaries must preserve the contents that produced success. Before a lipid envelope achieved that bargain, other kinds of compartment may have concentrated and sorted the chemistry that would later inhabit cells.

3. Compartments Could Precede Membranes

The Question

A cell is membrane-bound now, but origin is not obliged to copy the endpoint. Droplets, pores, mineral surfaces and films can localize reactants before a heritable lipid envelope exists, allowing cellularization to change its container as chemistry changes.

Some polymers spontaneously separate from water-rich surroundings into coacervate droplets. The interface is not a lipid bilayer, yet selected molecules partition strongly into the dense phase. Concentration can accelerate reactions that would be negligible in a dilute ocean and can keep partners near one another. It can also remain porous and dynamic. Those same properties create a heredity problem: if contents exchange rapidly, a successful droplet may not keep its distinctive chemistry long enough to found a lineage.

Bogdan Drobot and colleagues placed an RNA catalyst inside membrane-free coacervate protocells and showed that compartmentalization changed RNA reaction behaviour.[15] The droplets were real reaction environments, not merely drawings. They were also made from prepared components and did not autonomously reproduce their catalytic organization. The experiment separates two claims often fused together: compartmentalized function can precede a membrane, but function inside a droplet is not automatically inherited by daughter droplets.

A non-membrane compartment can also become a scaffold for a membrane. Tyler Tang and colleagues assembled fatty-acid layers around coacervate microdroplets, producing hybrid protocells that combined a dense internal phase with an amphiphile boundary.[14] This makes a staged transition physically imaginable: concentration first, membrane enclosure later. It does not show that early Earth followed that order. Designed polymers, prepared fatty acids and controlled solution conditions created the opportunity.

Other environments replace a floating compartment with structured space. Mineral pores can retain reactants and expose catalytic surfaces; wet-dry films repeatedly concentrate solutes; ice veins create briny microchannels; hydrothermal gradients can maintain continuous chemical differences.[29,31] Each solves a different dilution or energy problem. Each also risks trapping products, destroying fragile molecules or depending on a narrow setting. A useful origin scenario must trace materials and descendants through the environmental cycle, not merely name a favourable place.

Boundaries may therefore have changed during cellularization. Surface-associated chemistry could have become droplet-confined, then enveloped by simple amphiphiles, and finally equipped with synthesized lipids and transport proteins. The sequence is plausible, not recovered. Modern cells preserve no fossil membrane inside themselves, and later replacement can erase the chemistry of an earlier envelope.[21,25] The strongest experiments will connect stages without an investigator moving purified products from one apparatus to the next.

Where That Leaves Us

Compartment first and membrane first are not mutually exclusive labels if boundaries evolved. A sequence of changing containers could concentrate chemistry before enclosing it durably. But every new enclosure inherits the same practical test: it must feed the reactions it protects. That turns permeability from a material property into the next integration problem of an emerging cell.

4. A Membrane Must Admit and Retain

Membrane evolution is a moving compromise. A loose fatty-acid boundary exchanges small solutes without proteins but struggles in high salt, with divalent ions and with retention of steep gradients. A modern phospholipid bilayer is stable and less permeable, but then a cell needs channels and pumps. There is no reason the chemistry optimal before encoded proteins should be the chemistry retained after them. The first cell-like lineages may have survived by changing both membrane composition and metabolism together.

One famous incompatibility could be softened chemically. Non-enzymatic RNA copying often needs magnesium ions, which can disrupt fatty-acid vesicles. Katarzyna Adamala and Szostak showed that citrate protected model membranes while permitting template-directed RNA synthesis inside. [10] The achievement joined two previously conflicting modules. Its boundary conditions matter: activated monomers, substantial citrate, prepared vesicles and controlled exchange were supplied. Compatibility was demonstrated; a self-supplying citrate economy was not.

A second route makes the membrane from simpler soluble chemistry. In 2026 Marian Ebeling and colleagues used an organocatalytic network beginning with small carbonyl compounds to generate longer amphiphilic products that spontaneously formed protocell-like structures from nanometres to micrometres.[16] The compartments tolerated varied pH, temperature and salts and retained catalytic activity. The defined organocatalyst was a laboratory input, and no genetic lineage reproduced the structures. Bottom-up formation is not yet bottom-up life.

Another 2026 experiment attacked the assumption that a membrane must descend from a pre-existing membrane. Satyam Khanal and colleagues used soluble enzyme cascades to synthesize lipids de novo from small precursors, then added model influx and proton-gradient functions.[17] This is a powerful engineering answer to membrane heredity. It used enzymes from modern organisms, ATP, CoA chemistry, NADPH, a pore-forming peptide, cholesterol and defined buffers. The bilayer did not grow, divide and transmit an evolving system.

These experiments transform an old verbal puzzle into a ledger of dependencies. Can amphiphiles arise continuously? Can the boundary tolerate catalytic ions? Can nutrients enter without emptying the cell? Can useful gradients persist? Can internal chemistry make more boundary? Each module now has credible demonstrations.[8,10,16,17] No experiment has closed them all with bounded geochemical inputs. That remaining gap is narrower and more instructive than saying membranes either formed easily or were impossibly complex.

Where That Leaves Us

A viable membrane is not one substance but a managed flux: material enters, products remain, energy differences persist and new boundary is produced. Laboratory systems now satisfy those demands in overlapping subsets. Reproduction begins only when the subsets become one recurring cycle, because a cell that solves transport once but cannot rebuild its solution leaves no cellular descendants.

5. Growth Must Be Coupled to Inheritance

The Question

A compartment can double its membrane and still fail as a lineage. If division leaves one daughter without the catalyst, template or boundary machinery that caused growth, reproduction destroys the organization it was supposed to propagate.

Boundary reproduction can be chemically autocatalytic. Peter Walde and colleagues supplied a fatty-acid precursor whose hydrolysis generated more membrane-forming molecules, allowing vesicle populations to reproduce their structure.[13] The result deserves its name: existing vesicles accelerated formation of more vesicle material. Yet the cycle carried little individualized information. A change that made one vesicle chemically superior was not encoded in a sequence and reliably copied into descendants. Repetition had been achieved before open-ended heredity.

Physical division can also emerge without molecular motors. Zhu and Szostak fed model membranes until they formed elongated filaments; gentle shear then divided them while retaining contents.[9] Kensuke Kurihara and colleagues coordinated amplification of encapsulated DNA with reproduction of giant vesicles.[12] These experiments show that genome and boundary cycles can coexist. External fatty acids, mechanical conditions, PCR reagents and synthetic lipids still closed major parts of those cycles from outside.

Internal chemistry can confer competitive growth. In Chen's experiment, encapsulated nucleic acid altered osmotic pressure and drove membrane uptake.[7] In Adamala's, an internal catalyst produced a molecule that enhanced growth.[11] The bridge is important because selection cannot favour a genome for a membrane benefit unless the benefit stays associated with that genome. The remaining step is reciprocal encoding: descendants must copy the cause of success, reproduce the boundary and keep the two linked across many generations.

Partitioning adds a numerical constraint. A small protocell containing only a few copies of an essential catalyst can divide unevenly, producing a daughter with none. A larger compartment buffers that loss but becomes more bulk-like and may shelter parasites. Molecular attachment, reaction localization and coordinated division can reduce the risk. None requires perfect equality. They require a distribution good enough for successful organizations to leave more successful packages than unsuccessful ones.

The historical order remains open. A reproducing boundary may have captured replicators; replicators may have altered pre-existing compartments; metabolism may have supplied membrane precursors before high-fidelity genomes; or these functions may have matured in different places and later merged.[18,25,29] One successful laboratory ordering would demonstrate possibility, not exclusivity. The decisive comparison is whether a pathway can keep matter, energy and inherited function continuous without researchers repeatedly resetting the cycle.

Where That Leaves Us

Cellular reproduction is not membrane fission plus genome copying written on separate lines. It is their causal synchronization across descendants, including tolerable errors in partition and timing. That integration may once have occurred with membranes unlike any living cell's. Modern biology preserves a conspicuous clue—and a complication—in the chemical divide between bacterial and archaeal lipids.

6. The Lipid Divide Hides the Ancestral Boundary

Bacteria generally build membranes from fatty acids ester-linked to sn-glycerol-3-phosphate. Archaea generally use isoprenoid chains ether-linked to the mirror glycerol-phosphate stereochemistry. Enzymes and pathways differ as well.[21] This lipid divide is striking because both groups share translation, genetic code and other evidence of common ancestry. If their deepest common population already possessed a fully modern membrane, which type was it? The present does not give a single answer.

One proposal places a simpler or mixed membrane before the split, followed by independent refinement or replacement. Another places early lineages in geochemical compartments and makes modern membranes later innovations. A third emphasizes ancient divergence in lipid biosynthesis.[21,25] Each interpretation must account for shared ancestry, pathway distribution and membrane physiology. The divide is not a licence to declare two unrelated origins of life; the conserved molecular evidence for common ancestry remains much broader than lipids alone.[27]

A supposed chemical impossibility has been tested directly. Antonella Caforio and colleagues engineered *Escherichia coli* to synthesize archaeal-type ether lipids, which reached roughly 20–30 percent of the membrane alongside bacterial lipids.[19] The heterochiral hybrid membrane supported growth and slightly increased robustness under some stresses. The experiment disproves a blanket claim that mixed stereochemistry cannot sustain a cell. It does not identify the membrane of an ancestor billions of years ago.

Nature also crosses the textbook border. Laura Villanueva and colleagues found that bacteria in the FCB superphylum possess genes with the potential to synthesize archaeal ether lipids and reported corresponding lipid evidence.[20] Gene transfer, retention or convergence could help explain the pattern. Whatever its direction, a perfectly binary classification is too simple. Modern membrane chemistry has been exchanged and modified, which makes ancestral reconstruction both richer and less direct.

The honest inference is negative but useful. We cannot take either modern membrane and merely remove complexity to obtain the first cellular boundary. Later selection, replacement and horizontal transfer have rewritten the trail. Hybrid viability widens the possible transitions; it does not choose one. QTC-023 will use conserved genes to reconstruct a common ancestor, but the lipid divide warns that even a reconstructed ancestor need not preserve the chemistry of cellularization unchanged.

Where That Leaves Us

The membrane divide blocks a simple backward movie from modern cells to the first one. Shared ancestry survives the complication, but ancestral boundary chemistry remains underdetermined. Removing genes from a living cell seems to offer another route backward. It too can mislead, because subtraction begins with an organism whose uncounted structures and compatibilities have already evolved.

7. Minimal Cells Are Not Primitive Cells

The Question

Deleting genes from a modern cell asks what that descendant can lose while a laboratory keeps it alive. The first cell faced the opposite problem: how a system with no cellular parent gained enough mutually compatible functions to leave descendants.

In 2016 Clyde Hutchison and a large collaboration reported JCVI-syn3.0, a Mycoplasma-derived cell with a 531-kilobase genome containing 473 genes.[22] It could grow and divide in a rich medium. The number was an experimental minimum for one chassis under particular support, not the minimum genome of life. Remove a nutrient from the medium, change temperature or demand ecological independence, and genes dispensable in one laboratory can become essential.

The minimal genome also contained an instructive surprise: roughly one-third of its retained genes initially lacked a specifically assigned function.[22] Reduction had discovered necessity without fully explaining it. Jonathan Breuer and colleagues later combined experiments and modelling to map essential metabolism and environmental dependencies in the minimal cell.[24] The lesson is not that life requires exactly 473 genes. It is that even a highly characterized descendant contains causal work hidden behind labels such as unknown or supplied by medium.

Division exposed another hidden system. JCVI-syn3.0 produced irregular forms. James Pelletier and colleagues restored 19 genes to create a more regular derivative and found that seven acting together—including known division genes and several membrane-associated genes of unknown function—were sufficient to recover near-normal morphology.[23] A cell can satisfy a population-growth criterion while individual divisions are physically disorderly. Minimal survival, reliable reproduction and understood mechanism are different endpoints.

Top-down reduction inherits far more than DNA. The starting cytoplasm already contains ribosomes, membranes, metabolites, molecular concentrations and spatial organization produced by a living mother cell. Its proteins have evolved to work together. Rich medium replaces biosynthetic tasks. Those inheritances are precisely what an origin model must explain rather than assume. Minimal cells remain valuable dependency maps, but evolution cannot be run backwards by deleting genes until history appears.

Bottom-up synthetic cells ask the complementary question. In 2026 Ana María Restrepo Sierra and colleagues enclosed a six-gene system that coupled DNA replication, transcription–translation and phospholipid synthesis in liposomes.[18] Only a minority of vesicles displayed both central functions; newly synthesized lipid averaged about 0.7 percent of total lipid and did not create detectable growth. PURE translation, phage replication proteins, bacterial lipid enzymes, prepared liposomes and supplied substrates did enormous inherited work. Integration advanced without creating a historical or autonomous first cell.

Where That Leaves Us

Minimal and synthetic cells approach integration from opposite directions, exposing hidden dependencies as they remove or add functions. Neither direction is a replay of origin. Their value is sharper: they identify which loops remain externally supported. Once those supports are listed, the search shifts from one first cell to a transition among populations whose organization was still becoming cellular.

8. Cellularization Was a Transition, Not an Instant

The Question

Every organism alive today can descend from one shared ancestral population even if earlier chemistry produced many lineages, exchanged inventions or failed repeatedly. The genealogy of survivors is not a census of everything that once approached life.

Douglas Theobald formally compared common-ancestry and separate-ancestry models for conserved protein sequences and found overwhelming support for universal common ancestry among sampled living lineages.[27] The conclusion is powerful and narrower than it sounds. It does not count how many origin attempts occurred, locate the first replicator or prove that one isolated cell sat at the root. It says the organisms whose conserved machinery survives today share ancestry.

Carl Woese argued that the deepest ancestor may have been a communal progenote state rather than one fully integrated modern cell.[25] Components and innovations could move among loosely organized lineages before translation and other systems stabilized. Kalin Vetsigian, Woese and Nigel Goldenfeld later modelled how horizontal exchange could help a shared genetic code become universal.[26] Models do not recover a lost population, but they show why early history can resemble a network before later inheritance becomes predominantly tree-like.

Cellularization fits that possibility. Membrane recipes, catalysts, replicators and metabolic pathways need not have matured inside one uninterrupted vesicle lineage. Compartments could fuse, leak, exchange polymers or occupy connected pores. Selection could act on molecules, packages and communities at different times. Eventually tighter coupling made a boundary reproduce the chemistry that reproduced it. The transition may contain genuine thresholds without offering one uniquely nameable first cell.

Recent reconstruction places LUCA—the last universal common ancestor—around 4.2 billion years ago and infers a genome of at least roughly 2.5 megabases with about 2,600 proteins and ecological interactions.[28] Those estimates remain model-dependent, but their implication is clear enough for this boundary: LUCA was probably already far more organized than a fragile first protocell. It belongs to the history of established cellular life, not automatically to the instant life or cells began.

We can now state what the evidence does. Rocks establish that cellular communities existed early but begin too late. Laboratory protocells prove that boundary, copying, growth and catalysis can be connected in subsets. Synthetic and minimal cells reveal hidden support. Lipid chemistry prevents a simple backward reconstruction. Phylogeny identifies shared descendants and possible communal ancestry.[1,6,18,21,22,27,28] No line uniquely orders the transition. Together they bound a real open problem rather than an empty mystery.

Where That Leaves Us

The first cells are absent as objects but increasingly constrained as a process. Cellular life emerged when boundaries, inherited chemistry, energy and reproduction became mutually sustaining across descendants. We may never name the first participant in that transition. QTC-023 asks the next, answerable question: what can surviving genomes tell us about the later ancestor from which all living lineages descend?

What We Know, and How

- Persuasive Archean biosignatures already record microbial communities rather than the first cellular transition.[1,2]
- Fatty-acid vesicles and coacervates can compartmentalize chemistry, and several model systems grow, divide or host copying.[6–15]
- Internal polymers or catalysts can change protocell growth, physically linking compartment contents to competition.[7,11]
- Bacterial and archaeal membrane chemistry differs, but viable engineered hybrid membranes show that mixing is not intrinsically impossible.[19–21]
- Minimal and synthetic cells inherit substantial biological machinery and do not recreate the first historical cell.[18,22–24]

What We Still Don't Know

- Which physical compartment, if any, first transmitted a stable inside–outside distinction across descendants.
- The historical order in which boundary synthesis, heredity, metabolism, energy coupling and division became interdependent.
- Whether the earliest cellular populations used fatty acids, mixed lipids, mineral confinement or boundary chemistries now lost.
- How much exchange occurred among early lineages before stable vertical cellular inheritance emerged.
- How long cellular evolution preceded the ancestor reconstructed as LUCA.

What Could Change Our Minds

- An independently dated, exceptionally preserved cellular fossil older than accepted community biosignatures.
- A geochemically bounded protocell lineage sustaining membrane synthesis, transport, energy, copying and division across many generations.
- Ancestral enzyme reconstruction that decisively identifies the membrane chemistry before the bacterial–archaeal split.
- Convergence of top-down and bottom-up synthetic cells on a small, autonomous architecture without inherited cellular support.
- Phylogenomic evidence that sharply distinguishes a single cellular ancestor from a communal early population.

If You Remember Only One Thing

No experiment or fossil preserves the first cell. Cellularization was likely a gradual unresolved transition coupling boundaries, heredity, energy and reproduction; LUCA is a later reconstructed ancestor, not life's beginning.

Related Articles

- QTC-021 — When Chemistry Began to Evolve
- QTC-023 — LUCA: The Ancestor We Reconstructed

References

- [1] Abigail C. Allwood; Malcolm R. Walter; Balz S. Kamber; Craig P. Marshall; Ian W. Burch. Stromatolite Reef from the Early Archaean Era of Australia. *Nature* 441, 714–718 (2006). DOI 10.1038/nature04764. <https://doi.org/10.1038/nature04764>
- [2] Tara Djokic; Martin J. Van Kranendonk; Kathleen A. Campbell; Malcolm R. Walter; Colin R. Ward. Earliest Signs of Life on Land Preserved in ca. 3.5 Ga Hot Spring Deposits. *Nature Communications* 8, 15263 (2017). DOI 10.1038/ncomms15263. <https://doi.org/10.1038/ncomms15263>
- [3] Allen P. Nutman; Vickie C. Bennett; Clark R. L. Friend; Martin J. Van Kranendonk; Allan R. Chivas. Rapid Emergence of Life Shown by Discovery of 3,700-Million-Year-Old Microbial Structures. *Nature* 537, 535–538 (2016). DOI 10.1038/nature19355. <https://doi.org/10.1038/nature19355>
- [4] Abigail C. Allwood; Minik T. Rosing; David T. Flannery; Joel A. Hurowitz; Christopher M. Heirwegh. Reassessing Evidence of Life in 3,700-Million-Year-Old Rocks of Greenland. *Nature* 563, 241–244 (2018). DOI 10.1038/s41586-018-0610-4. <https://doi.org/10.1038/s41586-018-0610-4>
- [5] Matthew S. Dodd; Dominic Papineau; Tor Grenne; John F. Slack; Martin Rittner; Franco Pirajno; Jonathan O’Neil; Crispin T. S. Little. Evidence for Early Life in Earth’s Oldest Hydrothermal Vent Precipitates. *Nature* 543, 60–64 (2017). DOI 10.1038/nature21377. <https://doi.org/10.1038/nature21377>
- [6] Martin M. Hanczyc; Shelly M. Fujikawa; Jack W. Szostak. Experimental Models of Primitive Cellular Compartments: Encapsulation, Growth, and Division. *Science* 302, 618–622 (2003). DOI 10.1126/science.1089904. <https://doi.org/10.1126/science.1089904>
- [7] Irene A. Chen; Richard W. Roberts; Jack W. Szostak. The Emergence of Competition between Model Protocells. *Science* 305, 1474–1476 (2004). DOI 10.1126/science.1100757. <https://doi.org/10.1126/science.1100757>
- [8] Sheref S. Mansy; Jason P. Schrum; Mathangi Krishnamurthy; Sylvia Tobé; Douglas A. Treco; Jack W. Szostak. Template-Directed Synthesis of a Genetic Polymer in a Model Protocell. *Nature* 454, 122–125 (2008). DOI 10.1038/nature07018. <https://doi.org/10.1038/nature07018>
- [9] Ting F. Zhu; Jack W. Szostak. Coupled Growth and Division of Model Protocell Membranes. *Journal of the American Chemical Society* 131, 5705–5713 (2009). DOI 10.1021/ja900919c. <https://doi.org/10.1021/ja900919c>
- [10] Katarzyna Adamala; Jack W. Szostak. Nonenzymatic Template-Directed RNA Synthesis Inside Model Protocells. *Science* 342, 1098–1100 (2013). DOI 10.1126/science.1241888. <https://doi.org/10.1126/science.1241888>
- [11] Katarzyna Adamala; Jack W. Szostak. Competition between Model Protocells Driven by an Encapsulated Catalyst. *Nature Chemistry* 5, 495–501 (2013). DOI 10.1038/nchem.1650. <https://doi.org/10.1038/nchem.1650>
- [12] Kensuke Kurihara; Mieko Tamura; Koh-ichiroh Shohda; Taro Toyota; Kentaro Suzuki; Tadashi Sugawara. Self-Reproduction of Supramolecular Giant Vesicles Combined with the Amplification of

Encapsulated DNA. *Nature Chemistry* 3, 775–781 (2011). DOI 10.1038/nchem.1127.
<https://doi.org/10.1038/nchem.1127>

[13] Peter Walde; Roger Wick; Massimo Fresta; Annarosa Mangone; Pier Luigi Luisi. Autopoietic Self-Reproduction of Fatty Acid Vesicles. *Journal of the American Chemical Society* 116, 11649–11654 (1994). DOI 10.1021/ja00105a004. <https://doi.org/10.1021/ja00105a004>

[14] T.-Y. Dora Tang; C. Rohaida Che Hak; Alexander J. Thompson; Marina K. Kuimova; D. S. Williams; Adam W. Perriman; Stephen Mann. Fatty Acid Membrane Assembly on Coacervate Microdroplets as a Step Towards a Hybrid Protocell Model. *Nature Chemistry* 6, 527–533 (2014). DOI 10.1038/nchem.1921. <https://doi.org/10.1038/nchem.1921>

[15] Björn Drobot; Juan M. Iglesias-Artola; Kristian Le Vay; Viktoria Mayr; Mrityunjoy Kar; Moritz Kreysing; Hannes Mutschler; T-Y Dora Tang. Compartmentalised RNA Catalysis in Membrane-Free Coacervate Protocells. *Nature Communications* 9, 3643 (2018). DOI 10.1038/s41467-018-06072-w. <https://doi.org/10.1038/s41467-018-06072-w>

[16] Marian Simon Rafael Ebeling; Otto Berninghausen; Khang Hoang Nguyen; Roland Beckmann; Oliver Trapp. Organocatalyzed Bottom-Up Formation of Protocells. *Nature Communications* 17, 1983 (2026). DOI 10.1038/s41467-026-69597-5. <https://doi.org/10.1038/s41467-026-69597-5>

[17] Satyam Khanal; Alessandro Fracassi; Alexander Harjung; Michael D. Burkart; Neal K. Devaraj. Breaking the Membrane Heredity Paradox Through De Novo Protocell Formation. *Nature Communications* 17, 6920 (2026). DOI 10.1038/s41467-026-73667-z. <https://doi.org/10.1038/s41467-026-73667-z>

[18] Ana María Restrepo Sierra; Federico Ramirez Gomez; Mats van Tongeren; Laura Sierra Heras; Christophe Danelon. A Synthetic Cell with Integrated DNA Self-Replication and Lipid Biosynthesis. *Nature Communications* 17, 2727 (2026). DOI 10.1038/s41467-026-69531-9. <https://doi.org/10.1038/s41467-026-69531-9>

[19] Antonella Caforio; Melvin F. Siliakus; Marten Exterkate; Samta Jain; Varsha R. Jumde; Ruben L. H. Andringa; Servé W. M. Kengen; Adriaan J. Minnaard; Arnold J. M. Driessen; John van der Oost. Converting *Escherichia coli* into an Archaeobacterium with a Hybrid Heterochiral Membrane. *Proceedings of the National Academy of Sciences* 115, 3704–3709 (2018). DOI 10.1073/pnas.1721604115. <https://doi.org/10.1073/pnas.1721604115>

[20] Laura Villanueva; F A Bastiaan von Meijenfeldt; Alexander B Westbye; Subhash Yadav; Ellen C Hopmans; Bas E Dutilh; Jaap S Sinninghe Damsté. Bridging the Membrane Lipid Divide: Bacteria of the FCB Group Superphylum Have the Potential to Synthesize Archaeal Ether Lipids. *The ISME Journal* 15, 168–182 (2021). DOI 10.1038/s41396-020-00772-2. <https://doi.org/10.1038/s41396-020-00772-2>

[21] Jonathan Lombard; Purificación López-García; David Moreira. The Early Evolution of Lipid Membranes and the Three Domains of Life. *Nature Reviews Microbiology* 10, 507–515 (2012). DOI 10.1038/nrmicro2815. <https://doi.org/10.1038/nrmicro2815>

[22] Clyde A. Hutchison, III; Ray-Yuan Chuang; Vladimir N. Noskov; Nacyra Assad-Garcia; Thomas J. Deerinck; Mark H. Ellisman; John Gill; Krishna Kannan; Bogumil J. Karas; Li Ma; James F. Pelletier; Zhi-Qing Qi; R. Alexander Richter; Elizabeth A. Strychalski; Lijie Sun; Yo Suzuki; Billyana Tsvetanova; Kim S. Wise; Hamilton O. Smith; John I. Glass; Chuck Merryman; Daniel G. Gibson; J.

- Craig Venter. Design and Synthesis of a Minimal Bacterial Genome. *Science* 351, aad6253 (2016). DOI 10.1126/science.aad6253. <https://doi.org/10.1126/science.aad6253>
- [23] James F. Pelletier; Lijie Sun; Kim S. Wise; Nacyra Assad-Garcia; Bogumil J. Karas; Thomas J. Deerinck; Mark H. Ellisman; Andreas Mershin; Neil Gershenfeld; Ray-Yuan Chuang; John I. Glass; Elizabeth A. Strychalski. Genetic Requirements for Cell Division in a Genomically Minimal Cell. *Cell* 184, 2430–2440.e16 (2021). DOI 10.1016/j.cell.2021.03.008. <https://doi.org/10.1016/j.cell.2021.03.008>
- [24] Marian Breuer; Emmy E Earnest; Chuck Merryman; Kim S Wise; Lijie Sun; Michaela R Lynott; Clyde A Hutchison; Hamilton O Smith; John D Lapek; David J Gonzalez; Valérie de Crécy-Lagard; Drago Haas; Andrew D Hanson; Piyush Labhsetwar; John I Glass; Zaida Luthey-Schulten. Essential Metabolism for a Minimal Cell. *eLife* 8, e36842 (2019). DOI 10.7554/eLife.36842. <https://doi.org/10.7554/eLife.36842>
- [25] Carl Woese. The Universal Ancestor. *Proceedings of the National Academy of Sciences* 95, 6854–6859 (1998). DOI 10.1073/pnas.95.12.6854. <https://doi.org/10.1073/pnas.95.12.6854>
- [26] Kalin Vetsigian; Carl Woese; Nigel Goldenfeld. Collective Evolution and the Genetic Code. *Proceedings of the National Academy of Sciences* 103, 10696–10701 (2006). DOI 10.1073/pnas.0603780103. <https://doi.org/10.1073/pnas.0603780103>
- [27] Douglas L. Theobald. A Formal Test of the Theory of Universal Common Ancestry. *Nature* 465, 219–222 (2010). DOI 10.1038/nature09014. <https://doi.org/10.1038/nature09014>
- [28] Edmund R. R. Moody; Sandra Álvarez-Carretero; Tara A. Mahendrarajah; James W. Clark; Holly C. Betts; Nina Dombrowski; Lénárd L. Szánthó; Richard A. Boyle; Stuart Daines; Xi Chen; Nick Lane; Ziheng Yang; Graham A. Shields; Gergely J. Szöllősi; Anja Spang; Davide Pisani; Tom A. Williams; Timothy M. Lenton; Philip C. J. Donoghue. The Nature of the Last Universal Common Ancestor and Its Impact on the Early Earth System. *Nature Ecology & Evolution* 8, 1654–1666 (2024). DOI 10.1038/s41559-024-02461-1. <https://doi.org/10.1038/s41559-024-02461-1>
- [29] Nick Lane; William F. Martin. The Origin of Membrane Bioenergetics. *Cell* 151, 1406–1416 (2012). DOI 10.1016/j.cell.2012.11.050. <https://doi.org/10.1016/j.cell.2012.11.050>
- [30] M. G. Sacerdote; J. W. Szostak. Semipermeable Lipid Bilayers Exhibit Diastereoselectivity Favoring Ribose. *Proceedings of the National Academy of Sciences* 102, 6004–6008 (2005). DOI 10.1073/pnas.0408440102. <https://doi.org/10.1073/pnas.0408440102>
- [31] Jack W. Szostak; David P. Bartel; P. Luigi Luisi. Synthesizing life. *Nature* 409, 387–390 (2001). DOI 10.1038/35053176. <https://doi.org/10.1038/35053176>