Exploratory Research and Hypothesis in Medicine **2026** vol. 11(1) | e00041
DOI: 10.14218/ERHM.2025.00041

Review Article

The Oncodarwinian Hypothesis: Cancer as a Potential Immunoadaptive Response and Artificial Intelligence-based 3D Printed p53 Superproteins

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Received: August 16, 2025 | **Revised:** November 10, 2025 | **Accepted:** November 26, 2025 | **Published online:** January 22, 2026

Abstract

This review presents the Oncodarwinian Hypothesis, which proposes a new medical paradigm: that of cancer as a potential macro-immunoadaptive response (susceptible to fine-tuning or reprogramming/management via artificial intelligence-based 3D printed p53 superproteins). A traditional hypothesis-generation method was adopted; it entails observing a biophenomenon longitudinally (tumor-precursor out-of-control cell division), formulating and refining targeted research questions, and then, rooted in a prior interdisciplinary theoretical framework, outlining (per deductive reasoning) a testable answer or statement apt to predict outcomes. Two main theoretical findings emerge from this review: the plausibility of a wireless p53 superprotein molecular biochip (3D printed) and cancer cells' dual-focus immunological nature. It will be necessary to approach the key issue and prognosis of (supposedly meaningless) uncontrolled cell division in a different light. Basically, the same diseasing cancer also constitutes a self-replicating immunoadaptive algorithm that needs to be deciphered. An interdisciplinary quest to unravel its "source code" involves genomic palaeontology and learning the natural selection programming language — for developing (personalized) artificial intelligence-assisted p53 superproteins.

Introduction

Is cancer ontologically just a disease? What if we are misrepresenting it? Has rationalist pathology (or science's unimaginative specialization) eclipsed a broader perspective of cancer as a response/expression of evolutionary biology? In this context, is it theoretically permissible to approach cancer as some immunoadaptive endeavor (autopoiesis) of healing, or at least of coping with exogenous/endogenous risk factors, despite its absence of control?

A traditional hypothesis-generation method was adopted,[1] which entails observing a biophenomenon longitudinally (tumor-precursor out-of-control cell division), formulating and refining targeted research questions, and then, rooted in a prior interdisciplinary theoretical framework, outlining (per deductive reasoning) a testable answer or statement apt to predict outcomes. Thus, from the earliest cancer records found on a 7th-century BC Egyptian papyrus — and Mukherjee's cancer historiography[2] — down to Muñoz-Castiblanco's 3D bioprinting,[3] plus García-Reyes' and Bella's artificial intelligence (AI)-driven protein electrochemical chip engineering,[4,5] across Fussenegger's genetic software computational biodesign,[6] we begin to surface a consistent investigation landscape.

The goal is to address the above survey questions in order to substantiate our Oncodarwinian Hypothesis (OdH), which proposes a new medical paradigm: that of cancer as a potential macro-immunoadaptive response — susceptible to fine-tuning or reprogramming/management via AI-based 3D printed p53 superproteins. Such an autopsy of the illness–cancer binomial will be instrumentalized by a phenomenology of cancerous cells' biological creativity, suggesting the existence of a Darwinian "intelligence" of the cell cycle.

Cancer as biological fatalism

Cancer is expressed through uncontrolled cell division. Its onset and prognosis are usually linked to a series of alterations in the activity of cell cycle regulators, associated with risk factors: congenital conditions, infections, smoking, ageing, excessive exposure to solar radiation, alcoholic beverages, etc. For instance, cell cycle

Keywords: Cancer; Uncontrolled cell division; Oncodarwinian Hypothesis; Immunoadaptive response; Artificial intelligence-based 3D printed p53 superproteins; Cancer cells' dual-focus immunological nature.

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How to cite this article: Araújo A. The Oncodarwinian Hypothesis: Cancer as a Potential Immunoadaptive Response and Artificial Intelligence-based 3D Printed p53 Superproteins. *Explor Res Hypothesis Med* 2026;11(1):e00041. doi: 10.14218/ERHM.2025.00041.

inhibitors prevent cells from dividing when inopportune, so low activity of these inhibitors may trigger cancer. Similarly, positive regulators of cell division can lead to cancer if they are too active.[7] In most cases, such changes occur due to mutations in the genes that code for cell cycle regulatory proteins.[8]

The cancer cell (CC) has distinct properties compared with other cells. Many of these differences are related to its circumstantial behavior during cell division. Indeed, CCs can multiply in a petri dish without the addition of growth factors or growth-promoting protein signals. In contrast, normal cells require growth factors to divide in culture.[9] Furthermore, CCs manufacture their own growth factors. They also show growth factor pathways stuck in the "on" position.[10] Within the body, CCs induce neighboring cells to produce growth factors to support them.[11]

A lab-grown normal cell is surrounded by several neighboring cells, whose presence blocks division (contact inhibition). However, CCs ignore the signals that should interrupt their division and pile up on top of each other in irregular layers. It is obvious that the ecosystem of a petri dish differs from that of a human body. However, the oncological literature speculates that the loss of contact inhibition in CCs outside the organism reflects the switching off or inactivation of a mechanism in charge of directing tissue balance in the body.[12]

This replicative perennialization/immortality is a hallmark that identifies CCs, allowing us to understand their functioning and latent potential. They divide many times more than a normal cell, which performs about 40–60 rounds of replication before losing such capacity, ageing, and dying.[13,14] CCs can exponentially outpace the average division rate of other cells mainly because they express the enzyme telomerase, whose assignment is to reverse the fraying (usual during each cell division) of the chromosome ends.[15,16]

There are differences between CCs and non-cancerous cells that do not relate directly to the cell cycle, but to the genesis of tumors. The CC is able to migrate (metastasis) to other parts of the body, as well as increase its own supply chain by forming new blood vessels (angiogenesis), which optimizes the logistics of inputs — oxygen and nutrients — to tumor cells.[17] In addition, CCs do not manifest programmed cell death (apoptosis), at least not under the same conditions as normal cells, for example, due to DNA damage. Recent studies have also provided evidence that CCs experience metabolic changes that interfere with and amplify or potentiate their growth and division.[18]

Cells are programmed to restrict their own division, repair DNA, and prevent cancer etiology. Hence, presumably, cancer is a multi-step process in which several containment barriers (or defense lines) must fail before a critical mass forms and cells become cancerous. Most cancers arise when cells undergo a series of mutations (changes in DNA) and begin to divide more rapidly, escaping the internal and external controls of that division and thus avoiding predestined cell death.[19] How does this whole circuit of events unfold? Hypothetically, a cell might first lose the activity of a cell cycle inhibitor, causing its descendants to divide slightly faster. Such offspring are unlikely to be cancerous but may constitute a benign tumor: a mass of cells that, although they divide excessively, do not have the potential to invade other tissues or promote metastasis.[20]

Over time, a cell may experience enough mutations to expand the action of positive regulators of the cell cycle, giving rise to CCs and a malignant tumor capable of invading other tissues. In general, the mitotic progression of this same tumor leads to the ever-greater spread of mutations in its cells.[21] Advanced-stage cancers tend to develop major changes in their genomes, including large-scale mutations such as the loss or duplication of entire chromosomes.[22,23] They appear to result from inactivating mutations in genes that keep the genome stable, precisely by blocking the onset, transfer, and proliferation of mutations.[24,25]

These genes encode proteins that sense and repair DNA damage or faults, intercept DNA-binding chemicals, preserve telomere caps at the ends of chromosomes, and play other key maintenance roles. If one of them (genomic stability factors) turns out to be mutated and non-functional, it is possible for multiple mutations to accumulate rapidly in a progenitor cell. Then, its parental lineage may reach a critical mass of cancer-generating mutations. Different types of cancer involve distinct classes of mutations, and each individual tumor displays a unique set of genetic alterations.[26,27] However, mutations in two kinds of cell cycle regulators usually induce cancers: (i) overactivation of positive regulators, which become oncogenic; and (ii) inactivation of negative regulators, also labelled tumor suppressors.[28]

In CCs, a growth factor receptor gene may send signals even when there are no growth factors, or cyclin (a family of proteins that controls the cell's advancement through its cycle by activating enzymes such as kinases) may be expressed at alarming levels. The hyperactive versions and copies of these genes — cancer vectors — correspond to oncogenes, while their not-yet-mutated forms define proto-oncogenes.[29]

Mutations that convert proto-oncogenes into oncogenes follow varied routes. Some of them modify the amino acid sequence of the protein itself, changing its shape and locking it into an "always-on" status. Other mutations imply replicative elasticity, in which a cell acquires extra copies of a gene and starts producing too many proteins. There are also cases in which a failure in DNA repair connects the proto-oncogene to a foreign gene, yielding an unruly "combo" protein.[30]

A large number of Ras proteins — regulators of signal transduction and targets for cancer treatments and therapies — that convey signaling enzyme (or growth factor) signals are encoded by proto-oncogenes. Ordinarily, these proteins direct cell cycle progression only when growth factors are available. However, if one of them becomes overactive due to mutations, it transmits signals even when there is no growth factor.[31] For example, oncogenic Ras mutations can be found in approximately 90% of pancreatic cancers.[32] Ras is a G-family protein acting as a binary molecular switch. It alternates between an inactive mode (bound to a small guanosine diphosphate molecule) and an active mode (linked to a similar molecule, guanosine triphosphate). Carcinogenic mutations often change the Ras structure so that it loses the ability to revert to the inactive form or remains stuck in a "non-stop proliferation" maze.[33]

As for negative regulators of the cell cycle (tumor suppressor genes), they become less active — perhaps non-functional — in CCs.[34] In this case, a protein that breaks cell cycle development in response to DNA damage may no longer detect it or may fail to respond properly, preventing the suppression of cancerous tumors. An important tumor suppressor is the p53 protein, which performs a key function in DNA repair. This protein acts primarily at the G_1 end (controlling the transition from G_1 to S), where it blocks cell cycle advancement in response to corrupted DNA and other unfavorable conditions.[35]

When a cell's DNA is injured, a sensor protein activates p53, which triggers the production of a cell cycle inhibitor, interrupting the cycle at the end of G_1. This pause allows time for DNA remediation, also dependent on p53, whose second priority is to

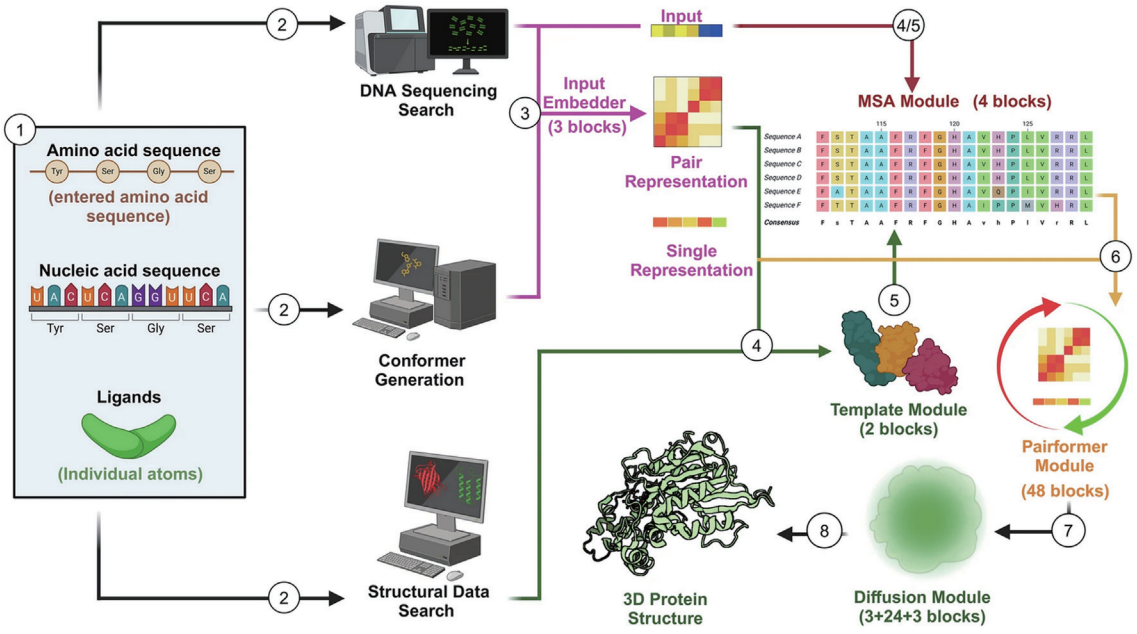

Fig. 1. AlphaFold 3's artificial intelligence (AI) biomolecule prediction/design scheme. Source: García-Reyes and colleagues.[4] "AlphaFold 3 can predict the structure of proteins, DNA/RNA molecules, and ligands. 1) Once a sequence has been entered, 2) the software concurrently engages with multiple databases to assess potential genetic sequences, conformational prototypes, and structural configurations. 3) The input embedder then uses the sequencing and conformer information to encode and generate a composite that results in a single and pair representation. 4) The template module then integrates known structures obtained from the structural data search into the pair representation. 4/5) In tandem, the Multiple Sequence Alignment (MSA) Module incorporates the sequencing, pair representation, and template models to iteratively build novel base templates. 6) From here, the pairformer module uses MSA information to test different interacting elements, refining the predicted molecule interactions and repeatedly updating the pair and single representations. 7) Finally, the diffusion module applies and removes noise into the algorithm to improve local stereochemistry and global structures."

activate DNA recovery enzymes.[16] If the damage is rectified, p53 will release the cell, permitting it to proceed through the cell cycle. Should the lesion not be corrected, p53 will command its third and final mission: to initiate apoptosis (programmed cell death) in order not to pass on damaged DNA.[36]

In CCs, p53 is absent, non-functional, or less active than normal. Many cancerous tumors have a mutated expression of p53 that may no longer bind to DNA. As p53 acts by binding to target genes and propelling their transcription, the unbound mutant protein is unable to fulfill its scope.[37]

Therefore, when p53 is deficient, a cell with tampered DNA divides, and its replicas will inherit mutations due to unrepaired DNA from the parent cell. Over generations, cells containing defective p53 accumulate mutations that *(i)* convert proto-oncogenes into oncogenes, or *(ii)* disable other tumor suppressors. CCs without mutations in p53 have probably inactivated it via alternative mechanisms (e.g., heightened intervention of p53-neutralising proteins).[38]

Cancer as biological creativity and AI-based 3D printed p53

Let's delve into a paradigm that presupposes an essential cancer propaedeutic, whose cell division is only uncontrolled until we learn to control it. However, the construction of knowledge inducing cell division governance has been postponed or impaired by the dogma (or premise) of this same cell splitting as an anomalous and ontologically pathogenic process — rather than an attempt at a specific, individual, and adaptive immune response to risk factors. In our OdH, one must simply learn to manage such an attempt.

Although biotechnology prefers to fight back, decrease, mitigate, and does not know how to fully control this immunoreaction,[39,40] it may soon be susceptible to manipulation or direction by nano-bioengineering, in a disruptive breakthrough concerning cell replacement. This represents a feasible challenge within an interdisciplinary environment based on cooperation (mutually reinforcing feedback) with 3D bioprinting and biocomputing technologies.[41]

On this point, a promising intervention field remains the evidence that the p53 protein encodes the most frequently mutated gene in human cancers.[23] It is speculated that biocomputing research could have already been encouraged, aiming at remodeling and printing nanostructures of creative or self-taught (tumor suppressor) p53 proteins, inoculated — via a tailor-made molecule delivery method — by viruses with an oncogenic tracer (e.g., a marker for overactive Ras proteins), to carry out a key task in DNA repair.

As a low-cost, easy-to-use pre-printing experimental protocol (according to our expertise in progress), it is advisable to download a p53 protein molecule file from the *Protein Data Bank* (PDB) via the internet by searching for "<molecule name> PDB File".[42] Import such a PDB file into *MoluCAD* (File → Import → PDB File),[43] a free-to-download software with a non-complex learning curve — where p53 protein molecules might also be drawn or modelled, instead of downloading from the PDB. Although PDB files accept direct import into *Blender* (a free and open-source 3D creation suite for editing PDB files),[44] note that atoms are often loaded without bonds.

Once the PDB file has been drawn in or imported into *MoluCAD*, export its output (File → Export → PDB File) to *Blender* through an add-on dubbed *Atomic Blender* (integratable with protein-designer AIs, e.g., *AlphaFold 3*) (Fig. 1).[4,45] The next level involves using *Blender* to reconfigure or customize p53 protein molecules (PDB files), converting them (PDB File → OBJ File) into

a wireless p53 superprotein molecular chip (p53-MoleChip),[46,47] i.e., p53-MoleChips able to decode and transmit specific tumor genesis signals online with an AI algorithm (a smart bet could be to calibrate or train *ChatGPT* for this role) which,[48] by autonomously diagnosing these signals (under physicians' mobile monitoring), will deliver guidelines for repairing or activating tumor suppression or containment components.

Having set the scale and additional parameters of the p53-MoleChip saved as an OBJ file, 3D printing is about to begin. Depending on p53-MoleChip geometry and complexity, support software (e.g., *Meshmixer*) will be required to print it successfully.[49] Freely downloadable, *Meshmixer* not only generates printing support but also allows the user to execute molecular rescaling. Then choose export or print as an STL file.

Anthony Atala and colleagues introduced the challenge of 3D printing and therefore the predictive dilemma of intelligent life production lines,[41] counterposing an elegant mirror to medicine. Léo Pio-Lopez follows him, exploring a connected issue: how would an artificially manufactured human being behave?[50,51] In this regard, the prototyping of (non-rejectable) personalized p53 simulacra may illustrate the next evolutionary step towards understanding cancer as a chance for cell cycle governance, which presupposes re-signifying or recycling the malignancy of a tumor.

We are facing the convergence of oncoengineering's multiple synapses. Martin Fussenegger learns to program or control gene expression in response to ribonucleic acids (RNAs) as genetic software, using protein-anchored central processing units. Furthermore, he has built and deployed — inside lab-grown cells — a dual-core central processing unit combining two orthogonal processors in a single cell to compute and metabolize a wide range of RNA inputs.[52] This represents an opportunity to master and design the algorithmic architecture (for nanoimplantation into CCs) of "intelligent" p53: synthetic, printable, AI-based superproteins that constantly adapt (self-learn), updating their tumor suppressor status.

Consider a human tissue with billions of cells, each one having its own organically integrated dual-core processor, i.e., molecular microprocessors fabricated by 3D printing and implanted in lab-grown cells, whose level of accuracy would be able to perform a wide range of (individual bits) bitwise computations, allocating biochemical logic gates to a surgical repair arithmetic.[6,53,54] In principle, this tissue would acquire an unprecedented processing capacity,[55,56] far superior to that of a digital supercomputer, while consuming less energy.[57–59]

By enabling rational programming of mammalian single-cell behavior, circuit-synthetic biology drives innovation across multicore-based design, which may detect and encourage proteomic biocomputing opportunities (with highly accurate protein sequencing prediction) to provide applications in cancer management and handling.[52,60–65]

OdH arises from the spectrum of Evolutionary Medicine (EM), which is also often referred to as "Darwinian Medicine". This new medical approach delves into the conceptual framework of evolution by natural selection to comprehend even human cell health.[63,64] In other words, EM can explain uncontrolled cell division and disease via evolutionary or historical causes. The high frequency, for example, of alleles related to sickle cell anaemia, especially among Afro-descendants, could only be properly understood after identifying the role of these same alleles in malaria resistance within endemic regions.[63]

According to EM, the human body is not defect-free, despite all its sophistication, and our body's evolutionary adaptations appear to stem from selective natural processes that, today, would have made an organism perfectly adapted to survival.[65,66] However, historically, these adaptations are vulnerable for at least two reasons: *(i)* environmental circumstances modify over the course of paleontological time, and so fitness changes too; and *(ii)* due to the limits of natural selection. On the other hand, human existence spaces are permeated or shared with risk factors and countless biological species, including pathogens that adapt to humans as their habitat.[67]

Functional biological properties derive from evolutionary processes, mainly adaptive ones. Every detail of the physiological or behavioral structure that has a current (or past) function or utility must be the result of natural selection processes acting on intrapopulational genetic variation. Consequently, it is acceptable to re-signify the idea of "uncontrolled cell division" as maladjustments of the body to modern risk factors, reflecting vulnerabilities of adaptations bequeathed by our phylogenetic heritage.[68]

Adaptive maladjustments arise because natural selection gradually and slowly reprograms human bodies (from primate ancestors) considering an environment or lifestyle — e.g., devoid of a significant smoking prevalence — that no longer exists, and there was no chance or time to adjust to the novel living conditions by natural selection.[67] In this scenario, a complete prospecting or demonstration of OdH presupposes decoding, through further research, certain vulnerabilities (potentialized by risk factors) intrinsic to the evolutionary history of the cell cycle itself.

Many interesting and important controversies remain unresolved within the Darwinian model of carcinogenesis. For example, tumor evolution is often portrayed as a linear sequence of genomic mutations and epigenetic changes synchronous with progressive drift of cellular populations from normal through premalignant lesions to invasive cancer. This approach, however, while useful conceptually and pedagogically, is highly simplified, ignoring, for example, the stochastic nature of mutations, mitigating intracellular processes such as the chaperone function of heat shock proteins, and extracellular factors such as the potential influence of microenvironmental selection factors. Similarly, the role of the mutator phenotype remains unclear.[69]

OdH: CCs' dual-focus immunological nature

Latest studies (borderline to our specific hypothesis), found through Google Scholar surveys using keywords (e.g., "cancer as immunoadaptive reply", "cell intelligence"), support cancer as an evolutive process which may elicit, become a target of, deflect, and resist immunoadaptive responses.[70–77] However, as stated earlier, the OdH assumes cancer is itself immunoadaptive; it involves an ongoing evolutive, non-pathological process (self-learning path) whose goal consists of adapting cell division biochemistry to epigenetics-reflected environmental or behavioral risk factors, such as diet, radiation, tabagism, sedentary lifestyle, etc.

Thus, cancer would not merely be the random target of a chain immune reaction (micro-immunological perspective) — since "immune evasion" allows tumors to bypass immunomodulation and tumor suppression attempts[71] — but rather part of an immunoadaptive response or journey (macro-immunological perspective) at an evolutionary timescale, equivalent to geological chronology in wide or deep intervals (eon, era, period, and epoch) (Fig. 2).[78] As per fossil stratigraphy,[79] *Homo sapiens* (a baby in evolutionary dating) arose within the current geological period (Quaternary) around 200,000 years ago, and some of the earliest cancer records were found on a 7th-century BC Egyptian papyrus.[2] So far, a very short time in Darwinian terms.

From an integrative (dual-focus) approach to these macro- and

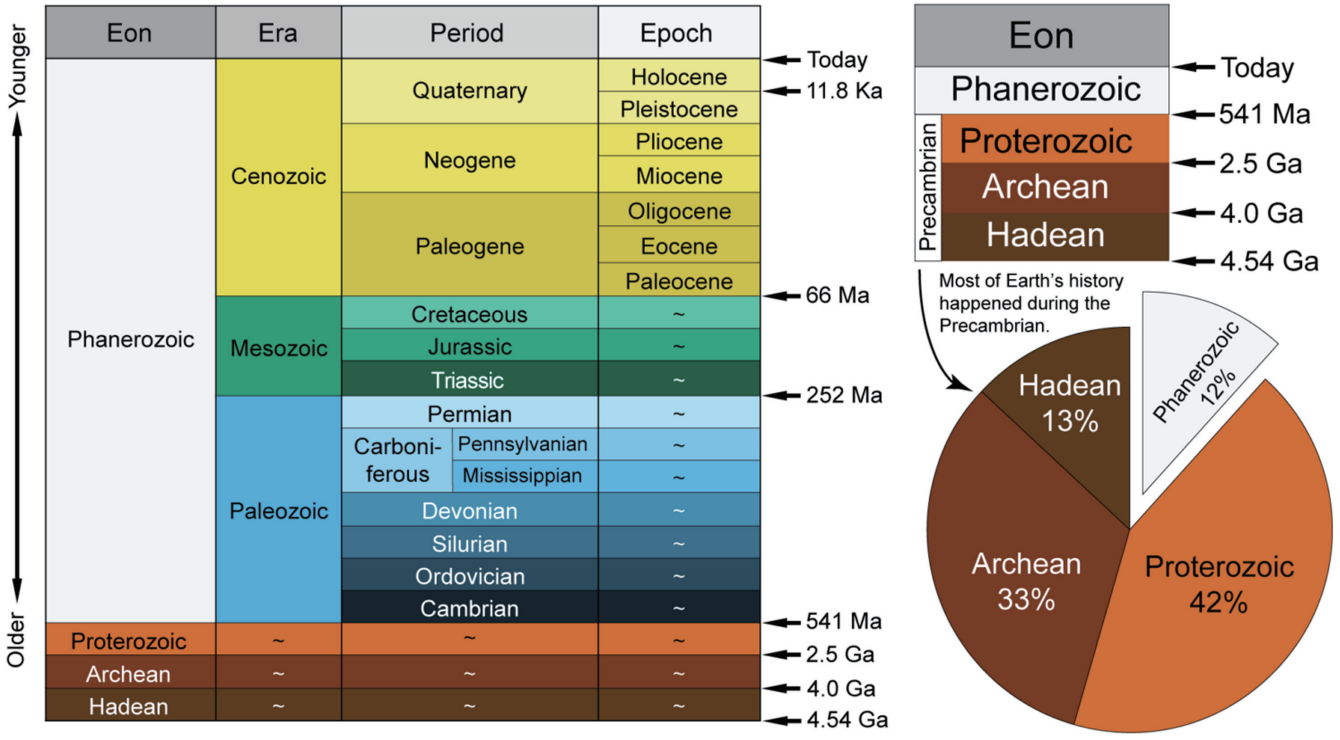

Fig. 2. Geological timescale. Source: Hendricks.[78]

micro-immunological dimensions, our hypothetical model (OdH) formulates and suggests that cancer, unlike how it has been diagnosed for millennia, corresponds to a pathological stage of a non-pathological immunoadaptive self-learning process. Somehow, this hypothesis (OdH) portrays the serialist *ratio* of Marx's and Engels' historical materialism, whereby the capitalist production system represents a necessary step towards communism (the overflow of historical materialism from sociology into biological sciences has long been occurring,[80–82] analogously, but in the opposite direction, to social Darwinism).

Under such circumstances, in theory, it is expected that AI-run 3D printed p53 superproteins collaborate with and speed up this macro-immunological cancer dimension as adaptive "cell intelligence",[83] while synchronously reinforcing tailored oncotherapies at the micro-immunological level. In any case, as far as is known, OdH seems to translate a radically innovative hypothesis, not yet incorporated into standard literature or covered by current discoveries or preliminary research findings. Always a first time.

AI-environmented 3D protein printing: a graphical immersion

A comprehensive (or in-depth) analysis of AI-based 3D printed p53 superproteins includes, with regard to *AI-driven protein design* (Figs. 1 and 3),[4,84–97] and *3D bioprinting* (Fig. 4),[3,98–101] highlighting their potential accuracy and feasibility with respect to the following variables (Table 1).

AI-designed p53: clinical translation and possible limitations/biases

Relative to clinical translation, how could AI-engineered p53 superproteins enhance current oncotherapies? Bacteria and viruses' potential to selectively replicate in tumors prompted microbial cancer treatments amid synthetic bioengineering.[102–111] An impressive study (from 2025), conducted by scholars at Columbia University, describes a symbiotic ecosystem "whereby [attenuated] *Salmonella typhimurium* bacteria transcribe and deliver the Senecavirus-A RNA genome inside host cells, launching a potent oncolytic viral infection".[112]

Hypothetically, such transcription or delivery might also aggregate AI-based 3D printed p53 superproteins. In fact, encapsulated within bacteria, viral genomes and synthetic p53 would further evade circulating antiviral antibodies to reach tumors, where they will trigger replication or dissemination in already immunized organisms (Fig. 5, per analogy).[112]

Until the efficacy of AI-based 3D printed p53 superproteins is proven, this review paper will remain partly confined to speculative territory (limitation), something typical of disruptive proposals. Let us consider another example. Einstein, who for years worked at Bern's Federal Bureau of Patents, mathematically predicted (1905) that during light ray propagation emitted by a point source, energy is not distributed continuously over larger and larger spaces but is comprised of a finite number of energy quanta located at space spots, each one moving without splitting and only being absorbed or generated in blocks. The concept of the photon — the name given to the light quantum after 1926 — was born, and with it the modern quantum physics era (however, years would pass before Einstein's equation was validated in 1915 for experiments carried out by American physicist Robert Millikan).[113]

Here, there could be confirmation bias, i.e., the tendency to interpret or seek information that corroborates a hypothesis,[1] whilst ignoring or disregarding evidence liable to contradict it. Preventing such bias demanded compilation of references with a broad

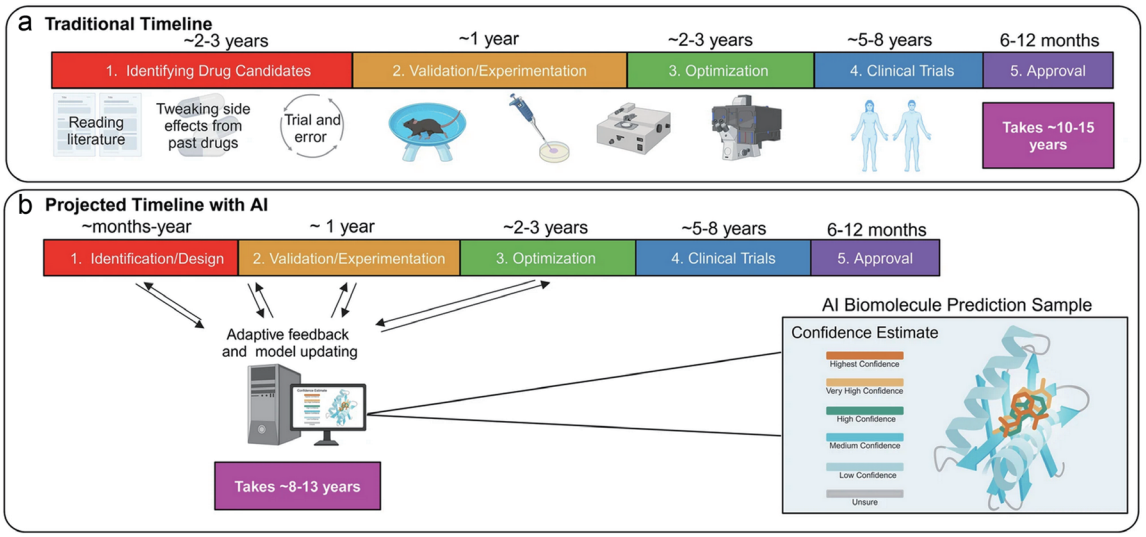

Fig. 3. Comparison of traditional vs. artificial intelligence (AI)-run biomolecule design pipelines. Source: García-Reyes and colleagues.[4] "(a) Traditional timeline for creating new drugs. a1-5) Partitioned timeline showing major categories of drug development (vivid colors). Subcategories describing unique elements are below major categories. Overall timeline from drug candidate identification to approval is ~10–15 years. (b) Projected timeline for creating new drugs with AI assistance. b1-5) Same as a1-5, but with notably shorter durations driven by continued AI optimization at each step. Generative AI models based on validation and clinical evidence can enhance the trajectory to approval by ~3 years."

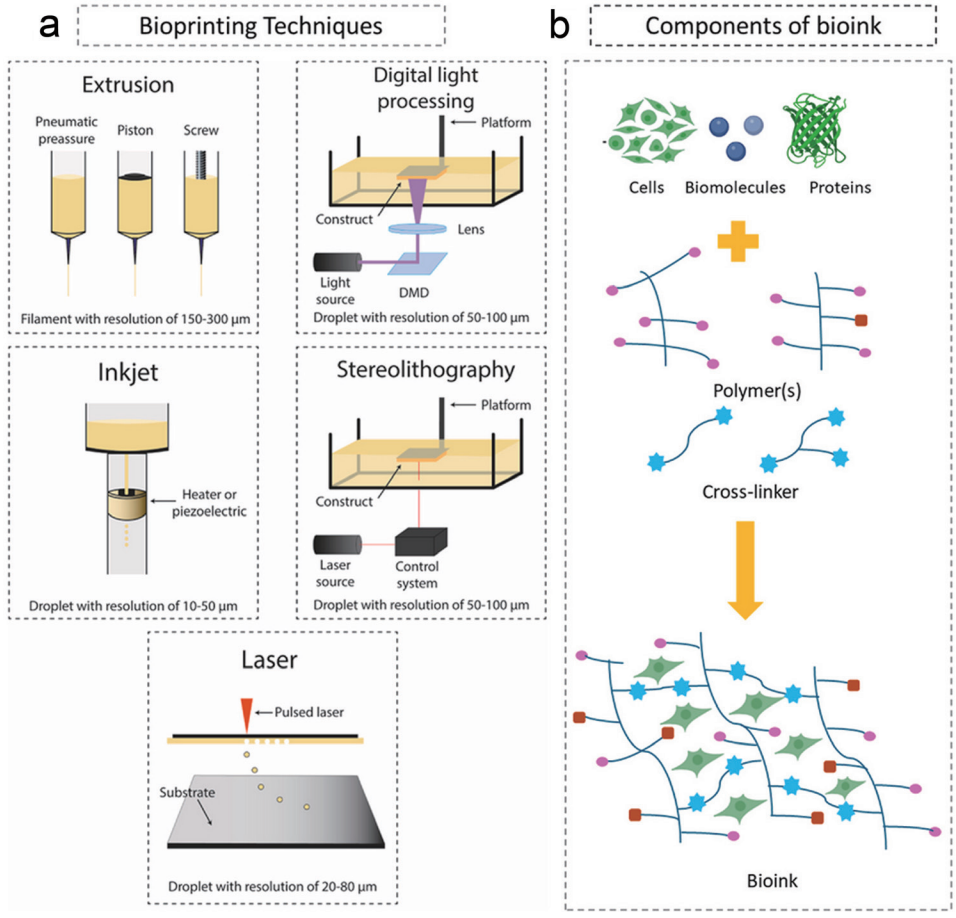

Fig. 4. 3D bioprinting. Source: Muñoz-Castiblanco and colleagues.[3] DMD, digital micromirror device.

DOI: 10.14218/ERHM.2025.00041 | Volume 11 Issue 1, January 2026

Table 1. Projections upon the AI-assisted 3D printed p53 superproteins

	AI-driven protein design	3D bioprinting
Operational constraints	How to integrate cutting-edge AI tools (e.g., AlphaFold 3) into bespoke synthetic protein workflows (no digital hallucinations), including devices for structural and functional prediction, beyond generative language models in molecular design	Challenges arising from variability in molecular properties, besides cross-linking efficiency (polymer chains joining to build a stable, resistant 3D network), emphasize the urgency of a protocol/method for determining standard bioinks. Type of bioinks: *natural polymers as inks* (gelatin; collagen; silk; fibrin; alginate, an anionic polysaccharide found in seaweeds; hyaluronic acid-based; chitosan), *decellularized extracellular matrix as inks*, and *synthetic polymer-based inks* (pluronic; PEG-based hydrogels; poly-lactic-co-glycolic acid, or PLGA; poly-ε-caprolactone, or PCL; polyurethane; poly-vinyl alcohol, or PVA)
Theoretical challenges	Deciphering (AI-based) the vast complexity of protein sequence space and overcoming structural/functional data limitations	Increase the versatility or autonomy of bioprinting so as to solve challenges through generative self-learning (AI-run), establishing a symbiotic and interchangeable nexus between 3D printers (fed bioinks made from bioprintable materials mixed with living cells) and 4D bioprinting, employing thermal-, electric field-, pH-, magneto- and photoresponsive (smart) polymers in self-assembly
Development schedule	Protein engineering made remarkable progress over the last decade. The priority — regarding a plausible schedule — for the coming decade will perhaps be to migrate from *protein design* (still focused on α-helix bundles, limiting its potential towards generating sophisticated enzymes, small molecules, and diverse protein ligands) into *proteomic engineering*, targeting an inter-relational (of governing dynamics) and large-scale analysis centered on protein structure, function, sequence, modifications, and interactions, to further advance concerning: *(i)* complex eukaryotic protein stability/activity; *(ii)* antigen generation for vaccines, antivirals; *(iii)* nanovehicle computational architecture used in drug delivery	The next five years will prove decisive for consolidating 3D bioprinting techniques that use bioinks based on natural macromolecules (NMs). NMs play a key role due to their ability to mimic, simulate, or mirror the extracellular matrix, increasing tissue adhesion and integration (i.e., with decreased histological rejection), enabling the precise manufacturing of tissue-like structures, as well as significant gains in personalization/customization and scalability to benefit regenerative medicine, drug testing via 3D models, and organ transplantation
Improvement demands	Train/validate AIs which deliver accuracy and speed in novel protein design (with customized functions) to unlock enzymatic mechanisms and reprogram biomolecular systems — shortening or optimizing experimental cycles	Among emerging trends in 3D bioprinting, the most promising seems to be hybrid bioinks, which combine natural macromolecules (NMs) with extracellular matrix components, associating them with polymers and cross-linkers (structural integrity vectors)
Verification methods	It was necessary to address unreliability in exclusively structure-anchored design methods, which limited their application and, hence, the development of more impactful therapeutic interventions (via high-complexity synthetic protein molecules). Indeed, recent methodological strategies combining structure- and sequence-level calculations, plus machine learning tools, have exponentially improved protein engineering	Extrusion-format 3D bioprinting using customized bioinks now ranks as the top method (extrusion denotes mechanical process whereby materials get forced through a cylindrical die or mold to acquire preset shapes)

AI, artificial intelligence; PEG, polyethylene glycol.

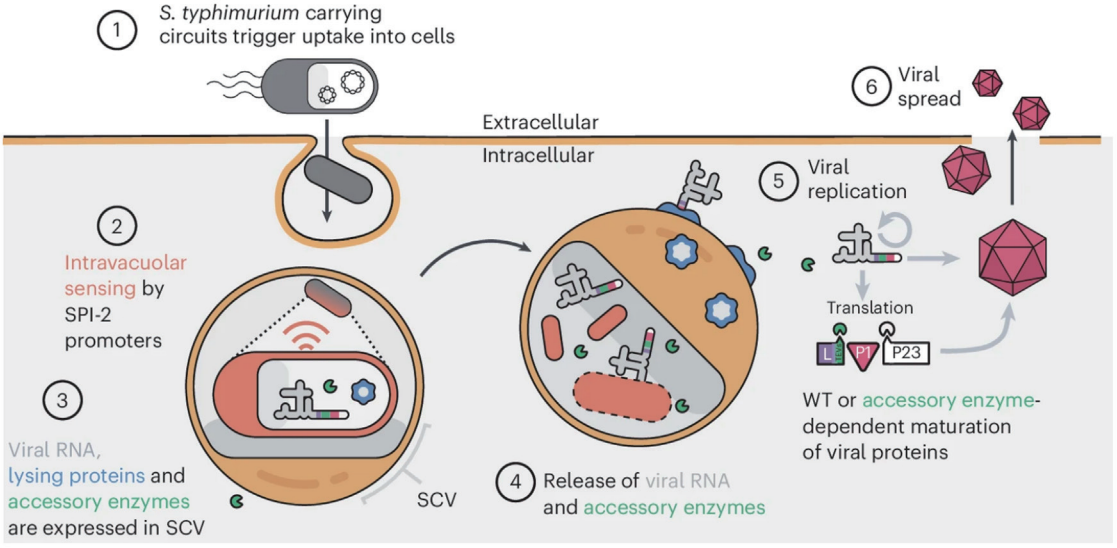

Fig. 5. Dose-related toxicity microbe consortium as an oncotherapeutic scheme for viral genomes/proteins in host cytoplasm. Source: Singer and colleagues.[112] "(1) *S. typhimurium* carrying synthetic circuits enter mammalian cells via natural effectors encoded on *Salmonella* pathogenicity island 1 (SPI-1). (2) Internalized *S. typhimurium* within a *Salmonella* containing vacuole (SCV) sense the intravacuolar space and trigger activation of SPI-2 promoters. (3) Engineered SPI-2 promoters are then used to drive the production of viral RNAs (poliovirus replicon, Senecavirus A (SVA) or engineered SVA), lysing proteins hemolysin E (HlyE) and E from phage ϕX174, and accessory enzyme. (4) Upon successful bacterial and vacuolar lysis, viral RNAs and accessory enzyme are released into the host cytoplasm. (5) Wild-type (WT) viral RNAs are translated in the cytoplasm and viral replication is initiated. The maturation of viral particles may be engineered to require the accessory enzyme for complete maturation. (6) Infectious particles are released into the extracellular space to infect neighbouring cells. Since *S. typhimurium* bacteria act as a viral 'capsid', we have named the platform Coordinated Activity of Prokaryote and Picornavirus for Safe Intracellular Delivery (CAPPSID)."

longitudinal and interdisciplinary spectrum.

Future directions

In the general context of what Miao Cui, Chao Cheng, and Lanjing Zhang would call "High-throughput proteomics",[114] the development of a protocol for the clinical translation only sketched out in the previous section clearly recommends a forward direction to specific viability tests around p53 viral protein as an AI-run wireless "electrochemical biochip" (3D printed),[5] signaling routes for its experimental validation, interdisciplinary partnerships, and long-term research aims. A premise is that once comparative statistical significance (overall, $\alpha = 0.05$, assuming a 95% confidence interval and p-value < 0.05) of AI-customized p53 in tumor inhibition, containment (no metastasis), or prevention has been shown, the OdH will gather traction to bridge major knowledge gaps surrounding CCs' macro-immunoadaptive (non-pathological dimension) responsivity and resilience — properties collaterally inferable from well-established literature at the onco-Darwinian interface (Evolutionary Theory of Cancer).[115–117]

Conclusions

Regarding cancer, we must overcome the dogma or diagnosis that defines it as nothing more than a disease whose malignancy and mutation collection mirror a constant: runaway cell division. Ultimately, what is fatal about cancer represents a one-dimensional dogma. Fighting this uncontrolled or cancerous cell division instead of learning to control it could be tantamount to killing or aborting a valuable evolutionary or regenerative mechanism.

It will be necessary to approach the key issue and prognosis of (supposedly meaningless) uncontrolled cell division in a different light. Basically, for the OdH, the same diseasing cancer also constitutes a self-replicating immunoadaptive algorithm that needs to be deciphered. The interdisciplinary quest to unravel its "source code" involves genomic palaeontology and learning the natural selection programming language — for developing (personalized) AI-based 3D printed p53 superproteins.

Acknowledgments

I would like to express my special gratitude to Lanjing Zhang and Amy Xu for their constructive suggestions and rigorous editorial treatment.

Funding

The author declares no funding.

Conflict of interest

The author declares no conflict of interest.

Author contributions

AA is the sole author of the manuscript.

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