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Perspective

Two decades of induced pluripotent stem cell research: From discovery to diverse applications

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SUMMARY

Twenty years have passed since the first demonstration of mouse induced pluripotent stem cells (iPSCs). What began as an unexpected observation in Kyoto quickly transformed stem cell biology and regenerative medicine worldwide. Over the past two decades, we have gained profound insights into the molecular mechanisms underlying cellular reprogramming and pluripotency. The technology has continued to evolve—becoming safer, more efficient, and more versatile. Today, iPSCs serve as a foundation for wide-ranging applications, from disease modeling and drug discovery to regenerative therapies and rejuvenation research. In this review, I reflect on the scientific journey of iPSCs, highlight key milestones in our understanding of reprogramming, and discuss the expanding clinical and societal impact of iPSCs.

INTRODUCTION

"Dr. Yamanaka, please come and check the cells. They look like ES cells."

It was the summer of 2005 when Kazutoshi Takahashi rushed into my office with this announcement. He had introduced 24 candidate genes—identified as highly expressed in mouse embryonic stem cells (ESCs)—into mouse embryonic fibroblasts (MEFs). To monitor reprogramming, we had modified the MEFs so that they would survive G418 selection only if they activated ESC-specific gene expression.[1] Under the microscope, I saw several colonies that resembled mouse ESCs in morphology (Figure 1). I told Kazutoshi, "Don't get excited. Most likely this is contamination." I was wrong.

I began thinking seriously about cellular reprogramming around 2000, when I became a principal investigator for the first time. Nuclear transfer experiments[2,3] and studies of transcription-factor-mediated cell fate conversion[4] had suggested that differentiated states were reversible in principle. However, whether pluripotency—the most extreme form of cellular plasticity—could be induced by defined factors alone remained entirely unclear, and I assumed that solving this problem might take decades.

What gave me confidence to attempt this experiment was the idea that pluripotency is maintained by a relatively small core regulatory network rather than by hundreds of independent components.[5] ESCs appeared to be stabilized by a limited number of transcription factors connected through reinforcing feedback loops.[6] If so, enforcing expression of the right combination might be sufficient to reset cell identity. Still, we did not expect the initial experiment to succeed. Our original plan was to use retroviral cDNA libraries for large-scale screening, and the 24-factor experiment was conceived as a pilot to validate our selection system. Had it failed, we would have proceeded with unbiased library-based discovery.

Kazutoshi repeated the experiments and consistently obtained similar colonies. Through systematic elimination, he narrowed the gene set down to four—Oct3/4, Sox2, Klf4, and c-Myc (OSKM). Cells induced by these four factors displayed properties of pluripotent stem cells. This was the birth of induced pluripotent stem cells (iPSCs).[7]

By the time we submitted our paper to *Cell*, we had confirmed the reproducibility of iPSC induction in our laboratories. Still, we were anxious about whether others could reproduce it using different hands, reagents, and equipment. Our concern proved unnecessary—within a year, multiple laboratories around the world successfully generated iPSCs with mouse[8,9] and human[10,11] cells. Whereas ESC research required 17 years to move from mouse to human, the foundation built by ESC studies enabled iPSC technology to make that transition in just 1 year. Since then, thousands of studies have explored nearly every aspect of this technology, from molecular mechanisms to translational applications.

In this article, I highlight landmark discoveries that shaped our understanding and medical applications of iPSC reprogramming (Figure 2) and discuss the broad range of current and future applications that continue to emerge two decades after that pivotal summer in Kyoto (Figure 3).

REVISITING REPROGRAMMING EFFICIENCY: A NUANCED RESOLUTION TO THE ELITE-STOCHASTIC DEBATE

Reprogramming was initially startling not only because it was possible but also because it was inefficient. Early reports indicated that only a tiny fraction of cells successfully reactivated the pluripotency program. This inefficiency sparked a lively debate between proponents of the elite model and the stochastic model.[12]

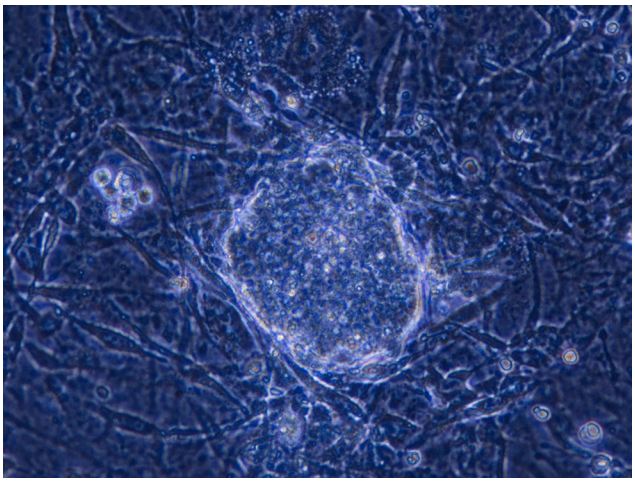

Figure 1. One of the first iPSC colonies observed in the summer of 2005

The elite model presumed that only rare cells within a heterogeneous population—perhaps progenitor or stem-like cells—retained an intrinsic plasticity that allowed them to respond to OSKM. These cells were thought to possess a more permissive chromatin landscape or a more favorable proliferative capacity.

The stochastic model proposed a far more radical idea: that all somatic cells had the capacity to reprogram, but the process required a sequence of rare molecular events that occurred with low probability. From this perspective, inefficiency reflected the complexity of the task, not a limitation of the starting population.

As the field accumulated data, it became clear that both models captured part of the truth. The development of the secondary iPSC induction system greatly enhanced the data accumulation.[13] The early phase of reprogramming is profoundly heterogeneous. Single-cell transcriptomic analyses revealed that cells pass through unstable intermediate states marked by partial loss of somatic identity and sporadic activation of early pluripotency-associated genes.[14] Only some of these cells advance far enough to activate the core pluripotency network, while others veer into dead ends or revert to somatic expression patterns.

Yet the field also learned that the initial state of the somatic cell matters deeply. Keratinocytes reprogram far more efficiently than fibroblasts because their chromatin landscape is inherently more accessible.[15] Blood progenitors reprogram more readily than terminally differentiated lymphocytes.[16] Aging, oxidative stress, mitochondrial dysfunction, and metabolic inflexibility all alter reprogramming susceptibility. Thus, while stochasticity dominates early events, the epigenetic "distance" between a somatic state and pluripotency shapes the likelihood that a cell will traverse the reprogramming landscape.

This nuanced understanding highlights the interplay between intrinsic cell properties and probabilistic transitions. Reprogramming is neither fully deterministic nor entirely random—it is a hybrid process influenced by both the starting state and the sequence of molecular events that reshape identity.

MECHANISMS OF CELLULAR REPROGRAMMING: DECODING THE LOGIC OF PLASTICITY

Reprogramming is a dramatic biological event.[17–19] It requires not only the suppression of somatic identity but also the reconstruction of a pluripotent state that resembles the early embryo. This transformation unfolds through intertwined waves of transcriptional reorganization, epigenetic remodeling, metabolic rewiring, and changes in cellular structure.

The first observable transformations occur within the initial days of OSKM induction.[20,21] Somatic transcription factors begin to lose dominance, and their enhancers progressively close. Meanwhile, the cell undergoes a mesenchymal-to-epithelial transition (MET), an event that surprised the field because it revealed that cell adhesion and polarity signals were critical in enabling the shift to pluripotency.[22,23] MET reflects the cell's movement away from the fibroblast identity and toward a more epithelial, embryonic-like state. Keratinocytes reprogram more efficiently than fibroblasts because they are already epithelial in nature, bypassing the need for MET.[15]

This transition is often accompanied by metabolic changes. Somatic cells that rely heavily on oxidative phosphorylation reduce mitochondrial activity and begin to favor glycolysis, a hallmark of pluripotent stem cells. Mitochondria themselves undergo morphological restructuring, becoming smaller and less elongated—a visual manifestation of the metabolic shift.[24,25]

Reprogramming requires an extensive reconfiguration of chromatin. Pluripotency genes are often locked within repressive chromatin adorned with H3K9me3 or DNA methylation.[20,26] OSKM expression initiates a slow, intricate process of chromatin opening. Ten-eleven translocaton (TET) enzymes catalyze the demethylation of pluripotency enhancers, and histone-modifying complexes remove repressive marks.[27,28] Chromatin remodelers such as Brahma-related gene 1 (BRG1) help reposition nucleosomes, creating a permissive environment for pluripotency gene activation.[29]

The removal of somatic enhancers and the gradual emergence of pluripotency enhancers highlight the dynamic interplay between chromatin architecture and transcription. Enhancer-promoter distances shift, looping interactions rearrange, and previously silent genomic regions become poised for activation.[30]

The activation of core pluripotency regulators represents a tipping point in reprogramming. Nanog, Oct4, Sox2, and Esrrb form interconnected feedback loops that stabilize the pluripotent identity. Once this network is established, the cell transitions from an unstable intermediate state to a more deterministic phase where the outcome becomes predictable.[31]

During this stage, the cell cycle accelerates, the G1 checkpoint shortens, and DNA repair pathways adapt to support the increased proliferation characteristic of pluripotent cells.[32] Chromatin becomes globally more accessible, reflecting a pluripotent genome that is poised for rapid differentiation into multiple lineages.[26]

As multi-omic technologies matured, it became evident that transcription factors alone do not govern reprogramming. Small RNAs fine-tune gene expression during the transition

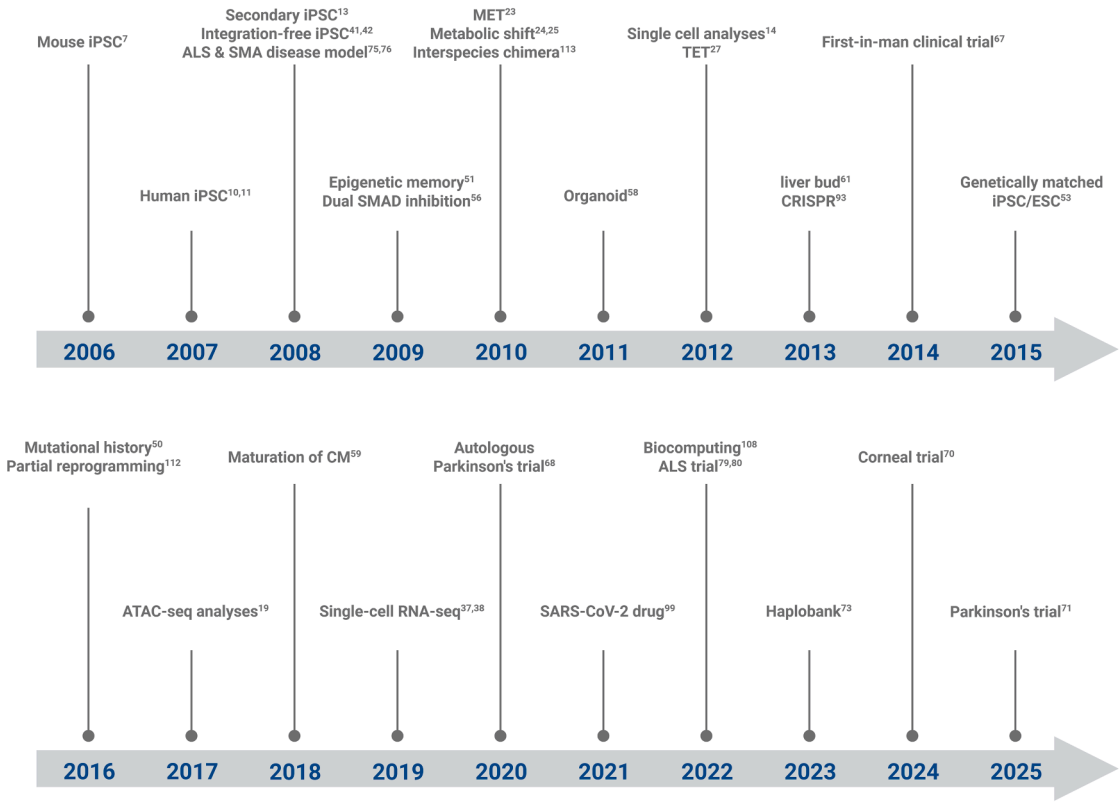

Figure 2. Landmark publications on the mechanisms of reprogramming and the medical applications of iPSCs and related technologies are shown, with reference numbers corresponding to those in the main text

The first-in-human clinical trial was initiated in 2014, and its outcomes were reported in 2017. Created in BioRender. Yamanaka, S. (2026) https://BioRender.com/o32og2c.

from somatic to pluripotent identity.[33,34] RNA-binding proteins influence splicing patterns crucial for identity transitions,[35] while long noncoding RNAs modulate enhancer activity and stabilize intermediate states.[36] Together, these regulators help orchestrate the intricate dance of molecular events that define reprogramming.

With the integration of single-cell transcriptomics, assay for transposase-accessible chromatin (ATAC)-seq, methylation profiling, proteomics, and metabolomics, the field now approaches a comprehensive understanding of the reprogramming trajectory. Computational frameworks such as optimal-transport modeling allow researchers to reconstruct the trajectories of thousands of individual cells, revealing alternative routes, detours, and bottlenecks.[37–39]

Reprogramming is no longer viewed as a simple pathway but as a multidimensional landscape shaped by the interplay of transcription, chromatin, metabolism, and cellular physiology.

MEDICAL APPLICATIONS OF iPSCs: FROM EARLY SKEPTICISM TO A MATURE TRANSLATIONAL PIPELINE

From the outset, iPSCs held enormous promise for regenerative medicine. Yet the journey from concept to clinic was far from straightforward. The early years were marked by legitimate concerns about safety, reproducibility, genomic integrity, and differentiation potential.[40] Over time, careful experimentation and methodical refinement transformed these challenges into opportunities for innovation.

Early iPSC generation relied on integrating viral vectors that carried risks of insertional mutagenesis. These approaches, though effective, raised concerns about clinical application. The development of non-integrating systems—episomal plasmids,[41] adenovirus,[42] Sendai virus,[43] piggyBac,[44] synthetic mRNA,[45] and eventually small-molecule-based methods[46]—represented a turning point. Not only did these platforms eliminate the risk of genomic integration, but they also simplified downstream quality control and improved scalability.

Initial studies reported worrisome levels of copy-number variation and mutations in iPSCs.[47–49] However, deeper analysis revealed that most were preexisting somatic mosaic mutations rather than artifacts of reprogramming.[50] Nevertheless, these findings prompted widespread adoption of rigorous genomic quality-control pipelines. Deep sequencing, methylation profiling, karyotyping, and mitochondrial-genome analysis now form standard components of iPSC characterization.

Residual epigenetic memory—the persistence of donor-cell-specific methylation patterns—also posed challenges by biasing differentiation potential.[51] Improvements in reprogramming kinetics, passaging protocols, and factor expression have largely resolved these issues, producing iPSCs that closely mirror ESCs in molecular and functional properties.[52]

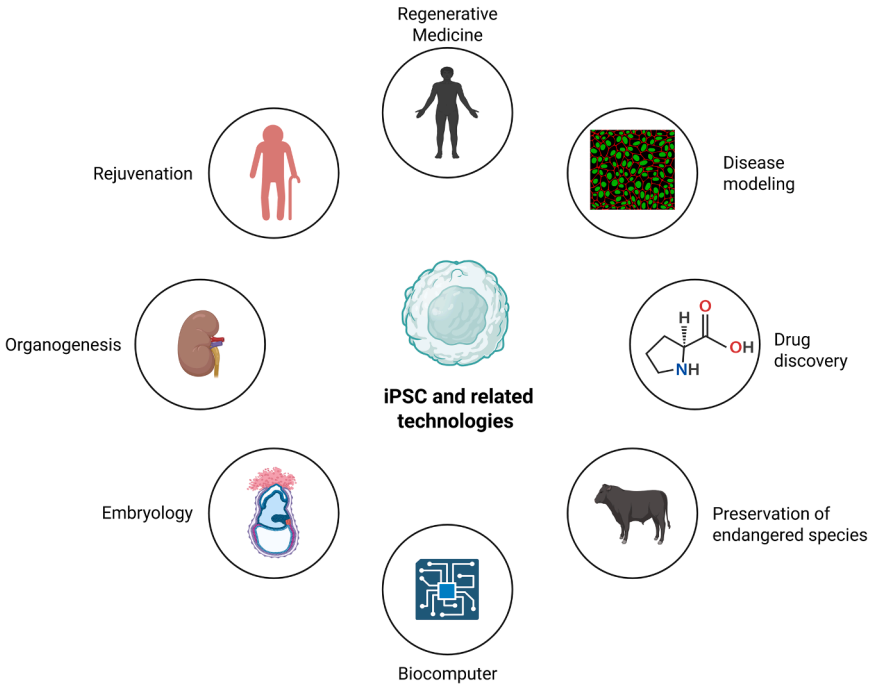

Figure 3. Diverse applications of iPSC and related technologies
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Genetically matched comparisons indicate that human ESCs and iPSCs are largely molecularly and functionally equivalent, and genetic background is a major confounder in apparent differences.[53] Nonetheless, line-to-line variability and incomplete reprogramming events—particularly at specific epigenetic features such as imprinting, X chromosome state, and higher-order genome programs—can influence phenotypes in a context-dependent manner.[54]

Achieving mature cell types from iPSCs and ESCs was one of the early bottlenecks in the field. Initial differentiation protocols yielded cells that resembled fetal rather than adult tissues.[55] Over time, advances in developmental biology enabled the creation of stepwise protocols that recapitulate embryonic signaling pathways with increasing precision.[56,57] Organoid technologies further improved differentiation outcomes by providing 3D contexts that mimic *in vivo* microenvironments.[58]

Today, iPSC-derived cardiomyocytes exhibit more matured phenotypes,[59,60] vascularized and functional liver tissue can be generated from human iPSC-derived organoid buds,[61] and iPSC-derived neurons form functional synaptic networks.[62] While perfect adult-like maturation remains a frontier, the field has progressed from proof-of-principle demonstrations to highly sophisticated cellular models.

One of the hallmarks of a mature field is the development of global standards.[63] The iPSC community embraced this necessity early, adopting pluripotency scorecards, standardized reporting frameworks, and guanosine monophosphate (GMP)-compatible workflows. International consortia now coordinate best practices to ensure that iPSC lines distributed across the world meet consistent benchmarks, such as the International Stem Cell Banking Initiative (ISCBI, https://www.iscbi.org/) and the Human Pluripotent Stem Cell Registry (https://hpscreg.eu/).

iPSC-BASED REGENERATIVE THERAPIES: FROM CONCEPTUAL PROMISE TO CLINICAL REALITY

Preclinical studies established that iPSC-derived cells could survive, integrate, and function within host tissues. In models of Parkinson's disease, transplanted dopaminergic neurons restored dopamine production and improved motor function.[64] In cardiac injury models, iPSC-derived cardiomyocytes synchronized with host myocardium.[65] Retinal pigment epithelium (RPE) cells derived from iPSCs demonstrated structural integration and photoreceptor support.[66]

These successes provided the justification needed to advance into first-in-human trials. The early iPSC-based trials, one for age-related macular degeneration[67] and the other for Parkinson's disease, demonstrated not only the feasibility but also the safety of autologous iPSC-derived grafts.[68] These trials highlighted the importance of meticulous manufacturing, long-term monitoring, and genomic screening—all elements that have since been incorporated into global clinical practice.

Following these early trials, clinical programs expanded rapidly. More than a hundred clinical trials have been conducted with iPSC and ESC.[69] Promising results of some of them have been published. Corneal epithelial cells offered new hope for treating blindness.[70] Dopaminergic progenitors entered trials for Parkinson's disease,[71,72] in which iPSC- and ESC-derived cells have thus far shown comparable safety profiles and encouraging signals of efficacy. Longer-term follow-up in larger patient cohorts will be required to establish durability, efficacy, and broad clinical feasibility.

While autologous therapies are conceptually appealing, they are slow and expensive to produce. The creation of human leukocyte antigen (HLA)-homozygous iPSC banks—collections of donor lines that match large portions of national populations—opened the door to scalable allogeneic therapies.[73] These cells can be prepared in advance, quality-tested, and stored for immediate clinical use. In parallel, immune engineering has produced "universal" iPSC lines with reduced immunogenicity, offering the possibility of truly off-the-shelf regenerative products.[74]

The clinical rise of iPSC therapy introduces ethical challenges that echo those seen with organ transplantation and genetic therapy but with unique nuances. Because iPSCs can be generated from any individual, issues of consent, privacy, and data governance take on heightened importance. Public engagement remains critical to maintaining trust as regenerative technologies become more powerful and more widely applied.

DISEASE MODELING AND DRUG DISCOVERY: HUMAN BIOLOGY IN A DISH

If regenerative therapies represent one pillar of iPSC science, disease modeling represents another—arguably the one with the broadest current impact.

Patient-specific iPSC models have enabled the study of diseases previously inaccessible due to the difficulty of obtaining primary human tissues. Amyotrophic lateral screrosis (ALS),[75] spinal muscular atrophy (SMA),[76] and Parkinson's disease[77] models exhibited hallmark neuronal degeneration. Long-QT syndrome cardiomyocytes displayed the electrophysiological signatures associated with arrhythmia risk.[78] These early successes demonstrated that iPSC-derived cells could recapitulate meaningful disease phenotypes. The outcomes of early-phase clinical trials support the potential of iPSC-based approaches for drug discovery, particularly drug repurposing.[79,80]

The field quickly moved beyond monogenic diseases. Psychiatric conditions such as schizophrenia,[81] bipolar disorder,[82] and autism[83] have been modeled using iPSC-derived neural cultures and organoids, revealing subtle differences in synaptic formation, network activity, and developmental trajectories. Complex cardiac diseases,[84] metabolic disorders,[85,86] and immune dysfunctions[87] have all been explored using similar approaches.

Organoids introduced a new dimensionality to disease modeling. Following the pioneering work in retinal organoids by the Sasai group,[58] other groups developed brain organoids that replicate aspects of cortical layering and neuronal migration,[88] and kidney[89] and intestinal[90] organoids that provide platforms to study cystic disease, infection, and epithelial dysfunction. The fusion of organoids into assembloids has enabled the study of long-range interactions, such as interneuron migration from the ventral forebrain into the cortex.[91,92]

The integration of iPSCs with CRISPR genome editing revolutionized causal inference.[93] By comparing isogenic pairs that differ only by a single pathogenic variant, researchers can identify the direct consequences of genetic lesions without confounding background variation. This strategy has clarified mechanisms underlying diverse disorders, including cardiomyopathies, autism spectrum disorders, and metabolic diseases.[94]

iPSC-derived tissues now serve as platforms for drug discovery and safety testing. Cardiomyocytes can predict arrhythmogenic potential,[95] hepatocytes assess metabolic and toxic responses,[96] and neural cultures provide information about neurotoxicity.[97,98] During emerging infectious disease outbreaks, iPSC-derived tissues have provided windows into viral tropism and host response.[99,100]

Large iPSC biobanks that include donors from diverse ancestries are critical for capturing the full spectrum of human genetic variation. Existing repositories show a strong European-ancestry bias, highlighting the need for broader representation to support equitable discovery.[101] Studies using large iPSC cohorts demonstrate that inherited variants shape cellular phenotypes, including gene regulation and stress responses.[102] Since genetic background influences therapeutic response, diverse iPSC biobanks provide essential infrastructure for advancing personalized medicine and human functional genomics.

THE EXPANDING HORIZONS OF iPSC SCIENCE

Though often associated with therapy and modeling, iPSCs have influenced a surprising range of scientific domains (Figure 2).

iPSCs derived from endangered species offer tools for preserving genetic diversity and studying developmental trajectories in organisms where experimental work is otherwise impossible.[103] Comparative studies using primate iPSCs have revealed species-specific differences in early neurodevelopment, synaptic maturation, and immune responses.[104]

Gastruloids and blastoids recreate early developmental events that are otherwise inaccessible in humans.[105] These models have clarified mechanisms of gastrulation, axis specification, and germ-layer formation. *In vitro* gametogenesis extends iPSC applications into reproductive biology, allowing investigation of fertility pathways and potential future treatments for infertility.[106]

Recent work coupling iPSC-derived neuronal networks with electronic systems has produced hybrid constructs capable of learning patterns, responding to stimuli, and adapting behavior.[107,108] These systems challenge conventional distinctions between biological and artificial intelligence, raising profound questions about computation, cognition, and the ethical limits of engineered living systems.

It is also fair to say that the discovery of reprogramming to pluripotency helped foster the development of direct lineage reprogramming. Demonstrating that defined transcription factors could override a stable somatic identity fundamentally changed how the field viewed cell fate, opening the door to the idea that one differentiated state could be converted directly into another. Subsequent work on induced neurons,[109] cardiomyocytes,[110] and other lineages built on conceptual and technical foundations established during iPSC research, even as these approaches followed distinct mechanistic routes.

Perhaps one of the most provocative frontiers is the field of rejuvenation biology. Partial reprogramming—transient exposure to OSKM or modified factor variants—offers a way to reset epigenetic age without fully erasing cellular identity. Early studies in animal models suggest that such approaches can restore metabolic resilience, reverse molecular markers of aging, and improve tissue function.[111,112] If these findings translate safely to human cells and tissues, partial reprogramming may help address age-associated diseases not by treating symptoms but by restoring youthful cellular states. The implications for public health, longevity, and chronic disease management are profound, and they invite careful consideration of both therapeutic promise and potential risks, such as tumorigenicity.

Another provocative extension of iPSC technology is interspecies organogenesis, which seeks to generate human organs in large animal hosts such as pigs via blastocyst complementation.[113] Advances in naive pluripotent states may enable human iPSC contribution in pig and sheep embryos.[114] Although major biological and ethical challenges remain, continued progress in genome engineering and developmental control sustains interest in this approach as a potential strategy to address organ shortages.

OUTLOOK: THE NEXT 20 YEARS

As the iPSC field enters its third decade, the boundaries between stem cell biology, computation, synthetic biology, and translational medicine are dissolving. The next era will be defined not simply by incremental refinements to reprogramming or differentiation protocols, but by a deeper integration of disciplines that traditionally developed separately. At the center of this convergence lies a simple but profound question: if we can control cell identity, can we also predict, design, and perhaps even optimize it?

One of the most transformative developments on the horizon is the integration of artificial intelligence into stem cell biology. Multi-omic datasets now capture the transcriptional, epigenetic, metabolic, and structural states of cells at unprecedented resolution. These datasets are too complex for intuition alone, but AI-driven models trained on them are beginning to uncover hidden patterns in fate decisions. Such systems may soon predict which cells are most amenable to reprogramming, identify the earliest molecular signatures of successful transitions, or even propose synthetic routes that bypass classical transcription-factor combinations. Instead of discovering reprogramming factors through trial and error, researchers may one day simulate reprogramming landscapes *in silico*, testing thousands of hypothetical factor combinations before validating the most promising candidates *in vitro*.

Synthetic biology is poised to reshape the field just as dramatically. Advances in programmable transcription factors, CRISPR-based epigenetic modifiers, and synthetic gene circuits allow increasingly precise manipulation of cell identity. It is not difficult to imagine pluripotency programs that can be turned on and off with small molecules or differentiation protocols guided by engineered feedback loops that sense and correct deviations in real time. Safety circuits may prevent uncontrolled growth, while synthetic enhancers could stabilize lineage commitment in tissues that historically have been difficult to differentiate. These innovations foreshadow a future in which the behavior of stem cells is not merely observed or nudged but designed.

Biomanufacturing—the often underappreciated backbone of translational cell therapy—will also undergo profound changes. Closed-system, automated culture platforms will reduce variability, increase scalability, and enhance safety. These systems will allow continuous monitoring of pluripotency markers, metabolic state, and genomic integrity, transforming cell production from an artisanal process into an industrial one. Universal donor cells, engineered to evade immune rejection, may drastically expand access to regenerative therapies, shifting clinical practice from bespoke treatments toward readily deployable off-the-shelf solutions. Alternatively, the closed and automated system may enable the generation of autologous iPSC for each patient at a reasonable cost and time. Depending on the types of cells to be transplanted and the immunological and systemic conditions of patients, autologous iPSCs may be required.

These scientific advances carry ethical, social, and philosophical implications. As iPSC-derived systems begin to encroach on aspects of early human development, reproduction, cognition, and environmental stewardship, society will be forced to confront questions that extend beyond conventional bioethics. Synthetic embryoid models challenge our definitions of developmental boundaries. *In vitro* gametogenesis raises questions about parenthood, inheritance, and reproductive autonomy. Biohybrid systems that couple neurons to computational hardware may provoke new debates about consciousness, learning, and the moral status of engineered biological networks. Even conservation biology—where iPSCs could aid in de-extinction efforts or the rescue of endangered species—raises questions about ecological responsibility and the long-term consequences of human intervention.

Navigating these questions requires not only scientific expertise but also sustained public dialogue, transparent regulatory frameworks, and a commitment to global equity. Access to regenerative therapies must not be limited to those with financial means or proximity to advanced medical centers. Likewise, international standards will be necessary to govern the creation, sharing, and therapeutic use of iPSC-derived materials.

In many ways, the story of iPSCs is emblematic of modern science: a testament to the power of curiosity-driven inquiry, interdisciplinary collaboration, and the willingness to challenge entrenched assumptions. What began as an unexpected observation in a single laboratory has reshaped the contours of biology and medicine. If the past 20 years revealed that barriers between cell fates are more permeable than once imagined, the next 20 years will show that the boundaries between biology, technology, and society are equally fluid. The challenge ahead is to harness this emerging potential with imagination, caution, and a sense of shared responsibility for the world we are creating.

Advances in robotics, AI, and machine learning will increasingly automate experimentation and accelerate data analysis, fundamentally changing the daily workflow of scientists. Nevertheless, transformative discoveries will continue to rely on human curiosity, intuition, and the willingness to pursue unconventional ideas, with technology serving as a powerful amplifier rather than a substitute for creative experimental thinking.

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DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the author used ChatGPT in order to collect citations and refine language. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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