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*CORRESPONDENCE
Fahmi Achmad Darojat,
fahmiayakina@gmail.com

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iPSC-Derived Biological Microrobots for Targeted Cancer Therapy: A Conceptual and Translational Framework

Fahmi Achmad Darojat[1*], Lubna Fatiha Moh[2]

[12]Walisongo State Islamic University, Central Java, Indonesia

Abstract

Targeted delivery remains a major challenge in cancer therapy, particularly in solid tumors and metastatic disease, where chemotherapy, radiotherapy, and surgery are limited by systemic toxicity and poor tumor specificity. Induced pluripotent stem cell (iPSC) technology has emerged as a promising platform for generating engineered immune effector cells due to its unlimited expansion capacity and susceptibility to precise genetic modification. iPSC-derived engineered cells can be conceptually framed as biological microrobots — a functional framework rather than a literal mechanical description — based on their capacity for tumor-directed migration, environmental sensing, programmable anti-tumor activity, and controllable therapeutic responses. This study evaluates iPSC-derived engineered cells as biological microrobots for targeted cancer therapy, integrating iPSC engineering, gene editing, and biorobotics principles within a unified translational framework. A systematic literature review following PRISMA 2020 guidelines was conducted using Scopus and PubMed with predefined keywords, independent dual-reviewer screening, and standardized quality appraisal. Of 329 identified records, 30 met eligibility criteria and were included in the qualitative synthesis. Key iPSC-derived microrobot archetypes identified include CAR-engineered iNK cells with IL-15/IL-21 cytokine armoring, iNPC carriers for oncolytic virus delivery, and NKG2D-CAR-functionalized iMSCs with enhanced tumor-homing ability. The evidence suggests promising translational potential for iPSC-derived biological microrobot systems; however, current data remain predominantly preclinical, and challenges related to safety, scalability, regulatory translation, and long-term in vivo behavior must still be addressed.

KEYWORDS

Induced pluripotent stem cells; biological microrobots; cancer therapy; targeted therapy

Introduction

Cancer remains one of the most complex and devastating diseases in modern medicine and is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2022 (World Health Organization, 2026). Despite progress in surgical oncology, chemotherapy, and radiotherapy, major limitations remain, including systemic toxicity, drug resistance, immunosuppression within the tumor microenvironment (TME), and limited ability to penetrate solid tumors (Martín-Antonio et al., 2024). In recent years, cellular immunotherapy has emerged as a major development, particularly chimeric antigen receptor T (CAR-T) cell therapy, which has shown strong results in hematological cancers. However, its effectiveness in solid tumors is still limited. This is mainly due to antigen heterogeneity, physical barriers in the TME, side effects such as cytokine release syndrome (CRS), and the high cost of autologous manufacturing (Goldenson et al., 2022). Because of these

challenges, alternative immune-based strategies are being explored, including the use of induced pluripotent stem cell (iPSC)-derived immune cells.

Induced pluripotent stem cells were first described by Shinya Yamanaka in 2006 and are generated by reprogramming somatic cells into a pluripotent state. These cells can self-renew and differentiate into multiple cell types(Bae et al., 2025; Baik et al., 2023) (Q. Li et al., 2025). In the context of cancer therapy, iPSCs offer several advantages. They can be expanded in large numbers, genetically modified with high precision before differentiation, and engineered for immune compatibility in allogeneic "off-the-shelf" applications (Haider, 2024). In addition, they can be used to generate standardized populations of immune effector cells, such as natural killer (NK) cells, T cells, macrophages, and dendritic cells, with controlled and programmable functions (Kaufman, 2022; Takahashi, 2023).

A different way to understand these cells is to view them through the concept of biological microrobotics. In this study, the term "biological microrobot" refers to engineered living cells capable of autonomous tumor-directed migration, molecular sensing of the surrounding environment, controlled therapeutic actuation, and targeted payload delivery. Unlike mechanical microrobots, these systems rely on intrinsic biological mechanisms such as chemokine-guided migration, receptor-mediated recognition, and programmable cytotoxic responses.

In this context, therapeutic cells are considered active biological systems that can move, sense their environment, and respond in a targeted manner. iPSC-derived effector cells, especially when genetically engineered, can be designed to home to tumor sites, respond to local molecular signals, and deliver cytotoxic effects. This allows them to function as "living biological microrobots" operating within the body (Q. Hu et al., 2025; B. Xu et al., 2025).

Based on this perspective, the present systematic literature review aims to synthesize current evidence on iPSC-derived biological microrobots for cancer therapy. Previous reviews have primarily discussed iPSC-derived immunotherapy, gene editing, or engineered cell therapy as separate topics. However, limited literature has integrated these approaches within a unified biorobotics framework that links cellular behavior with microrobot-like functions such as navigation, sensing, actuation, payload delivery, and safety control. This study addresses that gap by organizing current evidence according to functional biological microrobot archetypes while also evaluating translational, manufacturing, and safety challenges. By integrating concepts from stem cell biology, immunotherapy, gene editing, and biorobotics, this study proposes a conceptual and translational framework for future clinical development.

Comparison with Previous Reviews and Novel Contribution of the Present Study

Several recent reviews have examined iPSC-derived therapies for cancer, yet each has maintained a relatively narrow disciplinary scope. Goldenson et al. (2022) provided a comprehensive overview of iPSC-derived NK cell expansion and targeting strategies, focusing primarily on hematological malignancies. Xu et al. (2025) reviewed gene editing strategies for CAR-NK cell therapy, emphasizing immunological barrier reduction. J. Chen et al., (2023) discussed iPSC-derived immune cell therapies broadly but did not integrate these platforms within a functional systems framework. Kaufman (2022) highlighted the manufacturing advantages of iPSC-derived NK cells for off-the-shelf applications, while X. Li et al., (2024) and Y. Hu et al., (2026) reported preclinical efficacy data for engineered iNK cells without situating their findings within a broader microrobotic paradigm.

The limitations of these previous reviews are threefold. First, they typically treat iPSC biology, gene editing, and cell-based immunotherapy as separate domains rather than as integrated components of a unified therapeutic system. Second, none have explicitly framed iPSC-derived effector cells as biological microrobots—that is, programmable living systems capable of autonomous navigation, environmental sensing, and targeted actuation. Third, existing reviews have not systematically organized evidence according to functional microrobot archetypes (iNK, iT/iCAR-T, iMSC, iNPC, iMac), making it difficult to compare engineering strategies and translational readiness across platforms.

The present review addresses these gaps through both conceptual and methodological innovations. Conceptually, this study integrates principles from stem cell biology, immunotherapy, gene editing, and biorobotics into a single translational framework. By framing iPSC-derived cells as biological microrobots, we emphasize their functional capabilities—locomotion, sensing, actuation, and payload delivery—rather than treating them merely as passive therapeutic agents. Methodologically, this review employs a systematic PRISMA 2020 approach with predefined quality appraisal, enabling evidence-based comparison across distinct iPSC effector archetypes. This integration allows us to evaluate not only whether these platforms work, but how they function as coordinated therapeutic systems within the tumor microenvironment. To further illustrate the distinctions between previous reviews and the present study, a concise comparison is provided in Table 1.

Table 1. Comparison with Previous Reviews

Review	Primary Focus	iPSC Platforms Covered	Gene Editing Discussed	Biorobotics Framework	Key Limitation
Goldenson et al. (2022)	iNK expansion & targeting	iNK only	Limited	No	Narrow platform scope
X. Xu & others, (2024)	Gene editing for CAR-NK	iNK only	Extensive	No	Platform-specific
(G. Chen, 2025)	iPSC immune cell therapies	Multiple	Moderate	No	Descriptive, non-integrative
Kaufman (2022)	Off-the shelf iNK manufacturing	iNK only	Minimal	No	Manufacturing focus only

J. Li et al., (2025)	Preclinical iNK efficacy	iNK only	Moderate	No	Single-platform evidence
Hu et al. (2026)	Multi-gene engineered iNK	iNK only	Extensive	No	No comparative framework
Presnt Review	Integrated microrobot framework	iNK, iT, iMSC, iNPC, iMac	Systematic	Yes (core concept)	Preclinical evidence predominance

Methods

Research Type

This systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). An internal review protocol was prepared prior to the study, outlining the eligibility criteria, search strategy, study selection process, data extraction procedures, and quality appraisal methods. The protocol was not formally registered in PROSPERO or the Open Science Framework (OSF). Formal registration was not performed because the review was conducted as an independent academic study. A PRISMA flow diagram and checklist were used to document and report the study selection process and ensure methodological transparency.

Population and Sample/Informants

Studies were included based on the following Population, Intervention, Comparator, Outcome, and Study design (PICOS) framework: (P) cancer cell lines, animal tumor models, or human patients with malignancies; (I) iPSC-derived biological effector cells, including iNK cells, iT cells, iMSCs, iNPCs, or engineered constructs, applied as tumor-targeted therapies; (C) conventional therapies, parental non-iPSC cell lines, or untreated controls;

(O) anti-tumor cytotoxicity, tumor regression, cell homing, persistence, safety profiles, and translational feasibility; and (S) original research articles and preclinical translational studies published in peer-reviewed Scopus- or PubMed-indexed journals between January 2018 and April 2026.

Systematic reviews, meta-analyses, and narrative reviews were used only to provide background information and support conceptual interpretation and were not included as primary therapeutic evidence in the qualitative synthesis.

Studies published in English were included. Exclusion criteria included single case reports, conference abstracts lacking full-text data, review articles without primary data synthesis, studies examining iPSCs exclusively for non-oncological applications without translational oncology relevance, and articles with insufficient methodological or outcome data.

Research Location

The study was conducted through database-based research using international electronic databases, primarily Scopus and PubMed.

Instrumentation or Tools

Quality assessment was performed using appropriate Critical Appraisal Skills Programme (CASP) checklists according to study design and the Cochrane Risk of Bias tool for randomized controlled trials. An adapted CASP scoring approach was used for summary purposes, whereby studies meeting a greater number of appraisal criteria were categorized as high (8–10), moderate (5–7), or low quality (<5). Risk-of-bias assessment was conducted to evaluate methodological rigor and identify potential sources of bias that could influence interpretation of the findings. A summary table of quality assessment results was prepared and used to guide interpretation of study strengths, limitations, and overall evidence quality during qualitative synthesis. The included studies demonstrated methodological quality ranging from moderate to high (scores ≥5). Of the 30 studies included in the qualitative synthesis, 22 were classified as high quality (CASP score 8–10) and 8 as moderate quality (CASP score 5–7); no studies were classified as low quality. Study quality was considered during evidence synthesis and interpretation, with findings from higher-quality studies given greater evidentiary weight when drawing overall conclusions. Detailed quality assessment outcomes for individual primary studies are provided in Supplementary Table S1. A standardized data extraction form was used to systematically record study characteristics, intervention details, outcome measures, and key findings.

Data Collection Procedures

Electronic database searches were conducted in Scopus and PubMed on April 23, 2026. The search covered studies published between January 2018 and April 2026 and was limited to English-language publications. Complete search strategies for each database are provided in the Appendix.

The search string for Scopus was: TITLE-ABS-KEY ("induced pluripotent stem cell*" OR "iPSC*") AND ("cancer therapy*" OR "tumor target*" OR "CAR-NK" OR "oncolytic" OR "biological microrobot" OR "natural killer" OR "solid tumor" OR "immunotherapy*" OR "drug delivery*"), resulting in 242 records.

The PubMed search used equivalent Medical Subject Headings (MeSH) and keywords: ("Induced Pluripotent Stem Cells"[MeSH]) AND ("Neoplasms/therapy"[MeSH] OR "Immunotherapy, Adoptive"[MeSH] OR "Natural Killer Cells"[MeSH]), resulting in 87 records.

A total of 329 records were identified across both databases. Duplicate articles were removed prior to screening, resulting in 276 records for title and abstract assessment. Title and abstract screening were conducted independently by two reviewers according to predefined inclusion and exclusion criteria. Discrepancies in study selection were resolved through discussion and consensus. Following screening, 89 articles underwent full-text eligibility assessment. Of these, 49 studies were excluded due to a non-oncology focus or insufficient outcome data. The remaining studies underwent quality and relevance assessment, resulting in 30 studies meeting the predefined inclusion criteria and being included in the qualitative synthesis.

Data Analysis

Data extracted from each study included author,

publication year, study design, iPSC source, differentiation protocol, engineering strategy, cancer model, primary outcomes, safety data, and translational readiness level (TRL). Due to heterogeneity in study design, cancer models, and outcome measures, a quantitative meta-analysis was not performed. Instead, a qualitative narrative synthesis was conducted. Studies were thematically organized according to iPSC effector archetypes: (i) iNK cell platforms, (ii) iT cell and CAR-T platforms, (iii) iMSC delivery systems, (iv) iNPC oncolytic virus carriers, and (v) iPSC-derived macrophage platforms. Within each category, findings were analyzed with attention to engineering strategies, therapeutic efficacy, safety profiles, and translational potential.

Table 2. Summary of Quality Assessment Results of Included Studies

Study category	Number of studies (n)	CASP criteria assessed	Final score	Main methodological strengths	Main methodological limitations	Impact on interpretati on
Original research studies (primary evidence)	22	Objectives, methodology, validity, outcomes, bias	8-10	Clear experimental objectives, defined engineering strategies, measurable therapeutic outcomes	Small sample sizes and limited long-term validation	Findings interpreted as supportive but requiring further validation
Preclinical translationa l studies (primary evidence)	5	Objectives, methodology, animal model validity, outcomes, bias	6-8	Use of animal models and efficacy assessment	Limited randomization/ b linding and uncertain human applicability	Findings interpreted cautiously due to translational limitations
Contextual/ backgroun d studies	3	Relevance to review objectives, comprehensiv eness of literature synthesis, methodologic al transparency	5-7	Broad overview of emerging technologies, translational challenges, and future directions	Limited original experimental data and reliance on secondary interpretation	Used to contextualiz e and support discussion of findings rather than provide direct therapeutic evidence

Result and Discussion

Search Results and Study Characteristics.

The database search yielded 242 records from Scopus and 87 records from PubMed, resulting in a total of 329 records. Following the removal of 53 duplicate records, 276 unique articles remained for title and abstract screening. Of these, 187 articles were excluded for being outside the scope of the review or otherwise irrelevant to the research objectives, leaving 89 articles for full-text eligibility assessment. Following full-text review, 49 articles were excluded due to a non-oncology focus or insufficient data. The remaining studies underwent quality and relevance assessment, resulting in 30 studies meeting the predefined inclusion criteria and included in the qualitative synthesis. The study selection process is summarized in the PRISMA 2020 flow diagram (Figure 1).

Thirty studies were included in the qualitative synthesis. Of these, 22 were original research articles (in vitro and/or in vivo preclinical studies) and 5 were preclinical translational studies, which together constituted the primary evidence base for efficacy claims. Three additional studies provided contextual background and were used to support interpretation of findings rather than direct therapeutic conclusions. Methodological references, including PRISMA 2020 guidelines, quality appraisal frameworks, and epidemiological sources, were cited separately to support review methodology and background context and were not included in the qualitative synthesis. Study-level quality assessment results are presented in Supplementary Table S1. Overall, most included studies were rated as high quality, with the remainder rated as moderate quality and no studies classified as low quality. No publications from 2018 met the inclusion criteria; included publications spanned 2019–2026, with 78% published between 2022 and 2026, reflecting growing research activity in this domain. Studies were published in journals including Science Advances, Trends in Biotechnology, Nature Communications, STEM CELLS Translational Medicine, and Critical Reviews in Oncology/Hematology. A summary of the included primary studies is presented in Table 2.

iPSC-Derived Natural Killer (iNK) Cells as Biological Microrobots: Differentiation and Engineering Approaches

Among the different iPSC-derived platforms, natural killer (NK) cells represent the most developed model for use as biological microrobots in cancer therapy. This is supported by a relatively large body of preclinical

studies, along with emerging early-phase clinical data. The differentiation of iPSCs into functional NK cells.

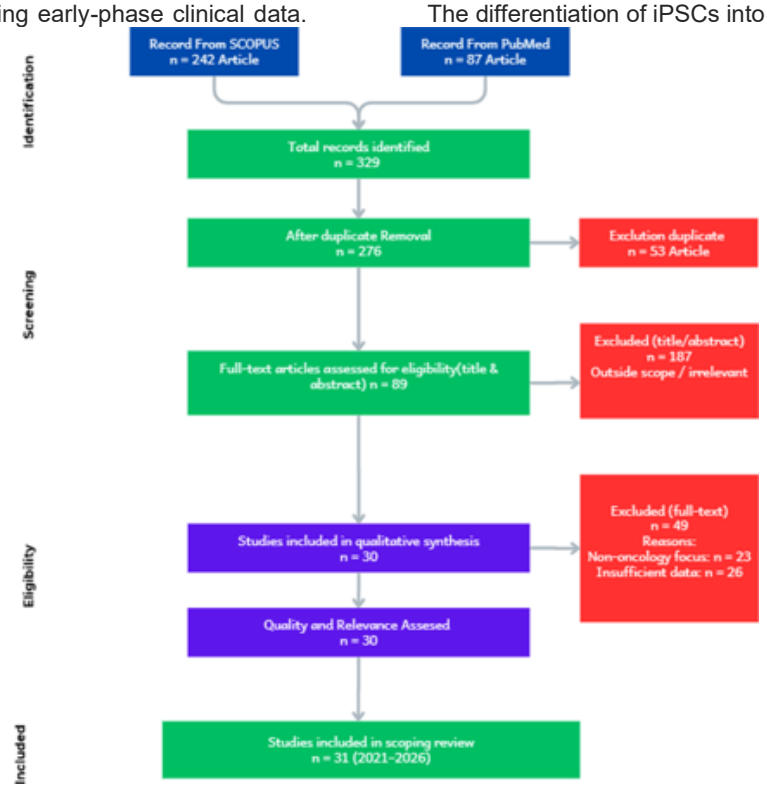

Figure 1. PRISMA 2020 flow diagram of study selection process

Table 3. CRISPR Gene Editing Strategies as the Programming Interface of iPSC Biological Microrobots

Editing Target	CRISPR Tool	Microrobot Module	Effect	Reference
CAR transgene (AAVS1)	CRISPR-Cas9 / AsCas12a Ultra	Navigation / recognition	Stable clonal expression; ~100% efficiency	Zetsche & others, (2021)
B2M knockout	CRISPR-Cas9	Immune evasion (T-cell)	HLA-I loss; host T-cell recognition blocked	Xu et al., 2025
HLA-E overexpression	CRISPR activation	Immune evasion (NK)	Missing-self restored; NK rejection blocked	Xu et al., 2025
CD47 overexpression	CRISPR activation	Immune evasion (macrophage)	Don't eat me' signal; phagocytosis inhibited	Xu et al., 2025
TIGIT deletion	CRISPR-Cas9	Enhanced cytotoxicity	Restored NK activation in immunosuppressive TME	Xu et al., 2025
IL-15 knock-in	HDR template	Cytokine armoring / persistence	Autocrine survival; improved in vivo longevity	Li et al., 2025
iCasp9 / HSV-TK	Lentiviral / HDR	Safety switch	Selective elimination on dimerizer/prodrug trigger	Bhatt & Bhatt, 2022
CISH / TGFBR2 KO	CRISPR-Cas9 dual KO	TME resistance	Effector function preserved in hypoxic TGF-β milieu	Li et al., 2025

typically follows several hematopoietic stages, including hemangioblasts, hematopoietic progenitors, and NK progenitors, under specific cytokine and feeder conditions (Kaufman, 2022; Goldenson et al., 2022). One advantage of the iPSC platform is that genetic modification can be introduced at the undifferentiated stage, allowing the generation of clonal cell populations with more consistent and controlled functional properties Li et al. (2025) demonstrated that the LiPSC-GR1.1 line, engineered with a mesothelin (MSLN)-targeting CAR and IL-15, differentiated into activated iNK cells with improved tumor-killing capacity, enhanced chemokine-directed migration, and sustained proliferation in vitro. Single-cell transcriptomic analysis revealed high expression of NK activation markers and low levels of exhaustion-associated genes (CISH, TGFBR2, BATF). Importantly, these cells maintained metabolic activity under hypoxic and TGF-β-rich TME conditions, fulfilling the sensing and persistence criteria of the biological microrobot framework (Science Advances, 2025). These findings derive from in vitro and CDX models; validation in humanized immune system models remains an important next step.

Hu et al. (2026) engineered a five-gene-modified iPSC-NK construct incorporating CCL19 (T-cell recruitment), CCR2B (tumor homing), high-affinity CD16 (ADCC enhancement), IL-15 (persistence), and the NKG2D-DAP10 signaling complex. In vitro, sustained cytotoxic activity was demonstrated across lung cancer cell lines. In vivo, near-

complete tumor regression was observed in orthotopic and subcutaneous CDX models (n = 8/group, p < 0.01 vs. control). In PDX models, tumor growth inhibition reached 28% as monotherapy and 53% in combination with cetuximab (Cancer Immunology, 2026). These results are promising but require confirmation in larger animal models and immune-competent settings.

iPSC-Derived Natural Killer (iNK) Cells as Biological Microrobots: Immune Evasion Strategies

One of the main challenges in using allogeneic iPSC-derived cells is their susceptibility to immune rejection by the host. This can occur through both T-cell–mediated recognition of major histocompatibility complex (MHC) molecules and NK cell–mediated "missing self" recognition. To address this, recent studies have focused on multiplex gene engineering approaches to reduce immunogenicity while preserving anti-tumor function.

Several strategies have been consistently reported. Knockout of β2-microglobulin (B2M), combined with overexpression of HLA-E, can reduce recognition by both T cells and NK cells. In addition, overexpression of CD47 provides a "don't eat me" signal that helps protect the cells from macrophage-mediated phagocytosis. Deletion of inhibitory receptors such as TIGIT has also been shown to enhance cytotoxic activity. Together, these modifications contribute to the development of so-called "universal" or hypoimmunogenic iPSC-derived NK cell platforms (J. Xu et al., 2022).

Advances in CRISPR technology have enabled multiplex implementation of these strategies. The AsCas12a Ultra nuclease (Zetsche et al., 2021) achieved editing efficiencies approaching 100% at targeted loci in the LiPSC-GR1.1 iPSC line under specific delivery conditions, with multiplex editing of multiple genes exceeding 90% and transgene knock-in rates reaching up to 60%. These efficiencies are locus-, line-, and delivery-method-dependent and should not be generalized across all iPSC backgrounds. Off-target editing rates and long-term genomic stability require dedicated safety evaluation in each new construct. This level of precision nonetheless enables combining immune evasion with CAR expression in a single clonal iPSC line (Nature Communications, 2021).

iPSC-Derived Natural Killer (iNK) Cells as Biological Microrobots: Clinical and Translational Evidence

Clinical data on iPSC-derived therapies are limited but growing. A scoping review identified 10 published clinical studies and 22 ongoing registered trials involving iPSC-derived products across cardiac, ocular, cancer, and GvHD indications, involving 115 total patients treated to date. Of these, cancer-specific iPSC-derived immunotherapy trials are the most advanced category (Goldenson et al., 2022). It should be noted that a significant portion of these trials involve non-NK cell iPSC products; the cancer-specific iPSC-NK trial data are derived primarily from Phase I studies.

CAR-NK therapy (including iPSC-derived and cord blood-derived NK platforms) has shown remission rates of up to 73–83% in lymphoma patients in early clinical studies. The specific iPSC-derived NK contribution to this clinical evidence base requires clarification, as some cited trials used cord blood-derived NK cells rather than iPSC-NK. These findings provide initial proof-of-concept for allogeneic NK cell-based immunotherapy but should be interpreted with caution regarding iPSC-specificity (Critical Reviews in Oncology/Hematology, 2025).

iPSC-Derived Neural Progenitor Cells (iNPCs) as Oncolytic Virus Carriers: Tumor-Tropic Delivery Function

Neural progenitor cells (NPCs) are known for their natural ability to migrate toward tumor sites, particularly in the central nervous system. This tumor-homing property makes them useful as delivery vehicles in cancer therapy (Uwishema et al., 2025). In this context, iPSC-derived NPCs have been explored as carriers for oncolytic viruses, with the aim of improving viral distribution within tumors compared to direct administration.

Chen et al. (2025) investigated the use of the CF17 oncolytic virus delivered either alone or through human pluripotent stem cell-derived NPC carriers. In vitro, both approaches showed inhibitory effects on glioblastoma stem cells (GSCs). However, in vivo results demonstrated clearer advantages when NPCs were used as carriers. Mouse models treated with NPC-delivered CF17-GFP showed better tumor targeting, a greater reduction in tumor cell numbers, and longer survival compared to direct viral injection alone (Oncotarget, 2025).

This approach is often described as a "Trojan horse" strategy, where cells are used to transport therapeutic agents directly into the tumor microenvironment. Similar concepts have been reported in studies using mesenchymal stem cells (MSCs) as viral carriers (Gabashvili et al., 2021). Overall, these findings highlight how iPSC-derived NPCs can function as active delivery systems, supporting their role as biological microrobots in targeted cancer therapy.

iPSC-Derived Mesenchymal Stem Cells (iMSCs): Enhanced Tumor Homing via NKG2D-CAR Engineering

iPSC-derived MSCs offer advantages over primary bone marrow MSCs, including greater phenotypic uniformity, non-invasive sourcing, large-scale expansion capacity, and flexible genetic modification. Li et al. (2025) developed NKG2D-CAR-modified iPSCs by inserting the NKG2D extracellular domain as a CAR construct into the B2M locus, followed by differentiation into iMSCs. In vitro, these cells showed improved migration and adhesion toward NKG2D-ligand-expressing solid tumor cell lines, supported by RNA-seq data indicating upregulation of cell adhesion and migration genes. In an A549 xenograft model, NKG2D-CAR-iMSCs demonstrated a 57% increase in tumor homing compared to unmodified iMSCs, without evidence of ectopic tissue formation (Cell Research, 2025). Beyond surface engineering, iMSCs can modulate the tumor microenvironment through immunological mechanisms. iMSC-mediated suppression of NF-κB signaling has been shown to influence macrophage polarization toward anti-inflammatory phenotypes in preclinical models (Stem Cell Research & Therapy, 2025). This dual function — targeted homing combined with TME modulation — supports the conceptualization of iMSCs as multi-functional biological microrobots. Evidence from non-cancer (inflammatory bowel and periodontal) models is noted but excluded from direct cancer efficacy claims.

iPSC-Derived T Cells, CAR Platforms, and Hypoimmunogenic Strategies

CAR-T cell therapy faces limitations in manufacturing scalability, cell exhaustion, and GvHD risk in allogeneic settings. iPSC-derived T cell platforms address these constraints by enabling stable genetic programming at the pluripotent stage. (L. Sun et al., 2025) developed human chemically reprogrammed iPSC-derived eosinophils (R-iEOs) that, when activated with TLR7/8 agonist R848, demonstrated enhanced anti-tumor activity, tumor site localization, and T-cell recruitment with reduced lung accumulation. In combination with CAR-T cells, R-iEOs produced superior tumor growth suppression in mouse models compared to monotherapy (Frontiers in Immunology, 2025). Because eosinophils represent a

functionally distinct iPSC-derived effector type, this evidence is presented as a distinct combinatorial modality rather than within the CAR-T subheading.

Wang et al. (2023) described hypoimmunogenic iPSC generation through B2M knockout, HLA-G1 overexpression, and CD47 upregulation, combined with CAR engineering and IL-15/NKG2D functional modules, to produce a universal "off-the-shelf" platform. This approach eliminates autologous manufacturing requirements, with potential implications for cost reduction and global accessibility (Chinese Medical Journal, 2023).

iPSC-Derived Macrophages as Phagocytic Microrobots

Macrophage-based therapies leverage natural tumor infiltration capacity and phagocytic function. True iPSC-derived macrophage (iMac) platforms engineered with chimeric antigen receptors (CAR-M) allow recognition of specific tumor antigens while retaining phagocytic activity, supporting their categorization as targeted anti-tumor effectors (Trends in Biotechnology, 2023).

R. Sun & others, (2024) described a distinct approach using direct reprogramming of fibroblasts into macrophage-like cells via c-Myc overexpression, bypassing an iPSC stage. Although this methodology does not involve iPSCs, it is included as background context for macrophage reprogramming principles. In leukemia, breast cancer, and PDX models, these cells demonstrated improved persistence and reduced tumor progression (Journal of Hematology & Oncology, 2024). iPSC-specific macrophage evidence remains limited and should be a priority for future primary research.

Extracellular vesicle (EV)-based cell-free systems derived from iPSC-MSCs represent an extension of the microrobot concept. These vesicles can be functionalized with aptamers, peptides, or tumor-specific antibodies, and exhibit lower immunogenicity compared to synthetic nanoparticles (Y. Xu et al., 2023).

Gene Editing as the Programming Interface of iPSC Biological Microrobots

Gene editing constitutes the core programming interface of iPSC-derived biological microrobots, enabling precise control of differentiation, environmental sensing, migration, and therapeutic actuation. CRISPR-Cas9, base editing, and prime editing permit simultaneous introduction of multiple functional modifications at the pluripotent stage.

Established strategies include: (1) CAR transgene insertion into genomic safe harbor sites (e.g., AAVS1) for stable expression; (2) multiplex knockout of immune checkpoints (TIGIT, PD-1, LAG-3) to maintain effector function under immunosuppressive TME conditions; (3) incorporation of safety switches (inducible caspase-9, HSV-TK) for controlled cell elimination; and (4) synthetic gene circuits that enable conditional therapeutic activation in response to tumor-specific signals such as hypoxia or tumor-associated antigens (Goldenson et al., 2022; Xu et al., 2025). The AsCas12a Ultra system has achieved near-100% single-locus efficiency with >90% multiplex editing in defined iPSC lines, enabling integration of multiple functional layers in a single clonal platform (Zetsche et al., 2021).

Safety Profile and Tumorigenicity Considerations

The primary safety concern for iPSC-derived systems is tumorigenicity from residual undifferentiated or partially differentiated cells forming teratomas post-transplantation. Mitigation strategies include stringent terminal differentiation protocols, removal of residual OCT4/NANOG-positive cells, and safety switch incorporation (iCasp9, HSV-TK). The PAR-4/ceramide apoptosis pathway selectively eliminates tumorigenic progenitors from NPC transplants (D. L. Bhatt & Bhatt, 2022).

Preclinical evidence supports acceptable safety profiles for appropriately engineered platforms. iNPC-GDNF constructs showed no tumor formation over 9 months in athymic nude rats (Limoli et al., 2023). NKG2D-CAR-iMSCs demonstrated tumor-selective homing without ectopic tissue formation in A549 xenograft models (Li et al., 2025). Compared to CAR-T cells, iPSC-derived NK cells carry lower CRS risk due to non-TCR-mediated mechanism and reduced GvHD potential (Kaufman, 2022; Xu et al., 2025). Comprehensive off-target cytotoxicity profiling and long-term engraftment monitoring remain critical requirements before clinical translation.

Interpretation of Key Findings

This study supports the conceptualization that induced pluripotent stem cell (iPSC)-derived cells can be conceptualized as biological microrobots based on their ability to perform core microrobotic functions, including locomotion, sensing, actuation, and navigation. In this framework, iPSC-derived effector cells exhibit autonomous migration through chemokine-mediated pathways, environmental sensing through receptor systems such as chimeric antigen receptors (CARs) and natural cytotoxicity receptors, and targeted actuation via cytotoxic mechanisms including perforin-granzyme release and cytokine secretion (Hu et al., 2025).

The tumor microenvironment (TME) functions as a complex operational environment that challenges the effectiveness of these biological systems. Factors such as hypoxia, immunosuppressive cytokines, and metabolic constraints require iPSC-derived cells to possess not only cytotoxic capacity but also adaptive and persistent functionality. Evidence from included studies demonstrates that engineered iPSC-derived cells, such as CAR-IL-15 iNK cells, are capable of maintaining functional stability even within highly suppressive TME conditions (Li et al., 2025). These findings support the concept that iPSC-derived cells can operate as programmable, autonomous therapeutic systems within complex biological environments.

Comparison with Previous Studies

The findings of this study are consistent with previous research demonstrating the therapeutic potential of iPSC-derived immune cells in cancer treatment, particularly in improving scalability and engineering precision compared to conventional autologous therapies (Goldenson et al., 2022). Prior studies have highlighted the limitations of CAR-T therapy, especially in solid tumors, due to manufacturing constraints and tumor microenvironment resistance. The current synthesis extends these findings by integrating iPSC biology with principles of biorobotics, providing a unified framework for understanding these cells as functional therapeutic systems rather than isolated biological tools.

In contrast to earlier studies that examined gene editing, iPSC-derived therapies, or cell-based immunotherapy independently, this study emphasizes their convergence. The integration of gene editing technologies, such as CRISPR-Cas systems, with iPSC platforms enables the design of multifunctional cells capable of immune evasion, targeted navigation, and controlled activation. This perspective aligns with emerging literature on synthetic immunology but advances it by explicitly framing these systems within a microrobotic paradigm.

Practical Implications

A defining practical implication of this review is that

iPSC-derived biological microrobots enable scalable, off-the-shelf manufacture from master cell banks, avoiding the patient-specific leukapheresis and weeks-long individualized production (and associated costs) required by autologous CAR-T therapies. Strategic HLA-matched iPSC banking—particularly using homozygous donor lines—can provide broad population coverage with a limited number of lines, improving global accessibility and lowering per-patient cost (AlZahrani et al., 2023; Shi et al., 2022; Wang et al., 2023). Producing therapeutics at the pluripotent stage also permits stable, multiplex genetic modifications to combine tumor-targeting constructs with immune-evasion features and safety switches in a controlled, standardized product, positioning iPSC-derived biological microrobots as a practical, next-generation precision oncology platform for both high-resource and resource-limited settings.

Limitations and Cautions

Despite the promising findings, several limitations should be acknowledged. First, formal inter-reviewer agreement statistics, such as Cohen's kappa coefficient or percentage agreement, were not calculated during the screening process. Although title and abstract screening were conducted independently by two reviewers and disagreements were resolved through discussion and consensus, the absence of a quantitative measure of reviewer agreement may limit methodological transparency.

Second, the majority of included studies are preclinical, relying on in vitro systems and animal models, which may not fully replicate human physiological conditions. As a result, the predictability of in vivo behavior, including migration patterns, persistence, and off-target effects, remains uncertain.

Third, heterogeneity in study design, cancer models, and outcome measures limits the ability to perform quantitative synthesis and may introduce variability in the reported results. Furthermore, safety concerns, particularly tumorigenicity and immune-related adverse effects, remain significant challenges. Although multiple studies report reduced tumorigenicity following differentiation and engineering, the risk cannot be completely eliminated.

Finally, regulatory and manufacturing complexities pose additional barriers to clinical translation. iPSC-derived therapies exist at the intersection of cell therapy, gene therapy, and biologically engineered systems, requiring the development of new regulatory frameworks and standardized production protocols ((Y. Liu et al., 2022; Z. Liu & others, 2025) et al., 2025).

Recommendations for Future Research

Future research should focus on advancing iPSC-derived biological microrobots toward clinical application. This includes the use of more representative preclinical models, such as large animal studies, to better evaluate safety and efficacy in physiologically relevant systems.

Further investigation is also needed to optimize gene editing strategies, particularly in improving precision, reducing off-target effects, and enabling more complex multifunctional programming. In addition, the development of standardized GMP-compliant manufacturing protocols will be essential to ensure consistency and scalability of therapeutic products.

Finally, long-term safety studies and ethical considerations should be prioritized, including monitoring of tumorigenicity, immune responses, and the long-term behavior of engrafted cells. Establishing clear regulatory guidelines and ethical frameworks will be critical for the responsible clinical implementation of these technologies.

Conclusion

This study examined the application of induced pluripotent stem cell (iPSC)-derived cells as biological microrobots for targeted cancer therapy, with the aim of evaluating their functional capabilities and translational potential. The evidence reviewed indicates that iPSC-derived systems are able to perform key therapeutic functions, including directed migration toward tumor sites, controlled cytotoxic activity, and sustained performance within the tumor microenvironment. Across multiple studies, platforms such as engineered iNK cells, iMSC-based carriers, and iNPC delivery systems demonstrate the ability to combine tumor targeting with programmable anti-tumor responses.

An important contribution of this work is the integration of iPSC biology, gene editing, and biorobotics into a single conceptual framework. Rather than being developed in isolation, these components can be understood as part of a coordinated system in which cells are engineered to sense, navigate, and respond to tumor environments in a controlled and adaptive manner.

This approach highlights the potential of iPSC-based therapies as scalable and adaptable tools for precision oncology. At the same time, several limitations remain, particularly the predominance of preclinical evidence, variability across experimental models, and ongoing concerns related to safety, tumorigenicity, and regulatory complexity.

Further research should prioritize clinical translation through the use of more representative in vivo models, refinement of gene editing strategies, and the development of standardized manufacturing and safety protocols. Addressing these challenges will be essential for advancing iPSC-derived therapeutic systems into practical clinical applications (See table 3).

Author contributions

FAD: Conceptualization, Writing – Original Draft, and Investigation (literature search and reference collection). LFM: Writing – Review & Editing, including sentence restructuring, grammatical correction, and paraphrasing.

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