

Review

hPSC models in cancer mechanisms and therapeutic discovery

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Despite major advances in cancer genomics and immunotherapy, the field remains limited by experimental models that fail to faithfully recapitulate human tumor initiation, genetic context, and immune-tumor interactions. Traditional animal and immortalized cell models often lack predictive power for therapeutic response and toxicity. Recent advances in human pluripotent stem cell (hPSC) technology have transformed this landscape, enabling the generation of patient-specific cancer models, multicellular organoids and assembloids, and scalable immune effector cells. These platforms now permit mechanistic dissection of tumorigenesis, reconstruction of human tumor microenvironments, and development of off-the-shelf immunotherapies. This review will synthesize these emerging findings, define key technological and biological gaps, and outline future directions for integrating hPSC-based modeling into precision oncology and translational cancer research.

Human pluripotent stem cells transform cancer research and therapy

Cancer remains one of the leading causes of death worldwide and is driven by complex interactions among genetic alterations, cell-state transitions, and the surrounding tissue microenvironment [1]. Despite major advances in cancer genomics and immunotherapy, many fundamental questions regarding tumor initiation, progression, immune evasion, and therapeutic resistance remain unresolved. A major obstacle has been the lack of experimental systems that fully recapitulate human development, genetic diversity, and multicellular interactions throughout the course of cancer development. Conventional cancer cell lines and animal models have provided invaluable biological insights but often fail to fully capture real biological mechanisms, highlighting the need for more physiologically relevant human platforms for studying cancer biology and developing new therapies [2].

Human pluripotent stem cells (hPSCs) are stem cells capable of indefinite self-renewal and differentiation into virtually any cell type in the human body. hPSCs encompass two major cell types: **embryonic stem cells (ESCs)** (see [Glossary](#)), which are derived from the inner cell mass of preimplantation embryos, and **induced pluripotent stem cells (iPSCs)**, which are generated through the reprogramming of differentiated somatic cells into a pluripotent state [3–5]. Because of their unique capacity to generate diverse human cell types while maintaining long-term proliferative potential, hPSCs have become powerful platforms for disease modeling, mechanistic studies, drug discovery, and regenerative medicine. In contrast to human embryonic stem cells (hESCs), which offer significant scientific and clinical promise but have been limited in their widespread adoption due to ethical and safety concerns associated with embryo use [6], iPSCs are generated by reprogramming somatic cells using four transcription factors (octamer-binding transcription factor 3/4 (OCT3/4), SRY-box transcription factor 2 (SOX2), cellular-MYC proto-oncogene (c-MYC), and Krüppel-like factor 4 (KLF4)) and provide an alternative source of ESC-like cells without the use of human embryos [4,7] ([Box 1](#)). iPSCs share many functional characteristics with hESCs and can be generated from patient-derived somatic cells, providing an attractive and ethically acceptable alternative for disease modeling and regenerative medicine.

Highlights

Induced pluripotent stem cell-based platforms enable patient-specific modeling of tumor initiation, progression, and genetic context, providing unique insight into early oncogenic mechanisms that are inaccessible in conventional systems.

Induced pluripotent stem cell-derived immune cells, including T, natural killer, macrophage, and dendritic cells, offer scalable, off-the-shelf immunotherapy platforms with enhanced engineering potential and reduced variability.

Integration of induced pluripotent stem cell-derived organoids, assembloids, and bioengineered 3D systems reconstructs human tumor microenvironments, allowing mechanistic dissection of tumor-stroma-immune interactions.

Coupling induced pluripotent stem cell technologies with AI-driven differentiation and precision modeling advances translational prediction, enabling biomarker discovery, drug screening, and personalized therapeutic development.

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Box 1. Reprogramming and genome engineering strategies for cancer research

Cellular reprogramming technologies have become important tools for studying tumor initiation, cellular plasticity, and lineage-specific oncogenic mechanisms [8–10]. By altering cell identity through transcription factor expression or genome engineering, researchers can recreate early stages of tumorigenesis and investigate how genetic mutations interact with the developmental context. Several complementary reprogramming and genome engineering strategies are now used to model human cancers, as described below.

Programming cancer-prone genetic-disorder somatic cells: somatic cells from patients with cancer-predisposition syndromes (e.g., Li-Fraumeni syndrome (LFS), RB, Rothmund-Thomson Syndrome (RTS), or BRCA1 and BRCA2 DNA repair associated cancers) provide a powerful platform for modeling tumor susceptibility in a native genetic background [11–14]. These cells can be reprogrammed using Yamanaka factors into iPSCs or differentiated into lineage-relevant cell types while retaining germline mutations that confer elevated cancer risk. Isogenic controls can be generated by correcting these mutations using genome editors such as clustered regularly interspaced short palindromic repeats–CRISPR-associated protein 9 (CRISPR-Cas9), transcription activator-like effector nucleases (TALENs), and zinc-finger nucleases (ZFNs) [15], enabling precise dissection of genotype–phenotype relationships. Compared with engineered models, this approach captures patient-specific genetic context, including modifier variants and epigenetic features that influence tumor progression. Upon differentiation, these cells often exhibit early oncogenic phenotypes, such as impaired differentiation, genomic instability, or altered stress responses, allowing the study of tumor initiation before overt transformation. This strategy has been applied to model cancers associated with tumor protein p53 (p53), RB transcriptional corepressor 1 (RB1), and DNA repair deficiencies, providing a valuable system for studying early tumorigenesis and testing therapeutic interventions [11–14,16,17].

Engineering oncogenic mutations in normal iPSCs: another strategy introduces cancer-associated mutations into genetically normal iPSCs and hESCs using genome-editing technologies. Differentiation of these engineered iPSCs into tissue-specific lineages enables investigation of how defined mutations initiate tumorigenesis within appropriate developmental contexts. This approach allows modeling of mutation combinations observed in human cancers and has been widely applied to study hematological malignancies, neuroblastoma, and retinoblastoma [18–20].

Cancer cell reprogramming to pluripotency: tumor cells can be reprogrammed into iPSCs through the expression of Yamanaka factors [21,22]. These cancer-derived iPSCs retain the oncogenic mutations present in the tumor genome but undergo extensive epigenetic resetting. Upon differentiation into lineage-relevant cell types, malignant phenotypes can re-emerge, effectively phenocopying the original tumor [21,23]. This approach has been applied to several cancers, including pancreatic ductal adenocarcinoma and leukemia, where reprogrammed cells regained tumorigenic properties following differentiation into pancreatic or hematopoietic lineages [21,23].

Direct lineage reprogramming: direct lineage reprogramming, also known as transdifferentiation, converts one somatic cell type directly into another without passing through a pluripotent state. This process typically relies on lineage-defining transcription factors that drive rapid changes in cell identity [24]. Although less commonly used in cancer modeling, this approach has been applied to generate immune populations, such as DCs, and to reprogram tumor cells into DCs for the development of novel immunotherapies [25,26].

Patient-derived and genetically engineered hPSCs have been widely used to model a broad spectrum of cancers, including sarcomas, retinoblastoma (RB), myelodysplastic syndrome (MDS), leukemia, and multiple solid tumors (Table 1), yielding critical insights into the mechanisms of tumor initiation, progression, and therapeutic response (see *Clinician's corner*) [48]. These studies establish hPSCs as powerful human-specific platforms that complement conventional cancer models. In this review, we provide an integrated perspective on the expanding role of hPSC-based platforms in cancer research, spanning cancer modeling and regenerative immunotherapy (Table 2). We discuss how patient-derived hPSCs, **organoid** and **assembloid** systems, and hPSC-derived immune cells are advancing mechanistic discovery, therapeutic development, and precision oncology, and we highlight the remaining challenges and future opportunities for clinical translation.

hPSC-derived cells and organoids for cancer modeling and therapeutic development

Sarcoma

Sarcomas are a heterogeneous group of relatively rare malignancies. Among them, osteosarcoma, the most common primary malignant bone tumor, occurs at markedly increased frequency in individuals with hereditary cancer predisposition syndromes, including hereditary RB, Rothmund–Thomson syndrome (RTS), and Li–Fraumeni syndrome (LFS) [8]. Patient iPSC-based modeling has enabled mechanistic dissection of osteosarcoma initiation in these genetic contexts. RB-iPSC-derived

Glossary

Artificial intelligence (AI): computational approaches, including machine learning and deep learning, that analyze high-dimensional biological datasets to optimize differentiation protocols, predict cell identity, and accelerate disease modeling.

Assembloids: advanced 3D models created by combining multiple lineage-specific organoids or differentiated cell populations. Assembloids enable the study of intercellular interactions, tissue–tissue crosstalk, and microenvironmental dynamics that are difficult to capture in single-organoid systems, making them particularly useful for modeling complex tissues and TMEs.

Embryonic stem cells (ESCs): derived from the inner cell mass of preimplantation blastocysts, can self-renew indefinitely and differentiate into all adult cell lineages, and their behavior, whether maintaining pluripotency or undergoing differentiation, depends on the surrounding culture conditions.

Hematopoietic progenitor cells

(HPCs): intermediate progenitor cells derived from hematopoietic stem cells that can differentiate into multiple blood lineages, including lymphoid and myeloid cells.

Induced pluripotent stem cells

(iPSCs): generated by reprogramming somatic cells into a pluripotent state through the introduction of defined transcription factors, commonly known as the Yamanaka factors (OCT4, SOX2, KLF4, and c-MYC). These reprogrammed cells acquire the capacity for unlimited self-renewal and the potential to differentiate into any adult cell type.

Isogenic controls: control cell lines that are genetically identical to the experimental cell line, except for the specific genetic change being studied.

Organoids: 3D structures derived from pluripotent or adult stem cells that self-organize into tissue-like architectures. Organoids recapitulate key cellular compositions, spatial organization, and functional characteristics of their tissue of origin, providing physiologically relevant models for development, disease, and drug screening.

Patient-derived iPSCs: generated from somatic cells obtained from individuals with specific genetic backgrounds or diseases. These cells retain the patient's germline mutations and provide personalized platforms for

osteoblasts, corresponding to the presumed cell of origin of osteosarcoma, exhibit neoplastic features and aberrant expression of the RB1/E2F3a onco-spliceosome signature (REOSS), which is associated with widespread RNA splicing abnormalities [11]. Notably, RB1 expression is inversely correlated with REOSS gene expression, and pharmacological inhibition of the spliceosome using sudemycin D6 (SD6) and pladienolide B selectively suppresses tumorigenesis in RB1-mutant osteosarcoma models, underscoring the utility of this system for therapeutic screening. In parallel, osteoblasts derived from iPSCs of patients with RTS type II display enhanced mitochondrial respiratory complex I expression and activity, leading to increased ATP production [12]. Inhibition of mitochondrial respiratory complex I using its inhibitor, IACS-010759, selectively reduces RTS cell viability by inducing apoptosis and cellular senescence, revealing a metabolic vulnerability associated with RecQ like helicase 4 (RECQL4) deficiency. Similarly, iPSC-based models of LFS-associated bone malignancy have uncovered multiple pathogenic mechanisms, including dysregulation of the long noncoding RNA (lncRNA) H19 imprinted maternally expressed transcript (H19)/small nucleolar RNA, H/ACA box 7A (SNORA7A) axis that impairs osteogenic differentiation, upregulation of secreted frizzled related protein 2 (SFRP2) that promotes tumor angiogenesis, and altered mitochondrial morphology that enhances glycolytic flux, collectively contributing to p53 mutation-driven tumor initiation and progression [9, 13, 16, 27, 28]. Therapeutic targeting of these pathways, including blockade of the SFRP2 and cysteine-rich angiogenic inducer 61 (CYR61) axis using anti-SFRP2 antibodies in combination with topoisomerase II inhibitors, represents a potential personalized treatment strategy.

Ewing's sarcoma is characterized by the Ewing sarcoma breakpoint region 1 (EWS)–Friend leukemia integration 1 (FLI1) fusion transcription factor, which enforces oncogenic gene expression programs [54]. A study using iPSCs generated from Ewing's sarcoma cells demonstrated that pluripotent reprogramming alters sensitivity to inhibitors targeting EWS–FLI1-dependent pathways, despite persistence of the fusion oncogene [29]. Importantly, restoration of lineage-specific differentiation reinstated drug responsiveness, indicating that epigenetic and differentiation states strongly modulate treatment efficacy. Together, these studies demonstrate that **patient-derived iPSCs** capture early premalignant states and conserved oncogenic mechanisms, elucidating mutation-driven pathological alterations, while also revealing cell state-dependent therapeutic vulnerabilities in sarcomas, thereby informing the development of rationally targeted therapies (Figure 1A).

Nervous system tumors

The human nervous system, comprising the central nervous system (CNS) and peripheral nervous system (PNS), controls nearly all bodily functions, and cancers arising within these systems are among the most aggressive and difficult to treat. Recent advances in iPSC-derived *in vitro* and *in vivo* models have improved our understanding of the molecular mechanisms driving CNS and PNS tumors and facilitated therapeutic drug screening. A number of studies have utilized iPSC-derived cells to model the genetic drivers of nervous system cancers. For example, iPSC-derived astrocytes and cerebral organoids from patients with LFS uncovered a mutant p53–Supervillin (SVIL)–mixed-lineage leukemia 1 (MLL1) transcriptional complex that drives YTH N6-methyladenosine RNA binding protein F2 (YTHDF2) expression, promoting degradation of tumor-suppressive transcripts and neoplastic transformation [17, 30]. Importantly, pharmacologic inhibition of the Menin–MLL1 interaction selectively suppressed the growth of LFS-derived astrocytes and organoids, highlighting a potential therapeutic strategy for LFS-associated brain malignancies. Collectively, these findings provide new insights into early gliomagenesis and identify MLL1 as a promising therapeutic target in LFS-associated brain tumors. Similarly, cerebral organoids harboring the epidermal growth factor receptor variant III (EGFRvIII) mutation demonstrated mutation-driven astrogenesis, enhanced proliferation, and selective sensitivity to temozolomide, establishing organoid platforms as functionally relevant systems for evaluating anticancer therapies in a human developmental context [31]. Additionally, iPSC-derived neural crest cells engineered to express

studying disease mechanisms and therapeutic responses.

Tumor-on-a-chip: microfluidic platforms that recreate aspects of tumor architecture, vascular flow, and microenvironmental gradients to model tumor biology and therapeutic responses under physiologically relevant conditions.

Table 1. Current evidence supporting the predictive validity of iPSC-derived cancer models

Cancer type	hPSC/iPSC-derived model	Genetic context/driver	Key biological insight	Therapeutic implication	Validation status	Refs
Osteosarcoma	iPSC-derived osteoblasts	RB1 mutation (hereditary retinoblastoma)	Activation of REOSS and aberrant RNA splicing	Spliceosome inhibitors (SD6 and pladienolide B) suppress tumorigenesis	Mechanistic modeling and target discovery	[11]
		RECQL4 mutation (RTS)	Increased mitochondrial complex I activity and ATP production	Complex I inhibitor IACS-010759 reduces tumor cell viability	Mechanistic modeling and target discovery	[12]
		TP53 mutation (LFS)	Dysregulation of H19/SNORA7A axis, SFRP2 signaling, and altered mitochondrial metabolism	Targeting SFRP2–CYR61 signaling	Mechanistic modeling and target discovery	[13,16,27,28]
Ewing sarcoma	Reprogrammed EWS iPSC model	EWS–FLI1 fusion	Cell differentiation state alters drug sensitivity	Differentiation state influences therapeutic response	Mechanistic modeling	[29]
Glioma	iPSC-derived astrocytes and cerebral organoids	TP53 mutation (LFS) and EGFRvIII	Mutant p53–SVIL–MLL1 complex promotes tumorigenesis; EGFRvIII drives astrogenesis	Platform for evaluating targeted therapies	Mechanistic modeling and target discovery	[17,30,31]
Neuroblastoma	iPSC-derived neural crest cells	MYCN and ALK (F1174L) mutations	POSTN–WNT signaling loop promotes tumorigenesis	Potential targeting of WNT-associated signaling pathways	Mechanistic modeling	[18]
MB	iPSC-derived NES cells and ectodermal cells	PTCH1 mutation (Gorlin syndrome)	Dysregulated SHH signaling	Identification of subgroup-specific therapeutic strategies and modeling MB formation	Mechanistic modeling and target discovery	[32,33]
AML	Patient-derived leukemic iPSCs	Representative MLL-rearranged AML model	Epigenetic resetting and restoration of leukemogenic phenotype upon differentiation	Identification of drug-resistant clones and relapse risk	Retrospective translational support	[34]
	CRISPR-engineered normal iPSCs and patient-derived RUNX1-FPD iPSCs	ASXL1 truncation; SRSF2(P95L) and NRAS (G12D) mutations	Modeling leukemogenesis and mutation cooperation	Drug screening and pathway targeting; identification of resistance of RAS-mutant leukemia cells to BCL2 inhibitor therapy	Mechanistic modeling and target discovery	[19,35]
JMML	NS iPSC model	PTPN11 mutation	Modeling NS-associated JMML and identifying dysregulation of miR-223 function	Identification of genotype–phenotype associations in JMML and the discovery of therapeutic targets	Mechanistic modeling	[36]
CML	BCR::ABL1 iPSC model	BCR::ABL1 fusion	Modeling genomic instability and disease progression	Identification of therapeutic vulnerabilities	Mechanistic modeling and target discovery	[37]
DS-ML	iPSC hematopoietic models	GATA1 and STAG2 mutations	Modeling syndromic leukemogenesis	Insight into mutation-driven leukemia development	Mechanistic modeling	[38]
	Genetically matched trisomy 21 and disomic iPSC models	Targeted correction of trisomy 21	Investigating chromosome 21 dosage-dependent phenotypes	Generation of isogenic disomic controls and identification of trisomy-associated defects in cell proliferation and endothelial differentiation	Mechanistic disease modeling	[39]
MDS	iPSC-derived HSPCs	del(7q). U2AF1 and SRSF2	Abnormally activated MEK signaling	MEK inhibitors trametinib, cobimetinib, selumetinib,	Mechanistic modeling and	[40,41]

Table 1. (continued)

Cancer type	hPSC/iPSC-derived model	Genetic context/driver	Key biological insight	Therapeutic implication	Validation status	Refs
		mutations		and CH5126766	target discovery	
MDS-RS	Patient-derived, genetically matched iPSC-derived HSPCs	SF3B1(K700E) mutation	Disease-associated RNA mis-splicing and altered transcriptional and chromatin-accessibility programs	TEAD transcription factors identified as potential therapeutic targets	Mechanistic modeling and target discovery	[42]
Lung cancer	iPSC-derived lung progenitors and organoids	RET(C634Y) and HER2 amplification	Oncogenic signaling activation and tumor-like morphology	RET inhibitor pralsetinib and pathway-targeted therapies	Mechanistic modeling and target discovery	[43,44]
Colorectal cancer	iPSC-derived colonic organoids	EPCAM deletion (CMMRD) and APC mutation (FAP)	Mismatch repair deficiency and early tumorigenesis	Platform for studying tumor initiation and drug responses	Mechanistic modeling and target discovery	[45,46]
Breast cancer	iPSC-derived mammary epithelial cells	BRCA1 mutation	S100P promotes stemness and tumorigenesis	Identification of targets beyond PARP inhibition	Target discovery	[14]
Retinoblastoma	iPSC/hESC-derived retinal organoids	RB1 mutation (hereditary retinoblastoma)	Organoids recapitulate tumor histology and transcriptomic features	Identification of SYK as a potential therapeutic target	Mechanistic modeling and target discovery	[20]
PDAC	Reprogrammed PDAC-derived iPSCs	KRAS mutation	Recapitulation of PanIN. PDAC progression and HNF4 α regulatory network	Identification of early-stage therapeutic targets	Mechanistic modeling	[21,47]

ABL1: ABL proto-oncogene 1, nonreceptor tyrosine kinase; ALK: ALK receptor tyrosine kinase; AML: acute myeloid leukemia; APC: APC regulator of WNT signaling pathway; ASXL1: ASXL transcriptional regulator 1; ATP: adenosine triphosphate; BCL2: BCL2 apoptosis regulator; BCR: BCR activator of RhoGEF and GTPase; BRCA1: BRCA1 DNA repair associated; C634Y: substitution of cysteine (C) with tyrosine (Y) at amino acid position 634; CML: chronic myeloid leukemia; CMMRD: constitutional mismatch repair deficiency; CRISPR: clustered regularly interspaced short palindromic repeats; CYR61: cysteine-rich angiogenic inducer 61; del(7q): deletion of the long arm of chromosome 7; DS-ML: Down syndrome associated myeloid leukemia; EGFRvIII: epidermal growth factor receptor variant III; EPCAM: epithelial cell adhesion molecule; EWS: Ewing sarcoma; EWS-FLI1: Ewing sarcoma breakpoint region 1–Flt-1 proto-oncogene fusion; F1174L: substitution of phenylalanine (F) with leucine (L) at amino acid position 1174; FAP: familial adenomatous polyposis; FPD: familial platelet disorder; G12D: glycine (G) $\rightarrow$ aspartic acid (D) substitution at amino acid 12; GATA1: GATA binding protein 1; H19: H19 imprinted maternally expressed transcript; HER2: human epidermal growth factor receptor 2; HNF4 α : hepatocyte nuclear factor 4 alpha; JMML: Juvenile myelomonocytic leukemia; K700E: substitution of lysine (K) with glutamic acid (E) at amino acid position 700; KRAS: KRAS proto-oncogene, GTPase; LFS: Li-Fraumeni syndrome; MB: medulloblastoma; MDS: myelodysplastic syndrome; MDS-RS: myelodysplastic syndrome with ring sideroblasts; MEK: mitogen-activated protein kinase kinase; miR-223: microRNA-223; MLL1: mixed-lineage leukemia 1; MYCN: MYCN proto-oncogene, bHLH transcription factor; NES: neuroepithelial stem; NRAS: NRAS proto-oncogene, GTPase; NS: Noonan syndrome; p53: tumor protein p53; P95L: proline (P) $\rightarrow$ leucine (L) substitution at amino acid 95; PanIN: pancreatic intraepithelial neoplasia; PARP: poly(ADP-ribose) polymerase; PDAC: pancreatic ductal adenocarcinoma; POSTN: periostin; PTCH1: patched1; PTPN11: protein tyrosine phosphatase nonreceptor type 11; RAS: rat sarcoma; RB1: retinoblastoma 1; RECQL4: RecQ-like helicase 4; REOS: RB1/E2F3a onco-spliceosome signature; RET: RET proto-oncogene, receptor tyrosine kinase; RTS: Rothmund–Thomson syndrome; RUNX1: RUNX family transcription factor 1; S100P: S100 calcium-binding protein P; SD6: sudomycin D6; SF3B1: splicing factor 3b subunit 1; SFRP2: secreted frizzled-related protein 2; SHH: sonic hedgehog; SNORA7A: small nucleolar RNA, H/ACA box 7A; SRSF2: serine and arginine rich splicing factor 2; STAG2: stromal antigen 2; SVIL: supervillin; SYK: spleen associated tyrosine kinase; TEAD: TEA domain transcription factor; TP53: tumor protein p53; U2AF1: U2 small nuclear RNA auxiliary factor 1; WNT: wingless-type MMTV integration site family.

the oncogenic MYCN proto-oncogene, bHLH transcription factor (MYCN) and ALK receptor tyrosine kinase (ALK)(F1174L) mutations mimicked the features of neuroblastoma. While MYCN alone is sufficient to initiate tumor formation, ALK(F1174L) enhances malignancy through a periostin (POSTN)–WNT signaling loop that promotes cell adhesion, migration, and growth [18].

Medulloblastoma (MB) is a malignant pediatric brain tumor that arises from disruptions in tightly regulated developmental programs of the cerebellum. Dysregulation of Sonic Hedgehog (SHH) and WNT signaling driven by mutations in patched 1 (PTCH1), smoothened, frizzled class receptor (SMO), SUFU negative regulator of Hedgehog signaling (SUFU), and APC regulator of WNT signaling pathway (APC) defines molecularly distinct MB subgroups and contributes to both hereditary and sporadic forms of the disease [55]. Patient-derived iPSC neuroepithelial

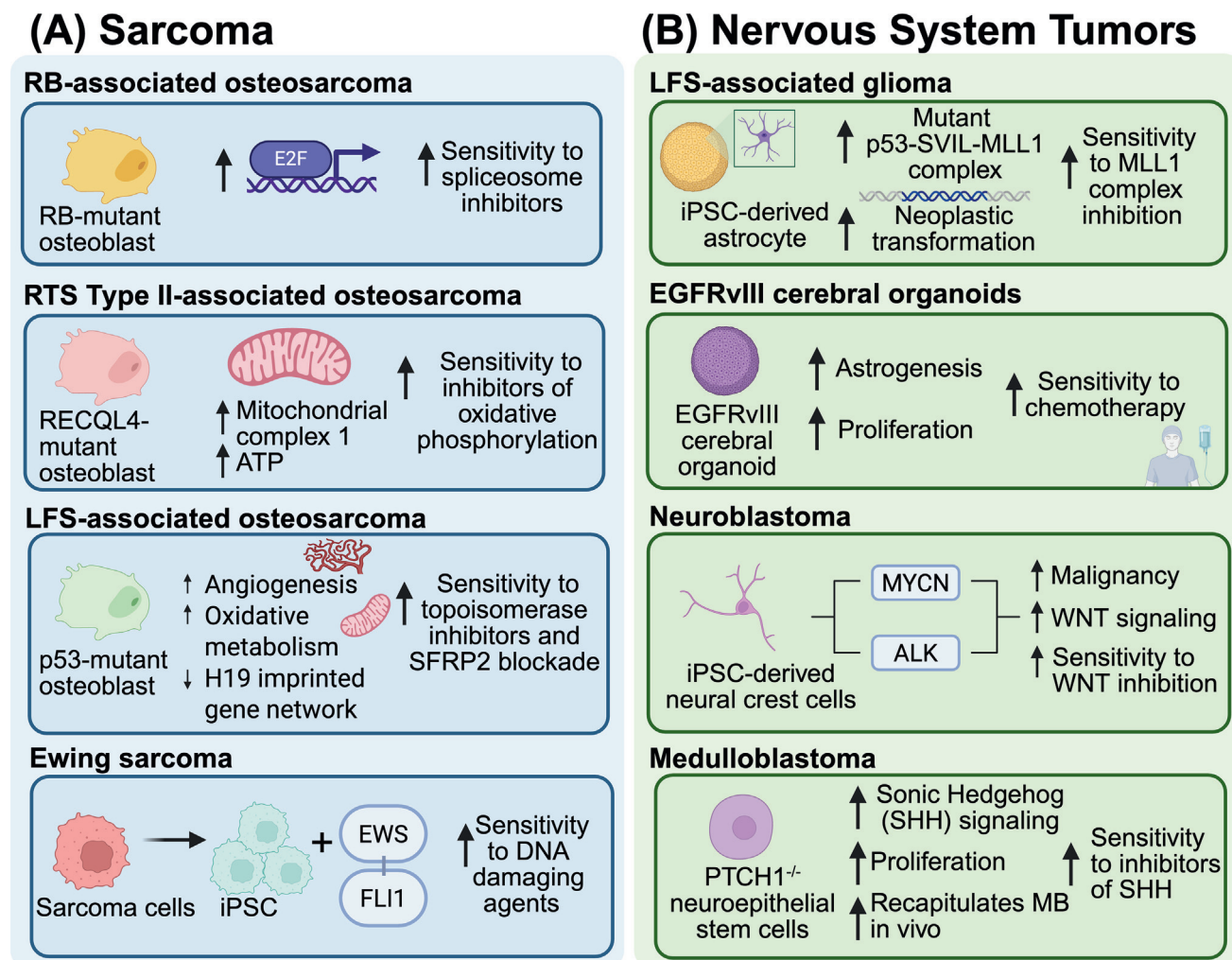
Table 2. Recent clinical trials for iPSC-derived immune-cell therapies for cancer

Cell type	Trial/product	Phase	Current status	Engineering strategy	Cancer indication	Sample size	Primary endpoint	Response/toxicity	Clinical reference
T cell	FT819	1	Active, not recruiting	iPSC-derived TCR-less CD19 CAR-T; CAR inserted into the TRAC locus	R/R B-cell lymphoma, CLL, and B-ALL	54 actual	Safety, DLTs, and AEs	No peer-reviewed final outcome reported	NCT04629729
T cell	FT825/ONO-8250	1	Recruiting	iPSC-derived HER2 CAR-T with multiplex synthetic controls	HER2+ or other advanced solid tumors	351 estimated	Safety, DLTs, TEAEs, and AEs	No peer-reviewed final outcome reported	NCT06241456
NK cell	FT500	1	Completed	Non-CAR iNK cells	Advanced solid tumors	37 actual	Safety and DLTs	No peer-reviewed final outcome reported	NCT03841110
NK cell	FT516	1	Terminated	iPSC-NK + hnCD16	AML; R/R B-cell lymphoma	72 actual	Safety, DLTs, and AEs	R/R B-cell lymphoma: ORR 58% (32/55); no DLTs; G1 CRS 2%; no neurotoxicity; G $\geq$ 3 neutropenia 84%, thrombocytopenia 36%, anemia 27%	NCT04023071 [127]
NK cell	FT516 + avelumab	1	Terminated	iPSC-NK + hnCD16	Advanced solid tumors	12 actual	Safety and DLTs	No peer-reviewed final ORR	NCT04551885
NK cell	FT516 + IL-2 ($\pm$ enoblituzumab)	1	Completed	iPSC-NK + hnCD16	Recurrent ovarian/fallopian/peritoneal cancer	3 actual	Safety, DLTs, and AEs	No DLTs (0/3); 6-mo PFS 1/3; enoblituzumab cohorts not enrolled	NCT04630769
NK cell	FT596	1	Terminated	CD19 CAR-iNK + hnCD16 + IL-15RF	R/R B-cell lymphoma and CLL	98 actual	Safety, DLTs, and AEs	FL: ORR 100%, CRR 85%; LBCL: ORR 38%, CRR 25%; no G $\geq$ 3 CRS, no ICANS/GVHD	NCT04245722 [50]
NK cell	FT596 + rituximab (relapse prevention)	1	Completed	CD19 CAR-iNK + hnCD16 + IL-15RF	Diffuse large or high-grade B-cell lymphoma after autologous HSCT	7 actual	Safety, DLTs, and AEs	No DLTs (0/7); 12-mo relapse/progression 3/7 and PFS 4/7	NCT04555811
NK cell	FT538	1	Terminated	iPSC-NK + hnCD16 + IL-15RF + CD38 knockout	AML; MM with mAbs	42 actual	Safety and DLTs	Early reports only; no peer-reviewed final ORR	NCT04614636
NK cell	FT538 + daratumumab	1	Completed	iPSC-NK + hnCD16 + IL-15RF + CD38 knockout	R/R AML	9 actual	Safety and DLTs	No DLTs (0/9); CR/CRi 2/9; 12-mo PFS 3/9 and OS 3/9	NCT04714372 [51]

NK cell	FT538 ± enoblituzumab	1	Terminated	iPSC-NK + hnCD16 + IL-15RF + CD38 knockout	Recurrent ovarian/fallopian/peritoneal cancer	1 actual	Safety and DLTs	Terminated after 1 patient; outcome data not collected	NCT05708924
NK cell	FT576	1	Completed	BCMA CAR-iNK + hnCD16 + IL-15RF + CD38 knockout	R/R multiple myeloma	31 actual	DLTs, RP2D, and AEs	Interim: no DLTs/CRS/ICANS/GvHD (0/9); VGPR (1/9), PR (1/9), and MR (1/9)	NCT05182073
NK cell	FT522	1	Completed	CD19 CAR-iNK + hnCD16 + IL-15RF + CD38 knockout + alloimmune defense receptor	R/R B-cell lymphoma	20 actual	DLTs and severity	Interim: 8/12 responses (5 CR, 3 PR) in Regimen A; 1/5 PR in Regimen B; no DLTs/CRS/ICANS	NCT05950334 [52,128]
NK cell	FT536	1	Terminated	MICA/B CAR-iNK + hnCD16 + IL-15RF + CD38 knockout	Advanced solid tumors	5 actual	RP2D, and AEs	No outcome reported	NCT05395052
NK cell	FT536 ovarian	1	Active, not recruiting	MICA/B CAR-iNK + hnCD16 + IL-15RF + CD38 knockout	Recurrent ovarian, fallopian tube, and primary peritoneal cancer	3 actual	PFS	No outcome reported	NCT06342986
NK cell	FT536 glioma	1	Recruiting	MICA/B CAR-iNK + hnCD16 + IL-15RF + CD38 knockout	Recurrent WHO grade 4 astrocytoma	9 estimated	Safety and tolerability	No outcome reported	NCT07560865
NK cell	CNTY-101	1	Terminated	CD19 CAR-iNK + siIL-15 + Allo-Evasion edits + EGFR safety switch	R/R CD19 ⁺ B-cell malignancies	28 actual	MTD/DLTs and RP2R	Interim: ORR/CRR up to 67%/33%; no DLTs/GvHD/ICANS; G1–2 CRS	NCT05336409 [53]
NK cell	CD33/CLL1 dual CAR- NK, CD33 CAR-NK, or super NK	1	Completed	CD33/CLL1 dual CAR-NK, CD33 CAR-NK, or super NK	R/R AML or AML with MRD	2 actual	DLTs, and TEAEs	No outcome reported	NCT05987696
NK cell	CLL1 or CD33 CAR-iNK	1	Recruiting	CLL1- or CD33-targeted CAR-iNK	R/R AML	24 estimated	TEAEs	No outcome reported	NCT06367673

Only iPSC-derived immune-cell therapy trials for cancer registered in [ClinicalTrials.gov](https://clinicaltrials.gov) were included. Trial status, sample size, cancer indication, and primary endpoints were extracted from [ClinicalTrials.gov](https://clinicaltrials.gov). Response and toxicity data were summarized from peer-reviewed clinical reports when available; otherwise, data from conference abstracts were labeled as interim, and trials without published efficacy or safety results were listed as ‘no outcome reported’.

AE: adverse event; AML: acute myeloid leukemia; B-ALL: B-cell acute lymphoblastic leukemia; BCMA: B-cell maturation antigen; CAR: chimeric antigen receptor; CLL: chronic lymphocytic leukemia; CLL1: C-type lectin-like molecule 1; CR: complete response; CRi: complete remission with incomplete hematologic recovery; CRR: complete response rate; CRS: cytokine release syndrome; DLT: dose-limiting toxicity; EGFR: epidermal growth factor receptor; FL: follicular lymphoma; G1/2/3: grade 1/2/3; GvHD: graft-versus-host disease; HER2: human epidermal growth factor receptor 2; hnCD16: high-affinity non-cleavable CD16 receptor; HSCT: hematopoietic stem cell transplantation; ICANS: immune effector cell-associated neurotoxicity syndrome; IL-15: interleukin-15; IL-15RF: interleukin-15 receptor fusion protein; IL-2: interleukin-2; iNK: iPSC-derived natural killer cell; LBCL: large B-cell lymphoma; mAbs: monoclonal antibodies; MICA/B: major histocompatibility complex class I polypeptide-related sequence A/B; MM: multiple myeloma; MR: minor response; MRD: minimal residual disease; MTD: maximum tolerated dose; NK: natural killer cells; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; RP2D: recommended Phase 2 dose; RP2R: recommended Phase 2 regimen; R/R: relapsed/refractory; TCR: T-cell receptor; TEAEs: treatment-emergent adverse events; TRAC: T-cell receptor alpha constant; VGPR: very good partial response; WHO: World Health Organization.



Trends in Molecular Medicine

Figure 1. hPSC/iPSC-based sarcoma and nervous system tumor models capture tumor-specific mechanisms. (A) Sarcoma. Induced pluripotent stem cell-derived osteoblast models recapitulate osteosarcoma-associated mechanisms across hereditary cancer predisposition syndromes. Retinoblastoma-associated models reveal an aberrant RB1/E2F3a-regulated splicing program that sensitizes RB1-mutant cells to spliceosome inhibition. Rothmund-Thomson syndrome models uncover increased mitochondrial complex I activity and selective sensitivity to complex I inhibition. LFS models identify p53 mutation-associated defects in osteogenic differentiation, angiogenic signaling, and cellular metabolism, revealing potential sensitivity to combined SFRP2 blockade and topoisomerase II inhibition. In Ewing sarcoma, iPSC reprogramming demonstrates that EWS-FLI1-associated therapeutic dependencies are cell state-dependent, with lineage-specific redifferentiation restoring drug responsiveness. (B) Nervous system tumors. iPSC-derived neural models capture early oncogenic events in human neurodevelopment. LFS-associated glioma models identify a mutant p53-SVIL-MLL1 transcriptional complex that promotes YTHDF2 expression and neoplastic transformation, revealing sensitivity to inhibition of the Menin-MLL1 interaction. EGFRvIII-mutant cerebral organoids exhibit enhanced astrogenesis and proliferation and selective sensitivity to temozolomide. Neuroblastoma models demonstrate that MYCN-driven tumor initiation is potentiated by ALK(F1174L) through a POSTN-WNT signaling loop. PTCH1-mutant iPSC-derived neuroepithelial stem cells model sonic hedgehog medulloblastoma by recapitulating increased Hedgehog signaling, proliferation, tumorigenicity, and sensitivity to the SHH inhibitor vismodegib. This figure was created using BioRender (<http://biorender.com/>). ALK: ALK receptor tyrosine kinase; E2F: E2F transcription factor family; EGFRvIII: epidermal growth factor receptor variant III; EWS-FLI1: Ewing sarcoma breakpoint region 1-Flt-1 proto-oncogene fusion; H19: H19 imprinted maternally expressed transcript; ATP: adenosine triphosphate; DNA: deoxyribonucleic acid; iPSC: induced pluripotent stem cell; LFS: Li-Fraumeni syndrome; MB: medulloblastoma; MLL1: mixed-lineage leukemia 1; MYCN: MYCN proto-oncogene, bHLH transcription factor; p53: tumor protein p53; PTCH1: patched 1; RB: retinoblastoma; RB1: retinoblastoma 1; RECQL4: RecQ-like helicase 4; RTS: Rothmund-Thomson syndrome; SFRP2: secreted frizzled-related protein 2; SHH: sonic hedgehog; SVIL: supvillin; WNT: wingless-type MMTV integration site family.

stem (NES) cells carrying a germline PTCH1 mutation associated with Gorlin syndrome were used to model SHH-subgroup MBs [32]. These Gorlin NES cells formed cerebellar tumors in mice that recapitulated human MBs, and tumor-derived cells showed accelerated growth,

increased stem-like properties, and enhanced sensitivity to the SHH inhibitor vismodegib. Using this model, galectin 1 (LGALS1) was identified as a GLI family zinc finger transcription factor (GLI)-regulated target gene upregulated in both tumor cells and SHH-subgroup MBs, highlighting its potential role in disease progression. Moreover, PTCH1 loss in patient-derived, gene-edited iPSCs activates Hedgehog signaling, leading to enhanced proliferation and the formation of MB-like immature ectodermal tissues, supporting a human iPSC-based model of Hedgehog-driven tumorigenesis [33]. Together, these findings highlight the versatility of iPSC-based platforms in modeling both the initiation and progression of nervous system cancers, as well as their potential in identifying new therapeutic strategies (Figure 1B).

Hematological malignancies

iPSC models have proven invaluable for studying hematological malignancies, including MDS and leukemia [36,40]. One challenge in hematological cancer research is replicating the complex genetic and phenotypic heterogeneity of these diseases. Currently, iPSC-based models have addressed this gap by enabling the generation of patient-specific and genetically engineered blood progenitors that closely mirror disease states. For example, patient-derived iPSCs carrying the recurrent Serine/arginine-rich splicing factor 2 (SRSF2)(P95L) and U2 small nuclear RNA auxiliary factor 1 (U2AF1)(S34F) mutations, a hallmark of MDS with ring sideroblasts (MDS-RS), recapitulate disease-associated splicing abnormalities and transcriptional programs in iPSC-derived hematopoietic stem and progenitor cells (HSPCs), providing mechanistic insight into MDS pathogenesis and identifying mitogen-activated protein kinase kinase (MEK) signaling as a potential therapeutic vulnerability [41]. Similarly, iPSCs harboring the splicing factor 3b subunit 1 (SF3B1)(K700E) mutation demonstrate that mutant SF3B1 drives MDS pathogenesis through coordinated alterations in RNA splicing, chromatin accessibility, and transcriptional regulation, including activation of transcriptional enhanced associate domain (TEAD)-associated programs [42]. Additionally, CRISPR-Cas9 has been used to introduce leukemia-associated mutations such as ASXL transcriptional regulator 1 (ASXL1) truncation, SRSF2(P95L), and NRAS proto-oncogene, GTPase (NRAS)(G12D) into healthy iPSCs, thereby successfully recapitulating the phenotypic and molecular features of MDS and acute myeloid leukemia (AML) [19]. Importantly, iPSC-derived models of AML harboring MLL1 rearrangements generate aggressive myeloid disease upon hematopoietic differentiation, enabling functional comparison of clonal populations. These studies reveal differences in drug sensitivity and identify cytarabine-resistant subclones associated with an increased risk of relapse [34]. Similarly, iPSCs derived from the bone marrow and peripheral blood mononuclear cells (PBMCs) of patients with AML have been used to generate HSPCs that recapitulate key leukemic features *in vitro* and *in vivo* while preserving subclone-specific drug-response phenotypes, providing a powerful platform to investigate therapeutic resistance and clinically relevant mechanisms of treatment failure [23]. Although reprogramming resets many leukemia-associated epigenetic states, AML-derived iPSCs retain oncogenic mutations and regain leukemogenic potential only after hematopoietic differentiation, underscoring the critical role of cell identity and developmental context in leukemogenesis [23,34]. This concept parallels observations from LFS and RB-associated osteosarcoma models, in which disease-associated phenotypes emerge specifically in iPSC-derived osteoblasts, the cell of origin for osteosarcoma, but not in mesenchymal stem cells, highlighting the lineage-specific manifestation of oncogenic mutations [11,13].

Beyond modeling leukemic subpopulations and subclone-specific drug-response phenotypes, patient-derived iPSCs have emerged as powerful platforms for investigating disease progression in hematologic malignancies. Inducing genomic instability in BCR activator of RhoGEF and GTPase-ABL proto-oncogene 1, non-receptor tyrosine kinase fusion (BCR::ABL1)-positive iPSCs has been used to model the progression of chronic myeloid leukemia (CML), whereas patient-derived iPSCs have been used to model blast crisis driven by the stepwise accumulation

of genomic abnormalities [37]. Similarly, trisomy 21 iPSCs derived from patients with Down syndrome (DS), together with isogenic disomy 21 iPSCs, have been established as a human model to investigate DS-associated leukemia susceptibility and therapeutic vulnerabilities [39]. Using this platform, sequential introduction of globin transcription factor 1 (GATA1) and stromal antigen 2 (STAG2) mutations recapitulated the multistep progression of DS-associated myeloid leukemia (DS-ML) [38]. In addition, rat sarcoma (RAS) mutations in AML were studied using CRISPR-Cas9-edited iPSCs and primary HSPCs to model stepwise leukemogenesis [35]. These mutations arise as late events that transform committed myelomonocytic progenitors and generate distinct leukemic stem cell populations with lineage-restricted properties. Importantly, RAS-mutant leukemic stem cells drive clinical resistance to the B-cell lymphoma 2 (BCL2) inhibitor venetoclax, leading to relapse characterized by monocytic disease. These advancements highlight the potential of iPSC-based models to study genetic heterogeneity, clonal evolution, and disease progression in hematologic malignancies (Figure 2A).

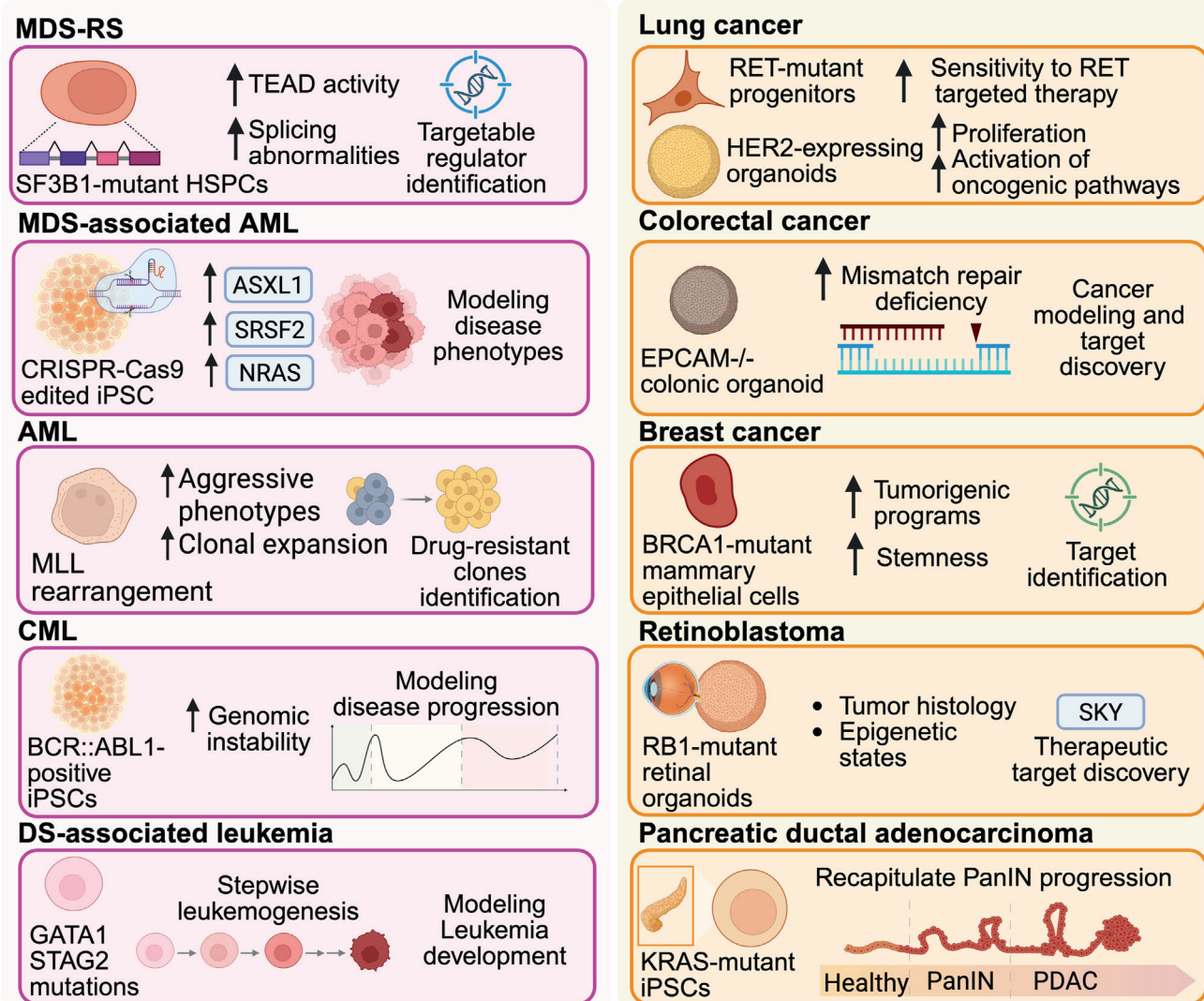
Current hPSC/iPSC hematologic cancer models focus on cell-intrinsic genetic alterations, while emerging bone marrow niche-mimicking organoids are beginning to address the role of the microenvironment in hematopoietic disorders. Recent advances have enabled multicellular organoids incorporating stromal, endothelial, osteogenic, and hematopoietic compartments that better recapitulate the human bone marrow niche, supporting long-term hematopoiesis and enabling studies of leukemia-niche interactions, clonal evolution, and therapeutic response [56–58]. Continued integration of iPSC-derived niche components with bioengineering and organoid technologies may further enhance the physiological relevance and translational potential of hematologic disease models.

Other solid tumors

In the context of solid tumors, iPSCs have also been instrumental in modeling lung cancer, colorectal cancer, breast cancer, retinoblastoma, and pancreatic cancer. For example, lung progenitor cells derived from patient-specific iPSCs with the RET proto-oncogene (RET) (C634Y) mutation displayed aberrant gene expression and oncogenic markers, such as prominin 2 (PROM2) and C1q and TNF related 6 (C1QTNF6), which are associated with poor prognosis in non-small cell lung cancer (NSCLC) [43]. Treatment with the RET inhibitor pralsetinib selectively suppressed oncogenic signaling, demonstrating the model's potential for studying RET-driven NSCLC and screening targeted therapies. In a parallel study, lung organoids derived from human epidermal growth factor receptor 2 (HER2)-overexpressing human iPSCs exhibited tumor-like features, including irregular morphology, enhanced proliferation, and activation of oncogenic pathways such as RAS/rapidly accelerated fibrosarcoma (RAF)/mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/AKT serine/threonine kinase 1 (AKT)/mechanistic target of rapamycin kinase (mTOR), mirroring clinical lung cancers with HER2 amplification [44]. In addition, iPSC-based models have proven valuable for studying colorectal cancer. iPSC-derived colonic organoids from patients with familial adenomatous polyposis (FAP) have been used to investigate the molecular mechanisms underlying colorectal tumorigenesis [45]. Likewise, colonic organoids derived from iPSCs harboring a homozygous epithelial cell adhesion molecule (EPCAM) gene deletion, a genetic alteration associated with constitutional mismatch repair deficiency (CMMRD), exhibited MutS homolog 2 (MSH2) promoter hypermethylation and loss of MSH2 protein expression, leading to a hypermutated genome and mismatch repair deficiency [46].

Furthermore, patient-derived iPSCs carrying germline BRCA1 mutations were differentiated into mammary-like cells that recapitulate key transcriptional programs, genomic alterations, and tumorigenic phenotypes of breast cancer [14]. S100 calcium binding protein P (S100P) was

(A) Hematological Malignancies (B) Other Solid Tumors



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Figure 2. hPSC/iPSC-based models of blood and solid tumors recapitulate tumor-specific mechanisms. (A) Hematological malignancies. iPSC-derived hematopoietic progenitors model myelodysplastic syndrome (MDS), leukemia, and disease progression by preserving oncogenic mutations while enabling differentiation into disease-relevant blood lineages. Representative examples include SF3B1-mutant HSPCs, engineered MDS/AML models carrying ASXL1, SRSF2, or NRAS mutations, patient-derived AML iPSCs, including MLL-rearranged lines that regain leukemogenic potential following hematopoietic differentiation, chronic myeloid leukemia (CML) progression models, and syndromic leukemias such as Down syndrome-associated myeloid leukemia. These systems enable studies of clonal evolution, genetic heterogeneity, and therapeutic response. (B) Solid tumors. hPSC-derived systems model tissue-specific oncogenic programs across solid cancers: lung cancer models capture RET-targeted therapeutic sensitivity and HER2-driven proliferation and oncogenic signaling, colorectal organoids recapitulate mismatch repair deficiency, BRCA1-mutant mammary models exhibit enhanced tumorigenic programs and stemness, enabling target identification, and retinal organoids model retinoblastoma, recapitulating tumor histology, epigenetic states, and transcriptomic signatures while revealing SYK as a therapeutic target whose inhibition induces marked apoptosis in tumor organoids. PDAC-derived iPSCs also recapitulate early tumor progression following pancreatic differentiation, forming pancreatic intraepithelial neoplasia-like lesions that progress toward invasive disease. This figure was created using BioRender (<http://biorender.com/>). AML: acute myeloid leukemia; ASXL1: additional sex combs-like 1; BCR::ABL1: breakpoint cluster region–Abelson 1 fusion gene; BRCA1: breast cancer susceptibility gene 1; Cas9: CRISPR-associated protein 9; CML: chronic myeloid leukemia; T CRISPR: clustered regularly interspaced short palindromic repeats; DS: Down syndrome; EPCAM: epithelial cell adhesion molecule; GATA1: GATA binding protein 1; HER2: human epidermal growth factor receptor 2; hPSC: human pluripotent stem cell; HSPCs: hematopoietic stem and progenitor cells; iPSC: induced pluripotent stem cell; KRAS: KRAS proto-oncogene; MDS: myelodysplastic syndrome; MDS-RS: MDS with

(Figure legend continued at the bottom of the next page.)

identified as a downstream effector of BRCA1 loss that drives stemness and tumorigenesis, highlighting this iPSC-based platform as a model for dissecting breast cancer driven by BRCA1 loss and for discovering novel therapeutic strategies beyond poly(ADP-ribose) polymerase (PARP) inhibitors. Additionally, using three-dimensional organoid systems derived from hESCs or iPSCs to reconstruct tumor initiation in developmentally relevant tissues, researchers have shown that retinal organoid models of retinoblastoma recapitulate tumor histology, epigenetic states, and transcriptomic signatures and have identified spleen associated tyrosine kinase (SYK) as a therapeutic target whose inhibition induces robust tumor cell apoptosis [20].

hPSC-based models have also proven valuable for studying pancreatic cancer. hPSC-derived pancreatic acinar and ductal organoids have been used to investigate lineage-specific oncogenic responses during exocrine development, in which KRAS proto-oncogene, GTPase (KRAS)(G12D) preferentially induces acinar-to-ductal metaplasia and tumorigenic features in acinar organoids, whereas GNAS complex locus (GNAS)(R201C) drives cystic growth more effectively in ductal organoids [47]. In addition, iPSCs derived from pancreatic ductal adenocarcinoma have been shown to recapitulate early stages of tumor progression upon redifferentiation, forming pancreatic intraepithelial neoplasia (PanIN)-like lesions that progress toward invasive disease, with intermediate lesions exhibiting an hepatocyte nuclear factor 4 alpha (HNF4 α)-associated transcriptional network [21]. Taken together, these studies highlight the power of iPSC-derived cells and organoid models to capture tissue-specific molecular alterations underlying solid tumor initiation and progression while enabling mechanistic dissection of oncogenic pathways in physiologically relevant systems that recapitulate tissue architecture, developmental context, and intratumoral heterogeneity [59] (Figure 2B).

hPSC-based cancer models offer unique advantages over conventional cancer cell lines and animal models by bridging reductionist *in vitro* systems and complex *in vivo* studies. The ability to generate patient-specific iPSCs and engineered **isogenic controls** enables precise interrogation of driver mutations within a homogeneous genetic background, facilitating studies of early tumorigenic events, genotype–phenotype relationships, and interpatient variability. Meanwhile, stepwise engineering supports modeling of cancer initiation and progression, and differentiation into otherwise inaccessible cell types allows investigation of lineage-specific cancers and the influence of cellular context on oncogenic transformation. However, despite these strengths, key limitations remain: reprogramming resets hallmarks of aging, including epigenetic alterations, telomere dynamics, and senescence-associated features, producing embryonic-like cells that may not reflect aged tissues where most cancers arise [60–62]; although strategies such as progerin expression, long-term culture, and engineered systems partially restore aging phenotypes, they remain incomplete. Additionally, epigenetic resetting may erase disease-relevant states accumulated during tumor evolution; hPSC-derived cells often display immature, fetal-like phenotypes; and current systems incompletely reconstruct the tumor microenvironment (TME), including stromal, vascular, and immune components critical for tumor progression and metastasis, particularly in complex or desmoplastic tumors [63]. As a result, while hPSC-based models are powerful for studying hereditary cancers, developmental malignancies, and early oncogenic events, faithfully modeling tumor heterogeneity, metastatic dissemination, and long-term tumor evolution remains challenging.

hPSC-derived immune cells

Cancer immunotherapies, including immune checkpoint blockade targeting cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1)- or programmed death-ligand 1 (PD-L1) and adoptive cell therapies such as chimeric antigen receptor (CAR) T cells, have

ring sideroblasts; MLL: mixed lineage leukemia; NRAS: neuroblastoma RAS viral oncogene homolog; PanIN: pancreatic intraepithelial neoplasia; PDAC: pancreatic ductal adenocarcinoma; RB1: retinoblastoma 1; RET: rearranged during transfection; SF3B1: splicing factor 3B subunit 1; SRSF2: serine and arginine rich splicing factor 2; STAG2: stromal antigen 2; SYK: spleen tyrosine kinase; TEAD: transcriptional enhanced associate domain.

transformed oncology by harnessing the immune system to eradicate tumors and achieve durable responses, often unattainable with conventional chemotherapy or radiotherapy [64–67]. These advances have yielded remarkable clinical benefits, particularly in hematologic malignancies [68, 69]. However, current autologous immune-cell therapies remain constrained by individualized manufacturing, patient-to-patient variability, limited scalability, and impaired T-cell fitness in heavily pretreated or elderly patients [70–72]. These limitations have motivated the development of hPSC-derived immune-cell platforms, which enable renewable, genetically engineerable, and batch-manufactured immune effectors with defined potency and reduced variability [50,73–75].

Several clinically advancing hPSC-derived immunotherapy platforms use allogeneic iPSC lines derived from healthy donors rather than autologous patient-specific iPSCs [50,76]. This strategy supports clonal selection, extensive genome engineering, quality control, banking, and scalable production of standardized off-the-shelf cellular products. However, allogeneic hPSC-derived immune cells also introduce challenges, including host-versus-graft immune rejection, limited long-term persistence, and potential incompatibilities arising from human leukocyte antigen (HLA) mismatch [50,76–78]. Accordingly, substantial efforts have focused on generating hypoinmunogenic universal donor hPSC lines through HLA engineering and immune-evasion strategies [77,78]. In contrast, autologous iPSC-derived immune products may reduce alloreactivity but remain limited by lengthy manufacturing timelines, high production costs, and variable starting material quality, particularly in heavily pretreated patients with cancer [77]. Thus, balancing scalability, immune compatibility, persistence, and safety remains a central challenge in the clinical translation of hPSC-derived immunotherapies.

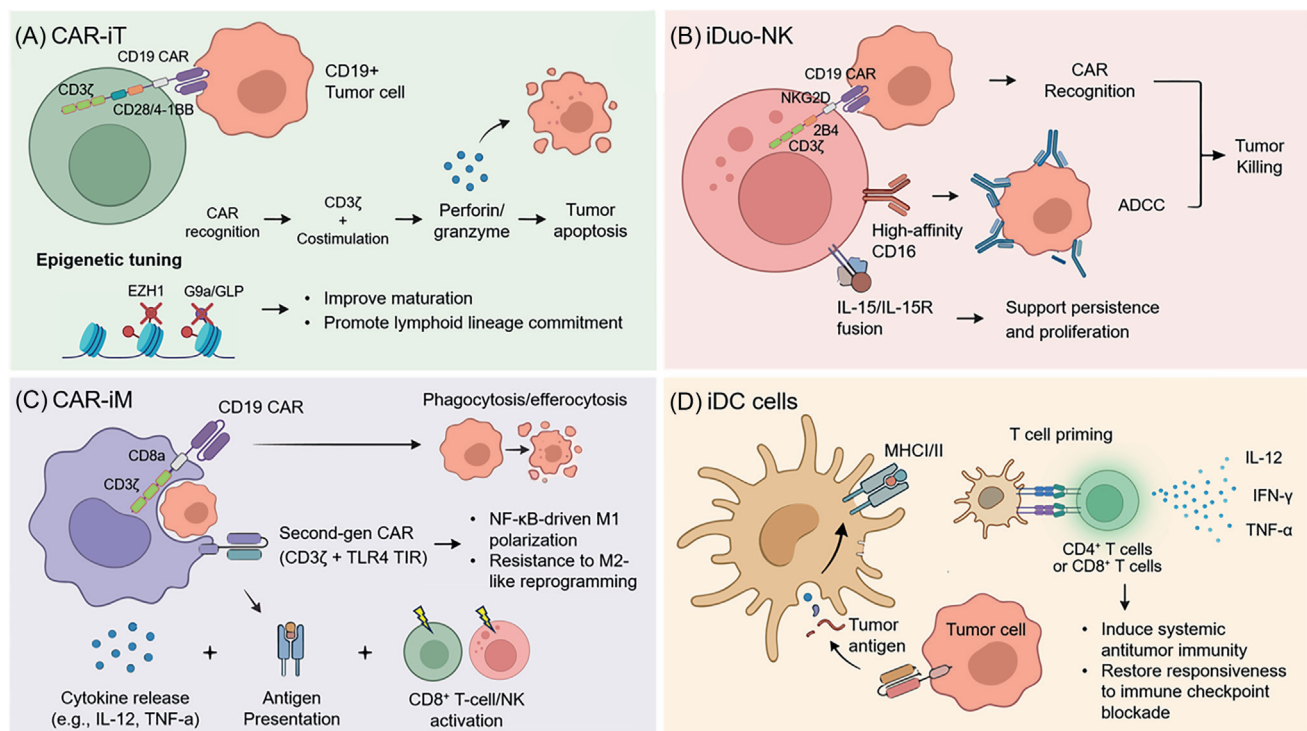
A key manufacturing and developmental feature shared by many hPSC-derived immune-cell platforms is convergence on CD34⁺ **hematopoietic progenitor cells (HPCs)** or a hemogenic endothelial intermediate [79–83]. In oncology, CD34⁺ hematopoietic progenitor dose and quality remain clinically relevant in hematopoietic cell transplantation for hematologic malignancies, underscoring the importance of defining progenitor identity, potency, and manufacturability in stem cell-derived immune platforms [84]. Within hPSC-derived immunotherapy pipelines, a standardized and cryopreservable CD34⁺ progenitor stage could provide a shared upstream source for multiple immune lineages, enabling quality control, banking, and genetic engineering before terminal differentiation [83]. However, most iPSC-derived CD34⁺ populations remain developmentally heterogeneous and are not yet equivalent to adult long-term repopulating HSCs, making the achievement of definitive hematopoietic specification, engraftment capacity, genomic safety, and control of residual undifferentiated cells key translational barriers [83].

From this common hematopoietic progenitor stage, hPSCs can be differentiated into multiple immune lineages that perform complementary functions in antitumor immunity. T cells mediate antigen-specific cytotoxicity, natural killer (NK) cells provide rapid MHC-independent killing, macrophages regulate phagocytosis and reshape the TME, whereas dendritic cells (DCs) initiate adaptive immune responses through antigen presentation. Collectively, these immune populations represent the major cellular platforms currently being developed for hPSC-based cancer immunotherapy. The following sections summarize recent advances in the generation of hPSC-derived T cells, NK cells, macrophages, and DCs, together with their emerging applications in cancer immunotherapy.

T cells

T cells are central to adaptive immunity and cancer immunotherapy, recognizing neoantigens via T-cell receptors (TCRs) that engage major histocompatibility complex (MHC) molecules to elicit targeted cytotoxicity [82]. This principle underlies adoptive cell therapies such as tumor-infiltrating lymphocyte therapy and CAR T-cell therapy [81,85]. While current CAR T-cell products

rely on patient-derived peripheral blood T cells, advances in stem cell biology now enable the generation of functional T cells from hPSCs (iT cells), providing a scalable, off-the-shelf alternative that can be genetically engineered to express defined antigen receptors for enhanced antitumor activity. iT cell differentiation typically proceeds through embryoid body (EB) formation, followed by isolation of CD34⁺ hematopoietic progenitors or hemogenic endothelial-like intermediates [79,81,82]. These intermediates subsequently undergo hematopoietic specification and Notch-dependent lymphoid commitment, giving rise to progenitor T cells, immature T cells, CD4⁺CD8⁺ double-positive cells, and ultimately mature CD4⁺ or CD8⁺ T cells, thereby partially recapitulating thymic T-cell development [86]. Further investigations have led to the development of stroma-free systems instead of murine stromal cell coculture to enhance T-cell production and differentiation specificity, while also supporting the generation of a diverse TCR repertoire, minimizing xenogeneic contamination risk, and facilitating clinically scalable T-cell manufacturing [79].



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Figure 3. iPSC-derived immune cell platforms for cancer immunotherapy. Schematic illustration of iPSC-derived immune effector cells and representative engineering strategies. (A) CAR-iT cells express a CD19-targeting CAR with CD28 and/or 4-1BB costimulatory domains and CD3ζ signaling, with epigenetic modulation (EZH1 repression and/or G9a/GLP inhibition) to enhance function. (B) iDuo-NK cells combine a CD19-targeting CAR containing NKG2D transmembrane, 2B4 costimulatory, and CD3ζ signaling domains with high-affinity non-cleavable CD16 and a membrane-bound IL-15/IL-15R fusion protein to support CAR-mediated recognition, ADCC, persistence, and proliferation. (C) Representative CAR-iMac designs include CD19-targeting CARs that promote antigen-dependent phagocytosis and second-generation CARs incorporating tandem CD3ζ and TLR4 TIR signaling domains, which enhance NF-κB-dependent pro-inflammatory polarization, resistance to M2-like reprogramming, efferyocytosis, cytokine release, and antigen presentation. (D) iPSC-derived dendritic cells capture and present tumor antigens through MHC class I and II molecules and promote CD4⁺ and CD8⁺ T-cell priming, supporting systemic antitumor immunity and responsiveness to immune checkpoint blockade. This figure was created using BioRender (<http://biorender.com/>). 2B4: CD244 natural killer cell receptor; 4-1BB: CD137; tumor necrosis factor receptor superfamily member 9; ACOD1: aconitate decarboxylase 1; ADCC: antibody-dependent cellular cytotoxicity; CAR: chimeric antigen receptor; CAR-iM: chimeric antigen receptor-expressing iPSC-derived macrophage; CAR-iT: chimeric antigen receptor-expressing iPSC-derived T cell; CD3ζ: CD3 zeta chain; EZH1: enhancer of zeste homolog 1; G9a/GLP: G9a and G9a-like protein; ID3: inhibitor of DNA binding 3; iDC: iPSC-derived dendritic cells; iDuo-NK: iPSC-derived dual-functional natural killer cell; IFN-γ: interferon-gamma; IL-15: interleukin-15; IL-15R: interleukin-15 receptor; iPSC: induced pluripotent stem cell; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NK: natural killer; NKG2D: natural killer group 2 member D; TIR: Toll/interleukin-1 receptor; TLR4: Toll-like receptor 4; TNF-α: tumor necrosis factor-alpha.

Despite these advances, CAR-iT cells exhibit less robust antitumor activity than peripheral blood-derived CAR-T cells, particularly in solid tumors [73]. Recent studies indicate that third-generation CAR constructs containing a CD19-targeting single-chain variable fragment (scFv), CD3 ζ , and the costimulatory molecules CD28 and 4-1BB can promote iPSC differentiation toward the CD4⁺CD8⁺ stage. To improve iT cell persistence and tumor infiltration, additional modifications, such as knockout of the negative regulator of TCR signaling diacylglycerol kinase, are under active investigation [73,87]. Epigenomic modulation further enhances differentiation: EZH1 inhibition improves T-cell fidelity and reduces CD1a expression toward a more mature phenotype, while suppression of G9a/GLP favors lymphoid over erythro-myeloid differentiation from HPCs [79,82]. Dual inhibition of EZH1 and G9a/GLP synergistically promotes lymphoid lineage commitment and lymphopoiesis, offering a promising strategy to enhance iT development (Figure 3A).

To improve the function of iT cells, recent efforts have focused on T cell-derived iPSCs (T-iPSCs) as a preferred starting source. T-iPSC-derived iT cells retain rearranged TCR loci from their parental T cells, enabling the derivation of antigen-defined T-cell clones [88]. Reprogramming also restores a more youthful cellular state, reversing exhaustion and promoting a naïve-like phenotype with superior expansion and persistence. T-iPSCs provide an effectively unlimited, genetically consistent reservoir for producing antigen-specific T cells, supporting standardized, off-the-shelf, and patient-tailored CAR T-cell products [81,89].

NK cells

NK cells are cytotoxic innate lymphoid cells that eliminate malignant targets via direct lysis, cytokine-mediated activation of adaptive immunity, and antibody-dependent cellular cytotoxicity (ADCC) [90]. Unlike allogeneic T-cell therapies, NK-cell immunotherapy does not require MHC recognition, reducing graft-versus-host disease risk and enabling off-the-shelf donor-derived products across HLA barriers [90]. Peripheral blood and cord blood NK cells are limited by scalability, donor variability, and reduced amenability to genetic engineering and storage [90]. In contrast, iPSCs provide a renewable, standardized platform compatible with clonal selection, scalable manufacturing, cryopreservation, and multiplex engineering, positioning iPSC-derived NK cells (iNK cells) as a leading platform for universal immunotherapies [50,91]. Differentiation of iNK cells, such as iT cells, commonly proceeds through CD34⁺ hematopoietic progenitors, followed by NK-lineage specification using stromal, feeder-based, or feeder-free culture systems optimized for clinical-scale expansion [92].

The therapeutic potential of iNK cells is increasingly evident from recent clinical advances, particularly through the application of sophisticated genetic engineering to enhance antitumor efficacy. FT596, the first CAR-iNK cell therapy evaluated in a first-in-human trial for B-cell lymphomas [50], incorporates three key enhancements: (i) a CD19-specific CAR with natural killer group 2 member D (NKG2D) fused to NK cell receptor 2B4 and CD3 ζ for robust tumor recognition; (ii) a high-affinity, noncleavable CD16 receptor (hnCD16) to enhance ADCC with monoclonal antibodies; and (iii) an IL-15/IL-15 receptor α fusion (IL-15RF) to support autonomous persistence and proliferation. In clinical evaluation, iPSC-derived CD16/IL-15RF-expressing anti-CD19 CAR-NK cells (FT596) exhibited a favorable safety profile, with no severe cytokine release syndrome (CRS) or neurotoxicity, and achieved deep, durable responses even in heavily pretreated, CAR T-refractory patients [50]. Further engineering strategies have been employed to produce mesothelin (MSLN).CAR-IL-15-iNK cells, a novel product targeting MSLN, a membrane glycoprotein overexpressed on many solid tumors, and simultaneously expressing IL-15 to enhance cytotoxicity, intratumoral accumulation, and cellular expansion [93]. iPSC-derived CD16/IL-15RF-expressing CD38-eliminated NK cells (FT538) incorporate a CD38 knockout to mitigate NK cell fratricide during coadministration with CD38-targeting monoclonal

antibodies [94]. Collectively, these advances highlight the versatility and clinical potential of iNK cells. Although challenges such as exhaustion, limited infiltration, and poor *in vivo* persistence remain, design and genetic optimization are driving progress to enhance iNK cell function for effective deployment in the immunosuppressive TME (Figure 3B).

Monocytes and macrophages

Monocytes and macrophages are central to innate immunity, acting as frontline defenders and regulators of tissue remodeling, apoptotic clearance, and immune homeostasis through dynamic crosstalk with other immune cells. Within the TME, they exhibit functional plasticity, polarizing toward tumor-promoting or tumor-suppressive states [95]. Recent efforts have focused on driving proinflammatory polarization to harness their antitumor potential. For example, HER2-targeting CAR macrophages derived from PBMCs enhance cytokine secretion, remodel the TME, and stimulate adaptive immunity [96]. However, PBMC- or cord blood-derived macrophages are limited by donor variability, restricted expansion, low transduction efficiency, and exhaustion, impeding standardization and clinical scalability. In contrast, iPSC-derived macrophages (iM cells) offer a renewable, genetically tractable, and uniform platform for cell therapy development. The differentiation of iM cells follows a hematopoietic-to-myeloid trajectory distinct from lymphoid lineages. iPSCs, either unmodified or pre-engineered with CAR constructs, are first directed toward mesodermal and hematopoietic progenitor states, followed by myeloid specification and terminal macrophage differentiation using stage-specific hematopoietic and myeloid-promoting cues [97].

Extensive research has focused on iM cells, with CAR engineering playing a key role in conferring antigen-specific tumoricidal activity. Early studies showed that CAR-iM cells targeting CD19 or prostate stem cell antigen mediate robust phagocytosis and cytokine release, producing significant antitumor responses in both hematologic and solid tumor models [74,98]. The scalability of iPSC-derived progenitors supports the development of cryopreservable, off-the-shelf CAR-iM cell products [95]. Building on this foundation, second-generation CAR-iM cells incorporating Toll-like receptor 4 (TLR4) intracellular Toll/interleukin-1 receptor (TIR) domains with CD3 ζ promote nuclear factor kappa B (NF- κ B)-driven M1 polarization, enhance efferocytosis of apoptotic tumor debris, and confer resistance to M2-like reprogramming in the immunosuppressive TME [97]. Complementary strategies include metabolic reprogramming, such as aconitate decarboxylase 1 (ACOD1) deletion, which boosts reactive oxygen species (ROS) production, strengthens phagocytosis, and synergizes with immune checkpoint blockade by attenuating nuclear factor erythroid 2-related factor 2 (NRF2)-mediated anti-inflammatory signaling [99]. Another strategy is transcriptional engineering using factors such as inhibitor of differentiation 3 (ID3) to enhance tumor phagocytosis and inflammatory cytokine secretion, thereby activating CD8⁺ T cells and NK cells [100]. iM cells combining CAR engineering, innate pathway activation, metabolic rewiring, and transcriptional programming can overcome immunosuppression, sustain proinflammatory activity, and synergize with adaptive immune cells, providing a blueprint for next-generation macrophage-based therapies (Figure 3C).

Dendritic cells

DCs are professional antigen-presenting cells that activate CD4⁺ and CD8⁺ T cells via MHC class II and cross-presentation on MHC class I, respectively. Their key role in initiating adaptive immunity underpins vaccine development and cell-based cancer immunotherapy [101]. Autologous DCs have been used clinically to enhance tumor-specific T-cell responses, as shown in a Phase 2/3 trial in patients with resected pancreatic cancer, where antigen-loaded DCs elicited functional cytotoxic T cells [102]. However, primary DCs are limited by low yield, interpatient variability, and labor-intensive production. iPSC-derived DCs (iDC cells) and direct somatic cell reprogramming offer scalable, genetically modifiable alternatives for next-generation DC therapies.

Differentiation of hPSCs into DCs has been refined using feeder-free systems that are more suitable for clinical translation [80]. One approach begins with EB formation and stepwise induction of mesodermal, hematopoietic, and DC progenitor states, followed by directed differentiation into cDC1- and cDC2-like subsets using lineage-specifying culture conditions. This streamlined strategy enables the generation of conventional DC (cDC) subsets with improved yield and phenotypic fidelity compared with earlier iPSC-based differentiation methods [80].

Recent studies demonstrate that iDC cells are functionally competent in both murine and human systems. In mice, cDC2-like iDC cells trafficked to tumor-draining lymph nodes, primed CD8⁺ T cells, and synergized with radiotherapy to induce systemic antitumor immunity and restore responsiveness to PD-L1 blockade, delaying local tumor growth and suppressing distant lesions, indicative of robust systemic memory [103]. In human models, cDC1- and cDC2-like iDC cells exhibited phagocytic activity, secreted proinflammatory cytokines, and efficiently activated allogeneic CD4⁺ and CD8⁺ T cells [104]. Moreover, autologous iDC cells transfected with tumor-derived RNA from patients with colorectal cancer elicited the activation of neoantigen-specific cytotoxic T cells that selectively killed patient-derived tumor spheroids *in vitro* [105]. These findings indicate that iDC cells form functional subsets that initiate adaptive immunity and mediate antigen-specific antitumor responses in preclinical and patient-derived systems (Figure 3D).

Alongside iPSC-based strategies, direct lineage reprogramming has emerged as a transformative approach for DC therapeutics. Pereira and colleagues demonstrated that enforced expression of transcription factor PU.1, interferon regulatory factor 8 (IRF8), and basic leucine zipper ATF-like transcription factor 3 (BATF3) converts mouse and human fibroblasts into functional DCs with a cDC1-like phenotype [25] (Box 1). These induced DCs retain key functions, including antigen presentation and T-cell priming.

More recently, Ascić *et al.* used local adenoviral delivery of PU.1, IRF8, and BATF3 to reprogram tumor cells *in situ* into cDC1-like antigen-presenting cells. In mouse melanoma models, this strategy was associated with remodeling of the TME, including increased effector immune-cell infiltration, tertiary lymphoid-like structure formation, reduced exhausted or regulatory T-cell

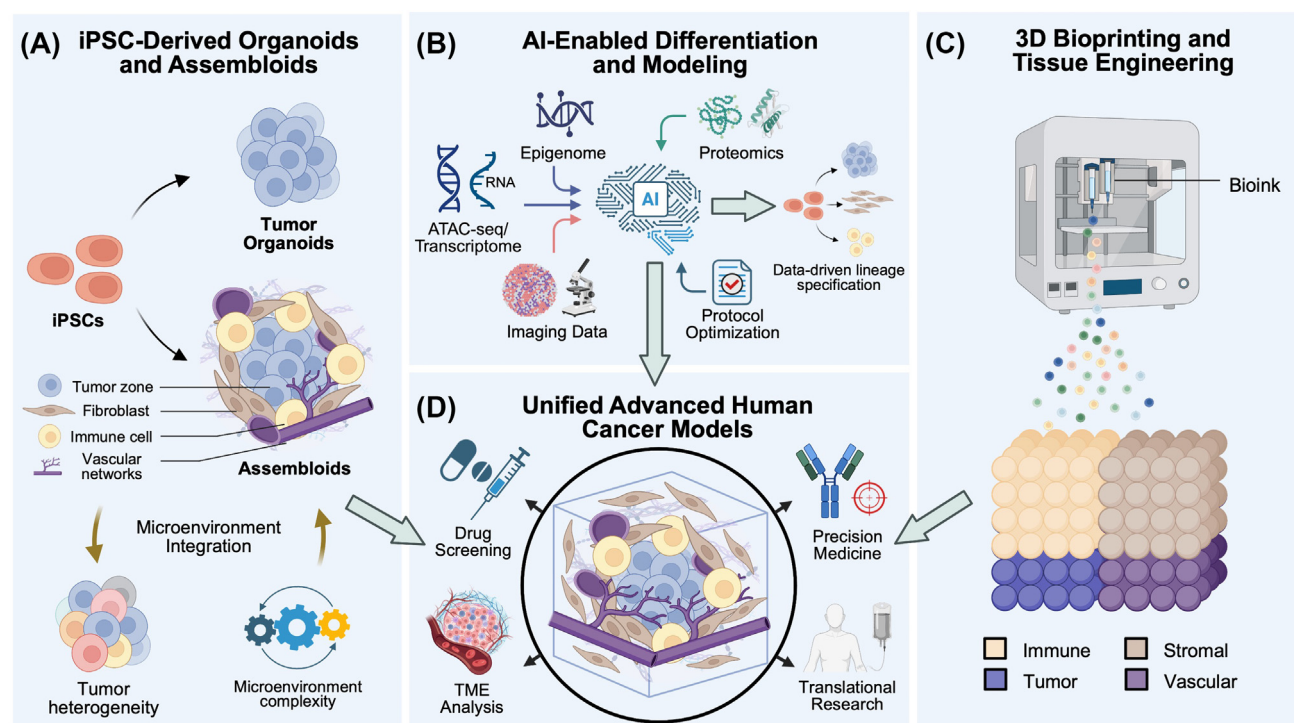
Table 3. Major translational barriers and potential solution pathways for the clinical implementation of hPSC-derived immunotherapies

Translational barrier	Key challenges	Potential solution path
Manufacturing and cost	Limited scalability; batch-to-batch variability; high GMP manufacturing costs	Closed-system automated GMP manufacturing; scalable bioreactors; standardized differentiation; HLA-homozygous or universal iPSC banks; continuous manufacturing
Supervision and quality control	Ensuring identity, purity, potency, genomic stability; residual pluripotent cells; lack of harmonized release criteria	Standardized release criteria, single-cell and multiomics quality assessment, genomic stability testing, validated potency assays, and GMP-compliant manufacturing
<i>In vivo</i> functional verification	Limited prediction of persistence, trafficking, efficacy, and long-term safety	Humanized mouse and orthotopic tumor models; <i>in vivo</i> tracking and barcoding; assessment of infiltration, persistence, exhaustion; biodistribution and cytokine profiling
Clinical endpoint correlation	Limited evidence linking preclinical findings to patient outcomes; patient heterogeneity; limited predictive biomarkers	Prospective clinical trials, biomarker-guided patient selection, correlation with clinical response and survival, and multicenter validation studies

GMP: good manufacturing practice.

states, expansion of memory T cells, systemic antitumor immunity, and enhanced responses to anti-PD-1 or anti-CTLA-4 therapy [26]. Extending transcription factor-based DC reprogramming beyond cDC1-like states, Henriques-Oliveira *et al.* used an anchored screening approach to identify subset-specific blueprints for generating diverse DC-like populations, including PU.1/interferon regulatory factor 4 (IRF4) /PR domain zinc finger protein 1 (PRDM1)-driven proinflammatory cDC2-like cells and Spi-B transcription factor (SPIB) /IRF8/IKAROS family zinc finger 2 (IKZF2)-driven immature lymphoid plasmacytoid dendritic cell (pDC)-like cells with distinct antitumor immune programs [106].

In summary, the integration of stem cell biology, advanced genetic engineering, and direct lineage reprogramming is creating a new frontier in cancer immunotherapy, where tailored T cells, NK cells, macrophages, and DCs can overcome current therapeutic limitations and provide potent, standardized, off-the-shelf treatments with curative potential. Despite this promise, clinical translation of iPSC-derived cell therapies remains limited by safety concerns, including tumorigenic risk from residual undifferentiated hPSCs, genomic and epigenomic alterations acquired during reprogramming and extended culture, and the lack of long-term *in vivo* safety data (Table 3). Current mitigation strategies include improving differentiation efficiency to enhance cell purity, applying cell sorting or selective depletion to remove undifferentiated cells, and implementing rigorous quality control with genomic and epigenetic profiling. In addition, good manufacturing



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Figure 4. Integrated platforms for advanced iPSC-based cancer modeling. iPSC-based technologies enabling next-generation human cancer models are illustrated. (A) iPSC-derived organoids and assembloids, which reconstruct tumor architecture and multicellular tumor microenvironments by integrating tumor cells with stromal, immune, and vascular components. (B) AI-enabled differentiation and modeling, where machine learning integrates multiomics and imaging datasets to guide lineage specification and optimize differentiation protocols. (C) 3D bioprinting and tissue engineering, which enable the spatially controlled assembly of tumor cells, stromal populations, immune cells, and vascular structures within engineered three-dimensional constructs. (D) The integration of these approaches supports the development of unified, advanced human cancer models for studying tumor biology, tumor-microenvironment interactions, drug screening, and precision oncology applications. This figure was created using BioRender (<http://biorender.com/>). 3D: three-dimensional; AI: artificial intelligence; ATAC-seq: assay for transposase-accessible chromatin using sequencing; iPSC: induced pluripotent stem cell; TME: tumor microenvironment.

practice (GMP)-compliant manufacturing and long-term preclinical evaluation are essential to ensure safety and enable clinical translation of iPSC-based therapies. Beyond these major lineages, continued progress in hPSC differentiation may further expand the immunotherapy toolbox to include B cells, $\gamma\delta$ T cells, other innate lymphoid cells, and additional antigen-presenting or regulatory immune populations for cancer treatment [75,107].

Emerging technologies for next-generation cancer modeling

iPSC-derived assembloids

iPSC-derived assembloids, generated by integrating two or more lineage-specific organoids or differentiated cell populations, offer a next-generation platform to model the complex interactions between multiple cell types within a single organoid or within predifferentiated populations of interest [108]. This is particularly important because malignancies are influenced by interactions between various cell types and tissue compartments, and this complexity cannot be fully captured by organoids. Assembloids allow the incorporation of tumor cells, stromal populations, immune components, and vascular-like structures within a single 3D system, providing a platform to model complex TME interactions, thereby permitting spatial and functional organization that more closely mimics *in vivo* tumors. For instance, iPSC-derived fibroblasts can be combined with epithelial or brain tumor organoids to study cancer-associated fibroblast-mediated remodeling, paracrine signaling, and immune modulation. Recent advances in iPSC differentiation have enabled the generation of multiple fibroblast subpopulations, including cardiac, hepatic, and dermal fibroblasts, demonstrating the capacity of iPSCs to produce heterogeneous stromal lineages resembling *in vivo* tissues [109]. This is especially important for solid tumors, where stromal cells influence extracellular matrix remodeling, immune exclusion, angiogenesis, and therapy resistance. However, challenges remain in generating cancer-relevant multicellular 3D models that faithfully distinguish malignant from normal tissues. For example, organoids derived from rectal tumors and matched adjacent normal tissues exhibit distinct gene expression profiles and differential therapeutic responses, highlighting the importance of accurately recapitulating tumor-specific molecular and functional characteristics when developing iPSC-derived multicellular 3D models, including organoids and assembloids, for cancer research [110]. As protocols become more standardized and reproducible, iPSC-derived assembloids are poised to become indispensable tools for modeling complex cancers that cannot be adequately captured by single-lineage systems (Figure 4A).

AI- and machine learning-optimized lineage differentiation for next-generation tumor models

Despite their promise, iPSC-based models remain limited by variability in reprogramming, differentiation efficiency, lineage fidelity, and reproducibility. In addition to biological variability, technical variability introduced by manual experimental procedures, such as pipetting inaccuracies and inconsistent reagent handling, can also compromise differentiation outcomes and reproducibility. Integrating laboratory automation platforms, including robotic liquid handling systems, can minimize operator-dependent variability by ensuring precise and consistent execution of differentiation protocols. Recent advances in AI and machine learning offer transformative opportunities to overcome these challenges and accelerate the development of robust cancer models. **Artificial intelligence (AI)** and machine learning approaches can be applied to optimize differentiation protocols by integrating high-dimensional datasets, including transcriptomics, epigenomics, proteomics, and live-cell imaging. Coupling AI-guided protocol optimization with automated experimental platforms enables iterative refinement of differentiation conditions while reducing human-induced variability, thereby improving reproducibility across laboratories. For example, these methods have been applied to phase-contrast microscopy images of iPSC-derived endothelial cells and retinal pigment epithelium sheets to predict cell identity and assess differentiation [111,112], as well as to refine liver lineage differentiation to improve efficiency and fidelity [113]. Additional developments include the use of high-throughput screening

Clinician's corner

iPSC-based cancer platforms are not merely experimental stem cell systems; they are emerging human-relevant models for studying tumor initiation, treatment response, and resistance in ways that conventional cell lines and many animal models cannot fully capture.

iPSC-derived immune cell products, including T cells, NK cells, macrophages, and DCs, are advancing the concept of off-the-shelf cell therapy. These approaches may eventually reduce manufacturing delays, product-to-product variability, and dependence on heavily pretreated or lymphopenic patients as autologous cell sources.

For clinicians, the near-term value of these platforms lies in translational prediction rather than routine diagnosis. Patient-specific iPSC-derived organoids, assembloids, and immune coculture systems may provide a unique and integrative platform to identify drug sensitivities, elucidate mechanisms of therapeutic failure, and refine biomarker-driven clinical trial design.

The most immediate clinical impact will likely be in precision oncology and early-phase therapeutic development. Integration of iPSC-based modeling with multiomics, bioprinting, and AI-guided differentiation could improve patient stratification, accelerate drug discovery, and support more rational design of immunotherapy combinations before these tools are broadly deployed in routine care.

Clinical interpretation should remain cautious. Although iPSC-derived models can better reflect human genetics and developmental context, current limitations include incomplete maturation, variable lineage fidelity, incomplete reconstruction of the TME, and uncertain correlation with patient outcomes across tumor types.

methods to identify various combinations of transcription factors to yield desired cell types. Liu *et al.* have developed a rapid screening process to generate microglia-like cells from human iPSCs through iterative screening of transcription factors [114]. Other approaches involve the generation of immune cells using a single-cell screening platform that can identify combinations of transcription factors to optimize immune reprogramming [115]. This approach can identify critical signaling nodes, temporal windows, and factor combinations required to drive specific cancer-relevant lineages with high fidelity. It is particularly valuable for generating developmentally restricted or poorly defined cell types that are implicated in cancer initiation (Figure 4B).

Tissue engineering strategies for advanced 3D cancer modeling

3D culture systems offer clear advantages over 2D models by more closely recapitulating native extracellular matrix architecture, but they remain limited by the absence of supporting tissue components, as well as increased costs and technical complexity [116]. In addition, difficulties lie in the generation of successful models that rely on the proper proportions of cells and the regeneration of the cellular microenvironment. Biological 3D printing, or bioprinting, has emerged as a tissue-engineering strategy to address these limitations by enabling controlled assembly of tissue-representative architectures [117]. Bioprinting workflows can incorporate either undifferentiated hPSCs, with differentiation induced after deposition onto 3D scaffolds [118], or lineage-committed derivatives printed into defined architectures, with differentiation induced first and then followed by printing of the cellular material [119]. Biomaterial choice also plays a critical role in maintaining cell viability and developmental potential. Approaches combining techniques such as hanging-drop spheroid formation with valve-based single-nozzle deposition have been followed by droplet- and extrusion-based bioink printing of differentiated hESCs [120,121]. These techniques have enabled the generation of functional corneal endothelial cells, human neurons, and cartilage from bioprinted progenitors (Figure 4C) [122]. Importantly, bioprinting offers unique opportunities for iPSC-based cancer modeling by enabling spatial control over tumor cells, stromal components, and extracellular matrices, thereby facilitating the study of TME interactions and supporting the development of complex, patient-specific tumor models for precision oncology [123].

Taken together, AI-guided differentiation offers the potential for adaptive and personalized cancer modeling, directing patient-specific iPSCs toward tumor-relevant lineages based on genetic background and disease context. Integrating AI-enabled differentiation with iPSC-derived organoids and assembloids, as well as tissue engineering approaches such as bioprinting-based platforms, can redefine tumor modeling by improving fidelity, scalability, and reproducibility. The ability to spatially organize tumor cells, stromal components, and extracellular matrices within engineered 3D constructs adds a critical layer of physiological relevance. This synergy between hPSC research and computational methods promises more accurate disease models, scalable drug screening, and deeper insights into complex tumor biology, ultimately providing new avenues to accelerate translational research and advance cancer therapies (Figure 4D).

Concluding remarks and future perspectives

Over the past decade, hPSCs have been increasingly applied to cancer research, offering a human-specific platform to model tumor initiation, progression, and therapeutic response. Despite their promise, widespread adoption has been hindered by technical challenges in achieving fully mature and context-appropriate cell types, as well as by the long-standing dominance of mouse models, which have served as the gold standard in cancer biology for over 30 years (see Outstanding questions). However, recent policy changes by the National Institutes of Health (NIH) and FDA mark a pivotal shift in this landscape. In 2025, the NIH announced that new funding opportunities would no longer focus exclusively on animal models but would instead prioritize human-based new approach methodologies, including iPSCs, organoids, tissue chips, and AI-

Outstanding questions

Can iPSC-based cancer models outperform conventional animal, organoid, and patient-derived models in predicting human tumor biology and therapeutic response?

How can reprogramming-based models preserve aging, epigenetic memory, clonal evolution, and tumor heterogeneity that are often reset during iPSC generation?

Can iPSC-derived organoids and assembloids reconstruct a clinically relevant TME with stromal, vascular, immune, and mechanical complexity?

Will universal hPSC-derived immune-cell therapies overcome rejection, limited persistence, and tumor immune escape sufficiently to compete with autologous approaches?

What evidence threshold is required for iPSC-based cancer platforms to move from mechanistic research tools to decision-support systems in precision oncology?

enabled systems, in alignment with parallel FDA efforts to reduce animal testing for select therapeutics. These policy shifts emphasize the need for models with greater relevance to human biology and improved translational predictability. Within this framework, iPSC-based cancer models are uniquely positioned to integrate genetic context, developmental lineage, and TME interactions in a human setting, marking the beginning of a new era for iPSC-driven cancer research. In addition to modeling oncogenic mechanisms, iPSC-derived systems have been applied to study treatment-associated toxicities that influence therapeutic decision-making [124]. These advances position iPSC-based systems as versatile, human-relevant platforms that not only model cancer initiation and progression but also enable therapeutic discovery, toxicity prediction, and precision medicine applications, ultimately bridging the gap between basic research and clinical translation.

Despite these advantages, several important challenges remain. First, human cell identity is not fixed. While classical classifications define approximately 200–300 cell types, single-cell and spatial profiling reveal from several hundred to over a thousand cell states, indicating a continuum of cellular identity. This incomplete definition of cell types, together with limited *in vitro* maturation of lineages, constrains accurate modeling of cells of origin, disease mechanisms, therapeutic responses, and TME reconstruction. In addition, patient-derived iPSCs preserve the genetic background of individual patients, introducing substantial interpatient heterogeneity as a major translational challenge. Even among patients harboring the same driver mutations, differences in germline genetics, epigenetic states, and environmental exposures can lead to marked variability in disease phenotypes and therapeutic responses, underscoring the need to account for patient-specific variability in preclinical modeling. To address this issue, iPSC-based studies should incorporate panels of patient-derived lines representing diverse genetic and clinical backgrounds rather than relying on single-donor models. Genome editing to generate isogenic controls can distinguish mutation-specific effects from patient-specific variation, while multipatient iPSC platforms integrated with multiomics profiling and drug screening enable identification of both broadly effective and patient-tailored therapeutic strategies.

Importantly, most current hPSC models primarily capture cell-autonomous mechanisms and do not fully recapitulate the complex extrinsic influences of the TME, including interactions with stromal, immune, vascular, and neural components. Distinguishing the relative contributions between intrinsic genetic alterations and microenvironmental cues remains a major challenge in the field. Accurately modeling tissue-specific niche conditions, such as extracellular matrix composition, mechanical forces, metabolic constraints, and normoxic versus hypoxic environments, also remains difficult. Additional limitations include variability in reprogramming and differentiation efficiency, incomplete cellular maturation, batch-to-batch variability, limited representation of tumor heterogeneity, and challenges in modeling long-term tumor evolution and clonal selection.

These limitations highlight key priorities for future development. Differentiation protocols are being refined through optimized signaling and computational approaches, while organoid and assembloid systems are being improved to better recapitulate tissue architecture and TME complexity. In parallel, integrating multicellular organoids, coculture systems, and assembloids with bioengineered matrices, **tumor-on-a-chip**, microfluidic platforms, and spatial multiomics can more faithfully reconstruct TME interactions and tissue-specific niches, enabling controlled fluid dynamics, microscale architecture, and spatiotemporal regulation of biochemical and mechanical cues to model processes such as tumor invasion, angiogenesis, and immune cell migration, while providing continuous nutrient and oxygen gradients that better reflect *in vivo* tumor progression [125,126]. Combining hPSC-based models with genome editing, single-cell

analysis, and high-throughput functional screening will further enable systematic dissection of cancer mechanisms and therapeutic vulnerabilities, and establishing standardized differentiation protocols, benchmarking criteria, and robust quality-control frameworks will be essential to improve reproducibility and accelerate clinical translation. Collectively, these advances position the hPSC platform as a powerful system for elucidating cancer biology, identifying therapeutic targets, and enabling cell-based therapeutic development.

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Declaration of interests

The authors declare no competing interests.

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