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Review

Pluripotent stem-cell-derived therapies in clinical trial: A 2025 update

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SUMMARY

Since the first derivation of human pluripotent stem cells (hPSCs) 27 years ago, technologies to control their differentiation and manufacturing have advanced immensely, enabling increasing numbers of clinical trials with hPSC-derived products. Here, we revew the landscape of interventional hPSC trials worldwide, highlighting available data on clinical safety and efficacy. As of December 2024, we identify 116 clinical trials with regulatory approval, testing 83 hPSC products. The majority of trials are targeting eye, central nervous system, and cancer. To date, more than 1,200 patients have been dosed with hPSC products, accumulating to >10^{11} clinically administered cells, so far showing no generalizable safety concerns.

INTRODUCTION

The derivation of human embryonic stem cells (hESCs) in 1998[1] enabled the production of non-cancerous human cells in practically unlimited quantities and provided access to therapeutically important human cell types, such as insulin-producing beta cells, retinal pigment epithelial cells, cardiomyocytes, and neurons. This discovery laid the foundation for the development of regenerative cell therapies engineered entirely in the lab, and it was thus anticipated that hESCs could revolutionize the treatment of chronic diseases. The generation of human induced pluripotent stem cells (hiPSCs) in 2007[2] further heightened this anticipation, allowing the reprogramming of somatic cells. It was now possible to create autologous cell lines and lines from human leukocyte antigen (HLA) homozygous donors, both serving to reduce or possibly eliminate the need for immunosuppression in transplanted individuals. Parthenogenesis and somatic cell nuclear transfer were alternative approaches to generating hPSCs.[3] However, complicated technical procedures and concerns regarding a lack of genomic imprinting[4] have limited their use clinically.

The translation of hPSC products into the clinic has been challenged by several technological and regulatory hurdles, which have made hPSC product development lengthy and expensive: (1) decades of research were required to understand human tissue specification and differentiation into functional cell types at high purity while avoiding potentially hazardous off-target cells.[5–7] (2) *In vivo* safety and efficacy studies have required the challenging development of animal models harboring disease-specific phenotypes combined with immunodeficient backgrounds to allow for long-term investigation of human xenografts.[8] (3) The adaptation of complex and lengthy manufacturing procedures involving many biological components and good manufacturing practice (GMP) has been challenged by a lack of commercially available GMP-grade and xeno-free stem cell reagents, requiring extensive sponsor-driven risk assessments and adventitious agent testing of raw materials. (4) The necessity for long-term toxicity, biodistribution, and tumorigenicity xenograft studies under good laboratory practice (GLP) has required laborious retraining of staff at *in vivo* contract research organizations (CROs). (5) Regulatory guidelines for the development of hPSC products were not in place for many years and are still challenged by a lack of consistency across jurisdictions. In addition, clinical testing of PSC-derived products required significant innovation in cell manufacturing as initial hESC culture conditions involved complex manual "picking" of colonies on mouse feeder cells and media containing bovine serum.[1] Many manufacturing improvements have been introduced, including feeder-free culture systems[9] and fully defined xeno-free culture media for derivation and propagation of hPSCs.[10] Coincident with the development of improved culture systems, hESC banks generated under GMP conditions were emerging in Israel, Singapore, and the UK during the years 2007–2012.[11–13] The first trials, however, used GMP master cell banks derived from research-grade hESC lines, such as the widely adopted H1/WA01 and H9/WA09 lines from WiCell (Tables 1 and 2).

Initial clinical trials were targeted toward indications requiring lower cell numbers (e.g., 0.1–10 million) and implantation into "immune-privileged" sites, such as the CNS and eye, which were not expected to require life-long immunosuppression. Geron Corporation was the first sponsor to successfully achieve United States Food and Drug Administration (FDA) clearance for a phase I trial with an hPSC-derived product: the hESC-derived oligodendrocyte progenitor product (GRN-OPC1) for the treatment of thoracic spinal cord injury (SCI) (NCT01217008).[104]

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Table 1. Ocular products

Product name	Product type	Source	Cell line	Allo/Auto	Repr. method	Indication	Sponsor	Trial ID	Study phase	Target enrollment	Actual dosed patients	Trial sites	Dose per eye	Immune suppr.	Start date	Status	Clin. ref.	Pre-clin. ref
MA09-hRPE	RPE suspension	hESC	MA09	Allo	–	dry AMD	Astellas	NCT01344993	I/II	ND	13	US	50,000, 100,000, 150,000, 200,000	Y	2011	C	Schwartz et al.[14–16]	Lu et al.[17]
							CHABiotech	NCT01674829	I/II	ND	12	KR	50,000	Y	2012	T[a]	Song et al.[18] and Shim et al.[19]	
						SMD		NCT01625559	I	ND	3			Y	2012	C	Song et al.[18] and Sung et al.[20]	
							Astellas	NCT01345006	I/II	ND	13	US	50,000, 100,000, 150,000, 200,000	Y	2011	C	Schwartz et al.[14–16]	
								NCT01469832	I/II	ND	12	UK		Y	2011	C	Mehat et al.[21]	
ASP7317-RPE	RPE suspension	hESC	AP7317	Allo	–	dry AMD		NCT03178149	I	42	ND	US	3 doses	Y	2018	A	–	–
iPSC-RPE sheet	RPE cell sheet	hiPSC	–	Auto	E	wet AMD	RIKEN	UMIN000011929	I/II	6	1	JP	1.3 × 3 mm (no scaffold)	N	2013	C	Takagi et al.[22] and Mandai et al.[23]	Kamao et al.[24] and Hirami et al.[25]
OpRegen (RG6501)	RPE suspension	hESC	HAD-C 102	Allo	–	advanced dry AMD	Hoffman-La Roche[b]	NCT02286089	I/II	ND	24	US, IL	50,000–200,000	Y	2015	A	Ho et al.[26] and Lineage Cell Therapeutics[27]	McGill et al.[28]
						GA secondary to dry AMD	Genentech[b]	NCT05626114	II	60	ND	US, IL	200,000	ND	2023	A	–	
PF-05206388	RPE on polyester membrane	hESC	Shef-1	Allo	–	wet AMD[c]	Moorfields Eye Hospital	NCT01691261	I	10	9	UK	6 × 3 mm, ~100,000	Y	2015	A	da Cruz et al.,[29] Soomro et al.,[30] da Cruz et al.[31]	Vugler et al.[32]
hESC-RPE	RPE suspension	hESC	Q-CTS-hESC-2	Allo	–	wet AMD, SMD	Southwest Hospital	NCT02749734	I/II	15	7	CN	SMD: 100,000, AMD: 1 M	Y	2015	U	Li et al.,[33] Liu et al.,[34] and Yin et al.[35]	Wu et al.[36]
CPCB-RPE1	RPE on a parylene membrane	hESC	WA09 (H9)	Allo	–	dry AMD	Regenerative Patch Technologies	NCT02590692	I/II	16	16	US	~100,000, 3.5 × 6.25 mm membrane	Y	2016	C	Kashani et al.[37–39] and Humayun et al.[40]	Fernandes et al.,[41] Koss et al.,[42] and Thomas et al.[43]
								NCT06557460	II	18[d]	0	US		Y	2025	X	–	Fernandes et al.,[41] Koss et al.,[42] and Thomas et al.[43]
hESC-RPE	RPE, monolayer or suspension	hESC	WA09 (H9)	Allo	–	wet/dry AMD, SMD	Federal University of Sao Paulo	NCT02903576	I/II	ND	15	BR	100,000	Y	2015	C	Brant Fernandes et al.[44]	
iPSC-RPE cell suspension	RPE suspension	hiPSC	QHJI01s04[f]	Allo/HLA	E	wet AMD	Kobe City Eye Hospital	UMIN000026003	I	5	5	JP	250,000	Y	2017	C	Sugita et al.[45]	Sugita et al.[46–48]
iPSC-derived RPE/PLGA	RPE on PLGA scaffold	hiPSC	–	Auto	E	dry AMD	NIH/NEI	NCT04339764	I/II	20	2	US	2 × 4 mm, ~70,000	N	2020	A	–	Khristov et al.[49]
hESC-RPE	RPE suspension	hESC	CTS-hESC-2, Q-CTS-hESC-78	Allo	–	dry AMD	Chinese Academy of Sciences	NCT02755428	I/II	10	5	CN	150,000	Y	2018	A	–	
				Allo/HLA		dry AMD		NCT03046407	I/II	10	6		150,000	Y	2017	A	–	
				Allo		retinitis pigmentosa		NCT03944239	I	10	10		150,000	Y	2020	A	Zhang and Jin[50]	

(*Continued on next page*)

Table 1. *Continued*

Product name	Product type	Source	Cell line	Allo/Auto	Repr. method	Indication	Sponsor	Trial ID	Study phase	Target enrollment	Actual dosed patients	Trial sites	Dose per eye	Immune suppr.	Start date	Status	Clin. ref.	Pre-clin. ref
aiPSC-RPE CSt	RPE cell strip	hiPSC	QHJI01s04[f]	Allo/HLA	E	RPE impaired disease	VCCT Inc	jRCTa050210178	I/II	3	3	JP	up to 400,000	Y	2022	A	–	Kajita et al.[51] and Nishida et al.[52]
Retinal organoid sheets	retinal photoreceptor organoids, cut into sheets	hiPSC	QHJI01s04[f]	Allo/HLA	E	retinitis pigmentosa	CiRA	jRCTa050200027	I	2	2	JP	0.5 × 1 mm sheet	Y	2020	C	Hirami et al.[53]	Watari et al.[54]
CLS-001	corneal endothelial cell suspension	hiPSC	QHJI01s04[f]	Allo/HLA	E	bullous keratopathy	Keio University	jRCTa031210199	I	3	1	JP	800,000	Y	2022	T	Cellusion[55]	Hatou et al.[56] and He et al.[57]
SCNT-hES-RPE	RPE suspension	SCNT-hESC	ND	Allo	–	dry AMD	CHA University	NCT03305029	I	3	1	KR	ND	N	2016	U	Sung et al.[58]	Chung et al.[59]
iPSC-RPE	RPE suspension	hiPSC	–	Auto	ND	dry/wet AMD	Beijing Tongren Hospital	NCT05445063	I	10	0	CN	ND	ND	2022	A	–	Zhang et al.[60]
BinaCell	RPE suspension	hESC	RoyanCell	Allo	–	GA secondary to dry AMD	Royan Institute	NA	I/II	10	0	IRAN	150,000	Y	2025	X	–	–
Patch ISTEM-01	RPE on human amniotic membrane in gelatin	hESC	RC-9	Allo	–	retinitis pigmentosa (monogenic)	iStem	NCT03963154	I/II	ND	7	FR	14.5 mm^2, 4,800–15,000 cells/mm^2	Y	2019	A	Foundation Fighting Blindness[61] and Monville et al.[62]	Ben M'Barek et al.[63]
iCEPS	corneal epithelial cell sheet	hiPSC	YZWJs524[f]	Allo/HLA	E	limbal stem-cell deficiency	Osaka University	UMIN000036539	I	4	4	JP	ND	Y/N[e]	2019	C	Soma et al.[64] and Osaka University[65]	Yoshinaga et al.[66] and Hayashi, et al.[67]
OpCT-001	photoreceptors	hiPSC	ND	Allo	ND	primary photoreceptor disease	BlueRock Therapeutics	NA	I/II	ND	ND	US	ND	Y	2025	X	–	–
Eyecyte-RPE	RPE suspension	hiPSC	ND	Allo	ND	GA secondary to dry AMD	Eyestem	NCT06394232	I/II	36	3	IN	100,000, 200,000, 300,000	Y	2024	A	–	Surendran et al.[68]

Allo, allogeneic; Auto, autologous, Reprogr. method, reprogramming method; Immune suppr., immune suppression; (pre-)clin. ref, (pre-)clinical references; SCNT, Somatic cell nuclear transfer; HLA, HLA subtype in some cases matched to patient; Astellas, Astellas Institute for Regenerative Medicine; CiRA, Center for iPS Cell Research and Application; UCLA, University of California, Los Angeles; NIH, National Institute of Health (USA); NEI, National Eye Institute; ND, not disclosed; NA, not assigned yet. Reprogramming methods: E, episomal. Countries: BR, Brazil; CN, China; FR, France; IL, Israel; IN, India; JP, Japan; KR, Korea; NL, UK, United Kingdom; US, United States of America. Dose is provided as number of cells, unless stated otherwise. Trial status: C, completed; A, active; T, terminated; U, unknown; X, clinical trial approval obtained, trial not yet initiated.

[a]Sponsor decision.

[b]In partnership with Lineage Cell Therapeutics.

[c]Acute wet AMD and anti-VEGF non-responders.

[d]Additional 6 patients will receive sham treatment.

[e]2 out of 4 patients received systemic immunosuppression.

[f]HLA homoygous cell line

Table 2. CNS products

Product name	Product type	Source	Cell line	Allo/ Auto	Repr. method	Indication	Sponsor	Trial ID	Study phase	Target enrollment	Actual dosed patients	Trial sites	Dose	Immune suppr.	Start date	Status	Clin. ref.	Pre-clin. ref
GRN-OPC1	oligodendrocyte progenitor cells (OPCs)	hESC	H1	Allo	–	SCI (th)	Lineage Cell Therapeutics[a]	NCT01217008	I	ND	5	US	2 M	Y	2010	T	McKenna et al.[69]	Priest et al.[70] and Fessler et al.[71]
AST-OPC1					–	SCI (cer)	Lineage Cell Therapeutics[b]	NCT02302157	I/II	35	30	US	2 M, 10 M, 20 M	Y	2015	C	Fessler et al.[72]	Priest et al.,[70] Fessler et al.,[71] and Manley et al.[73]
hiPSC-NS-PCs	neural stem cells	hiPSC	YZWJs513[e]	Allo/ HLA	E	SCI (th, cer)	Keio University	UMIN000035074	I/II	4	4	JP	2 M	Y	2020	A	Sugai et al.[74]	–
PSA-NCAM(+) NPC	neural precursor cells (PSA-NCAM$^+$)	hESC	SNU-hES32	Allo	–	SCI (cer)	S.Biomedics	NCT04812431 KCT0005628	I/II	6	1	KR	10.8 M	Y	2021	A	–	Kim et al.[75]
hESC DA progenitors	DA progenitors	hESC	Q-CTS-hESC-2, Q-CTS-hESC-338	Allo/ HLA	P	PD	Chinese Academy of Sciences	NCT03119636 ChineseASZQ-003	I/II	50	24	CN	1 M, 4 M, 10 M	Y	2015	A	–	Wang et al.[76]
ISC-hpNSC	neural stem cells	hpESC	ND	Allo	P	PD	Cyto Therapeutics Pty Limited/ ISCO	NCT02452723	I/II	12	12	AU	30 M, 50 M, 70 M	N	2016	C	International Stem Cell Corporation[77]	Gonzalez et al.[78] and Garitaonandia et al.[79]
DA progenitors	DA progenitors	hiPSC	–	Auto	E	PD	McLean Hospital	–[c]	–[d]	1	1	US	8 M	N	2017	C	Schweitzer et al.[80]	Song et al.[81]
							Massachusetts General Hospital	NCT06687837	I/II	8	0	US	8 M, 16 M	N	2024	A	–	
iPSC-derived DA progenitors	DA progenitors	hiPSC	QHJI01s04[e]	Allo/ HLA	E	PD	Kyoto University Hospital	UMIN000033564	I/II	7	7	JP	4.8 M, 9.6 M	Y	2018	C	–	Kikuchi et al.[82]
Bemdaneprocel	DA progenitors	hESC	WA09 (H9)	Allo	–	PD	BlueRock Therapeutics	NCT04802733	I	12	12	US, CA	1.8 M, 5.4 M	Y	2021	C	BlueRock Therapeutics[83,84]	Kim et al.[85] and Piao et al.[86]
STEM-PD	DA progenitors	hESC	RC17	Allo	–	PD	Region Skåne	NCT05635409	I/II	8	8	SE, UK	7 M, 14 M	Y	2022	A	Lund University[87]	Kirkeby et al.[88] and Nolbrant et al.[89]
TED-A9	DA progenitors	hESC	SNU-hES32	Allo	–	PD	S.Biomedics	NCT05887466	I/II	12	12	KR	3.15 M, 6.3 M	Y	2023	A	S.Biomedics[90]	Park et al.[91]
ANPD001	DA progenitors	hiPSC	–	Auto	S	PD	Aspen Neuroscience	NCT06344026	I/II	9	3	US	5 M, 10 M	N	2024	A	–	Emborg et al.[92]
Autologous DA neurons	DA neurons	hiPSC	–	Auto	S	PD	McLean hospital	NCT06422208	I/II	6	2	US	ND	N	2024	A	–	Hallett et al.[93] and Osborn et al.[94]
NouvNeu001	DA progenitors	hiPSC	ND	Allo	ND	PD	iRegene Therapeutics	NCT06167681	I/II	40	ND	CN	ND	ND	2024	A	–	–
								NCT06608355	I/II	6	ND	US	ND	ND	2024	A	–	–
CT1-DAP001	DA progenitors	hiPSC	QHJI01s04[e]	Allo	E	PD	UCSD[d]	NCT06482268	I/II	7	ND	US	4.2–5.4 M	Y	2024	A	Sumitomo Pharma Co[95]	–
DSP-1083	DA progenitors	hiPSC	ND	Allo	ND	PD	Sumitomo Pharma	NA	I/II	ND	ND	US	ND	Y	2025	X	–	–
DopaCell	DA progenitors	hESC	RoyanCell	Allo	–	PD	Royan Institute	IRCT201607 04028786N2	I	4	0	IRAN	10 M	Y	2025	X	–	Naderi et al.[96]

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Table 2. ***Continued***

Product name	Product type	Source	Cell line	Allo/ Auto	Repr. method	Indication	Sponsor	Trial ID	Study phase	Target enrollment	Actual dosed patients	Trial sites	Dose	Immune suppr.	Start date	Status	Clin. ref.	Pre-clin. ref
AstroRx	astrocytes	hESC	HAD-C 100	Allo	–	ALS	Kadimastem	NCT03482050	I/II	21	10	IL	100 M, 250 M	Y	2018	C	Gotkine et al.[97] and Kadimastem[98]	Sonnenfeld et al.[99]
NR1-02	neural stem cells	hESC	WA09 (H9)	Allo	–	Stroke	Stanford University	NCT04631406	I/II	18	18	US	2.5 M, 5 M, 10 M, 20 M	Y	2021	A	Steinberg et al.[100]	Azevedo-Pereira et al.[101]
NRTX-1001	inhibitory interneurons	hESC	ND	Allo	–	Epilepsy, MTLE	Neurona Therapeutics	NCT05135091	I/II	16	10	US	2 doses	Y	2022	A	Neurona Therapeutics[102]	Bershteyn et al.[103]
						Epilepsy, MTLE bilateral		NCT06422923	I/II	10	0	US	2 doses	Y	2022	A	–	

Allo, allogeneic; Auto, autologous, Reprogr. method, reprogramming method; Immune suppr., immune suppression; (pre-)clin. ref, (pre-)clinical references; hpESC, human parthenogenetic ESC; HLA, HLA subtype in some cases matched to patient; DA, dopamine; PD, Parkinson's disease; SCI, spinal cord injury; th, thoracic; cer, cervical; ALS, amyotrophic lateral sclerosis; MTLE, mesial temporal lobe epilepsy; ISCO, International Stem Cell Corporation; UCSD, University of San Diego. ND, not disclosed; NA, not assigned yet. Reprogramming methods: E, episomal; P, partheno-genesis; S, Sendai virus. Countries: AU, Australia; BE, CA, Canada; CN, China; IL, Israel; IN, JP, Japan; KR, Korea; NL, SE, Sweden; UK, United Kingdom; US, United States of America. Dose is provided as number of cells, unless stated otherwise. M, million (10^6).Trial status: C, completed; A, active; T, terminated; X, clinical trial approval obtained, trial not yet initiated.

[a]Previously sponsored by Geron.

[b]Previously sponsored by Asterias Biotherapeutics.

[c]Single patient expanded access.

[d]In partnership with Sumitomo Pharma America.

[e]HLA homozygous cell line

Geron faced many hurdles when filing their 22,000 page Investigational New Drug (IND) application in 2008, as regulatory guidelines and standards for the manufacture, testing, and delivery of these types of therapeutics were not yet in place.[104] Preclinical safety testing for the Geron trial included a 12-month assessment of immunocompromised rats implanted with GRN-OPC1 product "spiked" with 1%, 5%, 10%, or 50% undifferentiated hESCs to assess the sensitivity of the animal model for tumor formation.[70] After being on hold for about 2 years, Geron was able to dose their first patient in 2010. However, 1 year later, after implanting 5 of the planned 10 patients, Geron announced that it was closing the SCI trial for financial reasons, causing considerable concern in the stem cell community.[105,106] In 2013, Geron's stem cell assets were acquired by BioTime and launched into a new company named Asterias Biotherapeutics, which reinitiated clinical trials with the OPC1 product in 2015 (Table 2). Only in 2022 were the results from these first dosed patients with the GRN-OPC1 product made available to the public.[69]

The next hPSC products to enter clinical trials were both based on retinal pigment epithelium (RPE) for treatment of ocular indications. The MA09-hRPE product from Advanced Cell Technology entered 5 trials from 2011 to 2015 (Table 1). Simultaneously, Masayo Takahashi and her team at the RIKEN institute in Japan developed the first autologous hiPSC product, which was tested in a Japanese investigator-driven clinical trial in 2013 for treatment of age-related macular degeneration (AMD, UMIN000011929). While typical Japanese investigator-driven clinical trials may have different regulatory requirements than FDA-approved phase 1 trials, the safety and efficacy testing required for this first Japanese trial was very extensive, similar to other trials with hPSC products. Only one patient was dosed in this first hiPSC study, as the complexities and significant cost of manufacturing for this autologous product precluded the continuation of the trial.[107]

These initial trials have paved the way for many subsequent trials, with significant developments seen in the past 5 years. In this review, we manually curated and filtered interventional hPSC product trials from publicly available trial registries, and we summarized the results in Tables 1, 2, 3, 4, 5, and 6; Figures 1, 2, and S1. Trials that were terminated or withdrawn without dosing of any patients, and trials that could not be verified through the sponsor or third-party sources or that did not have a planned initiation date, were excluded from the review and listed in Table S2. Additional information which was not available in the public domain has in some cases been provided through personal communication with sponsors. Individuals who have helped to fact-check information in the review as well as provided trial-related information per personal communication are listed in Table S3. Through this compiled information, we provide here a comprehensive overview of all previous and ongoing hPSC trials, including information on the number of patients enrolled in each trial, dose levels, trial results, and most relevant publications and press releases. Additional detailed information on immunosuppressive regimens is compiled in Table S1. As of December 2024, we count a total of 116 clinical trials in 19 countries testing hPSC-derived products for 34 different indications. The majority of these trials are phase I/IIa trials, designed to test safety and feasibility, with only few trials yet designed to test efficacy. Below, we summarize the products developed for each disease indication.

MACULAR DEGENERATION AND OTHER EYE DISEASES

Several macular degenerative diseases are caused by the dysfunction and loss of RPE, a monolayer of cells that provide support to the overlying photoreceptors. The loss of RPE results in the degeneration of photoreceptors and loss of vision.[168] Exploratory clinical studies replacing the damaged RPE by autologous transplantation of healthy RPE from the peripheral retina in the same eye showed potential beneficial effects.[169] To make such treatments more accessible to patients, several groups have worked to develop hPSC-derived RPE products for the treatment of AMD, Stargardt's macular dystrophy (SMD) and other degenerative diseases. Subsequently, newer products for ocular indications also include photoreceptors and corneal epithelial and endothelial cells. To date, at least 21 products targeting ocular diseases have entered clinical trial for different indications (Table 1).

Dry AMD and SMD

The first studies delivering hESC-derived cells for ocular disease were initiated in 2011 by the company Advanced Cell Technology (later acquired by Ocata Therapeutics and then by Astellas Institute for Regenerative Medicine).[14–16] In these studies, a hESC-derived cryopreserved RPE cell suspension (MA09-hRPE) was injected into the subretinal space using vitreoretinal surgery in patients with SMD (NCT01345006) or dry AMD (NCT01344993, Table 1). Although slight vision improvements were measured for SMD patients (−10 to 15 letters) and dry AMD patients (0–15 letters), the authors cautioned that the visual acuity measurements can be unreliable in these advanced disease patients.[14–16] In 2011, an additional trial of MA09-hRPE for SMD was initiated in the UK (NCT01469832). A more detailed analysis of spatial correlation of retinal structure and function was performed, but no significant benefit was found in any of the treated patients at 12 months, potentially due to the advanced disease stage of patients included in the study.[21] In 2018, a new phase I trial for dry AMD was initiated by Astellas using a different cell line and product formulation (ASP7317-RPE, NCT03178149), but results have not yet been published. CHABiotech in Korea also performed trials with MA09-hRPE and saw potential vision improvements by 12 and 19 letters in SMD patients at 1 year (NCT01625559)[18,20] and by 1–9 letters in dry AMD patients (NCT01674829).[18,19] However, although the untreated AMD eye decreased by 6 and 20 letters, the fellow untreated SMD eye showed an improvement of 9 letters, indicating that caution should be taken in the interpretation of clinical improvements.[18]

Next into clinical trial in 2015 was the OpRegen product developed by Cell Cure Neurosciences, Ltd., a subsidiary of Lineage Cell Therapeutics. OpRegen, a cryopreserved suspension of hESC-derived RPE cells, was delivered to the subretina using pars plana vitrectomy and retinotomy or via a suprachoroidal route (NCT02286089). Results showed that patients with low vision demonstrated normal disease progression; however, patients with less vision impairment demonstrated stable or improved visual acuity (−2 to +24 letters),[26,170] supporting the argument that visual improvement may be challenging to achieve in advanced disease patients. A phase II trial was initiated in 2023 with the same product (NCT05626114).

Table 3. Cardiomyocyte and muscle products

Product name	Product type	Source	Cell line	Allo/ Auto	Repr. method	Indication	Sponsor	Trial ID	Study phase	Target enrollment	Actual dosed patients	Trial sites	Dose	Immune suppr.	Start date	Status	Clin. ref.	Pre-clin. ref
HiCM-188	cardiomyocyte suspension	hiPSC	ND	Allo	S	heart failure	Help Therapeutics	NCT04982081	I	21	1	CN	50 M, 100 M, 150 M, 300 M, 450 M	Y	2021	A	–	Guan et al.[108]
								NCT05223894	I/II	20	0	CN	100 M	Y	2022	A	–	
								NCT05566600	I	32	1	CN	100 M, 200 M, 400 M	Y	2022	A	–	
								NCT03763136	I/II	20	20	CN	200 M	Y	2021	C	Zhang et al.[109]	
								NCT06340048	I/II	36	11	CN	50 M, 150 M, 450 M	Y	2023	A	–	
CD15+ Isl-1+ progenitors	cardiac progenitors in a fibrin gel patch	hESC	I6	Allo	–	heart failure	Assistance Publique-Hospitaux de Paris	NCT02057900	I	10	6	FR	5–10 M	Y	2013	C	Menasche et al.,[110] Menasche,[111] and Menasche et al.[112]	Bellamy et al.[113] and Menasche et al.[114]
iPSC-cardiomyocyte sheet	cardiomyocyte patch	hiPSC	QHJI14s04[c]	Allo/ HLA	E	ischemic cardiomyopathy	Osaka University Hospital	NCT04696328	I	10	3	JP	3 patches, 33 M cells/ patch, ~3.5 cm diameter	Y	2019	U	Kawamura et al.[115]	Kashiyama et al.[116]
							Osaka University Hospital	jRCT2053190081	I	10	1	JP	3 patches, 33 M cells/ patch	Y	2020	A	Miyagawa et al.[117]	
HS-001	cardiac spheres	hiPSC	ND	Allo	ND	heart failure	Heartseed, Inc.	NCT04945018	I/II	10	6[a]	JP	50 M, 150 M	Y	2022	A	Heartseed[118]	Kawaguchi et al.[119] and Kobayashi et al.[120]
EHM	patch of cardiomyocyte, stromal cells, and collagen	hiPSC	LiPSC-GR1.1 (TC1133)	Allo	E	advanced heart failure	University Medical Center of Göttingen[b]	NCT04396899	I/II	53	13	DE	200–800 M	Y	2020	A	Repairon[121]	Tiburcy et al.[122] and Riegler et al.,[123]
hESC-CMs	cardiomyocyte suspension	hESC	H7	Allo	–	chronic ischemic left ventricular dysfunction	Stanford University	NCT05068674	I/II	18	6	US	50 M, 150 M, 300 M	Y	2022	A	–	Tiburcy et al.[122] and Riegler et al.[123]
iPSC-CL	cardiac lineage	hiPSC	–	Auto	ND	congenital heart disease	HeartWorks, Inc.	NCT05647213	I	50	ND	US	dose escalation, intended clinical dose 100 M	N	2023	A	–	Scholz et al.[124]
MyoPAXon	muscle stem cells	hiPSC	LiPSC-GR1.1 (TC1133)	Allo	E	duchenne muscular dystrophy	University of Minnesota	NCT06692426	I	8	0	US	25 M, 50 M, 100 M, 200 M	Y	2024	X	–	Azzag et al.[125]

Allo, allogeneic; Auto, autologous, Reprogr. method, reprogramming method; Immune suppr., immune suppression; (pre-)clin. ref, (pre-)clinical referencesHLA, HLA subtype in some cases matched to patient. ND, not disclosed. Reprogramming methods: E, episomal; S, Sendai virus. Countries: CN, China; DE, Germany; FR, France; JP, Japan; US, United States of America. Dose is provided as number of cells, unless stated otherwise. M, million (10^6). Trial status: C, completed; A, active; U, unknown; X, clinical trial approval obtained, trial not yet initiated.

[a]10 patients anticipated to be enrolled by the end of 2024.

[b]In partnership with Repairon GmbH and German Center for Cardiovascular Research (DZHK).

[c]HLA homozygous cell line

Table 4. Endocrine products

Product name	Product type	Source	Cell line	Allo/ Auto	Repr. method	Indication	Sponsor	Trial ID	Study phase	Target enrollment	Actual dosed patients	Trial sites	Dose	Immune suppr.	Start date	Status	Clin.ref.	Pre-clin.ref
VC-01	pancreatic endoderm cells (PEC-01) in Encaptra device	hESC	CyT49	Allo	–	T1DM	ViaCyte	NCT02239354	I/II	66	19	US, CA	250–500 M cells (1–2 implants)	N	2014	T	Clinicaltrial.gov[126]	Schulz[127] and Kroon et al.[128]
								NCT04678557	I/II	70	31	US	9–12 implants	N	2019	C	–	
VC-02	pancreatic endoderm cells (PEC-01) in macroencapsulation device							NCT03162926	I	ND	3	CA	up to 6 VC-02-20 implants	Y	2017	C	Keymeulen et al.[129]	Schulz[128] and Kroon et al.[129]
								NCT03163511	I/II	60	49	US, CA, BE	75–300 M cells (1–4 implants)	Y	2017	C	Shapiro et al.,[130] Ramzy et al.,[131] and Keymeulen et al.[132]	
VCTX210A	gene-edited pancreatic endoderm cells in macroencapsulation device	hESC	CyT49, hypoimmune	Allo	–	T1DM	ViaCyte	NCT05210530	I	ND	7	CA	up to 7 units	N	2022	C	BioSpace[133]	–
VX-880	pancreatic islet cells	hESC	ND	Allo	–	T1DM	Vertex Pharmaceuticals	NCT04786262	I/II[a]	37	16	US, CA, UK, DE, FR, IT, NL, CH, NO	2 doses	Y	2021	A	Vertex Pharmaceuticals[134]	–
VX-264	pancreatic islet cells (VX-880, encapsulated)	hESC	ND	Allo	–	T1DM	Vertex Pharmaceuticals	NCT05791201	I/II	ND	17	US, CA, DE, IT, NL, CH, UK	2 doses	N	2023	A	–	–
CiPSC islets	islet-like cells	hiPSC	ND	Auto	C	T1DM	Tianjin First Center Hospital	ChiCTR2300072200	I	3	1	CN	~2 B cells	Y	2023	A	Wang et al.[135]	–
Hepato-cytes	hepatocytes	hESC	ND	Allo	–	liver failure	Xiangya Hospital of Central South University	ChiCTR2100052988[b]	0	10	ND	CN	ND	ND	2022	U	–	–
HAES	hepatocytes	hESC	ND	Allo	–	neonatal urea-cycle disorder, bridge to liver transplant	National Center for Child Health and Development	JMA-IIA00412	I/II	5	2	JP	50 M/kg	ND	2018	U	National Center for Child Health and Development[136]	–

Allo, allogeneic; Auto, autologous, Reprogr. method, reprogramming method; Immune suppr., immune suppression; (pre-)clin. ref, (pre-)clinical references; T1DM, type 1 diabetes mellitus; ND, not disclosed. Reprogramming methods: C, chemical reprogramming.[137] Countries: BE, Belgium; BR, Brazil; CA, Canada; CH, Switzerland; CN, China; DE, Germany; FR, France; IT, Italy; IL, JP, Japan; KR, NL, Netherlands; NO, Norway; UK, United Kingdom; US, United States of America. Dose is provided as number of cells, unless stated otherwise. M, million (10^6); B, billion (10^9). Trial status: C, completed; A. active; T, terminated; U, unknown.

[a]This trial has been announced to be converted into a phase I/II/III trial.

[b]This trial has not been verified by the sponsor.

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Table 5. Immune and blood products

Product name	Product type	Source	Cell line	Allo/ Auto	Repr. method	Indication	Sponsor	Trial ID	Study phase	Target enrollment	Actual dosed patients	Trial sites	Dose	Lympho-depletion	Start date	Status	Clin.ref.	Pre-clin.ref
FT500	NK cells	hiPSC	ND	Allo	ND	advanced solid tumors	Fate Therapeutics	NCT03841110	I	ND	37	US	100 M, 300 M	Y	2019	C	Hong et al.[138]	–
FT516	NK + hnCD16 (high-affinity, non-cleavable CD16)	hiPSC	ND	Allo	ND	advanced B cell lymphoma	Fate Therapeutics	NCT04023071	I	ND	72	US	single dose 30 M, 90 M, 330 M	Y	2019	T	BioSpace,[139] Fate Therapeutics,[140] and Strati et al.[141]	Zhu et al.[142]
						solid tumors		NCT04551885	I	ND	12	US	–	Y	2020	T	–	
						ovarian cancer		NCT04630769	I	ND	3	US	3 infusions of 90 M, 300 M, 900 M	Y	2021	C	–	
	NK cells + high-affinity, ADAM17 non-cleavable CD16 (Fc receptor)	hiPSC	ND	Allo	ND	COVID-19	Masonic Cancer Center, University of Minnesota	NCT04363346	I	ND	5	US	90 M, 390 M, and1.29 B	Y	2020	C	–	–
FT596 (FT516 derivative)	NK + hnCD16 + IL-15RF (receptor fusion) + CD19-CAR	hiPSC	ND	Allo	ND	relapsed/ refractory B-NHL and CLL	Fate Therapeutics	NCT04245722	I	123	98	US	single dose 30 M, 90 M, 300 M, 900 M	Y	2020	T	Fate Therapeutics[143]	Goodridge et al.[144]
						NHL, DLBCL and high-grade BCL.		NCT04555811	I	ND	3	US	single dose 30 M, 90 M, 300 M	Y	2020	A		
FT538 (FT516 derivative)	NK + hnCD16 + IL-15RF + CD38KO	hiPSC	ND	Allo	ND	AML, MM	Fate Therapeutics	NCT04614636	I	ND	42	US	300 M	Y	2020	T	–	–
						monocytic leukemia, AML, ML		NCT04714372	I	ND	10	US	3 infusions of 100 M, 300 M, 1 B, 1.5 B	Y	2021	C	–	–
						solid tumors		NCT05069935	I	ND	16	US	–	Y	2021	T	–	–
						ovarian, fallopian tube and primary peritoneal cancer	Masonic Cancer Center, University of Minnesota	NCT05708924	I	33	2	US	50 M, 100 M, 1 B, and 1.5 B	Y	2023	S	–	–
FT576 (FT516 derivative)	NK + hnCD16 + + IL-15RF + CD38 KO + BCMA-CAR	hiPSC	ND	Allo	ND	MM	Fate Therapeutics	NCT05182073	I/II	50–100	ND	US	single dose 100 M, 300 M	Y	2021	C	–	Cichocki et al.[145]
FT819	T cell + novel CAR19 1XX + TCR KO	hiPSC	ND	Allo	ND	B cell malignancies	Fate Therapeutics	NCT04629729	I	50–75	ND	US	90 M, 180 M, 360 M	Y	2021	C	Fate Therapeutics[146]	Eyquem et al.[147]
						systemic lupus erythematosus	Fate Therapeutics	NCT06308978	I	64	3	US	360 M	Y	2024	A	Fate Therapeutics[148]	–
FT536	NK + hnCD16 + IL-15RF + CD38 KO + α3 domain of MICA/B -CAR	hiPSC	ND	Allo	ND	ovarian, fallopian tube and primary peritoneal cancer	Fate Therapeutics	NCT06342986	I	33	6	US	3 M, 100 M, 300 M, 1 B	Y	2024	A	–	–
						advanced solid tumors		NCT05395052	I	ND	6	US	ND	Y	2022	T	–	–

(*Continued on next page*)

Table 5. ***Continued***

Product name	Product type	Source	Cell line	Allo/ Auto	Repr. method	Indication	Sponsor	Trial ID	Study phase	Target enrollment	Actual dosed patients	Trial sites	Dose	Lympho-depletion	Start date	Status	Clin.ref.	Pre-clin.ref
FT522	NK + hnCD16 + IL-15RF + CD38 KO + CD19-CAR + ADR	hiPSC	ND	Allo	ND	BCL	Fate Therapeutics	NCT05950334	I	166	ND	US	ND	Y	2023	A	–	–
FT825	T cell + IL7RF + hnCD16a + CAR-HER2 + CXCR2 + chimeric TGFb-R, TCR/CD38-null	hiPSC	ND	Allo	ND	solid tumors	Fate Therapeutics	NCT06241456	I	50	37	US	100 M 300 M	Y	2023	A	–	–
AST-VAC2	dendritic cell	hESC	H1	Allo	-	non-small cell lung cancer	Cancer Research UK	NCT03371485	I	ND	9	UK	6 infusions of 10 M	ND	2018	C	Lineage Cell Therapeutics[149]	–
iPSC-NKT	NKT cell	hiPSC	ND	Allo	ND	head and neck cancer	Chiba University Hospital	jRCT2033200116	I	9	ND	JP	ND	ND	2020	A	–	Yamada et al.[150]
ICAR-ILC/ N101	NK + GPC3-CAR	hiPSC	QHJI01s04[b]	Allo/ HLA	E	ovarian clear cell carcinoma	National Cancer Center Hospital East	jRCT2033200431	I/II	18	ND	JP	3 infusions of 500 K/kg, 1 M/kg, 3 M/kg	ND	2021	A	Harano et al.[151]	Ueda et al.[152]
QN-023a	NK + CD33-CAR	hiPSC	ND	Allo	ND	AML	Institute of Hematology & Blood Diseases Hospital	NCT05601466[a]	I	18		CN	ND	Y	2022	A	–	Wang et al.[153]
						AML	Zhejiang University	NCT05665075[a]	I	19		CN	ND	Y	2022	A	–	
CNTY-101	NK + IL-15 + CD-19-CAR + Allo-evasion + sFGFR	hiPSC	ND	Allo	E	CD19-positive B cell malignancies	Century Therapeutics	NCT05336409	I	75	20	US	1–3 infusions of 100 M, 300 M, 1,000 M, and 3,000 M cells per cycle	Y	2022	A	Century Therapeutics,[154] Patel et al.,[155] and Ramachandran et al.[156]	–
MEG-002	HLA homozygous platelets	hiPSC	YZWJs513[b]	Allo/ HLA	E	thrombocytopenia	Megakaryon	JRCT2053210068	I/II	10	1	JP	60 B platelets	N	2021	T	Megakaryon Cororation[157]	Ito et al.[158]
iPLAT1	Platelets	hiPSC	imMKCL clone, M35-1	Auto	E	thrombocytopenia	CiRA, Kyoto University Hospital	jRCTa050190117	I	1	1	JP	140 B in 3 sequential doses	N	2021	C	Sugimoto et al.[159]	Sugimoto et al.[160]

Allo, allogeneic; Auto, autologous, Reprogr. method, reprogramming method; Immune suppr., immune suppression; (pre-)clin. ref, (pre-)clinical references;NK, natural killer cells; NKT, natural killer T cell, HSCs, hematopoietic stem cells; HLA, HLA subtype in some cases matched to patient; B-NHL, B cell non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; BCL, B cell lymphoma; DLBCL; diffuse large BCL, AML; acute myeloid leukemia; MM, Multiple myeloma; CiRA: Center for iPS Cell Research and Application; ND, not disclosed. Reprogramming methods: E, episomal; S, Sendai virus. Countries: CN, China; JP, Japan; UK, United Kingdom; US, United States of America. Dose is provided as number of cells, unless stated otherwise. M, million (10^6); B, billion (10^9). Trial status: C, completed; A, active; T, terminated; S, suspended.

[a]This trial has not been verified by the sponsor.

[b]HLA homozygous cell line

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Table 6. Stromal products

Product name	Product type	Source	Cell line	Allo/ Auto	Repr. method	Indication	Sponsor	Trial ID	Study phase	Target enrollment	Actual dosed patients	Trial sites	Dose	Immune suppr.	Start date	Status	Clin.ref.	Pre-clin.ref
CYP-001	MSC	hiPSC	ND	Allo	E	steroid-resistant acute GvHD	Cynata Therapeutics	NCT02923375	I	16	15	AU, UK	1 M/kg, max 100 M or 2 M/kg, max 200 M	Y/N[a]	2017	C	Bloor et al.[161] and Kelly et al.[162]	Ozay et al.[163]
						high-risk acute GvHD		NCT05643638	II	60	–	US, AU		N	2023	A	–	
						COVID-19		NCT04537351	I	24	14	AU	2 M/kg, max 200 M	N	2020	C	–	
						kidney transplant	LUMC[b]	NL-OMON53310	I	16	1	NL	2 M/kg, 4 M/kg	Y	2024	A	–	
CYP-004	MSC	hiPSC	ND	Allo	E	osteoarthritis	University of Sydney	ACTRN12620000870954	III	320	160[c]	AU	25 M	N	2020	A	–	–
CYP-006TK	MSCs with polymer-coated silicon membrane	hiPSC	ND	Allo	E	diabetic foot ulcers	Cynata Therapeutics	NCT05165628	I	30	30	AU	8 administrations of 25,000 cells/cm^2	N	2022	A	–	–
MSC-like cells	MSC	hESC	ND	Allo	–	meniscus injury	Tongji Hospital	NCT03839238[d]	I	18		CN	ND	ND	2019	U	–	–
CAStem	MSC	hESC	Q-CTS-hESC-2	Allo	–	pulmonary fibrosis from COVID-19	Wuhan Jinyintan Hospital	ChiCTR2000031139	I	20	20	CN	2 doses of 3 M/kg	N	2020	C	–	–
						COVID-19	Chinese Academy of Sciences	NCT04331613	I/II	9	1	CN	3 M, 5 M, 10 M/kg	N	2020	A	–	–
MR-MC-01	MSC	hESC	SNUhES42	Allo	-	interstitial cystitis	Asan Medical Center	NCT04610359	I	3	3	KR	20 M	N	2020	C	Shin et al.[164]	–
MSCLC TWPOI	MSC	hESC	Q-CTS-hESC-2	Allo	-	primary ovarian insufficiency	Chinese Academy of Sciences	NCT03877471	I	18	18	CN	2 M, 5 M, 10 M	N	2019	C	–	–
MSC	MSC	hESC	Q-CTS-hESC-2	Allo	-	intrauterine adhesions	Chinese Academy of Sciences	NCT04232592	I	32	18	CN	3 M, 10 M, 30 M	N	2020	A	–	–
IMS001	MSC	hESC	ND	Allo	-	multiple sclerosis	ImStem biotechnology	NCT04956744	I/II	30	14	US	1 M/kg, 3 M/kg	N	2021	A	–	Wang et al.[165,166]
Cartilage	chondrocytes	hiPSC	ND[e]	Allo/ HLA	E	knee articular cartilage damage	Kyoto University Hospital	jRCTa050190104	I/II	4	ND	JP	ND	ND	2020	A	–	Yamashita et al.[167]

Allo, allogeneic; Auto, autologous, Reprogr. method, reprogramming method; Immune suppr., immune suppression; (pre-)clin. ref, (pre-)clinical references; LUMC, Leiden University Medical Center; MSC, mesenchymal stromal cells; GvHD, graft versus host disease; HLA, HLA subtype in some cases matched to patient; ND, not disclosed; M, million. Reprogramming methods: E, episomal. Countries: AU, Australia; CN, China; JP, Japan; KR, Korea; NL, the Netherlands; UK, United Kingdom; US, United States of America. Dose is provided as number of cells, unless stated otherwise. M, million (10^6). Trial status: C, completed; A, active; U, unknown.

[a]67% of patients were immunosuppressed.

[b]In partnership with Cynata.

[c]Plus an equivalently sized placebo group.

[d]This trial has not been verified by the sponsor.

[e]HLA homozygous cell line

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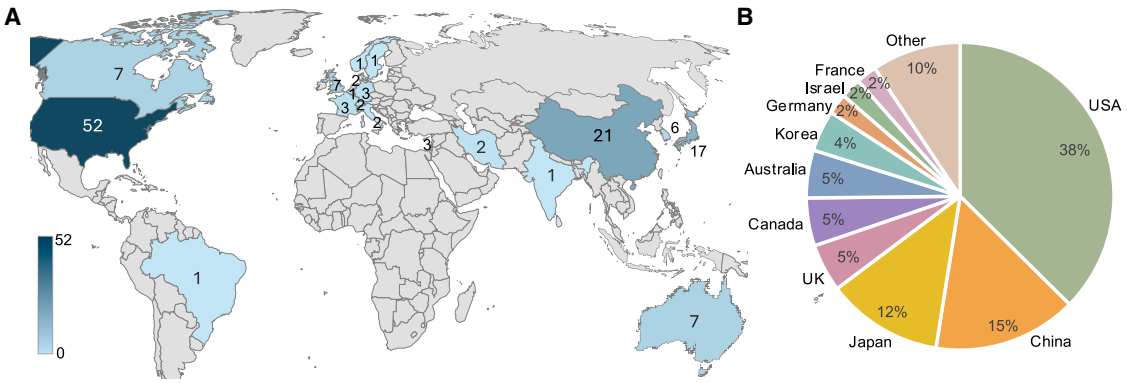

Figure 1. Distribution of hPSC trials per country

(A) Overview of number of hPSC clinical trials per country. The numbers indicate the countries' involvement in a trial as a trial site, and a trial with multiple sites in different countries will therefore be counted several times on the map. A trial with several sites within the same country is counted as just one trial. Chart made with Excel, Bing Maps.

(B) Pie chart showing fraction of hPSC clinical trial sites distributed per country.

In 2015, a study with non-cryopreserved RPE was initiated at the Southwest Hospital in China for SMD (NCT02749734). The study optimized cell delivery to avoid cell diffusion into the vitreous and proliferative vitreoretinopathy caused by exposure of RPE to vitreous cytokines, creating epiretinal membranes and potential retinal detachment. The study showed stable or transiently increased visual acuity at 1–4 months, but this achievement reverted to a visual acuity loss in 3 patients at 60 months.[33] Another study initiated by the University of Sao Paulo in 2015 aimed to compare transplantation of monolayer RPE and cell suspension in AMD and SMD (NCT02903576). Results are yet to be published for AMD and the comparison of suspension versus monolayer transplants, but the group reported a non-significant increase in visual acuity in transplanted SMD patients.[44]

In 2016, Regenerative Patch Technologies delivered hESC-derived RPE as a non-cryopreserved cell sheet on a synthetic membrane for treatment of dry AMD (NCT02590692). Delivering cells as a pre-made epithelium or with a supporting membrane improves survival and function of the transplanted RPE cells by mimicking the supportive functions of the Bruch's membrane.[24] Out of 16 patients implanted with RPE cell sheets, 4 showed a visual acuity gain of >5 letters at 12 months.[37,38] A 2-year post-mortem follow-up of a single patient showed survival of the allogeneic RPE cells without clinically detectable intraocular inflammation or serologic immune responses.[39] Median 3-year follow-up showed that implanted eyes were more likely to improve visual acuity by >5 letters, though the number of patients was not sufficient to detect statistically significant improvements.[40]

In addition to the allogeneic products, Kapil Bharti and colleagues at the NIH National Eye Institute (NEI) have pioneered the development of an autologous hiPSC-RPE product using a biodegradable scaffold, poly lactic-co-glycolic acid (PLGA), for dry AMD treatment (NCT04339764). This trial was initiated in 2020[171] and is the second autologous hiPSC trial to be initiated worldwide, with 2 patients dosed so far (Table 1).

Wet AMD

Neovascular/wet AMD (wet AMD) treatment using antibodies against vascular endothelial growth factor (anti-VEGF) to inhibit uncontrolled vascularization is quite effective; however, it does not address RPE degeneration in advanced cases.[22] Both hPSC-derived RPE cell suspension and cell sheets are currently in clinical trials for wet AMD.

The first RPE treatment to target wet AMD was also the first trial to test an hiPSC-derived product, initiated in 2013 by Masayo Takahashi and the RIKEN Institute in Japan (UMIN000011929).[34] A non-cryopreserved, autologous hiPSC-derived RPE cell sheet (1.3 × 3 mm) was detached from a collagen matrix and delivered to one eye of a patient with wet AMD in the absence of immunosuppression. In this study, graft survival was seen in the treated eye at 4 years, and visual acuity was stable in that eye at 1 and 4 years without additional anti-VEGF treatment.[22,23]

In a second wet/neovascular AMD study, initiated by Pete Coffey and colleagues at Moorfields Eye Hospital in 2015, an RPE monolayer on a polyester membrane was implanted into 2 patients (NCT01691261).[29] Improved visual acuity was seen at 12 months, with a >20 letter gain in both patients, marking clear signs of efficacy from an hPSC product.[29] The improved visual acuity, however, decreased to 2 letters below baseline for patient 1 at 5 years,[30] possibly indicating graft loss. For patient 2, the improved visual acuity was reduced but remained above baseline by 9 letters at 5 years.[30] Graft persistence up to 5 years was suggested by continued pigmentation and extension of pigmentation beyond the patch.[31] It is difficult to compare this study with others in wet AMD, as patients had a specific subform of wet AMD, RPE rip, where a part of the RPE layer acutely breaks and retracts but leaves the underlying Bruch's membrane and choroid intact. This characteristic AMD subtype may have contributed to the relatively favorable outcome.

At Southwest Hospital in China, the same non-cryopreserved RPE suspension product and delivery technique that was used for SMD patients[33] was also used for treatment of wet AMD, though with 10× more cells (1 million cells per eye) delivered (NCT02749734).[34] Some improvement in visual acuity was seen in all 3 patients, by 11–26 letters.[33,35] In 2021 Masayo Takahashi initiated a trial at the Kobe City Eye Hospital in Japan to treat wet AMD (UMIN000026003), delivering cryopreserved HLA-haplotyped allogeneic iPSC-derived cell suspensions to

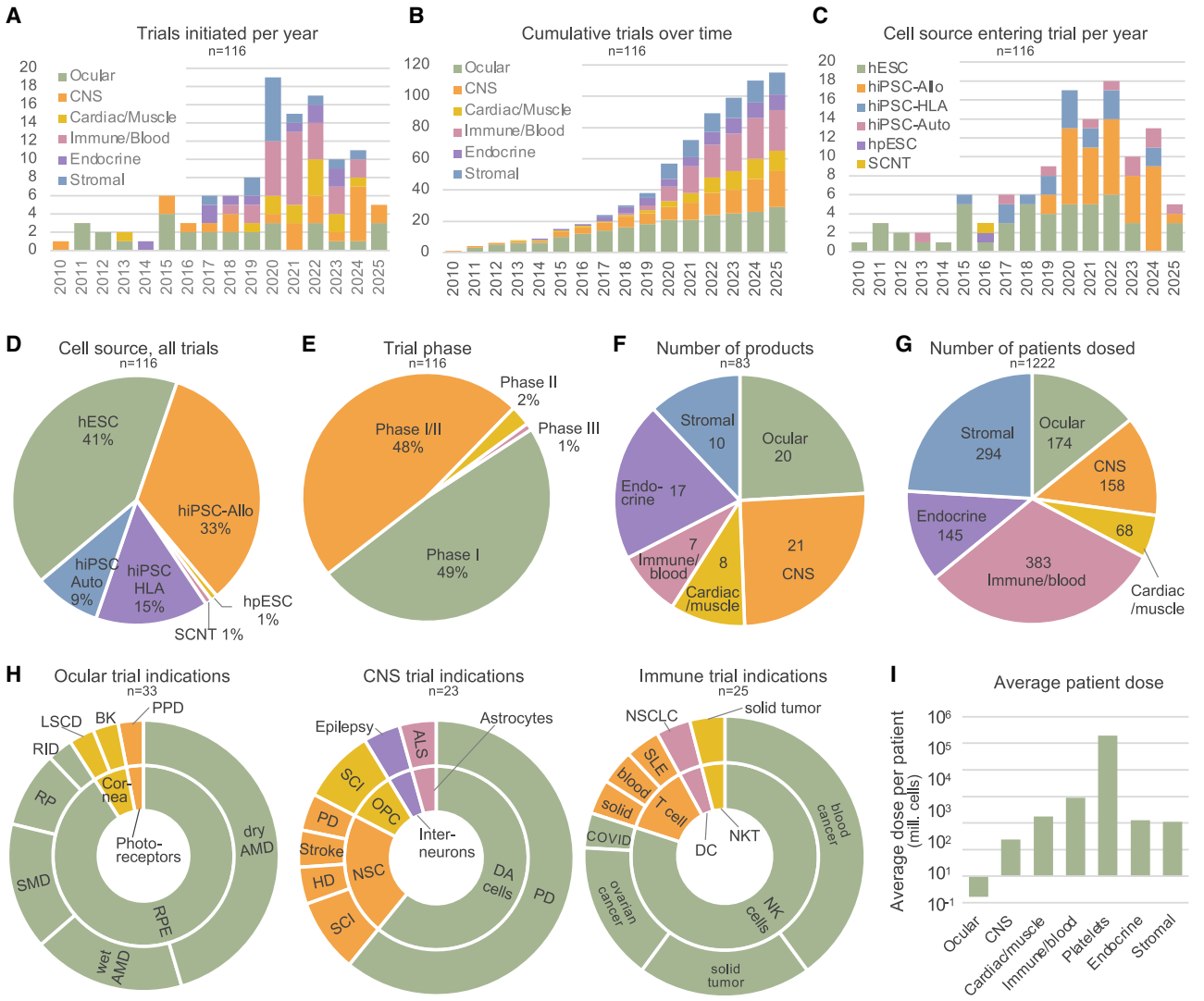

Figure 2. Overview of hPSC trials and dosed patients

(A) Number of trials initiated per year, since 2010, color-coded for product type. Numbers for 2025 are incomplete estimations based on currently approved trials.
(B) Cumulative number of initiated hPSC trials from 2010 to 2025, color-coded for product type.
(C) Number of trials initiated per year, color-coded for cell source used. Note that products from HLA-haplotyped hiPSCs (hiPSC-HLA) are not always matched to the patients in the trial.
(D) Pie chart showing fraction of trials with different cell sources.
(E) Pie chart showing fraction of trials in different clinical phases.
(F) Pie chart showing number of different product types approved for clinical trial.
(G) Pie chart showing number of patients dosed in total with each product type.
(H) Pie charts showing product cell types (inner circle) applied per disease indication (outer circle) for ocular, CNS and immune product trials.
(I) Average dose of cells administered to each patient for different product types. AMD, age-related macular degeneration; SMD, Stargardt macular degeneration; RP, retinitis pigmentosa; RID, RPE impaired disease; LSCD, limbal stem cell deficiency; BK, bullous keratopathy; PPD, primary photoreceptor disease; DA, dopamine; PD, Parkinson's disease; SCI, spinal cord injury; HD, Huntington's disease; NSCs, neural stem cells; OPCs, oligodendrocyte progenitor cells; ALS, amyotrophic lateral sclerosis, SLE, systemic lupus erythematosus; NSCLC, non-small cell lung cancer.

patients in the absence of immunosuppression (Table 1). Stable or improved vision was seen in these 5 patients (>10 letter gain in 2 patients and stable vision in 3 patients) and graft retention was confirmed at a 1 year follow-up.[45]

Other ocular indications

Three studies have been initiated for retinitis pigmentosa in France, Japan, and China (NCT03963154, jRCTa050200027, and NCT03944239). Initial results from the transplantation of hESC-RPE cell sheets in gelatin developed by Christelle Monville and colleagues at iSTEM in France showed possible stabilization of the nystagmus and fixation (NCT03963154).[62] Another study led by Masayo Takahashi and colleagues at the Kobe City Eye Hospital, using allogeneic iPSC-derived retinal organoid sheets (jRCTa050200027), showed cell survival at 2 years, though no improvement or worsening of visual acuity was seen

compared with the fellow eye.[53] A Japanese study from Kohji Nishida and colleagues at Osaka University, initiated in 2019 (UMIN000036539), investigated transplantation of hiPSC-derived corneal epithelial cell sheets for limbal stem cell deficiency, and showed no serious adverse events (SAEs) and improvement in disease symptoms in 3 out of 4 patients at a 2 year follow-up.[64] All patients were HLA-mismatched but systemic immunosuppression was used only in two patients (Table S1).[64] A single study for bullous keratopathy has also been initiated, delivering corneal endothelial cells (CLS001). Additionally, BlueRock Therapeutics announced IND clearance for an upcoming clinical trial using photoreceptor cells (OpCT-001) for the treatment of primary photoreceptor disease (Table 1).[172]

Learnings from ocular trials

Clinical studies with hPSC-derived products for ocular disease cover a wide diversity of indications, disease severity, and administration methods, making it challenging to distill broadly applicable learnings. Overall, the safety profile of the ocular hPSC products seems feasible, with no Serious Adverse Events (SAEs) due to delivered cells and no general signs of graft rejection, even in allogeneic settings. Dosage has increased over time and graft survival is generally reported. Proving graft function in the absence of a biopsy has been more challenging for RPE-based products, with only a single patient biopsy reported that suggested graft function at 2 years.[39] Though it may be possible to see pigments in the transplanted area, only biopsies can confirm that live, pigmented cells are present, rather than debris.

To date, all products with cell sheets have been delivered without cryopreservation post-manufacturing, whereas cell suspension products have been delivered from non-cryopreserved and cryopreserved states. It should be noted that the differentiation status of RPE cells is essential to survival of cryopreservation in both suspension[173,174] and sheets.[175] Optimization of product manufacturing to benefit from cryopreservation and guarantee optimal recovery and cell function may be necessary for products to eventually reach the market. Clinical data emerging in the coming years will provide more clarity about the clinical efficacy of RPE sheets, cell suspensions, autologous, and allogeneic products. Furthermore, trials are now increasingly including patients in less advanced disease states, which may enable more robust clinical responses to the transplanted tissue.

CNS INDICATIONS

PD

Most ongoing trials with CNS-targeted products involve the treatment of Parkinson's disease (PD), a debilitating motoric disease caused by the loss of dopamine (DA) neurons deep in the basal ganglia of the brain. Clinical replacement of DA neurons through intracerebral transplantation has been explored since the late 1980s, using donated human fetal tissue.[176] Although highly successful in some patients, this approach has been fraught with high variability, insufficient tissue availability, lack of standardized quality control, and ethical concerns. PD has therefore been regarded as a prime target for stem cell replacement therapy using replenishable sources of cells. The first hESC trial for PD was initiated in China in 2015 (NCT03119636) and has dosed 24 patients with DA progenitor cells, but with no clinical data released (Table 2). The second trial was initiated in Australia in 2016 by the company International Stem Cell Corporation (ISCO), using parthenogenetic stem cells (hpESCs). The trial reached its primary safety endpoint in 2021,[77] but the company has not announced plans to follow-up with further trials. The ISCO trial sparked concerns regarding their use of a generic neural stem cell (NSC) product, which was proposed to inhibit cell death of the endogenous DA neurons through trophic support, but which cannot itself replace dopaminergic function.[78,177]

The field subsequently moved toward better-defined products containing hPSC-derived progenitor cells patterned precisely toward the midbrain DA neurons, which are lost in PD. The first hiPSC product to enter clinical trials for PD was developed by Jun Takahashi at the Center for iPS Cell Research and Application (CiRA) in Japan, using an allogeneic HLA-haplotyped hiPSC line purified for the floor plate cell surface marker CORIN.[178] This trial, which was initiated in 2018 and included 7 patients, showed a good safety profile upon completion and moderate improvements in a subset of patients (J. Takahashi, personal communication). The CiRA product is now being pursued for further clinical trials in the USA by the Japanese company Sumitomo Pharma in collaboration with academic sponsors (Table 2).[95,179] BlueRock Therapeutics initiated an hESC trial in 2021, based upon the initial work of Lorenz Studer and colleagues at Memorial Sloan Kettering.[85,86] This trial dosed a total of 12 patients in US and Canada with the H9-derived Bemdaneprocel product (NCT04802733) and has reported a ~50% decrease in PD symptoms in the high-dose group at 18 and 24 months relative to baseline, prompting BlueRock Therapeutics to announce the expected initiation of a phase II study soon.[83,84] Similarly, S.Biomedics in Korea initiated an hESC-based trial in 2023 (NCT05887466) and reported a 25%–44% reduction in PD symptoms in their first 3 high-dose patients at 12 months.[90] An additional hESC trial for DA cell replacement (STEM-PD) was initiated in Sweden in 2022 by Skåne University Hospital, led by Malin Parmar, Roger Barker, and colleagues (NCT05635409).[87] These clinical trials in the USA, Japan, Sweden, and Korea all apply a relatively short differentiation protocol of 16–28 days.[180,181] In addition, a Chinese company, iRegene Therapeutics, has developed an allogeneic "chemical induction" hiPSC product (NouvNeu001), which entered clinical trials in China in January 2024 and received FDA clearance for a US trial in June 2024.[182]

Trials in PD have paved the way for autologous cell therapies, and a patient with PD at McLean Hospital in Boston was the second ever to receive an autologous hiPSC-derived transplant. This treatment took place in 2017 under a "single patient expanded access" protocol and was led by Kwang-Soo Kim and colleagues.[80] The transplanted patient displayed modest indications of graft survival by positron emission tomography (PET) imaging when assessed at 12 months post-transplantation.[80] Following this procedure, the same team received FDA approval in 2023 to expand the autologous DA cell transplantation to 8 patients (NCT06687837). Interestingly, two additional trials using autologous hiPSCs for PD were also cleared by the FDA in 2023: The ANPD001 trial by Aspen Neuroscience in which the first patient was dosed in the spring of 2024, and a trial

led by Penelope Hallett and colleagues at the McLean Hospital in Boston (NCT06422208), which has so far dosed two patients with autologous cells (Table 2, P. Hallett, personal communication). In total, 13 approved trials target PD. In the coming years, it will be informative to assess the efficacy data from patients with grafts that have reached full maturity at 2–3 years post-transplantation.

Spinal cord injury

Oligodendrocytes, which myelinate axons and provide trophic support, are lost after SCI. Replacing oligodendrocytes may therefore provide support to the damaged axons after injury.[70,183] An hESC-derived oligodendrocyte progenitor cell product was specifically developed by Geron Corporation to target SCI (GRN-OPC1) (Table 2). Preclinical studies in animal models demonstrated that the OPC1 product could produce neurotrophic factors, migrate into the spinal cord parenchyma, stimulate vascularization and induce remyelination of denuded axons at the site of injury,[70,183] supporting further clinical development. In 2010, the GRN-OPC1 product received regulatory approval by the FDA to enter clinical trials and became the first hPSC product worldwide to go into patients.[184]

The initial first-in-human trial (NCT01217008) tested the delivery of GRN-OPC1 in 5 patients with subacute thoracic injuries. 10-year safety data demonstrate that the product was well tolerated by patients with no SAEs related to the procedure, cell implant, or immunosuppression, and no ectopic tissues or teratomas were observed.[69] Patients, however, did not show significant clinical improvement, which was attributed to the relatively low dose of the cells.[69] Geron Corporation halted the GRN-OPC1 trial in November 2011,[105,106] and the technology was subsequently acquired by Asterias Biotherapeutics and launched as AST-OPC1 in another phase I/II dose escalation trial in patients with cervical SCI in 2015 (NCT02302157). In this trial, patients received 2, 10, or 20 × 10^6 ACT-OPC1 cells at 21–42 days post injury. Most of these patients (96%) recovered one or more levels of neurological function (i.e., levels corresponding to a specific spinal cord segment and its associated motor function) on at least one side of their body and 32% recovered 2 or more levels on at least one side at 1-year post-transplantation. These data support the safety profile of AST-OPC1, but given the limited size of the trial, it was difficult to attribute recovery to the AST-OPC1 product versus natural recovery from the injury.[72] As Asterias was later purchased by BioTime and rebranded as Lineage Cell Therapeutics, the product was renamed to LCTOPC1.

Two other groups have launched SCI clinical trials testing hPSC-derived neural stem or precursor cells, Keio University in Japan and S.Biomedics in Korea, respectively. The proposed mechanism of action of these products is the secretion of trophic factors at the injury site to promote repair and myelination. The S.Biomedics product is an hESC-derived neural precursor cell (PSA-NCAM+) that is administered intrathecally to patients with cervical subacute SCI. However, safety and efficacy data have not yet been released. The team at Keio University, led by Hideyuki Okano and colleagues, is testing hiPSC-derived NSCs in complete cervical/thoracic subacute SCI.[74] To date, 4 patients have received an injection of 2 million hiPSC-NSCs 2–4 weeks after injury and while efficacy data are not yet available, no SAEs have been observed (H. Okano, personal communication).

Epilepsy

Another CNS indication that has recently come into the spotlight of stem cell transplantation therapy is drug-resistant focal epilepsy. Focal epilepsy is caused by episodes of uncontrolled hyperactivity of excitatory neurons in isolated subregions of the brain, resulting in neuronal discharge that can manifest itself as motoric seizures and spasms. Work pioneered by Arturo Alvarez-Buyulla and colleagues at the University of California, San Francisco showed that transplantation of hESC-derived inhibitory GABAergic interneurons into the epileptic focus of the brain could dampen neuronal hyperactivity and reduce seizure occurrence in mouse models of genetic or mesothelial temporal lobe epilepsy (MTLE).[185] The team adopted a medial ganglionic interneuron differentiation protocol developed by Cory Nicholas, Arnold Kriegstein, and colleagues[186] and built the company Neurona Therapeutics in 2009. As a result, Neurona Therapeutics transplanted the first patient with the interneuron product NRTX-1001 in a trial on drug-resistant MTLE (NCT05135091) in 2022. Preliminary efficacy data released from the trial indicate that 4 out of 5 patients treated with the initial lower dose of NRTX-1001 experienced a >50% seizure reduction and that 3 patients were free from their most disabling focal seizure types.[102] Strikingly, the 2 patients with longest follow-up (16 and 21 months) showed >95% reduction in seizure episodes with one being seizure-free for 8 months. Neurona Therapeutics has expanded the trial to include 21 active clinical sites in the USA and has initiated a second trial for bilateral transplantation (NCT06422923). The results from the Neurona Therapeutics studies are encouraging to the field, not only because they confirm the ability of transplanted human neurons to survive and function in the human brain long-term but also because they corroborate previous data indicating that the brain can tolerate allogeneic grafts long-term even in the absence of immunosuppression. In this case, immunosuppression was withdrawn from the patients 12 months after transplantation.

Other CNS indications

Additional trials targeting the CNS include a study initiated by the company KadimaStem in Israel in 2018, administering hESC-derived astrocytes (AstroRx) intrathecally into the spinal cord of patients with amyotrophic lateral sclerosis (ALS). Ten patients, treated with two different doses, were included in the study. Although the patients showed a decline in disease progression rate during the first 3 months post-transplantation, there was no significant improvement above baseline at the 12-month follow-up in either dosing group.[97] Another trial was initiated by Stanford University in 2021 for treatment of ischemic subcortical stroke using an H9 hESC-derived NSC product. Interim data were released in early 2023 reporting that the treatment was well tolerated at 6 months in the first 6 transplanted patients.[100] Another NSC product for the treatment of Huntington's disease has been developed by Leslie Thompson and colleagues at University of California Irvine and received FDA clearance in 2024 (L. Thompson, personal communication, Table S2). While clinical testing has not yet been initiated,

preclinical studies suggest that the transplanted NSCs can decrease endogenous mutant Huntingtin accumulation and enhance production of neurotrophic factors to support the endogenous neurons.[187,188]

HEART FAILURE

Cell replacement therapies using various cell types are currently being tested in patients with myocardial infarction (MI) and chronic heart failure (CHF). After an MI, as many as 1 billion cardiomyocytes are lost and replaced by non-contractile scar tissue; a process that can secondarily progress to CHF. To this end, several laboratories are developing hPSC-derived cardiomyocytes to improve heart contractile function. Cardiomyocyte product doses range from 5 to 800 million cells (Table 3; Figure 2I) and are delivered in multiple formats, such as intracardially-injected cell suspensions, spheroids, cardiomyocyte patches, or sheets grafted to the external surface of the heart.

In 2013, Philippe Menasche and colleagues performed a clinical trial in which they tested epicardially delivered cardiomyocyte progenitors embedded into a fibrin scaffold and surgically delivered onto the infarct area (NCT02057900).[110] Six patients were treated in this trial, receiving only transient (1–2 months) immunosuppression (Table S1). One year after treatment, no product-related adverse events but some modest increase in heart function were reported, although the patient number was too low for definitive conclusions.[111,112] Interestingly, the team chose to discontinue the transplantation of cardiomyocytes and instead continue with a trial of hPSC-derived extracellular vesicles (NCT0577450),[189] possibly due to a lack of clear signs of cell engraftment.[111,190]

Additional cardiomyocyte trials were initiated in Japan, China, USA, and Germany between 2019 and 2023 (Table 3). The Osaka University team, led by Yoshiki Sawa and colleagues, reported no adverse events and improved cardiac function in the first patient of their trial (jRCT2053190081) at 1-year post-transplant after epicardial transplantation of 3 cardiomyocyte patches with transient immunosuppression.[117] A study from Wolfram Zimmerman and colleagues at University Medical Center of Goettingen in partnership with Repairon uses a combined fibroblast and cardiomyocyte patch engineered in collagen type I hydrogels (NCT04396899) and reported via press release evidence for sustained heart wall thickening and improved heart ejection fraction.[121] Combined, these studies give indicators of early symptomatic improvement, absence of ventricular arrhythmias, tumor formation, and immunosuppression-related adverse events.[110,111,117,121,191] However, these trials are not sufficiently powered for efficacy readouts. It is encouraging that the clinical studies involving cardiomyocyte sheets have not to this point reported arrhythmias in the transplanted patients; however, preclinical studies demonstrate that intramyocardial injection of cardiomyocytes in suspensions can in some cases lead to arrhythmia.[122,192–194] More recently, antiarrhythmic drugs and cell sorting have prevented arrhythmia from transplanted cardiomyocyte suspensions in large animal preclinical studies,[195,196] demonstrating that this can be a potential preventive approach for future trials using cells in suspension.

In China, Help Therapeutics[109] conducted a clinical trial in which cardiomyocyte suspensions were injected into multiple locations of the damaged tissue and supplemented with systemic antiarrhythmic therapy (NCT03763136). In 2022, HeartSeed initiated a trial with myocardially delivered cardiac spheroids (NCT04945018), and preliminary results from the two first patients showed left ventricular ejection fraction (LVEF) improvement of 2 and 11 percentage points 26 weeks post-transplantation.[197] Many factors affect the engraftment and function of hPSC-derived cardiomyocytes, including maturation, purity, product type (sheet, suspension, and spheroid), cryopreservation status, and delivery method. Achieving functional integration of the transplanted cells while at the same time avoiding arrhythmias will be fundamental for the success of future cardiomyocyte products.[111,190,198]

DIABETES

Type 1 diabetes mellitus (T1DM) is caused by an autoimmune-mediated loss of insulin-producing beta cells in the endocrine islets of the pancreas. Due to its early onset and severe health consequences, the transplantation of cadaver-derived islets has been explored as a therapeutic option already in the 1970s.[199] The protocols for clinical islet transplantation through infusion into the portal vein have since been improved, resulting in >50% of recipients gaining insulin independence for at least 1-year post-transplantation.[200] In 2023, cadaveric pancreatic islet transplantation (Lantidra) was officially approved in the USA by the FDA as a treatment for T1DM patients with recurrent episodes of severe hypoglycemia.[201]

Naturally, this historical proof of concept has sparked interest in the development of more easily accessible off-the-shelf hPSC-based products for T1DM patients. An early developer in the field was the company Viacyte, which initiated its first clinical trial in 2014 and subsequently launched 4 additional trials in the years 2017–2022 (Table 4). The technology developed by Viacyte involved a stepwise 12-day differentiation protocol, from hESCs to pancreatic endoderm progenitor cells (PEC-01).[128] The PEC-01 cells were loaded into a macroencapsulation device measuring up to 3 × 8 cm in size (Encaptra), designed to shield the transplanted cells against immune cell infiltration through an isolating membrane, enabling execution of the trial without immunosuppressive treatment.[202] This cell/device combination product (VC-01) was intended for subcutaneous implantation.[203] However, the device design resulted in poor graft survival in patients, presumably due to hypoxia within the core of the device.[204] Subsequently, Viacyte modified the design of the Encaptra device to allow ingrowth of blood vessels through small transversal pores,[130] and they implanted this device as a combination product with PEC-01 cells (VC-02) in two subsequent trials initiated in 2017 (NCT03162926 and NCT03163511). In these trials, patients received immunosuppression (Table S1); however, extensive host-derived fibrosis was evident within the devices, and graft cells only constituted 26%–40% of all cells in the device upon explanting the device at 12–24 months post-implantation. Modest increases in stimulated C-peptide release were observed in only 35% of patients.[130] Later, in 2019, a trial with a third version of the device, made from expanded polytetrafluoroethylene (ePTFE), and with both immuno-isolatory and pro-angiogenic properties was initiated without the use of

immunosuppression (NCT04678557). Data from this trial are still pending.

Viacyte was not alone in focusing on therapeutic pipelines for diabetes. In 2016, Viacyte merged with Johnson & Johnson's BetaLogics,[205] a competing company with an alternate beta cell differentiation protocol developed by Timothy Kieffer and colleagues at University of British Columbia.[206] Another competing company, Semma Therapeutics, was established by Douglas Melton and colleagues at Harvard University in 2014 and was later acquired by Vertex Pharmaceuticals in 2019.[207] This acquisition propelled the clinical development of Semma Therapeutics' hESC-derived mature pancreatic islet product forward. It resulted in the initiation of a first-in-human trial by Vertex in 2021, using non-encapsulated cells, VX-880, delivered through the portal vein to patients receiving a chronic immunosuppression regimen (NCT04786262). This phase I/II clinical trial delivered promising results in 2024, reporting that all 12 patients receiving the target dose of VX-880 as a single, one-time infusion showed evidence of islet cell engraftment, and 11 of 12 patients reduced or eliminated their need for exogenous insulin.[208] The 3 patients with more than 1 year follow-up demonstrated insulin independence and good glycemic control with no potentially life threatening, severe hypoglycemic events in the observation period.[208] The trial nonetheless met some hurdles along the way as it was paused for several months due to two deaths among the dosed patients—events which were deemed to not be related to VX-880.[209] In November 2024, Vertex announced that they are converting the initial phase I/II trial into a pivotal phase I/II/III trial,[210] bringing the VX-880 product closer toward a potential market launch.

Vertex subsequently initiated a second trial (NCT05791201) in 2023, also using the VX-880 cell product, but now encapsulated in a proprietary immunoprotective "channel array device" to avoid the need for immunosuppression in patients.[211] The device is designed to protect cells from the immune system, while enabling ingrowth of blood vessels in membrane-covered channels placed throughout the device.[202] An alternative approach to avoiding graft rejection is pursued by Hongkui Deng, Zhongyang Shen, and colleagues at the Tianjin First Center Hospital in China, who initiated a clinical trial in 2023 with autologous islet-like cells in an initial cohort of 3 patients (ChiCTR23000722009). The group published 12-month follow-up data on the first patient, reporting sustained insulin independence from day 75 after transplantation.[135]

LIVER DISEASE

PSC-derived hepatocytes for the treatment of acute liver failure have been among the most challenging products to develop. In patients with acute liver failure, administration of PSC-derived hepatocytes as a bridge therapy until the liver regenerates or an organ becomes available for transplantation can be a life-saving intervention. However, efficient generation of mature hepatocytes from hPSCs remains difficult as culture conditions for maintaining proliferation and function of hepatocytes are not well developed. Further, it is estimated that 1 to 10 billion hepatocytes will be required for effective treatment. Nevertheless, progress has been made, and 2 clinical trials are currently ongoing that test PSC-derived hepatocytes in liver disease (Table 4). Xiangya Hospital of Central South University in China is testing hESC-derived hepatocytes in patients with liver failure, with a target enrollment of 10 patients (ChiCTR2100052988). In Japan, the National Center for Child Health and Development has tested hESC-hepatocytes in 2 neonatal patients with urea-cycle disorder (JMA-IIA00412). The specifics of these products have not been disclosed, including the dose and requirement for immunosuppression and neither group has reported safety or efficacy data at this time.

IMMUNE AND BLOOD PRODUCTS

The development of autologous chimeric antigen receptor T cell (CAR-T) therapies has been transformative for patients with refractive hematologic malignancies. However, these autologous therapeutics are expensive, and the quality of patient-derived cells is often variable, making manufacturing of the CAR-T cell products challenging.[212] For these lifesaving therapies to become more accessible to patients, several groups are developing allogeneic off-the-shelf hPSC-derived natural killer (NK) and T cell products. Currently, 13 different PSC-derived NK or T cell products have been or are being tested in clinical trials (Table 5). As with autologous immunotherapies, the patients are lymphodepleted before administering the cell products (Table S1).

NK cells

Most trials to date have tested products developed by the California-based company Fate Therapeutics. Their initial product (FT500) consisted of non-engineered hiPSC-derived NK cells, which were administered to 37 patients with advanced solid tumors (NCT03841110). FT500 has since been replaced by improved NK products engineered to express transgenic molecules to enhance survival, durability and effectiveness of the cells (Table 5). These changes include gene edits, such as hnCD16 to enhance antibody-dependent cellular cytotoxicity and interleukin (IL)-15RF to enable NK persistence without the need for exogenous cytokine support. In addition, the company introduced disease-specific CARs, such as B cell maturation antigen for multiple myeloma and CD19 for diffuse large B cell lymphoma. This strategy allowed a stepwise building of safety data for their product pipeline, harnessing the unique potential of hPSCs to produce clonal immune cell products with multiple gene edits in all cells.

Several of the improved Fate Therapeutics iNK cell products (FT516, FT522, FT538, FT576, and FT596) have been tested in patients with blood cancers, such as acute myeloid leukemia, multiple myeloma, chronic lymphocytic leukemia, B cell lymphoma (Table 5). Although clinical data from these trials have not been published, a number of press releases and abstracts provide a high level view of the trial outcomes.[143,213] In general, the trials have demonstrated safety and tolerability with patient doses from 30 million to 1 billion cells. Available information confirms the absence of dose-limiting toxicity, immune effector-cell-associated neurotoxicity syndrome or graft versus host disease (GvHD), and only the occasional observation of cytokine release syndrome. In these trials, efficacy is measured by the number of patients achieving objective response ($\geq$30% reduction in tumor load or cancer) and complete response (all signs of cancer

disappear). Although some of these trials are still active, interim data from press releases indicate that 30%–50% of patients achieve a complete response after 30 days (Table 5).

More recently, Century Therapeutics initiated a trial testing hPSC-derived CAR19-iNK cells in patients with relapsed or refractory CD19-positive B cell malignancies (NCT05336409). This product includes several edits to facilitate immune evasion, including knockout of major histocompatibility complex (MHC) class I and II and overexpression of HLA-E, as well as a safety switch. A June 2024 press release[154] disclosed that 12 patients have been treated in a dose escalation trial. Seven patients treated with dose 1 (100 M) or dose 2 (300 M) on a once monthly dosing schedule showed a favorable safety profile and 2 complete remissions. Dose level 3 (1 or 3 doses of 1B cells) showed a favorable safety profile and 30%–60% complete remission. Findings from this trial will help to understand the effects of hypoimmune gene edits on the durability of allogeneic cell products.

As with autologous or allogeneic CAR cell products, the development of hiPSC-CAR therapies for the treatment of solid tumors has proven more challenging.[212,214] FT500, FT516, FT538, have been tested in solid tumors, but little data are available about the outcome of these trials. Additional hPSC-derived NK cell products in trial include an anti-GPC3 NK cell product developed for solid tumors in Japan (jRCT2033200431), and an anti-CD33 NK cell product (QN-023a) developed for blood cancer in China (Table 5).

T cells

The development of hiPSC-derived T cell products has proven considerably more difficult than NK cell products. Creating scalable manufacturing systems that mimic the thymic developmental steps required for generating T cells, such as positive and negative selection, remains a challenge. Fate Therapeutics entered the clinic with an hPSC-derived T cell product (FT819), which has a CD19 CAR inserted into the T cell receptor (TCR) alpha constant (TRAC) locus. This edit eliminates the endogenous TCR and is thought to decrease the risk of GvHD. An ongoing trial with FT819 in patients with relapsed/refractory B cell lymphoma (NCT04629729) has reported that the delivery of 90–360 million cells results in a favorable safety profile and complete remission in some patients.[146] Another version of their T cell product with 7 genetic modifications (FT825) also entered a clinical trial for solid tumors (Table 5).

In addition to using PSC-CAR-T cells for the treatment of cancers, clinical trials testing CAR-T cells targeting CD19 in patients with B cell-driven autoimmune disease have shown promise.[215] The required durability of the primary CD19 CAR-T cells is more limited in these diseases, with lower cell doses required and efficacy seen when cells persist for only 2 weeks.[216] Fate Therapeutics launched a second clinical trial testing FT819 in patients with systemic lupus erythematosus (SLE, NCT06308978). Remarkably, the company announced the achievement of drug-free clinical remission of the first SLE patient in this FT819 trial in November 2024,[148] providing hope for future B cell targeting in autoimmune indications.

In summary, off-the-shelf hPSC-derived CAR-NK and CAR-T cells might help develop transformative cancer therapies at much lower cost and with greater patient access compared with autologous CAR products. Early clinical data in hematologic malignancies indicate that these products are well tolerated, and some trials have shown early positive efficacy data, although not yet *en par* with autologous CAR-NK and CAR-T cells. These products are now being gene edited to increase potency and durability and more readily target solid tumors.

Dendritic cells

An hESC-derived dendritic cell product for the treatment of non-small cell lung cancer (GRN-VAC02) was developed by Geron and subsequently acquired by Asterias Biotherapeutics (renamed to AST-VAC2), and recently transferred to Lineage Cell Therapeutics (NCT03371485). Although data from this trial have not been released, it has been announced that AST-VAC2 was well tolerated and induced an immune response in the treated patients.[149]

Platelets

Platelet products derived from healthy blood donors can treat thrombocytopenia caused by hematopoietic diseases, chemotherapy, and other disorders. The increase in demand for blood-derived products, together with the irregular supply of donated blood, make the development of "off-the-shelf" iPSC-derived blood products very desirable. The manufacturing of iPSC-blood products has been challenged by the fact that platelet numbers required for each patient are very high (>100 B). Still, two groups have succeeded in testing iPSC-derived platelets in patients with thrombocytopenia. CiRA investigators Koji Eto and colleagues in Japan generated an autologous platelet product (iPLAT1) from a patient with alloimmune platelet transfusion refractoriness. The platelet manufacturing process included differentiating iPSCs into immortalized megakaryocyte progenitor cells (imMKCLs) through doxycycline-inducible c-MYC, BMI1, and BCL-XL transgenes. The overexpression of the 3 transgenes facilitates expansion of the imMKCLs before differentiation into platelets by the removal of doxycycline.[160] A total of 140 billion platelets were delivered to the patient in 3 escalating doses (jRCTa050190117). No safety concerns were raised 1 year after transplantation, but results also did not show direct evidence of increased platelet counts in the patient.[159,217] Similarly, Megakaryon Corporation, also in Japan, announced the successful delivery of 60 billion hiPSC-derived platelets (MEG-002) to one patient in 2022, with no adverse events observed (jRCT2053210068).[157]

STROMAL PRODUCTS

Mesenchymal stromal cells (MSCs) can be derived from bone marrow, adipose tissue, and cord blood and have been tested in clinical trials since the mid-1990s. MSCs are proposed to have immunosuppressive and trophic effects through secretion of cytokines and growth factors and have therefore been tested in conditions where immune dampening may be beneficial.[218] More than 1,000 clinical studies have been performed with MSCs from primary sources, targeting a variety of diseases, including GvHD, neurological disorders, cartilage damage, and COVID-19.[219,220] Despite the large number of clinical trials, only one MSC product, OSSM-001, has received market approval by the FDA for treatment of medically refractory

perianal fistulizing Crohn's disease. For other diseases, the efficacy of MSC transplantation is still debated.

Generating MSCs from PSCs is of interest given the manufacturing challenges from autologous sources, including donor variability and limited cell expansion. Although researchers have begun testing hPSC-MSC products in a variety of indications, these products will likely face similar hurdles as primary MSC products, including defining the mechanism of action. Cynata Therapeutics in Australia has tested hiPSC-derived MSCs in clinical trials for GvHD, COVID-19, kidney transplantation, diabetic foot ulcers, and osteoarthritis (Table 6). Their first phase I trial (NCT02923375) delivered the MSC product CYP-001 to 15 patients with acute steroid-resistant GvHD.[161] The treatment was well tolerated with no product-related SAEs, and the objective response and complete response rates at day 100 were 86.7% and 53.3%, respectively,[161] with 9 of 15 patients (60%) surviving at the 2-year follow-up.[162] These rates are potentially better than standard-of-care but require a parallel placebo comparison. It should be noted that some patients were given corticosteroids and/or other immunosuppressants in conjunction with CYP-001, and it is unclear how this may have impacted the outcome of the study (Table S1).[161]

Myung-Soo Choo and colleagues in South Korea treated 3 patients with hESC-derived MSCs for interstitial cystitis (NCT04610359). Some of these patients showed improvement in pain and lesion size, but the sample size was too small to draw definitive conclusions.[164] Another hESC-derived allogeneic MSC product (IMS001) has been developed by the company ImStem and is currently in clinical trial in the USA for treatment of multiple sclerosis (NCT04956744). The product is injected intravenously without immunosuppression, indicating that the company is aiming for transient immune modulatory effects via the blood system. The first of a target of 30 patients was dosed in 2021, but no subsequent trial information or patient data have been released.

Clinical trials testing PSC-derived MSCs in COVID-19 patients have been initiated by several groups including Cynata Therapeutics, Wuhan Jinyinyan Hospital, and the Chinese Academy of Sciences (NCT04537351, ChiCTR2000031139, NCT04331613). Given the anti-inflammatory and immune-suppressive effects of MSCs, it is reasoned that delivery of PSC-MSCs will reduce pulmonary inflammation. Although these studies were initiated in 2020, none of these groups have reported clinical results at the time of writing. In 2020, Cynata Therapeutics initiated a phase III, placebo-controlled, double-blinded trial testing CYP-004 in patients with osteoarthritis (ACTRN12620000870954). As of November 2023, the target sample size of 320 patients is reported on the Cynata website to have been reached,[221] but no data have yet been released. This study is to our knowledge the first phase III trial to be conducted with hPSC-derived products, and the outcome of this trial could be an important landmark for the field.

LOOKING TOWARD THE FUTURE—HOW TO AVOID IMMUNE REJECTION

As improved hPSC products are emerging, risks associated with long-term immunosuppression of patients become more pertinent. Overall, the field pursues four main strategies to circumvent immunosuppression of patients: (1) autologous transplantation of the patients' own cells, (2) use of HLA-haplotyped hiPSC banks for HLA-matching, (3) gene editing of hypoimmune cell lines, which can escape host immune cell recognition, and (4) immunoprotective encapsulation of transplanted cells to physically protect the transplant from host immune cells. Although 9 trials with autologous hiPSCs have been initiated, only a total of 11 patients have so far been treated with autologous cells, to our knowledge (Tables 1, 2, 3, 4, 5, and 6). Hence, the potential to expand the technology to many patients at reasonable cost still remains to be shown. Meanwhile, CiRA in Japan has worked to establish a GMP-grade haplobank of 27 hiPSC lines from HLA homozygous donors to match 40% of the Japanese population.[222] These haplotyped lines are already used in 12 clinical trials in Japan (and are indicated in Tables 1, 2, 3, 4, 5, and 6). However, the cells have been matched to the HLA subtype of the recipient only in some cases, and data on the long-term survival of these cells in the absence of immunosuppression are not yet available. Additionally, two trials by the Chinese Academy of Science are using HLA-matching for hESC-derived RPE and DA progenitor cells, but clinical data have not been released.

In turn, the generation of universally applicable hypoimmune cell lines, which evade immune recognition in their allogeneic host, is a strategy pharmaceutical companies are currently pursuing. Such hypoimmune lines can be generated through the deletion of genes for MHC class I and II expression, combined with forced expression of "don't eat me signals" such as CD47, CD64, HLA-E, or HLA-G.[223–225] Sana Biotechnologies demonstrated that gene-edited hypoimmune macaque iPSCs could survive for at least 4 months in an immune-competent allogeneic animal host with no signs of immune rejection.[225] These findings suggest that the same approach might also work in humans. Interim data from a Century Therapeutics trial using hiPSC-derived "allo-evasive" NK cells lacking MHC class I and II while overexpressing HLA-E reported signs of survival in patients with lymphoma.[154] Viacyte announced in February 2022 to have dosed its first patient with T1DM with a gene-edited immune-evasive cell product, VCTX210, developed in collaboration with CRISPR Therapeutics (NCT05210530).[133] However, the details of the cell line have not been disclosed. As Viacyte was acquired by Vertex in July 2022, it was announced that Vertex would not pursue the VCTX210 gene-edited product.[226] Instead, Vertex initiated its own trial with an immune-protected encapsulated cell product in 2023 (NCT05791201), indicating that they remain interested in encapsulation as an immune-evasive approach. While encapsulation can work successfully for a product with endocrine function, such as beta cells, the same approach cannot be applied for cells, which need to establish functional cellular contacts within host tissues, such as cardiomyocytes, neurons, or RPE cells. Nonetheless, the CNS and the eye are partially immunoprivileged sites, which may not require long-term immunosuppression for life-long graft survival. Encouragingly, data from RPE, PD, and epilepsy trials show functional graft survival for several months to years after withdrawal of initial immunosuppression.[83,102] This finding is in line with previous data from patients receiving non-matched fetal tissue transplants to the brain for treatment of PD, showing graft survival for >20 years in the absence of immunosuppression.[227] Therefore, immune-evasive strategies might not be required for the CNS and eye, and it is possible that patients can sustain

an allogeneic graft for many years at these sites with only initial immunosuppression for 6–12 months. Indeed, this is also the approach in most ongoing clinical trials focusing on allogeneic cell delivery into the CNS and eye (Table S1). As data from more transplanted patients become available, it will be possible to conclude with greater certainty whether allogeneic grafts in the CNS and eye can be sustained long-term in humans without sporadic rejection. Assessing the clinical results from HLA-matched, autologous and hypoimmune products in the coming years will be instrumental in determining the best path forward.

CONCLUSIONS

Patients have been receiving hPSC-derived products since 2010. As of December 2024, we count a total of 83 hPSC-derived products undergoing testing in 116 clinical trials worldwide. Numbers collected from national registries and sponsors show that at least 1,200 patients presenting with 34 different indications have been implanted with an accumulated dose of at least 190 billion cells + 200 billion platelets. Importantly, these data demonstrate that, to date, PSC-derived products under regulatory control are safe and well tolerated, even when followed up to 10 years post-transplantation, as for the GRN-OPC1 product.[69] One report of a patient with type 2 DM in China should be noted who received autologous hiPSC-derived beta islet cells and presented with an immature teratoma and lymph node metastases 2 months post-transplantation.[228] Information about the manufacture or characterization of the implanted cells is not publicly available, and, to our knowledge, the treatment of this patient was not part of a clinical trial approved by regulators. Importantly, proper manufacture, characterization, and release of PSC-products under regulatory oversight is crucial to avoid this type of outcome.

Whereas CNS and ocular products were dominating the clinical hPSC landscape in the first years, we are now seeing increasing numbers of trials with immune, cardiac, and endocrine cell products. The immune and blood cell product category now accounts for 31% of all treated patients (Figure 2G). Excitingly, we are beginning to see solid efficacy data emerging from several trials, in particular for diabetes, epilepsy, PD, and AMD. With these highly promising clinical data in sight, the next hurdle will be to design good solutions for pivotal phase II/III trials and provide evidence for product efficacy while balancing patient concerns against regulatory expectations for placebo-controlled studies. For invasive procedures such as intraocular and intracerebral transplantations, it is pertinent that alternative phase III trial designs are considered, to avoid exposing patient control groups to unnecessary sham surgeries and lengthy immunosuppression.[229] Additionally, companies will face challenges related to scaling up and scaling out of manufacturing to market-scale, as well as identifying the most promising immune evasion strategies for off-the-shelf products. Finally, hPSC products that successfully pass all criteria to reach the market will need to find sustainable pricing models to avoid a "second valley of death," as has occurred for other cell and gene therapies at the post-marketing stage.[230] Dealing with these obstacles now will be necessary to ensure that the field can steadily advance hPSC-based therapies from promising studies in animal models to accessible treatments for patients.

LIMITATIONS OF THE REVIEW

Since many of the listed trials are still not completed at the time of writing, we have relied in our reporting not only on scientific publications but also on clinical trial updates and interim results posted through press releases and abstracts from sponsors. These have been cited in the text, and website links can be found in the reference list. It should be noted that data published through press releases and abstracts have not gone through scientific peer review and should therefore be interpreted with caution. In some cases, additional information on trial status, patient enrollment and immunosuppressive regimens has been provided through personal communication with sponsor representatives. All sponsor representatives providing updated information to the review, or simply fact-checking the data in the tables, have been listed in Table S3. In addition, we have tried to acknowledge academic leaders for investigator-led clinical trials to the best of our knowledge, but due to textual constraints this information is not exhaustive.

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DECLARATION OF INTERESTS

A.K. is the owner of Kirkeby Cell Therapy APS, which holds royalty contracts and performs paid consultancy for Novo Nordisk A/S, Somite Therapeutics, and CCRM Nordic. A.K. is a co-inventor on several patents related to the generation of human neurons from stem cells and is engaged in the development of the STEM-PD product, which has been licensed to Novo Nordisk A/S for future development. H.M. is an owner of HOYA Consulting (ReGenMed Solutions AB), which provides consulting services on pluripotent stem cell start material including IP, quality, and commercial suitability. H.M. also holds a 50% role as project manager of ATMP Sweden. M.C. is president and owner of Carpenter Consulting Corporation, which provides consulting services for the development of stem cell therapeutics. M.C. is named inventor on a number of patents related to PSC manufacturing and product development.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.stem.2024.12.005.

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