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Concise Review

Pluripotent Stem Cells in Clinical Setting—New Developments and Overview of Current Status

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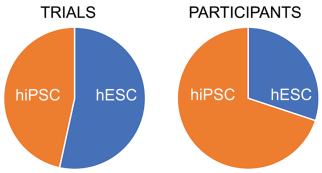
Abstract

The number of clinical trials using human pluripotent stem cells (hPSC)—both embryonic and induced pluripotent stem cells (hESC/iPSC)—has expanded in the last several years beyond expectations. By the end of 2021, a total of 90 trials had been registered in 13 countries with more than 3000 participants. However, only US, Japan, China, and the UK are conducting both hESC- and hiPSC-based trials. Together US, Japan, and China have registered 78% (70 out of 90) of all trials worldwide. More than half of all trials (51%) are focused on the treatment of degenerative eye diseases and malignancies, enrolling nearly 2/3 of all participants in hPSC-based trials. Although no serious adverse events resulting in death or morbidity due to hPSC-based cellular therapy received have been reported, information about safety and clinical efficacy are still very limited. With the availability of novel technologies for precise genome editing, a new trend in the development of hPSC-based cellular therapies seems to be emerging. Engineering universal donor hPSC lines has become a holy grail in the field. Indeed, because of its effectiveness and simplicity nanomedicine and in vivo delivery of gene therapy could become more advantageous than cellular therapies for the treatment of multiple diseases. In the future, for the best outcome, hPSC-based cellular therapy might be combined with other technological advancements, such as biomimetic epidural electrical stimulation that can restore trunk and leg motor functions after complete spinal injury.

Key words: clinical trials; embryonic stem cells; induced pluripotent stem cells; pluripotent stem cells.

Graphical Abstract



Significance Statement

The increase in the number of hPSC-based clinical trials, from 12 in 2015 to 90 in 2021, indicates that the field has matured enough to be taken seriously by Big Pharma and investors. Indeed, Fate Therapeutics is involved in 13, Astellas in 8, and ViaCyte in 5 clinical trials with 1587, 128, and 367 participants, respectively. The affordability of hPSC-based cellular therapies is likely to increase due to the development of universal donor iPSC lines for off-shelf treatment. The efficacy of hPSC-based cellular therapy might be improved in combination with other technological advancements.

In the last several years, the number of clinical trials with human pluripotent stem cells (hPSC)-based therapies is rapidly increasing, from 12 in 2015[1] to 54 in 2019,[2] and 90 in 2021 (Table 1, Fig. 1A). Although there are more human embryonic stem cells (hESC)-based trials, the number of participants enrolled in human induced pluripotent stem cells (hiPSC)-based trials is nearly 2-fold higher (1942 vs 979) (Fig. 1B, 1C). In a year or two, hiPSC-based trials will probably take over.[1]

Thirteen countries reportedly run hPSC-based clinical trials, although 78% of these trials (70 out of 90) are conducted in just three of these countries: US (35), China (17), and Japan (18). US, China, Japan, and the UK are the only countries conducting both hESC- and hiPSC-based trials.

The trials are focused mainly on four areas: degenerative diseases of the eye (30), malignancies (16), neural degenerative disorders (11), and cardiovascular diseases (10). Clinical

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Table 1. hPSC-based clinical trials by December 31, 2021.

Country	Sponsor	Title	Disease	Phase	Status (number of participants)	Study ID
Ocular Diseases						
hESC						
USA	Astellas Institute for Regenerative Medicine	Safety and Tolerability of Sub-retinal Transplantation of hESC-RPE (MA09-hRPE) Cells in Patients with Advanced Dry AMD	AMD	Phase I Phase II	Completed (13)	NCT01344993
USA		Long Term Follow Up of Sub-retinal Transplantation of hESC-RPE Cells in Patients with AMD		follow-up of a Phase I/II	Completed (11)	NCT02463344
USA		A Phase Ib Dose Escalation Evaluation of Safety and Tolerability and a Phase II Proof of Concept Investigation of Efficacy and Safety of ASP7317 for Atrophy Secondary to AMD		Phase I	Active, not recruiting (18)	NCT03178149
USA UK		A Safety Surveillance Study in Subjects with Macular Degenerative Disease Treated With hESC-RPE Cell Therapy	Macular degenerative disease	Phase I Phase II	Enrolling by invitation (36)	NCT03167203
USA		Sub-retinal Transplantation of hESC-RPE (MA09-hRPE) Cells in Patients with SMD	SMD	Phase I Phase II	Completed (13)	NCT01345006
UK		Safety and Tolerability of Sub-retinal Transplantation of hESC-RPE Cells in Patients with SMD		Phase I Phase II	Completed (12)	NCT01469832
USA		Long Term Follow Up of Sub-retinal Transplantation of hESC-RPE Cells in SMD Patients		Follow-up of a Phase I/II	Completed (13)	NCT02445612
UK		A Follow up Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of hESC-RPE Cells in Patients with SMD		Follow-up of a Phase I/II	Completed (12)	NCT02941991
USA Israel	Lineage Cell Therapeutics, Inc.	Safety and Efficacy Study of OpRegen for Treatment of Advanced Dry-Form AMD	AMD	Phase I Phase II	Active, not recruiting (24)	NCT02286089
USA	Regenerative Patch Technologies, LLC	Study of Subretinal Implantation of hESC-RPE Cells in Advanced Dry AMD	AMD	Phase I Phase II	Active, not recruiting (16)	NCT02590692
Korea	CHA Biotech CO., Ltd	A Phase I/IIa, Open-Label, Single-Center, Prospective Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of hESC-RPE (MA09-hRPE) Cells in Patients with Advanced Dry AMD	AMD	Phase I Phase II	Active, not recruiting (12)	NCT01674829
		Safety and Tolerability of MA09-hRPE Cells in Patients with SMD	SMD	Phase I	Unknown (3)	NCT01625559
Korea	CHA University	The Safety and Tolerability of Sub-retinal Transplantation of SCNT-hES-RPE Cells in Patients with Advanced Dry AMD	AMD	Phase I	Unknown (3)	NCT03305029
UK	Moorfields Eye Hospital NHS Foundation Trust	A Study of Implantation of hESC-RPE In Subjects with Acute Wet AMD And Recent Rapid Vision Decline	AMD	Phase I	Not yet recruiting (10)	NCT01691261
		RPE Safety Study for Patients in B4711001		Follow-up of a Phase I/II	Unknown (2)	NCT03102138
China	Chinese Academy of Sciences	Subretinal Transplantation of RPE in Treatment of AMD	AMD		Unknown (10)	NCT02755428
		Treatment of Dry AMD with RPE Derived from Clinical grade hESCs		Phase I Phase II	Unknown (10)	NCT03046407
		Safety and Efficacy of Subretinal Transplantation of Clinical hESC-RPE in Treatment of RP	Retinitis pigmentosa (RP)	Phase I	Recruiting (10)	NCT03944239
		Clinical study of subretinal transplantation of clinical hESC-derived RPE in treatment of retinitis pigmentosa diseases		Phase I	Not yet recruiting (10)	ChiCTR2100052988
	Southwest Hospital, Shapingba District, Chongqing	Clinical study of subretianl transplantation of human bone marrow mesenchymal stromal cells with or without embryonic retinal progenitor cells in treatment of retinal pigmentosa		Phase I	Unknown (10)	ChiCTR-ONB-15007477
	Eye Institute of Xiamen University	The clinical trial of hESC-derived epithelial cells transplantation in the treatment of severe ocular surface diseases	Severe ocular surface diseases	Phase I	Unknown (20)	ChiCTR-OCB-15005968
	Southwest Hospital	Clinical study of subretinal transplantation of hESC-RPE in treatment of macular degeneration diseases	Macular degenerative disease	Phase I Phase II	Unknown (15)	NCT02749734
France	Centre d'Etude des Cellules Souches	Interventional Study of Implantation of hESC-RPE in Patients with RP Due to Monogenic Mutation	Retinitis pigmentosa (RP)	Phase I Phase II	Recruiting (12)	NCT03963154
Brazil	Federal University of Sao Paulo	Stem Cell Therapy for Outer Retinal Degenerations	Outer retinal degenerations	Phase I Phase II	Completed (15)	NCT02903576

Table 1. continued

Country	Sponsor	Title	Disease	Phase	Status (number of participants)	Study ID
hiPSC						
Japan	Riken	A Study of transplantation of autologous iPSC-RPE cell sheet in subjects with exudative AMD	AMD	NS	Completed (6)	UMIN000011929
	Kobe City Medical Center General Hospital	A Study of transplantation of allogenic iPSC-RPE cell suspension in subjects with neovascular AMD	AMD	NS	Completed (5)	UMIN000026003
	Kobe City Eye Hospital	Clinical Research of allogeneic iPSC-RPE cell suspension transplantation for RPE impaired disease	RPE impaired disease	NS	Recruiting (50)	JRCTA050200122
	Osaka University Graduate School of Medicine	First-in-human clinical research of iPS derived corneal epithelial cell sheet transplantation for patients with limbal stem-cell deficiency	Limbal stem-cell deficiency	NS	Completed (4)	UMIN000036539
	Sumitomo Dainippon Pharma	Safety Study of allogenic hiPSC-retinas in Retinitis Pigmentosa	Retinitis pigmentosa	NS	Not yet recruiting (2)	JRCTA050200027
	Cellusion Inc. Keio University	Exploratory clinical study to examine safety and efficacy of iPS cell-derived corneal endothelial cell substitutes for bullous keratopathy (CLS001)	Bullous keratopathy	NS	Unknown (3)	JRCTA031210199
USA	National Eye Institute (NEI)	Autologous Transplantation of Induced Pluripotent Stem Cell-Derived Retinal Pigment Epithelium for Geographic Atrophy Associated with Age-Related Macular Degeneration	AMD	Phase I Phase II	Recruiting (20)	NCT04339764
Neural Disorders						
hESC						
USA	Asterias Biotherapeutics, Inc.	Safety Study of GRNOPC1 in Spinal Cord Injury	SCI	Phase I	Completed (5)	NCT01217008
		Dose Escalation Study of AST-OPC1 in Spinal Cord Injury	SCI	Phase I Phase II	Completed (25)	NCT02302157
Korea	S.Biomedics Co., Ltd. Linical Co., Ltd. Yonsei University	Safety and Exploratory Efficacy of Transplantation Therapy Using PSA-NCAM(+) NPC in AIS-A Level of Sub-acute SCI (SB-SCI-001)	SCI	Phase I Phase II	Not yet recruiting (5)	NCT04812431
USA Canada	BlueRock Therapeutics	Phase I Safety and Tolerability Study of MSK-DA01 Cell Therapy for Advanced Parkinson's Disease	Parkinson's disease	Phase I	Recruiting (12)	NCT04802733
USA	Neurona Therapeutics	FIH Study of NRTX-1001 Neural Cell Therapy in Drug-Resistant Unilateral Mesial Temporal Lobe Epilepsy	Epilepsy	Phase I Phase II	Not yet recruiting (40)	NCT05135091
Israel	Kadimastem	A Study to Evaluate Transplantation of Astrocytes Derived From hESC, in Patients with ALS	ALS	Phase I Phase II	Completed (16)	NCT03482050
hiPSC						
China	Allife Medical Science and Technology Co., Ltd	A Study on the Treatment of Parkinson's Disease with Autologous Neural Stem Cells	Parkinson's disease	Phase I	Unknown (10)	NCT03815071
Japan	Kyoto University Hospital, AMED, Sumitomo Dainippon Pharma Co., Ltd.	Kyoto Trial to Evaluate the Safety and Efficacy of iPSC-derived dopaminergic progenitors in the treatment of Parkinson's Disease		Phase I Phase II	No longer recruiting (7)	UMIN000033564
		Kyoto Trial to Evaluate the Safety And Efficacy Of Tacrolimus In The IPSC-Based Therapy For Parkinson's Disease		Phase 3	No longer recruiting (7)	UMIN000033565
	Keio University	Regenerative medicine for spinal cord injury at subacute stage using human induced pluripotent stem cell-derived neural stem/progenitor cells	SCI	Phase I Phase II	Suspended (4)	UMIN000035074
Other: hpNSC						
China	Cyto Therapeutics Pty Limited	A Study to Evaluate the Safety of Neural Stem Cells in Patients with Parkinson's Disease	Parkinson's disease	Phase I	Unknown (12)	NCT02452723
	Chinese Academy of Sciences	Safety and Efficacy Study of hESC-derived Neural Precursor Cells in the Treatment of Parkinson's Disease		Phase I Phase II	Unknown (50)	NCT03119636
	Allife Medical Science and Technology Co., Ltd	A Study on the Treatment of Parkinson's Disease with Autologous Neural Stem Cells		Phase I	Unknown (10)	NCT03815071

Table 1. continued

Country	Sponsor	Title	Disease	Phase	Status (number of participants)	Study ID
Cardiovascular Diseases						
hESC						
France	Assistance Publique - Hôpitaux de Paris	Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure (ESCORT)	Ischemic heart disease	Phase I	Completed (10)	NCT02057900
USA	Stanford University	hESC-Derived Cardiomyocyte Therapy for Chronic Ischemic Left Ventricular Dysfunction (HECTOR)		Phase I	Not yet recruiting (18)	NCT05068674
	Stanford University CIRM	A Safety and Tolerability Study of Neural Stem Cells (NR1) in Subjects with Chronic Ischemic Subcortical Stroke (ISS)	Stroke, Ischemic	Phase I Phase II	Recruiting (30)	NCT04631406
hiPSC						
China	Help Therapeutics	Treating Heart Failure With hPSC- CMs (HEAL-CHF)	Ischemic cardiomyopathy, Chronic heart failure	Phase I Phase II	Recruiting (20)	NCT03763136
		Treating Congestive HF With hiPSC-CMs Through Endocardial Injection		Phase I	Recruiting (20)	NCT04982081
	Beijing University of Chinese Medicine	IPS Differentiated Cardiomyocytes Vein Transplantation for Chronic Heart Failure (IDCVTCHF)		Phase II Phase 3	Not yet recruiting (3)	NCT03759405
Germany	University Medical Center Goettingen	Safety and Efficacy of iPSC-derived Engineered Human Myocardium as Biological Ventricular Assist Tissue in Terminal Heart Failure (BioVAT-HF)		Phase I Phase II	Recruiting (53)	NCT04396899
Japan	Osaka University (AMED)	Clinical trial of human (allogeneic) induced pluripotent stem cell-derived cardiomyocyte sheet for severe cardiomyopathy		Phase I Phase II	Completed (3)	UMIN000032989
	Osaka University Cuorips Inc	Clinical study of human (allogeneic) iPS cell-derived cardiomyocyte sheet for ischemic cardiomyopathy		NS	Recruiting (10)	JRCT2053190081
	Heartseed, Inc. Keio University	Safety study of iPSC-derived cardiac spheres transplantation		Phase I	Not yet recruiting (3)	JRCTA032200189
	Heartseed, Inc.	A phase I/II study of hiPSC-derived cardiomyocyte spheroids in patients with severe heart failure, secondary to ischemic heart disease, undergoing coronary artery bypass grafting		Phase I Phase II	Recruiting (10)	JPRN-JRCT2033210163
Other: iNSC, human Peripheral Blood Derived Induced Neural Stem Cells						
China	Allife Medical Science and Technology Co., Ltd	A Clinical Study of iNSC Intervent Cerebral Hemorrhagic Stroke	Stroke, Ischemic	Phase I	Unknown (12)	NCT03725865
Other: iEPC, Human Peripheral Blood Derived Induced EPCs						
China	Allife Medical Science and Technology Co., Ltd	A Clinical Study of iEPC Intervent Subjects with Cerebral Hemorrhagic Stroke	Stroke, Ischemic	Phase I	Unknown (12)	NCT03726814
Diabetes						
hESC						
USA Canada	ViaCyte	A Safety, Tolerability, and Efficacy Study of VC-01TM Combination Product in Subjects with Type I Diabetes Mellitus	Type 1 Diabetes Mellitus	Phase I Phase II	Terminated (19)	NCT02239354
USA Canada		One-Year Follow-up Safety Study in Subjects Previously Implanted with VC- 01TM		Follow-up of a Phase I/II	Enrolling by invitation (200)	NCT02939118
Canada		A Safety and Tolerability Study of VC-02TM Combination Product in Subjects with Type 1 Diabetes Mellitus		Phase I	Completed (3)	NCT03162926
USA Canada Belgium		A Safety, Tolerability, and Efficacy Study of VC-02TM Combination Product in Subjects with Type 1 Diabetes Mellitus and Hypoglycemia Unawareness		Phase I Phase II	Recruiting (75)	NCT03163511
USA		A Study to Evaluate Safety, Engraftment, and Efficacy of VC-01 in Subjects with T1 Diabetes Mellitus (VC01-103)		Phase I Phase II	Recruiting (70)	NCT04678557
USA	Vertex	A Safety, Tolerability, and Efficacy Study of VX-880 in Participants with Type 1 Diabetes		Phase I Phase II	Recruiting (17)	NCT04786262
hiPSC						
China	Allife Medical Science and Technology Co., Ltd	A Study of Autologous Induced Islet Body with Type 1 Diabetes	Type 1 Diabetes Mellitus	Phase I	Unknown (20)	NCT03728296

Table 1. continued

Country	Sponsor	Title	Disease	Phase	Status (number of participants)	Study ID
Hematopoietic Non-malignant Diseases						
hiPSC						
China	Allife Medical Science and Technology Co., Ltd	iHSCs With the Gene Correction of HBB Intervent Subjests With β- thalassemia Mutations	Beta-Thalassemia	Phase I	Unknown (12)	NCT03728322
China	Xiaofang Sun	Thalassemia Treatment Based on the Stem Cell Technology		Phase I	Unknown (2)	NCT03222453
Japan	Kyoto University Hospital (AMED)	iPSC-derived platelet transfusion trial1	Aplastic anemia	NS	Completed (1)	JRCTA050190117
	Megakaryon Corp.	Exploratory clinical study on the tolerability, safety and efficacy of iPS cell-derived platelets (MEG-002) in patients with thrombocytopenia	Thrombocytopenia	Phase I Phase II	Recruiting (10)	JRCT2053210068
Malignancies						
hESC						
UK	Cancer Research UK	AST-VAC2 Vaccine in Patients with Non- small Cell Lung Cancer	Non-small cell lung cancer in the advanced and adjuvant settings	Phase I	Recruiting (48)	NCT03371485
hiPSC-derived NK						
USA	Fate Therapeutics	FT516 in Subjects with Advanced Hematologic Malignancies	AML, B-cell lymphoma	Phase I	Recruiting (234)	NCT04023071
		FT516 in Combination with Monoclonal Antibodies in Advanced Solid Tumors	Advanced solid tumors	Phase I	Active, not recruiting (12)	NCT04551885
		Long-term, Non-interventional, Observational Study Following Treatment with Fate Therapeutics FT500 Cellular Immunotherapy	Advanced solid tumors	Follow-up of a Phase I/II	Recruiting (76)	NCT04106167
		FT500 as Monotherapy and in Combination with Immune Checkpoint Inhibitors in Subjects with Advanced Solid Tumors	Advanced solid tumors	Phase I	Recruiting (37)	NCT03841110
		FT596 as a Monotherapy and in Combination with Anti-CD20 Monoclonal Antibodies	CLL, B-cell lymphoma	Phase I	Recruiting (285)	NCT04245722
		FT576 in Subjects with Multiple Myeloma	Multiple myeloma	Phase I	Recruiting (168)	NCT05182073
		FT819 in Subjects With B-cell Malignancies	B-cell malignancies	Phase I	Recruiting (297)	NCT04629729
		FT538 in Subjects with Advanced Hematologic Malignancies	Advanced hematologic malignancies	Phase I	Recruiting (105)	NCT04614636
		FT538 in Combination with Monoclonal Antibodies in Advanced Solid Tumors	Advanced solid tumors	Phase I	Not yet recruiting (189)	NCT05069935
	Masonic Cancer Center, University of Minnesota	FT538 in Combination with Daratumumab in AML	AML	Phase I	Recruiting (50)	NCT04714372
		FT596 With Rituximab as Relapse Prevention After Autologous HSCT for NHL	NHL, B-cell lymphoma	Phase I	Recruiting (50)	NCT04555811
		Study of FT516 for the Treatment of COVID-19 in Hospitalized Patients with Hypoxia	COVID-19 disease	Phase I	Active, not recruiting (5)	NCT04363346
		FT516 and IL2 with Enoblituzumab for Ovarian Cancer	Ovarian cancer	Phase I	Recruiting (31)	NCT04630769
Japan	National Cancer Center Hospital East	A Phase I clinical trial of intraperitoneal administration of iCAR-ILC/N101 for ovarian clear cell carcinoma	Ovarian cancer	Phase I	Recruiting (18)	jRCT2033200431
Iran	Tehran University of Medical Sciences	A Clinical Trial to Evaluate the Effects of Autologous iPSC-Derived NK Cells in Personalized Treatment of Patients with Advanced Metastatic Breast Cancer	Metastatic breast cancer	Phase I	Not yet recruiting (32)	IRCT20200429047241N1

Table 1. continued

Country	Sponsor	Title	Disease	Phase	Status (number of participants)	Study ID
Other						
hESC						
China	National Cancer Center Hospital East	A Clinical Research on the Safety of Hepatocytes Therapy Generated from hESC for Patients with Acute or Acute-on-Chronic Liver Failure	Liver failure	Phase I	Not yet recruiting (5)	ChiCTR2100052988
Japan	National Center for Child Health and Development	Clinical Study of HAES Transplantation In Patients With Neonatal Onset Urea Cycle Disorder	Urea cycle disorder	Phase I Phase II	Recruiting (5)	JMA-IIA00412
hESC-derived MSC						
China	Tongji Hospital	Safety Observation on hESC Derived MSC Like Cell for the Meniscus Injury	Meniscus injury	Phase I	Unknown (18)	NCT03839238
	Tongji Hospital	Clinical Safety Study of hESC-Derived Mesenchymal Cells in the Treatment of Moderate and Severe Intrauterine Adhesions	Intrauterine adhesions	Phase I	Active, not recruiting (32)	NCT04232592
	Chinese Academy of Sciences	Mesenchymal Stem Cells (MSCs) - Like Cell Transplantation in Women with Primary Ovarian Insufficiency (MSCLCTWPOI)	Primary ovarian insufficiency	Phase I	Active, not recruiting (28)	NCT03877471
Korea	Asan Medical Center & MIRAE CELL BIO	Safety of Human Embryonic Stem Cell (hESC)-Derived Mesenchymal Stem Cells in Interstitial Cystitis	Interstitial cystitis	Phase I	Recruiting (3)	NCT04610359
USA	ImStem Biotechnology Rho, Inc	A Study to Evaluate the Safety, Tolerability, and Exploratory Efficacy of IMS001 in Subjects with Multiple Sclerosis	Multiple sclerosis	Phase I	Recruiting (30)	NCT04956744
hESC-derived M cells (immunity- and matrix-regulatory cells)						
China	Chinese Academy of Sciences	Safety and Efficacy of CAStem for Severe COVID-19 Associated with/without ARDS	COVID-19 disease	Phase I Phase II	Unknown (9)	NCT04331613
hiPSC						
Japan	Asahi Kasei Corporation, AMED	Development of treatment of knee articular cartilage damage with iPS-cell-derived cartilage.	Knee cartilage damage	NS	Not yet recruiting (4)	JRCTA050190104
hiPSC-derived MSC						
Australia UK	Cynata Therapeutics Limited	A Study of CYP-001 for the Treatment of Steroid-Resistant Acute Graft Versus Host Disease	GvHD	Phase I	Completed (16)	NCT02923375
Australia		The MEseNchymal coviD-19 Trial: MSCs in Adults with Respiratory Failure Due to COVID-19 or Another Underlying Cause (MEND)	COVID-19 disease	Phase I Phase II	Recruiting (24)	NCT04537351
		Safety, Tolerability and Efficacy of CYP-006TK in Adults with Diabetic Foot Ulcers	Diabetic foot ulcers	Phase I	Not yet recruiting (30)	NCT05165628
		Evaluating the efficacy and cost-effectiveness of stem cell injections in people with mild to moderate knee osteoarthritis: a randomised placebo-controlled trial (The SCUlpTOR trial)	Osteoarthritis		Unknown (440)	ACTRN12620000870954

Abbreviations: ALS, amyotrophic lateral sclerosis; AMD, age-related macular degeneration; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; GvHD, graft versus host disease; hESC, human embryonic stem cells; hiPSC, human induced pluripotent stem cells; hpNSC, homogeneous population of multipotent neural stem cells; iNSC, induced neural stem cells; MSC, mesenchymal stem cells; NHL, non-Hodgkin lymphoma; NS, non-significant; RPE, retinal pigment epithelium; SCI, spinal cord injury; SMD, Stargardt's macular dystrophy.

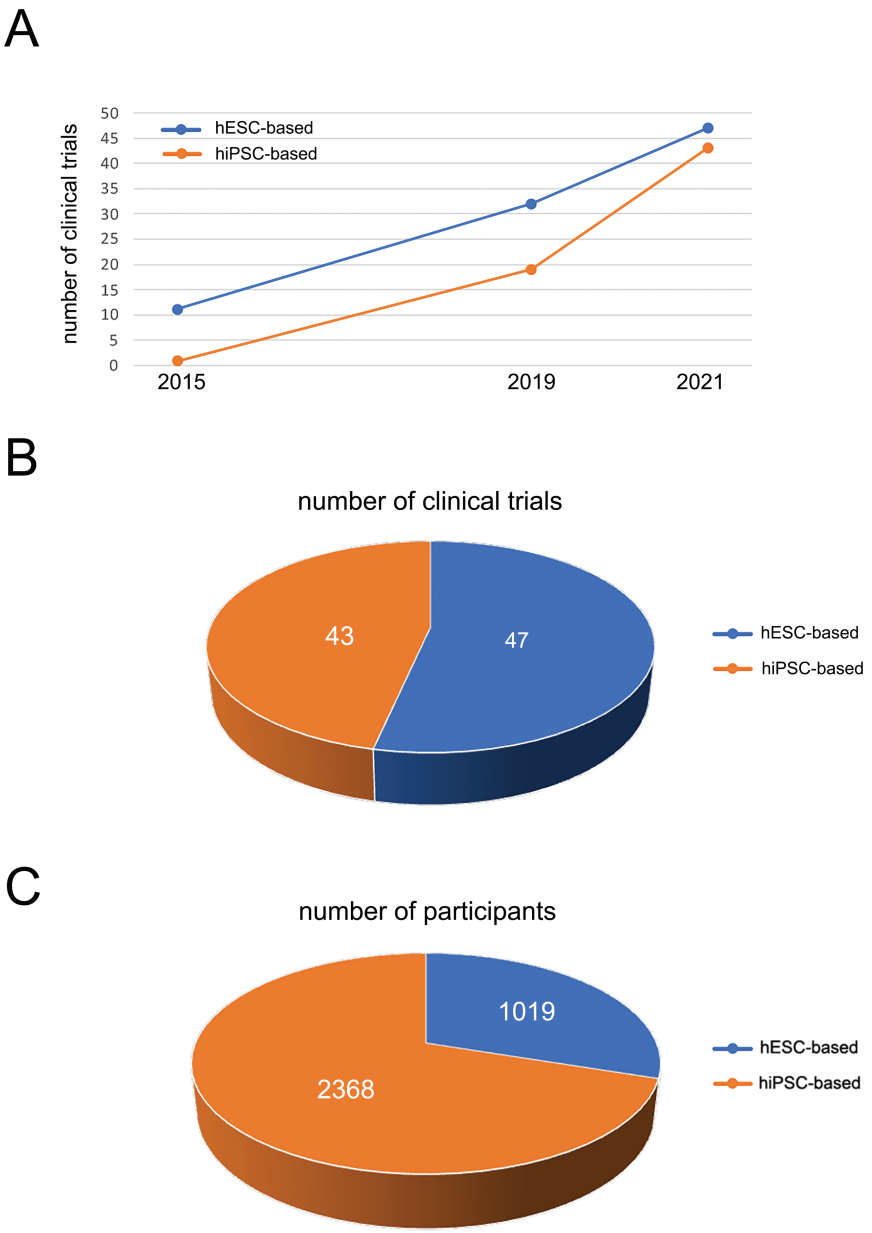

Figure 1. Clinical trials with hPSC-based therapies. **(A):** Number of clinical trials is rapidly increasing from 12 in 2015 to 54 in 2019, and 90 in 2021. **(B):** hESC-based clinical trials are still prevailing over the iPSC-based (47 vs 43). **(C):** Number of participants is higher in iPSC- than hESC-based clinical trials (2368 vs 1019).

trials for treatments of degenerative diseases of the eye, neural degenerative disorders, and type 1 diabetes are predominantly hESC-based, whereas cardiovascular diseases and malignancies are hiPSC-based (Fig. 2A). The highest number of participants (1637) were enrolled in hPSC-based treatment of malignancies, followed by degenerative diseases of the eye (407) and type 1 diabetes (405) (Fig. 2B).

The information summarized here may not be complete and/or fully accurate. We have collated data from the following databases: US Clinical Trials (http://clinicaltrials.gov), EU Clinical Trials Register (www.clinicaltrialsregister.eu), Human Pluripotent Stem Cell Registry (hPSC^{reg}; https://hpscreg.eu/browse/trials), Australian Clinical Trials (www.australianclinicaltrials.gov.au), Chinese Clinical Trial Registry (www.chictr.org.cn/enIndex.aspx), International Clinical Trials Registry Platform (ICTRP; www.who.int/clinical-trials-registry-platform), and the Japan Primary Registries Network Search Portal (https://rctportal.niph.go.jp/en/link), which covers the registries of four institutions: Ministry of Health, Labour and Welfare (JRCT), the University Hospital Medical Information Network Center (UMIN-CTR), the Japan Pharmaceutical Information Center (JAPIC), and the Japan Medical Association Center for Clinical Trials (JMACCT). Information were not always matched between databases. For example, cell therapy for advanced Parkinson's disease sponsored by *BlueRock Therapeutics* has a target of 12 participants on the US Clinical Trials site (NCT04802733), whereas on hPSC^{reg} the target is 10; two studies evaluating treatment of Parkinson's disease sponsored by Kyoto University were still active according to JMACCT, and not recruiting according to UMIN-CTR. Despite discrepancies, the presented overview largely

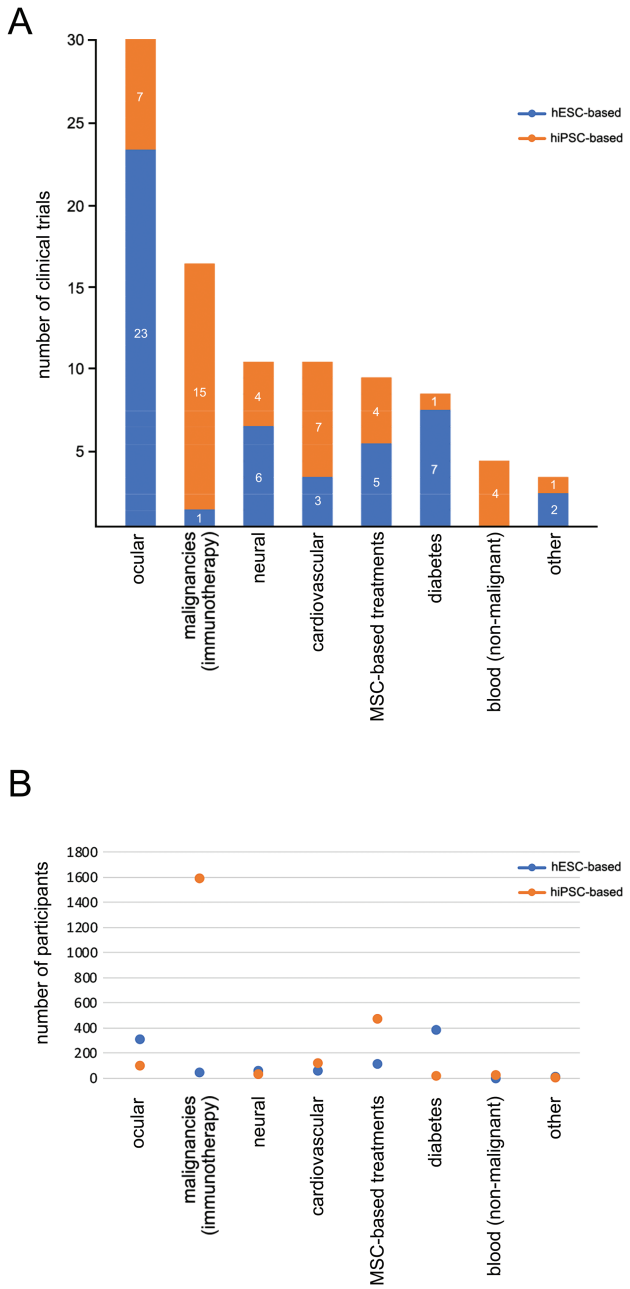

Figure 2. Distribution of hPSC-based clinical trials per condition treated. **(A):** Number of trials per condition treated. **(B):** Number of participants enrolled in hPSC-based clinical trials per condition treated.

reflects the current picture of hPSC-based clinical trials worldwide. We have also listed in the table three trials from China with insufficient information for full classification: induced neural stem cells (iNS) and induced endothelial progenitor cells (iEPC), both derived from the peripheral blood, and M cells or immunity and matrix-regulatory cells derived from hESC. Some of the information discussed has not been peer reviewed (eg, press releases or conference abstracts) and could not be independently verified.

Spinal Cord Injury—New Beginnings

In October 2010, the first patient was treated with hESC-based therapy at Shepherd Center, a 132-bed spinal cord and brain injury rehabilitation hospital and clinical research center in Atlanta, Georgia.[3] This was the first hPSC-based clinical trial worldwide. The trial was run by the California-based company *Geron*, and in phase I of the trial, 2 million oligodendrocyte progenitors were transplanted into the site of subacute spinal cord injury (SCI).[4] Although the initial data were encouraging and safety was demonstrated, the trial was abandoned after a year; the therapy did not show any signs of efficacy.[5] Another company, *Asterias Therapeutics*, acquired the technology and continued where *Geron* had stopped; in 2019, the Company reported the results from a trial using 5-10× higher doses of 10-20 million cells.[6] The higher doses were also safe, and no adverse events associated with the therapy were reported. The results were quite different from *Geron*'s trial—95% of these patients demonstrated improved sensory and motor function, indicating that a dose of 2 million cells was too low, and that at least 5× more cells should be transplanted to see any effect.

In 2021, a Japanese team published a design of a clinical trial treating patients with SCI with hiPSC-derived neural stem/progenitor cells (NS/PCs).[7] Disappointingly for the patients, the dose in phase I of the clinical trial was again 2 million cells. Even though plans to run dose-escalation trial are in place, the question remains is this subtherapeutic starting dose necessary, especially after the recently reported successful outcome of SCI treatment using a completely different approach.[8] This approach using only epidural electrical stimulation (EES) targeting the dorsal roots of lumbosacral segments, delivered with a multielectrode paddle, restored walking in patients with SCI with complete sensorimotor paralysis. Activity-specific stimulation programs enabled the three patients on which the device has been tested to stand, walk, cycle, swim, and control trunk movements in a single day.

Although the patients could move independently, the movements were not natural; they were enabled via biomimetic stimulation programs. During a 5-month rehabilitation period, two of the participants regained the ability to modulate some of the leg movements during EES, indicating that residual natural pathways were present and that their recovery might be boosted with biomimetic EES. Indeed, the same group had demonstrated previously that spatiotemporal neuromodulation therapies engaging muscle synergies improve motor control after SCI.[9,10] To enhance the recovery further and enable the patients with SCI to regain natural movement, a combination of biological repair interventions such as hPSC-based cellular therapy and neurorehabilitation supported by EES are probably the currently most promising way forward.

Revolution of iPSC-based Therapy—From a Personalized to the "Off-the-Shelf" Approach

Following the discovery of iPSCs,[11] the initial dream of personalized therapy was quickly shattered when developers faced the manufacturing costs. Only 8 years after the iPSCs were discovered, the world's first iPSC-based clinical trial was initiated in Japan for the treatment of age-related macular degeneration of the retina.[12] The patient had to wait over 10 months from the skin biopsy till the surgery. Reprogramming, differentiation, and Quality Control/Quality Assurance took their toll. The costs of the autologous transplantation of iPSC-derived retinal pigment epithelium (RPE) cells amounted to approximately USD 1 million.[13] Obviously, this was not sustainable.

To reduce the costs of an allogeneic approach, the ideal donors would be healthy with homozygous human leukocyte antigen (HLA)-A, HLA-B, and HLA-DR. It is estimated that 10, 75, and 140 cell lines would match approximately 50%, 80%, and 90% of the Japanese population.[14-16] Donor recruitment was achieved through the collaboration with the Japan Red Cross, Japan Marrow Donor Program, and several Japanese cord blood banks because they already had HLA typing data available for all stored blood samples. In a relatively short period, 36 donors agreed to participate in the project; 20 of them were homozygous for all 6, and 15 donors were homozygous for the 5 HLA loci.[13]

Clinical grade iPSC lines with three distinct homozygous HLA haplotypes, matching approximately 32% of the Japanese population, were released in 2015. In March 2017, one of these lines was used in the first allogeneic transplantation,[17] which was mimicking the procedure of the previous trial. The surgery time was shortened to about 1 month, and the overall cost was under USD 200 000 per patient.[13]

Although this strategy might work for a highly homogeneous population such as the Japanese, high ethnic diversity in other countries, such as in Europe or US, makes this task nearly insurmountable. The only plausible alternative would be to create hPSC lines with the capacity to evade the immune system—so-called, universal donor hPSC lines.

Chasing a Holy Grail—Universal Donor hPSC

A central role in allogeneic rejection is played by HLA class I molecules through their presentation of peptide antigens to $CD8^+$ T cells. To be expressed on the cell surface, they all require β_2-microglobulin (B2M), which is coded by a non-polymorphic gene. Several groups have generated $B2M^{-/-}$ hPSCs, eliminating class I surface expression and preventing the stimulation of allogeneic $CD8^+$ T cells, including University of Washington, Seattle, spin-off *Universal Cells*[18] and *Advanced Cell Technology*.[19]

This approach, however, did not work. HLA class I-negative cells were lysed by natural killer (NK) cells through the missing self-response. University of Washington/*Universal Cells* team solved the problem.[20] Using adeno-associated virus (AAV), they re-engineered $B2M^{-/-}$ hPSCs to express HLA-E as a single-chain protein fused to B2M, and thereby created the cells that express minimally polymorphic HLA-E as their only surface HLA class I molecule.

According to the *Universal Cells* website, the company is also working on a strategy of inactivating HLA class II molecules DP, DQ, and DR, which present peptides to $CD4^+$ T cells. They are composed of polymorphic alpha and beta chains and do not use B2M for cell surface expression. The common feature of class II molecules is that their promoters require the same set of transcription factors (*RFX5*, *RFXANK*, *RFXAP*, or *CIITA*). Mutations in these factors would prevent the expression of HLA class II molecules.

Astellas Pharma has acquired both companies; in February 2016, *Advanced Cell Technology*, which was renamed *Ocata Therapeutics*, and 2 years later, in February 2018, *Universal Cells*. By the end of 2021, *Astellas* has been sponsoring 8 clinical trials with hPSC, although all of them are evaluating hESC-based therapy (Table 1).

Although the strategy seemed to be well designed, it had some drawbacks. The HLA-E is the canonical activator of KLRC2 (NKG2C), a dominant activating receptor found on human NK cells. NK cells preferentially express several calcium-dependent (C-type) lectins, which have been implicated in the regulation of NK cell function. The cells engineered to over-express HLA-E, while effective in inhibiting KLRC1+ (NKG2A+) NK cells, were unable to inhibit but instead activated KLRC2+ (NKG2C+) NK cells.[21] These data suggested that other strategies are warranted.

It has been suggested that overexpression of NK inhibitory molecules in hPSC might allow the cells to "hide" from allogeneic T-cell recognition while inhibiting their NK-mediated lysis. Indeed, mouse iPSCs lose their immunogenicity when major histocompatibility complex (MHC) class I and II genes are inactivated and NK inhibitory ligand CD47 is over-expressed.[22] However, the data from the human system did not match expectations. The expression of the main CD47 interactor signal regulatory protein alpha (SIRPA) is mostly restricted to macrophages and dendritic cells and not human NK cells, and the observed effects of this immune-modulating strategy in the mouse system could offer only partial or incomplete immune evasion in the human system.[23] Furthermore, the entire strategy of overexpression of NK inhibitory molecules has a caveat. The expression patterns of NK inhibitory receptors are heterogenous,[24] and each NK inhibitory receptor is not expressed on all NK cells. Therefore, it is not easy to suppress NK cell activation in its entirety.[25]

Fate Therapeutics (CA, US; https://fatetherapeutics.com), known for its transgene-free reprogramming technology yielding ground state-like pluripotency stem cells,[26] went a step ahead of its competitors. Their iPSC-derived NK (iNK) cell therapy is multiplexed with a novel combination of immune-evasion modalities: (i) B2M knockout to prevent $CD8^+$ T-cell-mediated rejection; (ii) class II transactivator (CIITA) knockout to prevent $CD4^+$ T-cell-mediated rejection; and (iii) CD38 knockout to enable combination therapy with anti-CD38 monoclonal antibodies, which can be administered to deplete host alloreactive lymphocytes, including both NK and T cells.[23,27] When given in a combination with checkpoint inhibition therapies, such as PD-L1/PD-1 blockade, iNK cells further enhanced inflammatory cytokine production and exerted stronger cytotoxicity against an array of hematologic and solid tumors.[28] The company is currently a direct sponsor of 9 and a partner in additional 4 clinical trials involving their iNK cells (Table 1).

A Paradigm Shift?

The standard strategy for a cutting-edge cancer treatment requires extracting T cells from a patient, engineering them ex vivo, in a laboratory, to produce chimeric antigen receptors (CARs) on the surface that will enable them to latch on cancer cells, and then reintroducing them back to the patient. The entire process is expensive, which makes the therapy itself difficult to afford. A single dose of Kymriah (tisagenlecleucel) for patients in pediatric care is priced at USD 475 000 and Yescarta (axicabtagene ciloleucel) for certain types of non-Hodgkin lymphoma at USD 373 000.[29] These prices rival some of the most expensive medical procedures such as a kidney transplant that is priced at USD 415 000. Due to the shorter time and lower costs of manufacturing, universal donor hPSC-derived immune therapy of cancer is likely to replace such personalized CAR T-cell therapy in future. There is no need to extract T cells

and engineer them ex vivo. The off-the-shelf iNK cells could be available and ready to use right away. Any point of care that can perform a blood transfusion would be able to administer the iNK therapy too.

A new technology that can bypass ex vivo part, nanomedicine-mediated in vivo reprogramming, has recently emerged: a therapeutic approach to generate transient CAR T cells in vivo by delivering modified messenger RNA (mRNA) in T-cell-targeted lipid nanoparticles (LNPs) for the treatment of cardiac fibrosis has been reported.[30] This is only a preclinical study in a mouse model, and we cannot assume that it will work safely in humans. If the technology ends up being safe and effective enough in the treatment of human diseases, it may reduce the importance of the universal donor hPSC-derived immune therapy. However, due to its transient nature, this approach would not be applicable for regenerative therapies of solid organs.

How About hPSC-based Therapy of Diabetes?

Hundreds of articles have been published on stem cell-based treatment of diabetes (PubMed search with key words "stem cell therapy diabetes" yielded more than 5000 articles). However, despite all these predictions, the stem cell-based therapy of diabetes is still in clinical trials and out of reach. Insulin, a hundred years following its discovery, and islet transplantation that started about 20 years ago, are still the only effective treatment of diabetes. The encapsulation device as a strategy of delivering cellular therapy for diabetes was pioneered more than a decade ago. New Zealand-based *Living Cell Technologies* (https://lctglobal.com) successfully demonstrated the effectiveness of alginate-encapsulated neonatal porcine pancreatic islets in the first approved xenotherapy trial. However, the improvement was only short-lived, and this approach was not pursued. The development of a combined advanced therapy medicinal products (ATMP), especially encapsulation devices, for the therapy of diabetes is clearly warranted.

It seems that *ViaCyte* (CA, US; https://viacyte.com), a pioneer in the development of hPSC-based therapy of diabetes, has been the most successful. They changed the design of their proprietary encapsulation devices several times; the most recent one, composed of a medical-grade plastic called expanded polytetrafluoroethylene (ePTFE), was developed in collaboration with *Gore* (DE, US; www.gore.com). *ViaCyte* has recently reported interim results of a landmark stem cell therapy trial for type I diabetes.[31,32] The insulin-secreting cells were delivered to the patients in macroencapsulation device. The results from the first cohort of a phase I/II trial showed that the treated patients were on their way of achieving insulin independence. The implants were safe, and the data demonstrated evidence of meal-regulated insulin secretion by differentiated stem cells in patients.

In February 2022, *ViaCyte* (CA, US; https://viacyte.com) and *CRISPR Therapeutics* (Switzerland; www.crisprtx.com) announced a phase I clinical trials of VCTX210, an hESC-based therapy for type 1 diabetes without the need for immunosuppression. The CyT49 hESC line lacks the *B2M* gene and expresses a transgene encoding CD274 also known as programmed death ligand 1 (PD-L1) to further protect from T-cell attack. Thus, gene-edited, immune-evasive, hPSC-based cellular therapy is not reserved only for the treatment of malignancies.[33,34]

The Future of hPSC-based Therapies

It is quite likely that the upward trend will continue and that a number of hPSC-based clinical trials will grow rapidly in the next few years. US, Japan, and China will remain the leading countries. The closest "competitor," the UK, is still lagging behind. The primary reasons for segregation of the three leading counties are the costs of development and manufacturing of the hPSC-based therapies in line with the safety standards required by the regulatory agencies. Only well-financed businesses in countries with a developed infrastructure and large capital investments available can take advantage in the burgeoning field.

Inevitably, genetically engineered universal donor hPSCs and combined ATMPs will dominate the future of hPSC-based therapy. New quality standards can be established only by bringing together the most recent technology and diverse scientific state-of-the-art expertise in biotechnology, biomaterial sciences, and artificial intelligence. Working together across disciplines will foster the development and implementation of existing and new technologies, thus speeding up progress toward the use of hPSC-based therapies in translational medicine.

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Author Contributions

D.I. and C.O.: conception and design, manuscript writing.

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No new data were generated or analyzed in support of this research.

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