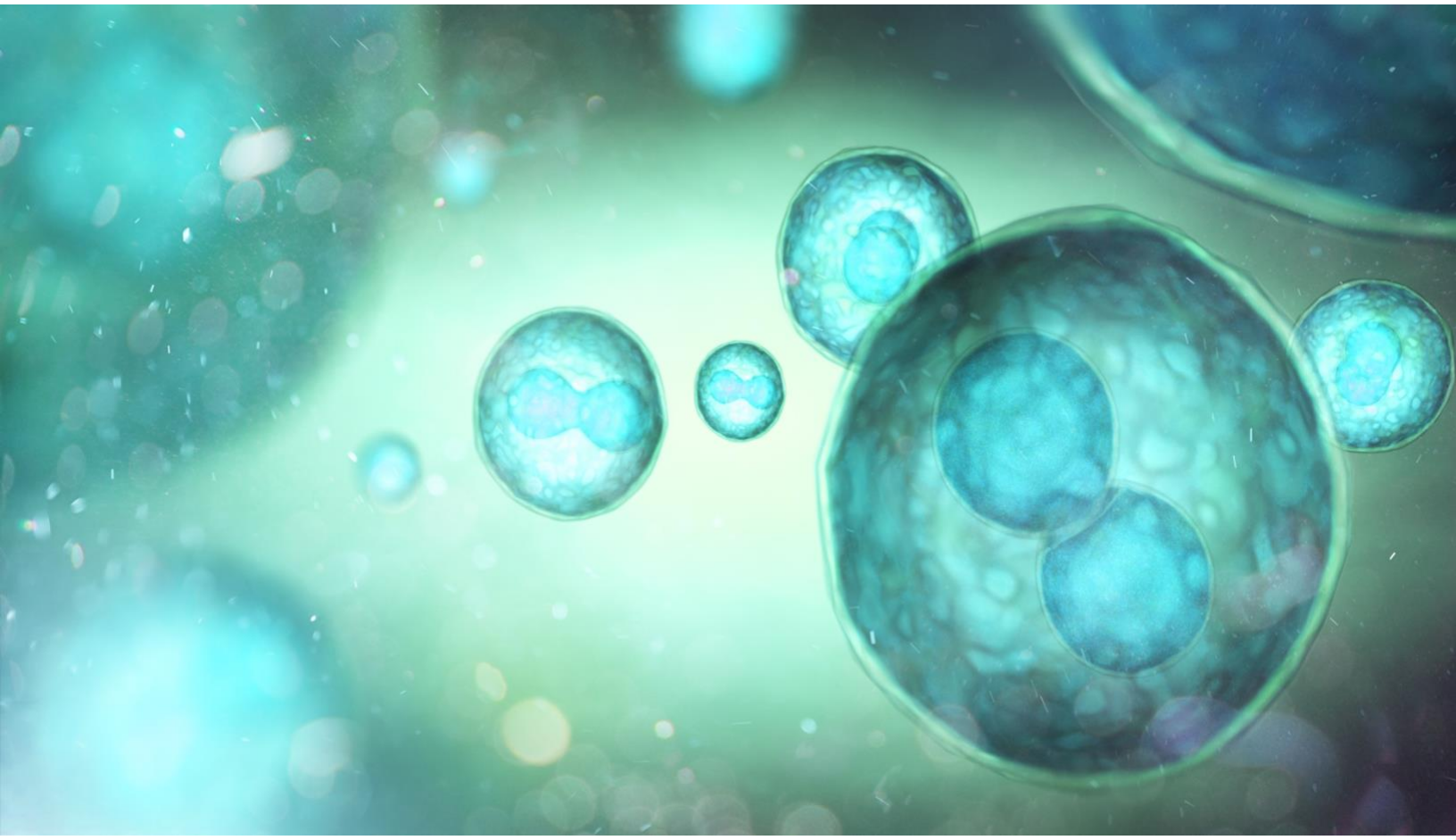

The iPSC Clinical Landscape: A Bright Future Ahead

Authors: Eugene Mironets, PhD, Associate Consultant

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I. Intro

Cell and gene therapies (CGT) are transforming how biopharma companies treat and potentially cure certain diseases. From viral vectors to CAR-T cells, the landscape of CGTs is evolving quickly before our eyes. One approach that combines many flavors of CGTs is the use of somatically-derived cells to produce pluripotent human stems cells that can be re-differentiated into terminal cell types to treat and study disease. In the past decade, significant advancements have been made in utilizing induced pluripotent stem cells hiPSCs) for modeling specific organ and niche cell systems, including cardiac, lung, liver, pancreatic, and central nervous systems (CNS)[1], among others (Fig. 1). The differentiation of human pluripotent cells into a state that closely resembles its primary counterparts morphologically, transcriptionally and functionally has been achieved through the use of transcription factors or small molecules. This enables the modeling of cell systems at various stages of maturity and disease (Fig. 1). Indeed, the capabilities of achieving diversity and specificity of desired cell types has dramatically improved since the discovery of this technology in 2006[2]. Combined with the recent surge in interest of CGTs, the potential for therapeutic interventions using iPSC technology is very promising.

Previously in "Unlocking iPSCs to Improve CNS Modeling and Drug Discovery", we discussed how iPSCs could play a critical role in R&D as a tool to improve in vivo modeling[3], particularly in neurological disease[4]. This paper delves into the current global clinical landscape of iPSC therapies, examines its distribution across various therapeutic areas and geographic territories, and discusses the implications for future therapeutic interventions using this technology.

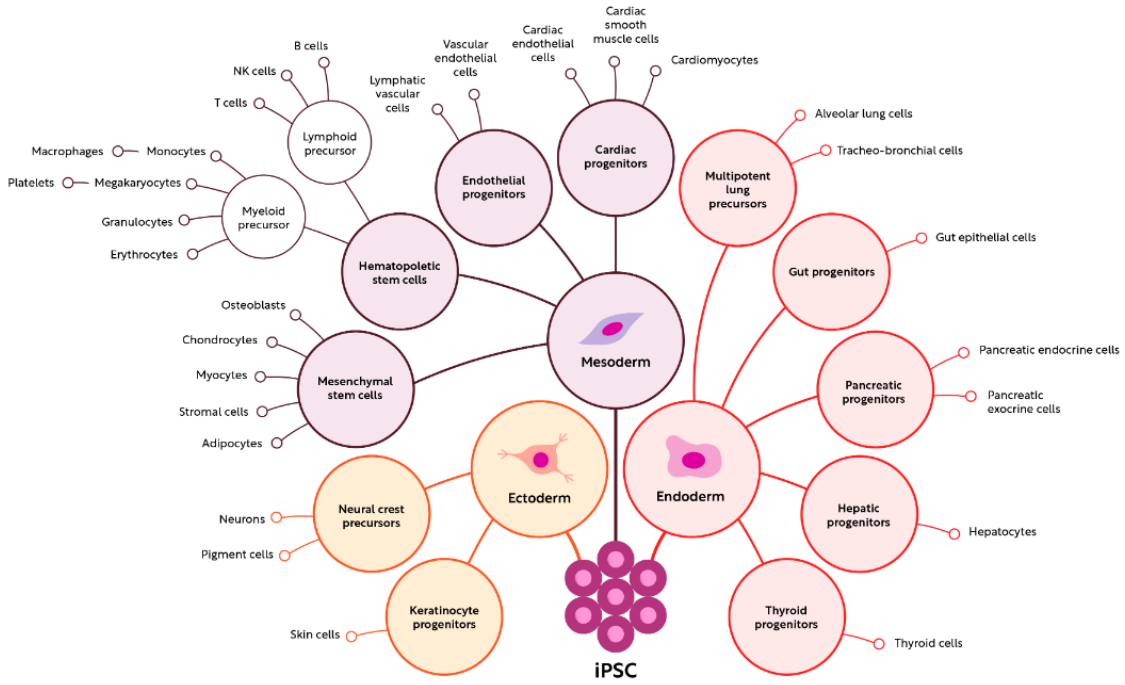

Figure 1. A bubble map showing the differentiation capacity of current iPSC lines[5]

II. iPSC Primer

Before diving into the landscape, a clear understanding of how iPSCs are sourced and generated is important to appreciate the developmental hurdles that need to be overcome. In the following section, we will describe some key iPSC terms that reference how these cells are sourced, generated, and used in clinical and R&D contexts. This will be important moving forward to understand how these different approaches to generating iPSCs produce unique challenges and considerations for patients, physicians and developers.

Key Types of iPSCs:

Virus-mediated iPSCs: Created by introducing genes that are known to be important for pluripotency into adult somatic cells using viruses, were the first type of iPSCs developed. This method is relatively efficient, but it can also introduce genetic changes into the iPSCs if using constructs that integrate into the genome (e.g., lentiviral and oncoretroviral vectors. Episomal iPSCs are generated using episomal vectors (e.g., adenoviral, adeno-associated viral, and herpes viral vectors), which are typically non-integrating viral genomes that express reprogramming factors. These vectors can be eliminated from iPSCs after reprogramming, resulting in iPSCs with a reduced risk of genetic alterations compared to viral-based methods that integrate into the genome.

Chemically-induced iPSCs: This type is created by exposing adult somatic cells to a combination of chemicals that are known to induce pluripotency. Traditional methods of generating iPSCs involve the use of viral vectors that carry reprogramming genes, known as transgenes. Transgene-free iPSCs are generated using non-integrating techniques, such as mRNA, proteins or small molecules, to reprogram cells without permanently altering their genomes. These transgene-free iPSCs have reduced concerns regarding genomic integration and potential side effects. This method is less efficient than virus-mediated reprogramming, but it does not introduce genetic changes into the iPSCs.

Direct reprogramming: A newer method uses a combination of genetic and chemical factors to directly reprogram adult somatic cells into a desired target differentiated cell without reprogramming to iPSCs as an intermediary. This method is the most efficient, but is also the most complex.

Autologous iPSCs: These iPSCs are derived from a patient's own cells, and are intended for use only in that patient. Since they are genetically identical to the patient, they are less likely to be rejected by the immune system when used for therapeutic purposes.

Allogeneic iPSCs: Allogeneic iPSCs are derived from a different individual than the patient to be treated, typically a healthy donor. These iPSCs can be used to create a cell bank that can serve multiple patients, making them more cost-effective. However, due to genetic differences between the donor and the recipient, there is a higher risk of immune rejection. However, if the haplotype is common in the population, many patients will benefit from this selected donor. To HLA match a reasonable proportion of patients in a population, a relatively high number of HLA haplotype-matched iPSC lines may be required.

Disease-specific iPSCs: These iPSCs are generated from patients with specific diseases or genetic disorders. By studying these cells, researchers can gain insights into the disease mechanisms, test

potential drug therapies, and develop personalized treatments. This approach has the potential to yield therapeutics for several diseases that may require genotype-specific approaches.

Gene-edited iPSCs: Gene editing technologies like CRISPR-Cas9 can be used to modify the genetic makeup of iPSCs. This allows scientists to introduce or correct specific genetic mutations associated with diseases, making gene-edited iPSCs valuable tools for disease modeling and potential therapies.

Each of the above has its advantages and applications and there is ongoing debate as to which strategy is best for generation of iPSC lines and for reprogramming to desired differentiated cells. One of the more common discussions revolves around whether allogeneic or autologous strategies are more appropriate in a given setting. Autologous iPSC products offer distinct advantages and disadvantages compared to allogeneic, off-the-shelf iPSCs. As mentioned, autologous transplants are less prone to immune rejection and therefore require fewer immunosuppressive therapies peri-transplantation, resulting in a lower risk of opportunistic infections. This is particularly significant in certain disease contexts, such as blood disorders, blood cancers, and graft-versus-host disease (GvHD).

However, there are also challenges associated with autologous iPSCs, such as the collection of a sufficient number of cells suitable for the manufacturing process, as well as the unpredictable durability of these cells ex vivo and long-term safety due to potential tumorigenicity. Many of these concerns diminish in well-validated allogeneic cell lines. The reprogramming of somatic cells into iPSCs is a time- and resource-intensive process. Therefore, the development of treatment regimens favors the use of allogeneic iPSCs over autologous counterparts more often than not. Currently, there is a global focus on generating allogeneic iPSC lines for the majority of indications. Additionally, significant efforts are dedicated to the development of human leukocyte antigen (HLA)-related CRISPR technology to reduce immune rejection[4, 5], as well as addressing tumorigenicity concerns associated with iPSCs in disease treatment.

III. Notable Therapeutic Areas of Interest in Clinical Development

Despite the significant roadblocks, there are several companies which are actively pushing through these barriers and developing products that are shifting the clinical landscape in its respective therapeutic areas. As is the case with gene therapies and CAR-T (among others), patients with certain diseases can go from having very few symptom relieving options to having a potentially curative approach with one or few treatments. In the subsequent sections, we explore global key players and their clinical pipelines. The following data were derived both from global and national clinical trials registries. Table 1 only includes interventional therapeutic studies trials and excludes non-therapeutic and physician-led trials[8].

Table 1: Clinical pipeline of iPSC therapeutics*

Drug Name	Sponsors	Active Indications	Stage of Development	Territory
CYP-004	Cynata Therapeutics Ltd	Osteoarthritis	Phase 3	AU
CYP001	Cynata Therapeutics	Graft versus host disease	Phase 2	AU

	Ltd; FUJIFILM Holdings Corp			
HS-001 CS	Heartseed Inc.	Heart Failure	Phase 1/2	JAPAN
BioVAT-HF	Repairon GmbH	Advanced Heart Failure	Phase 1/2	EU
iPSC-derived RPE/PLGA transplantation	National Eye Institute (NEI)	Age-Related Macular Degeneration	Phase 1/2	US
iPSC-CL	HeartWorks, Inc.	Congenital Heart disease, Heart Failure	Phase 1	US
CYP-006TK	Cynata Therapeutics Ltd; FUJIFILM Holdings Corp	Diabetic foot ulcer	Phase 1	AU
QN-019a	Hangzhou Qihan Biotechnology Co Ltd	B-cell acute lymphoblastic leukemia; B-cell lymphoma	Phase 1	CH
CNTY-101	Century Therapeutics Inc	B-cell lymphoma; Follicle center lymphoma; Marginal zone B-cell lymphoma; Non-Hodgkin lymphoma	Phase 1	US
FT-576	Fate Therapeutics Inc	Multiple myeloma	Phase 1	US
FT-819	Fate Therapeutics Inc	B-cell malignancies	Phase 1	US

* Table 1 only includes interventional therapeutic studies trials and excludes non-therapeutic and physician-led trials. Several >100 iPSC trials are not included in this table.

Although the technology is still in infancy, there is a rapidly expanding landscape of innovative iPSC-based strategies for addressing an increasing number of indications. What was once only feasible for a limited number of diseases a decade ago, has now evolved into a landscape with over 100 iPSC-based clinical trials. These trials explore the potential of iPSCs as therapeutics, encompassing a much wider range of diseases, as well as non-therapeutic and observational trials that aim to discover the suitability of this technology in several diseases. In this article, we will focus on just the interventional trials that assess therapeutic efficacy and safety in a specific disease.

Oncology

Fate Therapeutics is focusing on using clonal master-engineered iPSC lines to develop chimeric antigen receptor (CAR) cell therapy options for the treatment of hematological malignancies and tumors. It has two clinical-Phase assets in its pipeline: a pPhase 1 iPSC-derived NK cell (iNK) therapy for treating multiple myeloma and a Phase-1 iPSC derived T-cell therapy for treating B-cell malignancies. Notably, in its pipeline there are many different types of differentiated cell types including T-cells, dendritic cells, and NK cells. In 2016, iPSC-derived natural killer cells were demonstrated to be effective against ovarian cancer in an animal model[9]. Clinical trials using iPSC-derived NK cells are ongoing, and sponsored by researchers at the University of Minnesota and Fate Therapeutics, to assess their efficacy against various cancers. Fate currently has two active programs in clinical development, FT-576 and FT-819. In January 2023, Fate announced the discontinuation of FT-596 and FT-536, two iNK therapies to treat B-cell lymphomas and solid tumors [10]. The company has already produced clinical data on its FT-500 and FT-516 programs, which are no longer actively mentioned in its pipeline on its website, suggesting that it may be refocusing efforts into other clinical-stage and preclinical programs.

Century Therapeutics is also developing genetically-engineered immune effector cell therapies derived from iPSCs, targeting hematologic and solid cancers. Its comprehensive allogeneic cell therapy platform focused on the generation of immune effector cells from iPSCs using CRISPR-mediated precision gene editing to incorporate multiple transgenes and knock-outs to optimize cell product performance. It has six programs total in development, with CNTY-101 as the lead candidate[11]. Its platform has garnered interest from Bristol Myers Squibb as a collaborator on CNTY-104 and CTY-106 to treat acute myeloid leukemia and multiple myeloma, respectively.

Additionally, Hangzhou Qihan Biotech is currently developing QN-019a, allogeneic iNK cells that target CD19 for treating relapsed/refractory B-cell acute lymphoblastic leukemia[12]. Similar to Fate and Century, it applies genome-editing technology to develop novel cell therapies and organs for transplantation.

Central Nervous System

Several groups in Japan have pursued the use of iPSC-derived neural cells to tackle difficult indications such as traumatic spinal cord injury, ophthalmic disease and Parkinson's Disease (PD). However, these trials are largely physician-led and therefore hold a less obvious path to commercialization compared to trials backed by biotech, Big Pharma and national institutions[13]. We discuss more on this topic in the next section.

Ophthalmic

Born out of the efforts of Dr. Kapil Bharti's lab at the National Eye Institute, his team is developing a stem cell-based therapy to prevent and restore vision loss caused by age-related macular degeneration (AMD)[14]. This treatment aims to transplant autologous iPSC-derived retinal pigment epithelial cells into the subretinal space to treat refractory AMD.

Autoimmunity

In 2016, Cynata Therapeutics received a landmark approval to launch the world's first formal clinical trial of an allogeneic iPSC-derived mesenchymal stem cell (MSC) product (CYP-001) to treat GvHD. In collaboration with Fujifilm, Cynata Therapeutics completed this Phase I trial in December 2018, reporting positive results. As of April 2023, the FDA has cleared Cynata's application for a Phase 2 trial in aGvHD.

Cynata Therapeutics is also conducting a Phase III clinical trial using CYP-004, an allogeneic iPSC-derived mesenchymal stem cells (MSC) product, to treat patients with osteoarthritis. This trial is the world's first

Phase III clinical trial involving an iPSC-derived cell therapeutic and the largest one ever to be conducted, with an anticipated 440 patients enrolled[15].

Metabolic

In addition to Cyanata's two lead programs, there is also a third clinical program, CYP-006TK, to treat diabetic foot ulcers. This approach utilizes iPSCs differentiated to MSCs to facilitate skin restoration in foot lesions. Recruitment is underway and expected to finish by mid-2023.

Cyanata's approach to generating MSCs, dubbed Cymerus, aims to improve their manufacturing, which currently lacks consistency from inter-donor variability, scalability, and potency[16]. Cyanata's preclinical data consistently demonstrates superior efficacy to bone marrow MSCs. Its partnership with Fujifilm aims to commercialize its products with several more preclinical programs currently in the pipeline.

Cardiac Disorders

Repairon GmBH is working with the University Medical Center Göttingen in Germany to develop engineered iPSC-derived myocardium for targeting terminal heart failure. It is currently conducting a Phase I/II clinical trial to evaluate the safety and efficacy of iPSC-derived engineered human myocardium (EHM), as Biological Ventricular Assist Tissue (BioVAT) in Advanced Heart Failure[17]. In addition to Repairon, Heartworks Inc. and Heartseed Inc. are also conducting clinical trials for the treatment of heart failure using iPSC-based strategies.

In contrast to Heartseed and Repairon, who use allograft transplants, Heartworks is using autologous iPSC-derived cardiomyocytes, with a specific focus on congenital heart failure. Heartseed and Repairon both have a general focus, with the two programs differing only in the final form of the transplanted product. Heartseed's HS-001 utilizes cardiomyocyte spheroids that are injected intramyocardially in order to improve ventricular contractility[18], whereas Repairon has engineered contracting-heart-tissue containing cardiomyocytes and stromal cells in the shape of a laminar sheath, which is surgically patched to the outside of a patient's heart. Heartseed has entered a co-development agreement with Novo Nordisk to manufacture and commercialize HS-001 in all countries, except Japan. This deal include $55 million upfront but could balloon to $598 million with near-term milestone payments.

These products all produce contracting heart muscle cells that can help rebuild the weak muscle, which may be especially effective in older patients who have lost the ability to regenerate heart muscles on their own. This approach could be a critical breakthrough given the epidemiological burden of cardiovascular disease globally.

IV. Physician-Led Trials, Japan

Japan has paved the way for iPSC technology and is the foundational base for both its discovery and continued advancement. The original breakthrough was made there in 2006 by Shinya Yamanaka, MD, PhD, who was later awarded the Nobel Prize in Physiology or Medicine for the work. Considering this, it is unsurprising that Japan offers the most physician-led clinical trials in the world for iPSCs.

Kobe City Eye Hospital sponsors a clinical trial that focuses on transplanting allogeneic iPSC-derived retinal pigment epithelium (RPE) cells to treat patients with neovascular age-related macular degeneration (AMD). Researchers successfully transplanted a sheet of iPSC-derived corneal cells into a patient's cornea, and after one month, improved eyesight was confirmed[2,19]. Decimal visual acuity in the eye of the transplant recipient improved ~66% over a 4-year period. This trial carried out by RIKEN

Center in 2014 is the first known trial using iPSC technology. At the 4-year follow-up, multimodal imaging confirmed that the transplanted iPSC-derived RPE cell sheet was still viable and simultaneously supported the photoreceptors and choroidal vasculature[20].

A clinical trial sponsored by Kyoto University is transplanting dopamine progenitors into patients. Patient progress will be followed for two years and the study is currently enrolling [21].

Another clinical trial sponsored by Kobe City Eye Hospital involves the transplantation of autologous iPSC-derived RPE cells into patients with exudative AMD. In one case, a 77-year-old woman with AMD received a transplant of iPSC-RPE cells, resulting in the cessation of the degeneration process, photoreceptor recovery, and stable vision after one year.

At Keio University, clinical trials were approved to use neural progenitor cells derived from iPSCs in the treatment of patients with spinal cord injury. This piggybacks off of several preclinical studies in spinal cord injury models using iPSC derive neural progenitors[22].

In 2018, the Japanese government greenlit a plan for blood transfusions including platelets derived from iPSCs to treat individuals with aplastic anemia - a disease that diminishes red blood cells and platelets. Individuals with aplastic anemia are usually treated with blood transfusions, an approach for which the individuals in the trial are ineligible due to rejection, according to the researchers.

V. Noteworthy Preclinical Stage Therapeutics

Despite recent advancements, there are only a handful of companies and organizations with programs focused on iPSC-derived cell therapeutics. Several of these have preclinical programs in addition to their ongoing clinical programs. However, a number of companies are well on their way to first-in-human trials and a discussion on some of these follows below. The data below has been sourced from company/organization websites, press releases and journal publications (Table 2). This list is not exhaustive and excludes the many strategies being explored in academia.

Table 2: Companies with preclinical iPSC assets*

Disease Area	Indication(s)	Sponsor(s)	Effector Cell Type(s)	Territory
CNS	Parkinson's disease	Aspen Neuroscience	Dopaminergic Precursors	US
	Parkinson's disease	Ryne Biotech	Dopaminergic Precursors	US
	Parkinson's disease	Bluerock Therapeutics	Dopaminergic Precursors	US
	Stroke, TBI, Cerebral Palsy, ALS, Spinal Cord Injury	Hopstem Biotechnology	Forebrain Neural Progenitors, Motor Neuron Progenitors	China
	Muscular Dystrophies	Vita Therapeutics	Satellite Cell	US
Oncology	Undisclosed Solid Tumor and Metastasis	Vita Therapeutics	Myeloid Cell	US
	Metastatic Breast Cancer	Res Nova Bio Inc	Dendritic Cells	US

	Multiple Tumor Types	Cytovia/Cellectis	NK and CAR-NK Cells	US
	Multiple Tumor Types	Hebecells	NK Cells	US
	Multiple Tumor Types, T1D, CNS diseases	Sana Biotechnology	hypopimmune (HIP)-modified allogeneic cells	US
	Multiple Tumor Types	SCG Cell Therapy PTE/A*STAR	NK Cells	Singapore
	Multiple Tumor Types	Cytomed	NK and T Cells	Singapore
	Multiple Tumor Types	Shoreline Biosciences/ Editas Medicine	NK	US
	Multiple Tumor Types	Neukio Biotherapeutics/ EdiGene Inc	CAR-NK	China
	Multiple Tumor Types	Exacis Biotherapeutics	CAR-NK, CAR-T, and NK	US
	Multiple Tumor Types	CellOrigin Biotech/ Qilu Pharmaceuticals	CAR-Macs	China
Metabolic	T1D	Semma Therapeutics	Pancreatic Beta Cells	US
	T1D	SCM Lifescience/Allele Biotechnology	Pancreatic Beta Cells	US
	T1D	Orizuru (from CiRA/Takeda collab)	Pancreatic Beta Cells	Japan
Ophthalmic	Bullous Keratopathy	Cellusion	Corneal Endothelial Cells	Japan
	AMD	Healios K.K./ Sumitomo Dainippon Pharma	Retinal Pigment Epithelial Cells	Japan
Other	Connective Tissue Disorders	Implant Therapeutics	Mesenchymal Stem Cells	US
	Hair Loss Disorders	Stemson Therapeutics	Folliculogenic Cells	US

* The data have been sourced from company/organization websites, press releases and journal publications. This list is not exhaustive and excludes the many strategies being explored in academia.

Central Nervous System:

Aspen's lead product (ANPD001), an autologous neuron replacement therapy is currently undergoing IND-enabling studies for the treatment of sporadic Parkinson disease (PD). Aspen is also developing a gene-corrected autologous neuron replacement therapy for genetic variants that increase the risk of PD (ANPD002)[12].

Ryne Biotech is using allogeneic iPSCs to generate dopamine neuron progenitors to treat idiopathic PD, similarly to Aspen's products. Its lead product, RNDP-001, has successfully completed FDA-mandated preclinical safety studies and is now moving into clinical manufacturing for IND and a Phase 1 clinical trial[23]. There are two other preclinical assets, both aimed at treating different severities of PD.

PD presents as a particularly attractive indication to pursue using iPSC technology, given the known degenerating population of cells and how relatively consistent this is from patient to patient. Furthermore, the differentiation protocols for midbrain dopaminergic neurons and neural precursors has been extensively studied and validated preclinically[24,25]. Bluerock Therapeutics, a subsidiary of Bayer AG, is considered the leader in the field of iPSC-engineered cell therapies, emphasizing quality production and manufacturing practices to develop master cell banks, which provide advantages in cost and scale. It is the only company with a clinical stage therapeutic for PD using differentiated pluripotent stem cells to mature dopaminergic precursors. Bluerock's multiple programs span neurology, cardiology, immunology, and ophthalmology indications, with the lead focus on PD.

Despite Bluerock's stated emphasis on iPSC-derived cells, its lead product BRT-DA01 (MSK-DA01), is actually derived from human embryonic stem cells. Though, it has been shown that the dopamine progenitors derived from embryonic cells share remarkable similarity to iPSC-derived progenitors, both phenotypically and genotypically. Similar protocols are used to achieve such differentiation from pluripotency[24,26]. Bluerock has fully enrolled its Phase 1 study for PD - the first trial in the United States and Canada to study stem cell-derived dopaminergic neurons in patients with PD[27]. There is a lot of hope for this strategy given the unmet need of the patient population and the promising preclinical data out of the lab of Lorenz Studer, Bluerock's scientific co-founder, and Viviane Tabar, its founding investigator[24]. Results from the Phase 1 study are expected to be announced in the second half of 2023.

Vita Therapeutics is a cell engineering company that uses iPSCs to engineer specific cell types designed to replace those that are defective in patients with rare CNS diseases. Its lead program, VTA-100, is for the treatment of limb-girdle muscular dystrophy (LGMD2A). Vita is developing this proprietary cellular therapy following a dual development strategy beginning with autologous-derived cells before moving to a universal hypoimmunogenic cell line. It has one other program in preclinical development (VTA-120) and two additional programs in discovery (VTA-200 and VTA-300)[28].

Hopstem Biotechnology is one of the first iPSC cell therapy companies in China and a market leader in the manufacturing of clinical-grade iPSC-derived cells. Its listed pipeline assets are still early in development, but it has the most phenotypically diverse set of products compared to other CNS competitors. Hopstem utilizes forebrain neural progenitors aimed at treating stroke, traumatic brain injury, and cerebral palsy; motor neuron progenitors to treat ALS and spinal cord injury; and dopaminergic progenitors to treat PD. In 2021, it entered a strategic partnership with Neurophth Biotechnology, specialists in AAV-mediated gene therapies, for the treatment of ocular diseases[29].

Oncology

The ability of iPSCs to differentiate into a variety of immune cells with high fidelity makes for a highly-versatile platform that is the focus of several companies.

Emvolio Inc, a subsidiary of Therapeutic Solutions International, is currently developing StemVacs-V, an "off the shelf" cancer immunotherapy. StemVacs-V trains the immune system to selectively target and eliminate the blood vessels that feed cancer. Unlike first-generation cancer anti-angiogenesis immunotherapies, which relied on placental cells, StemVacs-V utilizes an established pluripotent stem

cell as a stable and reproducible source of the immunogen. StemVacs-V has been transferred to a spin-out company called Res Nova Bio, Inc[30], with the intention of conducting of a Phase 1/2 trial for metastatic breast cancer.

Cytovia Therapeutics, which is developing an allogeneic gene-edit NK and CAR-NK cell derived from iPSCs, entered into a collaboration with Cellectis to develop five TALEN® gene-edited products. Cellectis' approach aims to improve the potency, persistence and safety of its transplant products for a variety of cancers including solid tumors[31]. Collaborating with Cellectis will allow Cytovia to choose an optimal locus to cut DNA, before either repairing it to "knock-in" edits or disrupting it to "knock-out" undesirable genes. This precision targeting leads to homogeneous and predictable expression levels and allows for potentially more standardized manufacturing, allowing for increased safety and better therapeutic activity. Financial terms of the collaboration include a $20 million convertible note to be received by Cellectis as well as up to $805 million of development, regulatory, and sales milestones and single-digit royalty payments on the net sales of all partnered products commercialized by Cytovia.

Hebecell Corp's platform specializes in scalable NK cell technology. It has an extensive pipeline with ten listed assets, four of which are in collaborations (e.g., Jacobio, Proteintech, AC & Ankarys, TCellTech)[32]. Its products are positioned to potentially treat a number of indications, including ovarian, blood, gastric, colorectal, and brain tumors, among others[33].

Sana Biotechnology is another allogeneic iPSC platform for generating effector cells that escape immune detection in the absence of immune suppression. In vivo studies in fully immunocompetent non-human primates (NHPs) demonstrated that hypopimmune (HIP)-modified allogeneic cells survived without immunosuppression for the length of the studies (16 weeks and >40 weeks). Its pipeline is extensive and mainly focuses on oncology, but also has preclinical programs for type 1 diabetes using islet cells, and for various CNS diseases using glial progenitor cells[34].

SCG Cell Therapy Pte aims to develop first-in-class and best-in-class cell therapies to treat cancers. SCG has a worldwide license agreement with A*STAR to develop and commercialize iPSC-derived cell therapy products[35].

Cytomed, a Singaporean company, is combining iPSC technology and directed differentiation to generate a novel type of synthetic immune cells - γδ NKT cells - that express cancer recognition receptors of both γδ T cells and NK cells from iPSCs for a wide range of cancers, without genetic modification[36].

Earlier in 2023, Shoreline Biosciences entered a licensing agreement with Editas Medicine for its proprietary SLEEK (SeLection by Essential-gene Exon Knock-in) and AsCas12a gene editing technologies. In this agreement, it will also acquire Editas Medicine's preclinical gene-edited iPSC derived natural killer cell (iNK) programs and related manufacturing technologies[37].

Neukio Bioteherapeutics focuses on development of allogeneic iPSC-derived CAR-NK cells. It is in a partnership with EdiGene Inc, a China-based company with expertise in high-throughput genome-editing screening. The partnership aims to leverage complimentary expertise and its combined presence in the US (Cambridge, MA) and China to become a globally competitive gene-editing and iPSC player[38].

Exacis Biotherapeutics takes a unique approach compared to its competitors. It uses mRNA-based cell reprogramming and gene editing technologies to create engineered cell therapies (ExaNK™, ExaCAR-

NK™ and ExaCAR-T™). It claims its approach has distinct advantages due to a repeat dosing capability, capital efficiency for manufacturing, and decreased requirements for preconditioning[39].

CellOrigin Biotech is collaborating with Qilu Pharmaceutical to develop, manufacture and commercialize "off-the-shelf" iPSC-derived CAR macrophages for cancer immunotherapy[40]. This effort is demonstrating the capability of varying differentiation protocols. The ability of iPSCs to differentiate into a number of immune cell types suggests that it may be a useful strategy for a number of oncologic indications.

Given the boom in CAR immune cell therapies, it is unsurprising that iPSCs have become viable strategies for treating cancer. Among all therapeutic areas, it is clear that iPSCs have the greatest presence in oncology. It will be interesting to see which programs are able to successfully move forward.

Metabolic Diseases

Semma Therapeutics is focused on developing treatments for Type 1 diabetes using iPSCs. Semma is a wholly owned subsidiary of Vertex Pharmaceuticals. Semma was founded by Douglas Melton, PhD and others to develop transformative therapies for patients who currently depend on insulin injections. The company is focused on advancing Dr. Melton's method of generating billions of functional, insulin-producing beta cells grown from stem cells in the laboratory, which develop in islet-like clusters. Initial diabetes preclinical work in animal models has shown that transplantation of these cells by infusion into the liver is sufficient to control blood glucose levels. Semma is focused on combining these proprietary cells with a state-of-the-art cell device and immune protection strategy that can protect these cells from the patient's immune system and allow the beta cells to function as they do in non-diabetic individuals. Implantation of the islet cell-filled device has the potential to replace the missing beta cells in a diabetic patient without requiring patient immunosuppression. Semma is working to bring this new therapeutic option to the clinic.

Taking a similar approach to tackling type 1 diabetes, SCM Lifescience agreed to an exclusive licensing agreement with Allele Biotechnology to develop its iPSC-derived pancreatic beta cells to treat Type 1 diabetes, without requiring any assistive devices[41].

CiRA and Takeda Pharmaceutical Company Limited (Takeda) formed a partnership in April 2015 to create the Takeda-CiRA Joint Program for iPSC applications[42] or T-CiRA. The program aims to combine CiRA's expertise in iPSCs with Takeda's drug development capabilities to produce innovative iPSC-based medicines. The initial plan is to develop drugs or therapies in areas such as heart failure, diabetes mellitus, and neurological disorders. This collaboration has already yielded some success in iPSC-derived cardiomyocytes and iPSC-derived pancreatic islet cells, as seeds for regenerative medical products[43], and have been transferred to Orizuru Therapeutics Inc., a company established in April 2021. Takeda will provide research facilities at its Shonan Research Center and collaborative funding of $140 million over a 10-year period. In addition, Takeda will provide more than $84 million worth of research support (facility, equipment, Takeda researchers and various research services) over the 10-year collaboration period.

Ophthalmic Indications:

Cellusion, a Japanese company, is developing CECSi cells for corneal endothelial regeneration to cure bullous keratopathy, a condition accounting for more than half of all cases of corneal transplantation. To do so, Cellusion developed a novel mass culture system for corneal endothelial cells produced from iPSCs. In the future, it hopes to apply this breakthrough cellular technology to other conditions requiring a corneal transplantation beyond bullous keratopathy.

Healios K.K., in collaboration with Sumitomo Dainippon Pharma, is preparing a clinical trial to assess treatment options for patients with AMD. Its candidate, HLCR011, uses iPSC-derived RPE cells similarly to NEI[44].

Other Indications:

Implant Therapeutics develops iPSC-derived MSCs (a similar approach as Cyanata), with a focus on creating a platform highly amenable to gene editing and that can generate hypoimmunogenic cells at scale. CEO, Dr. Mahendra Rao, is a highly respected global leader in iPSC biology. Implant has signed a licensing agreement with panCELLa to develop therapies for diseases that require vascular reconstitution, such as connective tissues disorders. Implant has also agreed to collaborate with RxCell, which excels in developing cGMP grade iPSC lines. RxCell has engineered master cell banks that utilize Sigma/Merck CRISPR-based technology that incorporate 'safe harbor' technology. Safe harbors are sites in the genome that are able to accommodate the integration of new genetic material in a manner that ensures the newly inserted genetic elements function predictably and do not cause alterations of the host genome that could pose a risk to the host cell or organism[45]. The goal of this collaboration is to enhance Implant's ability to generate a wide variety of safe, therapeutic-grade products[46].

Perhaps the most unique company in our list is Stemson Therapeutics, which aims to combat hair-loss using iPSCs to generate de novo hair follicles. Though there is no listed pipeline on Stemson's website, the intention is to use autologous donor cells to create folliculogenic cells that can anchor effectively under the skin and grow a healthy follicle through the skin[47]. The goal is to ultimately use banked iPSC cells, rather than patient-derived cells, for scalability and cost. Stemson aims to treat several hair loss disorders including scarring alopecia, androgenic alopecia and chemo-induced alopecia.

VI. Conclusion

The early-stage iPSC programs discussed here vary greatly, both in innovation and in the diseases they hope to treat. Though iPSCs offer numerous possibilities as breakthrough treatments, when compared to other technologies, there are very few iPSC-based therapeutic agents in clinical development. Considering that iPSCs have been known to researchers since 2006, and the first iPSC-derived clinical trials were conducted in 2014, it is actually somewhat surprising that such little progress has been made in the development of therapeutic agents using iPSCs, and that iPSCs-derived products have only been administered to humans for approximately 7–8 years. The relatively small number of clinical trials focusing on the administration of iPSC-based therapies could be ascribed to the reported genomic instability of iPSCs[48] and the costs to generate the cells and ensure quality and consistency at scale?.

And yet, the preclinical environment suggests that iPSC platforms are on the upswing. We observe a wide range of therapeutics in development for various indications. A key catalyst for iPSCs is the broader growth of the CGT market, which is poised to continue. The early success of CAR therapies and gene editing technology, as well as a more amenable investment and regulatory environment, may yet catapult this technology - once just a promise - into the mainstream. The coming years look to be an exciting time in this space, as a host of untreatable diseases may now have viable, and potentially curable, options.

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About Alacrita

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For more information on our expertise please visit www.alacrita.com.

London Office:

London BioScience Innovation Centre
2 Royal College St
London
NW1 0NH
United Kingdom

+44 207 691 4915
europe@alacrita.com

Boston Office:

Cambridge Innovation Center
One Broadway, Floor 14
Cambridge, MA
02142
United States

+1 617-714-9696
usa@alacrita.com