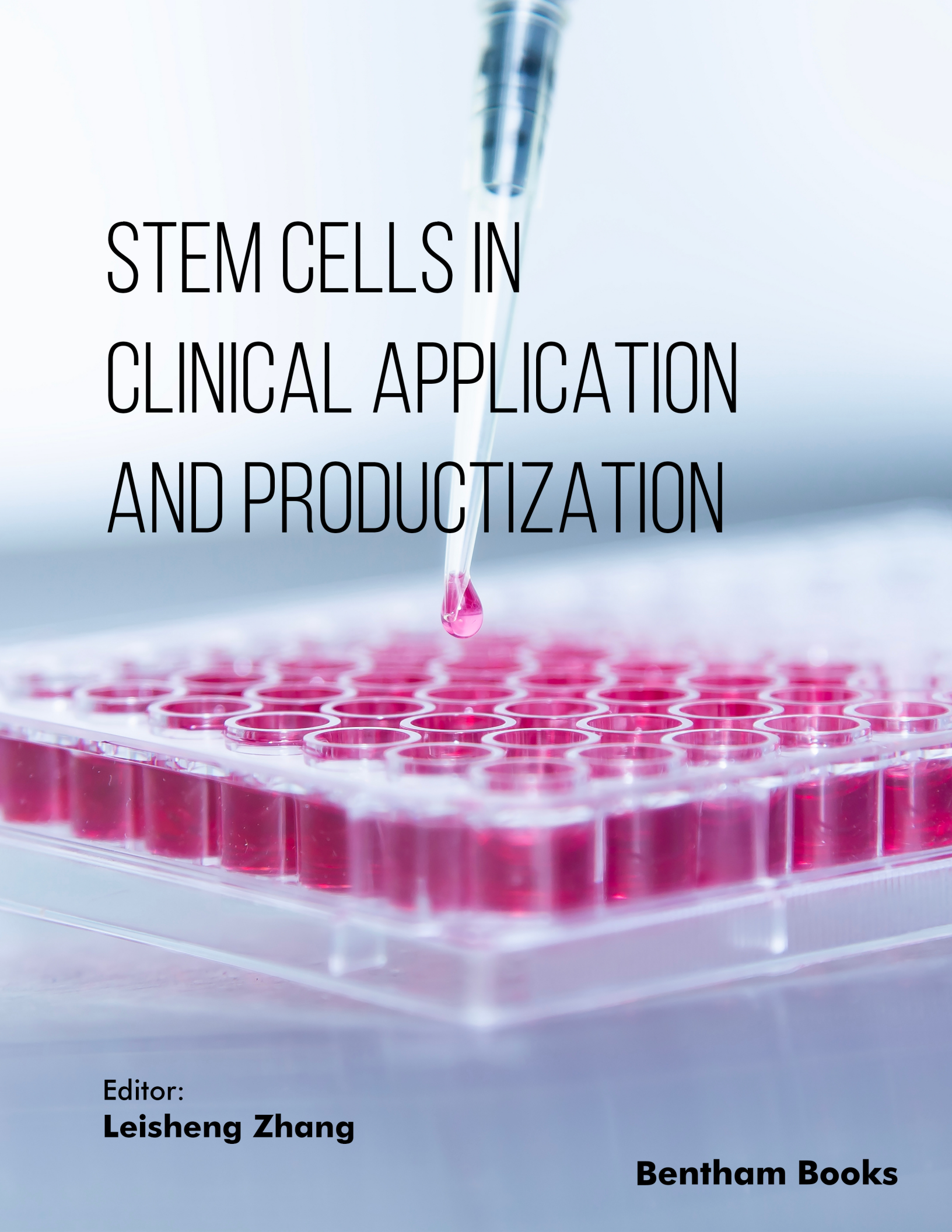

STEM CELLS IN CLINICAL APPLICATION AND PRODUCTIZATION

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Stem Cells in Clinical Application and Productization

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CONTENTS

FOREWORD

Stem cells possess self-renewal and multi-lineage differentiation potential, which are capable of differentiating into more than 200 types of functional cells in vitro and thus hold promising applications in regenerative medicine. Generally, stem cells can be divided into four types totipotent stem cells (*e.g*., zygotes), pluripotent stem cells (*e.g*., embryonic stem cells, induced pluripotent stem cells), multipotent stem cells (*e.g*., mesenchymal stem/stromal cells, neural stem cells), and unipotent stem cells (*e.g*., amniotic epithelial stem cells, hematopoietic stem cells).

State-of-the-art renewal has indicated the combination of biomaterials (*e.g*., hydrogels, hydroxyapatites, nano-materials, scaffolds) with mesenchymal stem/stromal cells (MSCs), which are heterogeneous populations with unique hematopoietic-supporting and immunoregulatory properties for tissue engineering purposes. For decades, we and other investigators have demonstrated the promising prospects of MSC-based tissue engineering in regenerative medicine, and in particular, for the administration of recurrent and refractory disease. Very recently, a number of talented experts took advantage of the biomaterial/MSC composite or scaffolds for applications in osteoarthritis, burn wounds, and refractory wounds associated with diabetic foot as well. Strikingly, the composite or scaffold showed superiority in the continuous improvement of the biological functions of the injured areas over biomaterials or MSCs, respectively. Therewith, stem cells, and biomaterials are recognized as "seeds" and "soils", which are of equal importance for tissue engineering. Collectively, stem cell and biomaterial-based tissue engineering is a core frontier area for disease remodeling and the accompanied regenerative medicine in the future.

Therewith, in this book, Professor Leisheng Zhang in our team and the coauthors have summarized the latest updates of biomaterial/stem cell composites in tissue engineering and put forward the hotspot issues in the future including 3D printing, biomaterial/MSC-exosomes in preclinical and clinical applications.

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PREFACE

Stem cells with self-renewal and multi-lineage differentiation potential have highlighted regenerative medicine for diverse refractory and recurrent disease administration. This book mainly focuses on the landscape of the biological properties and translational research of representative types of stem cells, including hematopoietic stem cells (HSCs), neural stem cells (NSCs), and mesenchymal stem/stromal cells (MSCs). Meanwhile, we are aiming to introduce the latest updates and development prospects of stem cells alone or in combination with advanced biomaterials and technological innovations toward large-scale standardization and productization. Collectively, the content will help enlighten the understanding and further development of stem cell-based innovative medicine and healthcare.

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CHAPTER 1

The Historical Overview of Stem Cells

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Abstract: Stem cells of hierarchical clustering have emerged as alternative and promising sources for tissue engineering and regenerative medicine. Owing to the unique self-renewal and multi-lineage differentiation attributes, stem cell-based cytotherapy has evoked great expectations in handling numerous refractory and recurrent diseases. Of note, quality control (QC), good manufacturing practice (GMP), and guidelines for stem cells and the derivations are prerequisites for evaluating the safety and efficacy of stem cell-based remedies. In this book, we principally focus on the definition, classification, signatures and functions, safety and efficacy of stem cells, together with the core concerns upon stem cell-based clinical applications and investigational new drug (IND) and new drug application (NDA). Collectively, this

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book will effectively benefit the novel stem cell-based tissue engineering and regenerative medicine.

Keywords: Amniotic stem cells, Constitutive microenvironment, Embryonic stem cells, Exosomes and small microvesicles, Hematopoietic stem cells, Hematopoietic-supporting effect, Immunomodulation, Immunoregulatory property, Induced pluripotent stem cells, Investigational new drug, Mesenchymal stem/stromal cells, Multipotent stem cells, Neural stem cells, Pluripotent stem cells, Refractory and recurrent disease, Regenerative medicine, Stem cells, Tissue engineering, Totipotent stem cells, Uni-potent stem cells.

INTRODUCTION

Stem cells are unique cell types of undifferentiated population, which are characterized by self-renewal and multi-lineage differentiation features, and thus hold promising prospects in tissue engineering and regenerative medicine [1]. State-of-the-art renewal has indicated the involvement of stem cells in a variety of physiological and pathological processes. On the one hand, numerous preclinical and clinical investigations have highlighted the therapeutic prospects in multiple refractory and recurrent disease administration, including hematological and circulatory diseases (*e.g.*, acquired aplastic anemia, acute lymphoblastic leukemia, graft-versus-host disease, acute myocardial infarction) [2 - 5], urogenital diseases (*e.g.*, premature ovarian failure, Turner's syndrome, intrauterine adhesion, thin endometrium, male erectile dysfunction, female stress urinary incontinence, interstitial cystitis) [6 - 10], neurological disorders (*e.g.*, Parkinson's disease, Alzheimer's disease, cerebral stroke, infantile cerebral palsy, spinal cord injury) [11 - 16], motor system diseases (*e.g.*, osteoarthritis, meniscus injury, osteonecrosis of the femoral head, critical limb ischemia) [17 - 19], respiratory diseases (*e.g.*, bronchopneumonia, chronic obstructive pulmonary disease, anaphylactic rhinitis, and even COVID-19-induced acute lung injury and acute respiratory distress syndrome) [20 - 24], cutaneous diseases (*e.g.*, decubitus, refractory wounds, allergic dermatitis) [25 - 27], immune diseases (*e.g.*, systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis) [28 - 32], endocrine and metabolic diseases (*e.g.*, diabetes and complications, osteoporosis, hyperuricemia and gout) [33 - 36], and digestive diseases (*e.g.*, decompensated liver cirrhosis, acute colitis, chronic acute liver failure, Crohn's disease, ulcerative colitis) [37 - 44]. On the other hand, we and other investigators in the field have also devoted to dissecting the potential pathogenicity of stem cells *via* secretion, dysimmunomodulation, and providing a constitutive microenvironment [20, 38, 45]. For instance, we recently reported the multifaceted variations in the biological phenotypes and transcriptomic features of bone marrow-derived mesenchymal

stem/stromal cells (BM-MSCs) in patients with acquired aplastic anemia and acute myeloid leukemia [45, 46].

Despite the detailed information of the mode of action of stem cells is still far from satisfaction, yet the overall ways of function have been extensively described, including direct-differentiation, trans-differentiation, dedifferentiation, autocrine and paracrine (*e.g*., exosomes, small microvesicles, cytokines, anti-inflammatory factors), bidirectional immunomodulation, and constitutive microenvironments [1, 13, 47 - 49]. For instance, Yuan *et al.* put forward the therapeutic applications and the concomitant "SMART" principles (including self-renewal, multi-lineage differentiation, apoptosis, rest, and trafficking) of hematopoietic stem cells (HSCs) for hematologic malignancy administration [50]. Instead, Zhao *et al.* highlighted the underlying mechanism of HSC-based cytotherapy for continuous blood cell generation *via* orchestrating cell proliferation, self-renewal, and cell differentiation in the microenvironment [51]. As to MSC-based remedies, we and the colleagues also verify the way of action such as differentiation, secretion, hematopoietic-supporting effect and bidirectional immunoregulation [4, 18, 20].

In this chapter, we mainly focus on the multifaceted characterization of the definition, classification, and the features of stem cells, which will supply overwhelming new references for further understanding the historical overview as well as dissecting the fundamental and clinical investigation of stem cell-based tissue engineering and regenerative medicine.

THE DEFINITION AND HISTORY OF STEM CELLS

In 1868, Ernst Haeckel and the colleagues originally put forward the definition of "Stammzelle" (stem cells) for the description of the ancestor unicellular organisms for the evolvement of all multicellular organisms, who were also the pioneering proponent of the "Anthropozoic Age"concept [52, 53]. In 1902, hematopoietic progenitor cells (HPCs) were identified from bone marrow, and HPC-based transplantation was accomplished for aplastic anemia treatment in 1939 [54]. In 1957, E. Donnall Thomas reported the first allogeneic transplantation of hematopoietic stem cell transplantation (HSCT) by combining the unfractionated mononuclear population with immune suppressive regimens [55 - 57]. In 1968, Friendenstein and the collaborators verified the distinctions between HSCs and stromal cells in the bone marrow environment, which were further named "mesenchymal stem/stromal cells" by Arnold I Caplan *et al* in 1991 [58, 59]. In 1990s and 2000s, pluripotent stem cells (PSCs) including embryonic stem cells (ESCs) and induced PSCs (iPSCs) were identified with the aid of OSKM factor (also known as "Yamanaka factors", including OCT4, SOX2,

KLF4, and c-MYC)-based reprogramming strategy, respectively (Fig. **1**) [60 - 64].

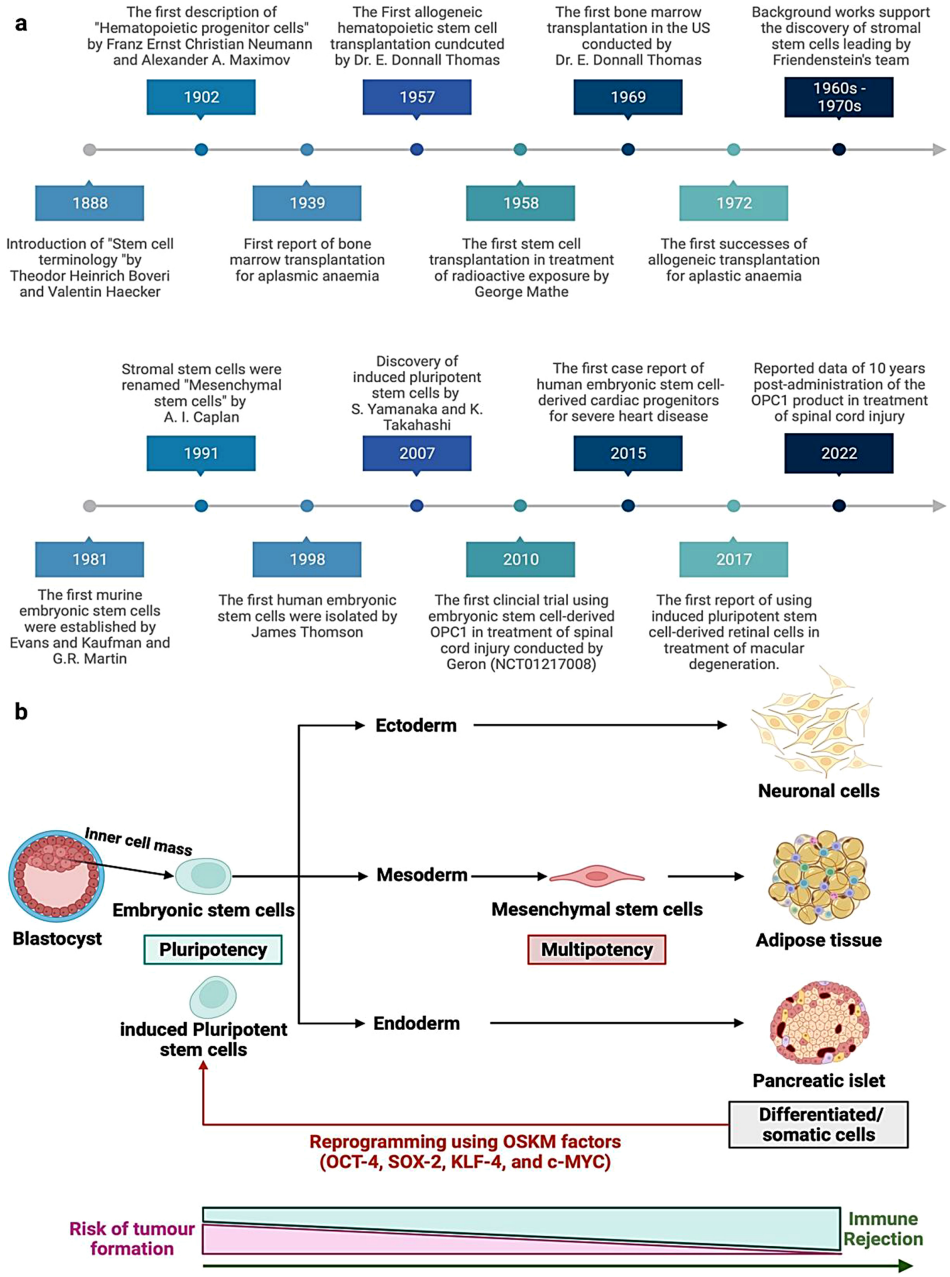

Fig. (1). The history and cell source of stem cell-based cytotherapy [54].

THE CHARACTERISTICS AND BIOLOGY OF STEM CELLS

As referred above, stem cells are populations with self-renewal and multi-lineage differentiation properties, yet vary in developmental potency and the concomitant range of specialized progeny [65]. Generally, PSCs have been considered with potency for generating three germ layers (*e.g*., ectoderm, endoderm, mesoderm) and all organism cells, whereas multipotent stem cells and unipotent stem cells can only regenerate specific tissues or lineages instead [65]. Distinguished from the aforementioned subtypes of stem cells, totipotent stem cells (*e.g*., spermatovum, gastrula stage cells, morula stage cells) are adequate to generate accessory tissue of embryos such as umbilical cord, placenta, amniotic membrane and amniotic fluid.

Currently, a variety of strategies have been involved and developed to define stem cell potency from the aspects of functional analyses, transcriptional expression pattern, single-cell heterogeneity, hallmarks of pluripotency, epigenetic and metabolic status [65]. For instance, PSCs with the robust expression of pluripotency-associated biomarkers (*e.g*., POU5F1, SOX2, and NANOG), while HSCs and MSCs with the abundant expression of hematopoiesis-related (*e.g*., CD34, CD45, CD43) and mesenchymal-related (*e.g*., CD44, CD73, CD105) surface biomarkers, respectively [4, 67, 68]. Murtha M, *et al*. took advantage of

the comparative FAIRE-seq analysis and verified the distinguishing features in the chromatin structure between ground primed- and state- pluripotent cells [69]. Instead, Tong *et al*. and Wang *et al*. reported the heterogeneity of HSCs and megakaryocytes by utilizing the single-cell transcriptomic analysis, respectively [70, 71].

Of note, one of the current research hotspots has turned to disclose the heterogeneity of stem cells and the specific subpopulations to better fulfill the requirements of tissue engineering and regenerative medicine. For instance, we and Zhang *et al*. respectively demonstrated multidimensional alterations and even contradictory outcomes of MSC-based cytotherapy for acute GvHD (aGvHD) and acute liver failure (ALF) due to the otherness in cell sources, which collectively indicated the impact of the heterogeneity of stem cells upon therapeutic effect [4, 72]. Therewith, more and more studies emphasize the necessity of identifying novel surface biomarkers for dissecting unique subpopulations with potentially specific bioactivity. For instance, Battula *et al*. and Studle *et al*. reported the MSCA-$1^{+}$$CD56^{+}$ subset and $CD56^{+}$ subset of MSCs with predominant differentiation bias towards pancreatic-like islets and chondrocytes over those negative counterparts, respectively [73, 74]. Similarly, Du and the colleagues verified that the content of VCAM-1^{+} subpopulation varied among BM-MSCs,

umbilical cord-derived MSCs (UC-MSCs), and placenta chorionic villi-derived MSCs (CV-MSCs), which displayed preferable pro-angiogenic activity *in vitro* and *in vitro* when compared with the VCAM-1^- subset [75]. Interestingly, with the aid of cytokine cocktail-based programming, we established a high-efficiency procedure for VCAM-1^+ UC-MSCs preparation within 48 hours, and the indicated cells revealed enhanced pro-angiogenic activity and efficacy for aplastic anemia mice over the VCAM-1^+ subset [3]. Very recently, we further demonstrated the preferable outcomes of cerebral infarction in rats and acute lung injury in mice, respectively [76, 77]. Overall, with the aid of systematic and detailed dissection of the heterogeneity in preclinical and clinical investigations, the potential variations and contradictoriness of stem cell-based cytotherapy can be hopefully well resolved.

THE CLASSIFICATION OF STEM CELLS

As mentioned above, stem cells and derivations (*e.g.*, exosomes, small extracellular vesicles) are advantaged sources with unique superiorities for tissue engineering and the resultant regenerative medicine [32, 78, 79]. Generally, according to the aforementioned differentiation potential, stem cells can be divided into totipotent stem cells (*e.g.*, germ cells), pluripotent stem cells (*e.g.*, embryonic stem cells, induced pluripotent stem cells), multipotent stem cells (*e.g.*, mesenchymal stem/stromal cells, amniotic stem cells), unipotent stem cells (*e.g.*, neural stem cells, hematopoietic stem cells, amniotic epithelial stem cells), and even the newly identified post-embryonic sub-totipotent stem cells (a hierarchical system of mesenchymal stem/stromal cells) [78, 80 - 82]. Meanwhile, stem cells can be classified into natural stem cells (*e.g.*, embryonic stem cells, perinatal stem cells, and adult tissue-derived stem cells) and artificial stem cells (*e.g.*, haploid stem cells, induced pluripotent stem cells, and nuclear transplanted stem cells) according to the origins [64, 79]. For instance, perinatal stem cells can be divided into umbilical cord-derived MSCs, umbilical cord blood-derived MSCs, amniotic epithelial stem cells (AESCs), amniotic mesenchymal stem cells (AMSCs), amniotic fluid-derived MSCs, placenta-derived stem cells, and placental chorionic villi-derived MSCs (CV-MSCs) [39, 75, 80, 82, 83].

THE SAFETY AND EFFICACY OF STEM CELLS

Due to the unique attributes of stem cells, the safety and efficacy issues after transplantation are the prerequisites of stem cell-based cytotherapy before large-scale clinical application. In particular, PSCs including ESCs and iPSCs are capable of differentiating into all types of functional cells and thus the safety issue has been considered as a long-disturbing problem in the field [38, 84, 85]. Meanwhile, numerous pending questions also hamper the PSC-based translational

medicine due to the intrinsic attributes, including technological, ethical, and regulatory complications [86]. In details, the variations and difficulties in clinically relevant features further hamper the large-scale application of PSC-based cytotherapy, such as generation methods for the development of autologous clinical-grade PSC lines, high-efficient procedures and good manufacturing practices (GMP) for cost-effective generation of functional cells, propensity to epigenetic abnormalities or genetic mutations, and the tumorigenicity [86].

Different from the aforementioned PSCs, MSCs of different origins reveal reliable hypoimmunogenicity and thus satisfy the demands for autologous and allogeneic infusion in tissue engineering and regenerative medicine, which therewith hold more robust prospects for conquering the recurrent and refractory diseases. Interestingly, Zhao *et al*. recently provided systematic and detailed description of the biological features (*e.g*., cellular immunophenotyping, tri-lineage differentiation potential, hematopoietic-supporting effect, efficacy upon aGvHD mice) and tumorigenicity (*e.g*., proto-oncogenes, tumor suppressor genes, chromosome structure, *in vivo* tumor formation test) of UC-MSCs at various passages, which collectively demonstrated the conservations and variations in continuous passages upon the safety and efficacy of UC-MSCs [4].

It's noteworthy that pioneering investigators in the field have turned their attention and aimed to solve the concomitant problems in safety and efficacy by releasing consensus and general requirements for stem cells [87]. For instance, the Chinese Society for Stem Cell Research (CSSCR) issued the first set of general guidelines for stem cell research and production in China named "General requirements for stem cells", which collectively specified the classification, quality requirements, ethical requirements, detection control requirements, quality control requirements, and waste disposal requirements of stem cells [87]. Meanwhile, Hao *et al*. and Chen *et al*. also respectively put forward general guidelines for human ESCs (hESCs) and MSCs, which were applicable to the quality control for the aforementioned stem cell subtypes and thus benefited the international standardization [88, 89]. Very recently, Nan and the colleagues highlighted the requirements for human haematopoietic stem/progenitor cells (HSPCs), including instructions for usage, technical requirements, inspection rules and methods, packaging requirements, labeling requirements, storage and transportation requirements [90].

Notably, Zhao *et al*. introduced the principles of clinical grade MSCs for investigational new drug (IND) in 2021 from the aspect of guidance, regulations, processes, quality management, pre-IND meeting as well as IND application for obtaining permission to launch clinical trials in China (Fig. **2**) [66]. In this review article, they discussed the major intermediate stages during MSC product

development in detail, such as the basic research stage (*e.g.*, cell isolation and purification, cell expansion, cell culture medium development, cell characteristics analysis, and the underlying mechanisms of action for specific indications), pharmacy stage (*e.g.*, product testing and release, chemistry manufacturing control, and stability programs), pharmacology stage (*e.g.*, definition of targeted indications and route of administration, solidification of anticipated mechanism of action, identification of biologically active dose, determination of efficacy, demonstration of safety and pharmacokinetics), toxicology stage (*e.g.*, a single dose toxicity test, reproductive toxicity, tumorigenicity research, immunotoxicity test, repeated administration toxicity test, antigenicity test, genetic toxicity, and local tolerance), IND application stage (*e.g.*, pre-IND meeting, IND application filing, IND submission), and clinical trials stage (*e.g.*, exploratory clinical trials, confirmatory clinical trials) [66].

In 2022, we and the collaborators further put forward the necessity and principles of quality control (QC) of UC-MSCs for acute GvHD (aGvHD) and chronic GvHD (cGvHD) during investigational new drug (IND) administration in China, which assure the consistency and feasibility of the safety and quality of UC-MSCs [2]. Furthermore, we emphasized the pivotal role of GMP for safety and efficacy evaluation during the large-scale preparation of therapeutic MSC drugs for carbon tetrachloride (CCl4)-induced acute-on-chronic liver failure (ACLF) [37]. Taken together, the published general requirements of guidelines and standards will benefit the decoding of the safety and efficacy assessment of stem cell-based tissue engineering and regenerative medicine in future.

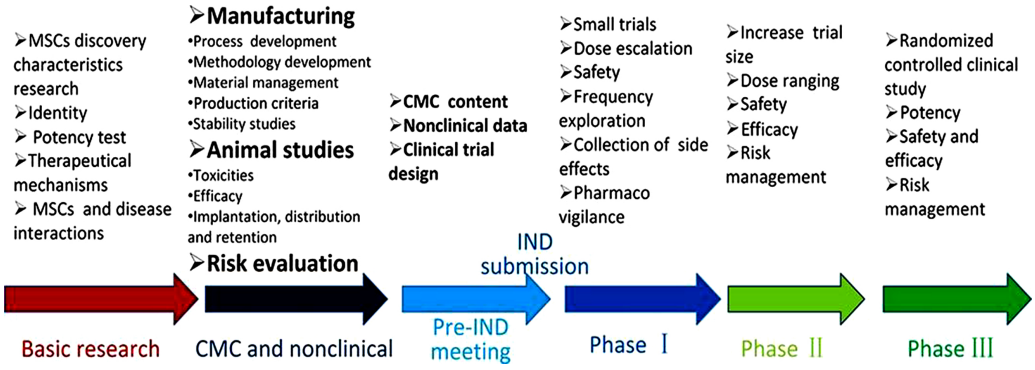

Fig. (2). Content and flow chart of MSC product development [66].

CONCLUSION

Stem cells are unique cell types with self-renewal and multi-lineage differentiation properties, which thus have potential application prospects in

conquering refractory and recurrent diseases as well as the concomitant tissue engineering and regenerative medicine. To better fulfill the aims of clinical application and investigational new drug application, it is of critical importance in systematic and detailed illustration of the principles and guidelines for biological features and the underlying mechanism. Overall, before large-scale application, the assessment of the safety and efficacy of stem cells are prerequisites for stem cell-based remedies and product development in future.

ABBREVIATIONS

PSCs	Pluripotent stem cells
ESCs	Embryonic stem cells
iPSCs	Induced pluripotent stem cells
MSCs	Mesenchymal stem/stromal cells
ASCs	Amniotic stem cells
AA	Aplastic anemia
ALL	Acute lymphoblastic leukemia
AESCs	Amniotic epithelial stem cells
AMSCs	Amniotic mesenchymal stem cells
GvHD	Graft-versus-host disease
AMI	Acute myocardial infarction
POF	Premature ovarian failure
PD	Parkinson's disease
AD	Alzheimer's disease
SCI	Spinal cord injury
OA	Osteoarthritis
ONFH	Osteonecrosis of the femoral head
CLI	Critical limb ischemia
COPD	Chronic obstructive pulmonary disease
AR	Anaphylactic rhinitis
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
AD	Allergic dermatitis
SS	Systemic sclerosis
SLE	Systemic lupus erythematosus
RA	Rheumatoid arthritis
ACLF	Acute-on-chronic liver failure
CD	Crohn's disease

UC	Ulcerative colitis
BM-MSCs	Bone marrow-derived MSCs
UC-MSCs	Umbilical cord-derived MSCs
HPCs	Hematopoietic progenitor cells
HSCT	Hematopoietic stem cell transplantation
aGvHD	Acute GvHD
cGvHD	Chronic GvHD
ALF	Acute liver failure
CV-MSCs	Chorionic villi-derived MSCs
GMP	Good manufacturing practices
CSSCR	Chinese Society for Stem Cell Research
HSPCs	Haematopoietic stem/progenitor cells
IND	Investigational new drug
QC	Quality control
CCl_4	Carbon tetrachloride

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CHAPTER 2

Biomaterials and Stem Cells

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Abstract: Longitudinal studies have indicated the involvement and performance of multitudinous biomaterials for stem cell-based cytotherapy and regenerative medicine largely attribute to their specific biocompatibility. Currently, stem cells and biomaterial scaffolds have been considered as the two essential elements of the cornerstone of tissue engineering. On the one hand, biomaterials are beneficial to provide suitable microenvironments for enhancing the cellular vitality and therapeutic effect of stem cells. On the other hand, biomaterial-induced fibrosis and inflammation remain a prominent challenge in designing and synthesizing appropriate materials to facilitate tissue repair and organ regeneration. In this book chapter, we summarize the classifica-

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tion and physicochemical properties of the indicated biomaterials, and appraise the latest literatures of biomaterial and stem cell composite for broad biomedical applications in tissue engineering and regenerative medicine. Collectively, we retrospect the current advancement of biomaterial engineering and science, and highlight the multifaceted biomaterial-assisted stem cell-based tissue engineering and regenerative medicine, and in particular, the biomaterial-based composites with mesenchymal stem/stromal cells (MSCs) and the derivatives (*e.g.*, exosomes, small microvesicles) for intractable disease administration.

Keywords: Biomaterials, Biocompatibility, Clinical trials, Cancer immunotherapy, Exosomes, Hyaluronic acid, Hydrogels, Immunomodulation, Mmesenchymal stem/stromal cells, Microenvironment, Nanomaterials, Organ regeneration, Physicochemical properties, Preclinical applications, Regenerative medicine, Stem cells, Small microvesicles, Scaffold, Tissue engineering, Three-dimensional printing.

INTRODUCTION

State-of-the-art renewal has indicated the superiority of biocompatible and biodegradable biomaterials in facilitating the ameliorative or therapeutic effect of stem cells upon numerous intractable diseases as well as enhancing immune cell manifestations during anti-cancer immunity [1 - 3]. Generally, biomaterials play an ancillary role with the objective of endowing the special ability of encapsulated constituents such as stem cells, immune cells, and derivatives (*e.g.*, exosomes). For example, the orientation and conformation of the proteins in dendritic cell-derived exosomes (DC-exo) can be altered and thus form “biomaterial-associated molecular patterns (BAMPs)” with the adsorbed biomaterial surfaces [4]. As to the immunogenicity problem, Jiang *et al*. reviewed alternative solutions with the aid of genetically modified cell-based biomaterials carrying particular immunomodulatory genes [5]. Even though, the intrinsic shortcomings of the current genetically modified stem cell-based or immune cell-based biomaterials remain to be overcome, such as nonspecific effects, uncertain biosecurity, and overlooked personalization [5]. In addition to that, we foresee that the next generation of biomaterials for tissue engineering and regenerative purposes will entail more effective interactions with the encapsulated cells including stem cells and the derivatives.

In this chapter, we are principally concerned with the latest updates in stem cell-based cytotherapy and tissue engineering by combing stem cells or derivatives with well-established biomaterials such as hyaluronic acid (HA) and nano-materials, which will supply new references and benefit the development of stem cell-based biomaterials and biomedicine.

HYDROGEL/STEM CELL COMPOSITE

Current studies have suggested the cell-laden hydrogels as a tissue-engineering platform with promising prospects for reinforcing the biological properties and biofunctions of the encapsulated objectives [6]. Of them, gelatin and hyaluronic acid (HA) have been recognized as the two major components of the extracellular matrix in various tissues, which are appealing for the generation of compatible hybrid hydrogels *via* orchestrating the scaffold structure, specific composition, and physico-chemical property [7]. For example, Madhusudanan *et al*. considered hydrogels rather than relative scaffolds as excellent candidates for the preparation of neural cells and the resultant neural tissue engineering (NTE) attributed to their intrinsic properties in orchestrating immune microenvironment and secreting the antagonists of neural growth inhibitors, neurotrophic factors, and relative neural growth-promoting agents [8]. Meanwhile, Xiao *et al*. and Celikkin *et al*. reviewed the Gelatin methacrylate-based hydrogels in tissue engineering applications based on the biofunctionality and mechanical tenability (*e.g*., chemical properties, physical strength, porosity, and conductivity) [9, 10].

Of note, state-of-the-art renewal has also highlighted the gelatin methacrylate-based hydrogels with controlled microstructures and excellent 3D scaffolds for facilitating cellular vitality and tissue engineering, including microfibers, microspheres, microgrooves, microridges, microchannels, microwells, and micropillars [11]. For instance, Khayambashi *et al*. figured out hydrogel encapsulation in enhancing the maintenance of the biological activity and controlling the release of paracrine factors from MSCs and MSC-exos [12]. Similarly, Tang *et al*. and Han *et al*. discussed the exosome-loaded thermosensitive hydorgels and 3D-cultured MSC-exo/hydrogel hybrid patch for corneal epithelium regeneration and spinal cord repair, respectively [13, 14].

Of note, current studies have also indicated that cryogels and other tissue equivalents could also act as good carriers for stem cells [15, 16]. As a specific hydrogel, cryogels are a category of macroporous and interconnective hydrogels that can polymerize at sub-zero temperatures, and thus form mechanically robust and elastic networks [17]. For stem cells, cryogels and the concomitant cryogelation are adequate to provide a unique and sponge-like structure for cell cultivation and the resultant tissue regeneration [18, 19].

Overall, a variety of hydrogel/stem cell composites have been continuously developed for regenerative purposes, including MSCs/thermosensitive hydroxy-propyl chitin hydrogel (HPCH),ε-caprolactone (PCL)/nano-hydroxyapatite (nHA) scaffold, injectable chitosan hydrogel, and PCL/nHA + HPCH hybrid scaffolds [20, 21].

COLLAGEN SCAFFOLD/STEM CELL COMPOSITE

Collagen has been used as biomaterials since 1881, which are subsequently used as natural scaffolds with high biocompatibility for tissue engineering [22, 23]. For example, renal extracellular matrix (ECM) is composed of elastin, collagens, glycoproteins and proteoglycans, which collectively form the interstitial space and basal membranes [24]. As a ubiquitous molecule and the primary component of ECM in the body, collagen is supposed to fulfill essential biofunctions in body tissues *via* serving as macromolecular scaffolds, the receptor binding site, and growth factor reservoir [25, 26].

On the basis of the high biocompatibility, collagen has been considered the pivotal component of the formulations being designed for tissue engineering, and in particular, for wound healing, homeostasis and surgical management as well as bone mineral formation [27 - 31]. For instance, Warth *et al*. and Patil *et al*. reviewed the implantation of resorbable collagen scaffolds and engineered collagen matrices for the remission of meniscus defects and relative tissue engineering applications, respectively [32, 33]. Notably, state-of-the-art updates indicated the bioprinting of pure collagen alone or combined with stem cells for regenerative purposes [34]. Collectively, collagens are perfect biomaterials and scaffolds for evaluating the synergistical effects with stem cells for surgical reconstruction and regenerative purposes.

NANOMATERIALS/STEM CELL COMPOSITE

Nanomaterials are nanoparticles with a diameter ranging from 1 nm to 100 nm, which are adequate to enhance the permeability and retention (EPR) effect of the target cells [35]. In general, nanomaterials can be categorized into organic nanomaterials, inorganic nanomaterials, and organic-inorganic hybrid nanomaterials, which have been continuously developed and optimized for diagnosis and treatment on the basis of their unique biomedical characteristics and biofunctions [36 - 39]. For example, Ang *et al*. emphasized the recent progress of advanced and multifunctional nanomaterials and concomitant cancer nanotheranostics [37]. Instead, Hofmann *et al*. and Kong *et al*. summarized the utilization of nanomaterials and nanostructure-mediated physical signals in mimicking the extracellular matrix (ECM) and driving stem cell fate determination [40, 41].

Current literatures have reported the interaction and the underlying molecular mechanism of the anchoring nanomaterial scaffolds and stem cells in tissue engineering and organoid research by activating specific signaling pathways [42 - 45]. For example, nanomaterials are often functioned as a scaffolding system to assemble imaging, targeting and therapeutic moieties into a unique and unitary

agent, which thus show ancillary effects with the encapsulated stem cells to modulate multidimensional biofunctions independently of engineered properties [35]. Instead, Shi *et al*. and Fan *et al*. demonstrated the auxiliary role of cell infiltrative inner connected porous hydrogel and a 3D biomimetic hydrogel for the functional recovery of spinal cord injury *via* orchestrating the cellular vitality and the cell fate of neural stem cells, respectively [46, 47].

Generally, the principles of nano-material design for nanomedicine mainly focus on two major aspects, functional considerations for clinical decision-marking and the potential clinical harm of adverse nanoparticle interactions with cell biology [35]. Taken together, nanomaterials facilitate stem cell-based cytotherapy *via* integrating or incorporating with the encapsulated stem cells, serving as substrates or scaffolds, benefiting cell migration and differentiation, and reinforcing the antioxidant property [46, 48, 49].

BIOMATERIALS AND DERIVATIVES OF STEM CELLS

Exosomes and small extracellular vesicles (sEVs) are the two major forms of derivatives of stem cells, and perform an important role in various physiological and pathological processes as well as tissue engineering [50 - 52]. Exosomes are nano-sized vesicles ranging from 20 nm to 200 nm, which include nucleic acids (*e.g*., mirRNAs, lncRNAs, tRNAs), proteins (*e.g*., cytokines, anti-inflammatory factors), lipids and relative bioactive substances [53].

Different from the parental stem cells, exosomes and sEVs are cell-free constituents as signalosomes and mediate the intercellular transportation of substances *via* adhesion or ligand molecules on or inside the membrane [54]. For example, MSC-exo have been proved to have considerable safety and efficient therapeutic effects on various diseases, including atherosclerosis, acute and chronic wound model [55, 56]. Meanwhile, exosomes have been involved in the pathogenesis of cancers and immune diseases, which can mediate epithelial mesenchymal transition (EMT) and exosome-inflammasome crosstalk, together with metastasis and chemoresistance of cancer cells [50, 57]. As reviewed by Zhang *et al*. and Shao *et al*., exosomes are widely distributed in the cellular system, and modulate cancer development and metastasis *via* anti-tumor and pro-tumor immunity, participation in tumor microenvironment, tumor targeting and drug delivery [54, 58, 59].

To date, exosome biogenesis has been recognized as a mechanism of protein-related quality control (QC), which displays functions and activities as diverse as transmitting molecules and signals, remodeling extracellular matrixes to other cells [60]. For example, Zhang *et al*. reported the chitosan hydrogel in boosting the stability and retention of placenta-derived MSC-exo and the contents (*e.g*.,

proteins, microRNAs) as well as the resultant enhanced therapeutic effects for hindlimb ischemia treatment [21].

Of note, current progress in technological advancements has highlighted the prospect of exosome biochemistry and nanotechnology, which have provided an unprecedented opportunity and a solid basis to bloom the developments of exosome-associated biology, pathology, chemistry, and next-generation therapeutics [61 - 63]. Collectively, stem cell-derived exosomes and sEVs are promising elements for human disease diagnosis, targeted drug delivery and tissue engineering, yet the clinical setting and relative regenerative purposes are restricted largely due to the deficiency of standardization in isolation, low yield, and analytical strategies [52, 59, 64].

CONCLUSION

Stem cells and the derivatives are advantaged sources for tissue engineering and regenerative medicine, which have been extensively investigated in numerous preclinical and clinical applications. State-of-the-art studies have also indicated the auxiliary role of biomaterials with specific biocompatibility in enhancing stem cell-based cytotherapy *via* providing suitable microenvironments as well as facilitating disease classificatory diagnosis. Overall, multitudinous biomaterials /stem cell composites will efficaciously enhance the cellular vitality, multifaceted biofunction and the therapeutic effect of stem cell-based therapeutic regimens in future.

LIST OF ABBREVIATIONS

MSCs	Mesenchymal stem/stromal cells
MSC-exo	MSCs-derived exosomes
DC-exo	Dendritic cell-derived exosomes
BAMPs	Biomaterial-associated molecular patterns
HA	Hyaluronic acid
NTE	Neural tissue engineering
HPCH	Hydroxypropyl chitin hydrogel
nHA	Nano-hydroxyapatite
PCL	ε-caprolactone
ECM	Extracellular matrix
EPR	Enhanced permeability and retention
sEVs	Small extracellular vesicles
EMT	Epithelial mesenchymal transition
QC	Quality control

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CHAPTER 3

Hematopoietic Stem Cells in Regenerative Medicine

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Abstract: Hematopoietic stem cells (HSCs) are a common origin of blood cells and the intermediate progenitor cells and precursor cells including the myeloid or lymphoid lineages, which are the footstones of short-term and long-term blood regeneration. HSCs are precisely orchestrated by the constituents in the hematopoietic microenvironment in the bone marrow niches such as stromal cells, immune cells, and cytokines. The dysfunction and genetic variations of HSCs might lead to hematopoietic abnormality, haematopoietic equilibrium and even hematologic malignancies. Meanwhile, the cellular and molecular mechanisms of HSC maintenance and differentiation according to the niche are of great importance for disease administration *via* hematopoietic stem cell transplantation (HSCT). In the chapter, we mainly focus on

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the works of literature on the definition, biological phenotypes, preclinical investigation and clinical trials of HSCs, which will collectively facilitate the clinical application of HSCT and the relative regenerative medicine for hematological diseases and immune diseases in future.

Keywords: Acute myeloid leukemia, Acute lymphocytic leukemia, Biological phenotypes, Bone marrow microenvironment, Biological features, Classification, Chronic lymphocytic leukemia, Chronic myeloid leukemia, Hematopoietic diseases, Hematopoietic stem cells, Hematopoietic stem cell transplantation, Homeostasis, Hematogenesis, Hematologic malignancies, Hematopoietic progenitors, Immune diseases, Molecular mechanisms, Regenerative medicine, Safety and efficacy, Stem cells.

INTRODUCTION

Hematopoietic stem cells (HSCs) are rare and unique cell populations with remarkable features of self-renewal and lineage differentiation potential towards differentiated hematological cell lineages [1, 2]. HSCs can be divided into the quiescent subpopulation and the activated subset, which are elaborately orchestrated by the hematopoietic microenvironment in the bone marrow [3]. HSCs reside in the microenvironment and are modulated by stromal cells and relative constitutive elements in the niches, which thus determine the quiescence of HSCs and the differentiation of hierarchy of blood cells [4, 5]. On the basis of the specific properties, HSCs sustain the lifelong generation of blood precursor cells and functional blood cells, together with immune cells at various stages of differentiation and maturation [6, 7]. Therewith, HSCs play a crucial role in both physiologic and pathological hematogeneis, and the concomitant HSCT [8].

In this chapter, we mainly summarize the state-of-the-art renewal and the challenges of HSCs from the aspects of definition, biological phenotype, hematopoietic microenvironment, regulation of hematopoiesis in physiologic hematopoiesis and pathological hematologic malignancies. Taken together, the contents in this chapter will help boost our understanding of HSC-based cytotherapy, and in particular, hematopoietic stem cell transplantation (HSCT) for blood production and hematopoietic reconstitution *via* the hierarchical organization of HSCs and their progenies including progenitor cells and precursor cells, which will collectively benefit HSC-based investigations for regenerative purposes.

THE OVERVIEW OF HEMATOPOIETIC STEM CELLS (HSCS)

HSCs present at the apex of the hematopoietic hierarchy of progeny cells and blood cells. As mentioned above, the typical property of quiescent HSCs is that

they principally maintain in the interphase of cell cycle (the G0 stage) and divide infrequently as well, while the activated HSCs are adequate to program into differentiated progeny and sustain the hematopoietic homeostasis [4, 9].

The maintenance of HSC pool and the derivatives is modulated by a complex network of stromal cells, endothelial cells, extracellular matrix, cell cycle proteins, nutrients, transcriptional factors, and microenvironment in an orchestrated fashion [10 - 12]. Nowadays, aging has been considered to show a broad impact upon the biofunction of hematopoietic system, and in particular, the heterogeneous HSC population [13]. Interestingly, mounting evidences have indicated the diversity and multi-layered hierarchy of the hematopoietic system, which will supply new insights into hematogenesis and facilitate *ex vivo* preparation of engraftable and functional multi-lineage blood cells [14].

Despite the widely application for HSCT and gene therapy, the amount of HSCs for large-scale treatments is still unavailable due to the deficiency in *ex vivo* preparation. For the purpose, numerous talents are devoted themselves to improving the yield and maturation of HSCs by utilizing small-molecule compound- or cytokine cocktail-based programming, and the direct-differentiation from human pluripotent stem cells (hPSCs) including human embryonic stem cells (hESCs) and the induced pluripotent stem cells (hiPSCs). Even though, the efficient procedures for expansion, purification and generation of HSCs are still urgently needed to be resolved in future [2].

THE ORIGINS AND DEVELOPMENT OF HSCS

State-of-the-art renewal in mice has challenged the current paradigm of single long-term HSCs for regenerating all the constituents of the mammalian immune system [15]. Of note, there are more and more studies upon the origins and the development of HSCs *via* dissecting the epigenetic and transcriptional signatures of HSCs and the progeny [4, 16]. To date, over 80 common gene expression modules have been involved in the assessment of distinct populations at various sub-stages of HSC differentiation [17]. For example, studies have shown the hierarchy within acute myeloid leukemia (AML), including the $CD34^{+}CD38^{-}$ fraction in leukemic stem cells (LSCs), $CD34^{+}CD38^{+}$ leukemia progenitor cells, and $CD34^{-}$ leukemic blasts [18 - 20]. At the meantime, the specific and differentiated hematopoietic microenvironment further complicates our understanding of the resident HSCs [21]. Very recently, Bigas and the colleagues highlighted the latest updates and the feasibility of using PSCs for further dissecting the normal and abnormal hematopoietic development, which were supposed to recapitulate the leukemic transformation processes *in vitro* and served as a promising model for the hematopoietic and leukemia development [22]. Even

though, further insights into the heterogeneity of HSCs are still of great importance, and the development of novel surface biomarkers, the establishment of functional assays, and the involvement of single-cell RNA-SEQ transcriptomics will be of great help for providing a comprehensive understanding. For example, long-term HSCs (LT-HSCs) and short-term HSCs (ST-HSCs) reveal variations in gene expression categories such as chromatin remodeling, cell cycle, and immune response [23].

Meanwhile, there are already theory and signs that not all the long-lived hematopoietic cells are derived from HSCs. This phenomenon indicates the existence of the classical HSC-dependent hematopoietic cells and HSC-independent tissue-resident blood cell lineages [14]. Additionally, HSCs reveal differ in multifaceted physical characteristics including the cell surface marker phenotype, cell cycle status, and lineage differentiation outputs after *in vivo* transplantation as well, which are also pivotal to HSC heterogeneity and affect leukemogenesis or treatment options [24]. However, the detailed information of how these cell populations arise from embryonic development and the subsequent HSCs is still largely unknowable. Notably, pioneering investigators in the field have taken an advantage of the classical genetic and embryological experiments, single-cell sequencing and imaging, cell fluorescence tracer technology, cell fate tracing data, transcriptome and whole-genome analyses to dissect the origins of HSCs and the progency, which has provided information on the cell/molecular trajectories of the integrated hematopoietic system [14, 25 - 28]. For instance, Bian *et al*. and Liu *et al*. deciphered the spatiotemporal transformation and hierarchical development of the human macrophage development and fetal innate lymphoid cells from hematopoietic stem/progenitor cells (HSPCs) with the aid of single-cell functional and transcriptomic analyses, respectively [29, 30].

THE PRECLINICAL AND CLINICAL APPLICATIONS OF HSCS

Due to the unique properties of HSCs, HSCT has obtained broad consensus as an advanced remedy for a variety of both non-malignant and malignant disorders as well as severe autoimmune diseases and neurological disorders in children and adults, such as acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), multiple myeloma (MM), myelodysplastic syndrome (MDS), multiple sclerosis (MS), severe aplastic anemia (SAA), chronic inflammatory demyelinating polyneuropathy (CIDP), chronic myeloproliferative disorders (CMD), juvenile myelomonocytic leukemia (JMML), myelodysplastic /myeloproliferative neoplasms (MDS /MPNs), acute biphenotypic leukemia (AB L), acute undifferentiated leukemia (AUL), non-Hodgkin's lymphoma (NHL), essential thrombocythemia (ET), and coincidental diseases [31 - 36]. Historically, HSCT started from four decades ago and appeared as an experimental medicine,

which has become a powerful and indispensable tool for intractable hematologic disorder treatment [37]. Up to January of 2023, there are a total of over 570 clinical trials of HSCT for various hematopoietic malignancies administration according to the clinicaltrials.gov website (https://www.clinicaltrials.gov/) (Table **1**).

Table 1. Clinical trials of HSC-based cytotherapy.

NCT No.	Status	Phases	Enrollment	Diseases
NCT05011422	Recruiting	Phase 1	32	Pediatric Hematologic Malignancies
NCT01341301	Completed	Phase 2	25	Hematologic Malignancy
NCT01374841	Recruiting	Phase 2	20	Hematologic Neoplasms
NCT02139280	Completed	Phase 2	58	Hematologic Malignancies
NCT00824135	Completed	Phase 1	34	Hematologic Malignancies
NCT03082677	Completed	Phase 2	20	Myeloid Hematologic Malignancy, Lymphoid Hematologic Malignancy
NCT05510089	Recruiting	Phase 4	62	Hematological Malignancy
NCT01788605	Unknown	Phase 2	65	Hematologic Malignancies
NCT02386332	Unknown	-	206	Hematologic Malignancies
NCT00770523	Completed	-	52	Hematologic Malignancies
NCT02990130	Active	-	60	Hematologic Malignancy
NCT05250362	Recruiting	Phase 1,2	56	Hematologic Malignancy
NCT04682314	No recruiting	-	60	Hematologic Malignancy
NCT01139164	Terminated	Phase 2	78	Hematological Malignancies
NCT01982682	Completed	Phase 2	41	Hematopoietic/Lymphoid Cancer
NCT03986086	Withdrawn	Phase 1,2	0	Hematologic Malignancy
NCT00429143	Completed	Phase 1,2	27	Hematologic Malignancies
NCT01237639	Completed	Phase 3	300	Hematologic Malignancies
NCT03575767	Completed	-	30	Hematologic Neoplasms
NCT00429416	Completed	Phase 1,2	14	Hematologic Malignancies
NCT03032783	Recruiting	Phase 2	63	Hematopoietic and Lymphoid Cell Neoplasm
NCT03149055	Completed	Phase 2	99	Hematologic Malignancy, Myeloproliferative Disorder
NCT03349372	Completed	-	227	Hematologic Neoplasms
NCT02696408	Completed	Phase 3	234	Hematologic Malignancy
NCT04684979	Recruiting	Phase 2	90	B-Cell Lymphoid Malignancies, Hematologic Malignancy, NHL
NCT00079391	Completed	Phase 2	50	Hematologic Malignancies

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05084027	Recruiting	Phase 2	50	Hematologic Malignancy
NCT04809181	Recruiting	Phase 2	95	Hematologic Malignancy
NCT01162096	Completed	Phase 1,2	34	Hematological Malignancies
NCT02301065	Completed	-	35	Hematologic Malignancies
NCT03106662	Completed	Phase 3	6	Hematopoietic Stem Cell Transplantation
NCT03531736	Recruiting	Phase 1	15	Myeloid Diseases
NCT02623309	Active	Phase 3	108	Hematologic Neoplasms
NCT00750126	Unknown	Phase 2	30	Solid Tumors, Hematologic Neoplasms
NCT04448184	Recruiting	Phase 3	662	Hematologic Neoplasms
NCT05147311	Active	-	70	Hematologic Malignancy, Hematopoietic/Lymphoid Cancer
NCT00056966	Completed	Phase 1,2	24	Hematologic Malignancy
NCT05654038	Recruiting	Phase 1,2	30	B-Cell Lymphoblastic Leukemia/Lymphoma
NCT05238376	Recruiting	-	70	Hematologic Malignancy
NCT04673175	Recruiting	Phase 1,2	20	Pseudomonas Aeruginosa, Pneumonia, Hematologic Malignancy
NCT01244906	Completed	Phase 2	26	Hematologic Neoplasms
NCT04323605	Unknown	-	50	Hematologic Neoplasms
NCT02194868	Completed	-	57	Hematological Malignancies
NCT02193399	Unknown	-	30	Hematologic Malignancy
NCT05536154	Recruiting	-	68	Lymphoma, MM
NCT00557817	Completed	Phase 2,3	125	Hematological Malignancies
NCT02668315	Completed	Phase 1,2	25	Hematologic Malignancy
NCT01217723	Unknown	Phase 3	198	Hematologic Malignancies
NCT05609227	Active	-	36	Hematologic Malignancy
NCT01621477	Terminated	Phase 2	34	ALL, AML, Chronic Myelocytic Leukemia, JMML, MS, Hodgkin or NHL, Sarcoma, Myeloid
NCT01349101	Completed	Phase 2	80	Hematological Malignancies
NCT00496340	Completed	Phase 2	42	Hematologic Malignancies
NCT00152139	Completed	Phase 3	33	ALLs, AML, CML, JMML, MS, Hemoglobinuria, Paroxysmal, NHL
NCT05570188	Withdrawn	Phase 1,2	0	B-cell Lymphoma, B-cell Leukemia
NCT01086735	Completed	Phase 1,2	11	Hematological Malignancy
NCT02500550	Completed	Phase 2	15	AML, ALL, MS

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02805075	Completed	Phase 1	15	Hematopoietic and Lymphoid Cell Neoplasm, Recurrent Hematologic Malignancy
NCT00984165	Terminated	Phase 2	18	Hodgkin's Lymphoma, NHL, CLLs, MM With Plasmacytoma
NCT05201183	Recruiting	Phase 1,2	53	AML,CML,ALL,MS
NCT04425642	Completed	-	120	Hematologic Malignancy
NCT03733340	Unknown	Phase 2,3	250	Hematological Malignancies
NCT01332006	Unknown	Phase 2	17	Hematologic Neoplasms
NCT00750737	Completed	Phase 3	46	Invasive Fungal Infections, Hematologic Malignancies
NCT01326728	Terminated	-	56	CML, AML, ALL, Hodgkins Lymphoma, Non-Hodgkins Lymphoma
NCT00582894	Completed	-	17	Hematological Neoplasms
NCT01063647	Completed	Phase 1,2	56	Hematological Malignancies
NCT01215981	Terminated	-	68	Hematologic Malignancy
NCT01315132	Completed	Phase 2	47	Hematological Malignancies, Leukemia, Lymphoma, MM, Hodgkin's Disease
NCT03654404	Completed	-	20	Hematologic Malignancy
NCT01794299	Completed	Phase 2	31	AML,ALL,MS
NCT01275534	Completed	-	375	Hematologic Neoplasms
NCT03091933	Unknown	Phase 1,2	20	AML, CLL, NHL, Hodgkin's Lymphoma, MS, MM
NCT02300571	Unknown	-	60	Hematological Malignancies
NCT01596257	Completed	Phase 2	116	Leukemia
NCT02728700	Terminated	Phase 1	1	MS, CML, MS, NHL
NCT04547049	Recruiting	Phase 3	160	Leukemia
NCT05629260	No recruiting		300	Hematological Malignancy
NCT00675831	Completed	Phase 1	24	Hematologic Malignancies
NCT05413356	Recruiting	Phase 2	50	Bronchiolitis Obliterans Syndrome, Hematologic Malignancy
NCT01384513	Completed	Phase 2	40	ALL, AML, CML, ET, JMML
NCT03320915	Unknown	Phase 2	88	Hematologic Neoplasms
NCT01807611	Completed	Phase 2	82	Leukemia, Lymphoma
NCT03712878	Recruiting	Phase 2	34	Hematopoietic and Lymphoid Cell Neoplasm
NCT05009719	Recruiting	Phase 1,2	50	Hematologic Malignancy
NCT00051311	Completed	Phase 2	62	Hematologic Neoplasms

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05216978	Recruiting	-	25	Hematologic Malignancy
NCT00930566	Unknown	Phase 1,2	20	Hematological Malignancies
NCT04024618	Unknown	-	40	Malignant Hematologic Neoplasm
NCT02566395	Completed	Phase 3	10	ALL, AML, MS, CML, NHL, Hodgkin Lymphoma
NCT00143559	Completed	Phase 2	17	ALL, AML, CML, Hodgkin's Lymphoma, NHL
NCT00914849	Completed	Phase 2	68	Hematologic Neoplasms
NCT04710212	Completed	-	168	Hematologic Malignancy, Acute Leukemia, Neutropenia
NCT01491958	Completed	Phase 2	40	AML, ALL, MS
NCT02639559	Active	Phase 2	50	AML, ALL, CML, NHL, Hodgkin Disease, Hodgkin's Disease, MM
NCT01860170	Completed	Phase 1,2	28	Hematological Malignancy
NCT02880293	Active	-	44	Hematologic Malignancy
NCT05290545	Recruiting	Phase 3	314	Hematological Malignancies
NCT04177004	Recruiting	Phase 1	36	Hematopoietic and Lymphoid Cell Neoplasm
NCT00476177	Completed	Phase 1	25	Hematologic Malignancy
NCT01350258	Terminated	Phase 1,2	8	MDS, Hodgkin's Lymphoma, NHL, CML
NCT01997918	Completed	-	60	Relapse of Hematological Malignancies
NCT02508038	Recruiting	Phase 1	22	AML, ALL, Hodgkin Lymphoma, NHL, MS
NCT04464889	Withdrawn	Phase 1	0	AML, ALL, MS, CML, Myelofibrosis, MM
NCT04237623	Recruiting	Phase 2	38	Transplant-Related Hematologic Malignancy
NCT01532635	Terminated	Phase 2	4	ALL, AML, CLL, Lymphoma, Hodgkin's Lymphoma, NHL, Myeloma
NCT00001748	Completed	Phase 1	35	GvHD, Hematologic Neoplasms, Lymphoma, MS, Myeloid Leukemia
NCT04195633	Recruiting	Phase 2	60	ALL, AML, CML, Hodgkin Lymphoma, MS, CLL
NCT02122081	Active	-	33	Adult ALL, Adult AML
NCT00423514	Completed	Phase 1,2	38	GvHD, Leukemia, MS
NCT02566304	Recruiting	Phase 2	35	AML, Aplastic Anemia, CML, MS
NCT00886522	Completed	Phase 2	23	Hematological Malignancies
NCT01760655	Completed	Phase 2	62	AML
NCT00731705	Withdrawn	-	0	Hematologic Malignancies
NCT01871441	Terminated	Phase 2	4	Malignant Neoplasm
NCT04762875	Terminated	Phase 2	7	AML, ALL, MS

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01627275	Completed	Phase 1	28	Hematological Malignancies
NCT05355675	Recruiting	-	300	Chronic GvHD, Complication
NCT02634294	Recruiting	Phase 2,3	50	Hematological Neoplasms
NCT05190653	Recruiting	-	152	Lymphoma, MM
NCT00067730	Completed	Phase 4	7	Sepsis, Hematologic Neoplasms, Infection
NCT00281879	Terminated	Phase 2	200	CMD
NCT05589844	No recruiting	Phase 1	12	Cytomegaloviral Infection
NCT00524784	Unknown	Phase 1,2	12	GvHD, Hematological Malignancies
NCT01719341	Unknown	-	21	Haematological Malignancies, Acquired Aplastic Anaemia
NCT00818961	Terminated	Phase 2	36	MS, MDS/MPNs
NCT03413800	Active	Phase 2	10	Relapsed Hematologic Malignancy, MM
NCT03198234	Recruiting	Phase 1	30	AML-AML, MDS, NHL-NHL, Hodgkin's Lymphoma, ALL
NCT00934557	Unknown	Phase 3	42	Haematological Malignancies
NCT02504047	Completed	-	40	Hematologic Neoplasms
NCT01652014	Withdrawn	Phase 2	0	CML, AML, Adult ALL
NCT00138112	Completed	Phase 3	126	Streptococcal Sepsis, Hematologic Malignancies
NCT00677859	Completed	Phase 1	36	Hematologic Malignancies
NCT04260698	Recruiting	Phase 3	60	Hematological Malignancies
NCT00005785	Completed	Phase 1	30	Hematologic Neoplasm, HIV Infection
NCT00732316	Completed	Phase 2	54	Leukemia, MS
NCT03531281	Withdrawn	Phase 1	0	Hematopoietic and Lymphoid Cell Neoplasm
NCT00049504	Completed	Phase 2	53	Accelerated Phase CML, Adult ALL, Adult AML
NCT02259348	Terminated	Phase 2	12	ALL,AML,MS,CML,MDS,NHL
NCT03146468	Active	Phase 2	14	Haematological Malignancy
NCT05170347	Recruiting	-	500	GvHD, Haematological Malignancy
NCT03023631	Active	Phase 4	48	Hematopoietic and Lymphoid Cell Neoplasm
NCT00245037	Completed	Phase 1,2	147	CMD, MM, MS,
NCT01186809	Completed	Phase 2	74	Hematologic Malignancies
NCT01474681	Completed	Phase 1,2	27	AML, ALL, CML, MS, CLL
NCT00566696	Completed	Phase 2	73	ALL, AML, CML, JMML, NHL, MDS
NCT00504803	Completed	Phase 2	30	Hematological Malignancies

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05672420	No recruiting	Phase 1,2	181	Hematologic Neoplasms, Thrombocytopenia, Infections
NCT00145626	Completed	Phase 2	40	AML, ALL, Myelodysplasia, CML, Histiocytosis
NCT03823651	Active	-	29	Hematologic Malignancy
NCT00006350	Completed	Phase 2	-	Leukemia, Lymphoma, MM and Plasma Cell Neoplasm, MS
NCT00001432	Completed	-	75	CML, Hematologic Neoplasm, Lymphoma
NCT03680092	Active	Phase 2	43	GVHD, Hematologic Neoplasms
NCT03800758	Active	Phase 3	405	Hematologic Malignancy
NCT03992352	Active	-	1229	Hematologic Malignancy
NCT01413568	Completed	Phase 1,2	38	AML, Adult ALL, CML, NHL, CLL,MM, MDS
NCT00004232	Completed	Phase 1	-	CMD, GvHD, MM, MS
NCT00241358	Completed	Phase 1,2	92	MS, MM, Non-Hodgkin, Hodgkin Disease
NCT03272633	Active	Early Phase 1	4	ALL, AML
NCT01572181	Completed	Phase 2	50	Hematologic Malignancy
NCT02129582	Completed	Phase 1	14	AML, ALL, NHL, Hodgkin Lymphoma, MM, MS, CLL, CML, MS
NCT00458250	Completed	Phase 1	10	Leukemia, Myeloid, Acute Leukemia
NCT03922035	Active	Phase 1	36	Hematopoietic and Lymphoid Cell Neoplasm
NCT01613066	Unknown	Phase 1,2	15	Advanced Haematological Malignancies
NCT04428918	Withdrawn	-	0	Hematologic Malignancies
NCT00593554	Terminated	Phase 2	9	AML, ALL, Myelodysplasia, CML
NCT00477542	Completed	Phase 1	18	Hematologic Malignancies
NCT01527838	Completed	Phase 1	10	NHL, Hodgkin's Disease, CLL, AML, ALL
NCT01350245	Completed	Phase 2	28	AML, MS, ALL, CML, CLL, Hodgkin's Disease, Aplastic Anemia
NCT00544466	Active	Phase 1,2	100	MS
NCT01166009	Recruiting	-	99999999	Solid Tumors, Blood Cancers
NCT00673114	Completed	Phase 1,2	3	Hematologic Malignancy, MDS, Aplastic Anemia
NCT02921685	Unknown	Phase 1	18	Hematologic Malignancies
NCT02650791	Completed	Phase 3	100	Hematologic Neoplasms
NCT00987987	Completed	Phase 1,2	21	Hematologic Neoplasms, Relapse
NCT02459743	Unknown	-	1000	Hematological Malignancies

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05103995	Completed	-	510	Hematological Malignancies
NCT02333058	Completed	Phase 2	70	ALL, AML, MDS
NCT03459170	Active	Phase 1	15	Hematologic Malignancy
NCT02487069	Completed	-	876	Acute Leukemia, CML, MS
NCT03377010	Completed	-	103	Hematopoietic Neoplasm
NCT02458235	Completed	Phase 2	17	AML, ALL, JMML, MS
NCT04733729	Recruiting	-	3000	COVID-19 Infection in Hematological Malignancies
NCT05537896	No recruiting	Phase 2	55	Hematological Malignancy, Neutropenia
NCT00062140	Completed	Phase 1	-	MS, MDS/MPNs
NCT00589602	Terminated	Phase 2	13	CMD, MM, MS
NCT04390542	Withdrawn	-	0	Blood Cancer
NCT00547196	Active	-	10	Leukemia, Lymphoma, MS
NCT00506948	Terminated	Phase 2	13	Hematological Malignancies, MS
NCT02806791	Unknown	-	300	Blood Diseases
NCT02988258	Suspended	Phase 1	10	Haematological Malignancies, CMV Infection
NCT01362179	Completed	-	21974	Hematologic Neoplasms
NCT03212560	Completed	-	30	Hematologic Malignancies
NCT02074436	Terminated	Phase 2	29	Hematological Malignancies, Thrombocytopenia
NCT04764513	Recruiting	Phase 1,2	20	AML, ALL, MS, Lymphoma
NCT01212796	Unknown	-	350	Allogeneic Stem Cell Transplantation
NCT03136445	Completed	Phase 3	616	Hematologic Neoplasms, Hemorrhage
NCT05270096	No recruiting		600	Hematologic Malignancy
NCT01069887	Completed	-	3000	Hematological Malignancies
NCT01627314	Terminated	Phase 2	62	Hematologic Malignancies
NCT04760184	Completed	-	20	MM, Hematologic Neoplasms
NCT00697671	Completed	Phase 1	48	ALL,CML,JMML,MS,NHL
NCT00640796	Completed	Phase 1	22	Myeloid and Acute Leukemia
NCT03622788	Recruiting	Phase 1,2	24	ALL, AML, CLL, CML, Hodgkin Lymphoma, MS, NHL
NCT01830010	Completed	Phase 1	23	Hematological Malignancies
NCT00806767	Completed	Phase 2	82	CMD, MM, MS, MN
NCT04935684	No recruiting	Phase 2	150	Acute Leukemia, MS, Hodgkin Lymphoma, Non-Hodgkin, CLL

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT03913026	Recruiting	Phase 2	20	High Risk Hematologic Malignancy
NCT05476770	Recruiting	Phase 1	54	AML,ALL,BPDCN,MDS,B-Cell, Lymphoma, AUL
NCT00001873	Completed	Phase 2	102	CLL, GvHD, Hematologic Neoplasm, MM, MS
NCT00427557	Completed	Phase 2	31	MM, Leukemia, Lymphoma
NCT01254578	Completed	Phase 1	17	Adult AML, Adult AML
NCT00763490	Completed	Phase 2	20	Hematological Malignancies
NCT00053989	Completed	Phase 2	41	CMD, MM, MS, MD, Fanconi Anemia, Aplastic Anemia
NCT02074839	Recruiting	Phase 1	291	AML, MS
NCT03806764	Enrolling by invitation	-	370	Haematological Malignancy
NCT02396134	Active	Phase 2	133	CML, Adult AML, Adult Hodgkin Lymphoma, Adult NHL,CML
NCT00782379	Completed	Phase 2	20	Leukemia, Lymphoma, MS
NCT04822974	No recruiting	-	20	Hematologic Cancer
NCT00003838	Completed	Phase 2	202	Myeloproliferative Disorders, AML, CML, MS, ALL
NCT03483324	Completed	Phase 1	10	AML, ALL, MS
NCT01930981	Completed	-	252	Hematologic Malignancies
NCT02372357	Completed	Phase 4	14	Hematological Malignancy
NCT05298930	No recruiting	-	15	Haematological Malignancy
NCT04331483	Withdrawn	-	0	Haematological Malignancy, Acute Leukemia, MS
NCT04582604	Recruiting	Phase 1,2	60	Peripheral Blood Stem Cell Transplantation
NCT03960619	Completed	-	8	Hematopoietic Neoplasms
NCT01287104	Completed	Phase 1	34	Leukemia, Lymphoma
NCT05377827	No recruiting	Phase 1	48	T-Cell NHL,AML,
NCT03609827	Completed	-	25	Hematologic Malignancies, Fanconi's Anemia, Thalassemia, Sickle Cell Disease
NCT04640987	Recruiting	Phase 1	22	Hematologic Diseases
NCT00001637	Completed	Phase 2	28	CLL, GvHD, Leukemia, MS, Myeloid Leukemia
NCT01220544	Unknown	Phase 1,2	30	AML, Advanced Hematological Malignancies
NCT02860598	Unknown	-	104	Anemia, AML
NCT02305979	Completed	-	61	Leukemia, Lymphoma

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT04720144	Recruiting	-	300	Hematologic Malignancy, Hematologic Diseases
NCT03609840	Active	-	25	Hematologic Malignancies, Immune Deficiency, Sickle Cell Disease
NCT01685411	Terminated	-	5	ALL, AML, MS
NCT02949427	Recruiting	-	60	AML, Hematologic Malignancy
NCT03192397	Recruiting	Phase 1,2	33	AML, CML, CML, GvHD, Hodgkin Lymphoma, MS, NHL, Severe Aplastic Anemia
NCT02167958	Completed	Phase 1	28	Leukemia, MDS, Myelofibrosis, Lymphoma
NCT01588015	Active	Phase 1	36	CML, Adult ALL, AML
NCT01521611	Completed	Phase 1,2	62	Acute Leukaemia, Chronic Leukaemia, Myeloma, Lymphoma
NCT00143845	Completed	Phase 2	54	MM, Lymphocytic Leukemia, Chronic Lymphoma, Low-Grade
NCT04372524	Recruiting	-	350	Chronic GvHD, Hematologic and Lymphocytic Disorder
NCT00611351	Completed	Phase 2	5	GvHD, MM, MS, MD
NCT02709993	Withdrawn	Phase 1,2	0	Cancer, Hematologic Malignancies
NCT03696537	Terminated	Phase 1	6	AML, CML, ALL, MS
NCT02223312	Withdrawn	Phase 1,2	0	Cancer, Hematologic Malignancies
NCT00301860	Terminated	-	8	Leukemia, Lymphoma
NCT00698685	Terminated	Phase 2	14	Lymphoma, Hodgkin's Disease, Hematologic Neoplasms, MM
NCT05352789	Completed	-	79	Haematological Malignancy
NCT00001623	Completed	-	41	GvHD, Hematologic Neoplasm, Leukemia, MM, MS
NCT01076270	Terminated	-	1	Accelerated Phase CML, Adult ALL, AML
NCT01930162	Completed	Phase 2	9	ALL, MS, NHL, MM, CLL
NCT00627666	Completed	Phase 2	52	Leukemia, MS, MN
NCT00054327	Completed	Phase 2	34	MS, MD
NCT03438344	Withdrawn	Phase 2	0	CML, AML, CLL, Hodgkin Lymphoma, MS, MN, NHL
NCT03275636	Recruiting	Phase 2,3	266	AML, ALL, MDS
NCT00110045	Completed	Phase 2	171	Cancer
NCT00005092	Completed	Phase 1	7	Leukemia, Lymphoma, MM and Plasma Cell Neoplasm, MS

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02477878	Active	Phase 1	10	Leukemia, MS, Lymphoma, MM, Hematologic Neoplasms
NCT05390671	Completed	-	260	CART Therapy
NCT04737785	Recruiting	-	130	Infectious Disease of Nervous System, Blood Disease
NCT00598624	Unknown	Phase 2	175	CML, MS, Diffuse Large Cell Lymphoma, Hodgkin Lymphoma, CLL, MM
NCT01789255	Completed	Phase 2	12	CML, Adult AML
NCT02900768	Unknown	-	120	Hematological Malignancy
NCT00004904	Completed	Phase 1	-	CMD, GvHD, MM, MS
NCT04103879	Recruiting	Phase 2	30	Hematological Malignancy
NCT00003107	Completed	Phase 1	-	Breast Cancer, Kidney Cancer, MM, MS, Ovarian Cancer, Testicular Germ Cell Tumor
NCT00725062	Terminated	Phase 1	3	GvHD, Leukemia, Lymphoma, MM and Plasma Cell Neoplasm, MS
NCT00089037	Completed	Phase 1,2	-	CMD, GvHD, MM, MS, MDS/MPNs
NCT00143884	Terminated	Phase 2	30	Leukemia, Lymphoma, NHL, MM, MS
NCT01822509	Completed	Phase 1	71	MPN, ALL, AML, CLL, CML
NCT00800150	Terminated	Phase 1	6	CMD, MM, MS, MN
NCT03434561	Completed	-	360	Hematopoietic Malignancy
NCT01028716	Terminated	Phase 2	46	ABL, Acute Erythroid Leukemia, ALL, AML, MS, AML
NCT02433483	Terminated	Phase 2	4	AML, MDS
NCT01025778	Completed	Phase 2	7	ALL, AML
NCT05493800	Recruiting	Phase 2	75	Oral Mucositis, Lymphoma, MM, Hematologic Cancer
NCT00028730	Completed	Phase 2	25	Leukemia, Lymphoma, MS, MN
NCT02966457	Completed	Phase 4	62	Hematological Infection
NCT00176839	Terminated	Phase 2,3	11	Leukemia, Lymphocytic, Acute AML, MDS
NCT01696461	Completed	Phase 2	128	AML, ALL, MS, CML, NHL, Hodgkin's Disease, CLL
NCT01231412	Completed	Phase 3	174	ALL, AML, Aggressive NHL, CLL
NCT04827446	Recruiting	-	138	Breast Cancer, Prostate Cancer
NCT00144703	Completed	Phase 2	55	Myelogenous Leukemia, ALL, MS, NHL, Hodgkin's Disease
NCT03097796	Suspended	Phase 1	18	Hematologic Diseases
NCT01517347	Terminated	-	90	Leukemia

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT04013685	Recruiting	Phase 1	255	AML, ALL, MS, CML
NCT01044745	Terminated	Phase 2	20	CML, ALL, AML, CML
NCT03395860	Unknown	Phase 2	100	GvHD, Prophylaxis
NCT02333162	Recruiting	Phase 1	30	MS, Adult ALL, Adult AML, Hematologic Malignancy
NCT00813501	Terminated	-	60	CMD, GvHD, Infection, Leukemia, Lymphoma, MM and Plasma
NCT00453206	Completed	-	66	CMD, Leukemia, Lymphoma, MM and Plasma Cell Neoplasm, MS
NCT04904588	Recruiting	Phase 2	200	ALL, AML, Acute Leukemia, MS, CML, CLL, Lymphoma
NCT00089011	Completed	Phase 2	150	CML, Adult ALL, Adult AML, AML
NCT00027820	Completed	Phase 1,2	106	Adult AML, Childhood ALL, AML, MS
NCT00186823	Completed	Phase 3	57	ALL, AML, CML, JMML, NHL, MDS
NCT05170828	No recruiting	Phase 1	30	MS, ALL, AML, ABL, AUL
NCT00536601	Completed	-	174	Adult ALL, Adult AML
NCT02598752	Completed	-	11	AML, MS, Hematological Malignancy, Leukemia, Lymphoma, Myeloma
NCT01093586	Completed	Phase 2	14	AML, Adult ALL
NCT00185679	Terminated	Phase 2	13	AML, CML, MDS, NHL, CLL
NCT00061581	Completed	Phase 2	14	ALL, CML, AML, MS, Myeloproliferative Disorders
NCT05445765	No recruiting	Phase 1	10	AML, High Risk Hematologic Malignancies
NCT00353860	Completed	Phase 2	70	Leukemia
NCT00179764	Completed	-	68	Hematological Malignancies
NCT00005799	Completed	-	55	CML, Adult ALL, Adult AML
NCT03739606	Withdrawn	Phase 2	0	ABL, Acute Leukemia, CML
NCT05316701	Recruiting	Phase 3	174	AML, ALL, MDS
NCT00078858	Completed	Phase 1,2	37	CML, Adult ALL, Adult AML
NCT04264039	Unknown	Early Phase 1	30	B-cell ALL, B-cell Lymphoma
NCT00040846	Completed	Phase 2	60	Adult AML
NCT00118352	Completed	Phase 2	12	AUL, Adult ALL, Adult AML
NCT04310592	Recruiting	Phase 1	94	AML
NCT01669005	Completed	-	84	Neutropenia
NCT00323518	Completed	Phase 2	390	Oral Mucositis, Stomatitis

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT00105001	Completed	Phase 2	210	CLL, CML, AML
NCT01620229	Withdrawn	Phase 1,2	0	Hematopoietic/Lymphoid Cancer
NCT00317785	Completed	Phase 2	50	Leukemia, Lymphoma, MS
NCT03168815	Active	-	98	Hematologic Malignancy, Pulmonary Infiltrates
NCT03246906	Recruiting	Phase 2	160	ALL, AML, CLL, MS
NCT03779854	Recruiting	Phase 2	68	ABL, ALL, AUL
NCT00469729	Completed	Phase 2,3	101	AML, CML, NHL, MS
NCT00881036	Completed	-	33	Hepatitis B
NCT00489203	Completed	Phase 2	140	CML, Adult AML
NCT00619645	Completed	Phase 2	8	Leukemia, Lymphoma, MM and Plasma Cell Neoplasm, MS
NCT05292664	Recruiting	Phase 1	92	MS, ALL
NCT04226989	Recruiting	Early Phase 1	72	ALL, NHL
NCT04689204	Recruiting	Early Phase 1	72	ALL, NHL
NCT04227015	Recruiting	Early Phase 1	72	ALL, NHL
NCT04691284	Recruiting	-	100	Hematologic Neoplasms
NCT00723099	Completed	Phase 2	73	ALL, AML, NHL, CML, CML, NHL, MS, CLL
NCT00186225	Completed	-	250	Blood Cancer
NCT00423826	No longer available		-	MM and Plasma Cell Neoplasm, MS
NCT00296023	Completed	-	25	CMD, Leukemia, Lymphoma, MM and Plasma Cell Neoplasm, MS
NCT00544115	Active	Phase 2	260	CMD, GvHD, MM, MS
NCT00997386	Completed	Phase 2	16	Hematologic Neoplasms, MM
NCT00295997	Unknown	-	35	CMD, Kidney Cancer, MS, MN
NCT01118013	Terminated	Phase 2	6	Lymphoproliferative Disorder, MM and Plasma Cell Neoplasm, MS, MN
NCT00856388	Completed	-	62	Accelerated Phase CML, AML, MS
NCT04217356	Recruiting	-	90	Myelofibrosis
NCT01529827	Completed	Phase 2	94	CML, Adult ALL, Adult AML
NCT01050764	Terminated	Phase 1,2	10	CML, MDS, NHL, CLL, AML, ALL
NCT01251575	Completed	Phase 2	77	Adult ALL, AML, NHL, Hodgkin Lymphoma
NCT01500161	Terminated	Phase 2	1	AML, ALL, CLL, CML, Hodgkins Disease, NHL, Aplastic Anemia, MM, MS

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT00719147	Completed	-	170	Avascular Necrosis, ALL
NCT00718757	Completed	Phase 1	4	NHL, Hodgkin's Disease, ALL
NCT04657965	No recruiting	Early Phase 1	144	Infectious Diseases, Hematological Malignancies
NCT00521859	Completed	Phase 1	5	Hematologic Malignancies
NCT02790515	Recruiting	Phase 2	52	ALL, AML, MS, CML, JMML, MDS, NHL
NCT04829136	Recruiting	-	30	Hematopoietic and Lymphoid Cell Neoplasm
NCT03128359	Active	Phase 2	38	CLL, CML, GvHD, Hodgkin Lymphoma, MS
NCT05443425	Recruiting	Phase 1	18	GvHD
NCT00534430	Active	Phase 2	50	Leukemia, MS
NCT00014235	Completed	-	160	AML, AUL, ALL
NCT04406285	Unknown	-	66	Fatigue, Leukemia, Lymphoma
NCT04098393	Recruiting	Phase 1	45	Hematologic Malignancies
NCT01527045	Completed	Phase 2	47	NHL
NCT00301912	Withdrawn	Phase 2	0	CMD,MM,MS,MD
NCT04290000	Recruiting	-	300	Lymphoma and ALL
NCT05618041	Recruiting	-	50	ALL, Lymphoma, MM
NCT02199041	Terminated	Phase 2	24	Hematological Malignancies
NCT03642626	Recruiting	-	120	ALL, Large B-cell Lymphoma
NCT00448201	Completed	Phase 2	71	CMD, Lymphoma, MM, MS
NCT04914338	Recruiting	-	40	Hematopoietic and Lymphoid Cell Neoplasm
NCT00075478	Completed	Phase 3	87	ALL, AML, NHL, CML
NCT00521430	Completed	-	30	MM,MS
NCT02861417	Active	Phase 2	204	MS, MN, ALL, AML, CML, NHL
NCT02999854	Terminated	Phase 3	63	AML, ALL, MS
NCT01916057	Completed	-	100	Neutropenia
NCT05658640	No recruiting	Phase 1,2	26	ALL
NCT01664910	Active	Phase 1,2	27	Hematopoietic and Lymphoid Cell Neoplasm
NCT05031897	Recruiting	Phase 2	67	ALL, AML, CLL, CML
NCT04282187	Recruiting	Phase 2	25	AML, MS, MN
NCT00968630	Completed	Phase 2	9	Hematopoietic and Lymphoid Cell Neoplasm, HIV Infection
NCT02452099	Completed	-	150	MM, Lymphomas, Leukemias
NCT00618969	Completed	Phase 2	2	Hematologic Neoplasms, MM
NCT01519648	Completed	-	808	Invasive Fungal Infections

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT03187756	Terminated	Phase 2	6	Hematopoietic Malignancies
NCT05589896	No recruiting	Phase 1,2	12	Acute Leukemia, ALL, AML, ABL, AUL
NCT03765177	Recruiting	Phase 1,2	60	ALL, NHL, CLL
NCT01427881	Completed	Phase 2	43	CML, ALL
NCT03802695	Recruiting	Phase 1	113	AML, ALL, MS, Acute Leukemia
NCT03875495	Terminated	Phase 1,2	9	MM
NCT00864227	Completed	Phase 2	54	Lymphoma
NCT03449953	Active	-	415	Hematologic Malignancy
NCT01630564	Terminated	Phase 1	2	Hematopoietic and Lymphoid Cell Neoplasm
NCT00304018	Completed	Phase 1	5	Leukemia, Lymphoma, MM, MS
NCT05236764	No recruiting	-	47	ALL, AML, MS, CML
NCT00112593	Completed	-	5	CML, AUL
NCT03229876	Suspended	-	20	ALL, NHL
NCT04191187	Active	Phase 2	37	AML, ALL, MS, CML
NCT01041508	Completed	Phase 1	36	Leukemia Lymphoblastic, AML
NCT05088356	Recruiting	Phase 1	24	CML, MS, MD
NCT01199562	Completed	-	153	CML, AUL, AML
NCT04191941	Unknown	Early Phase 1	9	B-cell NHL, B-cell ALL, MM
NCT00555048	Terminated	Phase 1,2	1	GvHD, MS, MD
NCT04112810	Recruiting	Phase 2	55	Hematologic Malignancies
NCT03919214	Suspended	-	40	Cancer of Prostate, CLL, Hematopoietic Malignancy
NCT00513474	Completed	Phase 1	46	CMD, GvHD, Leukemia, Lymphoma, MM, MS, MN
NCT00202917	Completed	Phase 1,2	61	Hematologic Malignancies
NCT04184414	Unknown	Early Phase 1	10	B-ALL,Mantle Cell Lymphoma,Follicular Lymphoma
NCT02988466	Recruiting	Phase 2	84	Hematologic Malignancies
NCT03849651	Recruiting	Phase 2	140	ALL, AML, MDS, Hodgkin Lymphoma, NHL, JMML, CML
NCT01713582	Completed	Phase 1	141	AML, Diffuse Large B-cell Lymphoma, ALL, MM
NCT00539656	Terminated	Phase 1,2	3	AML
NCT05288595	No recruiting	Phase 2	50	Hematologic Malignancy
NCT02409134	Completed	-	9	GvHD

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01379209	Completed	Phase 1,2	68	GvHD
NCT00003116	Completed	Phase 2	66	MM, MS, MD
NCT01254318	Completed	-	130	Mycoses, Leukemia
NCT02419755	Terminated	Phase 2	12	AML, ALL
NCT02188290	Completed	-	178	AML, ALL, MS
NCT00185692	Completed	Phase 2	16	GvHD, Malignancy, CLL, NHL, Hodgkin's Disease, MDS
NCT02743351	Completed	Phase 1,2	89	Hematologic Malignancies, AML, ALL, MS, CML, aGvHD
NCT00795132	Completed	Phase 2	47	Acute Leukaemia, Chronic Disease
NCT01119066	Completed	Phase 2	422	ALL, AML, MS, MM
NCT00052520	Completed	Phase 1,2	37	AML, CML, MS, CML, ALL, T-ALL
NCT04632316	Recruiting	Phase 1,2	33	AML
NCT03555955	Completed	Phase 1	21	Hematologic Malignancy, AML, ALL, MS
NCT04622956	Recruiting	Phase 1,2	47	GvHD, Hematopoietic Neoplasm
NCT00891137	Completed	Phase 1	30	Leukemia, Lymphoma, MM, Plasma Cell Neoplasm, MS
NCT03818334	Recruiting	Phase 2,3	50	GvHD, Infection Viral
NCT04796688	Recruiting	Phase 1	27	ALL, Chronic Lymphoblastic Leukemia, B-cell Lymphoma
NCT03125070	Active	Phase 3	548	Hematopoietic and Lymphoid Cell Neoplasm
NCT02593123	Active	Phase 2	31	Hodgkin's Lymphoma, ALL, NHL, CLL, MM, CML, MS, AML
NCT01684150	Completed	Phase 1	51	AML, ALL, MS, Myeloproliferative Disorders
NCT04083170	Recruiting	Phase 2	10	Acute Erythroid Leukemia, ALL, AML, CML, MS, NHL
NCT01854567	Completed	Phase 3	49	AML, ALL, NHL, Hodgkin's Disease
NCT05348889	Recruiting	Phase 1,2	165	NHL, ALL
NCT00328237	Unknown	Phase 2	20	AML, ALL, CML, NHL, MS
NCT03560752	Active	Phase 2	34	CML
NCT00006379	Completed	Phase 2	58	CMD, MM, MS, MD, Small Intestine Cancer
NCT02730299	Active	Phase 3	125	Hematological Malignancies, ALL, AML, CML, MDS
NCT00276159	Terminated	Phase 2	6	ALL, AML, NHL, Hodgkin's Lymphoma, MM, CLL
NCT01246206	Completed	Phase 2	21	Hematological Malignancies
NCT04545333	Recruiting	-	528	ALL, Adult B-Cell, CLL, MM, NHL

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01790295	Terminated	Phase 2	21	Primary Myelofibrosis, Post Polycythemia Vera Myelofibrosis
NCT03885947	Completed	Phase 1	7	Acute Leukemia, ALL, MS, NHL, Hodgkin Lymphoma
NCT03083327	Recruiting	-	408	Hematologic Neoplasms
NCT04282174	Withdrawn	Phase 2	0	ALL, AML, CML, CLL
NCT00027560	Completed	Phase 2	51	Leukemia, Lymphoma, MM and Plasma Cell Neoplasm, MS, MN
NCT00089596	Completed	Phase 1,2	10	ALL, AML, MS, NHL, CML
NCT02464098	Completed	-	200	Diarrhea
NCT00053196	Completed	Phase 2	82	Leukemia, Lymphoma, MM, MS, MPNs
NCT00990587	Completed	Phase 1	20	ALL, CLL, Myelodysplasia, AML, CML, Hodgkin's Disease
NCT02443831	Active	Phase 1	33	ALL, Burkitt Lymphoma
NCT00270881	Completed	Phase 1,2	33	AML, ALL, CML, MS
NCT02528682	Completed	Phase 1,2	10	Hematological Malignancies
NCT00838019	Unknown	Phase 4	10	Hematological Malignancies
NCT03419078	Completed	-	484	GvHD, Hematologic Malignancy
NCT02730312	Completed	Phase 1	120	AML, B-ALL, CML
NCT00674479	Completed	Phase 2	51	AML, ALL, MS, CML
NCT02338479	Active	-	340	ALL/Lymphoma, Myelodysplasia, AML, JMML, CML
NCT00513175	Completed	-	44	AML, ALL, CLL, MM, NHL, MD, CML, Aplastic Anemia
NCT03878199	Recruiting	Phase 1,2	47	ET, AML
NCT01885897	Completed	Phase 1,2	33	AML, ALL, MDS, Lymphoma, Myeloma, CLL, CML
NCT01110473	Completed	Phase 1	52	ALL, AML, B- CLL, CML, Myelodysplasia
NCT01163201	Withdrawn	Phase 1,2	0	Hematologic Malignancy, AML, ALL, CML, NHL
NCT01188798	Completed	Phase 3	6	ALL, AML, CML, Hodgkin's Disease, MS
NCT01321346	Completed	Phase 1	30	Lymphoblastic Leukemia, NHL
NCT05154474	No recruiting		150	Breast, Cancer Colon, Cancer
NCT00807677	Completed	Phase 1	31	AML, ALL, CML, CLL, MM, NHL
NCT03399773	Recruiting	Phase 2	15	ABL, ALL, CML
NCT00109707	Completed	Phase 1,2	507	CML, ALL
NCT01036009	Completed	Phase 2	43	AML, ALL, JMML, MS, CML

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT00002970	Completed	Phase 2	148	ALL, T-ALL
NCT01658319	Completed	Phase 1	20	NHL, CLL
NCT01344876	Completed	Phase 1	20	MM,NHL,AML,ALL,CML
NCT00077181	Completed	Phase 1	48	CML,AML
NCT01839916	Completed	Phase 2	77	CML,AML
NCT01745913	Terminated	Phase 2	2	AML, MS, ALL, Hodgkin's Lymphoma, NHL
NCT04681105	Recruiting	Phase 1	40	CML
NCT01175785	Completed	Phase 2	15	CML, AML, MS
NCT00246662	Completed	Phase 1	75	Acute Leukemia, MS
NCT00343798	Completed	Phase 1	23	CML, AML
NCT00923442	Enrolling by invitation		550	ALL, MDS, NHL, AML, Hodgkins Lymphoma
NCT05212584	Recruiting	Phase 1	24	Hematologic Malignancies-ALL/Lymphoma
NCT00666549	Completed	-	963	Myelofibrosis, ET
NCT03263637	Completed	Phase 1	44	AML, ALL, CLL, MS, CML, NHL, MM
NCT04033302	Recruiting	Phase 1,2	30	T-ALL, AML, NK Cell Lymphoma
NCT00460694	Completed	Phase 1,2	24	AML, ALL, CML, NHL, Hodgkin's Disease, MS, MM
NCT02533947	Unknown	-	80	Exercise Intervention
NCT03833180	Active	Phase 1	330	CLL, Large B-cell Lymphoma, NHL, ALL, AML
NCT03807063	Withdrawn	Phase 1	0	ABL, MN, ABL, ALL, AML, CML, MS
NCT00145613	Completed	Phase 2	25	ALL, AML, MDS, CML, JMML, NHL
NCT01221857	Completed	Phase 1,2	12	ALL, AML, MDS, NHL, Hodgkin's Disease
NCT03983850	Recruiting	Phase 1,2	400	GvHD, Hematologic Neoplasms
NCT00095797	Completed	Phase 1	60	Adult Acute Basophilic Leukemia, CML, AML
NCT00351975	Completed	Phase 1	56	AML, MS
NCT01015742	Unknown	Phase 2,3	10	Acute Leukemia
NCT00849147	Completed	Phase 2	55	B-CLL
NCT00008307	Unknown	Phase 2	52	Lymphoma, MM, MS
NCT00103272	Terminated	Phase 1	74	AML
NCT00963495	Terminated	Phase 1	11	AML, ALL, CLL, Myelodysplasia, Lymphoma, NHL, MM
NCT00176930	Terminated	-	330	AML, MDS, JMML, Hodgkin's Disease, NHL, MM
NCT03272789	Unknown	-	32	Haematologic Disease

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01423058	Completed	Phase 1,2	61	Myelofibrosis, ET Myelofibrosis
NCT00691015	Completed	Phase 2	48	CMD, MM, MS, MN
NCT05400122	Recruiting	Phase 1	12	AML, MS, ALL, CML, CLL, Hodgkin Lymphoma, NHL, MS
NCT01816230	Completed	Phase 1,2	36	Hematological Malignancies, ALL, AML, MDS
NCT01351545	Recruiting	-	99999	Hematologic Malignancies, ALL, Severe Aplastic Anemia
NCT00789776	Completed	Phase 1,2	41	ALL, AML, NHL, MS, CLL, CML, NHL
NCT00975975	Completed	Phase 2	17	AML, ALL, CML, CLL, Myelodysplasia, NHL, MM
NCT04532281	Recruiting	Early Phase 1	120	ALL, NHL of Soft Tissue
NCT04532203	Recruiting	Early Phase 1	72	ALL, NHL
NCT04188912	Recruiting	-	200	Hematopoietic and Lymphoid Cell Neoplasm
NCT01597219	Active	Phase 2	77	Hodgkin's Lymphoma, NHL, AML, ALL, MS, CML, CLL
NCT05322850	Recruiting	Phase 1,2	40	AML, ALL, AUL, CML
NCT00013533	Completed	Early Phase 1	30	Hodgkin Lymphoma, MS, NHL, CML, ALL, AML
NCT00522990	Terminated	Phase 1,2	48	AML, ALL, CML, MS, Myelofibrosis
NCT00361140	Completed	Phase 4	72	MS, MD, Lymphoma
NCT04014764	Completed	-	119	AML, MM, MS, ALL, CML
NCT04888338	Recruiting	-	100	Hematopoietic and Lymphoid Cell Neoplasm
NCT02960646	Active	Phase 1	11	ALL, AML, CML, MS
NCT01564277	Terminated	Phase 2	24	AML
NCT01416025	Completed	Phase 4	29	Fungal Infection
NCT01273766	Completed	Phase 2	16	AUL, Adult AML
NCT00923910	Completed	Phase 1,2	10	AML, ALL, CML, MDS, NHL
NCT01336712	Completed	Phase 2	30	Leukemia, Hodgkin's Disease, NHL, MS
NCT00354172	Terminated	Phase 2	16	Leukemia, MS
NCT03434730	Active	Phase 2	46	AML, ALL, MS, MMD, MD, NHL
NCT02991898	Terminated	Phase 2	3	ALL
NCT02793544	Completed	Phase 2	80	MDS, CLL, ALL, AML, ABL, AUL
NCT04951323	Recruiting	Phase 3	50	Covid19, Hematopoietic Neoplasms
NCT01943682	Completed	Phase 1	27	AML, ALL, Burkitt Lymphoma, Hodgkin Lymphoma

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02581007	Completed	Phase 2	30	CML, AML, MS, ALL, CLL, Hodgkin's Lymphoma, NHL, CMML, MM
NCT01660607	Active	Phase 1,2	68	AML, MDS, NHL, ALL, MS, AML, CML
NCT01663766	Terminated	Phase 1	12	GVHD, AML, ALL, MS, CML, MM, NHL, CLL
NCT01597778	Completed	Phase 3	368	ALL, AML, NHL
NCT00514722	Terminated	-	4	AML, Myelodysplasia, ALL, CML, MM
NCT01690520	Completed	Phase 2	163	ABL, ALL, AML, CML, MS
NCT01965171	Completed	-	24	ALL, AML
NCT00467961	Completed	Phase 2	61	CML, CLL, AML, ALL, MDS
NCT03678883	Recruiting	Phase 2	350	Pancreatic Cancer, NHL
NCT03333486	Active	Phase 2	31	CML
NCT00445744	Completed	-	52	AML
NCT00862719	Completed	Phase 2	29	Non-Hodgkin
NCT01685606	Terminated	Phase 2	6	T-ALL, AML
NCT00397813	Completed	Phase 2	77	CML, CML, MS
NCT03195010	Terminated	Phase 2	4	ABL, ALL, AML, B-Cell NHL, CLL, CML
NCT04603872	Recruiting	Early Phase 1	120	MM, MM, ALL, NHL
NCT00450450	Completed	Phase 3	27	ALL, CML, MS, CMLMS, JMML
NCT00010192	Completed	Phase 1	30	B-ALL
NCT00357708	Completed	Phase 1	50	AML
NCT01233921	Completed	-	6	CML, ALL, AML
NCT00796068	Completed	Phase 2	130	ABL, ALL, AML, CML, MS
NCT04975555	Recruiting	Phase 2	30	CRS, ICANS, NHL, MM, ALL
NCT01517035	Completed	Phase 1,2	43	MDS, CML, ALL, CML
NCT01866839	Completed	Phase 1,2	41	MDS, MD, NHL, ALL, AML
NCT04771572	Recruiting	Phase 1	100	NHL, MM, AML, ALL, MS, CLL
NCT00916045	Terminated	Phase 2	40	NHL, CLL
NCT01720264	Completed	Phase 2	15	AML, ALL
NCT00378534	Completed	Phase 2	116	CML, AML, CLL, ALL, MS
NCT03878524	Recruiting	Phase 1	40	CML, CML
NCT00301951	Completed	Phase 1	7	MM, MS
NCT03812705	Unknown	Phase 2	30	Hematopoietic and Lymphoid Cell Neoplasm
NCT01291784	Terminated	Phase 1	3	Myelofibrosis

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02141828	Completed	Phase 1	18	Leukemia, AML, ALL, Acute Leukemias
NCT00365287	Completed	Phase 1,2	148	Breast Cancer, Kidney Cancer, MM, MS
NCT02210065	Completed	Phase 2	6	Leukemia, Lymphoma
NCT05064787	Recruiting	-	50	Lymphoma, Lymphoma, MM
NCT03301168	Active	Phase 1,2	120	ALL, AML, MS
NCT02065869	Active	Phase 1,2	187	ALL, AML, NHL, MS, Sickle Cell
NCT03733249	Active	Phase 1,2	193	ALL, AML, NHL, MS, Sickle Cell
NCT00513318	Terminated	-	15	AML, ALL, CML, MM, NHL, CLL
NCT00890747	Completed	Phase 1	42	CML, AML
NCT01053494	Completed	-	80	CML, AUL, CML, ALL
NCT00025415	Completed	Phase 1	60	CML, AUL
NCT00588991	Active	Phase 1	12	AML, MS
NCT00357305	Completed	Phase 1	25	CML, AML, MS
NCT03852407	Recruiting	Phase 2	114	AML, MS, CML, MM, CLL, NHL
NCT00964873	Completed	Phase 1	29	AML, ALL, CML, AML, ALL, CML

To date, HSCs of different origins have been involved in conducting autologous and allogeneic HSCT, including mononuclear cells (MNCs) derived from bone marrow, peripheral blood, umbilical cord blood, and placenta blood [38, 39]. Generally, major procedures for bone marrow HSCs-based HSCT are bone marrow collection, followed by mobilization into peripheral blood, and apheresis [40]. Currently, the aforementioned bone marrow-based stem cells as cell sources for HSCT have been largely replaced by those derived from peripheral blood in autologous transplantation due to the better platelet and neutrophil recovery as well as faster immune reconstitution [41]. Additionally, the quiescence of HSCs is modulated both intrinsically and extrinsically, which has been recognized for refraining HSCs from exhaustion and preventing the accumulation of those mutations with malignant potential [4].

It is noteworthy that the adverse reaction of HSCT should also be seriously dealt with, including the well-known graft-versus-host disease (GvHD), neurologic complications, myelosuppression, infections and relapses caused by persistent T-cell immunodeficiency [42 - 45]. Meanwhile, the engraftment syndrome and hereditary bone marrow failure syndromes (IBMFS) after HSCT have also caused a significant morbidity but the underlying pathogenesis is still poorly understood [46, 47]. Taken together, HSCT has provoked the evolution of treatment algorithms for both adults and children.

CONCLUSION

Autogenous and allogeneic HSCs have served as common origins for both blood cells of lymphatic and myeloid lineage generation as well as immune cells, which have also been regarded as excellent models for hematogenesis and the mimic of complex differentiation landscape. Meanwhile the accumulation of recurrent mutations in haematopoietic cells usually initiates dysregulated HSC behavior and the resultant hematologic malignancies. Collectively, systematic and detailed dissection of the biofunction and the underlying molecular mechanisms of the stepwise manner for HSC-based hematogenesis and regenerative purposes are still urgently needed in the follow-up exploration.

LIST OF ABBREVIATIONS

HSCs	Hematopoietic stem cells
HSCT	Hematopoietic stem cell transplantation
AML	Acute myeloid leukemia
ALL	Acute lymphocytic leukemia
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
hPSCs	Human pluripotent stem cells
hESCs	Human embryonic stem cells
hiPSCs	Human induced pluripotent stem cells
LSCs	Leukemic stem cells
LT-HSCs	Long-term HSCs
ST-HSCs	Short-term HSCs
HSPCs	Hematopoietic stem/progenitor cells
MM	Multiple myeloma
MDS	Myelodysplastic syndrome
MS	Multiple sclerosis
SAA	Severe aplastic anemia
CIDP	Chronic inflammatory demyelinating polyneuropathy
CMD	Chronic myeloproliferative disorders
JMML	Juvenile myelomonocytic leukemia
MDS/MPNs	Myelodysplastic/myeloproliferative neoplasms
ABL	Acute biphenotypic leukemia
AUL	Acute undifferentiated leukemia
NHL	Non-Hodgkin's lymphoma

ET	Essential thrombocythemia
MNCs	Mononuclear cells
GvHD	Graft-versus-host disease
IBMFS	Hereditary bone marrow failure syndromes

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CHAPTER 4

Neural Stem Cells in Tissue Engineering

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Abstract: Neural stem cells (NSCs) are unique subsets of stem cells with self-renewal and multiple lineage differentiation potential, which are considered promising cell sources for neuron generation and complex cognitive and sensory functions, and the resultant NSC-based cryotherapy for regenerative purposes. Of them, distinguished from the small amount of activated subset, most of the NSCs are maintained in the quiescent state and reveal a low level of metabolic activity but a high sensitivity to the environment. The dynamic balance between quiescence and the activity of NSCs determines both the efficiency of neurogenesis and the long-term maintenance and self-renewal of the NSC pool as well as the neurogenic capacity of the brain. In this chapter, we mainly review the classification and biofunction of NSCs, and introduce the significant progress in the understanding of NSC-based applications and the underlying molecular mechanism for NSC quiescence, the dysfunction in neurogenesis, and the pathogenesis of neurological disorders. Collectively, these data will facilitate

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the development of NSC-based cytotherapy for a broad spectrum of refractory and recurrent diseases in the future.

Keywords: Alzheimer's disease, Amyotrophic lateral sclerosis, Biological features, Cerebral palsy, Classification, Definition, Fetal alcohol spectrum disorders, Human pluripotent stem cells, Microenvironment, Multiple lineage differentiation, Multiple sclerosis, Neural stem cells, Neurodegenerative diseases, Parkinson's disease, Peripheral arterial disease, Psychiatric illnesses, Safety and efficacy, Self-renewal, Stroke, Spinal cord injury.

INTRODUCTION

Neural stem cells (NSCs) have been recognized as tumor-tropic cells with self-renewal and multi-lineage differentiation properties towards all types of nerve cells and the concomitant complex nervous system [1, 2]. Two decades ago, NSCs were first identified in the adult brain with the capacity to produce new neurons for the repair of impaired nervous system [3]. Nowadays, it is well-known that the cell sources of NSCs are diverse from embryonic origins to adult origins, including human embryonic stem cells (hESCs), human induced pluripotent stem cells (hiPSCs), direct reprogrammed astrocytes, and neural stem /progenitor cells (NSPCs) derived from fetal brain [4]. Of note, recent works of literature have also indicated the variations in the NSC microenvironment, which is also known as NSC niche heterogeneity for the modulation of NSC differentiation potential towards specific nerve cells [5, 6]. Otherwise, the dysregulation of NSCs by the components in the niche usually leads to neurodegenerative diseases [7].

The stem cell niche, also known as the stem cell environment, is adequate to circumscribe and regulate stem cell fate in the naive state, which thus provides a complex contribution and impact to stem cells in various biological processes [6]. The development of NSCs and the progeny is precisely modulated by the close-knit and synchronized interactions between the enteric NSCs and the niche [8]. To date, NSCs and neuron progenitors have been employed for the treatment of various neurodegenerative diseases [9, 10]. For example, NSC-based transplantation (NSCT) for spinal cord injury (SCI) is recognized as one of the most promising and representative therapeutic remedies in pre-clinical practice [11]. Meanwhile, talented investigators in the field also turned to transcriptional analyses for the dissection of the genetic characteristics and gene expression profiling in NSCs during embryonic and adult neurogenesis [3, 12, 13].

In this chapter, we aim to review the basic knowledge of NSCs or neural stem/progenitor cells (NSPCs) and the concomitant NSCT, including the

conception, biological properties, origins and treatment of neurological diseases, and the underlying molecular mechanism as well. Collectively, the content in this chapter will benefit the development of novel remedies for neurodegenerative diseases and NSC-based regenerative medicine strategies for combating the central nervous system (CNS) injury in future.

THE OVERVIEW OF NEURAL STEM CELLS (NSCS)

Neural stem cells (NSCs) are a category of stem cells for neurogenesis, which are the origins of glia and neurons and possess the capacity for generating all kinds of differentiated neural cells via producing intermediate precursors, NSC secretomes according to neurodevelopment [14 - 16]. However, the failure or disorder in the regulation of NSCs might cause impaired memory and learning, brain malformation, neurodegenerative diseases, and tumor development [4, 17].

Therefore, the precise and dynamic control of NSC proliferation, migration and differentiation is very crucial and essential for the spatio-temporal development and biofunction of human brain [16, 18]. For example Kageyama *et al*. discussed the biofunction of basic helix-loop-helix (bHLH) family members (*e.g.*, Ascl1, Hes1, and Olig2) in the dynamic control of NSC vitality and cell-fate determination including the maintenance and proliferation, and in particular, the Hes5-mediated the switching of NSC competency and the development of the nervous system [19]. Furthermore, Ming *et al*. and Zhu *et al*. highlighted the emerging principles for NSC-based neurobiology, disease remodeling, electrical stimulation, and neural plasticity during adult neurogenesis in the brain [20, 21]. Currently, numerous literatures have indicated the promising perspectives of NSC-based cythotherapy for neurodegenerative disease management both preclinically and clinically such as Huntington's disease (HD), Alzheimer's disease (AD), stroke, glioblastoma multiforme, and amyotrophic lateral sclerosis (ALS) [10, 22 - 24].

THE ORIGINS AND DEVELOPMENT OF NSCS

State-of-the-art updates have elucidated the generation of NSCs with inherent plasticity from the neuroepithelium in the neural tube, which further develops into radial glial cells, and followed by receding at later developmental stages committed to the neural lineages and biofunctional nerve cells [25 - 27]. During the past decades, numerous procedures of neurogenesis have been established and various molecular biomarkers have been identified for the exploration of embryonic or adult NSCs [17]. NSCs are known to persevere in the postnatal brain and result in the generation of neurons and neuroglia [5, 17].

Therewith, NSCs can be enriched from both embryonic and adult brains, and new

strategies have been built for in vitro culture and expansion with the aid of defined medium and cytokine cocktails [17]. Additionally, numerous literatures have also indicated the feasibility of NSC generation from human pluripotent stem cells (hPSCs) including human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs), which also supply novel ex vivo models for mimicking neurogenesis and dissecting the pathogenesis of neurological disorders. For instance, Yan *et al*. and Avalian *et al*. reported the derivation of primitive NSCs, neural progenitors and brain subtype neurons from hPSCs and hiPSCs, respectively [28, 29]. Similarly, Aharonowiz and the colleagues demonstrated the neuroprotective effect of transplanted hESC-derived neural precursors for the administration of multiple sclerosis (MS) in mice with demyelinating manifestations in the central nervous system (CNS) [30]. Collectively, hPSCs including hESCs and hiPSCs have supplied splendid research models for dissecting the pharmacological and pathological studies of neuronal diseases in both preclinical and clinical investigations [31, 32].

State-of-the-art studies have also indicated the involvement of various biomaterials as a splendid substrate for NSC differentiation into neuronal lineage cells by constructing biomimetic and appropriate physiological microenvironment [33, 34]. Of them, conductive biomaterials have been regarded as one of the best choices for neurological diseases and nerve regeneration attribute to the property to mimic the microenvironment and regulate the growth, proliferation, alignment, and neuronal differentiation of NSCs [33]. To date, a variety of conductive biomaterials have been identified for modulating the activity of NSCs and the optimal reconstruction of the central nervous system, including polyaniline, polypyrrole, multi-walled carbon nanotubes, graphene, poly (3,4-ethylene dioxythiophene), graphite oxide, and single-wall carbon nanotubes [33]. Of note, Yousefifard and the colleagues put forward the superiority of the combination of neural stem/progenitor cells (NSPCs) and scaffolds over NSPCs or scaffolds alone upon locomotion recovery after spinal cord injury (SCI) in rodents, which also confirmed the safety and efficacy of the NSC-based remedies in preclinical applications [35, 36].

THE APPLICATION OF NSCS AND THE UNDERLYING MOLECULAR MECHANISM

Neurodegenerative diseases are a class of fatal and disabling neurological disorders with a poor prognosis and currently lack effective treatment strategies [5, 7, 37 - 39]. Distinguished from the traditional remedies, NSCs have offered renewable cell sources with inherent plasticity for neurological disorders and tissue regeneration [26, 31, 40 - 42]. Currently, NSC-based transplantation has provided the foundation for the development and optimization of potentially novel

cytotherapy for a broad spectrum of refractory and recurrent diseases, such as Parkinson's disease (PD), stroke, Alzheimer's disease (AD), psychiatric illnesses, cerebral palsy (CP), peripheral arterial disease (PAD), spinal cord injury (SCI), amyotrophic lateral sclerosis (ALS), fetal alcohol spectrum disorders, multiple sclerosis (MS) and cancers (*e.g.*, neuroglioma) (Table **1**) [4, 43 - 46]. For NSC-based transplantation, pertinent lab-to-clinic investigations of clinical therapeutic applications and translational requirements are of great importance, including the route of delivery, the establishment of optimal dosing, timing regimens, and the underlying molecular mechanism, which are the prerequisites of refining NSC-based remedies for debilitating neural disorders [43, 47]. However, the heterogeneity of neuroma or gliomas has impeded the efficient treatment of patients by traditional remedies, but the systematic and detailed molecular properties and novel NSC models can hopefully give opportunities for both fundamental and clinical research into new therapies [17].

Table 1. Clinical trials of NSC-based cytotherapy for neural disease administration.

NCT No.	Status	Phases	Enrollment	Conditions
NCT03128450	Unknown status	Phase 2,3	12	Parkinson Disease
NCT03684122	Active	Phase 1,2	10	Parkinson Disease
NCT03309514	Withdrawn	Phase 1,2	0	Parkinson's Disease
NCT01329926	Withdrawn		0	Parkinson's Disease
NCT03815071	Unknown status	Early Phase 1	10	Parkinson Disease
NCT02452723	Unknown status	Phase 1	12	Parkinson Disease
NCT01640067	Completed	Phase 1	18	Amyotrophic Lateral Sclerosis
NCT01730716	Unknown status	Phase 2	18	Amyotrophic Lateral Sclerosis
NCT01348451	Unknown status	Phase 1	18	Amyotrophic Lateral Sclerosis
NCT03119636	Unknown status	Phase 1,2	50	Parkinson's Disease
NCT02326662	Unknown status	Phase 1,2	30	Spinal Cord Injury
NCT03005249	Unknown status	Not Applicable	20	Cerebral Palsy
NCT01916369	Completed	Phase 1	5	Peripheral Arterial Disease
NCT03629275	Terminated	Phase 2	15	Ischemic Stroke, Chronic Stroke, Hemiparesis, Arm Paralysis
NCT03457870	Completed	Not Applicable	123	Aging, Cognitive Decline
NCT01772810	Unknown status	Phase 1	8	Spinal Cord Injury
NCT03269071	Completed	Phase 1	4	Progressive Multiple Sclerosis
NCT03282760	Completed	Phase 1	24	Secondary-progressive Multiple Sclerosis
NCT03296618	Unknown status	Phase 1	18	Ischemic Motor Stroke, Chronic

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Conditions
NCT02688049	Unknown status	Phase 1,2	30	Spinal Cord Injury
NCT03072134	Completed	Phase 1	13	Glioma, Anaplastic Astrocytoma, Astrocytoma, Brain Cancer
NCT04631406	Recruiting	Phase 1,2	30	Ischemic Stroke
NCT00581113	Terminated	Phase 3	8	Lung Cancer, Breast Cancer, Prostate Cancer
NCT01172964	Completed	Phase 1	15	Adult Anaplastic Astrocytoma, Glioma, Brain Tumor, Giant Cell Glioblastoma, Glioblastoma, Gliosarcoma
NCT03263390	Terminated		6	Obesity, Morbid
NCT02854579	Unknown status	Not Applicable	120	Hypoxic-Ischemic Encephalopathy
NCT03725865	Unknown status	Early Phase 1	12	Stroke, Ischemic
NCT02943850	Completed	Phase 1	18	Amyotrophic Lateral Sclerosis
NCT05306457	Recruiting	Phase 1	16	Amyotrophic Lateral Sclerosis
NCT03355365	Active	Phase 2	50	Multiple Sclerosis
NCT01933802	Completed	Phase 1	20	Multiple Sclerosis
NCT03822858	Temporarily not available			Multiple Sclerosis
NCT04052737	Active	Phase 2	80	Alzheimer Disease, Dementia
NCT04121468	Recruiting	Phase 1,2	30	Multiple Sclerosis
NCT05135091	Recruiting	Phase 1,2	40	Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis
NCT00073801	Completed		78	Endometriosis, Chronic Pelvic Pain

Modulation of NSCs in adult life and during the central nervous system development is connected with rigorous control [17, 48]. Signaling pathways that are involved in NSCs are important for cell self-renewal, direct-differentiation, apoptosis and survival, migration, and neurotrophic support [17, 49 - 51]. It is well-known that Notch-Hes signaling serves as the key regulator of NSC properties during the development of postnatal brain, and in particular, Hes1 functions as a major effector and strongly inhibits the process of neuronal differentiation and maintains the number of NSCs [52]. For example, Ohtsuka and the colleagues verified the biofunction of Hes1 overexpression in modulating the expansion of NSC pool during embryonic and postnatal brains as well as the generation of later-born neurons [52]. Very recently, Alkailani *et al*. put forward the latest renewal of Wnt signaling in cell migration, proliferation, differentiation, cell cycle and death of NSCs between brain tumorigenesis and neurogenesis [53].

Maucksch *et al*. and Patel *et al*. highlighted the somatic cell reprogramming effect of SOX2 or Oct4 alone or in combination with other transcription factors as a valuable and powerful tool for induced neural stem/precursor cell induction, which indicated the potential applications in the development of cell-based drug screening platforms, in vitro disease models, and the novel NSC-based cytotherapy and cell products, respectively [15, 47, 54, 55]. Instead, Aharonowiz *et al*. verified the therapeutic effect of multipotent neural precursors (NPs) upon multiple sclerosis by attenuating the inflammatory process, reducing axonal damage and demyelination, and inhibiting the proliferation and activation of T lymphocytes [30].

Interestingly, as reviewed by Khacho *et al*., more and more studies supplied new evidence suggesting mitochondria as central regulators of NSCs' fate, and in particular, accumulated damages and inherited mutations of mitochondria showed strong impacts upon both adult neurogenesis and neurodevelopment, and usually resulted in neurodegenerative diseases and neurodevelopmental disorders [56, 57]. These studies thus highlighted mitochondria as potent targets for NSC-based cytotherapy and interventions for neural defects and impaired neurogenesis [56, 58, 59]. At the molecular level, mutations in NSCs and the progency can effectively affect cell adhesion, migration and polarity, and thus collectively favor the progression of neurogenic diseases and enhance the invasive potential [53, 60]. Collectively, abnormalities in the underlying molecular mechanisms are adequate to impact the neurogenesis and trigger aneuploidy or genome instability, which collectively result in neoplastic transformation and the concomitant neuroma and glioma [61, 62].

Overall, NSCs-based regimens have provided the basis for novel cytotherapy for a variety of diseases such as stroke and psychiatric illnesses (*e.g.*, cancer, fetal alcohol spectrum disorders) [43, 63, 64]. Despite the rapid progress in NSCs-based cytotherapy, the detailed information for evaluating its efficacy is still largely obscure, including the route of delivery, the optimal dosing, timing regimens, and the underlying molecular mechanism as well [7, 43].

For instance, Radoszkiewicz *et al*. highlighted the variation in NSC biology (*e.g.*, neural differentiation stage, neurosphere formation potential) for cytotherapy between intra- and inter-species variability [65]. Instead, Ding and the colleagues figured out the importance of waking up quiescent NSCs and the concomitant mechanisms (*e.g.*, PI3K/TOR-Akt, Hippo, PDGF) and implications with the microenvironment (*e.g.*, endothelial cells, basal lamina, neuron, astrocytes, secreted factors) in the management of diverse neurodevelopmental disorders, which thereby discussed the NSCs transit and crosstalk between activation and quiescence [66 - 68]. Notably, Rosenblum *et al*. reported the intra-arterial NSC

therapy for the improvement of the outcomes after stroke, which could be further enhanced by pretreatment with 100 ng/ml brain-derived neurotrophic factor (BDNF) for 1 hour prior to NSC transplantation [69]. Furthermore, they found BDNF pretreatment could result in a faster migration of NSCs to stromal cell-derived factor-1 (SDF-1), higher secretion of macrophage colony stimulating factor (M-CSF), vascular endothelial growth factor (VEGF), and increased expression of chemokine C-X-C motif receptor 4 (CXCR4), vascular cell adhesion molecule 1 (VCAM-1), Thrombospondins 1 and 2 (TPO1, TPO2) and BDNF [69]. Collectively, before large-scale applications, numerous critical lab-to-clinic investigations are necessary to refine the NSCs-based cytotherapies for overcoming or debilitating human disorders [4, 17, 43].

CONCLUSION

NSCs are the fundamental basis for transplanting exogenous NSCs and boosting self-rehabilitation of the endogenous NSCs, and thus with promising prospect in regenerative medicine for conquering nervous system diseases. In this chapter, we review the gratifying progress in the rudimentary knowledge of NSC-based cytotherapy for neurogenesis and tumorigenesis, together with the abnormality in neurodegenerative diseases and neurodevelopmental disorders as well. Taken together, these data will benefit the further exploration and development in therapeutic opportunities of NSC-based remedies.

LIST OF ABBREVIATIONS

NSCs	Neural stem cells
bHLH	Basic helix-loop-helix
hPSCs	Human pluripotent stem cells
hESCs	Human embryonic stem cells
hiPSCs	Human induced pluripotent stem cells
CNS	Central nervous system
PD	Parkinson's disease
AD	Alzheimer's disease
NPs	Neural precursors
CP	Cerebral palsy
PAD	Peripheral arterial disease
SCI	Spinal cord injury
ALS	Amyotrophic lateral sclerosis
HD	Huntington's disease
MS	Multiple sclerosis

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CHAPTER 5

Biomaterials and Mesenchymal Stem Cells

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Abstract: Mesenchymal stem/stromal cells are splendid cell sources for tissue engineering and regenerative medicine attributed to the unique hematopoietic-support and immunomodulatory properties as well as the multi-dimensional differentiation potential towards adipocytes, osteoblasts, and chondrocytes *in vitro* and *in vivo*. To date, MSCs have been identified from various approaches, such as perinatal tissues, and adult tissues, and even derived from human pluripotent stem cells (hPSCs). Longitudinal studies have indicated the ameliorative effect and therapeutic efficacy upon a variety of refractory and recurrent disorders such as acute-on-chronic liver failure (ACLF), acute myeloid leukemia (ACLF), premature ovarian failure (POF), and intractable wounds. To date, MSCs have been a to have various origins, including mesoderm, endoderm and ectoderm. In this chapter, we mainly focus on the concepts, and biological and therapeutic properties of MSCs, together with the standardizations for industrial transformation. Overall, the descriptions would help promote a better

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understanding of MSCs in disease pathogenesis and management and benefit the preclinical and clinical applications in the future.

Keywords: Adipocytes, Biological features, Chondrocytes, Classification, Cytotherapy, Definition, Human pluripotent stem cells, Immunomodulation, Industrialization, Molecular mechanism, Multi-dimensional differentiation, Osteoblasts, Preclinical and clinical applications, Refractory and recurrent disorders, Regenerative medicine, Safety and efficacy, Secretion, Standardization, Stem cells, Tissue engineering.

INTRODUCTION

Mesenchymal stem/stromal cells (MSCs) were first identified from clinical samples of patients, which were different from the well-established hematopoietic stem cells (HSCs). In detail, Friedenstein *et al.* reported the first identification of MSCs from bone marrow (BM-MSCs) with long-spindle morphology in 19681. After that, MSCs of different origins have been isolated from various tissues such as adult tissues (*e.g.*, adipocyte tissue, dental pulp, bone marrow, tendon, smooth muscle) and perinatal tissues (*e.g.*, umbilical cord, amniotic membrane, placenta)2, and even derived from PSCs including ESCs and iPSCs3-7. Of them, BM-MSCs and the perinatal tissue-derived MSCs are considered with the most extensive applications in clinical trials and the most robust *in vitr*o proliferation capacity, respectively [8 - 11].

Nowadays, MSCs and their derivatives including exosomes and small extracellular vesicles (MSC-exo, MSC-sEVs) have been extensively explored as the key component in the microenvironment by both preclinical and clinical investigations for the pathogenesis of hematologic malignancies and the development of novel cytotherapy for relapse and recurrent disorders [12]. Interestingly, Zhang et al verified that the outcomes of rats with acute liver failure (ALF) were various due to the alterations of transplanted MSCs, whereas Zhao et al found that UC-MSCs at various passages (passages 3, 6, 15) revealed diversity in the efficacy upon mice with acute graft-*versus*-host disease (aGvHD) [11, 13].

In this chapter, we aim to present the latest updates of MSCs and the concomitant MSC-based tissue engineering, their definition, the historical overview, biological and molecular properties, their origin and development, and the standardizations and industrialization, which will benefit further investigation of MSCs with respect to the pathogenesis and the concomitant regenerative medicine in future.

THE BIOLOGICAL PROPERTIES OF MSCS

Mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells, multipotent stem cells, and medicinal signaling cells, are a heterogeneous population and have been regarded as advantaged cell sources with unique immunomodulatory and hematopoietic-supporting properties, together with tri-lineage differentiation potential towards adipocytes, osteoblasts, and chondrocytes [3, 11, 14].

For a long period, there were many definitions of MSCs due to the lack of unified understanding or consensus on MSCs. In 2005, the first version of the golden criteria for MSC clarification was published by the International Society for Cellular Therapy (ISCT). According to the documents, there are three contents including (1) fibroblast-like and plastic-adherent morphology; (2) the population with a high proportion of mesenchymal-associated surface markers over 95% (CD73, CD90, CD105) but the percentage with minimal hematopoietic- or immune -associated surface markers less than 5% (*e.g.*, CD34, CD45, HLA -DR); (3) The population revealed multi-lineage differentiation capacity towards adipocytes, osteoblasts and chondrocytes under indicated stimulations [15]. However, it is still noteworthy that the detailed information on MSCs contributing to the microenvironment and further classification of the subpopulations with specific properties are still pivotal and lack clarification as well.

To date, a series of functional experiments *in vitro* and *in vivo* have been explored to test the multifaceted biofunctions of MSCs. As mentioned above, besides the classical tests upon the immunophenotype and multi-dimensional differentiation, the relative experiments such as mixed lymphocyte culture (MLC), hematopoietic colony formation unit (CFU), Transwell assay, co-culture of mono-nuclear cells (MNCs) with MSCs, cobblestone area-forming cell (CAFC) test, Matrigel assay for angiogenesis evaluation, and immunohistological examination of subcutaneous tumorigenesis have been carried out [2, 11, 16, 17].

THE ORIGINS AND DEVELOPMENT OF MSCS

MSCs have been identified with heterogeneity, which are partially ascribed to the diverse origins with inherent properties of the origin areas [4, 18, 19]. For instance, the adipose tissue-derived MSCs (AD-MSCs) showed superiority in adipogenic differentiation potential over those derived from other counterparts such as bone marrow, dental pulp, and umbilical cord [20, 21]. Instead, bone marrow-derived MSCs (BM-MSCs) and dental pulp-derived MSCs (DPSCs) displayed preferable osteogenic differentiation potential and teeth repair capacity, respectively [22 - 24]. Of them, umbilical cord-derived MSCs (UC-MSCs), placenta-derived MSCs (P-MSCs), and pluripotent stem cell-derived MSCs (PSC-

MSCs) reveal better long-term proliferation ability over other subtypes [3, 10, 11, 25, 26]. Meanwhile, we and Du *et al.* found that CD106+ UC-MSCs and placenta chorionic villi-derived MSCs (CV-MSCs) rather than the CD106- counterpart displayed moderately enhanced bidirectional immunoregulatory properties and pro-angiogenesis, respectively [16, 17]. Similarly, Studle *et al.* and Battula *et al.* identified the preferable bias towards chondrocytes of the CD56+ subpopulation and pro-angiogenesis capacity of the MSCA-1+CD56+ subset when compared with the corresponding counterparts, respectively [27, 28].

In recent years, we and other investigators have been devoted to exploring the origins and development process of MSCs. To date, MSCs have been considered to mainly generate from mesoendoderm and the resultant mesoderm, together with other origins such as ectoderm, endoderm, neural crest stem cells (NCSCs), and trophoblasts [4, 25, 29 - 31]. For example, Lee *et al.* demonstrated the feasibility of MSCs generation from human embryonic stem cells (hESCs)-derived NCSCs by utilizing a co culture procedure with MS-5 stromal cells [32]. Instead, with the aid of the three-dimensional (3D) embryoid body (EB) model, Wang and his colleagues reported the generation of MSCs from hESCs *via* a TROP2+ trophoblast cell intermediate stage [33]. Recently, we and Kimbrel *et al.* and Maxim *et al.* reported the generation of MSCs from hESCs via a mesoderm stage [34, 35]. Of note, we obtained high-efficiency MSC preparation from hPSCs via the mesoderm or neural crest cell (NCC) intermediate stage based on the cell programming strategy, which were initiated and accelerated by specific transcription factors and chemical cocktails, respectively [3, 4, 25]. Taken together, the systematic and detailed study of the origins and development of MSCs will help understand the biological process, heterogeneity, and the underlying molecular mechanism of MSC-based pathogenesis and cytotherapy in tissue engineering in the future.

THE APPLICATION AND MOLECULAR MECHANISM OF MSCS

Since the first identification in the 1960s, MSCs and the derivatives alone or in combination with biomaterials have exhibited robust prospects in tissue engineering and regenerative medicine. To date, MSCs have been extensively explored for the management of a series of refractory and recurrent diseases via orchestrating the indicated mode of action, including paracrine, autocrine, bidirectional immunomodulation, direct-differentiation, and trans-differentiation, and serving as hematopoietic-supporting microenvironment [36, 37].

To date (up to January 16th, 2023), an amount of 1486 clinical trials have been registered according to the Clinical Trials.gov website (https ://www. clinical trials .gov). According to the distribution diagram, East Asia (438 items), the

United States (292 items), and Europe (254) occupied the top 3 numbers of clinical trials (Fig. **1**). Of them, 464 items were completed and 44 items were terminated, respectively. We also noticed that 1097 studies were found at the Phase 1/2 stage, 90 items, and 9 items were at the Phage 3 stage and Phage 4 stage, respectively.

As shown in Table **1**, numerous diseases have been taken into consideration for MSC-based trials alone or in combination with allogeneic HSCT. According to Table **1**, MSCs have been introduced for the administration of a variety of endocrine disorders and dermatosis, including type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), diabetic nephropathy, osteoporosis, corneal scars, vitiligo, dermatomyositis, diabetic foot ulcer, and even cleft palate.

For urinary system diseases, MSCs have been involved in various processes for disease management such as chronic renal failure, glomerulonephritis, prostate cancer, Peyronie's disease, interstitial cystitis, acute kidney tubular necrosis, end-stage renal disease (ESRD), chronic kidney diseases (CKD), stress urinary incontinence (SUI), faecal incontinence, acute kidney injury (AKI), lupus nephritis, and urinary incontinence.

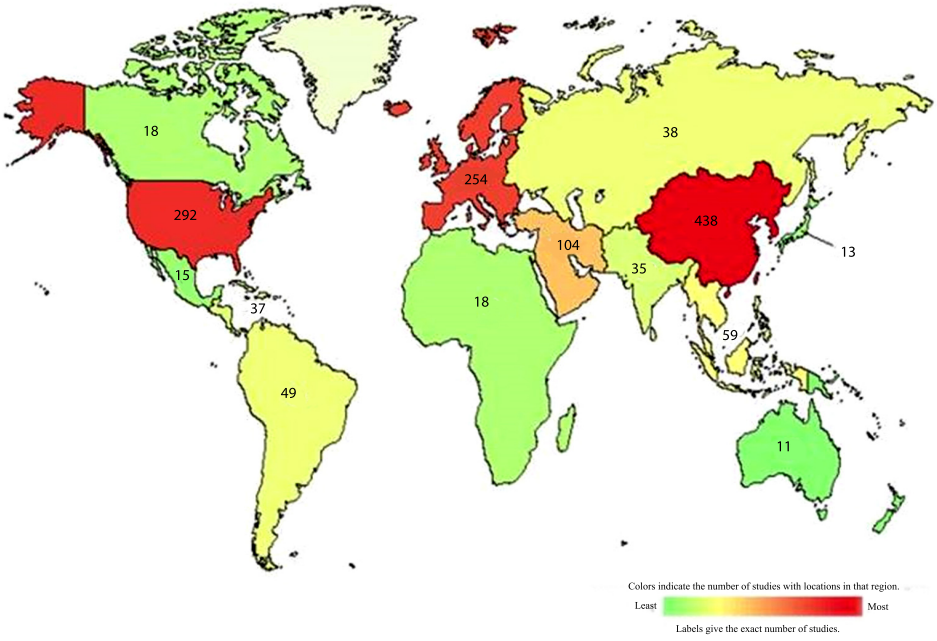

Fig. (1). The distribution diagram of all registered clinical trials worldwide.

Table 1. Clinical trials of MSC-based cytotherapy.

NCT No.	Status	Phases	Enrollment	Diseases
NCT04125329	Recruiting	Early Phase 1	15	Diabetic Nephropathy
NCT03558334	Unknown	Phase 1	12	Bronchopulmonary Dysplasia
NCT04073472	Withdrawn	Phase 1	0	Crohn's Disease, Fistula, Anal Fistula, Pouches
NCT03765957	Unknown	Early Phase 1	12	Psoriasis
NCT04318600	Completed	Phase 1	16	Lupus Nephritis
NCT03601416	Unknown	Phase 2	57	Bronchopulmonary Dysplasia
NCT02824393	Completed	Early Phase 1	10	Urticaria, Autoimmune Diseases, Immune System Diseases, Skin Diseases
NCT03778333	Completed	Phase 1	7	Multiple Sclerosis
NCT03106662	Completed	Phase 3	6	With HSCT
NCT03863002	Unknown	Phase 1,2	45	Acute on Chronic Liver Failure
NCT04078308	Unknown	Phase 1,2	20	Diabetes Mellitus, T1DM Diabetes Mellitus
NCT02804945	Completed	Phase 1	20	Adult Respiratory Distress Syndrome
NCT05468502	Recruiting	Phase 1	18	Idiopathic Pulmonary Fibrosis
NCT02118519	Completed	Phase 2	13	Knee Osteoarthritis
NCT05160831	Not recruiting	Not Applicable	50	Knee Osteoarthritis
NCT02112500	Unknown	Phase 2	10	Adult Respiratory Distress Syndrome
NCT02302599	Completed	Phase 2	103	T2DM
NCT03130374	Completed	Phase 1,2	12	Tracheal Stenosis, Laryngeal Stenosis
NCT01221428	Unknown	Phase 1,2	50	Ulcerative Colitis
NCT03683953	Unknown	Phase 1	200	Safety Issues, Effect of Drugs
NCT04441658	Unknown	Phase 1,2	30	T2DM
NCT04351932	Unknown	Phase 3	54	Osteo Arthritis Knee
NCT04414592	Recruiting	Not Applicable	20	Lumbar Disc Degeneration, Lumbar Disc Herniation
NCT01219465	Unknown	Phase 1,2	50	T1DM
NCT04791878	Recruiting	Phase 1	10	Perianal Fistula Due to Crohn's Disease
NCT02140528	Completed	Phase 2	40	Tibial Fracture

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT04446897	Completed	Phase 1,2	10	Chronic Periodontitis
NCT03068988	Unknown	Phase 1	50	Rotator Cuff Tear
NCT02824653	Completed	Phase 1,2	10	GvHD
NCT03956719	Unknown	Not Applicable	8	Knee Osteoarthritis
NCT01694927	Unknown	Phase 2	30	Spinal Cord Injury
NCT02285673	Unknown	Phase 1,2	10	Duchenne Muscular Dystrophy
NCT01763086	Unknown	Phase 2	60	With HSCT, Poor Graft Function, Hematological Diseases
NCT01219452	Unknown	Phase 1,2	30	Dilated Cardiomyopathy
NCT02945462	Completed	Phase 1	4	Erectile Dysfunction
NCT02166489	Completed	Phase 1	6	Chronic Renal Failure, Polycystic Kidney Disease
NCT02755922	Completed	Phase 3	20	Mandibular Fractures
NCT04446884	Completed	Phase 1,2	10	Stress Urinary Incontinence
NCT04302519	Unknown	Early Phase 1	24	COVID-19
NCT04501354	Unknown	Phase 2	5	Osteoporosis
NCT01956903	Completed	Phase 1,2	15	cGvHD
NCT02482194	Completed	Phase 1	9	Spinal Cord Injury
NCT04519671	Recruiting	Phase 1,2	40	Perianal Crohn Disease, Perianal Fistula, Crohn Disease
NCT01788059	Completed	Phase 2	19	Nonunion Fracture
NCT04194671	Not recruiting	Phase 1,2	80	Acute Kidney Injury
NCT03645525	Recruiting	Phase 1,2	180	Bronchopulmonary Dysplasia
NCT04519697	Recruiting	Phase 1,2	40	Rectovaginal Fistula, Crohn Disease, Crohn Disease of Vulva, Rectolabial; Fistula
NCT03346967	Unknown	Phase 1,2	30	Hormone Deficiency
NCT03668171	Unknown	Not Applicable	200	Acute-On-Chronic Liver Failure
NCT01763099	Unknown	Phase 2	60	With HSCT, Graft Failure, Hematological Diseases
NCT01941394	Unknown	Phase 2	70	Relapse GvHD
NCT03668145	Unknown	Not Applicable	140	Primary Biliary Cirrhosis
NCT01297972	Completed	Phase 1,2	9	Aplastic Anemia
NCT03219801	Unknown	Early Phase 1	10	Systemic Lupus Erythematosus

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01946048	Unknown	Phase 1	10	Ischemic Cardiomyopathy
NCT02172885	Completed	Phase 1	2	Osteogenesis Imperfecta
NCT01224327	Unknown	Phase 1,2	50	Liver Cirrhosis, Radiology
NCT03358654	Unknown	Not Applicable	9	Umbilical Cord Bleeding, Knee Osteoarthritis
NCT01068951	Completed	Not Applicable	20	T1DM
NCT02247973	Unknown	Phase 2	100	Severe Aplastic Anemia
NCT03055078	Unknown	Phase 1	10	Aplastic Anemia
NCT02116634	Withdrawn	Phase 1,2	0	Amyotrophic Lateral Sclerosis
NCT02440074	Withdrawn	Phase 1,2	0	Degenerative Disc Disease
NCT02249676	Completed	Phase 2	15	Devic's Syndrome, Devic's Neuromyelitis Optica, Devic Syndrome, Devic's Disease, Devic Disease
NCT03383081	Recruiting	Phase 2	60	Knee Osteoarthritis
NCT04520022	Completed	Phase 1,2	5	Recessive Dystrophic Epidermolysis Bullosa
NCT02409940	Unknown	Phase 1	17	Renal Transplant Rejection
NCT05672420	Not recruiting	Phase 1,2	181	Hematologic Neoplasms, Neutropenia, Anemia, Thrombocytopenia, Infections, Bleeding
NCT05535803	Enrolling	Phase 2	20	Tracheal Stenosis, Laryngeal Stenosis
NCT04104412	Recruiting	Phase 1	242	Lumbar Discogenic Pain
NCT04939077	Recruiting	Phase 1,2	20	Myocardial Ischemia, Ventricular Dysfunction, Left
NCT05578508	Withdrawn	Phase 1	0	Pouchitis, Crohn's Disease, Ulcerative Colitis Chronic, Inflammatory Bowel Diseases, Pouch, Ileal
NCT04234750	Unknown	Phase 1	20	Donor Sites
NCT02966951	Recruiting	Phase 1	10	Knee Osteoarthrosis
NCT01216865	Unknown	Phase 1,2	50	Diabetic Foot, Critical Limb Ischemia
NCT02963727	Recruiting	Phase 1	10	Knee Osteoarthrosis
NCT02344849	Completed	Phase 1	10	Erectile Dysfunction

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT03357575	Unknown	Not Applicable	14	Knee Osteoarthritis
NCT02460770	Withdrawn	Phase 1	0	Chronic Myocardial Ischemia
NCT03343782	Completed	Phase 1,2	30	T2DM
NCT01429012	Withdrawn	Phase 2	0	Nonunion Fracture
NCT03184935	Suspended	Phase 1,2	40	Myelodysplastic Syndromes
NCT04434794	Completed	Phase 1,2	27	Gingival Recession
NCT02266394	Completed	Phase 1	42	Renal Artery Stenosis, Ischemic Nephropathy, Renovascular Disease, Chronic Kidney Disease
NCT01874015	Unknown	Phase 1	10	Crohn's Disease
NCT04493918	Unknown	Phase 2	20	Spinal Tuberculosis
NCT01377870	Completed	Phase 1,2	22	Multiple Sclerosis
NCT04416139	Unknown	Phase 2	10	Covid 19
NCT05075811	Recruiting	Phase 1,2	20	Pouch, Ileal, Fistula
NCT03362424	Suspended	Phase 2	44	Rotator Cuff Tear, Tendon Injuries
NCT02763423	Unknown	Phase 2	30	Ketoacidosis, Diabetic
NCT01902082	Unknown	Phase 1	20	ARDS
NCT05227846	Recruiting	Phase 1	9	Decompensated Cirrhosis
NCT04235296	Unknown	Phase 1	30	Residual Burn Wound
NCT03180463	Suspended	Phase 1,2	30	Osteonecrosis of Femoral Head
NCT04432467	Completed	Phase 1,2	10	Chronic Endometritis, Uterus; Scar, Uterine Synechiae, Fallopian Tube Obstruction
NCT04184258	Completed	Phase 1,2	7	Systemic Lupus Erythematosus
NCT02414295	Completed	Not Applicable	1	Klinefelter Syndrome, Azoospermia
NCT04457037	Completed	Phase 1,2	18	Trophic Ulcer
NCT03186456	Suspended	Phase 1	40	Cerebral Infarction
NCT01962233	Unknown	Phase 1	10	Hypoxic Ischemic Encephalopathy
NCT01877759	Unknown	Phase 1,2	20	Liver Cirrhosis
NCT04444271	Unknown	Phase 2	20	COVID-19
NCT00504803	Completed	Phase 2	30	Hematological Malignancies
NCT02866721	Completed	Phase 1	14	Cystic Fibrosis
NCT01676441	Terminated	Phase 2,3	20	Spinal Cord Injury

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01775774	Completed	Phase 1	9	Acute Respiratory Distress Syndrome
NCT02181712	Completed	Phase 1	19	Lung Transplant Reject, Bronchiolitis Obliterans
NCT04713878	Completed	Not Applicable	21	Coronavirus Disease 2019 (COVID-19) Pneumonia
NCT03550183	Enrolling	Phase 1	20	Parkinson's Disease
NCT05167721	Recruiting	Phase 2	76	Multiple System Atrophy
NCT04519684	Recruiting	Phase 1,2	40	Ileal Pouch, Crohn Disease
NCT05345418	Recruiting	Phase 1,2	158	Male Sexual Dysfunction
NCT03386708	Completed	Phase 1	10	Uterus; Injury
NCT01765634	Unknown	Phase 2	40	aGvHD
NCT01504464	Completed	Phase 2	40	Osteoarthritis
NCT02387749	Completed	Not Applicable	10	Diabetic Peripheral Neuropathy
NCT02834858	Unknown	Phase 1	240	Peripheral Vascular Disease, Ischemia, Diabetic Foot
NCT01765660	Unknown	Phase 2	60	cGvHD
NCT02749448	Unknown	Phase 1	10	Pulmonary Disease
NCT02213705	Completed	Phase 1,2	20	Systemic Scleroderma
NCT04047810	Active	Phase 1	15	Chronic Obstructive Pulmonary Disease
NCT02484950	Recruiting	Not Applicable	100	Full Thickness Rotator Cuff Tear
NCT04357600	Recruiting	Phase 1,2	12	Liver Cirrhosis
NCT01157403	Unknown	Phase 2,3	80	Evidence of Liver Transplantation
NCT04650568	Enrolling	Not Applicable	100	Anterior Cruciate Ligament Injury, Anterior Cruciate Ligament Rupture
NCT05331872	Recruiting	Phase 1	20	Liver Cirrhosis
NCT04366323	Completed	Phase 1,2	26	Sars-CoV2
NCT04426643	Completed	Phase 1,2	10	Urinary Incontinence
NCT05520125	Not recruiting	Phase 1,2	20	Segmental Fracture - Bone Loss
NCT01649700	Completed	Phase 1,2	1	The Sequelae Caused by Severe Brain Injury
NCT00953485	Unknown	Phase 1,2	20	Sjogren's Syndrome
NCT05520112	Not recruiting	Phase 1,2	20	Recurrent Pregnancy Loss

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02492516	Completed	Phase 1	19	Amyotrophic Lateral Sclerosis
NCT03873506	Unknown	Phase 1	30	Bronchopulmonary Dysplasia
NCT03505034	Unknown	Phase 2	43	Spinal Cord Injuries
NCT03357770	Unknown	Not Applicable	9	Knee Osteoarthritis, Umbilical Cord Bleeding
NCT04382547	Completed	Phase 1,2	32	COVID -19 Pneumonia
NCT01741090	Unknown	Phase 2	12	Alcoholic Liver Cirrhosis
NCT04992832	Recruiting	Phase 1,2	40	Heart Failure, Systolic
NCT01056471	Completed	Phase 1,2	30	Autoimmune Diseases, Immune System Diseases, Demyelinating Diseases, Nervous System Diseases, Demyelinating Autoimmune Diseases, CNS, Autoimmune Diseases of the Nervous System
NCT04661644	Recruiting	Phase 1,2	20	Critical Limb Ischemia
NCT04216849	Unknown	Phase 1,2	54	T2DM With Renal Manifestations
NCT01360164	Unknown	Phase 1,2	20	Hereditary Ataxia
NCT03878628	Active	Early Phase 1	7	Dry Eye, Kerato Conjunctivitis Sicca, Aqueous Tear Deficiency
NCT03529136	Unknown	Phase 2	252	Decompensated Liver Cirrhosis
NCT04456361	Active	Early Phase 1	9	ARDS, Human, Covid-19
NCT04996966	Recruiting	Phase 1	16	Ischemic Heart Disease, Lung Injury, Non-cardiac Surgery
NCT02705742	Unknown	Phase 1,2	5	Liver Cirrhosis
NCT04390152	Unknown	Phase 1,2	40	Acute Respiratory Distress Syndrome
NCT04014166	Recruiting	Not Applicable	15	Thrombocytopenia
NCT04464213	Recruiting	Phase 1	43	Diabetic Foot Ulcer
NCT01730547	Unknown	Phase 1,2	15	Multiple Sclerosis
NCT01854957	Unknown	Phase 1,2	20	Multiple Sclerosis
NCT05039411	Recruiting	Phase 1	7	Perianal Fistula Due to Crohn's Disease, Fistula in Ano
NCT04130100	Unknown	Early Phase 1	60	Knee Osteoarthritis
NCT03826433	Recruiting	Phase 1	20	Hepatitis B
NCT02731586	Unknown	Early Phase 1	10	Edentulous Alveolar Ridge
NCT04326985	Completed	Early Phase 1	20	Knee Osteoarthritis

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT03299413	Unknown	Phase 1,2	20	Inflammatory Bowel Diseases
NCT01157650	Completed	Phase 1,2	15	Crohn Disease
NCT02304562	Unknown	Phase 1	50	Sweat Gland Diseases
NCT03673748	Not recruiting	Phase 2	20	Lupus Nephritis, Lupus Erythematosus
NCT04538885	Unknown	Phase 1	50	MSCs-PFs in Treating Poorly Healed Wounds of Postoperative Incision
NCT03378414	Not recruiting	Phase 2	45	Type 1,2,3,6 Spinocerebellar Ataxia
NCT01932164	Completed	Not Applicable	5	Cleft Lip and Palate
NCT02057211	Terminated	Phase 2	10	T1DM
NCT01895439	Completed	Phase 1,2	13	Multiple Sclerosis
NCT01919827	Completed	Phase 1	17	Idiopathic Pulmonary Fibrosis
NCT02987413	Completed	Phase 1	3	Motor Neuron Disease
NCT01573923	Unknown	Phase 1,2	320	Liver Cirrhosis
NCT03321942	Unknown	Not Applicable	100	Chronic Kidney Diseases, Renal Interstitial Fibrosis
NCT05522569	Temporarily not available	-	Acute Ischemic Stroke , Stroke, Acute Stroke/Brain Attack, Stroke	-
NCT02287831	Unknown	Phase 1,2	30	Diabetes, Peripheral Arterial Disease
NCT03180450	Suspended	Phase 1,2	60	Heart Failure
NCT02497443	Completed	Phase 1,2	60	Epilepsy
NCT02235844	Completed	Phase 1	1	Duchenne's Muscular Dystrophy
NCT00659620	Unknown	Phase 1,2	20	Kidney Transplant, Chronic Allograft Nephropathy
NCT00734396	Completed	Phase 1,2	15	Organ Transplantation
NCT03176498	Suspended	Phase 1,2	40	Cerebral Infarction
NCT03164083	Withdrawn	Phase 2	0	Osteoarthritis
NCT01436058	Completed	Phase 1	6	Osteoarthritis
NCT03979898	Completed	Early Phase 1	1	Cerebral Palsy
NCT05659095	Completed	Not Applicable	50	Hair Transplantation

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05240430	Recruiting	-	1	COVID-19 Acute Respiratory Distress Syndrome
NCT04522869	Unknown	Phase 1,2	34	Primary Biliary Cirrhosis
NCT02530047	Completed	Phase 1	5	Ovarian Cancer
NCT03570333	Active	Not Applicable	10	Gingival Recession, Lack of Keratinized Gingiva
NCT05127122	Not recruiting	Phase 1,2	81	ARDS
NCT03333681	Completed	Phase 1	15	Rheumatoid Arthritis
NCT01824069	Completed	Phase 1,2	10	Nonrevascularizable Critical Ischemia of the Lower Limbs
NCT01446614	Unknown	Phase 1,2	20	Parkinson's Disease
NCT02283879	Unknown	Phase 1	20	Cerebral Hemorrhage
NCT01446640	Unknown	Phase 1,2	20	Spinal Cord Injury
NCT03239535	Unknown	Phase 1,2	40	Critical Limb Ischemia
NCT03929120	Completed	Phase 1	10	Interstitial Lung Disease, Connective Tissue Diseases
NCT01228266	Terminated	Phase 2	9	Multiple Sclerosis
NCT03580291	Unknown	Phase 2	230	Lupus Nephritis
NCT02291926	Completed	Phase 1	20	Cartilage Diseases, Osteoarthritis
NCT02790762	Unknown	Phase 1	10	Pneumoconiosis
NCT01499459	Unknown	Not Applicable	25	Liver Cirrhosis
NCT04594850	Recruiting	Phase 2	54	Erectile Dysfunction
NCT03209986	Unknown	Not Applicable	200	Liver Cirrhosis
NCT01305694	Unknown	Phase 1,2	50	Aplastic Anemia
NCT02239393	Completed	Phase 2	31	Multiple Sclerosis
NCT05122234	Completed	Phase 3	40	COVID-19
NCT01809769	Completed	Phase 1,2	18	Knee Osteoarthritis
NCT01759784	Withdrawn	Phase 1	0	Amyotrophic Lateral Sclerosis
NCT02481440	Completed	Phase 1,2	102	Spinal Cord Injuries
NCT02652351	Unknown	Phase 1	20	Hepatic Cirrhosis
NCT01873625	Completed	Phase 2,3	60	Rheumatoid Arthritis
NCT04565665	Recruiting	Phase 1,2	70	COVID-19-Associated ARDS, Hematopoietic and Lymphoid Cell Neoplasm, Malignant Solid Neoplasm

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01322789	Unknown	Phase 1,2	10	Diabetes Mellitus
NCT04432545	Available	-	-	Systemic Sclerosis Pulmonary, Pulmonary Hypertension, Pulmonary Fibrosis
NCT01895413	Completed	Phase 1,2	10	Osteoarthritis
NCT01378182	Completed	Not Applicable	10	Wilson's Disease
NCT01849887	Withdrawn	Phase 1,2	0	Ischemic Stroke
NCT03562065	Recruiting	Phase 1,2	10	Lupus Erythematosus
NCT02633163	Recruiting	Phase 2	81	Systemic Lupus Erythematosus
NCT04499105	Unknown	Phase 2	10	Degenerative Disc Disease, Low Back Pain
NCT01392105	Completed	Phase 2,3	80	Acute Myocardial Infarction
NCT04055415	Unknown	Phase 1,2	60	Pulmonary Hypertension
NCT04823000	Completed	Phase 1,2	24	Multiple Sclerosis
NCT01649687	Completed	Phase 1,2	7	Cerebellar Ataxia
NCT01856140	Completed	Early Phase 1	12	Lateral Epicondylitis
NCT04062136	Unknown	Phase 1	10	Bronchopulmonary Dysplasia
NCT04821479	Completed	Phase 1,2	20	Amyotrophic Lateral Sclerosis
NCT00659217	Unknown	Phase 1,2	20	Lupus Nephritis
NCT04811651	Recruiting	Phase 2	200	Ischemic Stroke
NCT01985633	Unknown	Phase 1,2	24	Knee Osteoarthritis
NCT05495711	Recruiting	Phase 1	24	Female Infertility
NCT03288571	Unknown	Phase 1,2	20	Diabetic Nephropathies
NCT02472002	Suspended	Phase 1,2	14	Coronary Disease, Heart Transplant
NCT02945449	Completed	Phase 1	9	Erectile Dysfunction Associated With T2DM
NCT01459640	Unknown	Phase 2	50	Osteoarthritis
NCT02668068	Completed	Phase 1	80	Pneumoconiosis
NCT05018871	Suspended	Phase 1	15	Cerebral Palsy
NCT05152160	Recruiting	Phase 1,2	10	GvHD
NCT05018793	Suspended	Phase 1	15	Spinal Cord Injuries
NCT02443961	Active	Phase 1	10	Bronchopulmonary Dysplasia
NCT04651855	Active	Phase 1,2	20	Amyotrophic Lateral Sclerosis
NCT02574585	Unknown	Phase 2	40	Spinal Cord Injury
NCT04520373	Recruiting	Phase 2	40	Spinal Cord Injuries, Paralysis

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02477540	Withdrawn	Phase 1	0	Critical Limb Ischemia
NCT03487731	Withdrawn	Phase 1,2	0	Facetogenic Back Pain, Back Pain
NCT02152657	Completed	Not Applicable	5	Spinal Cord Injury
NCT02857010	Unknown	Phase 1	30	ACLF
NCT00883870	Completed	Phase 1,2	20	Critical Limb Ischemia
NCT03371329	Completed	Phase 1	9	Hemorrhagic Stroke, Intracerebral Hemorrhage
NCT04876326	Recruiting	Not Applicable	15	Multiple System Atrophy, Parkinsonism, Multiple System Atrophy, Parkinson Variant
NCT00813267	Unknown	Early Phase 1	15	Osteochondritis of the Femoral Head
NCT04615455	Active	Phase 2	40	Keratoconjunctivitis Sicca, in Sjogren's Syndrome
NCT00850187	Completed	Phase 1	6	Knee Osteoarthritis
NCT03751735	Completed	Phase 1,2	9	Erectile Dysfunction Associated With T2DM
NCT02574572	Unknown	Phase 1	10	Spinal Cord Injury
NCT02375568	Unknown	-	6	Knee Injuries
NCT02326935	Terminated	Phase 1	2	Multiple Sclerosis
NCT05167552	Not recruiting	Phase 1,2	60	Allergic Rhinitis, Rhinosinusitis Chronic
NCT00962923	Unknown	Phase 1,2	20	Systemic Sclerosis
NCT03745417	Unknown	Phase 1,2	5	Psoriasis, Drug Effect, Drug Toxicity
NCT01257776	Completed	Phase 1,2	33	Critical Limb Ischemia (CLI), Diabetes
NCT01745744	Completed	Phase 2	33	Critical Limb Ischemia
NCT01364246	Unknown	Phase 1,2	20	Progressive Multiple Sclerosis, Neuromyelitis Optica.
NCT02410239	Withdrawn	Phase 1	0	Cerebral Adrenoleukodystrophy
NCT00972660	Unknown	Phase 2	52	GvHD
NCT01456819	Unknown	Phase 2	50	Critical Limb Ischemia
NCT03171194	Completed	Phase 1	6	System Lupus Erythematosus
NCT05008588	Recruiting	Phase 1,2	15	Ischemic Stroke
NCT04388761	Recruiting	Phase 1	15	Ischemia Reperfusion Injury

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05329662	Not recruiting	Phase 2	130	Sexual Dysfunction Female
NCT00646724	Unknown	Phase 1,2	30	T1DM
NCT02677350	Withdrawn	Phase 1	0	Crohn's Disease, Fistulizing Crohn's Disease
NCT05011474	Enrolling	Phase 1,2	4	Chronic Low Back Pain
NCT01609283	Completed	Phase 1	27	Amyotrophic Lateral Sclerosis
NCT03608592	Unknown	Not Applicable	26	Acute Respiratory Distress Syndrome
NCT00294112	Completed	Phase 2	10	Crohn's Disease
NCT01461720	Unknown	Phase 2	50	Middle Cerebral Artery Infarction
NCT01983709	Terminated	Phase 1	7	Prostate Cancer
NCT02883803	Unknown	Not Applicable	66	Septic Shock
NCT05362786	Recruiting	Phase 1	20	Chronic Kidney Diseases
NCT03521323	Unknown	Phase 2	66	Spinal Cord Injuries
NCT03521336	Unknown	Phase 2	84	Spinal Cord Injury
NCT04224207	Completed	Phase 3	32	Retinitis Pigmentosa, Inherited Retinal Dystrophy
NCT02580019	Unknown	Phase 2	2	Stroke
NCT05308836	Recruiting	Phase 1	10	T1DM
NCT02292628	Completed	Phase 1,2	16	Faecal Incontinence
NCT04429763	Unknown	Phase 2	30	COVID-19
NCT05682586	Recruiting	Phase 3	60	COVID-19 Pneumonia
NCT03869229	Unknown	Phase 1,2	100	Knee Osteoarthritis, Hip Osteoarthritis, Glenohumeral Osteoarthritis, Osteoarthritis
NCT02675556	Terminated	Phase 1	1	Treatment Resistant Depression
NCT05284604	Not recruiting	Phase 1,2	36	Frailty
NCT00911365	Completed	Phase 2	27	Multiple System Atrophy
NCT01526850	Unknown	Phase 2,3	100	Chronic GvHD
NCT02403947	Terminated	Phase 1,2	1	Multiple Sclerosis
NCT00875654	Completed	Phase 2	31	Ischemia, Stroke
NCT04421274	Completed	Phase 2,3	43	Myocardial Infarction
NCT01720888	Unknown	Phase 2	80	Ischemic Dilated Cardiomyopathy
NCT01854125	Unknown	Phase 3	30	Immune Function in Blood, Liver Function in Blood, Variation of Ascites

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01440309	Unknown	Phase 1	20	Primary Biliary Cirrhosis
NCT03800810	Unknown	Early Phase 1	9	Knee Osteoarthritis
NCT04315987	Completed	Phase 2	90	COVID-19 Pneumonia
NCT00781872	Completed	Phase 1,2	24	Multiple Sclerosis
NCT04280003	Recruiting	Phase 2	30	Ischemic Stroke, Functional Status
NCT02751125	Completed	Phase 1	13	Bone Atrophy
NCT02218437	Unknown	Phase 4	20	Complications of Organ Transplant
NCT02643823	Unknown	Phase 1	40	Rheumatoid Arthritis
NCT01716481	Unknown	Phase 3	60	Ischemic Stroke
NCT04228666	Withdrawn	Phase 1,2	0	Alzheimer Disease
NCT01610440	Unknown	Phase 1,2	15	Duchenne Muscular Dystrophy
NCT02330978	Completed	Phase 1	2	Retinal Degeneration, Primary Open-angle Glaucoma
NCT02625246	Completed	Phase 1	6	Bronchiectasis
NCT01914887	Unknown	Phase 1,2	8	Ulcerative Colitis
NCT04235868	Unknown	Phase 1	30	MSC-derived Bioactivator for Treating Chronic Wounds
NCT04314661	Recruiting	Phase 1,2	20	Knee Osteoarthritis
NCT04506073	Active	Phase 2	45	Parkinson's Disease
NCT02564328	Unknown	Phase 1	40	Stroke
NCT02277145	Completed	Phase 1	10	Post-radiotherapy Pulmonary Fibrosis
NCT05631717	Recruiting	Phase 3	40	Systemic Lupus Erythematosus, Lupus Nephritis
NCT03259217	Unknown	Phase 1	40	Stem Cell Transplant
NCT01222039	Completed	Phase 1,2	19	Chronic and Expanded GvHD, Immune System Diseases
NCT04093336	Recruiting	Phase 1,2	120	Middle Cerebral Artery Infarction, Anterior Cerebral Artery, Cerebral Infarction, Stroke, Brain Infarction

NCT No.	Status	Phases	Enrollment	Diseases
NCT02068794	Recruiting	Phase 1,2	57	Fallopian Tube Clear Cell Adenocarcinoma, Ovarian Clear Cell Adenocarcinoma, Ovarian Endometrioid Adenocarcinoma, Ovarian Mucinous Adenocarcinoma, Ovarian Transitional Cell Carcinoma, Ovarian Undifferentiated Carcinoma, Primary Peritoneal Serous Adenocarcinoma
NCT04064879	Suspended	Not Applicable	10	Chronic Migraine, Headache
NCT04392206	Recruiting	Phase 1	15	End Stage Renal Disease
NCT02462330	Recruiting	Phase 2	90	Chronic Myocardial Ischemia
NCT01700920	Completed	Phase 2	3	Osteonecrosis of the Femoral Head
NCT04282928	Unknown	Phase 1	40	Severe Pneumonia
NCT05582226	Recruiting	Not Applicable	50	ACL Tear
NCT04898088	Completed	Not Applicable	30	COVID-19 Pneumonia
NCT01302015	Completed	Not Applicable	15	Buerger's Disease
NCT02808208	Enrolling	Phase 1,2	74	End Stage Renal Disease (ESRD), Vascular Access Complication
NCT03477942	Recruiting	Phase 1	16	Musculoskeletal Pain, Knee Osteoarthritis, Cartilage Injury, Cartilage Degeneration
NCT04312113	Recruiting	Phase 1	20	Ulcerative Colitis
NCT01552707	Completed	Phase 1,2	69	Lumbar Spondylolisthesis Involving L4-L5, Degenerative Discopathy Involving L4-L5
NCT01547091	Unknown	Phase 1,2	200	Rheumatoid Arthritis
NCT04326959	Unknown	Phase 1,2	24	Keloid
NCT02192749	Completed	Phase 1,2	20	Autism
NCT05262829	Not recruiting	Not Applicable	40	Crohn Disease
NCT01183728	Completed	Phase 1,2	12	Knee Osteoarthritis, Knee Degenerative Disease, Knee Osteoarthritis
NCT03798353	Completed	Phase 1	12	Myocardial Infarction

NCT No.	Status	Phases	Enrollment	Diseases
NCT00813969	Completed	Phase 1	24	Relapsing-Remitting Multiple Sclerosis, Multiple Sclerosis
NCT01586312	Completed	Phase 1,2	30	Knee Osteoarthritis, Arthritis of Knee, Knee Osteoarthritis
NCT03945487	Recruiting	Phase 2	200	Decompensated Liver Cirrhosis
NCT00836732	Completed	Not Applicable	35	Pened Chest Surgery for Programmes Coronary Bypass
NCT01540292	Terminated	Phase 1,2	13	Crohn's Disease
NCT01759797	Completed	Phase 1	6	Amyotrophic Lateral Sclerosis
NCT00891501	Unknown	Phase 2,3	25	Degenerative Arthritis, Chondral Defects, Osteochondral Defects
NCT01207193	Completed	Phase 1	6	Bone Cyst
NCT03279796	Unknown	Phase 2	200	Rotator Cuff Tear, Lateral Epicondylitis
NCT02941666	Terminated	-	20	Osteonecrosis
NCT02223897	Unknown	Phase 2,3	66	Ischemic-type Biliary Lesions
NCT02034188	Completed	Phase 1,2	20	Multiple Sclerosis
NCT02544802	Completed	Phase 1	4	Osteoarthritis Knee
NCT01758055	Unknown	Phase 1	12	Emphysema
NCT01389661	Completed	Phase 1,2	11	Maxillary Cyst, Bone Loss of Substance
NCT04153630	Unknown	Phase 1,2	9	Epidermolysis Bullosa Dystrophica, Recessive
NCT01985464	Unknown	Phase 1,2	20	Rheumatoid Arthritis
NCT01513694	Completed	Phase 1,2	15	Intervertebral Disc Disease
NCT00603330	Recruiting	Phase 2	100	GvHD, Poor Graft Function, Low Donor T-cell Chimerism
NCT05442437	Recruiting	Early Phase 1	24	HBV
NCT01374854	Unknown	Phase 1,2	44	T1DM
NCT01413035	Unknown	Phase 1,2	30	T2DM
NCT02981576	Completed	Phase 1,2	14	Spinal Cord Injuries
NCT01714167	Unknown	Phase 1	30	Stroke
NCT02881489	Unknown	Phase 1	30	Amyotrophic Lateral Sclerosis
NCT01643681	Withdrawn	Not Applicable	0	Lumbar Intervertebral Disc Degeneration
NCT05413148	Recruiting	Phase 2,3	135	Retinitis Pigmentosa
NCT01210950	Completed	Phase 1	6	Leg Length Inequality

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT03326505	Completed	Phase 1,2	60	Multiple Sclerosis
NCT01771640	Completed	Phase 1	8	Amyotrophic Lateral Sclerosis
NCT01076920	Completed	Phase 1,2	10	Chronic Myocardial Ischemia, Left Ventricular Dysfunction
NCT00476060	Unknown	Phase 2	36	Cirrhosis
NCT00314483	Unknown	Phase 1,2	25	Graft vs Host Disease
NCT04314011	Completed	Phase 1,2	30	Aging Frailty
NCT01207661	Completed	Phase 1	6	Osteoarthritis
NCT04543994	Recruiting	Phase 1,2	24	Ulcerative Colitis
NCT02855112	Unknown	Phase 1,2	10	Infantile Spinal Muscular Atrophy, Type I [Werdnig-Hoffman]
NCT05671796	Not recruiting	Phase 2	40	Spinal Cord Injuries
NCT01142856	Completed	Phase 1	1	Amyotrophic Lateral Sclerosis
NCT01218464	Unknown	Phase 1,2	70	Liver Failure
NCT03308565	Completed	Phase 1	10	Spinal Cord Injuries, Paralysis
NCT02298023	Completed	Phase 2	24	Rotator Cuff Tear
NCT04314687	Recruiting	Phase 1,2	78	Cerebral Palsy
NCT02338271	Unknown	Phase 1	10	Low Back Pain
NCT01739777	Completed	Phase 1,2	30	Dilated Cardiomyopathy
NCT04592640	Active	Not Applicable	7	Chronic Kidney Diseases, Calciphylaxis, Calcific Uremic Arteriolopathy, Treatment
NCT04371601	Unknown	Early Phase 1	60	COVID-19 Pneumonia
NCT01429038	Completed	Phase 1,2	40	Liver Failure, Kidney Failure
NCT04657458	Available	-	-	Covid19, ARDS, Hypoxia, Cytokine Storm
NCT02688049	Unknown	Phase 1,2	30	Spinal Cord Injury
NCT04064957	No longer available	-	Spinal Cord Injuries	-
NCT03816852	Suspended	Phase 2	12	Premature Ovarian Failure
NCT02770430	Unknown	Phase 2	90	Graft vs Host Disease
NCT00420134	Completed	Phase 1,2	30	Liver Failure, Cirrhosis
NCT03181087	Withdrawn	Phase 1	0	Uterine Scar
NCT02035514	Completed	Phase 1,2	9	Relapsing Remitting Multiple Sclerosis (RRMS)
NCT03414697	Unknown	Not Applicable	44	Cerebral Palsy

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02304588	Unknown	Phase 1	20	Diabetic Foot, Lower Limb Ischemia
NCT03361631	Unknown	Phase 1	13	Erectile Dysfunction, Stem Cells, T1DM
NCT04548583	Recruiting	Phase 1,2	24	Crohn Colitis
NCT05319106	Recruiting	Not Applicable	76	Venous Leg Ulcer
NCT04208646	Unknown	Phase 2	108	Knee Osteoarthritis
NCT01958502	Unknown	Phase 2	18	Nonunion of Fracture
NCT05016011	Recruiting	Phase 2	50	Knee Osteoarthritis
NCT02237846	Withdrawn	Phase 1,2	0	Osteoarthritis of the Knee
NCT02985346	Unknown	Early Phase 1	100	Idiopathic Pulmonary Hemosiderosis
NCT03265613	Active	Phase 1,2	7	Psoriasis, Drug Toxicity, Drug Effect
NCT01499056	Completed	Phase 1	6	Hip Osteoarthritis
NCT04602104	Unknown	Phase 1,2	169	Acute Respiratory Distress Syndrome
NCT00587990	Terminated	Phase 1,2	9	Ventricular Dysfunction
NCT04146519	Recruiting	Phase 2,3	50	Transplantation
NCT01668576	Terminated	-	4	Lung Transplantation
NCT05599087	Recruiting	Phase 1	10	Periapical Periodontitis
NCT01549665	Unknown	Phase 1,2	30	GvHD, GVHD, HSCT
NCT00395200	Completed	Phase 1,2	10	Multiple Sclerosis
NCT05187936	Recruiting	-	200	Hemophilia A or B Arthropathy
NCT02833792	Recruiting	Phase 2	40	Alzheimer Dementia
NCT00823316	Completed	Phase 1,2	10	Acute Leukemia
NCT01860417	Completed	Phase 1,2	25	Degenerative Disc Disease, Intervertebral Disc Disease, Low Back Pain
NCT02611167	Completed	Phase 1	20	Parkinson's Disease
NCT03237442	Unknown	Phase 1,2	100	Ocular Corneal Burn
NCT01092026	Unknown	Phase 1,2	20	Allogeneic Stem Cell Transplantation
NCT04692376	Recruiting	Phase 2	152	cGvHD
NCT04654286	Unknown	Not Applicable	24	Brachial Plexus Neuropathies

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT04366271	Withdrawn	Phase 2	0	COVID
NCT02108132	Unknown	Phase 1	20	Hemophilia
NCT03458156	Unknown	Not Applicable	30	Lupus Nephritis
NCT02594839	Completed	Phase 1,2	20	Idiopathic Interstitial Pneumonia, Interstitial Lung Disease, Idiopathic Pulmonary Fibrosis
NCT03692221	Withdrawn	Early Phase 1	0	Disc Degeneration
NCT00250302	Completed	Phase 1,2	24	Tibial Fracture
NCT03955497	Unknown	Phase 1,2	30	Knee Osteoarthritis, Cartilage Degeneration
NCT05499156	Active	Phase 1,2	80	Perianal Fistula in Patients With Crohn's Disease
NCT02307435	Unknown	Early Phase 1	9	Non Union Fracture, Metaphyseal Fibrous Defect
NCT02893306	Unknown	Phase 2	10	T1DM
NCT00447460	Unknown	Phase 1,2	15	Graft-vs-Host Disease (GVHD)
NCT03173638	Active	Phase 2	5	Non Arteritic Ischemic Optic Neuropathy
NCT03265808	Active	Phase 1,2	28	Major Depressive Disorder, Alcohol Use Disorder
NCT02034786	Unknown	Phase 1	25	Lipodystrophies, Aesthetics Procedure
NCT02315027	Active	Phase 1,2	30	MSA
NCT04834609	Completed	Not Applicable	27	Perianal Fistula, Adipose Tissue, Tissue Transplantation
NCT03648463	Withdrawn	Not Applicable	0	Cartilage Degeneration, Rotator Cuff Tear, Knee Osteoarthritis
NCT03137979	Unknown	Phase 1,2	30	Periodontitis
NCT04484402	Completed	Phase 1,2	25	Corneal Ulcer, Corneal Disease, Corneal Dystrophy
NCT05631444	Completed	Phase 1,2	24	Chronic Limb-threatening Ischemia, Diabetes Mellitus
NCT03044119	Unknown	Phase 1	15	Dental Implants
NCT02854579	Unknown	Not Applicable	120	Hypoxic-Ischemic Encephalopathy
NCT01162915	Suspended	Phase 1	10	Spinal Cord Injury
NCT03876197	Enrolling	Phase 1,2	30	Radiation Toxicity, Xerostomia, Dry Mouth, Hyposalivation

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02408432	Completed	Phase 1	7	Cardiomyopathy, Heart Failure
NCT01207869	Unknown	Phase 1	10	Bronchopulmonary Dysplasia, Extremely Premature Infants, Severe BPD
NCT04869761	Recruiting	Phase 1	40	Chronic Kidney Diseases, T1DM, T2DM, Diabetic Nephropathies
NCT04971980	Recruiting	Phase 1,2	9	Rheumatoid Arthritis
NCT03102879	Completed	Not Applicable	36	Periapical Periodontitis
NCT05152290	Recruiting	Phase 1	20	Spinal Cord Injuries
NCT03437759	Active	Early Phase 1	44	Macular Holes
NCT02776943	Unknown	Phase 1,2	20	Cartilage Damage, Degenerative Osteoarthritis
NCT05158127	Suspended	Phase 1	20	Skin Ulcer
NCT05158101	Recruiting	Phase 1	15	Stroke
NCT02685098	Recruiting	Phase 1	16	Peripheral Arterial Disease, Peripheral Vascular Disease, Arterial Occlusive Disease, Arteriosclerosis, Cardiovascular Disease
NCT05147675	Recruiting	Phase 1	20	Osteoarthritis, Spinal Arthritis
NCT05158933	Recruiting	Phase 1	20	Ovarian Failure
NCT05158439	Withdrawn	Phase 1	0	Tourette Syndrome
NCT05003908	Recruiting	Phase 1	20	Diabetes
NCT03484741	Unknown	Phase 1,2	15	T1DM
NCT05152394	Not recruiting	Phase 1	20	Parkinson Disease
NCT05147766	Recruiting	Phase 1	20	Congestive Heart Failure, Angina
NCT00366145	Completed	Phase 3	260	GvHD
NCT05152381	Suspended	Phase 1	20	Osteoporosis
NCT04061746	Recruiting	Phase 1	60	T1DM
NCT05003960	Recruiting	Phase 1	15	Autism
NCT04855955	No longer available	-	Alzheimer Disease	-
NCT03552848	Unknown	Not Applicable	60	Multiple Organ Dysfunction Syndrome
NCT05018819	Recruiting	Phase 1	15	Cerebral Palsy
NCT05018832	Not recruiting	Phase 1	20	Traumatic Brain Injury

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05147701	Recruiting	Phase 1	20	Retinitis Pigmentosa, Glaucoma, Diabetic Retinopathy, Macular Degeneration, Traumatic Optic Neuropathy, Optic Atrophy
NCT05003388	Recruiting	Phase 1	15	Multiple Sclerosis
NCT05078385	Not recruiting	Phase 1	10	Burns
NCT03449082	Active	Phase 2	30	Lateral Epicondylitis
NCT05018858	Recruiting	Phase 1	15	Lupus
NCT05016804	Recruiting	Phase 1	20	Systemic Sclerosis
NCT04642911	Active	-	91	Diabete Type 2
NCT05003947	Recruiting	Phase 1	15	Inflammatory Bowel Diseases
NCT05016817	Recruiting	Phase 1	20	Idiopathic Pulmonary Fibrosis
NCT03795974	Unknown	Phase 2	108	Cerebral Palsy, Spastic
NCT05147688	Recruiting	Phase 1	20	Pulmonary Disease, Asthma, Chronic Obstructive Pulmonary Disease
NCT04219657	Completed	Phase 1	110	Accidental Wound, Heel Injury
NCT02065167	Completed	Phase 2	26	Avascular Necrosis of the Femoral Head
NCT05018767	Recruiting	Phase 1	20	Frailty
NCT05018845	Recruiting	Phase 1	20	Chronic Kidney Diseases
NCT01724398	Unknown	Phase 1,2	120	Liver Failure
NCT05003921	Suspended	Phase 1	20	Amyotrophic Lateral Sclerosis
NCT02065245	Completed	Phase 1,2	65	Frailty
NCT05158114	Recruiting	Phase 1	20	Testicular Injury, Oligospermia
NCT03166865	Unknown	Phase 1,2	60	Osteoarthritis of the Knee
NCT05003934	Recruiting	Phase 1	20	Rheumatoid Arthritis
NCT03609905	Unknown	Phase 1,2	50	Ulcerative Colitis (UC)
NCT02208713	Unknown	Phase 1	21	Dystrophy
NCT05531266	Recruiting	Not Applicable	182	aGVHD
NCT03070275	Completed	Phase 1,2	20	Implant Therapy
NCT03726255	Completed	-	52	Perianal Fistula
NCT03969680	Recruiting	Not Applicable	60	Knee Osteoarthritis
NCT01322906	Unknown	Phase 2	120	Liver Failure
NCT04625738	Completed	Phase 2	30	COVID-19 ARDS

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05093725	Not recruiting	-	10	Umbilical Cord of Normal Labor
NCT04056819	Completed	Phase 1	10	Acute Myocardial Infarction
NCT01323894	Completed	-	3	Primary Disease
NCT02641860	Completed	Phase 1	22	Osteoarthritis
NCT01213953	Unknown	-	20	Lower Back Pain, Disc Degeneration
NCT01725698	Unknown	Phase 1	5	Union
NCT05042206	Recruiting	Phase 1	10	Stage 3B/4 Chronic Kidney Disease
NCT04385056	Unknown	Phase 1	15	Bradykinesia
NCT01751282	Terminated	Phase 1	5	Non Healing Wounds
NCT04313647	Completed	Phase 1	24	Healthy
NCT04346368	Unknown	Phase 1,2	20	Coronavirus Disease 2019 (COVID-19)
NCT04288102	Completed	Phase 2	100	Corona Virus Disease 2019(COVID-19)
NCT03384433	Unknown	Phase 1,2	5	Cerebrovascular Disorders
NCT03392311	Enrolling	Phase 1,2	8	Psoriasis, Drug Effect, Drug Toxicity
NCT00114452	Completed	Phase 1	60	Myocardial Infarction
NCT02570932	Completed	Phase 2	10	Spinal Cord Injury
NCT04104451	Active	Phase 1	16	Diabetic Foot Ulcer
NCT04822922	Not recruiting	Phase 2	16	Acute-On-Chronic Liver Failure
NCT04753476	Recruiting	Phase 2	48	Covid-19, Cytokine Storm
NCT05121870	Recruiting	Phase 2	240	Decompensated Cirrhosis
NCT01759212	Terminated	Phase 2,3	1	Heart Failure, Ischemic Cardiomyopathy
NCT02384499	Completed	Phase 1	21	Fecal Incontinence
NCT05224960	Not recruiting	Phase 2	240	Decompensated Cirrhosis
NCT04315025	Completed	Phase 1,2	18	Retinitis Pigmentosa
NCT04611256	Unknown	Phase 1	20	Covid19
NCT04433104	Recruiting	Phase 1,2	40	COPD
NCT01745783	Completed	Phase 1,2	26	Multiple Sclerosis
NCT01769872	Completed	Phase 1,2	15	Spinal Cord Injury
NCT01385644	Completed	Phase 1	8	Idiopathic Pulmonary Fibrosis
NCT05402748	Recruiting	Phase 1,2	80	Fistula Perianal
NCT01913886	Completed	Phase 1,2	10	Ischemic Cardiomyopathy

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05512988	Recruiting	Phase 1,2	44	Chronic Kidney Diseases
NCT02490020	Unknown	Phase 1	260	Disorder Related to Renal Transplantation
NCT01643655	Completed	Not Applicable	15	Avascular Necrosis of the Femoral Head
NCT05017298	Not recruiting	Phase 2	30	Corona Virus Infection, Covid19
NCT04212728	Recruiting	Not Applicable	60	Knee Osteoarthritis
NCT04551456	Unknown	Phase 2	300	Coronary Artery Disease
NCT02968459	Withdrawn	Phase 2	0	Uterine Scar
NCT05308342	Recruiting	Not Applicable	66	Premature Ovarian Insufficiency
NCT00136903	Completed	Phase 2	32	Graft Vs Host Disease
NCT03169231	Completed	Phase 2	150	Aging Frailty
NCT01591200	Completed	Phase 2	40	Alcoholic Liver Cirrhosis
NCT01605383	Completed	Phase 1,2	23	Avascular Necrosis of Femur Head
NCT02513238	Completed	Phase 2	30	Xerostomia
NCT01342250	Completed	Phase 1,2	20	Liver Cirrhosis
NCT01678534	Completed	Phase 2	19	Ischemic Stroke
NCT00752479	Terminated	Phase 1,2	4	Kidney Transplant
NCT01291329	Completed	Phase 2	160	ST-Elevation Myocardial Infarction
NCT04087889	Not available	-	-	Pancreatic Cancer
NCT05507762	Recruiting	Phase 1,2	20	Cirrhosis Due to Hepatitis B
NCT00955669	Completed	Phase 1	40	Autologous Transplantation, Diabetic Foot
NCT03967275	Completed	-	7	Bone Marrow Donor
NCT02449005	Completed	Phase 1,2	30	Chronic Periodontitis
NCT01484574	Completed	Phase 2	90	Critical Limb Ischemia, Buerger's Disease
NCT04749667	Recruiting	Phase 1,2	18	Multiple Sclerosis, Progressive Multiple Sclerosis
NCT02966717	Unknown	Phase 2	116	Renal Insufficiency, Chronic Nephrotic Syndrome
NCT01954147	Unknown	Phase 1,2	100	T2DM
NCT01728727	Unknown	Phase 1,2	240	Liver Cirrhosis, End Stage Liver Disease
NCT01274975	Completed	Phase 1	8	Spinal Cord Injury

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT03166189	Completed	Phase 2	46	Infertility of Uterine Origin, Asherman Syndrome
NCT01624779	Completed	Phase 1	15	Spinal Cord Injury
NCT01300598	Completed	Phase 1,2	18	Degenerative Arthritis
NCT02812121	Unknown	Phase 2	261	Liver Failure
NCT05501418	Active	Phase 1,2	75	COVID-19 Infection
NCT04889963	Recruiting	Early Phase 1	16	Ligament Rupture, Ligament Derived Conditioned Medium
NCT02336646	Completed	Phase 1	18	Critical Limb Ischemia
NCT03003364	Completed	Phase 1,2	10	Spinal Cord Injury, Chronic
NCT03743155	Unknown	Phase 2	10	Xerostomia Due to Radiotherapy
NCT02286128	Completed	-	75	T2DM
NCT05532943	Not recruiting	Phase 1,2	41	Multiple Sclerosis
NCT01233102	Suspended	Phase 1,2	200	Liver Cirrhosis
NCT01690247	Unknown	Phase 1	50	Evidence of Liver Transplantation
NCT04670302	Unknown	Not Applicable	24	Supraspinatus Tear
NCT02635464	Completed	Phase 1,2	50	Chronic Ischemic Cardiomyopathy
NCT04313322	Unknown	Phase 1	5	COVID-19
NCT02494752	Unknown	Not Applicable	30	Romberg's Disease, Craniofacial Microsomia, Lipodystrophy, Mixed Connective Tissue Disease
NCT01483248	Unknown	Phase 1,2	50	Liver Cirrhosis, Fibrosis, Liver Disease, Digestive System Disease
NCT04610359	Unknown	Phase 1	3	Interstitial Cystitis
NCT01453738	Completed	Phase 2	60	Osteoarthritis of Knee
NCT02957552	Unknown	Phase 1	7	Pediatric Liver Transplantation
NCT02083718	Unknown	Phase 2	120	Poor Graft Function, Hematological Diseases
NCT01606215	Completed	Phase 1,2	21	Multiple Sclerosis
NCT04252118	Unknown	Phase 1	20	COVID-19
NCT01844063	Unknown	Phase 1,2	210	Liver Failure
NCT02395029	Completed	Phase 1	5	Peyronie's Disease
NCT02398370	Completed	Phase 1	8	Erectile Dysfunction
NCT00885729	Unknown	Phase 1	50	Defect of Articular Cartilage
NCT04340609	Completed	Phase 1,2	4	Acute Myocardial Infarction

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02398604	Terminated	Phase 1	5	Hypoplastic Left Heart Syndrome
NCT01531348	Completed	Phase 1	14	Retinitis Pigmentosa
NCT03774537	Unknown	Phase 1,2	20	Bronchopulmonary Dysplasia
NCT01206179	Completed	Phase 1	6	Nonunion Fractures
NCT04174898	Unknown	Phase 1	100	Aging Well, Regenerative Medicine
NCT01443689	Unknown	Phase 1,2	20	Burns
NCT00993941	Unknown	Phase 2	60	Liver Cirrhosis
NCT04366063	Unknown	Phase 2,3	60	Covid-19
NCT04349631	Completed	Phase 2	56	COVID-19
NCT03766217	Completed	Phase 3	62	Cleft Lip and Palate
NCT03355365	Active	Phase 2	50	Multiple Sclerosis
NCT02698813	Unknown	Phase 1	30	Senescence Wrinkles, Acne, Pitting Scar
NCT02439541	Unknown	Phase 1,2	40	Chronic Ischemic Heart Disease, Heart Failure, Angina
NCT05106972	Recruiting	Not Applicable	30	Liver Cirrhosis
NCT02529566	Unknown	-	100	Lumbar Degenerative Disc Disease, Lower Back Pain, Chronic Lower Back Pain
NCT02013700	Terminated	Phase 1	9	Idiopathic Pulmonary Fibrosis (IPF)
NCT02442037	Unknown	Phase 1,2	30	Ulcerative Colitis
NCT03933995	Unknown	-	10	Erectile Dysfunction
NCT05116761	Not recruiting	Phase 1,2	60	Covid19, Postviral Syndrome, Dyspnea
NCT02444858	Unknown	Phase 1,2	40	Paraquat Poisoning, Lung Injury
NCT03291366	Unknown	Phase 1,2	30	Central Nervous System Injury
NCT04785027	Unknown	Phase 1,2	16	Traditional Chinese Medicine, Drug Effect, Drug Safety, Psoriasis
NCT02444455	Unknown	Phase 1,2	20	Acute Lung Injury, Acute Respiratory Distress Syndrome
NCT03866330	Unknown	Phase 1,2	100	Osteoarthritis, Hip Knee Osteoarthritis Osteoarthritis, Glenohumeral Osteoarthritis
NCT03187431	Unknown	Phase 1	12	Stem Cell Transplant Complications

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05261360	Recruiting	Phase 2	30	Meniscus Tear, Meniscus Lesion, Meniscus or Knee Injuries, Knee Pain Swelling, Arthralgia
NCT01144962	Completed	Phase 1,2	21	Crohn's Disease, Fistula
NCT01142050	Unknown	Phase 1	24	T2DM
NCT04336254	Recruiting	Phase 1,2	20	COVID-19
NCT04276987	Completed	Phase 1	24	Coronavirus
NCT03397095	Unknown	Phase 1,2	120	Ischemic Heart Disease
NCT04744051	Active	Phase 1	20	Post-Concussion Syndrome
NCT02368587	Unknown	Phase 2	160	Ischemic Cardiomyopathy
NCT03994666	Unknown	Phase 2	30	Critical Limb Ischemia
NCT03047772	Unknown	Phase 2	124	Myocardial Infarction, Angioplasty, Transluminal, Percutaneous Coronary
NCT02949414	Suspended	Phase 1	4	Tracheomalacia, Tracheal Stenosis
NCT01933802	Completed	Phase 1	20	Multiple Sclerosis
NCT05080465	Active	Phase 3	700	Liver Cirrhosis
NCT04457609	Unknown	Phase 1	40	COVID, Pulmonary Infection, Sars-CoV2
NCT00851162	Withdrawn	Phase 2,3	0	Bone Neoplasms
NCT04972890	Recruiting	Phase 2,3	12	Urologic Diseases, Erectile Dysfunction With Diabetes Mellitus
NCT03078621	Unknown	Phase 1,2	50	Cerebral Palsy
NCT02557724	Completed	-	35	Liver Failure, Liver Neoplasm
NCT02123368	Completed	Phase 1,2	30	Osteoarthritis
NCT05210309	Recruiting	-	150	Safety, Efficacy, Self
NCT01275612	Withdrawn	Phase 1	0	Solid Tumors, Acute Kidney Injury
NCT03602872	Withdrawn	Phase 1	0	Knee Osteoarthritis
NCT03378063	Recruiting	Early Phase 1	100	Bronchopulmonary Dysplasia
NCT00698191	Unknown	Phase 1,2	20	Refractory Systemic Lupus Erythematosus
NCT04213248	Recruiting	Phase 1,2	27	Dry Eye
NCT02327832	Unknown	Phase 1	10	Liver Regeneration
NCT05127369	Not recruiting	Not Applicable	48	Depression
NCT01957826	Unknown	Phase 1,2	70	Primary Idiopathic Dilated Cardiomyopathy

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT03356821	Completed	Phase 1,2	10	Perinatal Arterial Ischemic Stroke, Neonatal Stroke
NCT04029896	No longer available	-	Cerebral Palsy	-
NCT01494480	Unknown	Phase 2	30	Amyotrophic Lateral Sclerosis
NCT01879046	Completed	Not Applicable	35	Knee Osteoarthritis
NCT05043610	Recruiting	Phase 3	240	Acute Myocardial Infarction, Anterior Wall, Cardiac Remodeling, Heart Failure
NCT04863183	Not recruiting	Phase 1,2	30	, Knee Osteoarthritis, Cell Therapy
NCT05579665	Active	Phase 1,2	45	Knee Osteoarthritis
NCT04501341	Unknown	Phase 1,2	15	T2D
NCT02474342	Completed	Not Applicable	18	Rotator Cuff Disease
NCT05125562	Withdrawn	Phase 2	0	COVID-19
NCT02104440	Completed	Phase 2	15	Cytopenia
NCT01448434	Completed	Phase 2	72	Osteoarthritis of Knee Joint
NCT02290041	Completed	Phase 1,2	5	Discordant Immunological Response in HIV Infected Subjects
NCT02943889	Unknown	Phase 1,2	40	Liver Cirrhosis
NCT01489267	Unknown	Phase 2	20	Hereditary Cerebellar Ataxia.
NCT03798028	Unknown	Not Applicable	250	Rheumatoid Arthritis
NCT03069209	Unknown	Phase 1,2	50	Premature Ovarian Failure
NCT04998058	Not recruiting	Phase 1	20	Alveolar Bone Loss or Atrophy, Grafting Bone
NCT04356300	Not recruiting	Not Applicable	60	Multiple Organ Failure
NCT02501811	Completed	Phase 2	125	Ischemic Cardiomyopathy
NCT02365142	Unknown	Phase 1,2	38	Knee Osteoarthritis
NCT01840540	Completed	Phase 1	6	Atherosclerotic Renal Artery Stenosis, Ischemic Nephropathy, Renovascular Hypertension
NCT02881476	Unknown	Phase 1	30	Amyotrophic Lateral Sclerosis
NCT03724617	Completed	Not Applicable	18	Thin Endometrium, Intrauterine Adhesion
NCT04652908	Recruiting	Phase 1,2	55	Myelomeningocele

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01687777	Unknown	Phase 2	10	Chronic Disease
NCT02325843	Completed	Phase 2	16	Chemical Burns
NCT02587572	Not recruiting	Phase 2	40	Metabolic Disease, Endothelial Dysfunction
NCT01562002	Completed	Phase 1,2	27	Limbus Corneae Insufficiency Syndrome
NCT02587715	Unknown	Phase 1,2	69	Multiple Sclerosis, Relapsing-Remitting
NCT03585855	Terminated	Not Applicable	4	Interventional
NCT03592849	Completed	Not Applicable	20	Infertility, Female, Endometrium
NCT04273646	Unknown	Not Applicable	48	2019 Novel Coronavirus Pneumonia, COVID-19
NCT04490486	Withdrawn	Phase 1	0	COVID-19, Acute Respiratory Distress Syndrome, Corona Virus Infection
NCT02961725	Unknown	Phase 1	10	Bronchopleural Fistula
NCT02888704	Completed	Phase 1	13	Atopic Dermatitis
NCT01182662	Unknown	Phase 2	30	Aplastic Anemia
NCT03337243	Completed	Not Applicable	60	Knee Osteoarthritis, Osteo Arthritis Knee, Musculoskeletal Disease
NCT04448106	Not recruiting	Phase 2	300	Osteoarthritis (Knee, Hip, Shoulder)
NCT02445547	Completed	Phase 1,2	82	Crohn Disease
NCT02418325	Terminated	Phase 1,2	69	Multiple Sclerosis, Relapsing-Remitting
NCT04434768	Recruiting	Phase 1	14	Acute Stroke
NCT05018637	Enrolling	Phase 2	30	Vertebral Compression Fracture, Osteoporotic Fractures
NCT01420432	Unknown	Phase 1	10	Ankylosing Spondylitis
NCT00361049	Completed	Phase 1	49	Cancer
NCT04909892	Withdrawn	Phase 2	0	Covid-19
NCT00658073	Completed	Not Applicable	165	Renal Transplant Rejection
NCT05094011	Not recruiting	Phase 1	9	Idiopathic Parkinson's Disease
NCT03460223	Unknown	Phase 1,2	30	Renal Cirrhosis
NCT01129739	Unknown	Phase 2	30	Myelodysplastic Syndromes

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05095532	Recruiting	Phase 1	42	Chronic Pancreatitis
NCT04776239	Recruiting	Phase 1,2	30	Diabetes Mellitus, Ischemic Heart Disease
NCT02940418	Unknown	Phase 1	20	T1DM
NCT03058068	Withdrawn	Phase 1	0	Cystic Fibrosis
NCT01143168	Unknown	Phase 1	24	T1DM
NCT02509156	Completed	Phase 1	46	Cardiomyopathy Due to Anthracyclines
NCT01045382	Terminated	Phase 2	39	Acute Leukemia, Myelodysplastic Syndromes, Multiple Myeloma, Hodgkin's, Non-Hodgkin
NCT03028428	Unknown	Phase 2	1	Osteoarthritis
NCT02162693	Completed	Phase 2	53	Knee Osteoarthritis
NCT01741857	Unknown	Phase 1,2	40	Systemic Lupus Erythematosus
NCT02491658	Unknown	Phase 1,2	30	Psoriasis Vulgaris
NCT03684122	Active	Phase 1,2	10	Parkinson Disease
NCT04522986	Completed	Phase 1	6	SARS-Cov 2
NCT02853942	Unknown	Early Phase 1	100	Injury of Facial Nerve, Unspecified Side, Initial Encounter
NCT03877471	Active	Phase 1	28	Primary Ovarian Insufficiency
NCT04689152	Recruiting	Phase 3	200	Alcoholic Cirrhosis
NCT02331134	Recruiting	Not Applicable	40	Malignant Melanoma, Head and Neck Cancer
NCT03874572	Active	Phase 1	10	Xerostomia, Oropharynx Cancer, Salivary Gland Diseases, Dry Mouth
NCT03460795	Not recruiting	Phase 1,2	30	Liver Cirrhosis
NCT04063215	Active	Phase 1,2	24	Traumatic Brain Injury
NCT03137199	Terminated	Phase 1	3	Asthma
NCT03564808	Unknown	Phase 2	40	Skin Pigmentation Over Contour Deformities of Face, Trauma, Rhomberg Disease
NCT02338375	Unknown	Early Phase 1	28	Osteochondral Lesion of Talus
NCT00976287	Unknown	Phase 2	50	Liver Cirrhosis
NCT02379442	Terminated	Phase 1,2	1	GvHD
NCT03254758	Recruiting	Phase 1,2	27	Decompensated Liver Cirrhosis
NCT03691909	Completed	Phase 1,2	15	Rheumatoid Arthritis

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02013674	Completed	Phase 2	30	Chronic Ischemic Left Ventricular Dysfunction, Myocardial Infarction
NCT05130983	Recruiting	Phase 1	10	Crohn Disease, IBD-Irritable Bowel Disease
NCT03014037	Completed	Not Applicable	35	Osteoarthritis
NCT04905836	Recruiting	Phase 2	60	Covid-19
NCT04466007	Recruiting	Phase 2	90	Limb Ischemia, Diabetic Foot
NCT04992247	Not recruiting	Phase 2	60	Covid19
NCT04909879	Withdrawn	Phase 2	0	Acute Respiratory Distress Syndrome
NCT01875081	Completed	Phase 2	72	Alcoholic Liver Cirrhosis
NCT02687646	Completed	Phase 1,2	16	Acute GvHD
NCT02241018	Unknown	Phase 2,3	200	aGvHD
NCT05131412	Completed	-	107	Pneumonia, With HSCT
NCT04728698	Withdrawn	Phase 2	0	Covid19, ARDS
NCT04232592	Unknown	Phase 1	32	Intrauterine Adhesion
NCT04355728	Completed	Phase 1,2	24	Corona Virus Infection, ARDS, COVID-19
NCT04289194	Recruiting	Phase 1,2	26	ARDS
NCT02561767	Unknown	Phase 1,2	120	Kidney Transplantation, Acute Kidney Tubular Necrosis
NCT02064062	Unknown	Phase 2	10	Achilles Tendinitis, Achilles Tendon Thickening
NCT01301664	Available	-	-	-
NCT04953572	Not recruiting	Phase 1	252	Cartilage Injury
NCT00749164	Unknown	Phase 1,2	20	GvHD
NCT03174587	Completed	Phase 1	7	Lupus Nephritis
NCT02195323	Completed	Phase 1	7	Chronic Kidney Disease
NCT02962661	Recruiting	Phase 1	72	Cardiomyopathy, Heart Failure, Hematopoietic and Lymphoid Cell Neoplasm, Malignant Solid Neoplasm
NCT05595681	Not recruiting	Phase 1	30	Diabetic Foot Ulcer
NCT01087996	Completed	Phase 1,2	31	Stem Cell Transplantation
NCT04352803	Not recruiting	Phase 1	20	Covid-19 Pneumonia, Cyotokine Storm

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT03638154	Completed	Not Applicable	20	Periodontal Intrabony Defect
NCT00956891	Completed	-	158	Liver Failure
NCT01159899	Unknown	Early Phase 1	50	Knee Osteoarthritis Osteoarthritis, Osteochondritis Dissecans, Osteonecrosis
NCT04573270	Completed	Phase 1	40	Covid19, Prophylaxis
NCT03920397	Completed	Not Applicable	30	T1DM
NCT03822858	Temporarily not available	-	Multiple Sclerosis	-
NCT05279768	Recruiting	Phase 1,2	40	Polycystic Ovary Syndrome
NCT03943940	Unknown	Phase 1,2	60	T2DM
NCT03626090	Recruiting	Phase 1,2	20	Liver Cirrhosis
NCT02062931	Unknown	Phase 1,2	60	Premature Ovarian Failure
NCT03059355	Terminated	Phase 1,2	14	Endothelial Dysfunction, Metabolic Syndrome, Chronic Inflammation
NCT04706312	Not recruiting	Phase 1	12	Diminished Ovarian Response
NCT01532076	Terminated	Phase 2	8	Osteoporotic Fractures
NCT04368806	Recruiting	Phase 2,3	140	Knee Osteoarthritis
NCT02055625	Withdrawn	Phase 1,2	0	Graft -*Versus*-host-disease
NCT03325504	Active	Phase 3	46	Non Union Fracture
NCT03631420	Recruiting	Phase 1	9	Bronchopulmonary Dysplasia
NCT03522545	Recruiting	Phase 1	30	Treatment-resistant Bipolar Depression
NCT01652209	Recruiting	Phase 3	90	Acute Myocardial Infarction
NCT03847844	Unknown	Phase 1,2	40	Acute-GvHD
NCT00609661	Withdrawn	-	0	Wound Healing, Burn
NCT01297218	Completed	Phase 1	9	Dementia of the Alzheimer's Type
NCT01227694	Completed	Phase 1,2	15	Knee Osteoarthritis, Knee Injuries, Joint Diseases, Rheumatic Diseases, Cartilage Diseases
NCT05333029	Not recruiting	Phase 2	12	GvHD
NCT02666391	Unknown	Phase 1,2	64	Acute Myocardial Infarction, Myocardial Infarction, Ischemic Cardiomyopathy
NCT00976430	Terminated	Not Applicable	5	Parkinson's Disease

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01399749	Unknown	Phase 1,2	30	Articular Cartilage Lesion of the Femoral Condyle
NCT00883727	Completed	Phase 1,2	20	Myocardial Infarction
NCT00543374	Completed	Phase 3	98	Crohn's Disease
NCT04476901	Recruiting	Phase 2	136	Non-ischemic Dilated Cardiomyopathy
NCT00498316	Completed	Phase 1	98	Myelodysplastic Syndrome, Leukemia
NCT04776538	Recruiting	Phase 2	120	Xerostomia Following Radiotherapy
NCT02003131	Withdrawn	Phase 1,2	0	Osteoarthritis of the Knee
NCT01394432	Unknown	Phase 3	50	Acute Myocardial Infarction, Heart Failure
NCT05152368	Recruiting	Phase 1	20	Peripheral Neuropathy, Trigeminal Neuralgia
NCT02442817	Completed	Phase 4	10	Schizophrenia
NCT04914403	Recruiting	Phase 1	6	Frailty Syndrome
NCT02381366	Completed	Phase 1,2	12	Bronchopulmonary Dysplasia
NCT04206007	Active	Phase 1	9	Moderate COPD
NCT05132972	Recruiting	Phase 2,3	42	Covid 19
NCT04011059	Not recruiting	Phase 1,2	40	Cardiovascular Diseases, Heart Failure, Coronary Artery Disease Transplantation
NCT03562715	Completed	-	200	Preeclampsia
NCT05147779	Recruiting	Phase 1	20	Erectile Dysfunction, Peyronie's Disease, Interstitial Cystitis
NCT03925324	Terminated	Phase 2	4	Ischemic Heart Disease, Non-ischemic Cardiomyopathy
NCT00690066	Completed	Phase 2	63	Type 1 T1DM Diabetes, Diabetes Mellitus, Insulin-Dependent, Juvenile Diabetes
NCT01824121	Unknown	Phase 1,2	25	Progressive Supranuclear Palsy
NCT05640687	Active	-	26	Pulmonary Alveolar Proteinosis(PAP)
NCT01663376	Completed	Not Applicable	20	Critical Limb Ischemia
NCT05507697	Recruiting	Phase 1,2	42	Diabetic Peripheral Neuropathy Type 2
NCT05315661	Recruiting	Phase 1	12	Frontotemporal Dementia

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01981330	Completed	Phase 1	16	Improved Healing of Scarred Vocal Folds
NCT02848131	Enrolling	Phase 2	30	Chronic Kidney Disease
NCT04893174	Recruiting	Phase 1	6	Knee Osteoarthritis
NCT02192736	Unknown	Phase 1,2	20	Asthma
NCT04939337	Enrolling	Phase 1	24	Crohn's Disease
NCT05520086	Recruiting	Phase 1,2	20	Chronic Conjunctivitis, Stevens-Johnson Syndrome, Lyell Syndrome, Pemphigoid
NCT02982915	Completed	Phase 1,2	62	Aging Frailty
NCT03516006	Active	Phase 1,2	20	Primary Sclerosing Cholangitis
NCT02237547	Withdrawn	Phase 1,2	0	Spinal Cord Injury
NCT03799718	Completed	Phase 2	23	Chronic Progressive Multiple Sclerosis
NCT03631589	Unknown	Phase 2,3	50	Steroid-resistant Severe aGVHD
NCT03158896	Recruiting	Phase 1	10	Acute GvHD
NCT02083731	Unknown	Phase 2	120	Hematopoietic, CMV Infection, Hematological Diseases
NCT04919135	Not recruiting	Phase 1,2	44	Frailty
NCT04339660	Unknown	Phase 1,2	30	COVID-19
NCT03887208	Completed	Phase 1,2	100	Skin, Scar, Cutis Laxa, Keloid, Cicatrix
NCT04520945	Unknown	Phase 2	100	Knee Osteoarthritis
NCT00827398	Completed	Phase 1,2	50	GvHD
NCT05167188	Recruiting	-	25	GvHD
NCT05288725	Not recruiting	Phase 1,2	120	Knee Osteoarthritis
NCT03123458	Unknown	Phase 1	100	Immune Related Disorder, Tissue Damage
NCT03033277	Unknown	Phase 1,2	320	Primary Ovarian Insufficiency
NCT01844661	Completed	Phase 1,2	20	Children, Solid Tumors, Metastases
NCT02484560	Unknown	Phase 1	10	Duchenne Muscular Dystrophy
NCT02917681	Unknown	Phase 1,2	28	AMYOTROPHIC LATERAL SCLEROSIS
NCT03509025	Completed	Phase 2	11	Knee Osteoarthritis
NCT01742533	Unknown	Phase 1,2	40	Premature Ovarian Failure
NCT04527224	Recruiting	Phase 1,2	10	Covid19 Pneumonia

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02107118	Withdrawn	Phase 1	0	Erectile Dysfunction, Cardiac Disease
NCT02958267	Completed	Phase 2	32	Knee Osteoarthritis
NCT03706482	Active	Phase 1,2	18	Osteogenesis Imperfecta
NCT05354141	Recruiting	Phase 3	400	COVID-19 Acute Respiratory Distress Syndrome
NCT05669144	Recruiting	Phase 1,2	20	Myocardial Infarction, Myocardial Ischemia, Myocardial Stunning
NCT02352077	Unknown	Phase 1	30	Spinal Cord Injury
NCT02672280	Unknown	Phase 1,2	30	Wounds, Diabetic Foot Ulcers, Burns
NCT03865394	Completed	Phase 1,2	46	Diabetic Foot Ulcer
NCT01454336	Completed	Phase 1	3	Liver Fibrosis
NCT05176366	Recruiting	Phase 1	10	Ulcerative Colitis
NCT00482092	Completed	Phase 3	330	Crohn's Disease
NCT03589287	Completed	Phase 1,2	18	Knee Osteoarthritis
NCT01393977	Unknown	Phase 2	60	Spinal Cord Injuries
NCT02210624	Unknown	Not Applicable	4	Anoxic Brain Injury
NCT02809781	Unknown	Phase 2,3	250	Spondylitis, Ankylosis, Arthritis, Spondylarthritis, Spondylarthropathies
NCT00683722	Completed	Phase 2	62	Pulmonary Disease, Chronic Obstructive, Pulmonary Emphysema, Chronic Bronchitis
NCT01873547	Completed	Phase 3	300	Spinal Cord Injury
NCT01539902	Unknown	Phase 2	25	Lupus Nephritis
NCT03525418	Completed	Phase 1,2	10	HLHS
NCT05387278	Recruiting	Phase 1	20	COVID-19 Acute Respiratory Distress Syndrome, Respiratory Distress Syndrome
NCT05086939	Recruiting	Phase 3	120	Knee Osteoarthritis
NCT05349565	Recruiting	Not Applicable	26	Knee Osteoarthritis
NCT04497805	Unknown	Phase 2	64	Diabetic Foot Ulcer
NCT01696591	Unknown	-	14	Alzheimer Disease, Dementia, Central Nervous System Diseases, Tauopathies

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02789995	Completed	Not Applicable	93	Sepsis
NCT04428801	Not recruiting	Phase 2	200	COVID-19
NCT01318330	Completed	Phase 1	10	GvHD
NCT02923375	Completed	Phase 1	16	GvHD
NCT05279157	Recruiting	Phase 2	15	Ophthalmological Disorder, Corneal Dystrophy, Treatment, Therapy, Keratoconus
NCT04243681	Completed	Phase 4	5	Liver Cirrhosis
NCT03828344	Not recruiting	Phase 1	16	Rheumatoid Arthritis
NCT04536233	Unknown	Phase 1	50	MSCs Derived Pleiotropic Factors on Wound Healing in Endonasal Surgeries
NCT02045745	Unknown	Phase 1,2	10	Postoperative Air Leaks in Risk Patients
NCT01849159	Withdrawn	Phase 1,2	0	Pulmonary Emphysema
NCT05151133	Recruiting	Phase 1	18	Allergic Rhinitis
NCT04348461	Suspended	Phase 2	100	COVID, Respiratory Distress Syndrome
NCT01297205	Completed	Phase 1	9	Bronchopulmonary Dysplasia
NCT03369275	Unknown	Phase 2	114	Septic Shock, Sepsis, Shock, Infection, Systemic Inflammatory Response Syndrome
NCT05155657	Recruiting	Phase 1	36	Alcoholic Cirrhosis
NCT03855631	Completed	-	8	Kabuki Syndrome 1
NCT00515307	Completed	Phase 1	1	Familial Hypercholesterolemia
NCT02900014	Unknown	Not Applicable	5	Cleft Palate
NCT05292625	Recruiting	Phase 1,2	48	Ischemic Stroke
NCT01719640	Completed	Phase 1,2	22	T2DM
NCT00284986	Completed	Phase 2	11	GvHD
NCT04297813	Recruiting	Phase 3	150	Alveolar Bone Atrophy
NCT02054208	Completed	Phase 1,2	46	Alzheimer's Disease
NCT02407470	Unknown	Phase 1,2	90	Severe Aplastic Anemia
NCT04888949	Recruiting	Phase 2	20	SARS-CoV-2 Infection(COVID-19)
NCT04657315	Enrolling	Phase 1,2	10	Adult Gliosarcoma, Neoplasms, Brain, Recurrent Glioblastoma

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02334878	Completed	Phase 3	50	Urinary Incontinence, Stress
NCT01754454	Unknown	Phase 1,2	30	Acute GVH Disease
NCT02240992	Unknown	Phase 2,3	120	Delayed Platelet Engraftment, Hematological Diseases
NCT04288934	Completed	Phase 1	20	Spinal Cord Injuries
NCT04551443	Unknown	Phase 2	200	Acute Myocardial Infarction
NCT01220492	Completed	Phase 1,2	266	Liver Cirrhosis
NCT02815423	Unknown	Phase 1,2	40	Fracture, Bone Nonunion
NCT03818737	Completed	Phase 3	480	Osteoarthritis
NCT02290886	Completed	Phase 1,2	52	Amyotrophic Lateral Sclerosis
NCT01626625	Unknown	Phase 1	10	Healing of Fracture
NCT02648386	Unknown	Phase 1,2	34	Rectal Cancer, Erectile Dysfunction
NCT04281797	Enrolling	-	90	Kidney Transplant, Liver Transplant; Complications, Microbial Colonization
NCT00826046	No longer available	-	GvHD	-
NCT04544215	Recruiting	Phase 1,2	60	Drug-resistant
NCT04275024	Enrolling	Not Applicable	8	Psoriasis, Drug Effect, Drug Toxicity
NCT05508191	Active	Not Applicable	30	Skin Aging, Transepidermal Water Loss
NCT04850469	Withdrawn	-	0	Sepsis, Critical Illness
NCT03115749	Terminated	Not Applicable	2	Inflammatory Bowel Diseases
NCT04240873	Unknown	Phase 1,2	24	Knee Osteoarthritis
NCT04325594	Unknown	Phase 2	60	Chronic Heart Failure, Non-ischemic Cardiomyopathy, Non-ischemic Dilated Cardiomyopathy
NCT00877903	Completed	Phase 2	220	Myocardial Infarction
NCT03186417	Recruiting	Phase 1	20	Rheumatoid Arthritis
NCT02600130	Completed	Phase 1	33	Alzheimer's Disease
NCT04877067	Completed	Phase 3	18	Methanol Poisoning, Toxic Optic Neuropathy
NCT03857841	Terminated	Phase 1	3	Bronchopulmonary Dysplasia
NCT02890953	Unknown	Phase 2	22	Cell Transplantation
NCT05027581	Recruiting	Phase 2	70	Knee Osteoarthritis

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01409954	Enrolling	-	60	Pseudarthrosis After Fusion or Arthrodesis
NCT03860155	Terminated	Phase 1,2	5	ACLF
NCT01343511	Completed	Phase 1,2	37	Autism
NCT03639506	Unknown	Not Applicable	50	Repetition Failure
NCT03990805	Completed	Phase 3	260	Degenerative Arthritis, Knee Osteoarthritis
NCT02672267	Completed	Phase 3	50	Myocardial Infarction
NCT05216562	Recruiting	Phase 2,3	60	SARS-CoV2 Infection
NCT02566655	Completed	Phase 1	10	Osteoporosis, Spinal Fractures
NCT03000712	Completed	Not Applicable	26	Degenerative Arthritis, Knee Osteoarthritis
NCT01547689	Unknown	Phase 1,2	30	Alzheimer's Disease
NCT01496339	Unknown	Phase 1,2	50	T1DM
NCT01306513	Completed	Phase 1	10	Emphysema
NCT02672306	Unknown	Phase 1,2	16	Alzheimer's Disease
NCT04535856	Completed	Phase 1	9	Covid19, Corona Virus Infection, SAR
NCT04040348	Active	Phase 1	6	Alzheimer Disease
NCT04097652	Recruiting	Phase 1	9	Acute Ischemic Stroke
NCT01909154	Completed	Phase 1	12	Spinal Cord Injury
NCT03839238	Unknown	Phase 1	18	Meniscus Injury
NCT05305833	Recruiting	Phase 1,2	20	Temporomandibular Joint Osteoarthritis, Effusion
NCT03925649	No longer available	-	Spinal Cord Injury at C5-C7 Level	-
NCT04347967	Not recruiting	Phase 1	18	Acute Respiratory Distress Syndrome
NCT02641769	Unknown	Phase 1,2	50	Non-obstructive Azoospermia
NCT02563340	Unknown	Phase 1,2	60	Kidney Transplantation
NCT04461925	Unknown	Phase 1,2	30	COVID-19 Pneumonia
NCT00557635	Suspended	Phase 2	50	Tibia or Femur Pseudo-arthrosis
NCT04494386	Active	Phase 1,2	17	Covid19, Corona Virus Infection, SARS-CoV Infection, ARDS, Coronavirus
NCT02145897	Unknown	Phase 1,2	60	Critical Limb Ischemia

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT04739930	Completed	Not Applicable	33	Cartilage Injury
NCT01325103	Completed	Not Applicable	14	Spinal Cord Injury
NCT01733186	Completed	Phase 1,2	12	Degeneration Articular Cartilage Knee
NCT01213186	Unknown	Phase 2	72	Human Immunodeficiency Virus, Disorder of Immune Reconstitution
NCT04825730	Not recruiting	Not Applicable	14	Degenerative Arthritis, Knee Arthritis
NCT01803347	Completed	Phase 3	80	Anal Fistula
NCT00759018	No longer available	-	Graft vs Host Disease, GvHD	-
NCT04763369	Recruiting	Phase 2	50	Retinitis Pigmentosa (RP)
NCT04170426	Not recruiting	Phase 1,2	54	Rheumatoid Arthritis
NCT02669199	Completed	Phase 1	20	MSCs
NCT02563366	Unknown	Phase 1,2	120	Kidney Transplantation, Acute Kidney Tubular Necrosis
NCT03902067	Not recruiting	Phase 1	40	Left Ventricular Dysfunction, Acute Myocardial Infarction
NCT02313415	Completed	Not Applicable	26	Infertility, Intrauterine Adhesions
NCT04612465	Unknown	Phase 3	36	Crohn's Fistula
NCT02855073	Unknown	Phase 2	28	Defect of Articular Cartilage, Knee Osteoarthritis
NCT02917291	Recruiting	Phase 1,2	48	Acute Traumatic Spinal Cord Injury
NCT02543073	Unknown	Phase 1,2	60	With HSCT, Lung Diseases, Interstitial, Bronchiolitis Obliterans
NCT05658094	Recruiting	Not Applicable	20	Hair Loss, Alopecia
NCT05491681	Not recruiting	Phase 1	9	ARDS, Human
NCT03105284	Completed	Not Applicable	20	-
NCT05407766	Withdrawn	Phase 1	0	Rectal Fistula
NCT04951882	Recruiting	Early Phase 1	30	Acute Lung Injury
NCT04388982	Unknown	Phase 1,2	9	Alzheimer Disease
NCT04427930	Active	Phase 3	129	Knee Osteoarthritis

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02755376	Completed	Not Applicable	30	Deficiency of Anterior Cruciate Ligament
NCT04953663	Recruiting	Phase 1,2	60	Stroke
NCT03633565	Unknown	Phase 4	45	Myopathy
NCT02801890	Completed	Phase 1,2	10	Ultra-Filtration Failure
NCT02619877	Completed	Phase 2	59	Diabetic Foot Ulcer
NCT02619851	Active	Phase 2	22	Burn Injury
NCT04339504	Recruiting	Phase 1	12	Knee Osteoarthritis
NCT02767817	Unknown	Phase 1	30	Brain Injury
NCT03672825	Active	Phase 1	25	Cartilage Defect
NCT03389919	Unknown	Phase 3	20	MSC Transplantation
NCT04342325	Active	Phase 1	9	Glomerulonephritis , IGA
NCT01309061	Completed	Not Applicable	5	Progressive Hemifacial Atrophy, Romberg's Disease
NCT03838666	Terminated	Phase 1,2	9	Rotator Cuff Tear
NCT02947191	Unknown	Phase 1,2	12	Chronic Nasal Septum Perforation
NCT03265444	Completed	Phase 1	9	Multiple System Atrophy
NCT02786017	Unknown	Phase 1,2	40	Decompensated Cirrhosis
NCT01033552	Active	Phase 1,2	32	Epidermolysis Bullosa
NCT04675970	Active	-	86	Primary Ovarian Insufficiency, Premature Ovarian Failure
NCT03454737	Unknown	Not Applicable	20	Patellar Tendinopathy
NCT02166021	Completed	Phase 2	48	Multiple Sclerosis (MS)
NCT04954534	Not recruiting	Not Applicable	9	Alzheimer's Disease
NCT01091701	Withdrawn	Phase 1,2	0	Stroke
NCT04562025	Unknown	Not Applicable	38	Diabetic Nephropathy
NCT04074408	Recruiting	Phase 2	100	Basal Ganglia Hematoma
NCT03766139	Unknown	Early Phase 1	17	Intrabony Periodontal Defect
NCT01603836	Completed	Not Applicable	80	Spondyloarthrosis, Spondylosis
NCT04293692	Withdrawn	Not Applicable	0	COVID-19
NCT03056742	Withdrawn	Phase 2	0	Critical Limb Ischemia Due to Buerger's Disease

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02696876	Recruiting	Not Applicable	20	Defect of Articular Cartilage, Cartilage Injury, Knee Osteoarthritis
NCT01392625	Completed	Phase 1,2	37	Non-ischemic Dilated Cardiomyopathy
NCT04173650	Not recruiting	Phase 1,2	10	Dystrophic Epidermolysis Bullosa
NCT02796079	Unknown	Phase 1	240	Peripheral Vascular Disease, Ischemia, Diabetic Foot
NCT01314092	Terminated	Phase 2	15	Complex Perianal Fistula
NCT03370874	Unknown	Phase 3	164	Diabetic Foot Ulcer
NCT01922908	Withdrawn	Phase 1,2	0	Ischemic Stroke
NCT03325322	Enrolling	Phase 2	30	Chronic Kidney Diseases, Diabetes Mellitus, Diabetic Nephropathies
NCT02579148	Withdrawn	Phase 1	0	Erectile Dysfunction, Type 1 T2DM Diabetes Mellitus
NCT03754465	Recruiting	Phase 2	56	Diabetic Foot Ulcer
NCT02492490	Unknown	Phase 1,2	120	Uremia
NCT03183726	Completed	-	4	Diabetic Foot Ulcer
NCT02582775	Recruiting	Phase 2	84	Epidermolysis Bullosa
NCT05433298	Recruiting	Phase 1,2	60	COVID-19 Pneumonia, COVID-19
NCT03183661	Unknown	-	9	Crohn Disease
NCT04362189	Terminated	Phase 2	53	COVID-19
NCT00221130	Completed	Phase 1,2	10	Adult Periodontitis
NCT05283317	Completed	Phase 1,2	30	Sepsis, Septic Shock
NCT01662973	Unknown	Phase 1,2	100	Primary Biliary Cirrhosis
NCT05116540	Recruiting	Phase 2	24	Multiple Sclerosis
NCT05344157	Recruiting	Phase 1,2	54	Knee Osteoarthritis
NCT04003857	Recruiting	Phase 2	60	Bronchopulmonary Dysplasia
NCT04447833	Active	Phase 1	7	ARDS, Human, COVID
NCT04738981	Not recruiting	Phase 3	130	GvHD
NCT02378974	Completed	Phase 1,2	19	Cerebral Infarction
NCT01897987	Completed	Not Applicable	62	Bronchopulmonary Dysplasia
NCT01041001	Completed	Phase 3	104	Cartilage Injury, Osteoarthritis
NCT01828957	Completed	Phase 2	69	Bronchopulmonary Dysplasia
NCT03478215	Recruiting	Phase 2	24	Renal Transplantation

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT04493242	Completed	Phase 2	120	Covid19, ARDS, Pneumonia, Viral
NCT04903327	Terminated	Phase 2	43	Covid19
NCT01759823	Completed	Phase 2,3	30	T2DM
NCT04482413	Not recruiting	Phase 2	100	Alzheimer Disease
NCT04037345	Completed	Phase 1	12	Knee Osteoarthritis
NCT03117738	Completed	Phase 1,2	21	Alzheimer Disease
NCT02674399	Completed	Phase 2	28	Knee Osteoarthritis
NCT04684602	Recruiting	Phase 1,2	5000	Cardiovascular Disorders, Integumentary Disease, Musculoskeletal Disorders, Neurodegenerative Disorders, Neurologic Disorders, Pulmonary Disorders, Sexual Dysfunction, Urologic Disorders, Viral Illness
NCT03424629	Unknown	Phase 1	57	Moderate and Severe Plaque Psoriasis
NCT04623606	Unknown	Phase 1,2	15	Osteogenesis Imperfecta
NCT02384018	Completed	Phase 1	3	Chronic Pancreatitis, Diabetes
NCT03280056	Completed	Phase 3	263	Amyotrophic Lateral Sclerosis (ALS)
NCT01661842	Unknown	Phase 1,2	100	Autoimmune Hepatitis
NCT05549609	Recruiting	Phase 1,2	12	Venous Leg Ulcer
NCT04835883	Recruiting	Phase 2	10	Systemic Lupus Erythematosus
NCT03827096	Terminated	Phase 1,2	10	Degenerative Disc Disease
NCT05191381	Recruiting	-	40	COVID-19, Critical Illness, Hypercytokinemia, Lung Fibrosis
NCT00187018	Completed	Not Applicable	9	Osteogenesis Imperfecta
NCT04348435	Completed	Phase 2	53	COVID-19
NCT04452097	Not recruiting	Phase 1,2	39	COVID-19, ARDS
NCT05182034	Recruiting	Phase 2	90	Knee Osteoarthritis
NCT03489564	Completed	-	20	Pregnancy Related, Physical Activity
NCT02023788	Completed	-	8	Bronchopulmonary Dysplasia, Respiratory Tract Infections, Premature Birth of Newborn
NCT01709656	Completed	Not Applicable	120	Ankylosing Spondylitis

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT04492501	Completed	Not Applicable	600	Covid19, Cytokine Release Syndrome, Critical Illness, ARDS
NCT03264573	Completed	Not Applicable	40	Atrophic Scar
NCT00768066	Completed	Phase 1,2	65	Stem Cell Transplantation, Ventricular Dysfunction, Left
NCT01984450	Unknown	Not Applicable	100	Articular Cartilage Defect
NCT03912480	Unknown	Early Phase 1	24	Type1diabetes
NCT03472742	Recruiting	-	21	Decompensated Liver Cirrhosis
NCT03678467	Recruiting	Phase 1,2	6	Mandible Tumor, Mandibular Injuries, Mandible; Deformity
NCT04629105	Recruiting	Phase 1	70	ARDS, Covid19
NCT04928287	Active	Phase 2	24	Parkinson Disease
NCT00225095	Completed	Phase 1,2	60	Recovery Following Partial Medial Meniscectomy
NCT03529877	Completed	Phase 1,2	16	Recessive Dystrophic Epidermolysis Bullosa
NCT03943576	Recruiting	Phase 1,2	30	Knee Osteoarthritis
NCT04377334	Not recruiting	Phase 2	40	ARDS, COVID-19
NCT02161003	Unknown	Phase 1,2	50	Fecal Incontinence
NCT02706132	Unknown	Phase 1,2	15	Liver Transplantation
NCT04392778	Completed	Phase 1,2	30	Covid19, Pneumonia, Multiple Organ Failure, Corona Virus Infection
NCT01753440	Completed	Phase 2	11	Coronary Artery Disease, Ischemic Cardiomyopathy
NCT03067870	Unknown	Phase 1	100	RheumatoId Arthritis, Knee Osteoarthritis, Hip Osteoarthritis
NCT05165017	Not recruiting	Phase 1,2	26	Pitt Hopkins Syndrome
NCT02287974	Terminated	Phase 1,2	20	Critical Limb Ischemia (CLI)
NCT05443464	Withdrawn	Phase 1	0	GVHD,Acute
NCT01541579	Completed	Phase 3	278	Crohn's Disease
NCT04356287	Recruiting	Phase 1,2	18	Sclerosis, Systemic
NCT02079324	Unknown	Phase 1	12	Head and Neck Cancer
NCT01548092	Unknown	Phase 1,2	10	Recto-vaginal Fistula
NCT04995081	Recruiting	Phase 2	60	Parkinson Disease

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT04397796	Active	Phase 1	45	COVID
NCT02274428	Completed	Phase 1	9	Mesenchymal Stromal Cells
NCT05521672	Recruiting	Phase 1,2	20	Stenosis; Bowel, Crohn Disease
NCT04345601	Recruiting	Phase 1,2	66	Sars-CoV2, Acute Respiratory Distress Syndrome, COVID-19
NCT03404063	Completed	Phase 2,3	105	Myocardial Infarction
NCT04590118	Recruiting	Phase 1,2	60	Ischemic Stroke
NCT03905824	Recruiting	Phase 3	70	Osteochondral Fracture of Talus
NCT01233960	Completed	Phase 3	73	Crohn's Disease
NCT00702741	Completed	Phase 1,2	55	Recovery Following Partial Medial Meniscectomy
NCT02025270	Unknown	Phase 1,2	100	Male Infertility
NCT05113342	Recruiting	Phase 1,2	20	Multiple Myeloma, Relapse Multiple Myeloma
NCT04219241	Active	Phase 2,3	35	Huntington Disease
NCT03183804	Unknown	-	54	Diabetic Foot Ulcer
NCT03172117	Unknown	Phase 1,2	45	Alzheimer's Disease
NCT04713436	Completed	-	3	Anti-Bacterial Agents
NCT02016508	Unknown	Phase 1,2	1	Age Related Macular Degeneration
NCT04514952	No longer available	-	Amyotrophic Lateral Sclerosis	-
NCT04653077	Unknown	Not Applicable	50	Stem Cell Transplant Complications
NCT02495766	Completed	Phase 1,2	8	Relapsing-Remitting Multiple Sclerosis, Secondary Progressive Multiple Sclerosis
NCT04390139	Active	Phase 1,2	30	COVID-19, SARS-CoV 2, ARDS
NCT01632475	Active	-	9	Bronchopulmonary Dysplasia
NCT02135380	Unknown	Phase 1,2	60	Idiopathic Pulmonary Fibrosis
NCT02291770	Unknown	Phase 3	130	cGvHD
NCT02846883	Terminated	Phase 1	28	Abdominal Aortic Aneurysm
NCT02104713	Completed	Phase 1	15	Second Degree Skin Burn
NCT03901235	Recruiting	Phase 1,2	60	Efficacy and Safety
NCT02603744	Unknown	Phase 1,2	9	Premature Ovarian Failure
NCT04604288	No longer available	-	Knee Pain Chronic, Osteo Arthritis Knee	-

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT04269525	Unknown	Phase 2	16	Pneumonia, Viral, Pneumonia
NCT01351610	Completed	Phase 1,2	25	Critical Limb Ischemia, Peripheral Artery Disease
NCT01804153	Unknown	Phase 1,2	10	Urinary Incontinence
NCT02728115	Active	Phase 1	6	Huntington Disease
NCT03939741	Recruiting	Phase 1,2	31	Chronic Kidney Diseases
NCT05553132	Recruiting	Phase 1	15	Cartilage Defect
NCT02396056	Unknown	Not Applicable	10	Alveolar Ridge Augmentation
NCT01764100	Unknown	Phase 1	10	Graft vs Host Disease
NCT05322057	Completed	-	14	Crohn Disease, Fistula Perianal
NCT04815213	Recruiting	Phase 1	10	Premature Ovarian Failure
NCT02745379	Unknown	Phase 1	20	Alveolar Bone Loss
NCT04956744	Recruiting	Phase 1	30	Multiple Sclerosis
NCT02745366	Unknown	Phase 1	20	Alveolar Bone Loss, Atrophy
NCT02017912	Completed	Phase 2	48	Amyotrophic Lateral Sclerosis (ALS)
NCT04780685	Recruiting	Phase 2	40	Covid19
NCT01589549	Unknown	Phase 2	66	Acute GVH Disease
NCT02468492	Completed	Early Phase 1	18	Knee Osteoarthritis
NCT02504437	Unknown	Phase 1,2	200	Myocardial Infarction, Acute Myocardial Infarction, Ischemic Cardiomyopathy
NCT02975960	Completed	Not Applicable	7	Systemic Sclerosis
NCT05215288	Not recruiting	Early Phase 1	20	Solid Organ Transplant Rejection, Organ Rejection Transplants, Organ Rejection
NCT04681118	No longer available	-	Amyotrophic Lateral Sclerosis	-
NCT04798716	Not recruiting	Phase 1,2	55	Covid19, Novel Coronavirus Pneumonia, ARDS
NCT04308213	Recruiting	Not Applicable	30	Shoulder Arthritis
NCT00186914	Completed	Phase 1	8	Osteodysplasia
NCT03455335	Completed	Phase 1	12	Critical Limb Ischemia
NCT04410731	Active	Phase 1	10	Facet-Mediated Low Back Pain

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01929434	Completed	Phase 3	300	Cerebral Palsy
NCT03629015	Withdrawn	Phase 1	0	Acute Liver Failure, ACLF
NCT04018729	Recruiting	Phase 2,3	34	Severe COPD
NCT04034615	Withdrawn	Phase 2	0	Cicatrix
NCT01558908	Unknown	Phase 1,2	15	Peripheral Vascular Diseases
NCT02772289	Completed	Phase 2	90	Cicatrix
NCT05484856	Completed	Phase 1,2	140	Knee Osteoarthritis
NCT00260338	Completed	Phase 1,2	31	Myocardial Ischemia, Coronary Heart Disease
NCT05338099	Recruiting	Phase 1	12	Duchenne Muscular Dystrophy
NCT05333406	Recruiting	Phase 1	12	Charcot-Marie-Tooth Disease, Type IA
NCT02685722	Completed	Phase 1	20	Difficult to Healing of Skin Ulcers
NCT02467387	Completed	Phase 2	23	Non-Ischemic Heart Failure
NCT01166776	Completed	-	64	Varices of Umbilical Cord
NCT03248466	Unknown	Early Phase 1	60	Diabetic Foot Ulcer
NCT05280002	Completed	Phase 2	30	Knee Osteoarthritis
NCT00790764	Suspended	Phase 2	60	Heart Disease, Blocked Arteries, Coronary Ischemia, Coronary Disease, Coronary Artery Disease, Coronary Atherosclerosis
NCT03838250	Unknown	Phase 1	10	Alcoholic Liver Cirrhosis
NCT03896568	Recruiting	Phase 1	36	IDH1 wt Allele, Recurrent Anaplastic Astrocytoma, Recurrent Glioblastoma, Recurrent Gliosarcoma, Recurrent Malignant Glioma
NCT02492308	Unknown	Phase 1,2	120	Living-relative Kidney Transplantation
NCT02644447	Completed	Phase 1,2	23	Premature Ovarian Failure
NCT02745808	Unknown	Phase 1	30	Erectile Dysfunction, T1DM, T2DM
NCT03226015	Completed	-	27	Limbal Stem-cell Deficiency
NCT04758533	Recruiting	Phase 1,2	12	Diffuse Intrinsic Pontine Glioma, Medulloblastoma
NCT00988338	Completed	-	106	Tibiotalar Arthrodesis, Subtalar Arthrodesis, Calcaneocuboid Arthrodesis, Double Arthrodesis, Triple Arthrodesis

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT00418418	Unknown	Phase 2	60	Heart Failure, Myocardial Infarction, Coronary Artery Disease
NCT03042143	Recruiting	Phase 1,2	129	Acute Respiratory Distress Syndrome
NCT04340284	Completed	Phase 1,2	11	Nonunion of Fracture
NCT02579369	Unknown	Phase 1,2	5	Dystrophic Epidermolysis Bullosa
NCT01626677	Completed	Phase 3	103	Degenerative Osteoarthritis, Defect of Articular Cartilage
NCT01623453	Terminated	-	6	Perianal Fistula, Primary; Complex
NCT05066334	Recruiting	Phase 2	52	Intervertebral Disc Degeneration, Chronic Low-back Pain
NCT03418233	Completed	Phase 2,3	115	Heart Failure
NCT03423732	Active	Phase 2,3	50	Critical Limb Ischemia
NCT01770613	Withdrawn	Phase 2	0	ST Segment Elevation Myocardial Infarction (STEMI)
NCT03066245	Unknown	Phase 1,2	4	Aneurysmal Bone Cyst
NCT01719926	Completed	Phase 1	13	Colorectal Neoplasms, Esophageal Neoplasms, Ovarian Neoplasms
NCT05669261	Not recruiting	Phase 1	20	Long COVID
NCT05126563	Recruiting	Phase 2	80	Post COVID-19 Syndrome
NCT02138331	Unknown	Phase 2,3	20	T1DM
NCT01366911	Completed	-	203	Hip Arthroplasty
NCT03268603	Active	Phase 2	69	ALS
NCT03252535	Completed	Phase 2	35	Huntington Disease
NCT01449032	Completed	Phase 2	60	Chronic Ischemic Heart Disease
NCT02658344	Completed	Phase 2	24	Degenerative Arthritis, Knee Osteoarthritis
NCT03042572	Unknown	Phase 2,3	60	Peripheral Arterial Disease, Cardiovascular Diseases, Vascular Diseases
NCT04917744	Recruiting	-	15	Ovarian Carcinoma
NCT01931007	Completed	Phase 1	25	Bilateral Primary Osteoarthritis of Knee
NCT04821102	Not recruiting	Not Applicable	21	Degenerative Arthritis, Knee Arthritis
NCT04247945	Recruiting	Phase 2,3	120	Allogeneic HSCT
NCT02033525	Completed	Phase 1,2	20	Chronic Meniscal Injury

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT03392467	Unknown	Phase 2	60	Severe Bronchopulmonary Dysplasia
NCT04495582	Active	-	8	Multiple System Atrophy
NCT00913289	Terminated	Phase 1	6	Liver Cirrhosis
NCT03067831	Unknown	Phase 1,2	20	Duchenne Muscular Dystrophy
NCT02177565	Completed	Not Applicable	35	Non-union of Fractures
NCT05559801	Not recruiting	Phase 1,2	12	Type III Osteogenesis Imperfecta
NCT04998461	Not recruiting	-	60	Chronic Kidney Diseases, Obesity, T2DM
NCT05047276	Not recruiting	Phase 1,2	16	Uveal Melanoma, Metastatic
NCT04042844	Recruiting	Phase 2	99	Lumbar Disc Disease
NCT04537351	Completed	Phase 1,2	14	Covid19, ARDS
NCT02387723	Completed	Phase 1	10	Heart Failure
NCT03790189	Unknown	Not Applicable	25	Knee Osteoarthritis, Cartilage Degeneration
NCT04798066	No longer available	-	Post COVID-19 Syndrome	-
NCT01062750	Completed	Not Applicable	4	Liver Cirrhosis
NCT04714801	Recruiting	Phase 1,2	30	Lung Transplant Rejection
NCT02673788	Active	-	9	Intracranial Hemorrhages , Newborn Infant
NCT01709279	Unknown	Not Applicable	6	Ischemic Heart Failure
NCT04467047	Unknown	Phase 1	10	COVID-19, Sars-CoV2
NCT04772378	Available	-	-	Parkinson Disease
NCT04437823	Unknown	Phase 2	20	Corona Virus Infection
NCT03308006	Unknown	Phase 2	18	Knee Osteoarthritis
NCT04711811	No longer available	-	Chronic Pain	-
NCT02742857	Completed	Phase 1	20	Brain Death
NCT03379168	Active	Not Applicable	75	Knee Osteoarthritis
NCT00710411	Completed	-	48	Multiple Trauma
NCT01468064	Completed	Phase 1,2	20	Stroke, Infarction, Middle Cerebral Artery

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05018754	Completed	-	15	Graft Vs Host Disease, Oral Mucositis
NCT01663116	Completed	Phase 1,2	53	Aggravated Rheumatoid Arthritis
NCT01771679	Active	Phase 1,2	29	Chronic Effect of Ultraviolet Radiation on Photoaged Skin, Dermatologic Disorders
NCT04020367	Unknown	Not Applicable	25	Septoplasty, Turbinoplasty
NCT01849237	Unknown	Phase 1,2	30	Neutropenia, Aplastic Anemia
NCT03257098	Completed	Phase 1,2	31	Skin Ulcer Venous Stasis Chronic
NCT03267784	Completed	Phase 1,2	23	Diabetic Neuropathic Ulcer
NCT03676400	Completed	Not Applicable	84	Androgenic Alopecia
NCT04213131	Unknown	Not Applicable	42	Spinal Cord Injuries
NCT04230902	Unknown	Phase 3	48	Knee Osteoarthritis
NCT01065337	Completed	Phase 2	30	Diabetic Foot
NCT03968198	Recruiting	Phase 2	43	Critical Limb Ischemia, Peripheral Artery Disease
NCT01967186	Unknown	Not Applicable	36	T1DM, End Stage Renal Disease
NCT02181478	Completed	Early Phase 1	6	Acute Lymphoblastic Leukemia, Acute Myelogenous Leukemia, Myelodysplastic Syndromes, Myelofibrosis, Relapsed Non-Hodgkin Lymphoma, Refractory Hodgkin Lymphoma, Relapsed Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia
NCT02503280	Withdrawn	Phase 1,2	0	Chronic Ischemic Left Ventricular Dysfunction, Myocardial Infarction
NCT03069170	Unknown	Phase 1	50	Multiple Sclerosis
NCT01089387	Completed	Phase 1,2	18	Prostate Cancer, Erectile Dysfunction
NCT05177003	Active	-	27	Crohn Disease, Ano Fistula
NCT05165459	Recruiting	Not Applicable	10	Venous Leg Ulcer, Autologous Adipose Stromal Vascular Fraction
NCT03294759	Active	Not Applicable	40	ACL-Anterior Cruciate Ligament Rupture

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02582489	Recruiting	Not Applicable	100	Osteoarthritis Post-meniscectomy
NCT00629018	Completed	Phase 2	110	Dilated Cardiomyopathy
NCT05658237	Recruiting	Not Applicable	10	Myopic Chorioretinal Atrophy
NCT02899091	Unknown	Phase 1,2	24	Alzheimer's Disease
NCT05137821	Not recruiting	Not Applicable	4	Peri-Implantitis
NCT04234412	Unknown	Not Applicable	10	Knee Osteoarthritis
NCT03112122	Terminated	Phase 4	1	Bone Marrow Edema
NCT02932852	Unknown	Early Phase 1	12	Hereditary Corneal Dystrophy, Keratoconus
NCT01842477	Completed	Phase 1,2	30	Delayed Union After Fracture of Humerus
NCT03686449	Unknown	Not Applicable	33	Burn With Full-Thickness Skin Loss
NCT03194451	Unknown	-	40	Impacted Tooth
NCT03964922	Unknown	Not Applicable	104	Relapse Leukemia, Immune Evasion
NCT04398303	Unknown	Phase 1,2	70	COVID-19 Pneumonia
NCT05000593	Completed	Not Applicable	30	Knee Osteoarthritis
NCT02580617	Recruiting	Phase 1	9	Crohn's Disease
NCT02580695	Completed	Phase 1,2	30	Osteoarthritis
NCT01686139	Unknown	Phase 1	12	T1DM With Ulcer, T2DM With Ulcer
NCT02483364	Completed	Phase 2	12	Pseudoarthrosis
NCT04361942	Completed	Phase 2	24	COVID-19 Pneumonia
NCT04745299	Recruiting	Phase 3	115	Amyotrophic Lateral Sclerosis
NCT00816803	Completed	Phase 1,2	80	Chronic Spinal Cord Injury
NCT04299152	Not recruiting	Phase 2	20	Severe Acute Respiratory Syndrome (SARS) Pneumonia
NCT03840343	Recruiting	Phase 1	30	Diabetic Kidney Disease, Diabetic Nephropathies, T2DM, T1DM, Chronic Kidney Disease, Diabetic Nephropathy Type 2, Kidney Failure, Kidney Insufficiency
NCT04134676	Completed	Phase 1	38	Chronic Ulcer

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01649752	Unknown	Phase 1	60	Endometrial Receptivity
NCT04126603	Recruiting	Phase 3	40	T2DM
NCT04825613	Temporarily not available	-	Primary Lateral Sclerosis	-
NCT04064983	No longer available	-	Polyneuropathies	-
NCT03339973	Terminated	Phase 1,2	24	Peripheral Arterial Occlusive Disease
NCT04825626	No longer available	-	Chronic Inflammatory Demyelinating Polyneuropathy	-
NCT05643638	Not recruiting	Phase 2	60	aGvHD
NCT04925024	Recruiting	Phase 2	38	Hypoplastic Left Heart Syndrome
NCT00821470	Completed	Phase 1	21	Necrosis
NCT02394873	Completed	Phase 1	5	Burn
NCT03645460	Unknown	Not Applicable	10	Adenosine De Aminase Severe Combined Immuno-Deficiency (ADA-SCID)
NCT01557543	Terminated	Phase 1	24	Heart Disease, Ischemic Heart Disease, Coronary Artery Disease, Coronary Artery Disease (CAD)
NCT02351011	Completed	Phase 1,2	12	Osteoarthritis of Knee
NCT02645305	Unknown	Phase 1,2	20	COPD
NCT04333368	Completed	Phase 1,2	47	Severe Acute Respiratory Syndrome Coronavirus 2, Severe Acute Respiratory Distress Syndrome
NCT02403232	Unknown	Phase 2	10	Perianal Fistula, Crohn Disease
NCT04522505	Active	-	7	Lupus Nephritis
NCT02676921	Completed	-	10	Sinus; Empyema, Maxillary
NCT03351868	Unknown	Not Applicable	10	Fanconi Anemia
NCT04576468	Completed	Not Applicable	40	Periodontal Diseases
NCT02654925	Completed	-	59	Obesity
NCT00705120	Completed	Phase 1	9	Osteogenesis Imperfecta
NCT04371393	Terminated	Phase 3	223	Acute Respiratory Distress Syndrome, COVID

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT03563495	Completed	Not Applicable	10	Cleft Lip and Palate
NCT02394886	Completed	Phase 1	5	Diabetic Foot Ulcer
NCT05154851	No longer available	-	Congenital Muscular Dystrophy	-
NCT05210452	Not recruiting	Phase 1,2	30	Alopecia
NCT02005861	Unknown	Not Applicable	140	Osteochondritis
NCT04524962	Recruiting	Phase 1,2	30	Acute Respiratory Distress Syndrome, Covid19
NCT04310215	Completed	Phase 3	102	Chondral or Osteochondral Lesion of Talus
NCT04716803	Recruiting	Not Applicable	10	Osteo Arthritis Knee
NCT03676569	Completed	Phase 1	6	Refractory Epilepsy
NCT02386163	Completed	-	6	Knee Injuries
NCT03183934	Unknown	-	5	Dystrophic Epidermolysis Bullosa
NCT05494723	Not recruiting	Phase 1	6	POI
NCT03497780	Recruiting	-	38	ACL - Anterior Cruciate Ligament Rupture, ACL Injury
NCT03961243	Unknown	Phase 1	10	Hemophilia B
NCT02831075	Unknown	Phase 1	240	Peripheral Vascular Disease, Ischemia, Diabetic Foot
NCT04261335	Active	Phase 1	9	Hypoxia-Ischemia, Brain
NCT04138017	Enrolling	Phase 4	15	Ankle Deformity, Ankle Arthritis
NCT03217032	Unknown	Phase 1	10	Hemophilia A
NCT03747822	Unknown	Phase 3	12	Patients With Deficient Chin
NCT02964143	Unknown	Not Applicable	306	Knee Osteoarthritis
NCT04746599	Recruiting	Not Applicable	20	Critical Limb Ischemia, Peripheral Arterial Disease-PAD, Ischemic Ulcer, Diabetic Foot, Scleroderma, Ischemic Leg
NCT04475341	Not recruiting	Not Applicable	96	Osteochondral Lesion of Talus
NCT03861650	Completed	Not Applicable	12	Hemifacial Microsomia, Distraction of Bone

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02779374	Terminated	Not Applicable	10	Premature Ovarian Failure
NCT03252340	Active	-	11	Atopic Dermatitis
NCT03269409	Terminated	Phase 1	8	Osteonecrosis
NCT05162326	Not recruiting	Phase 1	9	Nasolabial Fold Wrinkles
NCT03788265	Unknown	Not Applicable	60	Knee Osteoarthritis
NCT05243368	Not recruiting	Not Applicable	30	Diabetic Foot
NCT04569409	Unknown	Phase 3	104	Diabetic Foot Ulcer
NCT02622464	Completed	Not Applicable	8	Dysphonia
NCT03838146	Active	Not Applicable	160	Exercise
NCT05509673	Completed	Not Applicable	34	Wound Healing Disorder
NCT03856021	Unknown	Not Applicable	70	Osteochondral Lesion of Talus
NCT03183648	Active	-	30	Burn
NCT03183622	Completed	-	5	Burn
NCT04602442	Unknown	Phase 2	90	SARS-CoV-2 Pneumonia, COVID-19
NCT04491240	Completed	Phase 1,2	30	SARS-CoV-2 Pneumonia, COVID-19
NCT05447767	Recruiting	Phase 2	240	Knee Osteoarthritis
NCT03688308	Withdrawn	Not Applicable	0	Rotator Cuff Tear, Rotator Cuff Injury
NCT02720146	Unknown	-	10	Platelet- Cell and Animal Model
NCT02448849	Unknown	Phase 2,3	60	Bone Fracture
NCT03601234	Unknown	Not Applicable	80	Gastrointestinal Stromal Tumors
NCT01061879	Completed	-	8	Pregnancy
NCT05165628	Recruiting	Phase 1	30	Diabetic Foot Ulcer, Cutaneous Ulcer
NCT01926327	Completed	Phase 3	150	Osteoarthritis
NCT01846533	Unknown	-	1200	T2DM, Osteoporosis
NCT04990128	Not recruiting	Phase 3	100	Hip Osteoarthritis
NCT01747681	Completed	-	110	Articular Chondral Defect

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT05429710	Not recruiting	-	60	Urinary Bladder Neoplasm
NCT01152580	Completed	Phase 1	19	Osteoporosis, Osteopenia
NCT05092724	Not recruiting	Not Applicable	20	COVID-19 Acute Respiratory Distress Syndrome
NCT00644410	Completed	Phase 1,2	59	Congestive Heart Failure
NCT03048773	Completed	Not Applicable	40	Shockwave Therapy, Knee Osteoarthritis
NCT05274295	Recruiting	Not Applicable	5	Diabetic Foot Ulcer, Leg Ulcer, Adipose Stromal Vascular Fraction
NCT01932021	Unknown	Not Applicable	10	Skin Ulcer
NCT00496795	Active	Phase 2	100	Stage III Breast Cancer AJCC V7
NCT04864509	Not recruiting	Phase 4	40	Osteoporosis, Postmenopausal
NCT05193877	Recruiting	Not Applicable	60	Treatment Complication
NCT05677672	Not recruiting	Phase 1,2	84	Complex Perianal Fistulas
NCT05227547	Recruiting	Not Applicable	186	Chronic Obstructive Lung Disease, Chronic Obstructive Pulmonary Disease
NCT05019287	Completed	Phase 1,2	29	Covid19, Cytokine Storm
NCT05207995	Not recruiting	Phase 1,2	30	Diabetes Mellitus
NCT04976140	Enrolling	Phase 1,2	18	Polymyositis, Dermatomyositis
NCT02421484	Completed	Phase 1	9	Septic Shock
NCT03013049	Unknown	Not Applicable	40	Vitiligo
NCT04346680	Unknown	Not Applicable	6	Neurotmesis of Peripheral Nerve (Disorder)
NCT01805388	Withdrawn	Phase 1	0	Dental Pulp Regeneration
NCT05120726	Recruiting	Phase 4	20	Pyoderma Gangrenosum
NCT02926079	Completed	-	18	Pregnancy, Gestational Diabetes Mellitus
NCT03015623	Active	Phase 1,2	24	Acute Kidney Injury
NCT01435434	Unknown	Not Applicable	-	Non Union/Delayed Fractures
NCT01510431	No longer available	-	Crohn's Disease	-
NCT01602328	Terminated	Phase 2	156	Acute Kidney Injury
NCT05157958	Not recruiting	Phase 2	6	Dystrophic Epidermolysis Bullosa

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01413061	Completed	Not Applicable	140	Degenerative Osteoarthritis, Arthrosis, Rheumatoid Arthritis of Subtalar Joint
NCT01860495	Completed	-	15	Periodontal Pocket
NCT03747913	Completed	Not Applicable	18	Healthy
NCT02256241	Unknown	-	90	Trauma Operation, Primary Tumors of Mesenchymal Origin
NCT04179760	Recruiting	Phase 1,2	92	Dermatitis, Atopic
NCT04189432	Recruiting	Phase 2	77	Chronic Graft-*versus*-host-disease
NCT04189419	Completed	Phase 1,2	36	Pancreatitis, Acute
NCT05270850	Recruiting	Not Applicable	20	Benign Airway Stenosis, Respiratory Tract Fistula
NCT03643614	Completed	Phase 1	16	Rectovaginal Fistula
NCT04541680	Recruiting	Phase 3	250	SARS-Cov-2 Induced Pulmonary Fibrosis
NCT01221454	Unknown	Phase 2	60	Liver Failure
NCT01223664	Unknown	Phase 2	60	Liver Cirrhosis
NCT03096782	Completed	Phase 2	6	Chronic Myelogenous Leukemia, Acute Biphenotypic Leukemia, Acute Lymphoblastic Leukemia, Myelodysplastic Syndrome
NCT05403164	Recruiting	-	80	Periodontitis, Periodontal Diseases, Gram-Negative Bacteria
NCT03696485	Not recruiting	Phase 1,2	12	Secondary Progressive Multiple Sclerosis (SPMS)
NCT04310852	Unknown	-	25	Knee Osteoarthritis, Cartilage Degeneration
NCT03715374	Completed	Not Applicable	60	Periodontal Attachment Loss, Periodontal Bone Loss, Periodontal Diseases
NCT03197623	Completed	Phase 1	58	Osteopenia, Osteoporosis, Osteonecrosis
NCT03470415	Unknown	-	100	Type2 Diabetes Mellitus
NCT04759105	Recruiting	Phase 2	52	Intervertebral Disc Degeneration, Chronic Low-back Pain
NCT05651997	Not recruiting	Not Applicable	80	Articular Cartilage Defect, Chondral Defect, Osteochondritis
NCT03060551	Completed	Early Phase 1	20	Systemic Sclerosis

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02890537	Completed	Phase 2	82	Avascular Necrosis of Femur Head
NCT04557514	Not recruiting	Not Applicable	60	Burn Scar
NCT03582800	Recruiting	Phase 2	40	Systemic Sclerosis, Dermatomyositis, iPPSD2
NCT02886884	Completed	Phase 1,2	16	T2DM
NCT04735185	Suspended	Not Applicable	106	Chronic Low Back Pain, Degenerative Disc Disease
NCT01529008	Terminated	Phase 3	68	Osteonecrosis of the Femoral Head
NCT04750499	Recruiting	Not Applicable	12	Anal Fistula
NCT03555357	Unknown	Not Applicable	10	Abdominoplasty Scar Revision
NCT03618784	Completed	Phase 1,2	33	Rheumatoid Arthritis
NCT04749758	Completed	Not Applicable	66	Knee Osteoarthritis
NCT03913910	Unknown	-	100	Perianal Fistula
NCT02566681	Unknown	Phase 1	10	Osteonecrosis of Jaw
NCT00562497	Completed	Phase 3	192	GvHD
NCT03410355	Terminated	Not Applicable	6	Osteoarthritis, Hip
NCT01297413	Completed	Phase 1,2	38	Ischemic Stroke
NCT03276312	Completed	Not Applicable	112	Diabetic Foot
NCT05497401	Not recruiting	Phase 3	300	Covid-related Pneumonia
NCT04453111	Unknown	Phase 1,2	45	Knee Osteoarthritis
NCT01298830	Terminated	Phase 1,2	11	Intracerebral Hemorrhage (ICH)
NCT02859025	Completed	Phase 1	10	Cleft of Alveolar Ridge
NCT02646007	Unknown	Phase 1	30	Kienböck's Disease
NCT00927355	Completed	Not Applicable	10	Osteoblast, Adipocytes, Bone Density, Osteocalcin, Adiponectin
NCT02145923	Unknown	Phase 1,2	16	Neutropenic Enterocolitis, Myeloablative Chemotherapy Induced Bone Marrow Aplasia
NCT04907188	No longer available	-	Stroke, Stroke, Ischemic	-
NCT04746586	Recruiting	-	30	Adolescent Idiopathic Scoliosis
NCT00629096	Completed	Phase 2	27	Dilated Cardiomyopathy

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT04105569	Completed	Not Applicable	6	Gingivitis
NCT01071577	Completed	-	65	Bone Marrow Stromal Cells
NCT03629002	Unknown	-	30	Systemic Scleroderma
NCT05660824	Not recruiting	Phase 4	195	Tendinopathy, Osteoarthritis
NCT05120700	Not recruiting	Phase 1,2	10	Cell- and Tissue-Based Therapy, Cartilage Injury, Knee Injuries
NCT04980261	Recruiting	Not Applicable	32	Bone Loss
NCT02165904	Completed	Phase 1	10	Spinal Cord Injury
NCT00815217	Unknown	Not Applicable	250	Diabetic Wounds, Venous Stasis Wounds
NCT02859415	Terminated	Phase 1,2	3	Esophageal Neoplasms, Lung Neoplasms, Mesothelioma, Thymus Neoplasms, Neoplasms
NCT04466098	Active	Phase 2	9	Acute Respiratory Distress Syndrome, ARDS, COVID-19 Pneumonia
NCT04695522	Unknown	Phase 1	6	D017202
NCT04685577	Recruiting	Phase 2	60	Second- or Third-Degree Burn
NCT04043819	Unknown	Phase 1	125	Knee Osteoarthritis
NCT03211793	Recruiting	Phase 1,2	20	Systemic Sclerosis, Digital Ulcer
NCT05330416	Recruiting	Not Applicable	108	Crohn Disease
NCT00790413	Active	Early Phase 1	15	Neuroblastoma
NCT00081055	Withdrawn	Phase 2	0	GvHD, Leukemia, Myelodysplastic Syndromes
NCT05081921	Recruiting	Phase 1,2	200	Osteoarthritis of Knee
NCT04132076	Unknown	-	200	Osteochondral Lesion of Talus, Ankle Arthritis
NCT01270139	Completed	Not Applicable	180	Stable Angina, Heart Failure, Atherosclerosis, Multivessel Coronary Artery Disease

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT03011541	Recruiting	Not Applicable	500	Age-Related Macular Degeneration, Retinitis Pigmentosa, Stargardt Disease, Optic Neuropathy, Nonarteritic Ischemic Optic Neuropathy, Optic Atrophy, Optic Nerve Disease, Glaucoma, Leber Hereditary Optic Neuropathy, Blindness, Retinopathy, Maculopathy, Macular Degeneration, Retina Atrophy
NCT01920867	Unknown	Not Applicable	300	Macular Degeneration, Hereditary Retinal Dystrophy, Optic Nerve Disease, Glaucoma
NCT01739504	Terminated	Not Applicable	10	Osteoarthritis
NCT01544712	Completed	Not Applicable	50	Non Traumatic Osteonecrosis of the Femoral Head
NCT02849613	Withdrawn	Phase 2,3	0	Stroke
NCT02807389	Completed	Phase 1	2	Surgical Leak Fistula
NCT04445220	Active	Phase 1,2	22	COVID-19, Acute Kidney Injury, Sepsis
NCT04007081	Completed	Not Applicable	12	Xerostomia, Head and Neck Cancer
NCT01771913	Completed	Phase 2	20	Breast Reconstruction, Contour Irregularities, Volume Insufficiency
NCT04961658	Recruiting	Phase 1	21	Septic Shock
NCT03220243	Completed	Phase 1	5	Fistula Vagina, Crohn Disease
NCT02802384	Active	-	11	Paget's Disease of Bone
NCT03296501	Unknown	Phase 1	30	Amyotrophic Lateral Sclerosis
NCT05602116	Not recruiting	Phase 1	10	Autism Spectrum Disorder, Gastrointestinal Dysfunction, Leaky Gut Syndrome , Inflammatory Bowel Diseases
NCT02829216	Unknown	-	50	Abnormal Hematopoiesis, Allogenic Disease, GvHD
NCT02000362	Unknown	Phase 1,2	24	Crohn's Disease
NCT04847739	Recruiting	Phase 2	60	Perianal Fistula, Crohn's Disease
NCT02926300	Unknown	-	24	Crohn's Disease
NCT04341610	Withdrawn	Phase 1,2	0	Respiratory Tract Diseases
NCT02328612	Completed	Phase 1	32	Sepsis

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT04222140	Unknown	Not Applicable	40	Post-Traumatic Osteoarthritis of Knee
NCT04223622	Recruiting	-	24	Osteoarthritis
NCT02037204	Completed	Phase 1,2	35	Foreign-Body Reaction, Inflammation, Effusion Knee, Knee Pain Swelling
NCT02323477	Terminated	Phase 1,2	46	Chronic Ischemic Cardiomyopathy, Coronary Artery Bypass Surgery
NCT02742844	Terminated	Phase 1,2	13	Skin Ulcer Venous Stasis Chronic
NCT02209311	Unknown	Phase 1,2	12	Partially Edentulous Maxilla, Alveolar Bone Atrophy, Alveolar Bone Loss
NCT02918123	Unknown	Phase 1	9	Psoriasis
NCT04137562	Recruiting	Phase 2	118	Atopic Dermatitis
NCT03079401	Active	Phase 1,2	19	Hypoplastic Left Heart Syndrome, Atrioventricular Canal
NCT00512434	Completed	Not Applicable	85	Tibial Fractures, Fractures
NCT03753711	Completed	Not Applicable	30	Lumbar Disc Herniation
NCT02589119	Completed	Phase 1	15	Perianal Fistula, Cryptoglandular Perianal Fistula
NCT03298399	Withdrawn	Phase 1	0	Sickle Cell Disease
NCT02372474	Completed	Phase 1,2	112	Premature Ovarian Failure
NCT01624701	Terminated	Phase 1,2	3	Acute Leukemia, Chronic Leukemia, Myelodysplastic Syndrome, Lymphoma, Myeloma
NCT04723303	Recruiting	Early Phase 1	22	Polymyositis, Dermatomyositis
NCT03381326	Active	-	94	Prostate Cancer, Metastatic Cancer, Castration-resistant Prostate Cancer
NCT03298763	Recruiting	Phase 1,2	46	Adenocarcinoma of Lung
NCT01915927	Completed	Phase 1	20	Perianal Crohn's Disease
NCT04629833	Recruiting	Phase 3	210	Steroid-refractory aGvHD
NCT03113747	Unknown	Phase 1,2	20	Second- or Third-degree Burns
NCT04400032	Completed	Phase 1,2	15	Acute Respiratory Distress Syndrome, Covid19
NCT03608579	Recruiting	Phase 1	24	Osteoarthritis, Hip
NCT02630836	Withdrawn	Phase 1,2	0	Femoral Neck Fracture

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT02525432	Enrolling	Phase 2	55	Brain Injuries, Traumatic, Brain Injuries, Acute, TBI (Traumatic Brain Injury)
NCT01585857	Completed	Phase 1	18	Osteoarthritis
NCT03295292	Unknown	Phase 1	15	Corneal Scars and Opacities
NCT01290367	Completed	Phase 2	100	Degenerative Disc Disease
NCT03233074	Recruiting	-	150	Myelodysplastic Syndromes, Acute Myeloid Leukemia, Cardio-vascular Surgery
NCT02052908	Completed	Phase 1	81	Lynch Syndrome
NCT02240823	Unknown	Phase 1	30	Delayed Graft Function
NCT00135850	Completed	Phase 1,2	48	Ischemic Heart Disease
NCT04255147	Not recruiting	Phase 1	9	Bronchopulmonary Dysplasia
NCT00731744	Unknown	Not Applicable	50	Normal Full-Term Deliveries
NCT02838069	Active	Phase 2	100	Osteoarthritis
NCT03828123	Completed	Phase 1,2	26	Motor Neuron Disease, Amyotrophic Lateral Sclerosis
NCT02382874	Unknown	Phase 1	5	Focal Segmental Glomerulosclerosis
NCT00957931	Completed	Phase 2	6	Sickle Cell Disease, Thalassemia, Diamond-Blackfan Anemia
NCT03449069	Recruiting	Phase 1	5	Fistula in Ano, Crohn Disease
NCT05523011	Completed	Phase 1	10	Psoriasis
NCT02103452	Completed	Not Applicable	80	Ovarian Endometriosis
NCT02336230	Completed	Phase 3	55	Grade B, Grade C, Grade D aGVHD
NCT01460901	Completed	Phase 1	5	Neuroblastoma
NCT04918706	Recruiting	Phase 2	30	Pulmonary Emphysema
NCT01436123	Terminated	Phase 1	62	Coronary Artery Disease, Atherosclerosis
NCT03918655	Active	-	186	Acute Myeloid Leukemia
NCT04089579	Active	Phase 2	164	Autism, Autism Spectrum Disorder
NCT01038596	Completed	-	30	Osteoarthritis
NCT05286255	Recruiting	Phase 1	10	COVID-19 Pneumonia, Viral Pneumonia
NCT00927784	Terminated	Phase 2	10	Heart Failure

(Table 1) cont.....

NCT No.	Status	Phases	Enrollment	Diseases
NCT01777646	Completed	Phase 2	14	Amyotrophic Lateral Sclerosis
NCT02688114	Enrolling	Not Applicable	20	Barrett Esophagus
NCT01781390	Completed	Phase 2	106	Acute Myocardial Infarction
NCT05348772	Not recruiting	Phase 1	18	COVID-19
NCT02619734	Unknown	Phase 1	40	Chronic Leg Ulcer, Sickle Cell Disease
NCT00810212	Withdrawn	Phase 1,2	0	Degenerative Disc Disease, Degenerative Spondylolisthesis, Spinal Stenosis
NCT01861054	Terminated	Phase 2	20	Breast Cancer
NCT00549913	Completed	Phase 1,2	6	Degenerative Disc Disease, Spondylolisthesis, Spinal Stenosis
NCT02412462	Completed	Phase 1	15	Solid Tumor, Metastatic Cancer
NCT01051882	Completed	Phase 1,2	12	Amyotrophic Lateral Sclerosis
NCT02001974	Completed	Phase 1	33	Metastatic Breast Cancer
NCT03473301	Completed	Phase 1,2	91	Cerebral Palsy
NCT02448121	Unknown	Phase 1,2	100	Avascular Necrosis of Bone, Sickle Cell Disease
NCT02032004	Completed	Phase 3	566	Chronic Heart Failure
NCT03973827	Active	Phase 1,2	15	Type1diabetes

For respiratory system diseases, MSCs are being explored in numerous lung and bronchial lesions, including bronchopulmonary dysplasia, pulmonary alveolar proteinosis(PAP), dysphonia, emphysema, asthma, pneumoconiosis, adult respiratory distress syndrome, acute respiratory distress syndrome (ARDS), idiopathic pulmonary fibrosis (IPF), coronavirus disease 2019 (COVID-19)-associated acute lung injury (ALI), and chronic obstructive pulmonary disease (COPD).

For diseases of the digestive system, MSCs are being tested in clinical trials for numerous diseases, such as Crohn's disease (CD), colorectal neoplasms, Barrett esophagus, esophageal neoplasms, familial hypercholesterolemia, inflammatory bowel diseases (IBD), ulcerative colitis (UC), acute-on-chronic liver failure (ACLF), primary biliary cirrhosis, liver cirrhosis, and alcoholic liver cirrhosis.

Meanwhile, MSCs have been employed for multitudinous immunological disorders management, including epidermolysis bullosa dystrophica, psoriasis, multiple sclerosis (MS), recessive dystrophic epidermolysis bullosa, residual burn wound, systemic scleroderma (SS), systemic lupus erythematosus (SLE), adenosine De aminase severe combined immuno-deficiency (ADA-SCID), hereditary ataxia, rheumatoid arthritis (RA), multiple organ dysfunction syndrome (MODS), and obesity.

For diseases of the reproductive system, MSCs have been used to improve the outcomes of the enrolled cases, such as Asherman syndrome, ovarian endometriosis, ovarian neoplasms, metastatic breast cancer, non-obstructive azoospermia, primary ovarian insufficiency (POI), premature ovarian failure (POF), thin endometrium, intrauterine adhesion, fallopian tube obstruction, male sexual dysfunction, ovarian cancer, erectile dysfunction, and female infertility.

For diseases of the movement system, MSCs of different origins are also reported for disease administration in numerous clinical trials, including osteoarthritis, motor neuron disease (MND), anterior cruciate ligament rupture, articular chondral defect, chronic meniscal injury, osteogenesis imperfecta, cartilage injury, Achilles tendinitis, lateral epicondylitis, osteochondritis of the femoral head, tibial fracture, Duchenne muscular dystrophy, amyotrophic lateral sclerosis (ALS), and lateral epicondylitis.

For hematological disorders and malignancies, MSCs have been extensively explored for symptom remission and hematopoietic reconstruction, such as graft-*versus*-host disease (GvHD), sickle cell disease (SCD), Thalassemia, Diamond-Blackfan anemia (DBA), acute Lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS), myelofibrosis, relapsed non-Hodgkin Lymphoma (NHL), refractory Hodgkin lymphoma, relapsed chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), multiple myeloma (MM), severe aplastic anemia (SAA), hemophilia, and thrombocytopenia.

Similarly, numerous clinical trials have also been registered for the management of circulation system diseases, including dilated cardiomyopathy, Buerger's disease, peripheral artery disease (PAD), intracerebral hemorrhage (ICH), ST-segment elevation myocardial infarction (STEMI), cerebral artery infarction (CAI), venous leg ulcer, ischemia-reperfusion injury, ischemic cardiomyopathy, critical limb ischemia (CLI), chronic myocardial ischemia (CMI), and coronary disease.

Finally, for the nervous system diseases, MSC-based regiments have been introduced in a large amount of clinical trials, such as spinal cord injury (SCI),

autism spectrum disorder (ASD), polyneuropathies, medulloblastoma, neuroblastoma, Huntington's disease, frontotemporal dementia, amyotrophic lateral sclerosis (ALS), ankylosing spondylitis, stroke, traumatic brain injury (TBI), brachial plexus neuropathies, Alzheimer's disease (AD), cerebral Palsy (CP), cerebral infarction, hypoxic ischemic Eencephalopathy (HIEH), Parkinson's disease (PD), and spinocerebellar ataxia. Taken together, MSC-based cytotherapy has become a promising medical therapeutic for conquering the numerous refractory and recurrent diseases and vastly facilitating the progression of MSC-based regenerative medicine.

THE STANDARDIZATION AND INDUSTRIALIZATION OF MSCS

As mentioned above, the heterogeneity of MSCs results in variations in their biological properties and the concomitant biofunction and therapeutic effects for regenerative purposes. Meanwhile, as reported by Zhang *et al.* and Zhao *et al.*, MSCs of different origins and passages revealed multifaceted conservations and variations in the cellular vitality (*e.g.*, proliferation, cell cycle, and apoptosis), biofunction (*e.g.*, hematopoietic-supporting effect, tri-lineage differentiation towards adipocytes, osteoblasts, and chondrocytes) and the transcriptomic characteristics (*e.g.*, proto-oncogenes, genetic mutations), which were of great importance for the outcomes of mice with ALF and aGvHD, respectively [2].

For this purpose, investigators in the field are devoted to verifying the detailed information and the standards for facilitating the MSCs-based cytotherapy, which are the prerequisites for large-scale clinical application and industrial transformation. Firstly, longitudinal studies have indicated the necessity of stem cell banks and the relevant indicators for MSC seed preservation and the concomitant large-scale preparation. For example, the recommended standards are cell number, cellular vitality (*e.g.*, proliferation, cell cycle, apoptosis), sterility and pathogenic microorganism (*e.g.*, hepatitis B virus, human immunodeficiency virus, cytomegalovirus, syphilis), and the source preparation (*e.g.*, collection, preservation, and transportation of perinatal tissues, dissociation and enrichment of primary "seeding cells" with culture medium and indicated cytokines, raw materials) [2]. Secondly, the establishment of standard operating procedure (SOP) for laboratories and manufacturing, including quality assurance (QA) (*e.g.*, process parameters, quality standards for product inspection), quality control (QC) (*e.g.*, quality system supervision, quality inspection of the production department, amendments of the product inspection specification, control plan, process parameter identification), and good laboratory practice (GLP). Thirdly, the establishment of constructive guidelines for safety and efficacy evaluation in preclinical practice (*e.g.*, drug toxicity, long-term toxicity test, pharmacokinetic experiment).

Fourthly, the clinical research plans should take all things into consideration including the therapeutic regimen (*e.g.*, inclusion and exclusion criteria, persons in charge, clinical examinations, emergency measures, treatment, and nursing), ethical risk, good clinical practice (GCP), the outcomes (*e.g.*, primary evaluation index, secondary evaluation index, acute and chronic adverse reactions), and indemnifying measures (*e.g.*, clinical trial associated business insurance and subsidies). Fifthly, the manufacturing systems for large-scale industrialization are also necessary, such as good manufacturing practices (GMP), ISO certification, and the criteria for the quality control of drug manufacturing, together with good manufacturing practices (GMP) for the collection, processing, manufacturing, and storage of MSCs and the components (*e.g.*, exosomes, small extracellular vesicles).

Additionally, more advanced technologies for developing the next generation of MSCs production are also necessary and promising. For instance, Du *et al.* and Wei *et al.* reported the unique attributes of vascular cell adhesion molecule 1 (VCAM-1) positive CV-MSCs and UC-MSCs in pro-angiogenesis and immunomodulation over the VCAM-1- counterparts, which indicated the feasibility of generating specific subpopulations with particular usefulness [16, 17]. Collectively, these indicated aspects will benefit the further exploration of standardizations for MSC product development and the MSC-based regiments in both preclinical and clinical practice in the future.

CONCLUSION

Overall, MSCs of different origins display multidimensional properties and biofunctions in both preclinical investigations and clinical applications worldwide based on extensive explorations. For a better understanding of the multifaceted signatures and underlying molecular mechanisms, the systematic and detailed dissection of the subpopulations and standardization of MSCs with advanced technologies and novel functional analyses will congruously benefit the development of MSC-based cell products and therapeutic regiments in the future.

LIST OF ABBREVIATIONS

PSCs	Pluripotent Stem Cells
ESCs	Embryonic Stem Cells
iPSCs	Induced Pluripotent Stem Cells
MSCs	Mesenchymal Stem/Stromal Cells
ASCs	Amniotic Stem Cells
AA	Aplastic Anemia
ALL	Acute Lymphoblastic Leukemia

GvHD	Graft-*Versus*-Host Disease
AMI	Acute Myocardial Infarction
POF	Premature Ovarian Failure
PD	Parkinson's disease
AD	Alzheimer's disease
SCI	Spinal Cord Injury
OA	Osteoarthritis
ONFH	Osteonecrosis of the Femoral Head
CLI	Critical Limb Ischemia
COPD	Chronic Obstructive Pulmonary Disease
AR	Anaphylactic Rhinitis
ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
AD	Allergic Dermatitis
SS	Systemic Sclerosis
SLE	Systemic Lupus Erythematosus
RA	Rheumatoid Arthritis
ACLF	Acute-On-Chronic Liver Failure
CD	Crohn's disease
UC	Ulcerative Colitis
BM-MSCs	Bone Marrow-Derived Mscs
UC-MSCs	Umbilical Cord-Derived Mscs
HPCs	Hematopoietic Progenitor Cells
HSCT	Hematopoietic Stem Cell Transplantation
aGvHD	Acute Graft-*versus*-host Disease
cGvHD	Chronic GvHD
ALF	Acute Liver Failure
CV-MSCs	Chorionic Villi-Derived Mscs
GMP	Good Manufacturing Practices
CSSCR	Chinese Society for Stem Cell Research
HSPCs	Haematopoietic Stem/Progenitor Cells
IND	Investigational New Drug
QC	Quality Control
CCl4	Carbon Tetrachloride
HSCs	Hematopoietic Stem Cells

MSC-exo	MSCs-Derived Exosomes
MSC-sEVs	MSCs-derived Small Extracellular Vesicles
MLC	Mixed Lymphocyte Culture
MNCs	Mononuclear Cells
CAFC	Cobblestone Area-Forming Cell
AD-MSCs	Adipose Tissue-Derived Mscs
DPSCs	Dental Pulp-Derived Mscs
P-MSCs	Placenta-Derived Mscs
PSC-MSCs	Pluripotent Stem Cell-Derived Mscs
NCSCs	Neural Crest Stem Cells
hESCs	Human Embryonic Stem Cells
EB	Embryoid Body
3D	Three Dimensional
NCC	Neural Crest Cell
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
ESRD	End-Stage Renal Disease
CKD	Chronic Kidney Diseases
SUI	Stress Urinary Incontinence
AKI	Acute Kidney Injury
ARDS	Acute Respiratory Distress Syndrome
IPF	Idiopathic Pulmonary Fibrosis
COVID-19	Coronavirus Disease 2019
ALI	Acute Lung Injury
COPD	Chronic Obstructive Pulmonary Disease
IBD	Inflammatory Bowel Diseases
ACLF	Acute-on-Chronic Liver Failure
MS	Multiple Sclerosis
ADA-SCID	Adenosine de Aminase Severe Combined Immuno-Deficiency
RA	Rheumatoid Arthritis
MODS	Multiple Organ Dysfunction Syndrome
POI	Primary Ovarian Insufficiency
POF	Premature Ovarian Failure
MND	Motor Neuron Disease
ALS	Amyotrophic Lateral Sclerosis

GvHD	Graft-*versus*-Host disease
SCD	Sickle Cell Disease
DBA	Diamond-Blackfan Anemia
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myelogenous Leukemia
MDS	Myelodysplastic Syndromes
NHL	Non-Hodgkin Lymphoma
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myelogenous Leukemia
MM	Multiple Myeloma
PAD	Peripheral Artery Disease
ICH	Intracerebral Hemorrhage
STEMI ST	Segment Elevation Myocardial Infarction
CAI	Cerebral Artery Infarction
CMI	Chronic Myocardial Ischemia
SCI	Spinal Cord Injury
ASD	Autism Spectrum Disorder
ALS	Amyotrophic Lateral Sclerosis
TBI	Traumatic Brain Injury
CP	Cerebral Palsy
HIEH	Hypoxic Ischemic Eencephalopathy
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
GCP	Good Clinical Practice
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure

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CHAPTER 6

Stem Cells-Based Technological Innovation in Tissue Engineering

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Abstract: Stem cells are a category of cells with self-renewal and multi-lineage differentiation capacity, which have been recognized as advantaged sources for tissue engineering and regenerative medicine. To date, stem cells and their derivatives alone or combined with biomaterials have aroused extensive and sustained attention to investigations in the field of fundamental research and clinical practice. In recent years, a series of novel technologies have been involved in stem cell-based cytotherapy, such as three-dimensional (3D) printing, organoid research, and multitudinous kinds of gene-editing technologies, which collectively facilitate the development of tissue engineering for disease administration. In this chapter, we summarized the rudimentary knowledge of the aforementioned new technologies, together with the promising perspective and the concomitant challenges, which would help increase the cognition of technological innovation for stem cell-based investigations and remedies in the future.

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INTRODUCTION

Stem cells of various origins in the niche, including those from the embryonic stage and the adult tissues, are a unique cell population with self-renewal and multi-lineage differentiation [1, 2]. Due to the abovementioned properties, stem cells can be divided into pluripotent stem cells (PSCs, including embryonic stem cells and induced PSCs), perinatal stem cells (*e.g.*, umbilical cord-, amniotic membrane-, amniotic fluid-, and placenta tissue-derived stem cells), and adult stem cells (*e.g.*, dental pulp-, apical papilla-, adipose tissue-, bone marrow-, and muscle tendon-derived stem cells) [3 - 5]. Of them, hematopoietic stem cells (HSCs) and mesenchymal stem/stromal cells (MSCs) function critically in hematogenesis and immunomodulation, respectively, which have been explored with the widest range of clinical applications for numerous refractory and recurrent disease management, such as hematologic disorders and malignancies (*e.g.*, acute myeloid leukemia, acquired aplastic anemia, multiple myeloma, myelodysplastic syndrome, acute lymphocytic leukemia), degenerative diseases (*e.g.*, Parkinson's disease, Alzheimer's disease, osteoarthritis, meniscus injury), and diseases associated with immune abnormalities (*e.g.*, rheumatoid arthritis, systemic lupus erythematosus, allergic asthma, graft-versus-host disease) [6 - 11].

In recent years, novel stem cell-based technologies have continuously emerged and further accelerated the development of concomitant cytotherapy and regenerative medicine [12 - 14]. To date, we and other investigators in the field are devoted to developing a variety of advanced technologies, including organoid, gene editing, three-dimensional (3D) printing, *in vivo* fluorescence tracer, and single cell sequencing, which conformably reveal promising prospective and vastly facilitate tissue engineering in combination with stem cells [15 - 20]. For example, Kim and colleagues summarized the application of 3D stem cell systems for tissue repair and regeneration, including the 3D stem cell spheroids and the 3D stem cell organoids for mimicking the *in vivo* environments [15]. In the chapter, we described the concepts and the instances of the aforementioned revolutionary technology in stem cell-based approaches for regenerative purposes.

THREE-DIMENSIONAL (3D) PRINTING

3D printing has emerged as an exciting branch of manufacturing technology by fusing single or varied materials together in a layer-by-layer manner for the construction of an integrated 3D product [21 - 23]. Therefore, compared with the traditional manufacturing process, 3D printing based on stem cells and appropriate biomaterials offers high flexibility in the design and preparation of personalized and off-the-shelf medical production that accommodate the needs of patients, which thus transforms the way of stem cell-based tissue engineering [18, 23]. For instance, 3D bioprinting products including the instrumentation and implants have indicated transformative bone and cartilage restoration procedures for treating inpatients with varying degrees of musculoskeletal injuries by combing orthopaedic surgery with stem cell-based medicine [23].

During the past decades, 3D bioprinting and additive manufacturing have achieved rapid development with decreasing costs due to the progress in new common printing methods, material synthesis, and education of patients and trainees [24, 25]. For example, the injectable conductive hydrogels have been considered an ideal biomaterial for 3D bioprinting and tissue engineering scaffolds, which are adequate to facilitate the communication of specific electrical signals among cells and thus simulate the physiological or pathological microenvironment of electroactive tissues [18]. To date, 3D bioprinting has been involved in a variety of refractory and recurrent disease management as well as multifaceted regenerative purposes, such as otorhinolaryngology, urology, spine surgery, the retina, minimally invasive cardiac surgery, orbital diseases, the reconstruction of congenital defects, orbital trauma, cardiovascular diseases, and tumor resection [22, 24, 26 - 29]. Collectively, 3D bioprinting has been employed in a series of surgical and medical specialties for the improvement of advanced resident physician training and the concomitant patient care [30].

ORGANOID

Organoids are three-dimensional (3D) ex vivo culture systems generated from self-organizing stem cells, which are 3D structures comprised of diverse cell types and self-organized to recapitulate and mimic the spatio-temporal processes of embryonic and tissue development *in vitro* [31 - 33]. Different from the two-dimensional (2D) culture methods, the 3D organoids with favorable architecture and microenvironment reveal multifaceted advantages of stem cell maintenance and differentiation, conducting high-throughput pharmaceutical screening, as well as mirroring architecture, functionality, and geometric properties of tissues *in vivo* [32]. Generally, organoids can be derived from various kinds of stem cells including human embryonic stem cells (hESCs) and patient-derived human

induced pluripotent stem cells (hiPSCs), which thus can fulfill the demands of mimicking human development and disease [16].

To date, remarkable progressions of organoid technology have been achieved over the past decade [34]. Currently, a variety of novel organoid technologies have been developed to control the processes involved in the process of organoid development, which efficiently meet the growing demand for constructing dynamic niches that resemble the dynamic procedures *in vivo* organogenesis to produce reliable and reproducible organoids for various clinical applications in future [35]. For example, Yi *et al*. reviewed the technological advances in organoid research and engineering, including the advanced engineering-based approaches and the innovative biomaterial-based and approaches, genetic modulation, and extracellular matrices [35]. Notably, Wu and the colleagues took advantage of the hPSC-derived kidney organoid and single-cell transcriptomics for the identification of the multifaceted transcriptomic networks related to fate decisions, and in particular, the biofunction of brain-derived neurotrophic factor (BDNF) and the receptor neurotrophic Receptor Tyrosine Kinase 2 (NTRK2) expressed in multiple neuronal lineage during the kidney organoid differentiation [36]. These abovementioned organoid models provide an excellent and powerful platform for systematically and meticulously elucidating the developmental processes, modeling diseases, underlying molecular mechanisms, and screening drug candidates [35].

Nowadays, organoid technology has been involved in modeling human physiological and pathological organ development 'in a dish", together with predicting candidate drug responses in a personalized fashion [37]. For instance, Qian and the colleagues highlighted current advances in brain organoid methodologies and compared them with embryonic human brain in mimicking multifaceted key features of the early brain development from the aspects of cellular, structural, molecular, and functional levels, together with brain development [38]. Instead, Chen *et al*. summarized the latest updates of organoids as an advantaged model for recapitulating pancreatic cancer, and supplied a new hope for guiding clinical practice, preclinical drug screening, and improving patient prognosis as well [39].

Currently, a variety of platforms have been developed for the construction of organoids, including the organ-on-a-chip systems on the basis of cell biology, microfluidics, and tissue engineering, which have been designed as a multiplex platform for automating the culture of individual organoids in distinct microenvironments [40, 41]. In the near future, organoid will hopefully facilitate the personalized medical decisions and profoundly improve patient outcomes by replacing the irreversibly and progressively diseased organs [17, 34, 42, 43].

Collectively, stem cell-based organoids are promising models for organ development, disease remodeling, drug discovery, and stem cell-based regenerative medicine [34, 44]. Organoid research will provide a wide range of preclinical and clinical applications such as organogenesis, stem cell biology, hereditary diseases, and host cell-microorganism interactions.

GENE EDITING AND STEM CELL-BASED GENE THERAPY

Gene-editing techniques based on the precise manipulation of cellular DNA sequences for specific organism traits and cell fates have acquired long-grown progress in the past decades [45 - 47]. For example, genome editing by utilizing the transcription activator-like effector nucleases (TALENs) and zinc finger nucleases (ZFNs) has reached a certain amount of clinical trials [48]. In recent years, the clustered regularly interspersed short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) system has shown preferable prospect in both preclinical and clinical application [12, 49]. For example, Maganti *et al*. summarized the role of CRISPR/Cas9 gene editing in improving the chimeric antigen receptor-transduced T (CAR-T) cell therapy for cancer treatment, including acute leukemia, glioma, melanoma and relative cancers [50]. Similarly, we recently reviewed the preclinical and clinical investigations in chimeric antigen receptor-transduced natural killer (CAR-NK) cells for adoptive cancer immunotherapy as well [51, 52]. Interestingly, Mo *et al*. put forward the latest renewal of deoxyribonucleic acid (DNA) hydrogel-based gene editing as drug delivery systems, together with the non-biological and biological stimuli as well, which collectively highlighted the promising prospects for combining gene editing toolbox with DNA hydrogels for tissue engineering and regenerative purposes [53].

In the past decades, we and other investigators in the field took advantage of various gene-editing technologies for understanding the biofunction and underlying molecular mechanisms of multiple candidate genes. For instance, with the aid of the Lenti-X™ Tet-On Advanced Inducible Expression System for the inducible overexpression of muscle segment homeobox 2 (MSX2), programming effect on initiating hPSCs differentiation towards mesendoderm was verified [5]. Furthermore, we respectively verified the initiating and/or accelerating effect of MSX2 and thrombopoietin (TPO) in MSC specification and platelet generation of hPSCs by conducting CRISPR/Cas9-based gene knock-out and gene knock-in, which would benefit the large-scale and cost-effective preparation of therapeutic-scale cell production from stem cells in future [3, 54]. As reviewed by Chen and the colleagues, the multidimensional opportunities and challenges of CRISPR-Cas9-based cancer therapy should be paid enough attention before large-scale clinical practices, such as delivery methods, editing efficiency, fitness of edited

cells, and potential off-target effects as well [55, 56]. It is noteworthy that state-of-the-art literatures have also put forward the feasibility and practice of CRISPR/Cas9-based *in vivo* therapeutics mediated by lipid nanoparticles (LNPs) as delivery approaches and novel remedies, which would tremendously accelerate the stem cell-based tissue engineering [14, 57 - 59].

IN VIVO FLUORESCENT TRACER

In recent years, investigators in the field of stem cells have aroused great interest in the fluorescent tracer system for understanding the early embryonic development, lineage differentiation, and spatio-termporal alterations of the transplanted cells [60 - 62]. For instance, with the aid of the fluorescence reflectance imaging (FRI), Satkunananthan and the colleagues verified the feasibility of *in vivo* imaging of diverse contents such as protease activity, MMP (matrix metalloproteinase) activity, and cathepsin K activity in post-traumatic osteoarthritis (PTOA) mice for up to 56 days in the body, which provided vital details about the variations in biological activity and inflammation following joint injury [63]. Notably, Heront *et al*. summarized the latest advances in molecular tracers in near-infrared spectrum for fluorescence image-mediated oncological surgery based on the ongoing clinical trials, preclinical investigations, and the latest developments of therapeutic antibodies and fluorescent dyes (*e.g.*, DiR, ^{111}indium-DTPA) [64].

To date, a variety of methods have been developed for accurate and efficient *in vivo* fluorescent tracer of transplanted stem cells and small extracellular vesicles (sEVs) biodistribution, including fluorescent, radioactive, microlymphatics, and bioluminescent tracers (*e.g.*, mCherry, Firefly and NanoLuc luciferase) [65 - 68]. Of them, the aforementioned DiR and ^{111}indium-DTPA have been recognized as the most sensitive tracers for sEVs imaging, which provide with the precise quantification of ex vivo analysis of tissue lysates and *in vivo* physiological biodistribution of sEVs [65]. For example, Devraj and the colleagues reported the feasibility of fluorescently labeled tracers for blood-brain barrier (BBB) permeability analysis in mice [69]. Recently, we took advantage of the firefly and nanoLuc luciferase-based dual fluorescent tracer, and verified the spatio-termporal metabolokinetics and the therapeutic effect of transplanted CD106$^+$ umbilical cord-derived MSCs (UC-MSCs) and placenta-derived MSCs (P-MSCs) for acute lung injury (ALI) and refractory Crohn's-like enterocutaneous fistula administration, respectively [9, 62]. Similarily, Cao *et al*. verified the *in vivo* biofunction of MSC-derived EVs (MSC-EVs) in improving the outcomes of renal ischemia-reperfusion injury *via* enhancing mitochondrial function according to the DPA-SCP-based real-time imaging [70]. Instead, Akgul Caglar *et al*. explored

the utilization of retrograde dyes (*e.g*, Di-8-ANEPPQ, DiI) with a retrograde tracer for labeling heart *in vivo* and cardiac cultures *in vitro* [71].

Of note, as reviewed by McCarthy *et al*., considerable impressive advancements have been achieved in cancer immunotherapy on the basis of *in vivo* innovative imaging technologies, such as computed tomography (CT), magnetic resonance imaging (MRI), scintigraphy, ultrasound, positron emission tomography (PET), and single-photon emission computerized tomography (SPECT) [72 - 74]. Collectively, *in vivo* fluorescent tracer has become an important branch and methodology for detailed analysis of the spatio-termporal metabolokinetics and the therapeutic effect of stem cell-based tissue engineering in both preclinical investigations and clinical application.

SINGLE-CELL RNA SEQUENCING (SCRNA-SEQ)

State-of-the-art studies have continuously highlighted the promising prospects of single-cell RNA sequencing in stem cell-based biological and medical issues [75 - 77]. Nowadays, scRNA-seq technology has emerged as a powerful platform and transformational technology for elucidating biological phenotypes, characterizing individual cells, and providing a deep insight into the cell-to-cell variation [78, 79]. For hematological malignancies, scRNA-seq displays a solid prospect for unraveling disease pathogenesis, cellular subpopulations, therapeutic responses, tumor heterogeneity, and patient stratification, which also allows high-resolution analyses of the concomitant pathogenic mechanisms, paves ways to individualized cytotherapy, and affords considerable clinical utilities in future [79 - 81]. For example, Gandhi *et al*. put forward the current perspectives in multiple myeloma (MM) variability after autologous stem cell transplantation (ASCT) from the aspects of population pharmacogenetics, single cell technology, and molecular signal transduction, which collectively supplied new references for understanding the myeloma microenvironment and providing a basis for developing MSC-based remedies to combat the malignancy as well [82, 83].

At the meantime, talented investigators in the field have also attempted to study the physiological development and cellular heterogeneity of stem cells. For instance, Bao *et al*. and Gladka *et al*. identified somatosensory neuron types and adult mammalian heart by high-coverage scRNA-seq and functional heterogenetity, respectively [84, 85]. Instead, Gudiseva *et al*., Tong *et al*., Xu et al ., Liu *et al*. and Wang *et al*. examined the distinct molecular signatures and subtypes of retinal ganglion cells, megakaryocytes and erythoroid precursors derived from human pluripotent stem cells or hematopoietic stem cells, respectively [86 - 90]. Taken together, the scRNA-seq technology has emerged with the widest application in the current genomics tool box for unravelling the

complexity of RNA transcripts and the heterogeneity and composition (*e.g.*, genetic variations, epigenetic changes, gene and protein expression pattern) of individual cells, which revolutionize the process of stem cell-based pathogenesis and regenerative medicine [91 - 94].

CONCLUSION

Overall, in this chapter, we outlined the overview of technological innovation in stem cell-based tissue engineering and regenerative medicine. Of note, the state-of-the-art literatures have highlighted the promising prospect of the aforementioned novel technologies in combination with stem cells, which strikingly inspire the preclinical investigations and clinical practice and new drug application (NDA) of the combined remedies.

LIST OF ABBREVIATIONS

3D	Three-dimensional
2D	Two-dimensional
hESCs	Human embryonic stem cells
hiPSCs	Human induced pluripotent stem cells
BDNF	Brain-derived neurotrophic factor
NTRK2	Neurotrophic Receptor Tyrosine Kinase 2
TALENs	Transcription activator-like effector nucleases
ZFNs	Zinc finger nucleases
CAR-T	Chimeric antigen receptor-transduced T
CAR-NK	Chimeric antigen receptor-transduced natural killer
DNA	Deoxyribonucleic acid
MSX2	Muscle segment homeobox 2
TPO	Thrombopoietin
LNPs	Lipid nanoparticles
CRISPR/Cas9	Clustered regularly interspersed short palindromic Repeats/CRISPR-associated protein 9
MSCs	Mesenchymal stem/stromal cells
UC-MSCs	Umbilical cord-derived MSCs
P-MSCs	Placenta-derived MSCs
ALI	Acute lung injury
AD	Alzheimer's disease
ALL	Acute lymphocytic leukemia
HSCs	Hematopoietic stem cells
MDS	Myelodysplastic syndrome

PD	Parkinson's disease
AD	Alzheimer's disease
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
GvHD	Graft-*versus*-host disease
PTOA	Post-traumatic osteoarthritis
sEVs	Small extracellular vesicles
BBB	Blood-brain barrier
MSC-EVs	MSC-derived EVs
CT	Computed tomography
MRI	Magnetic resonance imaging
PET	Positron emission tomography
SPECT	Single-photon emission computerized tomography
scRNA-seq	Single-cell RNA sequencing
MM	Multiple myeloma
ASCT	Autologous stem cell transplantation
NDA	New drug application

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CHAPTER 7

MSCs as Biological Drugs: From Manufacturing to Commercialization

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Abstract: Mesenchymal stem/stromal cells (MSCs) can be used as a therapeutic agent in regenerative medicine, owing to their unique self-renewal, multi-lineage differentiation, and immunoregulation properties. The manufacturing of authorized MSC products should depend on good manufacturing practices (GMP), Good Laboratory Practice (GLP), and Good Clinical Practice (GCP). Until now, many biotech companies have invested in developing the clinical application of MSC product all over the world. Meanwhile, the application of MSC products for human use must comply with regulations and guidance for a biotech company. In this chapter, we discuss the process and development of MSC products from production-manufacturing to commercialization.

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INTRODUCTION

Mesenchymal stem/stromal cells (MSCs) are a cohort of heterogeneous populations with multifaceted biological properties such as splendid hematopoietic-supporting effects, immunological tolerance, and multi-lineage differentiation potential [1, 2]. Since the 1960s, MSCs have been isolated and identified from adult tissues (*e.g.*, adipose tissue, bone marrow), perinatal tissues (*e.g.*, placenta, umbilical cord), and so forth [3]. Until now (~2023 years), there are more than 1400 MSCs clinical trials underway worldwide, as well as over sixty thousand scientific publications published about MSCs from 2013 to 2023 years. Currently, MSC products and the derivatives must be manufactured under Good Manufacturing Practice (GMP) conditions according to investigational new drug (IND) regulations, in other words, identification and assessment of critical quality attributes (purity, potency, and safety) for release criteria as early as the process development stage would ensure product consistency during commercial manufacturing [4, 5]. Meanwhile, the pharmaceutical Non-clinical Trial of MSC products should comply with the "Good Laboratory Practice" (GLP). Subsequently, the researchers should follow the requirements of the "Good Clinical Practice" (GCP) in the phase of clinical trials. There is an increasing need to understand the regulatory issues that have led to the development of the MSC as a medical drug product. For example, in the European Union, the development and authorization of MSCs-based products and derivatives are regulated by the European Medicines Agency (EMA), which is in charge of the certification and evaluation procedures of MSCs [6]. In Korea, the development and authorization of MSCs-based product is regulated by the Ministry of Food and Drug Safety (MFDS) and the Pharmaceutical Affairs Act (PAA), which governs the release or commercial launch of cell and gene therapy products [7]. Meanwhile, in China, the development and authorization of MSCs-based products are regulated by the National Center of Drug Evaluation (CDE) on the basis of the National Medical Products Administration (NMPA) regulations [8]. Therewith, in this chapter, we mainly describe a route for scientists, biotech companies, and clinical trial investigators toward the successful development of MSC-based therapeutic products.

PROCESS DEVELOPMENT OF MESENCHYMAL STEM CELLS PRODUCTS

In general, the process of approval for MSCs-based products is developed following a rigorous procedure as shown in Fig. (**1**). (1) The basic research stage:

it mainly includes cell isolation, expansion, processing, formulation, and mechanisms of action (MOA). (2) The CMC stage: it mainly includes chemistry manufacturing control (CMC), product testing and releasing, stability programs, and so forth. (3) The non-clinical stage: it mainly includes pharmacology and toxicology. (4) The IND stages: these stages mainly include pre-IND meetings, IND applications, and submission. (5) The clinical trials stage: these mainly include exploratory and confirmatory clinical trials.

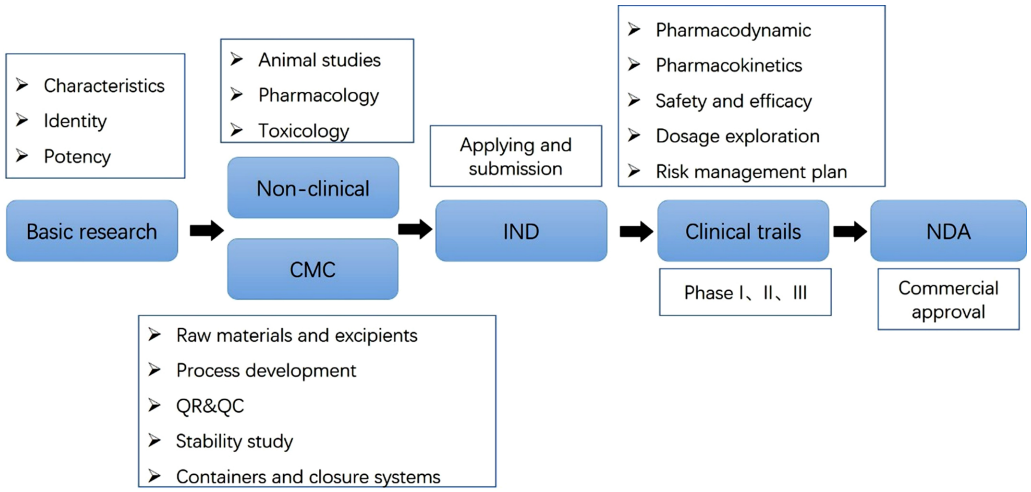

Fig. (1). Process for the generation of MSC-based clinical product in compliance with regulatory requirements of CFDA.

CHEMISTRY, MANUFACTURING, AND CONTROLS (GMP)

Stem cell products that are developed and registered as pharmaceutical products are subject to the supervision of the State Drug Administration (NMPA) and comply with the requirements of the Drug Administration Law of the People's Republic of China, the Administrative Measures for Drug Registration, and the Pharmacopoeia of the People's Republic of China and other relevant laws and regulations. The whole production process of stem cell products for human use should comply with the basic principles and relevant requirements of the Good Manufacturing Practice (GMP). The quality assurance system should supervise all production activities, from the control of raw materials, processing, testing, staff, equipment, labeling, check of production records, error detection and correction, and authorization for the final release of the product [9, 10].

Raw Materials and Excipients

Materials for production include all raw materials and excipients used in the production of MSCs products. Raw materials include starting materials

(production cells, helper cells, and *in vitro* gene delivery and modification systems) and other raw materials (such as culture media and biochemical reagents such as cytokines, cell separation and combination devices and other consumables). The use of excipients should comply with the requirements of the pharmacopoeia and the Rule of Joint Review and Approval Combining Excipients and Package Materials with Drug requirements. Materials used for production are directly related to product quality and are subject to risk assessment and quality control with reference to the relevant requirements of the Chinese Pharmacopoeia.

Raw Materials

Stem cell products developed in accordance with pharmaceuticals are generally derived from donors (autologous or allogeneic) and may also be derived from cell banks. The source of stem cells and related operations should comply with relevant national laws and regulations and ethical requirements, and their use should obtain informed consent and authorization from the owner. The production of stem cell products should establish a stable source of cells for production and ensure consistent quality. If human embryonic stem cells are involved, appropriate donor screening procedures and criteria should be established according to the characteristics of the product, and the safety and reasonableness of the production cell application should be comprehensively assessed [11].

Excipients

The source, dosage, and quality control of excipients used in stem cell products developed in accordance with the drug should be based on the principle of risk assessment, full research and validation by prescription screening, *etc*., and should comply with relevant requirements of "General Rules for the quality control of raw materials and excipients used in the manufacture of biological products". In the current version of the Chinese Pharmacopoeia, we should try to choose low-risk excipients, giving priority to pharmaceutical-grade excipients. For excipients with high-risk levels, the necessity of using these excipients should be evaluated in the early stage of product development, and other alternatives or alternative sources should be sought [12].

Process

The process of stem cell products is complex. The batch-to-batch differences may be different from those of general drugs. For stem cell products developed as drugs, the research of their production process should follow the general rules of the drug production process as far as possible, the relationship between the production process and product quality, residue removal, and establishment of a robust and reliable production process should be comprehensively studied. Since

the early stage of R&D, it is necessary to gradually define the production process steps and operating parameters, as well as the production process control, acceptable ranges and abandon limits, to keep the process relatively stable and reliable, and gradually determine the product target product quality profile (QTPP) and critical quality attributes (CQA). The process of stem cell products generally includes the upstream cell culture process and the downstream formulation process. The process flow may include several process steps in cell recovery, expansion, induction of differentiation, gene delivery and modification, harvesting, canning, freezing, storage, transportation, *etc*. The production scale and the definition of batches and lots should be clarified. Upstream and downstream process scales should be compatible. If there are combined batches or split batches in the process, adequate studies and corresponding principles need to be conducted [5, 13, 14].

Compared with general pharmaceuticals, the batch-to-batch variation in stem cell products may be larger and process validation is more difficult, but it is still necessary to ensure product consistency and quality controllability. At the market authorization application stage, the production of multiple consecutive batches of stem cell products at commercial production scale should be conducted, and the process and product quality of each batch should be fully characterized to confirm the robustness of each process and the consistency of product quality. The process validation process is recommended to focus on the *in vitro* assessment of genotypic instability, tumorigenicity and phenotypic characteristics (including expected and unintended cell populations) of the product at key production stages. The process validation should ensure the safety of the product. In addition, validation of the production process of key raw materials, storage conditions and the time of intermediates, medium/buffer preparation and placement conditions, filter validation, transport validation, aseptic mock filling validation, cleaning validation, and container seal integrity validation should be completed [14 - 16].

Quality Research and Quality Control

As MSC products are diverse, variable, and complex, quality studies should be conducted on representative production batches and appropriate production stage samples (including initially isolated cells or cell seeds, cell banks, intermediate products, stock solutions, and finished preparations) as shown in Table **1**. If possible, a series of state-of-the-art and orthogonal analytical techniques should be used, and the analytical methods should be confirmed by research to ensure that the methods are applicable and reliable [5, 8, 16, 17].

Stability Studies of MSC Products

The stability study can be carried out with reference to the general requirements

of the Chinese Pharmacopoeia Guidelines for Stability Testing of Biological Products and ICH Q5C. The purpose of stability studies is to support the storage, transportation, and use of stem cell products. Stability studies generally include impact factor tests (temperature, light, mechanical force, *etc*.), acceleration tests, long-term tests, transportation tests, and stability tests in clinical use. The test conditions should fully consider the difference between fresh and frozen cells, the special requirements of stem cell product preservation, packaging, transportation, clinical compounding, and actual drug administration, and the influence of the cumulative preservation time of each link of sample storage on the stability of the final product. The stability data at the clinical trial application point should support the clinical trial. The stability data of the proposed representative batches should be provided to support the determination of storage conditions, conditions of use, and expiration date, and the sensitivity conditions, inactivation pathway, and inactivation rate of the product should be clarified [14, 18, 19].

Table 1. Characterization/CQA for MSC products.

QC	Description
Cell characterization	Cell morphology (light microscopy); Cell activity (viability and number of live cells, population multiplication time, cell cycle); Cell identification (short tandem repeats (STR) mapping, mid-term karyotype analysis, and isozyme profiling or genetic polymorphism); Cell marker assays (flow cytometry).
Physical and chemical characterization	Appearance; color; clarity; pH; visible foreign matter; molar concentration of osmolality; loading capacity.
Cell purity analysis	The ratio of live cells; the ratio of cell subpopulations; the ratio of functional cells; a ratio of non-intended cell populations.
Biological safety	Tumorigenicity and oncogenicity; abnormal immune responses; Unintended differentiation.
Microbiological safety	Aseptic testing - bacteria, fungi; Mycoplasma testing; Mycoplasma testing; Bacterial endotoxin detection.
Biological activity analysis	Secretion of relevant bioactive substances (*e.g.*, growth factors, enzymes and cytokines), formation of cells and extracellular matrix/structures, cellular interactions (*e.g.* immune activation or inhibition), and migration differentiation or self-renewal potential of cells.

Packaging and Closed Container Systems

The object of the suitability assessment of the packaging and containment container system is the packaging container and the containment system that are in direct contact with the product. The route of product administration (intravenous administration, local administration, ophthalmic preparations) should be in compliance with the nature of the preparation (fresh cells, frozen

preparations), *etc*. to select the appropriate inner packaging materials (bottles, soft bags, *etc*.). With respect to the relevant guidelines, compatibility studies of samples (collected tissues or cells, cells in the preparation process) and finished products in the process of stem cell products and direct contact packaging materials should be carried out, using small size packaging containers of the same material, and must also cover the density and volume range of the products to be packaged. Extractable/leachable studies should be carried out and safety assessments should be conducted. Toxicological assessment of extracts should be based on good scientific principles and consider specific container sealing systems, drug prescriptions, dosage forms, routes of administration, and dosing regimens (chronic or short-term dosing) [14, 20].

PHARMACOLOGICAL AND TOXICOLOGICAL STUDIES (GLP)

The safety evaluation of MSCs-based products should comply with the requirements of the quality management practice for good laboratory practice (GLP). It is recommended to follow the GLP specification to the maximum extent. However, due to the obvious technical complexity in the safety evaluation of MSCs-based products, the impact of indicator detection in some non-GLP conditions on the reliability and integrity of the test results should be described and evaluated, so as to evaluate its impact on the safety evaluation of MSCs products. In general, the pharmacological and toxicological research and evaluation of MSC products should comply with the "Good Laboratory Practice" (GLP), which includes pharmacodynamics, pharmacokinetics, safety pharmacology studies, single dose toxicity tests, repeated dose toxicity studies, immunogenicity and immunotoxicity studies, reproductive and genetic toxicity studies, and special safety studies [4, 15].

MESENCHYMAL STEM CELLS: CLINICAL TRIALS (GCP)

During the clinical trial phase, they should follow the requirements of Good Clinical Practice (GCP). In principle, the research content of clinical trials should include clinical safety evaluation, pharmacokinetic study, pharmacodynamics study, dose exploration study and confirmatory clinical trial. In view of the special biological characteristics of cellular preparations, it is necessary to adopt a holistic strategy of clinical trials, which is different from other drugs in clinical trials. In order to achieve the desired therapeutic effect, MSC products may need to be administered by specific surgical measures, administration methods, or combination therapy strategies. Therefore, it should be considered in the design of clinical trial protocol. Many unique properties of MSC products can also influence the design of clinical trials, including product characteristics, manufacturing characteristics, and results of pre-clinical studies [21 - 23].

Pharmacovigilance and traceability of products should be addressed in the development of a risk management plan. At the same time, the possible differences in the efficacy and safety caused by cell preparations in drug administration, individualized preparation, special treatment, or adjuvant therapy should be considered. Cell preparations may require specific long-term studies to monitor the issues of safety, such as infection, immunogenicity immunosuppression, and malignant transformation should be evaluated. Adequate follow-up time is needed to evaluate its safety.

MSC-BASED PRODUCTS IN THE MARKET

As the most common stem cell type being used within regenerative medicine today, there is huge potential for growth within the MSCs market, which is attributed to the escalated need for pluripotent tissue as MSCs banking, tissue engineering, drug discovery, and development, among others. Until now (~2023 years), there are more than 1400 MSCs clinical trials underway worldwide, as well as over sixty thousand scientific publications published about MSCs from 2013 to 2023 years. While many MSC clinical trials have indicated safety and efficacy, only a small number of MSC products have reached commercialization, indicating that the therapeutic market for MSCs has huge potential. Today, some market competitors are developing various types of MSC therapeutics, as summarized in Table **2**. For example, Procgymal® (Remestemcel-L) is an allogeneic bone marrow derived-MSC therapy developed by Osiris Therapeutics Inc in 2009, which received conditional approval to treat pediatric steroid-refractory Graft-vs-Host Disease (GvHD) in Canada and New Zealand. Temcell®, an equivalent manufactured MSCs product to remestemcel-L, was approved in Japan based on small single-arm studies by using a regulation for regenerative medicine in 2016, which is priced at eight-sixty yen per dosage ($7000 U.S. dollars), and is taken $120000 per each course of treatment. Meanwhile, Cartistem® has recorded more than 10 billion krw ($9 million U.S. dollars) in each year from 2017 to 2020. The sales of Cartistem® have increased at an average annual rate of 40% since lunch, and the total number of operations has exceeded 20,000.

Table 2. Mesenchymal stem cell products in the market.

Product Generic Name®	Manufacturer	Stem Cell Type	Clinical Use	Years and Country
Queencell	Anterogen	Autologous adipose tissue derived-MSCs	Subcutaneous tissue defect	2010 (Korea)
Cellgram	Pharmicell	Autologous bone marrow derived-MSCs	Acute myocardial infarction	2011 (Korea)

(Table 2) cont.....

Product Generic Name®	Manufacturer	Stem Cell Type	Clinical Use	Years and Country
Cartistem	Medipost	Allogenic Umbilical cord blood derived-MSCs	Knee joint osteoarthritis	2012 (Korea)
Cupistem	Anterogen	Autologous adipose tissue derived-MSCs	Complex perianal fistulas in Crohn's disease	2012 (Korea)
Prochymal	Osiris/mesoblast	Allogenic bone marrow derived-MSCs	Acute graft-versus-host disease	2012 (Canada)
NeuroNata-R	Corestem	Autologous bone marrow derived-MSCs	Amyotrophic lateral sclerosis	2014 (Korea)
Temcell	JCR pharmaceutics	Allogenic bone marrow derived-MSCs	Acute graft-versus-host disease	2015 (Japan)
Unique access medical	Stemirac	Autologous bone marrow derived-MSCs	Spine cord injury	2018 (Japan)
RNL-Astrostem	NatureCell/Biostar	Autologous adipose tissue derived-MSCs	Alzheimer's disease	2018 (Japan)
Stempeucel	Stempeutics	Allogenic bone marrow derived-MSCs	Critical limb ischemia	2020 (Indian)
Alofisel	TiGenix/Takeda	Allogenic adipose tissue derived-MSCs	Complex perianal fistulas in Crohn's disease	2018 (EU) 2021 (Japan)

According to the research report published by Polaris Market Research, the global mesenchymal stem cells market was valued at USD 2.49 billion in 2021 and is expected to grow at a CAGR (Compound Annual Growth Rate) of 12.9% during the forecast period, but also, the global mesenchymal stem cell market is expected to reach $7.25 billion by 2030. Mesenchymal stem cell products are praised as the next-generation drugs in clinical application. Drug companies are investing heavily in increasing their MSCs product portfolios, thereby demonstrating definite indications that MSC products are entirely plausible in treating various life-threatening diseases [24 - 26].

REGULATIONS AND GUIDANCE OF MSC PRODUCTS

The process and development of all biological products for human use must comply with regulations and guidance for a biotech company, as shown in Table **3**. For example, in the European Union, MSC-based products are classified as advanced therapy medicinal products (ATMP) according to the European Regulation 1394/2007/EC 2007. The development of MSC products-based ATMP must obey these guidelines as shown below: (1) The guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006); (2) The reflection paper

on stem cell-based medicinal products (EMA/CAT/571134/2009); (3) The guideline on potency testing of cell-based immunotherapy medicinal products for the treatment of cancer (CHMP/BWP/271475/06); (4) The reflection paper on clinical aspects related to tissue engineered products (EMA/CAT/573420/2009). (5) Guidelines on safety and efficacy follow-up and risk management of advanced therapy medicinal products (EMEA/149995/2008). In the United States, MSC-based products fall under the remit of the Center for Biologics Evaluation and Research (CBER), specifically the Office of Cellular Tissue and Gene Therapies (OCTGT), which is performed following the guidelines shown as follows: (1) Good tissue practices (GTP) under Part 1271 of CFR Title 21 in research phase; (2) Good laboratory practice (GLP) facility following 21 CFR 58 and 21 CFR 610. (3) Good manufacturing practice (GMP) facility following 21 CFR 210 and 21 CFR211. (4) 21 CFR 312 refers to procedures and requirements governing the use of investigational new drugs. (5) Throughout all phases of clinical trials, the following FDA regulations are applied as 21 CFR50, 21 CFR54, 21 CFR56, and 21 CFR11. In China, stem cell products that are developed and registered as pharmaceutical products are subject to the supervision of the State Drug Administration (NMPA) and comply with the requirements of the Drug Administration Law of the People's Republic of China, the Administrative Measures for Drug Registration, and the Pharmacopoeia of the People's Republic of China and other relevant laws and regulations. The whole production process of stem cell products for human use should comply with the basic principles and relevant requirements of the Good Manufacturing Practice (GMP). NMPA drafted the “Technical Guidelines for Clinical Trials of Human-derived Stem Cells and Derived Cell Therapeutics (Draft for Comment)” on August 4, 2020. Meanwhile, NMPA also drafted the title of “Technical Guidance for Research and Evaluation on Chemistry, Manufacturing, and Control (CMC) of Human-derived Stem Cell Products (Draft for Comment)” on August 17, 2021. This guideline is to provide advice on the technical aspects of CMC research from the development to the marketing stage of stem cell products developed as drugs [27 - 30].

Table 3. Regulatory agencies in different countries.

Country	Regulatory Agency	Website Link
Australia	Therapeutic Goods Administration (TGA)	https://www.tga.gov.au
Canada	Health Canada	https://www.canada.ca/en/health-canada/services/drugs-health- products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions.html

(Table 3) cont.....

Country	Regulatory Agency	Website Link
China	National Medical Products Administration (NMPA)	https://www.nmpa.gov.cn
Europe	European Medicines Agency (EMA)	https://www.ema.europa.eu/en
Germany	The paul ehrlich institute	https://www.pei.de/EN/home/home-node.html
India	Cental Drugs Standard Control Organization (CDSCO)	https://cdsco.gov.in/opencms/opencms/en/Home
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	https://www.pmda.go.jp/english/
Korea	Pharmaceutical Affairs Act (PAA); Ministry of Food and Drug Safety (MFDS)	https://www.mfds.go.kr/eng/index.do
United states	Food and Drug Administration (FDA)	https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products

CONCLUSION

In general, the development of MSCs products has been rapid for their potent application to the management of different diseases. Regulatory guidelines on the development of MSC products are associated with the national and NMPA recommendations, which include the compliance process of product preparation, quality testing, quality management, and so forth. From the perspective of biotechnical company, the development of a regulatory strategy is advisable. Communication and cooperation with the regulatory authority throughout the processing of MSCs product which will make the regulatory pathway straightforward.

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