Abstract:
Herewith, we review an updated progress of regenerative medical products using human embryonic stem cells (ESCs) in Japan. Two groups from Kyoto University and the National Center for Child Health and Development (NCCHD) established a novel derivation/cultivation system of ESCs for potential application in translational and clinical research. At the first stage of ESC derivation, murine feeder cells have been used in line with Japanese guidelines on public health associated with the implementation of the xenograft. To avoid exposure of ESCs to animal products in culture media, a xeno-free cultivating system has been established. Twelve ESCs (KhES-1, KhES-2, KhES-3, KhES-4, KhES-5, SEES-1, SEES-2, SEES-3, SEES-4, SEES-5, SEES-6, and SEES-7) are now available under a clinically relevant platform for industrially and clinically applicable regenerative medical products. NCCHD submitted an investigative new drug application to the Pharmaceuticals and Medical Devices Agency (PMDA) for using ESC-based products in patients with hyperammonemia due to genetic defects on March 2018 under the Pharmaceutical Affairs Law (now revised to the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act). Currently, up to ten ESC-based products are being prepared for intractable and rare disorders in Japan.

Key Words:
embryonic stem cells, ESCs, regulation, Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act, The Act on the Safety of Regenerative Medicine

Embryonic Stem Cell (ESC) Lines for Regenerative Medical Products in Japan

Human ESCs have high potential to be raw material to produce a variety of cell types due to their pluripotency when compared with somatic stem cells which have limited abilities in differentiation and self-renewal (1), (2). Once effective and efficient differentiation protocols are established to obtain a target cell, human ESCs are expected to stably supply a major portion of raw cell substrate materials used for manufacturing regenerative medical products. Kyoto University and the National Center for Child Health and Development (NCCHD) strictly complied with the Guidelines for Derivation and Distribution of Human Embryonic Stem Cells (3) and the Guidelines for Utilization of Human Embryonic Stem Cells (4) for human dignity to establish ESCs in Japan. In these two guidelines, the basic issues concerning the protection of personal information and protocols of derivation and usage of human ESCs are defined from the viewpoints of bioethics. The guidelines are now for development of novel treatments and pharmaceuticals/medical devices (5), (6).

Twelve human ESC lines (KhES-1, KhES-2, KhES-3, KhES-4, KhES-5, SEES-1, SEES-2, SEES-3, SEES-4, SEES-5, SEES-6, and SEES-7) are available as a resource of cell substrates to manufacture regenerative medical products at present for clinical usage under the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act, formerly Pharmaceutical Affairs Law) (7), (8), (9). KhES-1, KhES-2, and KhES-3 can be maintained in culture for up to 2 years without significant alteration in differentiated capability and karyotypes (7). Meanwhile, SEES-4, SEES-5, SEES-6, and SEES-7 can also be stably cultivated under xenogeneic-free conditions (9). SEES-1, SEES-2, and SEES-3 have been established by utilizing murine feeder cells. For a quality evaluation,
we thus need to follow “Derivation and Characterization of Cell Substrates Used for the Production of Biotechnological/Biological Products,” “Guidelines on Public Health Infection Issues Accompanying Xenotransplantations,” and “Guidelines on Epithelial Regenerative Therapy Using 3T3J2 Strain or 3T3NIH Strain Cells as Feeder Cells” in order to prevent contamination of feeder cells and transmission of bacteria, fungi, viruses, and prions. KthES11, KthES12, KthES13, and KthES14 cells were established by Kyoto University in a feeder-free culture system to avoid contamination of murine cell components. Suemori has been generating KhESC lines at Kyoto University and has inserted a letter “t” to a name of newly established ESC, which are called KthES-11 cells, because he intends to apply KthES cells for therapeutic purpose in a clinical setting.

Two Acts on the Regulation of ESC-Based Medical Products

A new regulatory framework to supervise regenerative medicine, i.e., the “Act on the Safety of Regenerative Medicine” and the “Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act,” was enacted in November 2015 (10). The Act on the Safety of Regenerative Medicine, in place of the Medical Practitioners Act and the Medical Care Act, provides regulations on medical professionals’ practices and clinical studies on regenerative medicine. Under the new “Act on the Safety of Regenerative Medicine,” regenerative medicine is classified into three categories depending on each therapy’s potential risk factor. The risk of regenerative medicine studies using ESCs is considered high; thus, ESC-based therapy will be placed in the high-risk medical technology category (Class I). Regardless of risk factor, all plans of using regenerative medicine must be submitted to the Ministry of Health, Labour and Welfare (MHLW). Moreover, before submitting plans to the MHLW, a certified special committee must submit their opinion on the preliminary plan created by the medical institution that intends to offer ESC-based therapy. This committee fulfills the legal accreditation criterion laid down by the MHLW. Once the committee gives its opinion, regardless of the recommendation, the medical institution may submit their preliminary plan for practicing regenerative medicine along with the committee’s opinion to the MHLW. In addition, medical institutions are obligated to conduct follow-up reports detailing the adverse effects and annual details about their regenerative medicine plan implementation, including the treatment provided, the number of patients treated, and the effectiveness of the treatment to the MHLW and the committee.

“Donors’ Protection” versus “Patients’ Safety”

We follow two regulations for different legal benefits, namely, “safety and quality” (Guideline on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Human Embryonic Stem Cells) and “ethics” (Guidelines on the Derivation of Human Embryonic Stem Cells, Guidelines on the Distribution and Utilization of Human Embryonic Stem Cells) (11,15,16). These guidelines have different standpoints and, therefore, conflict: the former guideline focuses on protection of donors’ personal information and human dignity, and the latter prioritizes safety of raw materials.

Safety of Raw Materials as Regenerative Medical Products

If human ESC lines are established for the purpose of clinical use, donors need to be selected appropriately. Selection criteria and eligibility of the donors are important. Infection with hepatitis B virus, hepatitis C virus, human immunodeficiency virus, adult human T-lymphotropic virus, or parvovirus B19 shall be ruled out via physician-donor interviews and clinical laboratory tests, such as serological tests and nucleic acid amplification tests. Infection controls at the right time need to be done by retesting, taking into consideration the window period; however, such retesting is not practically allowed for ESCs according to the Guidelines on the Derivation of Human Embryonic Stem Cells (9). Infection with cytomegalovirus, Epstein-Barr virus, or West Nile virus shall also be ruled out, if necessary, via appropriate clinical laboratory tests. In addition, the eligibility of donors should be assessed whether he or she ever received a blood transfusion or underwent a transplantation procedure. Alternatively, it is conceivable to assess infectious pathogens at intermediate products during differentiation from the viewpoint of ethical and scientific rationality.

Banking of Intermediate Products during Practical Manufacturing

ESCs are considered the most undifferentiated cells similar to inner cells of blastocysts. Thus, the manufacturing process from undifferentiated ESCs to functional differentiated cells or final products is complicated and requires a long timeline, which may be challenging to perform. From the viewpoint of consistency and robustness, the most ideal foundation in the sustainable manufacture of ESC-based products is intermediate cell products/lines that have been well characterized (Figure 1). Preferably, the intermediate products should be stable per se and possess the ability to be propagated under relevant conditions. Furthermore, banks of the intermediate products should be renewed and must be able to differentiate properly into target cells. For certain final products, the proper establishment of sustainable intermediate cell products/lines as a cell bank at the intermediate stage of manufacturing process may be more significant and scientifically rational for the consistent manufacturing of desired safe products in addi-
tion to characterization, evaluation, or control of cells at the raw material stage. To minimize issues/concerns as much as possible, the most important concept and measures common to all types of biologics production are to ensure consistency and robustness in the manufacturing process. One of the core technical elements for proper and consistent production of biologics is to establish a base camp, i.e., to prepare production substrates at a relevant stage in the manufacturing process, which is applicable to extensive characterization and control, stable in quality, and from which constant processing to next intermediates and finally to a desired product is achievable.

ESC-Based Candidate Products in the Development Pipeline

Human ESC-based products have been developed for clinical trials worldwide (11), (12), (13), (14), (15), (16), (17), (18), (19), (20). Clinical trials using hESC-derived cells for transplantation were identified by exploring the public database (Table 1). We used the search term “human embryonic stem cell” in reviewing “ClinicalTrials.gov,” from the US National Library of Medicine (https://clinicaltrials.gov/) database. We also evaluated original research articles and the sponsor’s websites on the respective clinical trials and/or transplant products for additional information. For example, ESC-derived products are being tested for use to patients with age-related macular degeneration, Stargardt disease, type 1 diabetes, and spinal cord injury in the United States; age-related macular degeneration and Stargardt disease in South Korea, the United Kingdom, China, and Brazil; age-related macular degeneration in Israel; severe heart failure in France; and Parkinson’s disease in Australia. We have filed a new investigational drug application to PMDA for ESC-based regenerative medical products to patients with congenital metabolic disorders and have ESC-derived mesenchymal stromal cells, epidermal cells, intestinal organoids, and hepatocytes in the development pipeline (21), (22).

Figure 1. Schematic diagram of intermediate product bank for practical manufacturing

ESC-Based Candidate Products in the Development Pipeline

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Table 1. Clinical Trials Using hESC-derived Cells for Transplantation.

| Study title                                                                                                                   | Cell type (product name)                              | Sponsor/ collaborator                      | Trial location | Disease                        | Stage of trial | Cell delivery | Status of trial | Registration number | Estimated or actual study completion date | Note/Reference                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|--------------------------------------------|----------------|--------------------------------|----------------|---------------|-----------------|-------------------------------|------------------------------------------|--------------------------------------------------------------------------------|
| **A. Eye disease**                                                                                                            |                                                      |                                            |                |                                |                |               |                 |                               |                                          |                                                                                 |
| Safety and tolerability of sub-retinal transplantation of hESC-Derived RPE (MA09-hRPE) Cells in Patients with Advanced Dry Age-Related Macular Degeneration (Dry AMD) | hESC-derived RPE (MA09-hRPE)                          | Astellas Institute for Regenerative Medicine | United States  | Dry AMD                        | Phase I/II     | Cell suspension | Completed       | NCT01344993                  | August 1, 2015                          | < Progress report > Lancet. 2015 Feb 7:385(9967):509-16. Lancet. 2012 Feb 25;379(9817):713-20. < Follow-up study > Invest Ophthalmol Vis Sci. 2016 Apr 1(57)(3):ORSFc1-9. |
| Sub-retinal transplantation of hESC-derived RPE (MA09-hRPE) cells in patients with SMD                                          | hESC-derived RPE (MA09-hRPE)                          | Astellas Institute for Regenerative Medicine | United States  | Stargardt’s macular dystrophy (SMD) | Phase I/II     | Cell suspension | Completed       | NCT01345006                  | August 1, 2015                          |                                                                                  |
| Long Term Follow Up of Sub-retinal Transplantation of hESC Derived RPE Cells in Stargardt Macular Dystrophy Patients            | hESC-derived RPE (MA09-hRPE)                          | Astellas Institute for Regenerative Medicine | United States  | Dry AMD                        | Phase I/II     | Cell suspension | Active, not recruiting | NCT02445612                  | December 1, 2019                      | Follow-up study for NCT1345006                                                   |
| Long Term Follow Up of Sub-retinal Transplantation of hESC Derived RPE Cells in Patients With AMD                              | hESC-derived RPE (MA09-hRPE)                          | Astellas Institute for Regenerative Medicine | United States  | Dry AMD                        | Phase I/II     | Cell suspension | Active, not recruiting | NCT02465344                  | December 1, 2019                      | Follow-up study for NCT1349993                                                   |
| Safety and tolerability of sub-retinal transplantation of hESC-RPE cells in patients with SMD                                 | hESC-derived RPE (MA09-hRPE)                          | Astellas Institute for Regenerative Medicine | United Kingdom | Stargardt’s macular dystrophy (SMD) | Phase I/II     | Cell suspension | Completed       | NCT01469832                  | September 1, 2015                     | < Progress reports > Ophthalmology. 2018 Nov;135(11):1765-1775.                 |
| A Follow up Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of Human Embryonic Stem Cell Derived Retinal Pigmented Epithelial (hESC-RPE) Cells in Patients With Stargardt’s Macular Dystrophy (SMD) | hESC-derived RPE (MA09-hRPE)                          | Astellas Institute for Regenerative Medicine | United Kingdom | Stargardt’s macular dystrophy (SMD) | Phase I/II     | Cell suspension | Active, not recruiting | NCT02941991                  | December 1, 2019                      | Follow-up study for NCT14e9832                                                 |
| A Phase 1b Dose Escalation Evaluation of Safety and Tolerance and a Phase 2 Proof of Concept Investigation of Efficacy and Safety of ASP7317 for Atrophy Secondary to Age-related Macular Degeneration (AMD) | hESC-derived RPE (ASP7317)                            | Astellas Institute for Regenerative Medicine | United States  | AMD                            | Phase I/II     | Cell suspension | Recruiting       | NCT03178149                  | October 1, 2026                       | Clinical study of ASP7317, a new cell line to replace MA09-hRPE                  |
| A Phase I/IIa, Open-Label, Single-Center, Prospective Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of Human Embryonic Stem Cell Derived Retinal Pigmented Epithelial (MA09-hRPE) Cells in Patients With Advanced Dry Age-Related Macular Degeneration (AMD) | hESC-derived RPE (MA09-hRPE)                          | CHA Biotech (licensed from Astellas Institute) | Korea          | Dry AMD                        | Phase I/II     | Cell suspension | Unknown         | NCT01674829                  | April 1, 2016                         | < Progress report > Stem Cell Reports. 2015 May 12;4(5):860-72. < Progress report of NCT01674829 > JAMA Ophthalmol. 2017 Mar 1;135(3):287-289. |
| Study title                                                                 | Cell type (product name) | Sponsor/collaborator | Trial location       | Disease                      | Stage of trial | Cell delivery          | Status of trial         | Registration number     | Estimated or actual study completion date | Note/reference                                                   |
|---------------------------------------------------------------------------|--------------------------|----------------------|----------------------|-----------------------------|----------------|------------------------|-------------------------|--------------------------|---------------------------------------------|-----------------------------------------------------------------|
| Safety and Tolerability of MA09-hRPE Cells in Patients with Stargardt’s Macular Dystrophy (SMD) | hESC-derived RPE (MA09-hRPE) | CHABiotech (licensed from Astellas Institute) | Korea                  | Stargardt’s macular dystrophy (SMD) | Phase I | Cell suspension | Unknown                 | NCT01625559               | June 1, 2015                        | < Progress report including nonclinical and clinical studies > Nat Biotechnol. 2018 Mar 19. doi: 10.1038/nbt.4114. |
| A study of implantation of RPE in subjects with acute wet age-related macular degeneration | hESC-derived RPE (PF-05206388) | Pfizer/University College, London | United Kingdom       | Wet AMD                    | Phase I | Membrane-immobilized monolayer sheet | Active, not recruiting | NCT01691261               | December 1, 2019                        | Follow-up study for NCT01691261                                                      |
| Retinal Pigment Epithelium Safety Study For Patients In Br711001            | hESC-derived RPE (PF-05206388) | Pfizer               | United Kingdom       | Wet AMD                    | Phase I | Membrane-immobilized monolayer sheet | Active, not recruiting | NCT03102138               | October 4, 2020                         | < Progress report including nonclinical and clinical studies > Transl Vis Sci Technol. 2017 Jun; 6(3): 17  < Nonclinical study > Graefes Arch Clin Exp Ophthalmol. 2016 Aug;254(8):1553-65.  < Progress report of clinical study (phase I/II) > Science Translational Medicine 04 Apr 2018: Vol. 10, Issue 435, eaao4097  http://www.sankeibiz.jp/business/news/180405/prl1804051101040-n1.htm |
| Safety and Efficacy Study of OpRegen for Treatment of Advanced Dry-Form Age-Related Macular Degeneration | hESC-derived RPE (OpRegen) | Lineage Cell Therapeutics (former BioTime)/Cell Cure Neurosciences | United States and Israel | Dry AMD                    | Phase I/II | Cell suspension | Recruiting | NCT02286089               | December 1, 2024                        | < Progress report of clinical study (phase I/II) > Science Translational Medicine 04 Apr 2018: Vol. 10, Issue 435, eaao4097  http://www.sankeibiz.jp/business/news/180405/prl1804051101040-n1.htm |
| Study of subretinal implantation of human ESC-derived RPE cells in advanced dry AMD | hESC-derived RPE (CPCB-RPE1) | Regenerative Patch Technologies | United States & geographic Atrophy | Dry AMD/AMD | Phase I/II | Membrane-immobilized monolayer sheet | Active, not recruiting | NCT02590692               | January 1, 2023                       | < Nonclinical study > Transl Vis Sci Technol. 2017 Jun; 6(3): 17  < Progress report of clinical study (phase I/II) > Science Translational Medicine 04 Apr 2018: Vol. 10, Issue 435, eaao4097  http://www.sankeibiz.jp/business/news/180405/prl1804051101040-n1.htm |

(Table continued on next page)
| Study title | Cell type (product name) | Sponsor/ collaborator | Trial location | Disease | Stage of trial | Cell delivery | Status of trial | Registration number | Estimated or actual study completion date | Note/reference |
|-------------|-------------------------|-----------------------|----------------|---------|----------------|---------------|----------------|-------------------|--------------------------------------------|----------------|
| Stem Cell Therapy for Outer Retinal Degenerations | hESC-derived RPE | Federal University of São Paulo | Brazil | Dry AMD/wet AMD/Stargardt | Phase I/II | Cell suspension or monolayer in a polymeric substrate | Unknown | NCT02903576 | June 1, 2019 | No available information |
| A Safety surveillance study in subjects with macular degenerative disease treated with human ESC-derived retinal pigment epithelial cell therapy | hESC-derived RPE (MA09-hRPE) | Astellas Institute for Regenerative Medicine | United States | Macular degeneration | Phase I/II | Cell suspension | Enrolling by invitation | NCT03167203 | December 1, 2029 | A long-term (up to 15 years) safety surveillance study |
| Safety and Efficacy of Subretinal Transplantation of Clinical Human Embryonic Stem Cell Derived Retinal Pigment Epitheliums in Treatment of Retinitis Pigmentosa | hESC-derived RPE | Qi Zhou/Beijing Tongren Hospital | China | Retinitis pigmentosa | Phase I | - | Recruiting | NCT03944239 | December 1, 2020 | No available information |
| Interventional Study of Implantation of hESC-derived RPE in Patients With RP Due to Monogenic Mutation | hESC-derived RPE | Centre d’Etude des Cellules Souches | France | Retinitis pigmentosa (due to monogenic mutation) | Phase I/II | - | Recruiting | NCT03963154 | December 15, 2021 | No available information |

**B. Other disease**

| Study title | Cell type (product name) | Sponsor/ collaborator | Trial location | Disease | Stage of trial | Cell delivery | Status of trial | Registration number | Estimated or actual study completion date | Note/reference |
|-------------|-------------------------|-----------------------|----------------|---------|----------------|---------------|----------------|-------------------|--------------------------------------------|----------------|
| Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure (ESCORT) | hESC-derived CD15+ Isl-1+ cardiac progenitors | Assistance publique, Hôpitaux de Paris | France | Severe heart failure | Phase I | Cells embedded in fibrin patch | Completed | NCT02057900 | March 22, 2018 | < Nonclinical study > Eur Heart J. 2015 Mar 21;36(12):743-50. < Progress reports of clinical study > Eur Heart J. 2015 Aug;36(30):2011-7. J Am Coll Cardiol. 2018 Jan 30;71(4):429-438. VC-01<sup>TM</sup>, a combination product (PEC-01<sup>TM</sup> cells + Encaptra® DDS) (see PMID: 29369575) <Manufacturing information > Stem Cells Transl Med. 2015 Aug;4(8):927-31. VC-01<sup>TM</sup> (PEC-Encap<sup>TM</sup>) deliver the PEC-01 pancreatic progenitor cells in a immunoprotective device https://viacyte.com/products/pec-encap-tc-01 |
| A Safety, Tolerability, and Efficacy Study of VC-01<sup>TM</sup> Combination Product in Subjects With Type I Diabetes Mellitus | hESC-derived pancreatic precursor cells (VC-01<sup>TM</sup> combination product) | ViaCyte/ California Institute for Regenerative Medicine (CIRM) | United States/ Canada | Type 1 diabetes | Phase I/II | PEC-01 cells encapsulated in a medical device | Active, not recruiting | NCT02239354 | January 1, 2021 | |
| One-Year Follow-up Safety Study in Subjects Previously Implanted With VC-01<sup>TM</sup> | hESC-derived pancreatic precursor cells (VC-01<sup>TM</sup> combination product) | ViaCyte | United States | Type 1 diabetes | Observational study | PEC-01 cells encapsulated in a medical device | Enrolling by invitation | NCT02939118 | November 1, 2021 | |

(Table continued on next page)
### Table 1. Continued.

| Study title                                                                 | Cell type (product name)                                                                 | Sponsor/ collaborator | Trial location | Disease          | Stage of trial | Cell delivery | Status of trial               | Registration number | Estimated or actual study completion date | Note/reference                                                                 |
|----------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------|----------------|------------------|----------------|----------------|----------------------------------|---------------------|------------------------------------------|--------------------------------------------------------------------------------|
| A Safety and Tolerability Study of VC-02™ Combination Product in Subjects With Type 1 Diabetes Mellitus | hESC-derived pancreatic precursor cells (VC-02™ combination product, aka PEC-Direct) | ViaCyte Canada        | Type 1 diabetes | Phase I          | PEC-01 cells loaded into a delivery device | Completed | NCT03162926 | February 15, 2018 | < Nonclinical study >                        |
| A Safety, Tolerability, and Efficacy Study of VC-02™ Combination Product in Subjects With Type 1 Diabetes Mellitus and Hypoglycemia Unawareness | hESC-derived pancreatic precursor cells (VC-02™ combination product, aka PEC-Direct) | ViaCyte United States | Type 1 diabetes | Phase I/II       | PEC-01 cells loaded into a delivery device | Recruiting | NCT03163511 | March 1, 2022 | https://viacyte.com/products/pec-direct |
| Safety Study of GRNOPC1 in Spinal Cord Injury                               | hESC-derived oligodendrocyte progenitors (GRNOPC1/AST-OPC1)                           | Astera Biotherapeutics | United States | Spinal cord injury | Phase I        | Cell suspension | Completed (took over from Geron) | NCT01217008 | July 1, 2013 | < Nonclinical study >                        |
| Dose Escalation Study of AST-OPC1 in Spinal Cord Injury                     | hESC-derived oligodendrocyte progenitors (AST-OPC1)                                   | Astera Biotherapeutics | United States | Spinal cord injury | Phase I/II     | Cell suspension | Completed | NCT02302157 | December 1, 2018 | < Nonclinical study >                        |
| A Study to Evaluate the Safety of Neural Stem Cells in Patients With Parkinson’s Disease | Human parthenogenetic stem cell-derived neural stem cells (MSC-hpNSC)                 | Cyto Therapeutics/ International Stem Cell Corporation Australia | Parkinson’s disease | Phase I          | Cell suspension | Active, not recruiting | NCT02452723 | June 1, 2020 | < Nonclinical study >                        |
| Safety and Efficacy Study of Human ESC-Derived Neural Precursor Cells in the Treatment of Parkinson’s Disease | Human embryonic stem cells-derived neural precursor cells                             | Chinese Academy of Sciences/The First Affiliated Hospital of Zhengzhou University | China Parkinson’s Disease | Phase I/II       | Cell suspension | Recruiting | NCT03119636 | December 1, 2020 | < Nonclinical study >                        |
| A Study to Evaluate Transplantation of Astrocytes Derived From Human Embryonic Stem Cells, in Patients With Amyotrophic Lateral Sclerosis (ALS) | Astrocytes derived from human embryonic stem cells (AstroRx)                       | Kadimastem Israel | ALS (amyotrophic lateral sclerosis) | Phase I/II | Cell suspension | Recruiting | NCT03482050 | August 1, 2020 | < Nonclinical study >                        |
| Safety Observation on hESC Derived MSC-Like Cell for the Meniscus Injury    | hESC-derived MSC-like cell                                                               | Tongji Hospital/ Chinese Academy of Sciences China | Meniscus injury | Phase I          | -              | Active, not recruiting | NCT03839238 | September 30, 2020 | < Nonclinical study >                        |

**Notes:**
- AMD: Age-related macular degeneration
- hESC: Human embryonic stem cell
- SMD: Stargardt’s macular dystrophy
- RPE: Retinal pigment epithelium
- DDS: Drug delivery system

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