



May 10, 2019
Gene Techno Science Co., Ltd.
Code: 4584 (TSE Mothers)
Masaharu Tani, President & CEO

Announcement of signing a joint research and development agreement
with ORTHOREBIRTH for cleft lip/cleft palate

Tokyo, May 10, 2019 — Gene Techno Science (“GTS”, TSE Mothers 4584) today announced that GTS and ORTHOREBIRTH Co., Ltd. (“ORTHOREBIRTH”) have signed a joint research and development agreement (“this Agreement”) to develop new therapeutic treatment for cleft lip/cleft palate.

1. Purpose and Background of this Agreement

GTS announced GTS 3.0 “Biotech Engineering Company, striving for value creation” a new business stage starting from this fiscal year, which targeted the pediatric disease in addition to the areas GTS has been engaged in such as the orphan disease and intractable disease. By leveraging the know-how and expertise about biotechnology acquired in the past business activities and also utilizing our cell therapy platform of stem cells from exfoliated deciduous teeth (SHED), in which GTS acquired on April 1st 2019 - Advanced Cell Technology and Engineering Ltd., GTS is working on the development and provision of new medicines and therapeutic treatment for the purpose of achieving comprehensive healthcare solutions for the patients suffering from these diseases as well as families and caregivers. Among the R&D themes pertaining to pediatric diseases, this Agreement aims to create valuable therapeutic treatments for such diseases.

Cleft lip/cleft palate is a disease caused by congenital defects in the oral cavity, and one of the congenital diseases in which the split (cleft) remains due to the incomplete closure of one side of the palate during the developmental phase. The disease is divided into three categories, cleft lip, cleft palate, and alveolar cleft according to the site of onset, and the treatment of alveolar cleft, which causes cracks in the alveolar bone in maxilla, is considered to be the most difficult. Alveolar bone graft is a treatment that promotes regeneration of alveolar bone by removing own hip bone from a pediatric patient and implanting them in the cleft. However, there are several issues such as having to wait for treatment at an age that allows sufficient amounts of own hip bone to be removed, the treatment being

invasive, accompanying walking disorders, and hospitalizing for about ten days. To address these issues, GTS aims to develop new non-invasive therapeutic treatment by means of regenerative medicine/cell therapy using SHED.

Cleft lip/cleft palate is a disease that is caused by an abnormality in neural crest cells that play an important role in craniofacial development, and is classified as neurocristopathy. Since SHED are embryologically derived from neural crest cells and have superior osteogenesis capability, it is considered to be an optimal cell source for cell therapy for alveolar cleft grafting. In addition, engraftment of SHED at the treatment region would improve by combining with appropriate scaffolds, and more stable alveolar bone regeneration is expected due to the synergetic effect by the osteogenesis capability of SHED and scaffolds. We believe that this scaffolding material has many advantages when combining with SHED, the bio-cotton artificial bone ReBOSSIS® produced by OROTHOREBIRTH. ReBOSSIS® has already been approved by US FDA as the material using for a treatment of fractures, and proven as safe and highly capable of inducing bone regeneration. In addition, since ReBOSSIS® has cotton-like structure, it provides larger surface area than solid filling materials and it can be expected that more SHED can be engrafted. Furthermore, ReBOSSIS® is made of biodegradable materials and disappears after bone regeneration, therefore the regenerated alveolar bone is replaced with a patient's own bone, which means that there is no concern about remaining artificial components in grafted area. GTS and ORTHOREBIRTH will conduct joint research by the collaboration of bio-cotton artificial bone and SHED, optimize a treatment method for cleft lip/cleft palate, and demonstrate bone regeneration ability on animal models in non-clinical studies.

As described above, GTS will promote research and development activities in collaboration with ORTHOREBIRTH. Prior to this Agreement, in November 10, 2014, GTS resolved to conduct a capital and business alliance with ORTHOREBIRTH for the product development of the artificial bone business, however, it has been concluded at this time that it is the best for both companies to shift the focus of collaboration for development of regenerative medicine/cell therapy product as the business associated with the previous alliance has come to reach at a certain stage. As a result of discussions with ORTHOREBIRTH, GTS and ORTHOREBIRTH agreed and decided to terminate the previous capital and business alliance agreement upon the execution of this Agreement between the companies. For clarity, although the previous agreement terminated this time, the Agreement means GTS and ORTHOREBIRTH enter into a renewal business partnership so that GTS continues to hold a certain amount of ORTHOREBIRTH common shares acquired in November 2014 for the medium to long term.

2. Outlines of this Agreement

Joint research and development agreement for new therapeutic treatment for cleft lip/cleft palate with SHED and artificial bone filling material.

A. Optimization study of SHED and artificial bone filling material in vitro

B. Demonstration of bone regeneration ability with SHED and artificial bone filling material in vivo

3. About ORTHOREBIRTH (as of March 31, 2019)

Company Name	ORTHOREBIRTH Co., Ltd.	
Representative	Yasutoshi Nishikawa, President & CEO	
Date of Establishment	June, 2011	
Address	15-3-303 Chigasaki-Chuo, Tsuzuki-ku, Yokohama-shi Kanagawa pref. Japan	
Business	Research and development, sales, manufacturing, and repair of medical equipment, expendable medical supplies, and others Sales of medical drugs, quasi-drugs, industrial chemicals, and others	
Capital	447,461,000 Japanese Yen	
Major Shareholders	Innovation Engine Inc.	15.2%
	Dexerials Corporation	9.7%
Relations between the companies	Capital relationship	Based on the agreement announced on November 10, 2014 - Collaboration on New Indication for ReBOSSIS™ and Business Development with ORTHOREBIRTH, GTS owns 909 common shares of ORTHOREBIRTH
	Personnel relationship	There is no reporting item applicable to this matter
	Transaction relationship	There is no reporting item applicable to this matter
	Status as a related party	There is no reporting item applicable to this matter

4. Financial Impact

The financial impact on FY2019 is expected to be minimal.

[Terms]

Cleft lip/cleft palate

Cleft lip/cleft palate is a congenital disease that occurs in 1 in 500 newborns, in which the split (cleft) remains due to the incomplete closure of one side of the palate during the developmental phase. Depending on the site of onset, it is divided into three categories, alveolar cleft, cleft palate, and cleft lip, but the disease is caused by the same mechanism of pathogenesis and often associated with each other. Among these symptoms, the most difficult to treat is alveolar cleft. A cleft is formed in the alveolar bone of the maxilla, thus in case it is not cured, regurgitation of nasal discharge, occlusal discrepancy due to atelognathia (defective jaw formation) will be caused and that results in back pain, headache, mastication disorder, and dysphonia, etc. For the treatment of alveolar cleft, the part of the hip bone is surgically extracted first according to the growth of the patient's jaw, and then crushed and implanted in the cleft region to regenerate ridge, alveolar bone. However, this surgery on patients in growth phase is highly invasive, therefore a less invasive alternative treatment is expected.

Neural crest cell

During the developmental process, it is known that fertilized egg performs cell divisions, and three germ layers are formed through cellular migration and the induction - ectoderm which forms skin and nerve, mesoderm which forms blood, heart, kidney, etc., and endoderm which forms visceral tubes. Neural crest cells arise at the boundary between non-neural ectoderm and neural ectoderm. Although neural crest cells are originated from the ectoderm, these cells migrate into various regions of whole body, and differentiated into the tissues derived from ectoderm as well as tissues and organs derived from mesoderm and endoderm at the point of migration in the developmental phase. Tissues originating from neural crest cells exist in the craniofacial bones and cartilages, teeth, vascular smooth muscle, pericytes, neural tissues such as sensory nerves and glial cells, pigment cells, cornea, iris and ciliary body in the eye, and also in choroids and adrenal medulla. Based on these characteristics, there is also a concept of defining neural crest cells as the fourth germ layer, and a multiple basic researches are elucidated.

The dental pulp stem cells, which our company promotes research and development, and also banking business, are the cells derived from cranial neural crest, delaminated and migrated from the anterior neural tube, and colonized in the dental pulp as stem cells.

Neurocristopathy

The disease caused by abnormalities in neural crest cells during developmental phase is called neurocristopathy, designated by Robert Bolande in 1974. Neurocristopathy is roughly classified into neoplastic forms that causes cancers due to the abnormal proliferation of neural crest cells, and dysgenetic forms in which the migration or differentiation of neural crest cells is abnormal. Neoplastic neurocristopathy includes pheochromocytoma (tumor of pheochromocytoma cells in

adrenal medulla) and neurofibromatosis type 1 (congenital nevus disease characterized by cafe-au-lait spot and neurofibroma). As a neurocristopathy of dysgenetic forms, Hirschsprung's disease (megacolon syndrome caused by a congenital defect of ganglion cells at the end of the intestinal tract) or Waardenburg syndrome (congenital syndromes that present sensory hearing loss, gray hair, and iris pigment abnormalities, are the typical diseases.