Kidswell Bio Co., Ltd

(4584 Growth) Issued: Jan. 18, 2023

SHED: Star Performer in Regenerative Medicine

Summary 1: SHED, with superior proliferative and tissue regenerative ability

Kidswell Bio Corporation is accelerating the development of a regenerative medicine known as SHED (stem cells from human exfoliated deciduous teeth) by generating the profit from biosimilar business. Attempts are being made to use bone marrow-derived mesenchymal stem cells in the most difficult of procedures, the regeneration of nerves after cerebral infarction and spinal cord injuries. These are being watched with interest, but none have yet been officially approved.

Establishing a manufacturing process for commercial production is essential for approval of regenerative medicine products, but it takes time and effort to obtain biological components such as bone marrow as raw materials. The stem cells are, in general, difficult to obtain, have limited proliferative capacity, and are prone to senescence, thus posing high hurdles to establishing commercial production which can produce at a sufficient level for numerous patients. In the case of SHED, proliferative capacity is higher than for other mesenchymal stem cells (MSC's) and relatively easier to obtain, thus providing the prospect of relatively lower hurdles.

SHED is also regarded as appropriate for nerve regeneration since it has a superior ability to secrete neurotrophic factors than other mesenchymal stem cells. Further, it has also been established that SHED acts in the acute phase of the initial onset to reduce inflammation and protect nerves. Also, in the chronic stage after inflammation subsides, it can contribute to nerve regeneration. In the future, the accumulation of SHED itself, or SHED-induced immune system cells, in the brain, may help provide an amelioration of symptoms.

Summary 2: First generation -regenerative medicine

Kidswell Bio is carrying out a number of projects to develop "first-generation SHEDs" that use unmodified SHEDs as cell therapy drugs. The illnesses targeted using SHED attributes are related to neurology and osteogenesis, many of which are classified as pediatric or orphan diseases and for which there is no effective cure, creating an area of high unmet medical need. Many development projects are being conducted under medical leadership in collaboration with academia, and the clinical studies will start in the coming year. From the 2024 fiscal year, there will be a shift to company sponsored clinical trials on multiple disorders for which proof of concept (POC) has been established. The target date for a final commercial product is estimated to be 2030. In order to avoid what has been called the "Galapagos effect", there has from the start been a focus on building human resources and platforms with an eye to overseas development. With regard to establishing critical manufacturing processes the company in August 2022 has established the world's first SHED master cell bank, thereby overcoming the first hurdle. In addition, in order to reinforce GMP-compliant manufacturing of investigational new drugs, the plan is to initiate development initiatives with Minaris Regenerative Medicine and other partners.

Summary 3: Second generation - "designer cell "applications

The development of SHED modified by gene transfection (second generation SHED) is also making progress. In November 2022 it was disclosed that, in collaboration with Hamamatsu University School of Medicine, SHED, modified by gene transfection and incorporating a suicide gene, was effective against glioma cells. This research also demonstrated the existence of a "bystander effect", killing not only the cancer cells to which SHED is induced but also neighbouring cells successively. Using the fact that SHEDs are attracted to the cytokines secreted from tumour cells, SHED has demonstrated a bystander effect by using the toxin produced by the suicide gene as a DDS to induce suicide genes into tumour cells. The expectation is that SHED will be used with other techniques, not just suicide genes. The company is currently targeting various diseases with a view to introducing external technologies.

Note: This report is the English-language version of the original Japanese-language report issued on January 18, 2023, to which you should refer for precise details.

R&D Report

Fair Research Inc.

Tsuyoshi Suzuki

Company Outline	
Location	Chuo-ku Tokyo
President	Masaharu Tani
Established	March 2001
Capital	JPY1,433 million
Listed	November 2012
URL	www.kidswellbio.com
Industry	Pharma
Employees	39(non-consol)
Key Indicators (Jan. 17, 2023)	
Share price	254 JPY
52-week high	494 JPY
52-week low	201 JPY
Shares outstanding	31,896thousand
Trading unit	100 shares
Market cap	JPY8,102 mil.
Dividend (est.)	0.0
Forecast EPS	-31.8 JPY
Forecast PER	NA
Actual BPS	47.66 JPY
Actual PBR	5.33X

(Note: EPS、PER、BPS、PBR based on shares outstanding (excl. treasury shares)

Results	Revenues JPY-mil.	YoY %	Op. Income JPY- mil	YoY %	Rec. Profit JPY-mil.	YoY %	Net Income JPY-mil.	YoY %	EPS JPY	Stock Price High	Stock Price Low
2021/3 Actual	996	-7.5	-969	NM	-991	NM	-1,001	NM	-34.7	888	466
2022/3 Actual	1,569	57.5	-919	NM	-952	NM	-535	NM	-17.3	858	410
2023/3 Forecast	2,900	NM	-980	NM	-999	NM	-1,000	NM	-31.8		
2021/9 1-2Q Actual	740	324.5	-450	NM	-463	NM	-462	NM	-15.3	858	410
2022/9 1-2Q Actual	1,116	NM	11	NM	-42	NM	-42	NM	-1.3	480	231

Company Outline and Management Philosophy

＜Company outline＞

Solid earnings from biosimilars business

Kidswell Bio Corporation started out as Gene Techno Science Co., Ltd., a bio-venture launched by Hokkaido University to pursue the development of biosimilars and new biologics. After starting its biosimilars business in 2007 it received its first regulatory approval, for the filgrastim biosimilar, in 2012 and now has three products on the market, with a plan to increase this to four products within a few years. The biosimilars business has already generated profits that exceed working capital (fixed costs), and in fiscal 2025 the company is aiming to achieve sales of JPY3 billion and operating income of JPY1 billion yen. Looking ahead, the company's plan is to deploy its advanced manufacturing technology, and its accumulated know-how and experience of development and commercialization, to expand its business with new biosimilars and reduced manufacturing costs.

Moving into the area of regenerative medicine as its next earnings driver

Pediatric diseases, with a particular focus on rare diseases

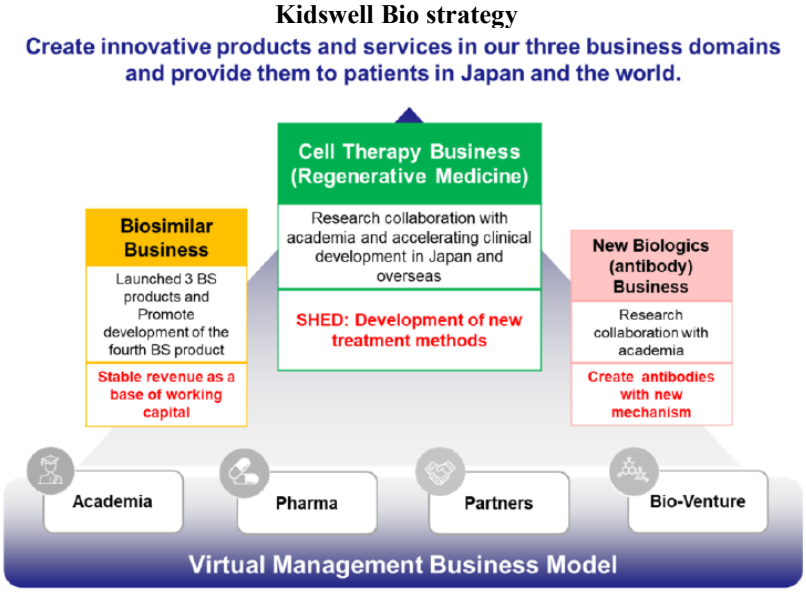
Developing stem cells from human exfoliated deciduous teeth (SHED), a novel modality

With a view to overseas development, it is now concentrating the company's internal resources on SHED's realisation and market launch by 2030

In addition, in 2021 it expressed its intention of lifting corporate value by using the proceeds of its biosimilars business to develop a new earnings driver in the form of cell therapy business (regenerative medicine). Around the same time, it formally changed its name to Kidswell Bio Corporation and made pediatric medicine, particularly rare pediatric disorders, its main area of interest.

In the company's cell therapy business Kidswell Bio uses mesenchymal stem cells for regenerative medicine. However, it is distinguished by its development of a novel modality known as SHED (Stem cells from Human Exfoliated Deciduous teeth). Since 2021, the company has been accelerating investment in SHED as a regenerative medical product based on the favorable results of non-clinical trials. It aims to market a product in 2030 and is currently focusing its internal resources on achieving that. Development in Japan has advantages, such as a conditions-based rapid approval system to support the commercialization of regenerative medicine products. However, market growth will necessitate development in the overseas markets also, notably the US market. For that reason, Kidswell Bio is now preparing to undertake R&D overseas in addition to its development work in Japan.

Kidswell Bio strategy



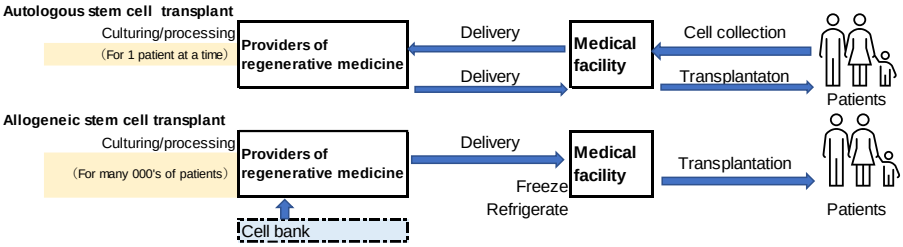
(Source: Kidswell Bio company briefing)

＜What is SHED?＞

In regenerative medicine, the use of allogeneic cells in cell therapy is mainstream

There are two types of regenerative medicine: cell transplantation, which aims to engraft cells to function as part of the tissue at the site of the damage or defect; and cell medicine, which involves the release of growth factors to enhance the regenerative power of the remaining tissue. Further, there are two methods: one using autologous cells, and a second using allogeneic cells. In the former case, the patient's own cells are cultured, processed and returned to the patient. This method tends to be high cost. However, in the case of allogeneic cells, mass cultured cells taken from healthy donors are administered to patients. The cells can be used for numerous different patients and high volume production keeps the costs down.

The business model for autologous and allogeneic cell transplants



(Source: Compiled by Fair Research Inc.)

Much was expected of pluripotent stem cells, such as induced pluripotent stem cells (iPS), but a variety of problems have croppped up

Cells used for cell transplantation may be somatic cells in skin transplantation, or pluripotent stem cells such as iPS cells or ES cells. Somatic cells have low proliferative capacity, and are mostly autologous because of the problem of rejection. What is really needed are pluripotent allogeneic stem cells, but these present a variety of problems in terms of bioethics, cancer risk, production methodology and production cost, and we are still a long way from realisation.

Types of cell

	Mature cells	Tissue stem cells		Pluripotent stem cells		
	Somatic cells	Somatic stem cells	Mesenchymal stem cells	ES cells	iPS cells	MUSE cells
Origin	Various tissue	Various tissue	Bone marrow, dental pulp, adipose tissue etc.	Fertilised eggs	Genetic manipulation of somatic cells	Slight presence in mesenchymal stem cells
Proliferation	Low	Depends on tissue	Very high	Very high	Very high	Very high
Differentiation	None	Limited	Limited	Unlimited	Unlimited	Unlimited
Viral infection	None	None	None	No risk	No risk	No risk
Cancer risk	None	None	None	No risk	**Yes**	No risk
Bioethics	None	None	None	Problematic	None	None

(Source: Compiled by Fair Research from various sources)

Much development work uses MSCs

In cell medicine, however, mesenchymal stem cells (MSC's) are often used. These are somatic cells derived from mesenchyme, widely found in bone marrow, adipose tissue, placenta, umbilical cord and dental pulp and capable of self-replication (proliferation). When cultured in a flask, MSC's attach themselves to the bottom surface exhibiting a spindle shape, and can differentiate into various lineages such as osteoblasts, adipocytes, and chondrocytes depending on the culture conditions. Allogeneic bone marrow-derived MSCs have already been approved and administered in Japan (Temcell® 2015; indication for acute graft-versus-host disease after hematopoietic stem cell transplantation: GVHD).

A lot of attention is focused on bone marrow-derived MSCs (BMMSC) to treat nerve regeneration

Recently, with the aim of regenerating the central nervous system, which is the most difficult organ to repair, the development of regenerative therapeutic drugs for treating cerebral infarction and spinal cord injury has attracted attention. Examples include SanBio's SB623 and Helios's HLCM051, both of which are bone marrow-derived MSCs (BMMSCs).

<SHED characteristics>

Kidswelll Bio is focused on SHED: Stem cells from Human Exfoliated Deciduous teeth

As noted above, unlike other companies, Kidswell Bio uses stem cells from human exfoliated deciduous teeth (SHED). Below we compare the characteristics of SHED with other MSCs.

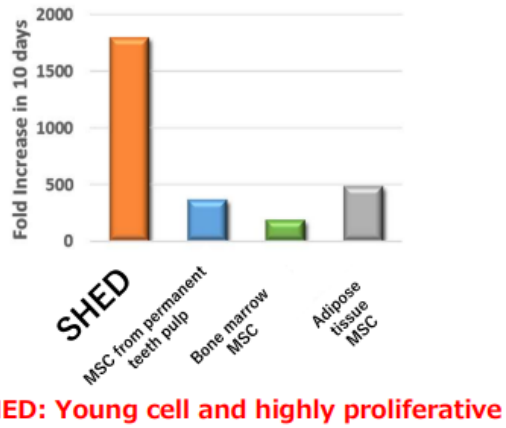
(1) Ease of availability and high proliferation

SHED are superior to other MSCs because it is easier to obtain and has a higher proliferative capacity

Bone marrow-derived mesenchymal stem cells are a potent source of stem cells, but the burden imposed on patients by bone marrow aspiration, the reduction in stem cells due to ageing and the relatively long culturing period make them expensive to manufacture. Meanwhile, umbilical cord blood or umbilical cord-derived stem cells can have a low frequency of mesenchymal stem cells, which affects the reliability of collection. Additionally, adipose-derived stem cells (adipose tissue MSC – ATMSC) require liposuction or other surgery at time of extraction, and this can put a heavy burden on the patient. Dental pulp stem cells, however, are from permanent teeth that are no longer needed (dental pulp stem cells – DPSC), or deciduous dental pulp cells from deciduous teeth that have been discarded after falling out (SHED). These cells, therefore, are relatively easy to obtain.

Further, compared to BMMSC, ATMSC and DPSC, SHED has a much higher proliferative capacity.

Comparison of proliferative capacity



(Source: Kidswell Bio company)

Drugs from other companies that use BMMSCs are finding it difficulet to get approval, but this is due to the difficulty of establishing a system for mass-production of homogeneous cell medicines.

SanBio's SB623 was submitted for approval under the fast track system in March 2022, but six months after the priority review deadline it has still not received approval. We assume the reason for this is that, in the case of BMMSCs, there are difficulties in establishing a system for stable commercial production and supply, such as limited proliferation. We believe Kidswell Bio's SHED is superior to other mesenchymal stem cells because of the ease with which it may be obtained and its high proliferative ability.

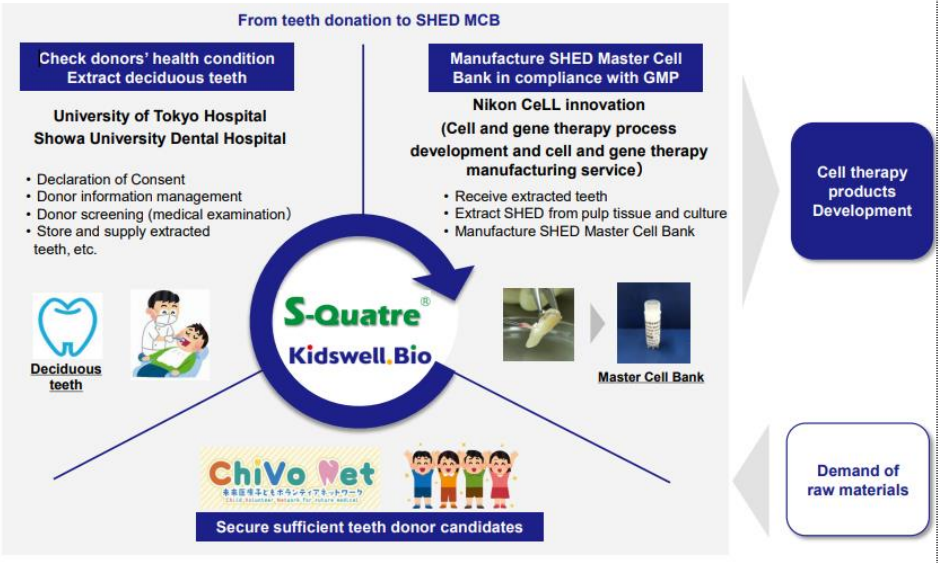
In August 2022 Kidswell Bio became the first company in the world to complete construction of a SHED master cell bank

In the field of cell medicines, many companies are struggling to build a manufacturing process capable of providing a stable supply. Kidswell Bio, however, has already overcome this first hurdle by establishing, in August 2022, a master cell bank of GMP standards. It has also built the world's first system called S-Quatre® to link up partners who develop the pharmaceuticals using the master cell bank by teaming up with an organization (ChiVo Net) to obtain deciduous teeth donors, Tokyo University Hospital and Showa University Dental Hospital to extract teeth, and Nikon Cell Innovation Co., Ltd. to manufacture the SHED master cell bank.

The system is now in place – from engaging donors to manufacture and supply

S-Quatre® （SHED Source Supply Service）

Stable manufacturing & supply system of SHED MCB



(Source: Kidswell Bio company briefing)

MSCs release various cytokines to promote tissue regeneration

(2) Tissue repair function

Mesenchymal stem cells (MSCs) have the ability to differentiate into not only mesodermal cells such as osteoblasts/bone cells, cardiomyocytes, chondrocytes, and adipocytes, but also different germ layer cells such as glial cells and hepatocytes. The mechanism involved does not differentiate MSCs into various cells in the body to replace damaged cells. Instead, it is thought that various cytokines secreted by MSCs act on the cells of the patient to promote tissue regeneration.

As shown in the table below, the various cytokines secreted by the MSCs exhibit various therapeutic effects, including the promotion of tissue repair and the regulation of inflammation and immunity

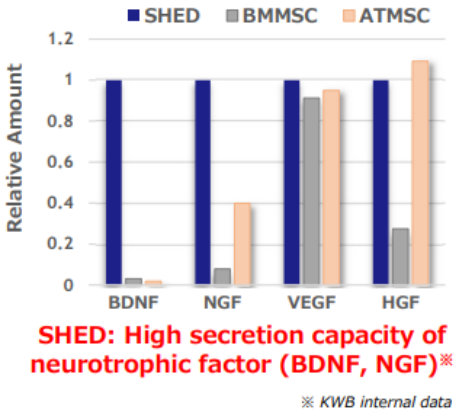
Effects of cytokines secreted by MSCs

Anticipated effect		Effective factors secreted
Tissue repair	Angiogenesis	VEGF, FGF2 ,ANG-1, MCP-1, EPO, HGF
	Cell proliferation	SCF, LIF, M-SCF, SDF-1, FGF2, VEGF, IGF, PDGF, HGF
	Anti-apoptosis of weak cells	FGF2, IGF, ANG-1, IL-6, VEGF, MCP-1, G/M-CSF, STC-1 ,EPO, TGF-β, HGF
	Nerve cell protection	**BDNF, NGF, GDNF**
	Suppression of liver fibrosis	IL-10, TNF-α, HGF,MMP-9
	Suppression of scarring	HGF,FGF2, ANG-1
	Stem cell support	TPO, SCF, TGF-β
	Accumulation at target site	SDF-1, HGF, LIF IGF, G/M-CSF, VEGF
Immunoregulation	Immune cell suppression	TGF-β, PGE-2, HGF, IDO etc.
	Suppression of inflamatory fact	MCP-1etc.

(Source: Compiled by Fair Research Inc. using Atsushi Yokoyama, J-Vet 2013)

SHED are believed to be better than other MSCs for treating nerve disorders, and have a greater ability to rebuild bone

Compared to other MSCs, SHED have a greater ability to secrete neurotrophic factors (BDNF and NGF) and also have a higher expression of neurogenesis-related genes. It is expected therefore they will offer treatment for neurological conditions (spinal cord injury, cerebral infarction, cerebral palsy). In addition, SHED are reported to have a greater bone regeneration ability than other MSCs and can be expected to play a role where such regeneration is called for (intractable bone fractures, femoral head necrosis).



(Source: Kidswell Bio company briefing)

References

- On the comparison of nervous system gene expression levels:
  Terunuma et al., Journal of Stem Cells and Regenerative Medicine May 2019, P10, Figure 2
  「Comparative transcriptomic analysis of human mesenchymal stem cells derived from dental pulp and adipose tissues」

- On the comparison of nervous system growth factors:
  Mead et al. PLOS ONE, October 2014, P7 Table 2
  「Paracrine-Mediated Neuroprotection and Neuritogenesis of Axotomised Retinal Ganglion Cells by Human Dental Pulp Stem Cells: Comparison with Human Bone Marrow and Adipose-Derived Mesenchymal Stem Cells」

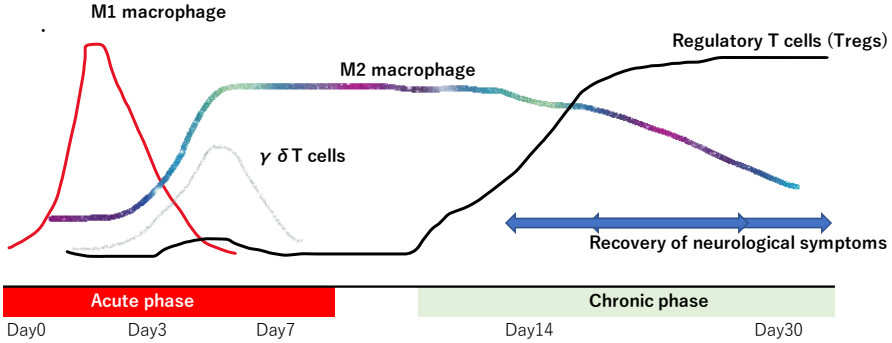
In addition, in the same way as with other MSCs, immunoregulatory and anti-inflammatory effects can also be expected. These are extremely important in the context of spinal cord injury and cerebral infarction.

Immunoregulatory function and anti-inflammatory effect are also important

In the acute phase of spinal cord injury or cerebral infarction, an injury or inflammation can cause a number of events around the area of the injury. This causes a sharp halt to the repair of the damaged neural circuits. For example, inflammatory cells such as macrophage type I (M1) and neutrophils infiltrate the brain 1 to 3 days after brain tissue necrosis. M1 stimulates inflammation by producing inflammatory cytokines such as IL-1β, IL-23 and TNF-α. From day 3 onwards, IL-1β and IL-23 stimulate γδT cells to produce IL-17 (which activates neutrophils and promotes inflammation).

In the acute phase of brain injury, macrophage type 1 (M1) releases inflammatory cytokines

Image of infiltration of cells in the inflammatory process after cerebral infarction



(Source: Compiled by Fair Research Inc. from Experimental Medicine, August 2019: "Innate and Acquired Immunity in Repairing Brain Injury", etc.)

SHED secretes MCP-1 (monocyte chemoattractant protein-1) and sSiglec-9 (secreted ectodomain of sialic acid-binding Ig-like lectin-9), which have an anti-inflammatory effect, and convert pro-inflammatory M1 into macrophage type II (M2). M2 has been shown to act in inflammatory resolution and neuronal repair. It

In SHED, M1 converts to M2, which acts in inflammatory resolution and neural repair

In addition, it accumulates regulatory T cells (Treg) in the chronic stage after inflammation subsides and supports improvement of neurological symptoms

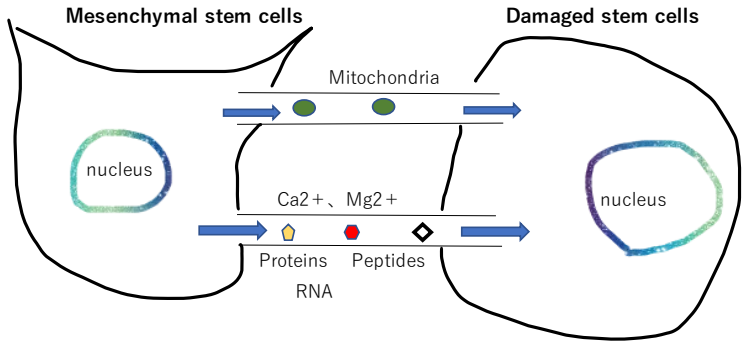
is expected to be effective in the subacute stage when M1 infiltration peaks. (From Fumiya Kano et al. Stem Cells 2017;35).

Of course, in SHED, as in other MSCs, cytokines such as TGF-β and PGE2 can suppress the proliferation of T cells and NK cells, and the operation of immunoregulatory functions can be expected through the induction of Tregs (regulatory T cells). The accumulation of Tregs in the brain in the chronic stage after inflammation subsides controls excessive activation of astrocytes, and is expected to control the deterioration of nerve functions and regenerative disorders due to the formation of glial scars, as well as supporting an improvement of neurological symptoms.

(3) Intercellular communication

Tunneling nanotubes is one method of direct communication between adjacent cells. These are thin tubules that connect cells to each other and are made up of actin. Numerous studies have shown that these tunneling nanotubes transport various substances from one cell to another.

Various substances are transferred from MSCs to injured cells through thin tubules that directly connect cells.



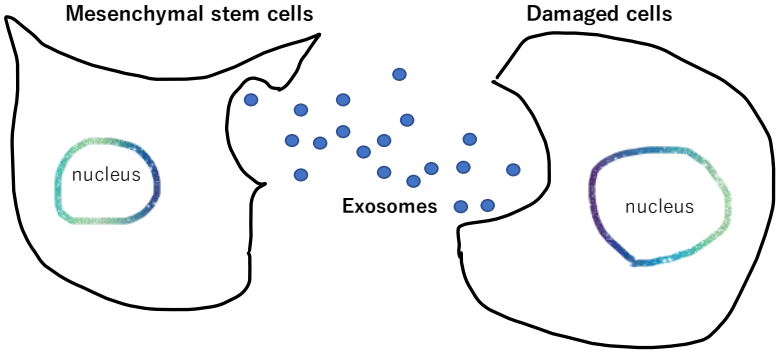
Generally, not only SHED but also BMMSC-derived cell drugs developed by other companies are administered intravenously (not locally). These MSCs migrate closer to damaged cells (homing effect) and supply mitochondria from MSCs to damaged cells via tunneling nanotubes, and transport intercellular signals such as calcium signals and intracellular proteins. The transduction of information is thus achieved and tissue repair promoted.

(4) Exosomes secreted from MSCs

Exosomes are a type of extracellular endoplasmic reticulum with a lipid bilayer membrane structure of about 30-100nm secreted from cells and containing numerous proteins and micro-RNAs. It is now thought that they may contribute to transmitting information between widely separate cells, and there is a recent view that MSC-derived exosomes have a therapeutic effect on various diseases. Kidswell Bio is now considering providing SHED to a partner for the purpose of developing an exosome drug derived from SHED.

Transmission of information between widely separate cells through the release of exosomes

Development of exosome drugs is also a promising possibility



Developing SHED itself as a cell therapy for paediatric and rare diseases with high unmet medical need

Physician-led clinical research to start within a year, followed by company-sponsored trials of POC-qualified product candidates

To avoid the "Galapagos effect" developers have eyed international development from the start

The company is at the same time progressing an upgrade to manufacturing processes

＜First generation SHED＞

Kidswell Bio is now carrying out a number of trials using the peculiar features of SHED to develop cell therapy drugs, dubbed "first generation SHED". The diseases being targeted, shown in the chart below, are in areas where SHED's attributes are most effective, such as neurology and bone repair. Many are classified as paediatric or rarely occurring and for which no effective treatment exists, constituting areas of high unmet medical need.

As of December 2022, many product pipelines are being developed in collaboration with physicians under tie-ups with academia. Within the next year, physician-led trials will start and from the second half of FY2024 the plan is to progress with company-sponsored trials on some diseases for which POC has been confirmed. Kidswell Bio is positing FY2030 as the target date for a final commercial product.

Preparations are being made to undertake SHED research and development beyond Japan. Development in Japan has some systemic advantages, such as the existence of an expedited approval system to support the development of regenerative medicine. But this also limits the market to Japan and, to avoid this, overseas development is also being eyed.

Therefore, in the next two to three years, in line with overseas expansion and the start of company-sponsored clinical trials, it will be necessary to develop the manufacturing process for a scale up of GMP manufacturing of SHED investigational drugs as well as additional manufacturing of master cell banks. At the present time, the company is scheduling the process development of GMP products with several companies, including Minaris Regenerative Medicine, a subsidiary of Showa Denko Materials.

Development Product	Target disease	Symptom	Existing Treatment	Therapeutic target	Partners	Number of patients (Domestic) ※2	Number of patients (Global) ※2
1st generation SHED	Pediatric disease Cerebral palsy	Quadriplegia and Posture disorder	None	Nerve protection, activation and regeneration	Nagoya University, Tokyo Medical and Dental University	2,000 patients per year, 30,000 patients in total	100,000 patients per year, 1.7 millions patients in total
	Pediatric disease Congenital Isolated Hypoganglionosis	Intestinal obstruction	Enterectomy, colostomy	Ganglion regeneration	Mochida Pharmaceutical	100 patients	–
	Including Pediatric disease Spinal cord injury	Loss of motor function and sensation	None	Nerve protection, activation and regeneration	Nagoya University	5,000 patients per year, 100,000 patients in total	25,000 patients per year, 500,000 patients in total (US, EU and Japan)
	Non-union fractures	Chronic pain, gait disturbance	Surgery	Bone regeneration	Hokkaido University and Spinal Injuries Center	100,000 patients per year	–
	Ophthalmologic disease	※1	※1	※1	Gifu Pharmaceutical University	※1	※1
	Peripheral nerve palsy	Motor function and sensation disorder	Nerve reconstruction (Autologous nerve transplantation)	Peripheral nerve regeneration	Oita University	8,000 surgeries per year	–
	Pediatric disease Cleft lip and palate	Eating and speech disorder	Lip arthroplasty + iliac bone graft	Maxilla bone regeneration	ORTHOREBIRTH	2,000 patients per year	15 out of 10,000 newborns

Note*1 Not disclosed *2 Kidswell Bio's estimation using publically available information
(Source: Kidswell Bio company briefing)

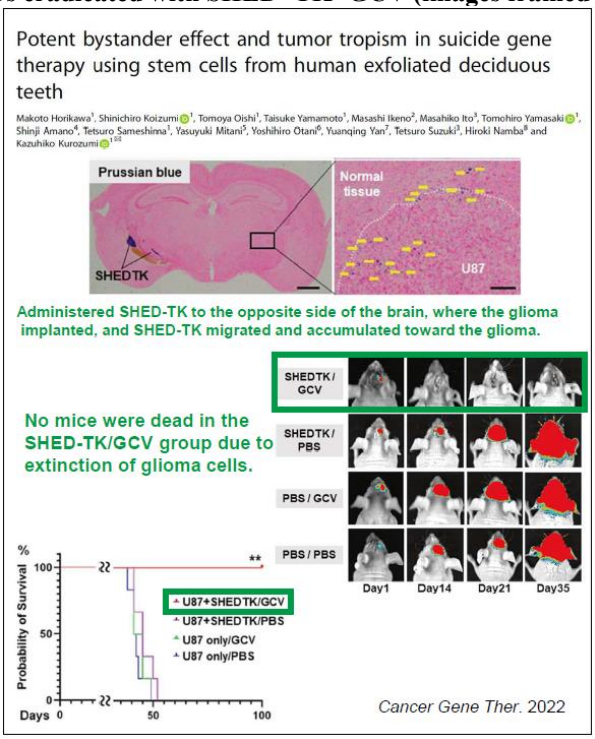
On December 7, 2022, Kidswell Bio published a research paper jointly with Nagoya University Hospital demonstrating that SHED improve neurological symptoms in an animal model of chronic cerebral palsy. Kidswell Bio is thus actively promoting the acquisition of intellectual property related to SHED. Below is an except from that paper.

Reference: Outline of results from research collaboration with Nagoya University

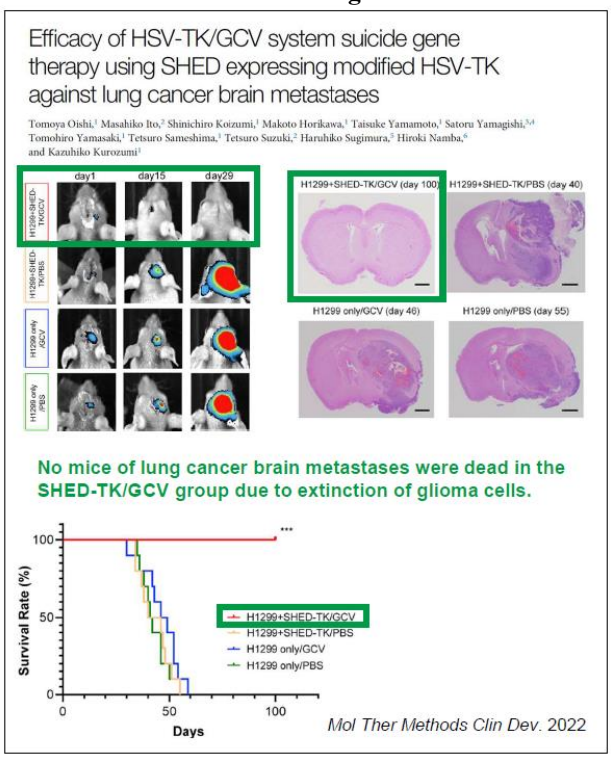
Cerebral palsy is a disease in which neurological symptoms, such as mobility problems, manifest themselves as a result of oxygen deficiency or contraction of an infectious disease during the perinatal period before and after birth. The symptoms are often not clearly apparent in the acute phase immediately after birth. What is needed is a new method of treatment that is effective even if initiated in the chronic

	phase, after the acute phase has passed and the disease has taken hold. Research on stem cell treatments for perinatal brain injury has so far been mainly directed at the acute phase, and there have been no reports of animal experiments demonstrating the efficacy of later interventions. In the research under consideration here, when SHED was administered at a later phase to perinatal encephalopathy model animals which had developed neurological symptoms, brain weight was restored, and motor deficit and learning/memory were improved.
	＜Second generation SHED＞
Anti-cancer drug using SHED as a DDS also under development	In November 2022 Kidswell Bio revealed the details of a second-generation SHED being developed. According to this, the second-generation SHED focuses on SHED's attractiveness to cytokines secreted by tumour cells, thus acting as a DDS (drug delivery system).
Suicide gene therapy using HSVtk and GCV also acts on healthy cells	Originally, suicide gene therapy using herpes virus-derived thymidine kinase (HSVtk) and ganciclovir (Gancicolovir, GCV) was noted for its "bystander effect" in that it could treat many cancer cells rather than only some. It utilizes the fact that ganciclovir is converted by thymidine kinase into a highly toxic substance called 3-phosphorylated ganciclovir. A "bystander effect" is produced by transferring the toxic substance from cell to cell without flowing out of the cells. However, the problem is that HSVtk expression is also induced in healthy cells and 3-phosphorylated GVC causes various forms of cytotoxicity.
Uses the fact that SHED are attracted to cytokines secreted by tumour cells Tumour shrinkage by SHED-TK also confirmation of bystander effect	Kidswell Bio and Hamamatsu University School of Medicine then jointly conducted research focusing on the properties of SHED being induced by four growth factors (SCF, PDGF-BB, CXCL12, VEGF) and attracted to tumor cells. Specifically, SHED (SHED-TK), genetically modified to express thymidine kinase, was administered locally to mice with brain tumours, and GCV was then intravenously administered. As a result, a remarkable reduction in tumour size was observed and tumour cells were killed successively by bystander effects (note: SHED was administered locally because it cannot penetrate the blood-brain barrier).

Tumours eradicated with SHED+TK+GCV (images framed in green)



Effect also confirmed for lung cancer brain metastases



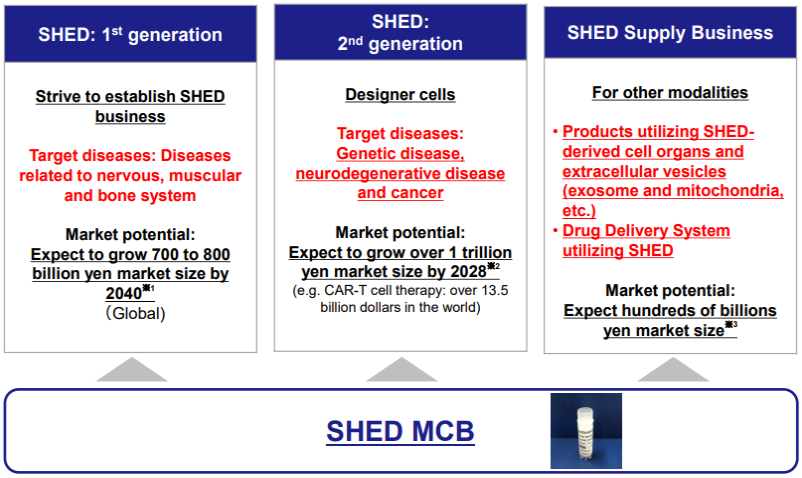
(Source: Both from Kidswell Bio R&D briefing materials)

Secondary effect of nerve regeneration by SHED is also expected

In addition, a secondary effect is expected by which the nerve regeneration action of SHED leads to the regeneration of nerves destroyed by brain tumours.

In addition to SHED-TK, the company is also looking at the development of "designer cells" incorporating various genetic modifications and exosome drugs derived from SHED

As part of second generation SHED, Kidswell Bio is also planning to develop "designer cells" incorporating a variety of genetic modifications, and will aggressively pursue tie-ups with other companies, thereby maximising the value of SHED. Targeted diseases include not only cancer, but could also include genetic diseases and neurodegenerative diseases. In addition, the emergence of therapies using SHED-derived exosomes and other SHED applications could generate new business opportunities.



(Source: Kidswell Bio company briefing)

Kidswell Bio estimates that first generation SHED has a market potential of JPY 700-800 billion, and for second generation SHED a market potential in excess of JPY1 trillion. In addition, other SHED businesses are thought to have potential in the region of several hundred billion yen.

＜Concluding Remarks＞

Kidswell Bio is accelerating the development of SHED, a regenerative medical product, using revenues from its biosimilars business.

SHED could prove to be a major force in regenerative medicine

In the field of regenerative medicine, attention is being paid to the development of bone marrow-derived mesenchymal stem cells (BMMSC) for the regeneration of nerves, said to be the most difficult to regenerate (for cerebral infarction and spinal cord injury). This development has, so far, not received complete regulatory approval. To receive such approval in cell medicine a manufacturing process capable of commercial production is essential, but the stem cells are difficult to obtain, have limited proliferative capacity, and are prone to senescence, thus posing high hurdles to establishing commercial production. SHED is expected to overcome this hurdle relatively easily because it has a higher proliferative capacity and is relatively easier to obtain than other mesenchymal stem cells (MSCs). In addition, SHED is more suitable for nerve regeneration than other mesenchymal stem cells because of its superior ability to secrete neuroprotective factors (e.g., BDNF and NGF). Furthermore, SHED has been shown to be effective in the early acute phase of disease onset, inflammatory convergence, and nerve repair. Hence, its reputation as a major force in regenerative medicine.

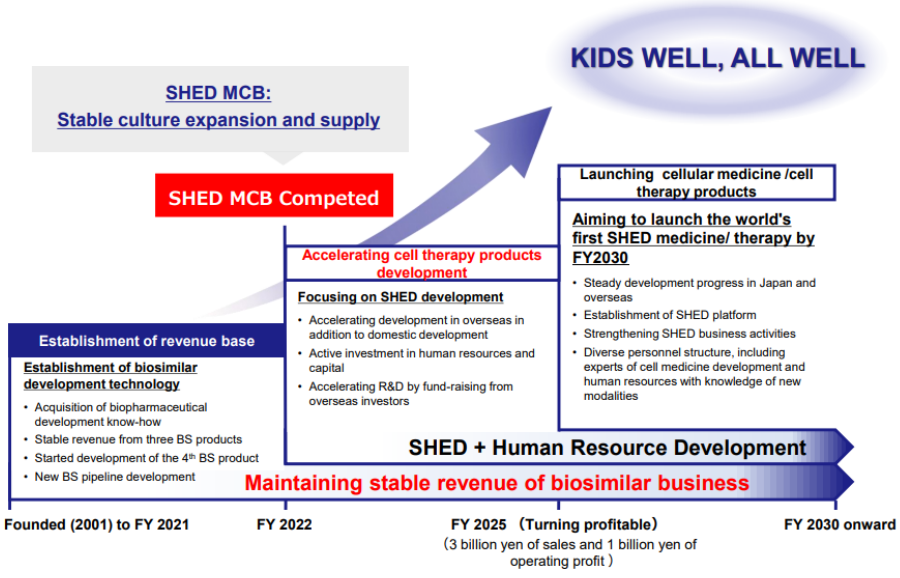
Avoiding the “Galapagos effect” restricting use to Japan only

In addition, in order to avoid the “Galapagos effect” which restricts application to Japan alone, Kidswell Bio has, from the beginning, been focusing on building human resources and platforms with a view to overseas development and expansion.

Establish POC in 2 years and move on to corporate clinical trials

In the summer of 2022, Kidswell Bio was the first in the world to establish a SHED master cell bank (MCB), overcoming a major hurdle. The company plans to establish proof of concept (POC) and move ahead with corporate clinical trials in the next two years, and hopes to achieve the world's first launch of a regenerative medicine product utilizing SHED by FY2030.

Medium term management plan



(Source: Kidswell Bio company briefing materials)

Fair Research Inc.
Floor 4, BIZ SMART Kayabacho
Shinkawa 1-3-21
Chuo-ku
Tokyo 104-0033
Tel. 03-6869-6518
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