First in-human trial protocol investigating a scaffold-free Bio 3D conduit developed from autologous dermal fibroblasts for peripheral nerve regeneration: a safety and feasibility study

Momoko Nagai-Tanima
Ryosuke Ikeguchi (ikeguchi@kuhp.kyoto-u.ac.jp)
Mika Ushimaru
Yoko Amino
Aoi, Ishikawa
Shizuka Akieda
Takashi Noguchi
Hiromu Ito
Tomoki Aoyama
Shuichi Matsuda

Method Article

Keywords: Peripheral nerve injury, Bio 3D conduit, scaffold-free, autologous, dermal fibroblasts, nerve regeneration

Posted Date: March 7th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1414422/v1

Abstract

Background

Autologous nerve grafting is considered to be the gold standard treatment for severe and/or wide-ranging damage resulting in neurotmesis. However, the technique has several disadvantages including donor site morbidity and the limited supply of donor nerves. B3CON-01 is a scaffold-free three-dimensional conduit composed entirely of autologous dermal fibroblasts and is designed to overcome these disadvantages. Herein, the authors propose a protocol to evaluate the safety and utility of B3CON-01 in humans with peripheral nerve injury as the first step before randomized clinical trial test.

Methods

Individuals with a severed peripheral nerve cutting or defect, measuring ≤ 20 mm in length and diameter ≤ 2 mm, will be recruited. After participants provide informed consent, autologous dermal fibroblasts will be collected from each via skin biopsy. B3CON-01 is produced using the fibroblasts and transplanted into each subject. To avoid contamination among tissues, the protocol will be performed separately in each subject. Outcomes will be assessed at baseline and post-intervention at each time point. Participants will be assessed at 12 months' follow-up. The primary outcome measure is the safety of the intervention. The safety endpoint will be the incidence of adverse events and defects. As a secondary assessment, efficacy will be assessed using nerve system and functional analyses.

Conclusion

The protocol of this study will be the first to assess the safety and efficacy of B3CON-01 in humans, and will contribute to not only the development of a treatment for peripheral nerve injury, but also to "made-to-order" personalized therapies in regenerative medicine.

1. Background

Several approaches have been used to treat traumatic peripheral nerve injuries, such as neurotmesis, axonotmesis and neurapraxia, according to the severity of the injury [1, 2]. Generally, follow-up and rehabilitation are accepted strategies for axonotmesis and neurapraxia depending on the degree of paralysis, while suturing both sides of the nerve stump is an accepted technique for neurotmesis. In cases of severe or wide-ranging damage in neurotmesis, it is difficult to bind the bilateral stump. In this case, autologous nerve grafting is considered to be the gold standard treatment to bridge the interstump gap [3, 4]. However, autologous nerve grafting has several disadvantages including donor site morbidity, limited supply of donor nerves, potential neuroma formation at the donor site and, frequently, disappointing functional outcomes [5, 6]. To overcome these disadvantages, a tubulization technique using a nonautogenous biological conduit and nonbiological conduit has been developed [7]. Several

tubulization techniques have been used in selected clinical settings [8]. Currently, however, the technique is not widely used because conduit(s) fabricated using artificial materials have limitations; more specifically, it is difficult to use near a joint and results in poor nerve regeneration, foreign body reaction(s), and the risk for infection. Regeneration likely fails due to the lack of neurotrophic support, blood vessels, and growth factors from the nerve end site because artificial conduits are insufficient to act as an extracellular matrix scaffold such as in end-to-end repair [7, 8]. As such, artificial conduits are not the primary choice for the treatment of nerve defects [9]. In addition, a meta-analysis of median and ulnar nerve repairs reported that satisfactory motor and sensory recovery was achieved in < 52% of cases [10]. Furthermore, the study revealed that many patients remained unsatisfied with function after nerve repair despite the existence of many treatment options for peripheral nerve injury.

To overcome these problems, we created the “Bio 3D” conduit as a novel material and assessed its efficacy using animal models. The Bio 3D conduit is a scaffold-free tubular tissue consisting entirely of homogenous multicellular spheroids fabricated without synthetic materials and constructed using a computer-controlled three-dimensional (3D) printer [11]. In our previous studies, we confirmed the efficacy of the Bio 3D conduit in peripheral nerve regeneration after nerve defects in rodents [12] and canines [13]. In these investigations, the Bio 3D conduit worked well for nerve regeneration—both functionally and morphologically—regardless of whether it was heterogenous or autologous. The proof of concept of this technique, feasibility, and efficacy as a treatment for peripheral nerve injury and segmental nerve defects was demonstrated using medium-size mammals [13]. Based on the results of these non-clinical trials, the Bio 3D conduit demonstrated three advantages: a high level of safety using non-scaffold and is biomaterial free; 3D tissue can be constructed using only homogenous multicellular spheroids; and a high potential for regeneration compared with other artificial conduit(s). Therefore, the Bio 3D conduit is anticipated to be a promising alternative to autologous nerve transplantation.

Accordingly, the primary objective of this study is to examine the safety and usability of a biological, scaffold-free, 3D conduit composed entirely of autologous dermal fibroblasts (i.e., B3CON-01) in human patients with peripheral nerve injuries undergoing nerve reconstruction. A secondary objective will be to evaluate the safety of the treatment.

2. Material And Methods

2.1. Primary objective

The safety and efficacy of B3CON-01 in patients with peripheral nerve cutting or defect in the distal part of the wrist joint will be assessed by measuring motor and sensory nerve function in the affected upper limb over a 48-week period after transplantation.

2.2. Study design

This single-institutional, nonblinded, non-randomized controlled trial received ethics approval from the Institutional Review Board (IRB) of Kyoto University Hospital (Kyoto, Japan) on March 25, 2020 (K069,

protocol version 1.0, February 2020). Any protocol modification(s) will be approved by the IRB before implementation. This study will be conducted in accordance with the study protocol and adhere to the principles of the Helsinki Declaration [14]. This study will confirm the safety of the experiment and quality management of transplantation materials after general toxicity tests and tumor tests, in agreement with the Pharmaceuticals and Medical Devices Agency.

2.3. Setting

The trial will be conducted at the Kyoto University Hospital, located in Kyoto, Japan. B3CON-01 is produced by the Center for Cell and Molecular Therapy (CCMT) at Kyoto University Hospital. The safety of B3CON-01, when applied for a 48-week period, has not been previously investigated in humans. Academic hospitals, where at least one investigator-initiated clinical trial was performed in accordance with good clinical practices (GCP) has been conducted, will be recruited.

2.4. Eligibility criteria

2.4.1. Inclusion criteria

Individuals (male or female) fulfilling the following criteria will be included: 1) (those with) severed peripheral nerve injuries or a defect in the region distal to the wrist joint not caused by a congenital anomaly; 2) defect ≤ 20 mm in length in a nerve with a diameter ≤ 2 mm; 3) available results data from sensory functional tests, including the Semmes-Weinstein monofilament test (SWT), static and moving 2-point discrimination sensory functional tests (s2PD and m2PD, respectively) failed on the dermatome distribution of the injured peripheral nerve; 4) able to register in the protocol within six months from the day of injury; 5) refused artificial nerve or autologous nerve transplantation; 6) age ≥ 20 to ≤ 60 years; and 7) willingness to participate and provide informed written consent.

2.4.2. Exclusion criteria

Individuals (male or female) fulfilling any of the following criteria will be excluded: 1) peripheral nerve injury including those in the fingers affected by injury from infection and severe damage of accessories including the skin, tendon and bone, injury at multiple sites of the nerve and wide area, direct suture is not feasible; 2) antibodies to hepatitis B, anti-human immunodeficiency virus, or anti- human T-cell leukemia virus; 3) active infection, such as hepatitis C, syphilis (*Treponema pallidum* antibody-positive in serological tests for syphilis), and human parvovirus B19; 4) a history of allergy or anaphylaxis reaction to a component(s) of the clinical trial products, such as aminoglycoside antibiotics, polyene macrolide antibiotics, bovine serum and/or metal(s); 5) one of the following complications including cardiovascular disease(s), diabetes mellitus, stroke (including history), cervical spondylosis, cervical myelopathy, polyneuropathy, Guillain-Barre syndrome, amyotrophic lateral sclerosis, peripheral circulatory failure, rheumatoid arthritis, collagen disease, depression, schizophrenia, automatic neuropathy, or dementia; 6) malignant disease and/or medical history thereof; 7) previous treatment with immunosuppressive agents and/or steroids excluding local effects; 8) simultaneous participation in another interventional trial and/or a clinical trial within the previous 3 months before enrolment in this trial; 9) history of participation

in studies investigating the transplant of the clinical trial products; 10) pregnant females, those lactating, and those unwilling to prevent pregnancy during the study period; and 11) individuals judged by the attending physician to be unfit or not suitable for the study.

2.5. Recruitment

Subjects will be recruited from the orthopedic surgery clinics at Kyoto University Hospital. Patients will be eligible only if they provide written informed consent, and if the investigator verifies they have fulfilled all of the inclusion criteria and none of the exclusion criteria.

2.6. Study flow

Because B3CON-01 is being used for the first time in humans, the study will be conducted according to the schedule shown in Table 1. The trial procedure includes participant registration, transplantation of B3CON-01, and the end of observation. The procedure can be divided into three distinct periods: material culture (from skin biopsy to culture of material); treatment (from hospitalization for transplantation to discharge); and observation (from discharge to the end of the observation period). A schematic illustrating the entire process and details of the culture process are shown in Fig. 1.

After carefully confirming safety in each participant in whom the product is transplanted, whether the next transplantation step can start will be judged. The safety assessment committee will be consulted and asked to advise on the appropriateness of starting the next study for each participant.

2.7. Material culture period

2.7.1. Before intervention

After participants provide written informed consent, an eligibility confirmation sheet, drafted by the attending physician, is sent to the data center to confirm any unclear points related to the study on the patients. After this process, participants will be added to the screening list. Screening will be performed by the attending physician to investigate medical background and eligibility for the study. When using the assessment results obtained before informed consent, participant agreement is required. Registration will be considered to be complete after these processes.

2.7.2. Production of B3CON-01

Skin biopsy for the transplanted materials: Intact skin tissue (> 1 cm^2) from each patient will be biopsied from the abdomen or inguinal region in the operating room at Kyoto University Hospital.

Fabricating the Bio 3D conduit from skin tissue: Skin tissue will be transferred to a cell culture room in the CCMT immediately after skin biopsy. Approximately 8 weeks before surgery, a piece of skin tissue is harvested.

The following protocol will be used [13]. Dermal fibroblasts from passages 4 to 5 are used in this study. Conduits are assembled from each patient fibroblast using a Bio-3D printer (Cystrix™, Cyfuse, Tokyo,

Japan) as previously described [11]. Fibroblast multicellular spheroids are created after cell aggregation process in a 96-well plate. Using a Bio-3D printer, spheroids are aspirated into a fine suction nozzle from the 96-well plate, skewered into a circular needle-array made from stainless steel, and permitted to develop into a tubular structure according to the pre-designed pattern. Approximately 1 week after this procedure, adjacent spheroids are conglutinated to create the Bio 3D conduit, and the needle-array is removed. The obtained Bio 3D conduits are transferred to a perfusion bioreactor, where a silicon tube with an external diameter of 5 mm is placed inside each Bio 3D conduit. Perfusion cultivation is continued until the desired function and strength is achieved. The mature conduit structure is > 20 mm in length and 2.5 ± 1 mm in diameter. This processes takes approximately 60 days. Process management assessment is conducted at the following time points: primary cell culture; after spread culture; after spheroid preparation; and before transfer to the operating room. In addition, material assessment is performed at the time of receiving the tissue sample before cell culture and the time before transferring B3CON-01 to the operating room.

2.8. Treatment period

2.8.1. Autologous transplantation of the 3D conduit

At the time of receiving the made-to-order conduit material from the CCMT in the operating room, each patient will be anesthetized and a skin incision is made on the nerve injured in the upper limb. The injured unilateral nerve is exposed by removing the subcutaneous tissue and creating an operational area. Each patient's own 20 mm Bio 3D conduit will be interposed between the proximal and distal stumps. Each stump is then pulled 1.5 mm into the conduit and anchored in place using epineural 10–0 nylon sutures, bridging the interstump gap in the conduit. The wound is closed in layers using 5–0 nylon sutures. Following this procedure, a cast is placed on the forearm for three weeks. After transplantation, the operation site will be treated with disinfection and/or removed nylon sutures, as appropriate. The timing of discharge is decided after confirming the good condition of the entire body and the treated site 3 days after transplantation. Rehabilitation will be provided and performed at each patient's home.

2.8.2. Discontinuation

The intervention may be discontinued due to adverse event(s) or any other reason(s) based on the discretion of the investigator, or the participant requests discontinuation/withdrawal from the study.

2.8.3. Observation period

Adherence assessments are scheduled at 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 weeks after transplantation. Functional analysis and hematological tests will be performed at 4, 12, 24, 36, and 48 weeks after transplantation to monitor the condition of the affected forelimb and the body's response.

2.9. Adherence assessment

Clinicians will interview and examine participants to assess adherence to the protocol. Participants condition will be confirmed subjectively or objectively, fault symptoms, and vital signs: blood pressure,

pulse, and body temperature. The occurrence of adverse events, failure of the body, and information regarding combination treatment will also be confirmed. These assessments are performed at each time point in the study protocol.

2.10. Measurements

The primary assessment is the safety of the intervention. The safety endpoint is the incidence of adverse events and defects. It is assumed that adverse events or defects will be induced by the materials in the trial, transportation, and/or skin biopsy for fabricating the material.

The secondary assessment is efficacy. Several analyses will be performed to capture aspects of the sensory and motor nerve systems and physical function of the affected forelimb, including: sensory functional test; impairment assessment of the upper limb; and motor nerve function analysis.

2.10.1. Sensory functional tests: SWT, s2PD, and m2PD

The median and ulnar nerves were compounded in the carpal tunnel. SWT is a widely used clinical test to quantify sensibility in patients with Carpal Tunnel Syndrome [15]. It measures the response to touching sensation of the monofilaments according to a numerical quantity. Based on the results, grading is divided into three categories: excellent, good, and poor [16]. The s2PD and m2PD are also common in the battery of sensory tests, and are used in subjects with median and ulnar nerve injuries on the upper limb [17, 18]. The length of the two-point discrimination was assessed. For each test, grading will be classified as excellent, good, or poor based on the results [18].

2.10.2. Assessment of impairment in the upper limb

The shortened Disabilities of the Arm, Shoulder, and Hand Questionnaire (QuickDASH) is an 11-item questionnaire used to assesses physical function and symptoms in individuals with any or multiple upper limb musculoskeletal disorders [19, 20]. It can assess impairment in the upper limb and is highly responsive and validated for different patient populations with upper limb pathologies. A higher value corresponds to greater disability/severity of symptoms.

2.10.3. Motor nerve function analysis

Three types of analyses will be performed to assess motor nerve function in the median and ulnar nerves. The “Perfect O” sign, which can be used to grossly verify function in the median nerve and specifically test the anterior interosseous nerve, is a common physical examination tool and is used in clinical practice [21]. The collapse of the Perfect O sign reflects reduced functionality and muscle weakness innervated by the median nerve. “Froment’s sign” is a well-known physical examination of the hand to test for palsy or disability of the ulnar nerve. It is used to evaluate the strength of the adductor pollicus of the thumb, which is innervated by the ulnar nerve. A positive sign reflects reduced functionality and muscle weakness in the pinch grip [22]. Similar to hand action, tip pinch and key pinch strength are widely used as functional tests of motor nerves in the hand [23]. The “manual muscle test (MMT)” is used as a motor nerve functional test to assess the quantitative maximum force of muscles associated with the median

and ulnar nerves. The MMT is widely used to evaluate the maximum force a muscle is capable of generating, and its reliability has been confirmed [24]. It is scored on a scale graded from 0 to 5, with grade 5 indicating normal muscle function and grade 0 indicating complete paralysis [25]. This will be applied to the participants, as appropriate.

2.11. Assessment of adverse events

All adverse events will be assessed and recorded according to trial site and patient, and reported in a predesigned booklet throughout the entire course of the study including: date of the initial event; policy decision date; details of adverse event(s); total number of adverse events; total number of follow-up days (number of days in the observation period). All adverse events including the number of patients who experienced at least one adverse event and number of patients who discontinued treatment due to adverse events will be reported to the data center and handled in accordance with regulatory requirements. The safety assessment committee will be asked to advise in cases in which the endpoint may be affected.

2.12. Data analysis

The efficacy analysis subject group will include participants who are assessed at least once after transplantation. Individuals committing a serious violation of the study process or GCP, and/or demonstrate noncompliance after registration, will be excluded. The safety analysis subject group includes participants who undergo skin biopsies after registration. Problematic data will be discussed and judged by the physician and the chief of statistical data analysis to determine whether they will be included in the analysis. Missing data will not be imputed. Details regarding problematic data (e.g., item name, content, and decision date) will be recorded. Intermediate analysis is not scheduled to be performed. Demographic data will be assessed for the proportion of each item. Measurable demographic data will be assessed using summary statistics.

The main analysis, is safety analysis, will be conducted for the safety analysis subjects. The number of adverse and fault events that are likely related to the products in or processes of transplantation after skin biopsy will be counted. In addition, the percentage of each event will be calculated using the results from all samples.

The results of the sensory functional analysis will be used for sub-analysis. In the efficacy analysis subject group, the time transition from transplantation to 48 weeks after transplantation and the maintenance factor will be assessed for the results of SWT, s2PD, and m2PD. All analyses will be performed using JMP Pro 15 (SAS Institute, Cary, NC, USA).

2.13. Sample size

It takes 60 days to obtain the transplantation materials after skin biopsy because conduit maturation requires extensive processes and time; moreover, there is only one available device for the protocol. Furthermore, the device can culture only a single conduit at once to avoid contamination from other patient samples. Therefore, it is difficult to overlap the protocol duration for each patient because safety will be confirmed in each step of the study. From the perspective of feasibility and ensuring safety, a sample size of three, as the initial set up, was agreed upon to complete the clinical protocol.

2.14. Data collection and management

Investigators and clinical research coordinators will be advised to complete case report forms in the booklet while following instructions. Each completed booklet will be copied to the attending physician and submitted to the data center at the Institute for Advancement of Clinical and Translational Science (iACT). The data in the booklet will be entered into a database using a double-entry method. Data quality will be validated by checking for missing and out-of-range values.

The data will be stored in the data center and housed in a secure server to maintain participant anonymity. Participants will not be identified by their names, addresses, or telephone numbers, but by unique case registration numbers in combination with the date of the investigation.

2.15. Monitoring

An independent data monitoring committee has been established to assess safety data if serious adverse events should occur, and to assess whether the per-protocol set requires any modification(s). A qualified and independent auditor has been appointed to audit the trial systems and trial conduct before and during the study in accordance with a written procedure.

2.16. Reporting checklist

The Standard Protocol Items: Recommendations for Interventional Trials (i.e., SPIRIT) reporting guidelines were used to compile the checklist for this protocol (Supplemental Fig. 1).

3. Discussion

Currently, artificial conduits are not the primary choice in the treatment of nerve defect(s) due to difficulties introduced by the degradability of materials, such as silicon, and inadequate results. B3CON-01 will enable the bridging of nerve gaps without unnecessary tension owing to its high potential for regeneration compared with other artificial conduits. This study is designed as a non-randomized, controlled clinical trial as an initial step to confirm the efficacy and safety of B3CON-01 while ensuring the safety of the sample population. To our knowledge, this is the first human experimental study using a scaffold-free tubular tissue composed entirely of homogenous multicellular spheroids without synthetic

materials. A positive outcome with B3CON-01 would not only improve the treatment of peripheral nerve injuries, but also contribute to the development of “made-to-order” therapies in personalized regenerative medicine. To evaluate B3CON-01 as a clinically effective treatment, a randomized controlled trial will be conducted following this study.

Abbreviations

3D: three-dimensional; IRB: institutional review board; CCMT: Center for Cell and Molecular Therapy; GCP: Good clinical practices; SWT: Semmes-Weinstein monofilament test; s2PD and m2PD: Static and moving 2-point discrimination sensory functional test; QuickDASH: The shortened Disabilities of the Arm, Shoulder and Hand Questionnaire; MMT, manual muscle test; iACT, Institute for Advancement of Clinical and Translational Science; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Declarations

Ethics approval and consent to participate

This trial received ethics approval from the Institutional Review Board at Kyoto University Hospital on March 25, 2020 (K069, protocol version 1.0, February 2020). The protocol was evaluated and approved by the Japan Registry of Clinical Trials (jRCT2053200022, Registered on June 1, 2020). Informed written consent to participate in the study will be obtained by the investigator from all eligible participants and housed at Kyoto University Hospital.

Availability of data and materials

Not applicable.

Competing interests

Shizuka Akieda, the President of Cyfuse, contributed to the fabrication of the 3D conduits, and Cyfuse provided the bioprinter to fabricate the conduit.

Funding

This study was funded, in part, by grants from the Japan Agency for Medical Research and Development (AMED) under Grant Numbers 17lm0203034h0001, 18lm0203053h0001, and 19lm0203053h0002.

Authors' contributions

RI, CP, MU, YA, SA, TN, HI, TA, and SM contributed to the definition of intellectual content. RI, TA, and YA conceptualized the study. RI, TA , AI, and YA will conduct the products, collection, and data analysis. MN, RI, TA, and YA were involved in drafting. All authors have written, reviewed, and approved the manuscript.

Acknowledgements

The authors thank the staff involved in this trial in the CCMT and iACT at Kyoto University.

References

1. Seddon HJ. A classification of nerve injuries. Br Med J. 2 (1942) 237–239. https://doi.org/10.1136/bmj.2.4260.237.
2. Grinsell D, Keating CP. Peripheral nerve reconstruction after injury: A review of clinical and experimental therapies. BioMed Res Int. 2014 (2014) 698256. https://doi.org/10.1155/2014/698256.
3. Lundborg GA. A 25-year perspective of peripheral nerve surgery: Evolving neuroscientific concepts and clinical significance. J Hand Surg Am. 25 (2000) 391–414. https://doi.org/10.1053/jhsu.2000.4165
4. Matsuyama T, Mackay M, Midha R. Peripheral nerve repair and grafting techniques: A review. Neurol Med Chir. 40 (2000) 187 – 99. https://doi.org/10.2176/nmc.40.187
5. Kim DH, Han K, Tiel RL, Murovic JA, Kline DG. Surgical outcomes of 654 ulnar nerve lesions. J Neurol Surg. 98 (2003) 993–1004. https://doi.org/10.3171/jns.2003.98.5.0993
6. Moore AM, Ray WZ, Chenard KE, Tung T, Mackinnon SE. Nerve allotransplantation as it pertains to composite tissue transplantation. Hand. 4 (2009) 239 – 44. https://doi.org/10.1007/s11552-009-9183-x
7. Griffin MF, Malahias M, Hindocha S, S, KW. Peripheral nerve injury: Principles for repair and regeneration. Open Orthop J. 8 (2014) 199–203. https://doi.org/10.2174/1874325001408010199
8. Konofaos P, Ver Halen JP. Nerve repair by means of tubulization: Past, present, future. J Reconstr Microsurg. 29 (2013) 149 – 64. https://doi.org/10.1055/s-0032-1333316
9. Mafi P, Hindocha S, Dhital M, Saleh M. Advances of peripheral nerve repair techniques to improve hand function: A systematic review of literature. Open Orthop J. 6 (2012) 60–8. https://doi.org/10.2174/1874325001206010060
10. Ruijs ACJ, Jaquet JB, Kalmijn S, Giele H, Hovius SER. Median and ulnar nerve injuries: A meta-analysis of predictors of motor and sensory recovery after modern microsurgical nerve repair. Plast Reconstr Surg. 116 (2005) 484–496. https://doi.org/10.1097/01.prs.0000172896.86594.07
11. Itoh M, Nakayama K, Noguchi R, Kamohara K, Furukawa K, Uchihashi K, et al. Scaffold-free tubular tissues created by a bio-3D printer undergo remodeling and endothelialization when implanted in rat aortae. PLOS ONE. 10 (2015) e0136681. https://doi.org/10.1371/journal.pone.0136681
12. Yurie H, Ikeguchi R, Aoyama T, Kaizawa Y, Tajino J, Ito A, et al. The efficacy of a scaffold-free bio 3D conduit developed from human fibroblasts on peripheral nerve regeneration in a rat sciatic nerve model. PLOS ONE. 12 (2017) e0171448. https://doi.org/10.1371/journal.pone.0171448
13. Mitsuzawa S, Ikeguchi R, Aoyama T, Takeuchi H, Yurie H, Oda H, et al. The efficacy of a scaffold-free bio 3D conduit developed from autologous dermal fibroblasts on peripheral nerve regeneration in a canine ulnar nerve injury model: A preclinical proof-of-concept study. Cell Transplant. 28 (2019) 1231–41. https://doi.org/10.1177/0963689719855346

14. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. JAMA. 310 (2013) 2191–2194. https://doi.org/10.1001/jama.2013.281053
15. Raji P, Ansari NN, Naghdi S, Forogh B, Hasson S. Relationship between Semmes-Weinstein Monofilaments perception Test and sensory nerve conduction studies in carpal tunnel syndrome. Neurorehabilitation. 35(2014) 543–552. https://doi.org/10.3233/NRE-141150
16. McGill M, Molyneaux L, Yue DK. Use of the Semmes-Weinstein 5.07/10 gram monofilament: The long and the short of it. Diabet Med. 15 (1998) 615–617. https://doi.org/10.1002/(SICI)1096-9136(199807)15:7<615::AID-DIA641>3.0.CO;2-P
17. Fonseca MCR, Elui VMC, Lalone E, Da Silva NC, Barbosa RI, Marcolino AM, et al. Functional, motor, and sensory assessment instruments upon nerve repair in adult hands: Systematic review of psychometric properties. Syst Res. 7 (2018) 175. https://doi.org/10.1186/s13643-018-0836-0
18. Jerosch-Herold C. Measuring outcome in median nerve injuries. J Hand Surg Br. 18 (1993) 624–628. https://doi.org/10.1016/0266-7681(93)90019-c.
19. Su Y. QuickDASH. J Physiother. 60 (2014) 167. https://doi.org/10.1016/j.jphys.2014.06.003
20. Beaton DE, Wright JG, Katz JN, Amadio P, Bombardier C, Cole D, et al. Development of the QuickDASH: COmparison of three item-reduction approaches. J Bone Jt Surg - Ser A. 87 (2005) 1038–1046. https://doi.org/10.2106/JBJS.D.02060
21. Mohammed AA, Robertson FML, Shah N. Physical examination: Extended OK sign. MOJ Orthop Rheumatol. 9 (2017) 00353. https://doi.org/10.15406/mojor.2017.09.00353
22. Richardson C, Fabre G. Froment's sign. J Audiov Media Med. 26 (2003) 34. https://doi.org/10.1080/0140511031000091284
23. Sallam AA, El-Deeb MS, Imam MA. Useful functional outcome can be achieved after motor nerve transfers in management of the paralytic hand. An observational study. HSS J. 12 (2016) 2–7. https://doi.org/10.1007/s11420-015-9459-3
24. Cuthbert SC, Goodheart GJ. On the reliability and validity of manual muscle testing: A literature review. Chiropr Osteopat. 15 (2007) 4. https://doi.org/10.1186/1746-1340-15-4
25. Conable KM, Rosner AL. A narrative review of manual muscle testing and implications for muscle testing research. J Chiropr Med. 10 (2011) 157 – 65. https://doi.org/10.1016/j.jcm.2011.04.001

Table

Table 1 is available in the Supplementary Files section

Figures

Figure 1

Entire scheme and details of the cell culture schedule.

Cell culture is performed at the Center for Cell and Molecular Therapy (CCMT) at Kyoto University Hospital. Approximately 60 days are required to produce B3CON-01. Process management assessment (arrowhead) is performed at the following time points: primary cell culture; after spread culture; after spheroid preparation; and before transfer to the operating room. Receiving or transfer assessment (arrow) is performed at the time of receiving the tissue sample before cell culture and the time before transferring B3CON-01 to the operating room.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table.1.png
- SPIRITM.NagaiTanima.png