

# Standardized derivation and biobanking of dermal fibroblasts using explant culture: A pilot protocol for translational neurodegeneration research

## Obtención estandarizada y biobanco de fibroblastos dérmicos mediante cultivo de explantes: protocolo piloto para la investigación traslacional en neurodegeneración

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### ABSTRACT

**Objectives:** To describe a pilot standardized protocol for the collection, explant culture, cryopreservation, and biobanking of dermal fibroblasts derived from 4-mm skin punch biopsies. **Methods:** Dermal fibroblasts were obtained from 4-mm skin punch biopsies collected from two healthy donors. The protocol incorporated tissue microfragmentation, the use of pre-wetted glass coverslips to promote explant adherence, and an enriched fibroblast culture medium. **Results:** Fibroblast outgrowth was observed within 5–7 days after biopsy collection, and cultures reached sufficient density for expansion within 2–3 weeks. Cells displayed the characteristic spindle-shaped morphology of dermal fibroblasts under phase-contrast microscopy. Post-thaw viability exceeded 85% in both cryopreserved cell lines, while quality control testing confirmed sterility and the absence of mycoplasma contamination in all stored samples. **Conclusions:** This pilot study demonstrates the feasibility of establishing, cryopreserving, and biobanking dermal fibroblast cultures from small skin biopsies using an explant culture approach. The protocol provides a practical framework for the development of cellular biobanking resources and highlights the potential application of dermal fibroblast cultures in neurogenetic and neurodegenerative disease research.

**Keywords:** Biological Specimen Banks; Biopsy; Cell Culture Techniques; Fibroblasts; Genetics (source: MeSH NLM).

### RESUMEN

**Objetivos:** Describir un protocolo piloto estandarizado para la obtención, cultivo por explantes, criopreservación y biobanco de fibroblastos dérmicos derivados de biopsias cutáneas por punch de 4 mm. **Materiales y métodos:** Se obtuvieron fibroblastos dérmicos a partir de biopsias cutáneas por punch de 4 mm recolectadas de dos donantes sanos. El protocolo incorporó la microfragmentación del tejido, el uso de cubreobjetos de vidrio previamente humedecidos para favorecer la adherencia de los explantes y un medio de cultivo enriquecido para fibroblastos. **Resultados:** El crecimiento de fibroblastos se observó entre los 5 y 7 días posteriores a la obtención de la biopsia, y los cultivos alcanzaron una densidad suficiente para su expansión en un período de 2 a 3 semanas. Las células mostraron la morfología fusiforme característica de los fibroblastos dérmicos bajo microscopía de contraste de fases. La viabilidad posterior a la descongelación superó el 85% en ambas líneas celulares criopreservadas, mientras que las pruebas de control de calidad confirmaron la esterilidad y la ausencia de contaminación por micoplasma en todas las muestras almacenadas. **Conclusiones:** Este estudio piloto demuestra la factibilidad de establecer, criopreservar y almacenar en un biobanco cultivos de fibroblastos dérmicos obtenidos a partir de pequeñas biopsias cutáneas mediante un enfoque de cultivo por explantes. El protocolo proporciona un marco práctico para el desarrollo de recursos de biobancos celulares y resalta el potencial de aplicación de los cultivos de fibroblastos dérmicos en la investigación de enfermedades neurogenéticas y neurodegenerativas.

**Palabras clave:** Bancos de Muestras Biológicas; Biopsia; Técnicas de Cultivo de Célula; Fibroblastos; Genética (fuente: DeCS BIREME).

## INTRODUCTION

The explant culture method is a widely adopted strategy for fibroblast isolation and the establishment of primary fibroblast cultures from skin biopsy specimens [1,2]. This approach has been extensively used in biomedical research, including studies of rare neurogenetic disorders, providing a valuable platform for investigating disease mechanisms [3,4].

Rare neurogenetic diseases encompass a wide range of inherited conditions affecting the nervous system, including cerebellar ataxias [5], leukodystrophies [6], neurodevelopmental syndromes [7], and early-onset neurodegenerative disorders [8,9]. The development of reliable in vitro cellular models derived directly from affected individuals is a critical step toward understanding the pathogenic mechanisms of many neurogenetic diseases, as well as advancing therapeutic research. Dermal fibroblasts are a valuable resource in this context due to their ease of access, genetic stability, and compatibility with reprogramming and gene editing technologies [10].

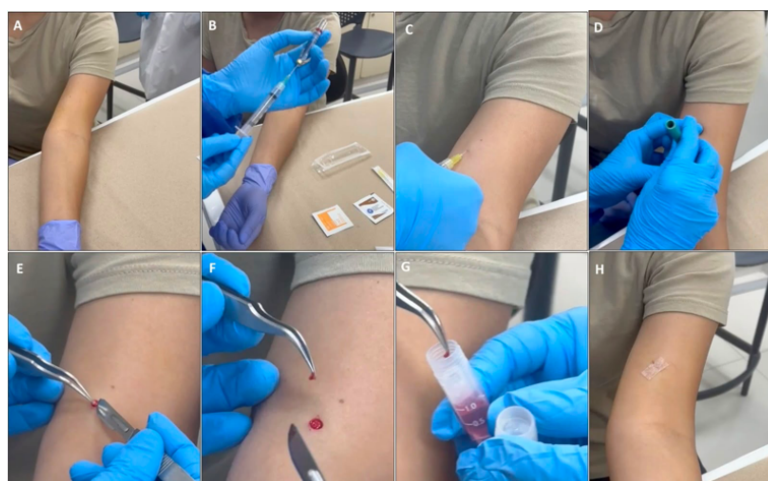
In Peru, Spinocerebellar ataxia type 10 (SCA10) is a neurodegenerative disorder reported as the most frequent spinocerebellar ataxia [11]. However, despite recent advances, the canonical repeat expansion associated with SCA10 remains insufficiently characterized at the functional level [12,13]. Further studies using cellular and animal models are needed to elucidate its pathogenic mechanisms. As part of an international collaborative study, we have been addressing some of these aspects by establishing a large Peruvian SCA10 cohort [13,14]. Although the explant culture method is well established, it has not been implemented in Peruvian research institutions to support the development of cellular models for SCA10 and other disorders.

As part of an ongoing Peruvian-U.S. collaborative study focused on SCA10, we implemented and pilot-adapted a protocol for the derivation and biobanking of dermal fibroblasts initially piloted in healthy individuals, with the aim of supporting future functional studies on multiple neurodegenerative disorders. This method integrates precise biopsy collection with optimized explant culture techniques, including the use of pre-wetted glass coverslips to promote tissue adherence and fibroblast outgrowth. The workflow has been implemented in Lima and provides a foundation for the development of a biorepository for both local and collaborative translational studies.

## METHODS

### *Skin biopsy collection*

Donated skin punch biopsies from two healthy individuals were obtained from the upper inner arm under aseptic conditions after appropriate informed consent following standard guidelines [15]. A 4 mm Visipunch was used to obtain the sample following the subcutaneous injection of 1 mL of 1% lidocaine with epinephrine (1:100,000). The biopsy site was disinfected with iodine and alcohol prep pads. The punch was inserted vertically to a depth reaching the dermis and the specimen was excised at the base using a sterile scalpel. The sample was transferred immediately into a 2 mL screw-cap tube containing 1.5 mL of cold transport medium consisting of Dulbecco's Modified Eagle Medium (DMEM; Gibco, Cat. No.12100061) with 20% fetal bovine serum (FBS; Biowest, Cat. No. S181H-500), Glutamax (Gibco, Cat. No. 35050061), non-essential amino acids (Gibco, Cat. No. 11140050), sodium pyruvate (Gibco, Cat. No. 11360070) and 1% penicillin-streptomycin (Gibco, Cat. No. 15140122) (Figure 1). Samples were transported to the laboratory on wet ice and processed the same day.



**Figure 1.** Skin biopsy procedure for fibroblast culture. (A) Arm preparation. (B) Syringe with local anesthetic. (C) Anesthetic injection. (D) Punch biopsy. (E) Skin incision. (F) Tissue extraction with forceps. (G) Transfer of biopsy to transport medium tube. (H) Wound dressing.

## Skin explant culture

For the explant culture, we followed the protocol of Vangipuram et al. [2]. Upon arrival, the tissue was rinsed with phosphate-buffered saline (PBS), and excess surface blood was gently scraped off with a sterile scalpel. The biopsy was dissected into 12–15 fragments (~1 mm<sup>2</sup>) using a sterile scalpel, ideally under a stereoscopic microscope, although successful dissection was also achieved using direct visual inspection. Two to three tissue pieces were placed into each well of a 6-well culture plate that had been pre-filled with 800 µL of fibroblast culture medium. Each well received a sterile 12 mm glass coverslip that had been pre-soaked in PBS to reduce surface tension. Pre-soaking the coverslip in PBS is recommended to reduce surface tension at the glass-medium interface, facilitating complete medium coverage of the tissue fragment and minimizing the risk of coverslip displacement during the initial adherence phase. While this step was not formally tested against a non-wetted control in the present study, it represents a practical optimization adopted from protocol development observations.

## Fibroblast culture medium and conditions

The fibroblast culture medium was prepared under sterile conditions inside a horizontal laminar flow hood. The components consisted of 0.2 µm filtered powder reconstituted high-glucose DMEM supplemented with 20% FBS, 1% Glutamax, non-essential amino acids, sodium pyruvate, 1% penicillin-streptomycin, and 3.7 g/L sodium bicarbonate adjusted to pH 7.0–7.4. Cultures were maintained at 37 °C in a humidified atmosphere with 5% carbon dioxide (CO<sub>2</sub>) in a Thermo Scientific HeraCell VIOS 160 incubator. Medium was changed every 3–4 days, and coverslips were left undisturbed to support adherence.

## Fibroblast expansion and passaging

Fibroblast outgrowth was typically visible by day 5–7. Once the explants exhibited sufficient outgrowth and cell density and reached the edges of the culture vessel, typically by 2–3 weeks, fibroblasts were detached using 0.25% trypsin, counted by trypan blue exclusion, and seeded into gelatin-coated T75 flasks for expansion. Cells were passed at a 1:4 to 1:5 ratio depending on confluency and health. Higher split ratios may slow cell proliferation and promote cellular senescence.

## Fibroblast cryopreservation

For cryopreservation, fibroblasts were resuspended in a freezing medium consisting of 90% FBS and 10% dimethyl sulfoxide (DMSO; Sigma, D2650) and aliquoted at  $1 \times 10^6$

cells per cryovial. Vials were placed in a cell freezing container (Corning® CoolCell®) at –80 °C overnight, then transferred to liquid nitrogen for long-term storage. Each line was cataloged with associated metadata and stored at Universidad Científica del Sur in Lima.

## Quality assessment

To ensure biospecimen quality and safety, all cell lines were tested for sterility and mycoplasma contamination prior to cryopreservation. Additional quality control assays, including G-banded karyotyping and single nucleotide polymorphism (SNP)-based identity confirmation, may be performed for selected lines or upon collaborator request.

## Biobanking procedures

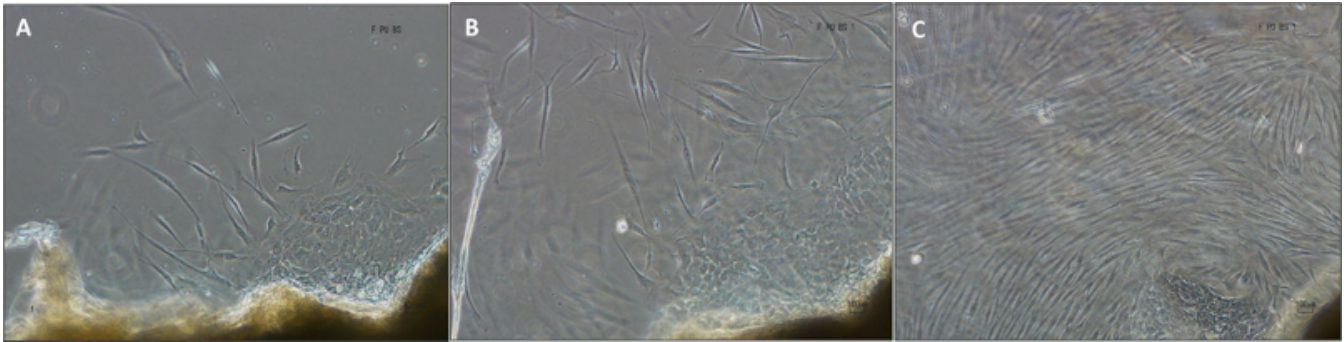
Samples were collected under appropriate informed consent for research and biobanking and were stored for future research use through Biobank-Científica. Standardized biobanking procedures ensured sample traceability, de-identification and data management, following local and international regulations for donor data protection and handling procedures.

## Ethical aspects

The development of this standardized protocol was conducted in accordance with ethical principles. The study was approved by the Institutional Research Ethics Committee at Universidad Científica del Sur (Approval N° 028-2025-PRO99), and the Institutional Research Ethics Committee of the Instituto Nacional de Ciencias Neurológicas (Approval N° 014-2025-CIECI-INCN).

## RESULTS

Fibroblast lines were successfully derived from all skin biopsy samples collected to date. In both donor samples, fibroblast outgrowth was observed by days 5–7 post-biopsy, and cultures reached sufficient density for expansion within 2–3 weeks. These observations are consistent with the use of tissue microfragmentation, glass coverslip-assisted tissue adherence, and an enriched culture medium, although no formal comparative control conditions were tested in this pilot study (Figure 2, Supplementary Material S1, S2, and S3). Cell identity as dermal fibroblasts was assigned based on characteristic morphological features observed under phase-contrast microscopy, including an elongated spindle-shaped morphology, a large flat cell body, and a prominent nucleus—consistent with previously described primary fibroblast cultures [2]. Cell viability was assessed



**Figure 2.** Progressive fibroblast outgrowth in primary explant culture. Phase-contrast micrographs of the same peripheral field at days 11 (A), 13 (B), and 18 (C), showing increasing cell confluence over time. Images were acquired from the peripheral outgrowth zone, the primary site of fibroblast migration in explant-based systems. Sequential imaging of the same field allows direct visualization of progressive cell outgrowth over time. Magnification 10x. Scale bar = 100  $\mu$ m.

at the time of cryopreservation by trypan blue exclusion using a hemocytometer. Post-thaw viability exceeded 85% across both cryopreserved lines processed under standard conditions, indicating adequate cell survival through the freeze-thaw cycle. Dedicated apoptosis quantification assays (e.g., Annexin V/propidium iodide staining by flow cytometry, or the TUNEL assay) were not performed in this pilot study. Quality control testing confirmed sterility and the absence of mycoplasma contamination in all frozen vials.

## DISCUSSION

This pilot explant culture protocol offers a feasible approach to generate dermal fibroblast lines from small skin biopsies with minimal invasiveness. Compared with enzymatic dissociation methods, explant culture minimizes tissue manipulation and avoids potential enzyme-induced cellular damage, while preserving the natural migration and expansion of fibroblasts from tissue fragments [16,17].

Our pilot protocol supported fibroblast isolation and expansion under the conditions evaluated in this study. Previous reports have demonstrated the successful establishment and reproducibility of dermal fibroblast cultures using small numbers of donors ( $n=6$ ). The results are consistent with the scale commonly reported in methodological and pilot studies of primary fibroblast culture [16]. Pre-soaking of coverslips in PBS was adopted as a recommended optimization step during protocol development, based on the rationale that reducing surface tension improves medium coverage and promotes tissue-substrate contact. The inability to determine dermis orientation at the microfragment level did not negatively affect outgrowth, as fibroblast migration occurred reliably when fragments were in stable contact with the substrate.

The protocol was designed for local research and laboratory contexts, including rapid dissection

and culture setup without the need for high-end imaging equipment. However, use of a stereoscopic microscope can facilitate more precise dissection and is recommended when available. Cell health metrics in this pilot study were limited to trypan blue exclusion viability at cryopreservation and post-thaw. All fibroblast lines are stored at a centralized facility with validated freezing and storage conditions, enabling long-term access and reproducibility. Optional advanced quality control procedures such as karyotyping and SNP identity testing enhance the utility of this biobank for collaborative research.

Primary skin fibroblasts provide a powerful and accessible patient-derived model for study neurodegenerative diseases, including ataxias, because they retain the donor's genetic background and often exhibit disease-relevant cellular phenotypes despite being non-neuronal. Mak et al. demonstrated that fibroblasts from a patient with SNCA triplication showed mitochondrial dysfunction, reduced ATP production, and increased sensitivity to oxidative stress [18]. These phenotypes were rescued by  $\alpha$ -synuclein knockdown, highlighting their utility for modeling pathogenic mechanisms of Parkinson's disease. Similarly, González-Casacuberta et al. reported that fibroblasts from *PRKN*-mutant Parkinson's disease patients exhibit impaired mitochondrial respiration and defective autophagic flux [19], and Antony et al. showed that fibroblasts from idiopathic PD patients display fragmented mitochondria and stress-induced bioenergetic deficits [20]. Importantly, several studies have applied this approach to ataxias: Torres et al. demonstrated that toxic RNA foci can be detected and quantified in skin fibroblasts from patients with spinocerebellar ataxia type 10 (SCA10) [21]. Wang et al. found that fibroblasts from Friedreich's ataxia patients show widespread lipid metabolism defects that correlate with frataxin deficiency and disease severity [22]. Onofre et al. demonstrated mitochondrial abnormalities and oxidative stress in fibroblasts from Machado-Joseph disease (SCA3) patients [23], and Haj et al. showed that

fibroblasts from ataxia-telangiectasia patients undergo premature senescence and display distinct transcriptional signatures even under physiological oxygen tension [24]. Collectively, these studies illustrate that patient-derived skin fibroblasts serve as a versatile platform to probe pathogenic mechanisms, cellular vulnerabilities, and potential therapeutic responses across inherited ataxias and diverse neurodegenerative disorders.

It is true that iPSCs and organoids have become central tools in neurodegenerative disease modeling due to their ability to generate disease-relevant cell types. Despite other approaches including iPSCs [25], organoids [26], and other advanced cellular models, dermal fibroblasts retain important and complementary roles: they serve as the primary starting material for iPSC reprogramming, retain the donor's genetic background without epigenetic reprogramming artifacts, and exhibit disease-relevant phenotypes including mitochondrial dysfunction, altered autophagy, and RNA foci. In addition, fibroblast culture is significantly more accessible in resource-limited settings, does not require specialized GMP infrastructure, and is appropriate for biobanking at scale. Our protocol is explicitly positioned as a foundational step toward future iPSC-based studies, not as a replacement for them.

We acknowledge several limitations in this pilot study that need to be considered when interpreting its results. As this is a pilot study, we did not have properly conducted experimental comparisons assessing fibroblast yield and viability under different culture conditions. Immunophenotypic confirmation using fibroblast-specific markers (e.g., fibroblast-associated markers or fibronectin) was not performed in this pilot study and should be further implemented as a quality control step, particularly prior to downstream applications such as induced pluripotent stem cells (iPSC) reprogramming or functional assays. Comprehensive assessment of apoptosis, necrosis, and metabolic activity during culture, using assays such as Annexin V staining, TUNEL, or resazurin-based metabolic assays would provide a more complete characterization of culture health and is recommended for future protocol validation studies. It should be noted that the technical recommendations described in this protocol—including the use of pre-wetted coverslips and enriched medium composition—are based on optimization observations during protocol development rather than formally controlled comparative experiments. Future validation studies incorporating control conditions (e.g., non-wetted coverslips, standard DMEM without supplementation) would provide stronger evidence for the relative contribution of each parameter to fibroblast yield and viability.

This pilot protocol, implemented as part of an ongoing collaborative study, establishes a feasible and standardized workflow for the collection, culture,

cryopreservation, and biobanking of dermal fibroblasts from skin biopsies. The successful implementation of this protocol provides an important step toward the development of cellular biobanking capabilities in Peru and creates a foundation for future research on neurodegenerative disorders. With further validation, these cellular resources may support disease modeling, induced pluripotent stem cell (iPSC) generation, drug screening, and other translational applications aimed at advancing precision medicine. Furthermore, the establishment of dermal fibroblast cell lines and their long-term preservation in a centralized biorepository provides a foundational resource with potential value for advancing disease modeling, therapeutic discovery, and functional genomics studies in rare neurological disorders.

### Supplementary Material

The supplementary material can be accessed at the following link: <https://revistas.cientifica.edu.pe/index.php/mecp/article/view/3625/1775>

### Author contributions

AMH: Conceptualization, investigation, experimental work, writing – review, final approval. MIM, MCO: Conceptualization, investigation, writing – review, final approval. STR, DOC, PGD, KML, ICA, CME: Investigation, experimental work, writing – review, final approval. BS: Conceptualization, experimental work, writing – review, final approval.

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### Conflicts of interest statement

The authors declare no conflicts of interest.

### Generative Artificial Intelligence use statement

During the preparation of this manuscript, the authors used ChatGPT solely to improve language clarity and readability. The content was subsequently reviewed and edited by the authors, who take full responsibility for the accuracy and integrity of the published work.

### Data availability statement

Not applicable.

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