Supplementary Figures

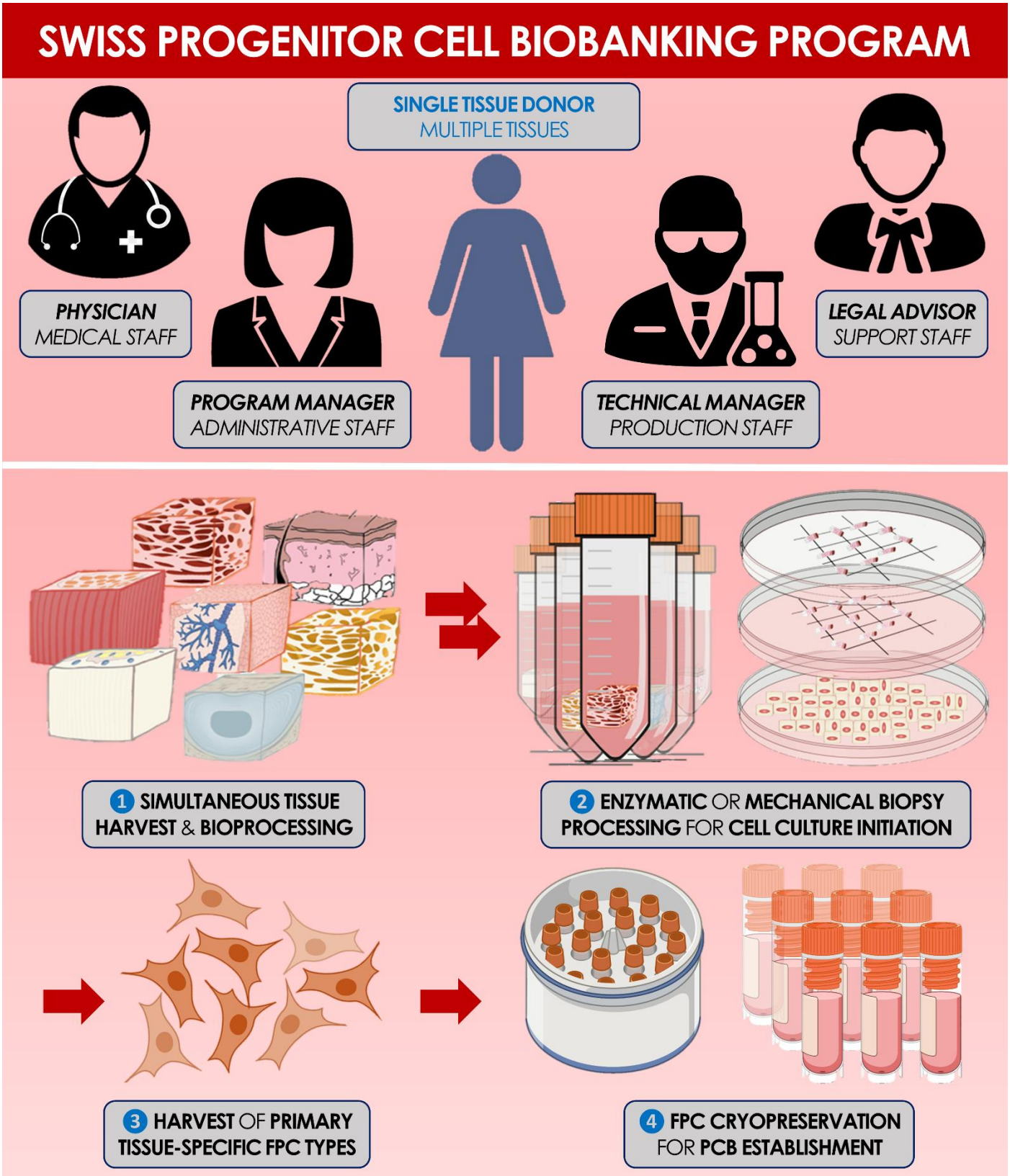

Figure S1. Schematic overview of the Swiss progenitor cell transplantation program organigram (i.e., as detailed in Table 1) and of the main technical steps for primary progenitor cell (e.g., FPC) in vitro culture initiation. The interdisciplinary collaboration within the cell transplantation program enables the optimal design and the implementation of the traceable yet anonymous procurement of the specific tissue biopsies for eventual bioengineering and therapeutic purposes. The compartmentalization of the different progenitor cell transplantation program stakeholders ensures the preservation of donor and of donation anonymity. FPC, fibroblast progenitor cells; PCB, parental cell bank. Adapted with permission from Laurent et al., 2021 [51].

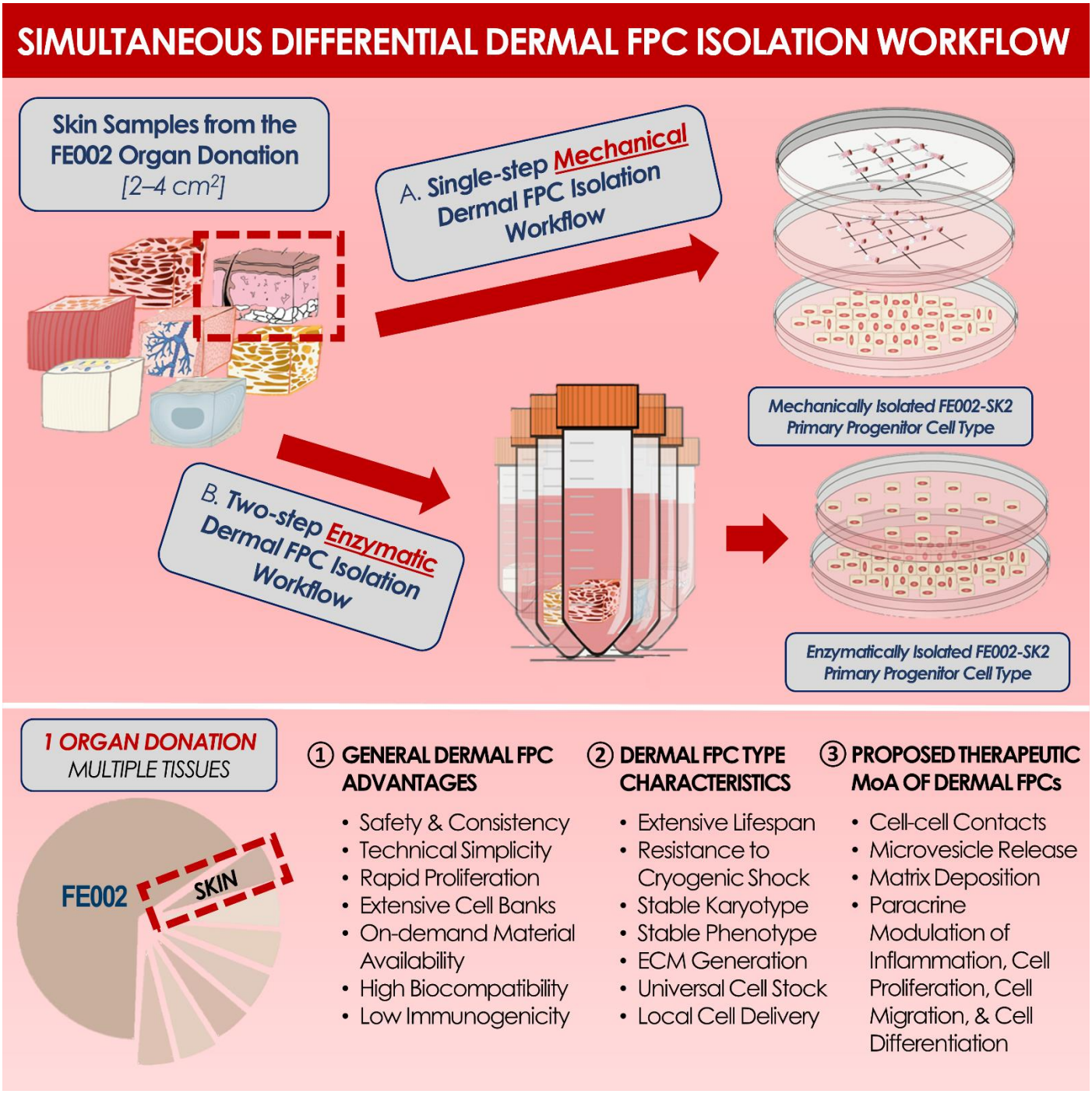

Figure S2. Schematic technical overview of the differential in vitro cell isolation workflow for skin-derived primary progenitor cells (e.g., FE002-SK2 cell types) under the Swiss progenitor cell transplantation program, along with some advantages of using such biological materials, as well as the proposed therapeutic mechanisms of action of progenitor cells. From a single organ donation included in a dedicated cell transplantation program, various tissue biopsies (e.g., bone, cartilage, intervertebral disc, lung, muscle, skin, tendon, etc.) may be simultaneously differentially treated for the primary progenitor cell isolation and the in vitro cell culture initiation process. ECM, extra-cellular matrix; FPC, fibroblast progenitor cells; MoA, mechanism of action. Adapted with permission from Laurent et al., 2021 [51].

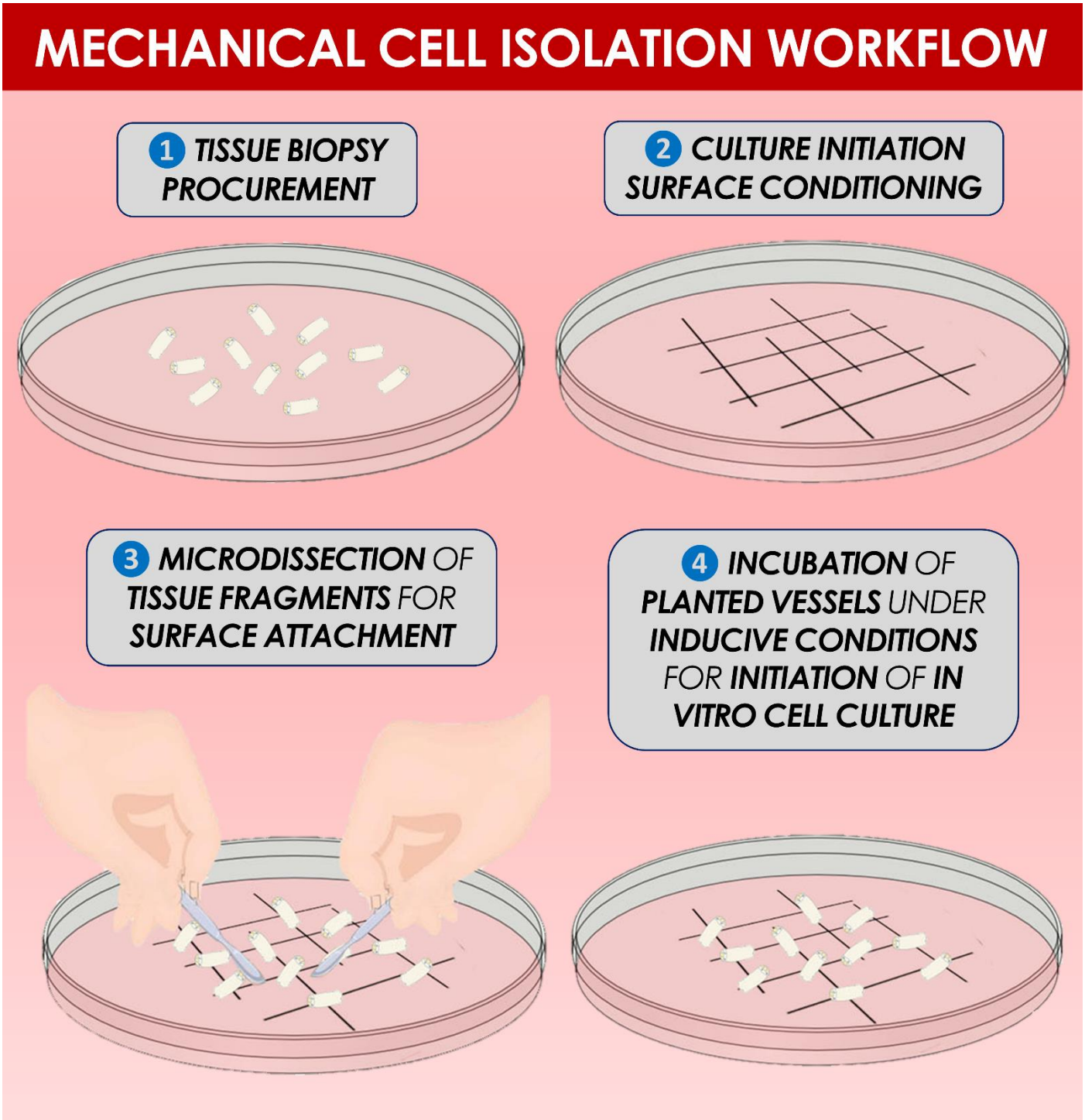

Figure S3. Schematic technical process overview for the in vitro non-enzymatic/mechanical isolation of primary progenitor cells and for the in vitro primary cell culture initiation under the Swiss progenitor cell transplantation program. The tissue culture vessels are appropriately conditioned by deep mechanical scoring of the plastic culture surfaces in a checkerboard pattern. The tissue fragments are then transferred to the vessels and are minced. Following homogenous distribution in the culture vessels, the fragments are attached to the plastic grooves. The vessels are then incubated to favor the adherent in vitro monolayer cell culture initiation. Adapted with permission from Laurent et al., 2021 [51].

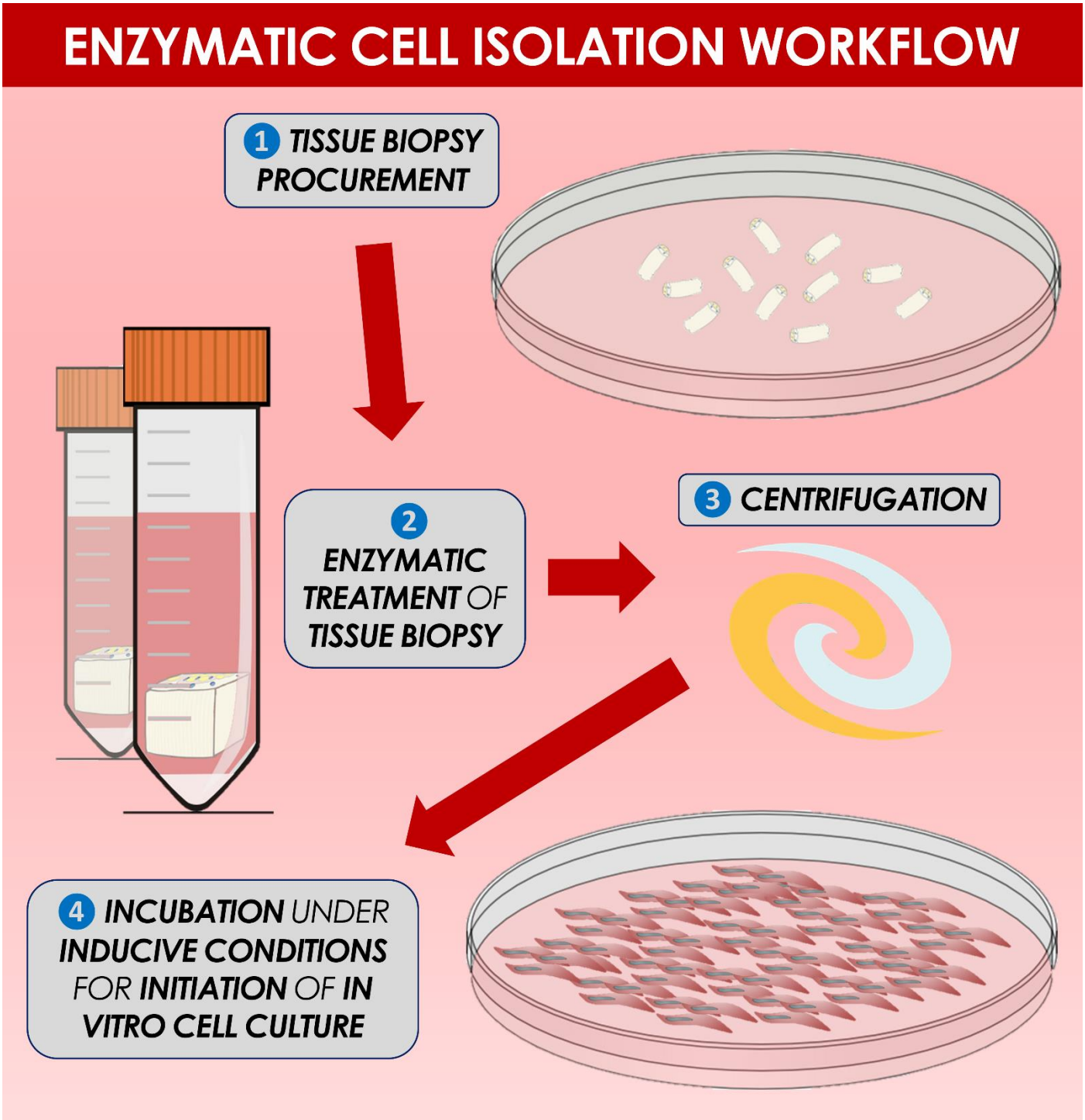

Figure S4. Schematic technical process overview for the in vitro enzymatic isolation of primary progenitor cells and for the in vitro primary cell culture initiation under the Swiss progenitor cell transplantation program. The tissue biopsies are processed into fragments and are transferred into the tissue digestion tubes. After an appropriate enzymatic treatment of the tissue (i.e., 10–20 min at 37 °C) with trypsin-EDTA, the dissociated cells are centrifuged, collected, and are resuspended in the appropriate cell culture medium for the subsequent in vitro adherent monolayer cell culture initiation. EDTA, ethylenediaminetetraacetic acid. Adapted with permission from Laurent et al., 2021 [51].

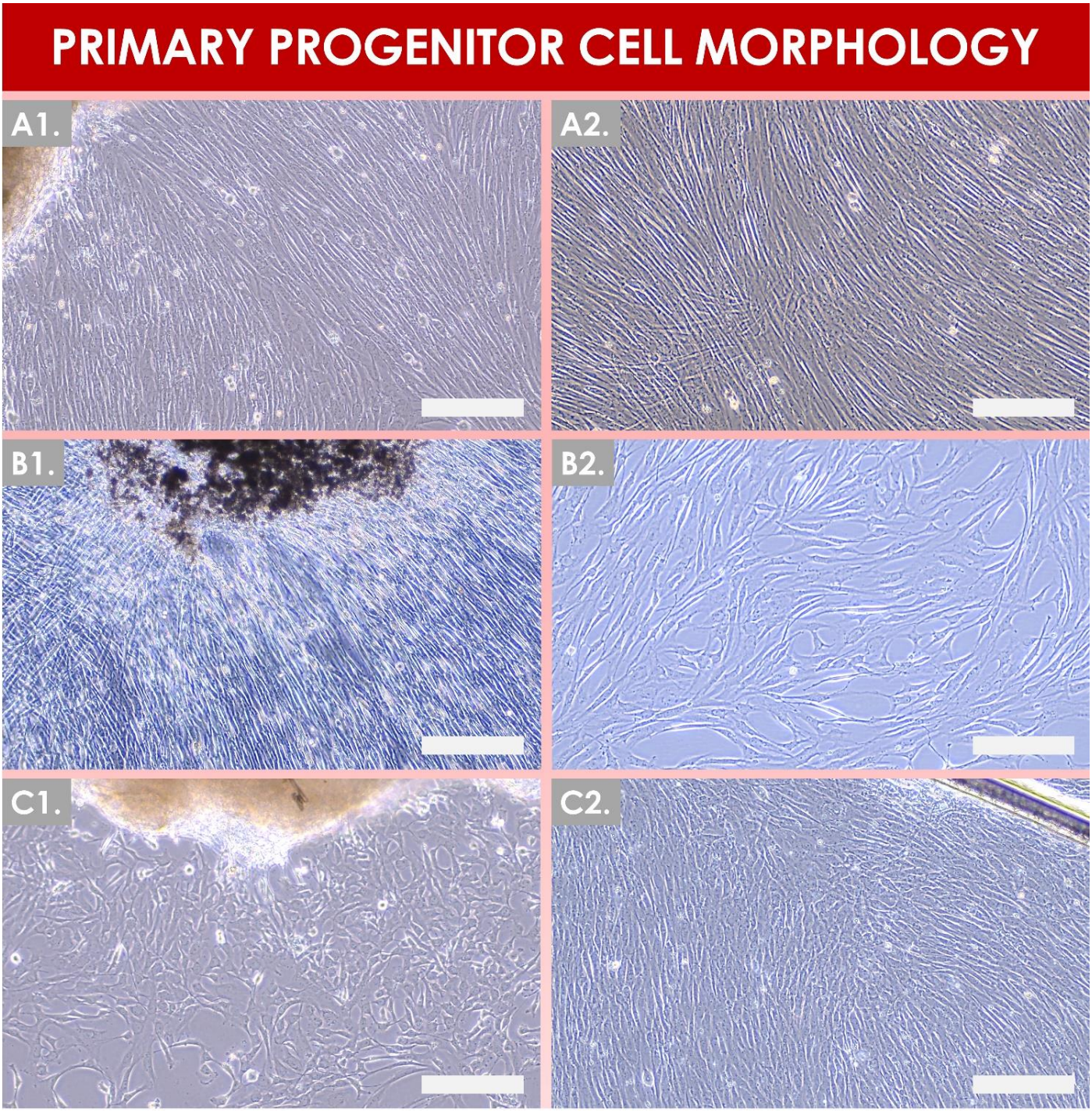

Figure S5. Photographic imaging records of various primary progenitor cell cultures following the respective mechanical in vitro cell isolation steps, as visualized by contrast phase microscopy. (**A**) Dermal fibroblast primary progenitor cells (e.g., FE002-SK2 cell type). (**B**) Primary progenitor tenocytes (e.g., FE002-Ten cell type). (**C**) Primary epiphyseal chondroprogenitors (e.g., FE002-Cart cell type). Scale bars = 50 μm.

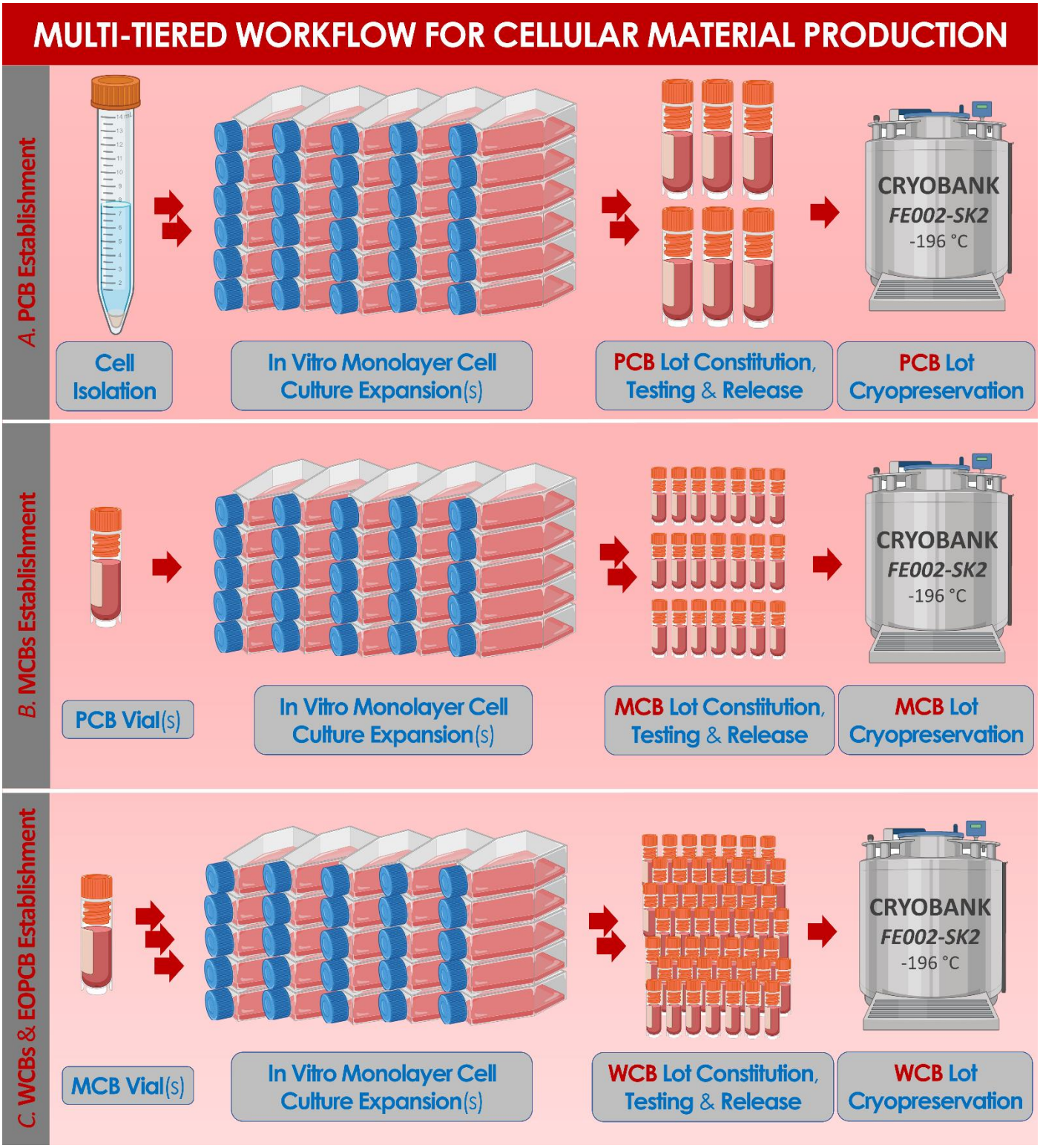

Figure S6. Schematic technical overview of the optimized multi-tiered in vitro cell biobanking workflow for the sustainable exploitation of primary dermal progenitor cell types (e.g., enzymatically isolated FE002-SK2 progenitor cell type) under the Swiss progenitor cell transplantation program. (**A**) Stepwise overview of the in vitro primary progenitor cell PCB establishment. (**B**) Stepwise overview of the in vitro primary progenitor cell MCB establishment. (**C**) Stepwise overview of the in vitro primary progenitor cell WCB or EOPCB establishment. EOPCB, end of production cell bank; MCB, master cell bank; PCB, parental cell bank; WCB, working cell bank.

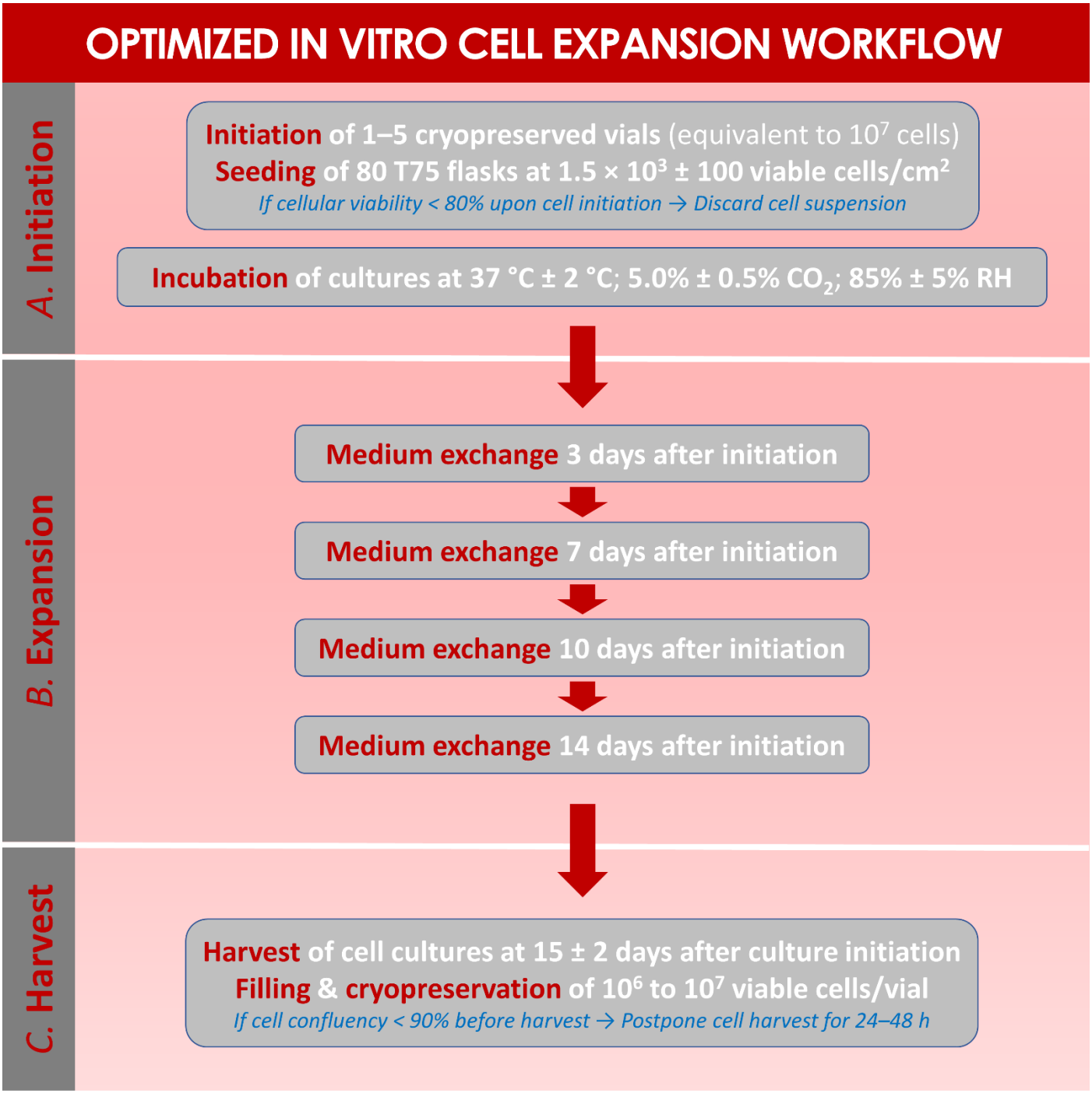

Figure S7. Example of a generic optimized schematic workflow for primary progenitor cell in vitro expansion under the Swiss progenitor cell transplantation program. (**A**) Cryopreserved cellular starting materials are initiated and are appropriately incubated in vitro. (**B**) Successive cell culture medium exchange procedures are performed during the in vitro monolayer primary progenitor cell expansion phase. (**C**) Once the predetermined endpoints have been reached, the primary progenitor cell cultures are harvested, and the obtained progenitor cell lot is appropriately cryopreserved. h, hours; RH, relative humidity. Adapted with permission from Laurent et al., 2021 [51].

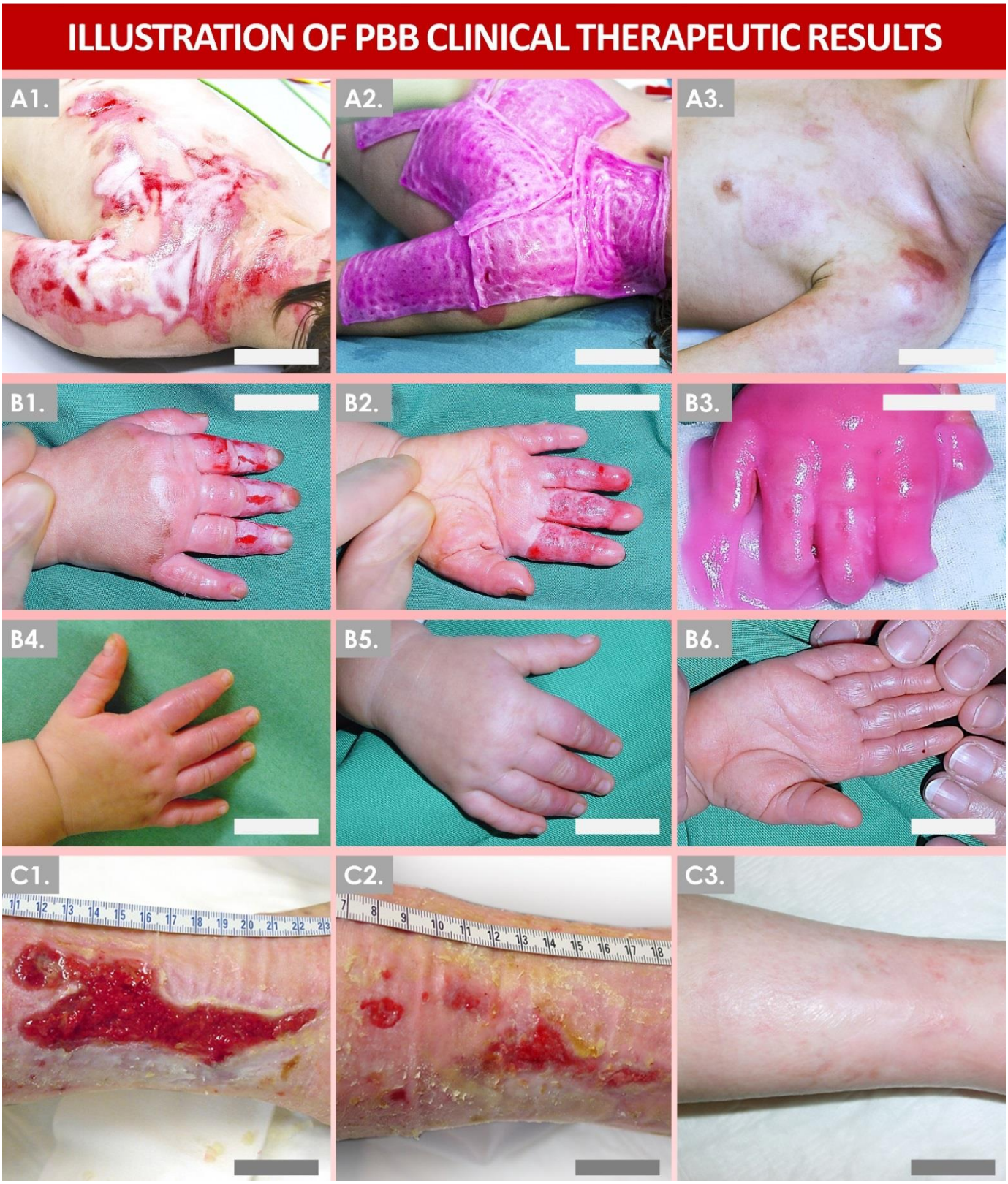

Figure S8. Illustration examples of PBB clinical therapeutic results in burn wound and cutaneous ulcer care. (**A**) Second-degree deep pediatric burn wounds of the torso caused by scalding liquid. Photographic representations of the cutaneous lesions after early wound debridement (**A1**), after PBB application (**A2**), and after six weeks of treatment (**A3**). Scale bars = 5 cm. (**B**) Second-degree and third-degree pediatric burn wounds of the hand caused by scalding liquid. Photographic representations of the cutaneous lesions after early wound debridement (**B1**,**B2**), after PBB application (**B3**), and after six weeks of treatment (**B4**–**B6**). Scale bars = 2 cm. (**C**) Refractory and painful post-thrombotic lower-limb cutaneous ulcer lesions treated weekly with PBBs. Photographic representations of the cutaneous lesions after treatment initiation (**C1**), 11 weeks later (**C2**), and 15 months later during follow-up wound care (**C3**). Scale bars = 3 cm. PBB, progenitor biological bandages. Adapted with permission from Laurent et al., 2020 [1].

Supplementary Tables

Table S1. General FE002-SK2 primary progenitor cell type characterization data overview, as summarily presented in the corresponding original FE002-SK2 cell type master file under the Swiss progenitor cell transplantation program. API, active pharmaceutical ingredient; CD, cluster of differentiation; ECACC, European collection of authenticated cell cultures; EOPCB, end of production cell bank; FIRDI, Food industry research and development institute; HLA, human leucocyte antigen; PD, population doubling.

Parameters	Recorded Data and Documented Experimental Results
Cell Type Identity	● "FE002-SK2" cell type, primary diploid progenitor cell type, isolated and serially cultured in vitro from pre-natal skin donated at 14 weeks of gestation in 2009
	● Cell type verified and deposited in the ECACC (N°12070301-FE002-SK2) and in the FIRDI (N°BCRC 960460) accredited biorepositories
	● Fibroblastic proliferative cellular phenotype, with stable cellular morphology in adherent monolayer in vitro culture
	● Defined basic cell surface marker profile; $CD34^-$, $CD45^-$, HLA-DP,DQ,DR^-, $CD14^+$, $CD26^+$, $CD44^+$, $CD73^+$, $CD90^+$, $CD105^+$, $CD166^+$, HLA-A,B,C^+, D7-FIB^+ cell surface markers
	● Specific levels of gene expression (e.g., TGF-β2, BMP-6, GDF-10) in culture as compared to adult skin fibroblasts
Safety of Tissue Donation	● Single and controlled organ donation (i.e., no pooling of biological sources or multiple donor testing)
	● Comprehensive traceability and full prospective informed donor consent obtention for material and derivative/progeny uses
	● Safety screening of tissue donor and of donated tissues for thorough qualification purposes
Safety of Cell Banks	● Universal allogeneic donor material (i.e., reduced repeated testing requirements)
	● Safety evaluated iteratively with thorough testing of EOPCBs
	● Documented safety of therapeutic use as an API (i.e., in vitro, ex vivo, pre-clinical, and clinical data available)
	● Non-immunogenic and non-tumorigenic APIs in vivo
Cell Type Stability	● Extensive manufacturing cell type lifespan with stable in vitro cell expansion kinetics
	● Establishment and testing of EOPCBs at passage level 12 [1]
	● Consistent proliferative in vitro cellular morphology in monolayer culture
	● Normal 46X,Y karyotype stable up to passage level 14 [1]
	● Stable evolution of protein expression levels throughout the clinically relevant in vitro passage levels
	● Cellular resistance to cryogenic shock and stability during cryogenic storage (i.e., validated for > 12 years)
	● Stable pre-terminally differentiated cellular phenotype
Cell Type Manufacturing	● Simple in vitro mitotic cell growth requirements
	● High rate of mitotic proliferation in vitro
	● High sustainability of optimized primary progenitor cell bank exploitation
	● Demonstrated cost-effectiveness of primary progenitor cellular APIs and of related therapeutic product use

Cell Type Cytocompatibility	● Cytocompatibility demonstrated with various hydrogel product and semi-solid scaffold formulations (e.g., collagen sheets and hyaluronan-based gels)
Cellular API Functionality	● Maintenance of selected biological activity by cell-derived APIs and by related preparations (e.g., primary progenitor cell lysates, lyophilizates) ● Stimulation of target cell proliferation and of target cell migration in vitro ● Prevention of cutaneous scar tissue formation and reduction of the corrective intervention need at clinical levels ● Potent cutaneous tissue repair stimulation (e.g., rapid and complete burn wound closure with little hypertrophy or retraction in pediatric patients) ● Non-persistence of therapeutic progenitor cells in patients after several weeks following administration ● Over two decades of safe clinical therapeutic uses and over 10 years of individual patient follow-up monitoring
Cellular API Postulated Effects & Mechanisms	● Intercellular contacts ● Reversal of apoptotic signals or mechanisms ● Release of microvesicles and of related cell secretome ● Generation and deposition of extracellular matrix ● Homologous specific cellular functions ● Paracrine and/or trophic modulation of endogenous cells ● Anti-inflammatory effects ● Scavenging of oxidative stress sources

[1] Passage level nomenclature is used for the characterization of cultured primary progenitor cell in vitro age in the Swiss progenitor cell transplantation program.

Table S2. Cell-based product monograph for PBBs in cutaneous regenerative medicine (e.g., early treatment of pediatric and adult burn wounds or of skin graft donor sites as first cover) under the Swiss progenitor cell transplantation program, as considered valid in the Lausanne Burn Center [41,57]. API, active pharmaceutical ingredient; FPC, fibroblast progenitor cells; GMP, good manufacturing practices; h, hours; PBB, progenitor biological bandages; WCB, working cell bank.

Product Parameters	Product Specifications and Instructions of Use Related to Progenitor Biological Bandages (PBB)
Product Definition	● PBBs are ready-to-use three-dimensional cell-based therapeutic constructs, composed of equine collagen sheet-scaffolds (i.e., carrier excipient) extemporaneously seeded with viable cultured allogeneic human dermal FPCs (e.g., FE002-SK2 dermal fibroblasts) as the API. ● Primary progenitor cells used as the PBB APIs are obtained under a defined progenitor cell transplantation program and are manufactured following optimized and defined technical specifications in a GMP multi-tiered cell banking system. ● Viable dermal FPCs (i.e., initiated from cryopreservation for extemporaneous reconstitution) adhere to the PBB collagen scaffold during an in vitro incubation period (i.e., 18–24 h) after the cell seeding.
Established Product Clinical Indications	● PBBs are clinically applied as early and temporary (i.e., bioresorbable) first covers on second-degree (i.e., superficial and deep) burn wounds, for prevention of hypertrophic scarring and for the reduction of the need for corrective surgeries. ● PBBs are clinically applied as early and temporary (i.e., bioresorbable) first covers on skin graft donor sites (e.g., skin harvest for autologous treatment of third-degree burn wounds). ● PBBs are clinically applied as temporary (i.e., bioresorbable) first covers on refractory lower limb cutaneous ulcers for the promotion of chronic wound healing.
Critical Product Properties	● PBBs possess planar dimensions of 9 cm × 12 cm and a thickness of 2 mm. ● Each PBB product is seeded with 5×10^5 viable dermal FPCs, initiated from a dedicated progenitor WCB. ● PBBs are manufactured on-demand in batches of 4 constructs in class A GMP conditions. ● The products are not submitted to terminal sterilization; the product aseptic processing should therefore guarantee the absence of adventitious agents in the liberated final product lot. ● All starting materials, raw materials, and ancillary materials used for the production of the API or of the final product are tested or are certified for the absence of zoonotic pathogens or contaminants. ● Cellular materials used as the APIs are cryogenically preserved in individual vials (i.e., 2×10^6 to 10^7 cells/vial) in the dedicated progenitor cell bank storage system. ● Final product quality is evaluated based on cellular morphology, homogeneity of PBB construct cellular colonization, physical integrity of the PBB product and of its packages (i.e., primary and secondary packaging).

Product Quality Control Requirements	● Cell viability (i.e., > 80% cell viability upon API cell initiation; maintenance of cell adherence/proliferation capacities in vitro). [1] ● Microbiological quality testing (i.e., aerobic and anaerobic bacteria, mycoplasma, fungi, endotoxins). [1] ● Construct structural integrity maintenance and integrity of primary/secondary product packaging. ● Products are delivered to the operating theatre with appropriate humidification in product transport medium.
Product Storage and Transport	● PBBs are extemporaneously manufactured on-demand following the medical prescription for a specific patient. ● PBBs are transported at ambient temperature (i.e., 15 °C–25 °C) in an isotherm and temperature-monitored transport container to the operating theatre. ● Freezing and high temperatures (i.e., > 37 °C) should be avoided during product handling and transport. ● The product validity period after manufacture is specified and the final product should not be stored in the operating theatre for a longer period (e.g., > 8 h).
Product Use Contra-indications	● Wound microbiological colonization. ● Wound microbiological infection. ● Bleeding wounds. ● Profusely exudating wounds. ● Third-degree burn wounds. ● Allergy to a product component.

Product Special Labelling and Accompanying Information	● Product name, reference, and unique lot number. ● Name of the patient (i.e., PBBs are manufactured and destined for defined patients). ● Date and time of the manufacture start, end, and of the final product liberation. ● Product expiry date and time. ● Name of the attending/prescribing physician. ● Transport conditions. ● Key product specifications. ● Instructions for appropriate product clinical application. ● Manufacturing lot liberation report. ● Manufacturer identification and contact details.
Product Special Warnings	● PBBs are single-use products which are to be applied on the patient within 8 h of the product liberation from the GMP manufacturing facility. ● PBBs must not be frozen and should be discarded if they are not used for the specified patient or if they are not used within the specified validity period. ● PBBs should be deconditioned and applied by trained medical personnel in aseptic conditions in the operating theatre. ● PBBs should be manipulated cautiously to avoid construct structural ruptures. Constructs may be cut and molded to individual wound surfaces in the operating theatre. ● Constructs should not be repositioned once applied. ● Product residues are to be washed away with an appropriate irrigation solvent during standard wound care and normal bandage exchange procedures. ● Antiseptic preparations may be applied during standard wound care but should be appropriately rinsed away before PBB product applications. ● Observed adverse reactions to the PBB products should be documented and should be notified to the product manufacturer.

[1] Post-process quality controls: Final product lot manufacturing reports are only made available after the product application on the patient, due to the extemporaneous reconstitution of the product APIs and the technical delays incurred by the quality control test assays.

Table S3. General risk analysis matrix established for PBB products containing cultured primary dermal progenitor fibroblasts (e.g., FE002-SK2 cell source), as considered valid in the Lausanne Burn Center [87]. The risk analysis matrix is applicable for the use of PBBs in cutaneous regenerative medicine (e.g., treatment of pediatric and adult burn wounds or of skin graft donor sites) under the Swiss progenitor cell transplantation program. Specified parameters were established based on API and on finished product specifications and on product key/critical quality attributes. API, active pharmaceutical ingredient; FPC, fibroblast progenitor cells; PBB, progenitor biological bandages; QC, quality control; WCB, working cell bank.

Product Parameters	**Pre-Mitigation**			**Risk Severity** (0–3) [1]	**Risk Likelihood** (0–2) [2]	**Risk Level** (0–2) [3]	**Mitigations** *(Cumulative)*	**Post-Mitigation Risk Levels** (0–2) [4]
	Risks	**Causes**	**Effects**					
Allogeneic Cell API Origin / API Immunogenicity	Immune reaction of recipient to allogeneic cellular API	Immune recognition of allogeneic cellular API by recipient organism	Treatment failure Iatrogenesis	3	1	1	Use of pre-immunocompetent cells (FPCs) as the therapeutic cellular APIs No pooling of cellular API starting materials from distinct donors Exclusion of potential recipients with known immunological/allergic risk factors	0
Cell Viability in the Final Product	Insufficient product efficacy in case of low API cell viability [5]	Inadequacy of product formulation Inadequacy of product storage and handling Inadequacy of product administration	Treatment failure	2	1	1	Qualification of finished combination product Validation of cell viability maintenance following product reconstitution, transport, and administration (i.e., full validity period) Viability determination QC at the time of finished product reconstitution (i.e., cell viability upon initiation and in recovery QC) Extemporaneous API cell reconstitution and short specified product validity period Appropriate specified finished product transport and administration modalities	0

Level of API Manipulation	Mutagenicity, oncogenicity, or tumorigenicity of cellular API	High in vitro manipulation of cells Extensive in vitro cell culture	Formation of tumors in patients	3	0	1	No genetic manipulation of cellular API No immortalization of cellular API No use of viral tools for API manufacture Testing for API cell type tumorigenicity Testing for API cell type genetic stability Use of cells limited at 2/3 of the qualified in vitro cell type lifespan No in vivo persistence of product/API in patient wounds	0
Adventitious Contamination During Finished Product Manufacturing	Introduction of extraneous contaminants by reagents, equipment, material, personnel	Inadequate manufacturing process (i.e., including storage and transport) Inadequate reagents, materials Inadequate control processes Presence of latent virus in materials Absence of purification regimen and of terminal sterilization	Contamination of the product Infectious risk for the patient	3	1	2	Testing and qualification of API WCBs Class A API manufacturing environment Selection of qualified and tested materials and reagents Environmental controls during open-container manipulations Minimization of open-container processes Minimization of contact processes Use of sterile single-use consumables Retention sample testing Post-production bulk API and final product testing and qualification	0
Product Mode of Administration	Systemic exposure to the topical product	Cutaneous barrier compromised by burn wounds Systemic distribution of APIs	Systemic effects of APIs Effect amplitude excess	1	1	1	Extensive safety and quality testing of API No persistence of allogeneic cellular APIs Historical clinical safety data on cellular APIs No evidence of high dose-related adverse effects of the APIs	0

Combination Product	Incompatibility between the API and the scaffold Formation of toxic degradation products	Biological or chemical incompatibility or reaction between the API and the scaffold	Treatment failure Iatrogenesis	3	0	1	Qualification of product scaffolds Qualification of finished combination product Historical clinical safety data with finished product	0
Duration of Exposure to the Product	Chronic toxicity of the product	Extensive and repeated exposure to the product, applied on wounded tissues	Treatment failure Iatrogenesis	3	0	1	Bioresorbable product formulation Product eliminated during bandage exchange procedures Limited number of product applications No persistence of product/API in patient wounds	0
Availability of Clinical Safety Data and of Historical Experience	Insufficient safety data/experience	No clinical recording of historical product uses	Absence of tangible evidence for retrospective product safety evaluation	2	0	0	Several decades of safe clinical product use Multiple peer-reviewed scientific publications on the safety and efficacy of the API/products Prospective and retrospective clinical trials performed for multiple similar indications of the product	0

[1] Pre-mitigation risk severity is classified as (**0**) = acceptable, (**1**) = tolerable, (**2**) = undesirable, or as (**3**) = intolerable. [2] Pre-mitigation risk likelihood is classified as (**0**) = improbable, (**1**) = possible, or as (**2**) = probable. [3] Pre-mitigation risk level is classified as (**0**) = low, (**1**) = medium, or as (**2**) = high. [4] Post-mitigation risk level is classified as (**0**) = low, (**1**) = medium, or as (**2**) = high. [5] Applicable to products which intend to maintain API cellular viability up to and beyond clinical administration, yet cellular viability may not be necessary for the deployment of the therapeutic effects by specific primary progenitor cell APIs.