Burn Center Organization and Cellular Therapy Integration: Managing Risks and Costs

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The complex management of severe burn victims requires an integrative collaboration of multidisciplinary specialists in order to ensure quality and excellence in healthcare. This multidisciplinary care has quickly led to the integration of cell therapies in clinical care of burn patients. Specific advances in cellular therapy together with medical care have allowed for rapid treatment, shorter residence in hospitals and intensive care units, shorter durations of mechanical ventilation, lower complications and surgery interventions, and decreasing mortality rates. However, naturally fluctuating patient admission rates increase pressure toward optimized resource utilization. Besides, European translational developments of cellular therapies currently face potentially jeopardizing challenges on the policy front. The aim of the present work is to provide key considerations in burn care with focus on architectural and organizational aspects of burn centers, management of cellular therapy products, and guidelines in evolving restrictive regulations relative to standardized cell therapies. Thus, based on our experience, we present herein integrated management of risks and costs for preserving and optimizing clinical care and cellular therapies for patients in dire need.

After the development of cultured cutaneous autografts in Boston in the 1980s, our Burn Center was the first in Europe to adopt therapeutic cultured cellular product protocols. To date, various autologous and allogenic cell therapies are elaborated and routinely produced in-house at our Burn Center and according to current Good Manufacturing Practices (GMP). Thus, our Burn Center has been at the forefront of high-quality regenerative therapies for almost 35 years, and has produced over these three decades an array of novel cell therapies in compliance with relevant local and European legislations. Cell therapies, both autologous and allogenic, have favored structural improvement and functional skin regeneration in diverse burn patient populations.[1–8]

In addition to the surgical and cellular therapeutic level, medical advances have also evolved, including restrictive fluid management protocols, "minimally restrictive" sedation protocols, and nutrition protocols based on careful early enteral nutrition focused on protein substitution, mirroring the current state-of-the-art in reference Burn Centers. Altogether, these advances have allowed for rapid treatment, shorter residence in hospital and intensive care units (ICUs), shorter durations of mechanical ventilation, fewer complications and surgeries, and decreasing mortality rates in our hospital. As a result, massively burned patients with over 90% to 95% of TBSA burns may be treated routinely and often survive.[9]

However, the naturally fluctuating admission rates of burn patients have generated increasing pressure toward optimized resource utilization and pragmatic operation of Burn Centers. We have identified the following risks that may hinder the quality of burn care management: on the one hand, the architectural and organizational setting of a Burn Center that has to evolve to maximize the efficiency and quality of individual patient care; on the other hand, the continuously restrictive and constraining regulatory environment for cell therapies, despite their demonstrated key roles in severe burn patient care.

The overall goal of the present work is to provide an overview and targeted considerations for optimized high-quality care provision to severe burn patients. Specifically, we present herein practical workflows for optimal operation of a Burn Center, GMP production of autologous and allogenic cutaneous cellular therapies, as well as evolving specific regulations governing integration of such therapies into clinical care.

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Conflict of interest statement. None.

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doi:10.1093/jbcr/irab080

With an aim toward an integrative and specific communication of current headways and hurdles of severe burn patient care, we describe herein key management of risks and costs, based on our experience, for preserving and optimizing lives of patients in dire need.

OPTIMIZED BURN CENTER ORGANIZATION

Open-Space Unit Design

Consideration of architectural and organizational parameters are paramount for optimal establishment and operation of specific clinical infrastructures (Figure 1 and Table 1). Conventionally, Burn Centers are closed-off units with a specific area attributed to burn patients. Over the last 15 years, the model of our Burn Center has evolved to become an efficient "open" unit located in the general ICU of the Hospital (Figure 1), with additional space available on the respective floors of the Plastic and Pediatric Surgery services. Practically, burn patients are prioritized for access to five dedicated intensive care beds, which may be reallocated to general ICU purposes in case of vacancy. Within this "open" unit, strict hygiene protocols specific to "closed" burn units have fallen out of favor, without leading to (from our experience) increases in the rate of infections, as might have been expected. In this design, adult and pediatric burn patients share a common clinical pathway, which often begins by an initial hospitalization in the Burn Unit, before dispatch in Reconstructive Surgery and Pediatric Surgery services, respectively.

Burn Center Logistic Workflows

On the main floor, the Burn Center (Figure 1) should comprise ICU rooms individually equipped with one patient bed and intensive care medical supplies, a workstation, a storage area, dedicated air conditioning and ventilation systems, and adequate clearance space for the staff. At minimum, one of these rooms should be specifically designed as an isolation room adapted to accommodate highly sensitive or particularly infected burn patients (eg, multiresistant *Pseudomonas aeruginosa* or *Acinetobacter baumannii* strains, Ebola or SARS-CoV-2 viruses). As such, it comprises an airlock, a hydrotherapy bed and sufficient clearance to accommodate transformation into an operating theater, while keeping the patient confined (Figure 1, isolation room). A crucial aspect in the design and workflows for the Burn Center is the air quality, ensuring both patient and staff safety, especially during epidemic outbreaks. In such case, laminar-flow type ventilation systems can provide fresh air, circulated through high efficiency filters, emanating from vents in the ceiling and directed vertically toward the floor. The latter is lined with corresponding vents that aspirate the air, creating local negative pressure pockets and limiting propagation of aerosols or airborne droplets. These systems are particularly important in the isolation box, the operating theater, and the hydrotherapy room.

The Burn Center should also comprise dedicated operating and hydrotherapy rooms for general use by the burn patients. Treated patients are showered in the main hydrotherapy room, usually under general anesthesia, for dressing changes or for scrubbing before going to the operating room (Figure 1, hydrotherapy room). The main operating room should be located right next to the main hydrotherapy room, but should not directly communicate with it, for microbiological risk mitigation (Figure 1, operation room). This operation room is mainly dedicated for burn patients, but can be used occasionally for other surgical interventions, such as organ retrieval for transplantation purposes.

Once patients no longer require intensive care, they are transferred to the regular floor of the Plastic and Reconstructive Surgery service, where a hydrotherapy room is also available for common use, in addition to an extra shower integrated in a spacious isolation room. As on the ICU floor, nonburn patients occupy these quarters in the absence of burn victims.

Multidisciplinary Clinical Care of Burn Victims

Due to lack of awareness about burn patient care outside the highly specialized and specific settings of Burn Centers, a multidisciplinary team should carry the complex management of severe burn victims. For instance, the care of severely burned patients is categorized in Switzerland as "Highly Specialized Medicine" (HSM).[2,10–13] This HSM organization ensures the highest quality and excellence in healthcare, provided by an integrative and dynamic collaboration of multidisciplinary specialists. This strategy of multidisciplinary clinical care is also widely used worldwide.

In an open design, ICU physicians and nurses would be the primary care providers from a nonsurgical standpoint, along with plastic and pediatric surgeons as consultants (while on the reconstructive surgery floor, surgeons would be the primary care providers). Given the multidisciplinary character of care management for severely burned patients, team meetings should be held to discuss all patients of the Burn Center, and in addition to respective primary care providers, attendance to these meetings should routinely comprise physiotherapists, nutritionists, anesthesiologists, psychiatrists, and other medical consultants as needed. In our hospital, biologists and engineers from the research unit of the Plastic and Reconstructive Surgery service also attend these meetings, as they lead research projects and ensure proper implementation of GMP cellular production protocols. Likewise, scientists from the CPC (Cell Production Center, ie, GMP-accredited manufacturing facility of our hospital) provide updates about the amount of available cultured skin grafts and expected dates of delivery, in order to plan showers and surgeries accordingly.

Regarding postburn care, Burn Centers should sign collaboration agreements with rehabilitation centers, in order to ensure a continuum of care for its burn patients after hospital discharge, until social and professional reintegration is established. For instance, our Burn Center signed collaboration agreements with two external rehabilitation centers, namely the "Clinique Romande de Réadaptation" or CRR (Vaud, Switzerland) and Lavey-Medical SA (Valais, Switzerland), which reduces the costs considerably, as it will be shown hereafter.

Managing the Risks and Costs in the Organization of a Burn Center

Due to the naturally fluctuating burn patient admission rates, Burn Centers bear increasing pressure

Table 1. Specificities and related advantages of an "open-design" Burn Center from an architectural and organizational perspective

Characteristic	Advantages
Open main Burn Unit	Facilitated clinical and logistic workflows
Merged adult and pediatric care	Centralization of personnel resources, clinical competencies, and dedicated equipment
Isolation box with operating theater and hydrotherapy capacity	Possibility to treat patients autonomously while maintaining isolation, for protection of the patient and the Burn Unit
Dedicated operating theater in the Burn Unit	Proximity with dedicated intensive care beds, limited transit distance, and high reaction capacity to emergencies
Burn Unit on main ICU floor	Proximity of intensive care providers and equipment in case of emergency, and limited transit distance
In-house GMP manufacturing facility	No dependency on external providers and direct control on procedures and quality
Isolators for cell therapy production chain	Facilitated accreditation and relatively low overall costs of operation

GMP, Good Manufacturing Practices; *ICU*, intensive care unit.

Figure 1. Illustration of a main Burn Unit located on the general ICU floor, with representation of an unconventional "open-space design" facilitating clinical and logistic workflows. Depicted locations comprise essentially the isolation box and regular rooms, the general ICU area, the main operating theater, and the hydrotherapy room, as well as other areas such as the reception desk, the technical room, the storage room, the meeting room, the office, and the waiting room. *ICU*, intensive care unit.

toward resource utilization optimization.[14,15] As mentioned hereabove, a notable characteristic of our Burn Center structure is the open-space design, facilitating clinical and logistic workflows while reducing costs, since space and personnel are attributed interchangeably to burn and nonburn patients, as a function of burn patient admissions. For instance, general ICU patients or routine plastic surgery patients are admitted to the Burn Center, when burn patients are scarce. These nonburn patients will occupy the same space and will be taken care of by the same personnel that take care of burn patients, when present. Programs that educate multidisciplinary staff for burn patient care are essential and result in increased commitment to the Burn Center.[16] Despite its benefits, the open-space setup does not resemble many other Burn Center structures that we have had the privilege to visit over the years (ie, Canada, India, and Taiwan), which is why we advocate for such design as set forth in our guideline.

On the same line of optimized resource utilization, the operating room that is dedicated mainly for burn patients can be used for other surgical interventions: in our hospital, this room is occasionally used for organ retrieval for transplantation purposes. In addition, both hydrotherapy and operating rooms should also be implicated in the treatment of severe cutaneous conditions such as Lyell and Stevens–Johnson syndromes or necrotizing fasciitis, as these cases necessitate similar medical care as for burns. In addition, minimizing infectious complications (Figure 1, isolation box) results in controlled morbidity and mortality. This can be achieved via specific structural designs, workflows, and use of therapies proven to decrease complications and hospital stays.[17–21] Further information on infrastructure optimization is discussed in the "Managing Risks and Costs of Cellular Therapies" section, namely for the manufacturing of cell therapies.

Finally, signing collaboration agreements with rehabilitation centers allows to reduce the costs of hospitalizations; in our case, from around 1000 Swiss Francs (CHF) per day on the regular floor in our hospital to around 400 CHF per day at CRR and 200 CHF per day at Lavey-Medical SA.

STANDARDIZED CELL THERAPY INTEGRATION FOR SEVERE BURN PATIENTS

Worldwide efforts in specialized hospital centers have been made to develop and implement novel cell therapy approaches to fill the gaps and unmet needs in conventional surgical treatment of severe burns.[22] Early surgical intervention and Tissue Engineering Products (TEPs) decrease morbidity and mortality of severely burned patients, as they allow for rapid wound coverage, thereby decreasing fluid loss and nosocomial infection risks.[23–25] In addition, cell therapies promote epithelialization of burn wounds as well as donor sites, thereby hastening the coverage process.[22,26] Medico-economic analyses have demonstrated the efficiency of established cell therapy protocols, enabling reimbursement by basic health insurance, especially when the remaining amount of skin may not be enough for conventional skin grafting (ie, >50% TBSA burns in adults and >30% TBSA burns in children). We will detail in this section different cell therapies known for burns (Table 2), with a discussion on the optimization and the costs of an "in-house" model of cell therapy manufacturing.

Platelet-Rich Plasma

Autologous platelet-rich plasma (PRP) treatments are used in superficial burns and on split-thickness skin graft donor sites, with good overall results and high relative cost-effectiveness.[5,27,28] They are safe and their manufacturing process is easily standardized. Acute burn wounds generally necessitate 1 ml of PRP preparation to treat surfaces of 100 to 150 cm^2, while chronic wounds are more demanding, with an average of 1 ml preparation for 10 cm^2 areas.

Autologous PRP preparations are obtained by a two-step differential centrifugation protocol applied to patient whole-blood (ie, ~20 ml, sodium citrate-stabilized) and isolation of autologous thrombocytes in restricted plasma volumes (Figure 2). The resulting cell suspension (ie, 1–2 ml, concentrated 2–3-fold) is then reinjected or applied topically. This intervention stimulates tissue repair and modulates responses to injury, thereby enhancing wound healing. Autologous PRP

Table 2. Overview of GMP cell therapies currently used in Burn Centers

Therapy	Treatment Unit Definition	Composition	Lot Composition	Manufacture Timeframe
PRP	2 ml ($5.0 \times 10^8 \pm 2.3 \times 10^8$ platelets)	Autologous plasma and thrombocytes	1 syringe	2 h
CEA	75 cm^2 sheet	Stratified autologous cultured keratinocytes Vaseline gauze Traces of rinsing medium and feeder-layer fibroblasts	50 units	3–4 weeks
CDEA	75 cm^2 sheet	Stratified autologous cultured keratinocytes and fibroblasts Vaseline gauze Traces of rinsing medium and feeder-layer fibroblasts	20–40 units	6–8 weeks
PBB	108 cm^2 construct ($5.0 \times 10^5 \pm 0.5 \times 10^5$ allogenic cells)	Human cultured progenitor dermal fibroblasts Equine collagen sheet Rinsing and incubation medium traces	2–50 units	18–72 h

CDEA, cultured dermal–epidermal autograft; *CEA*, cultured epithelial autograft; *PBB*, Progenitor Biological Bandage; *PRP*, platelet-rich plasma.

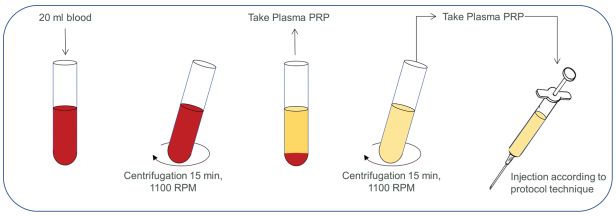

Figure 2. Illustration of platelet-rich plasma preparation by centrifugation.

may be sprayed on the wounds in combination with fibrin sealant (eg, Artiss® from Baxter, Evicell® from Ethicon).

Cultured Epithelial Autografts and Keratinocyte Suspensions

Cultured epithelial autografts (CEAs) were originally developed in Brigham Hospital in Boston, USA,[29] where successful patient treatments were published starting in the 1980s.[30–32] Extensive clinical data available today confirm the usefulness of CEAs in Burn Centers.[33–37]

CEAs are composed of autologous cultured and stratified keratinocyte sheets (Figure 3). They are prepared from a healthy epidermal biopsy isolated from the patient (ie, <10 cm^2, ideally from axillary or inguinal regions). Enzymatic digestion enables isolation of single-cell keratinocyte suspensions, which are used for serial in vitro culture expansions on feeder layers (ie, murine fetal 3T3-J2 fibroblast cell line). After 3 weeks of expansion, resulting keratinocyte sheets (ie, stratified, six to eight layers with epidermal phenotype and differentiation) are then harvested and transferred to Vaseline-covered bandages, which are subsequently applied to deep partial-thickness burns and stapled in place. Around 15 to 50 CEAs are usually prepared for each severe burn patient, and numbers are adapted according to wound size. Alternatively, expanded keratinocytes may be resuspended and applied in spray formulations based on wound type, topology, and urgency of treatment. This practice has been used periodically over the years when urgent clinical situations arose.[5,38–40]

Cultured Dermal–Epidermal Autografts

Cultured dermal–epidermal autografts (CDEAs) are an evolution of CEAs and broaden the scope of clinical applications (Figure 4), as they comprise both autologous cultured keratinocytes and fibroblasts.[41–44] They were developed and applied clinically since the 1990s, in deep partial- and full-thickness burns specifically. The biphasic composition of CDEAs provides a relatively stronger layer for skin reconstruction. The current clinical management strategy restricts their use to patients presenting over 70% TBSA burns, as reconstructive efforts are highly time-consuming and allow for lengthy cell production delays. A main advantage of these constructs is the relatively low induced retraction property, allowing for application in anatomical sites where skin retraction is to be avoided (eg, articulations, neck).

To obtain this type of construct, a full-thickness healthy skin biopsy is isolated from the patient and is differentially submitted to enzymatic and mechanical treatments in order to isolate the cell types of interest (Figure 5). After appropriate in vitro expansion and specific cell stimulation, resulting bicomponent cellular sheets are applied to the patient wounds in the same manner as CEAs. Comparative evaluations have shown that for deep wounds, CDEA constructs combined with commercial dermal substitutes provided relatively superior clinical outcomes, with reconstructed skin presenting ameliorated functional mechanical properties than samples from the CEA group. Indeed, CDEAs were the only products able to promote effective re-epithelialization of Integra® or Matriderm® constructs. Despite high utility in wound coverage and repair stimulation, both CEAs and CDEAs suffer from the inherent disadvantage of necessitating extensive manufacturing delays (ie, 3–4 and 6–8 weeks, respectively), due to cell culture procedures. Nevertheless, once the initial in vitro culture periods are over, new cultured autografts may be made available regularly by continuous production and cryopreservation of specific patient cells.

As reconstruction success has been limited to the epidermis and dermis to date, it will be necessary to further associate hypodermis and specific cell types from this tissue to abovementioned routine methods to improve the quality of regenerated skin. The inclusion of adipose stem cell culture could be this next step of reconstruction.[45]

Allogenic Cell-Based Therapy: Progenitor Biological Bandages

Progenitor Biological Bandages (PBBs) were developed and introduced since the 2000s as customized and safe products.[6,46,47] Due to their short manufacturing delays, PBBs provide a rapid wound coverage solution, without the need for skin grafts (Figure 6). They are currently classified as combined Advanced Therapy Medicinal Products (cATMP) under relevant European legislation and as Standardized Transplants under Swiss legislation. PBBs allow bioactive wound coverage and healing, based on allogenic primary progenitor dermal fibroblasts formulated on a moldable bioresorbable equine collagen sponge.[8] Primary progenitor dermal fibroblasts were isolated under a dedicated Transplantation Program and used to constitute tiered cryopreserved cell banks within GMP specifications.[22]

In addition to numerous technical and clinical advantages characterizing the robust progenitor cell source, clinical applications of PBBs have yielded promising results in particular for pediatric burn patients (Figure 7). In addition to rapid primary wound or donor site wound coverage, PBBs may lower pain, prepare wound beds for subsequent grafting when necessary, stimulate repair and regeneration, and minimize scar tissue formation by moderating host tissue functions via growth factor and cytokine paracrine signaling pathways.[22] With regard to wound depth, PBBs are supposed to optimally stimulate spontaneous skin healing and minimize scaring of superficial zones, reduce the risk of edema and capillary thrombosis in intermediate zones, which in turn implies a reduction of the body area to be grafted, and prepare deeply affected zones for skin grafting.[9] Notably, PBBs do not require stapling during clinical application, and are rapidly and naturally degraded without residual necrotic tissue formation. This results in an easy and relatively painless bandage exchange procedure.[8]

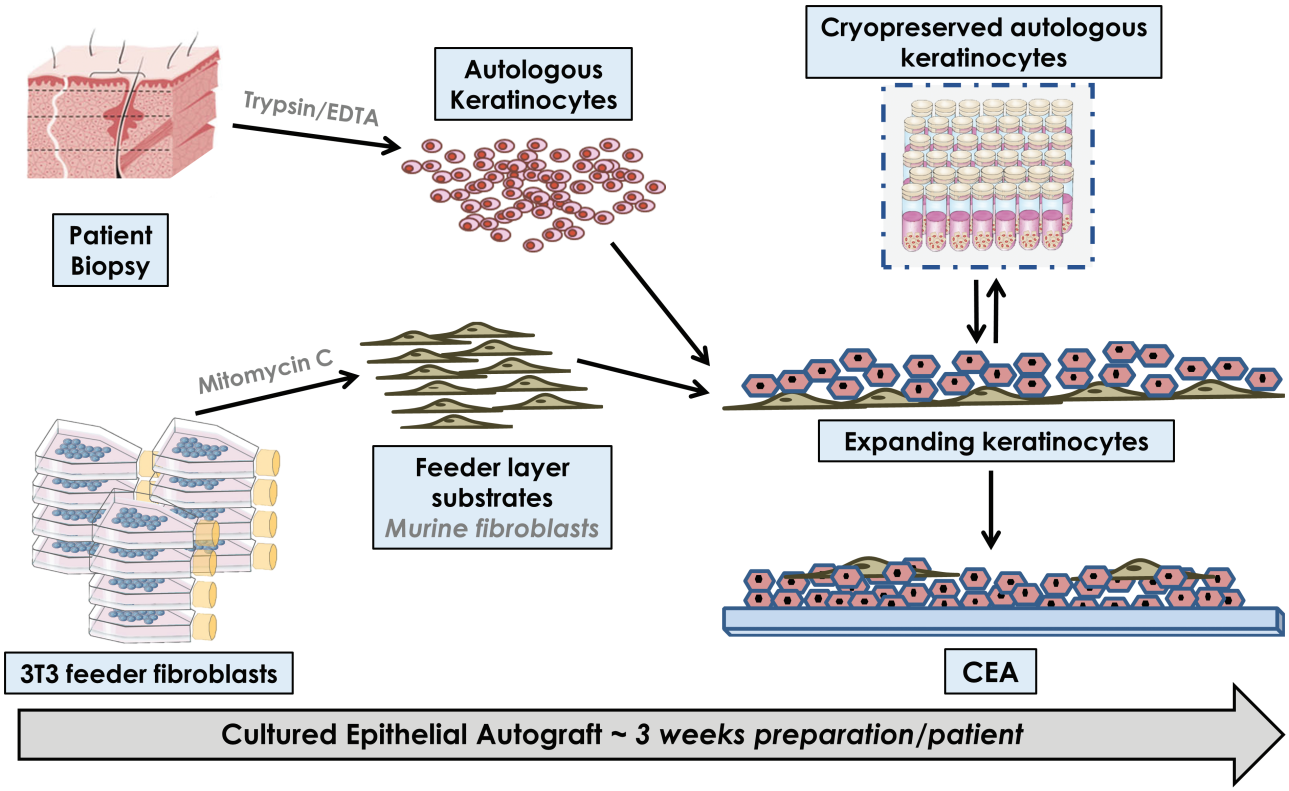

Figure 3. Graphical schematization of cultured epithelial autograft (CEA) GMP manufacture. An epidermal biopsy of healthy skin is harvested from the patient and enzymatically dissociated (trypsin 0.1%, mechanical agitation at 37°C, filtration on 100 µm cell strainers). Confluent 3T3-J2 murine fibroblasts are growth-arrested by adjunction of mitomycin C (4 µg/ml) and are used as feeder layers for coculture proliferation support. Keratinocytes are grown in culture medium composed of DMEM, HAM's F12, FBS, l-glutamine, EGF, hydrocortisone, cholera toxin, penicillin–streptomycin, insulin, and gentamycin. After expansion of sufficient keratinocyte populations (around 60% confluence), cells may be harvested in sheets for CEA preparation (dispase 0.25% treatment) or harvested (trypsin–EDTA, 0.05–0.01%) and suspended in cryopreservation medium (BIOFREEZE) and frozen for long-term storage. After incubation, cell sheets are rinsed with DMEM supplemented with penicillin–streptomycin. For transfer to the clinic, constructs are mechanically transferred and clipped onto Vaseline gauze (7.6 cm × 23 cm) and immersed in rinsing medium supplemented with gentamycin. The different manufacturing steps result in a production delay of about 3 weeks for a given patient before the autografts are available for therapeutic use.

Managing Risks and Costs of Cellular Therapies

Improvements of cellular therapy protocols may be attained through simplifying methods of manufacturing to reduce overall costs while the quality of the final product is guaranteed or even improved. Indeed, several cell therapy protocols are available to date at our institution following internal validated Standard Operating Procedures, with considerable efforts made toward compliance with local, national, and global quality rules and regulations. Hence, all products destined for clinical use (ie, in our hospital or sent abroad) are manufactured in-house by the accredited and authorized CPC, under current Good Manufacturing Practices (cGMP) standards.

Our in-house GMP manufacturing workflows unconventionally designed with all contact process steps carried out within a bioconfinement class A closed module and installed in class D production suites may be a cost-effective option (Figure 8). Contrasting with traditional open-system GMP infrastructures and equipment (ie, class A laminar flow hood in class B suites), this closed-system installation requires less overall maintenance, less personnel, and less cleaning procedures. The adoption of these closed-system GMP manufacturing chains also diminishes the frequency of product nonconformity. On the long run, these in-house dispositions allow for effective risk mitigation, control simplifications, and reduced overall manufacturing costs, for the following reasons: 1) the Burn Center does not rely on the supply of an outsourced structure or company in order to provide cell therapies for their patients; 2) each closed class A module is designed and controlled in order to allow the manufacture of cell therapy products for different cell types in parallel, which is pivotal in the case of cell therapies for acute wounds such as burns; 3) several closed class A modules ensure a continuous supply of cell therapies even in the case of maintenance, as other modules are available for manufacture.

Furthermore, the cost-effectiveness of wound coverage products is multifactorial, as improved clinical outcomes may shorten hospital stays and reduce overall costs, despite the relatively high individual product prices. As an example, a 24-hour stay in a Swiss Burn Center costs on average 4000 to 6000 CHF per day, therefore it is estimated that a 50% TBSA burn patient costs in excess of 150,000 CHF, which may be put into perspective with the costs of commercial wound coverages (ie, 3340 CHF for 1 m^2 porcine cover, around 12,000 CHF for 1 m^2 human cadaveric skin substitute).[1,2] These figures can

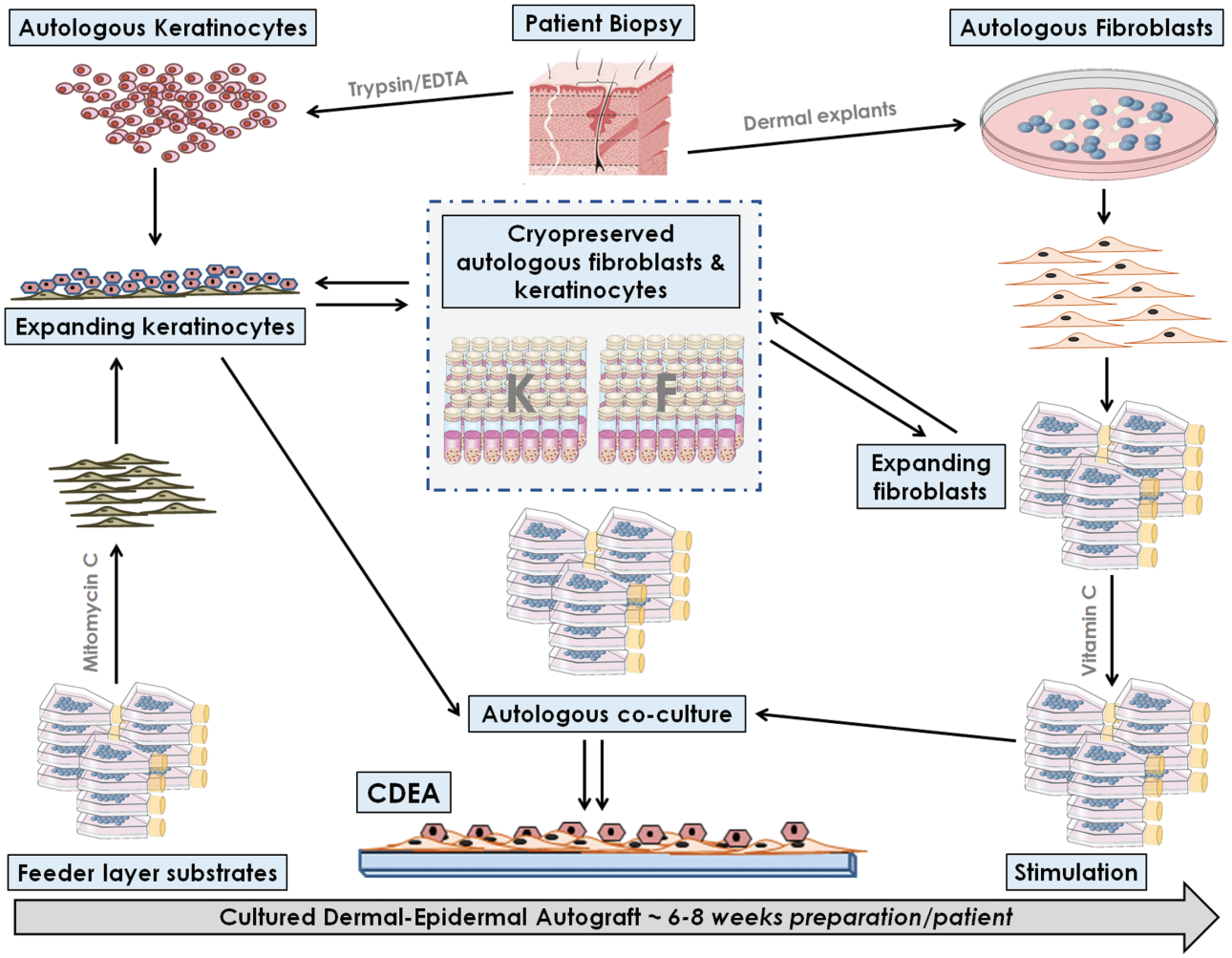

Figure 4. Graphical schematization of cultured dermal–epidermal autograft (CDEA) GMP manufacture. A full-thickness biopsy of healthy skin is harvested from the patient and submitted to thermolysin treatment (1 hour at 4°C in 0.05% thermolysin) before parallel enzymatic (trypsin–EDTA) and mechanical dissociation (trituration and explant method). Patient fibroblasts are culture expanded and may also be cryopreserved or cocultured for CDEA preparation, with an intermediary stimulation using vitamin C (100 µl of 20 mM solution, for stimulation of collagen production) in the second case. Coculture of both patient cell types results in rapid formation (~7 days) of stratified cell sheets to be harvested for CDEA preparation. Culture vessels are opened or thermally cut to extract the cell sheets. The different manufacturing steps result in a production delay of about 7 weeks for a given patient before the autografts are available for therapeutic use.

furthermore be compared to the costs of PBBs, which amount to about 2550 CHF for 1 m^2, constituting an additional argument for continued in-house manufacture and specific therapeutic use.

Continuous optimization and standardization of cellular therapy protocols are necessary to ensure safety and effectiveness of final products.[48] Such undertakings may comprise replacement of animal products in manufacturing processes, choice of therapeutic delivery systems allowing for shorter culture periods, or integration of ancillary autologous cellular components promoting product stability (eg, PRP).[5,49]

REGULATORY HURDLES AND SOLUTIONS FOR CELL THERAPIES IN HOSPITALS

Evolution of Regulatory Framework of Cell Therapies

The abovementioned cell therapies currently face potentially jeopardizing challenges on the policy front in Europe.[50–55] Indeed, evolution of requirements for use of ATMPs have brought market authorizations to a stall. Conjugation of cGMP manufacture and extended regulatory submission steps bear stifling costs for many key sponsors interested in bringing novel and salutary regenerative medicine products to patient bedsides.[50,56,57] This is exemplified at the level of University Hospitals actively resorting to cell therapies, for which industry-destined GMP guidelines are being enforced and result in pharaonic manufacture costs. This problematic resonates at multiple institutional levels and has opened wide debate around strategic operations of Burn Centers in particular, as many well-established hospital practices were denounced as illegal with respect to European directives or national regulations. According to these regulations, the hospital must hold, on the one hand, a manufacturing authorization specific to the concerned therapeutic products, and on the other hand, a market authorization (AMM) even to apply the therapeutic products to its own patients.

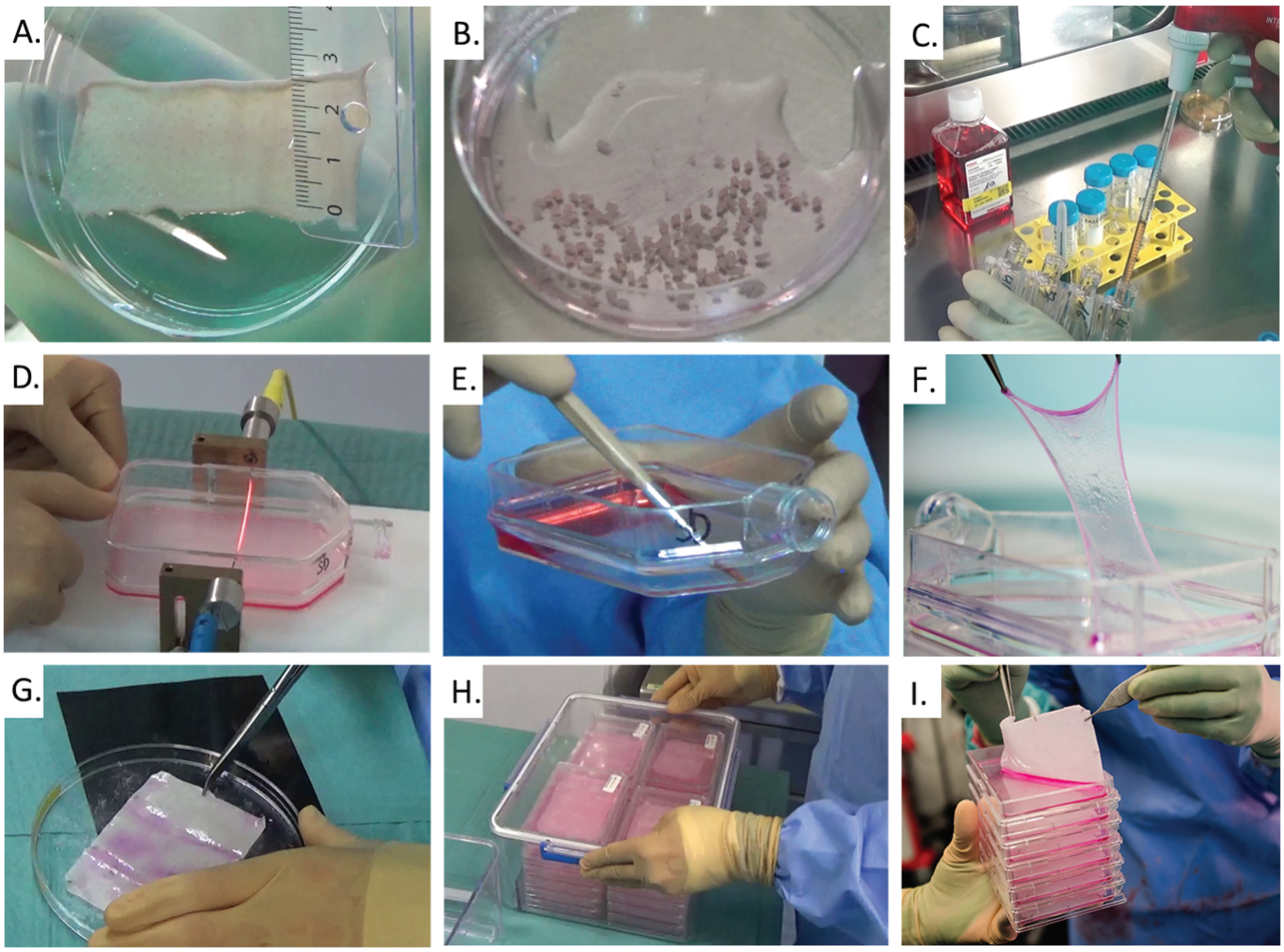

Figure 5. Graphical illustration of various manufacturing steps of cultured skin autograft (CEA or CDEA) manufacture. (A) A full-thickness 10 sq cm^2 biopsy is procured. (B) Patient dermal fragments are minced and cell cultures are initiated using seeding for keratinocytes or an explant method for fibroblasts. (C) Cells are culture expanded and harvested with trypsin–EDTA (0.05–0.01%). (D) Culture flasks are cut for stratified cell sheet harvest. (E and F) Cell sheets are carefully removed from the culture vessels. (G) Cell sheets are adjusted on adequate Vaseline gauze to form CEAs or CDEAs. (H) Sheets are put into square flasks contain a small quantity of medium and conditioned into a hermetic box (as secondary containment) for transport. (I) CEAs or CDEAs are processed for clinical application in the operating theater. *CDEA*, cultured dermal–epidermal autograft; *CEA*, cultured epithelial autograft.

Although the necessity of a manufacturing authorization may be reasonable in terms of patient safety, an AMM is not justified in the case where products to be administered are manufactured by the hospital laboratory/pharmacy specifically for their own patients. Therefore, hampering effects due to regulatory frameworks and implied costs has driven public institutions to seek specific policy exceptions enabling suitable and continued use of crucial personalized therapies (Table 3).[56–59]

In the specific context of burn patient care, it is important that the adequate choice of treatment, potentially including cellular therapy, is retained by the primary caregivers, as pragmatic, rapid, and effective wound management is often essential for patient survival. While maintaining the most stringent quality standards and requirements for the hospital manufacture of cell therapies, straightforward regulatory frameworks are paramount in assuring safe and effective care provision to burn patients.[51,52,56,60] For instance, in Switzerland, cell therapy manufacture for therapeutic use must submit to cGMP standards and comply with dispositions and ordinances of the federal therapeutic products legislation (ie, Federal Act on Medicinal Products and Medical Devices, Therapeutic Products Act, TPA, SR 812.21 and related Ordinances).

Practically, new European Directives (ie, 2001/83/EC) and Regulations (ie, 726/2004, with the amended Regulation 1394/2007) have been implemented and interpreted in variable manners throughout Europe over the last years.[61–63] Coupled to these frameworks, the renewed Swiss Transplantation Legislation has led to complex pathways to be implemented, which could potentially adversely affect severe burn patients and appropriate clinical care decisions. Indeed, before 2007, all new cell therapy techniques were presented before State Ethics Committees and were registered with the Department of Public Health once approved. Since the abovementioned regulatory shifts, all therapies that comprise cell culture techniques are by legal definition considered to be Standardized Transplant Products, as a consequence of the standardized in vitro processing of the biological products.[4] As a result, cell therapies such as CEA/CDEAs or PBBs are to be regulated similarly to classical or biological drugs for all development and therapeutic

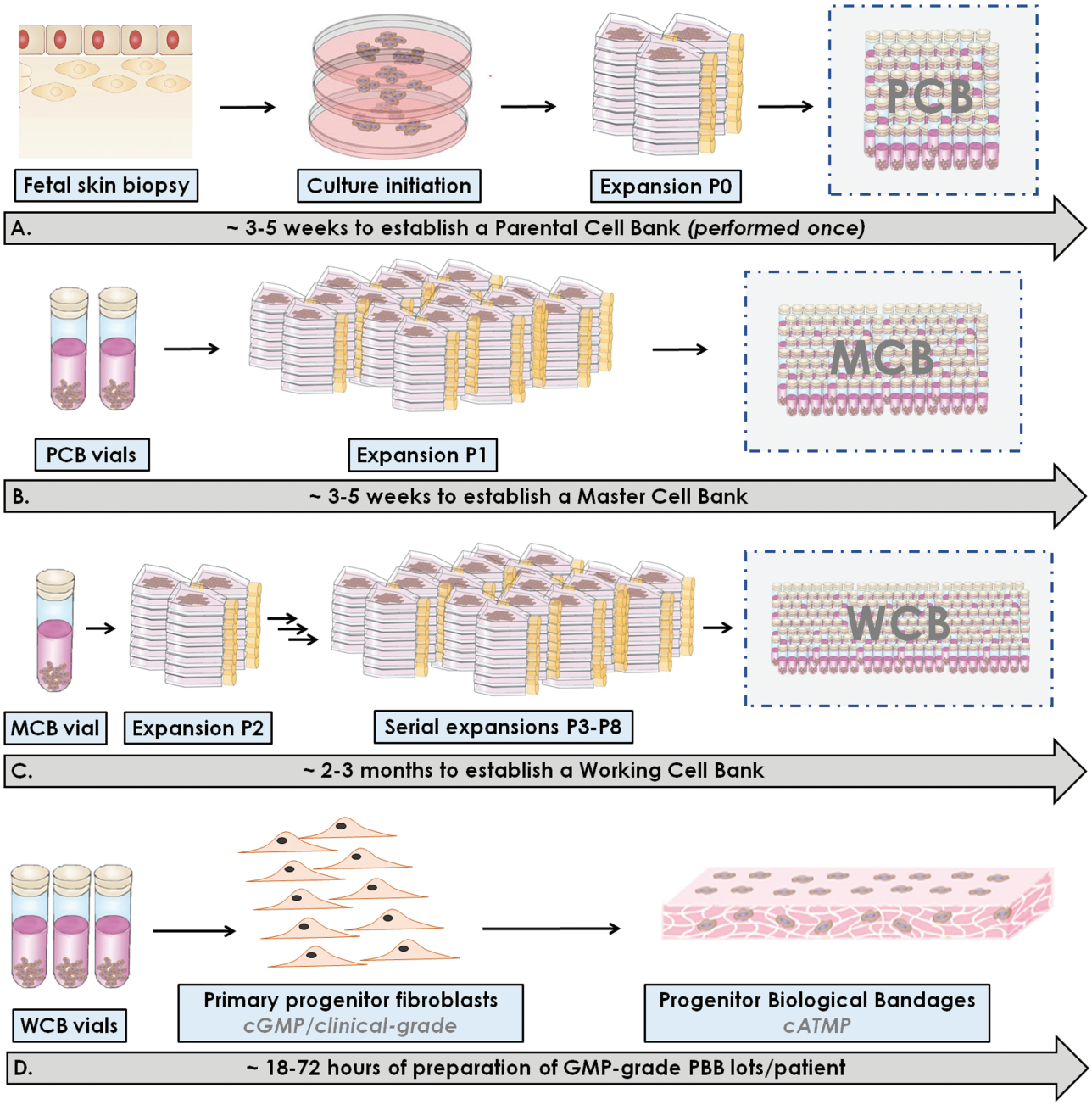

Figure 6. Graphical schematization of progenitor cell type isolation, tiered cell banking, and Progenitor Biological Bandage (PBB) GMP manufacture. (A) A small (<2 cm^2) fetal skin biopsy is processed using an explant method to establish a primary progenitor cell type (dermal fibroblasts). Cells are culture expanded and cryopreserved to constitute a Parental Cell Bank (PCB). This procedure is carried out only once, as the tiered banking system requires only one organ donation. (B) Using materials from the PCB, a culture expansion is conducted to establish a cryopreserved Master Cell Bank (MCB). (C) Using materials from the MCB, serial culture expansions are conducted to establish cryopreserved Working Cell Banks (WCBs). (D) Vials from the WCBs are initiated and cells are seeded on equine collagen scaffolds to form Progenitor Biological Bandages (PBBs).

use considerations (Article 49 of the Transplantation Act, Therapeutic Products Act, and Medicinal Products Licensing Ordinance MPLO, SR 812.212.1).[64,65] The authorization requirements for transplant products have thus been aligned more closely to those for medicinal products, even if adjustments have been admitted to be necessary according to the specific nature of TPs (Swissmedic Information Sheet I-313.AA.01-A15e, 2019). Direct and specific outcomes of such frameworks imply that University Hospitals, despite their general interest mission, are held to the same standards as pharmaceutical industries, which must seek exploitation authorizations for manufacturing cell-based products, licenses to conduct clinical trials, and full authorizations for market approval (AMM) as for commercial drugs.[65] Furthermore, regulation changes imply that hospital infrastructure must follow cGMP standards for production, Quality Assurance, and Quality Control of all processes for use

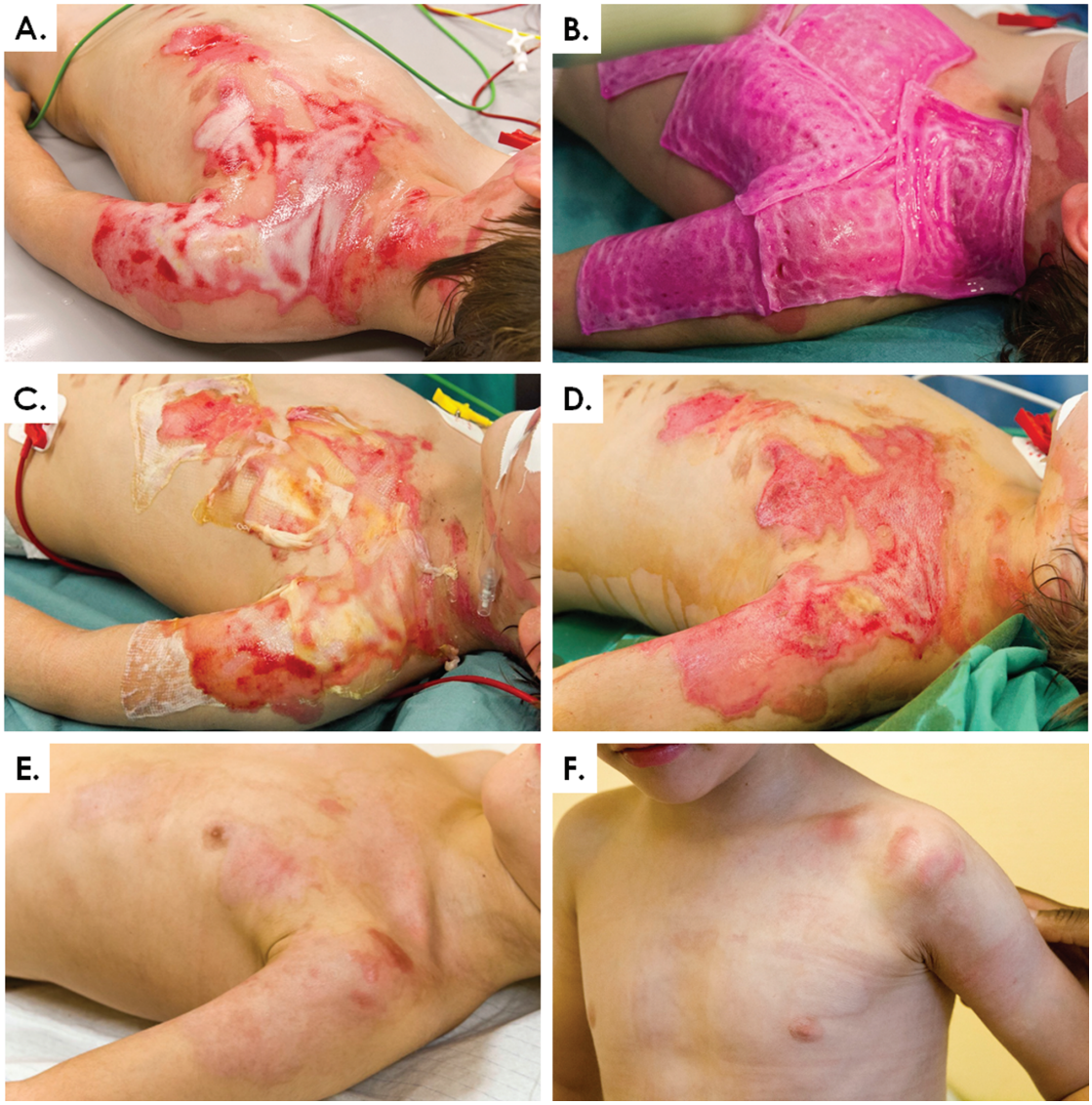

Figure 7. Photographic illustration of pediatric thermal burn wound (scalding injury) evolution after clinical application of PBBs. Second degree superficial and deep burns covered 12% of the TBSA. (A) Aspect of the burns after thorough cleaning and washing. (B) Application of PBBs the next day. (C) Aspect of the burns 48 hours after treatment initiation. (D) Aspect of the burns 4 days after treatment initiation. (E and F) Aspect of the burns 6 weeks after treatment initiation. Full structural and functional recovery were attained, without formation of scar tissue. *PBB*, Progenitor Biological Bandages. Adapted with permission.[66]

in the Burn Center. However, not many hospitals worldwide possess the necessary infrastructure, specialists, and financing to maintain these requirements following the letter of the new laws.

Along with the availability of such dedicated manufacturing platforms, the new product classification issues remain, which is problematic for protocols and therapies which have been safely and routinely used for decades.[51,53] Indeed, as ATMPs may be classified as standardized transplants (ie, substantial modifications of patient biological materials), they are normally required to be evaluated within standard clinical trials, notwithstanding extensive scientific and clinical hindsight of over 30 years. Pragmatically, developing a randomized controlled clinical trial for treating severe burn patients could present a significant ethical dilemma, as cell therapies such as discussed herein are firstly implemented to save lives in the race for sufficient burn wound coverage. Therefore, for these types of cell therapies, hospital exemptions, compassionate use, or resort to Hospital Magistral Preparation (HMP) frameworks would be most appropriate pathways circumventing regulatory deadlocks.[60]

Hospital Exemptions

Provided that hospitals possess or work with adequate accredited GMP infrastructures, it would be most logical to implement hospital exemptions in order to offer safe cell therapies for burn patient betterment.[56] According to Article 28 of the European Regulation 1394/2007 revision, the "*Hospital Exemption is applied to any ATMP which*

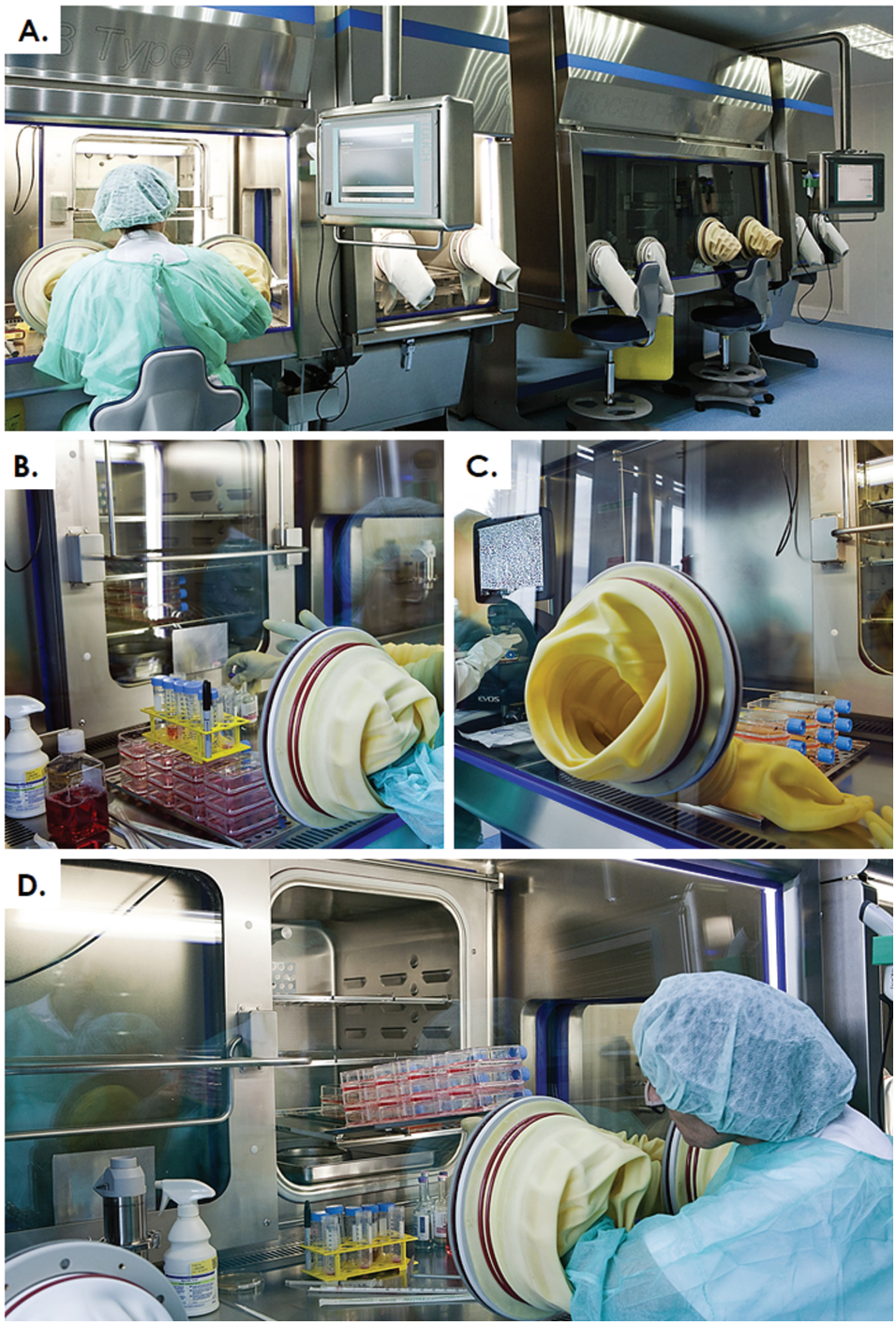

Figure 8. Photographic representation of the in-house Cell Production Center GMP production platform with isolator manufacturing chains. (A) Overview of the main production unit. (B) Handling of the cell cultures in the isolator workspace, before reincubation in the integrated controlled atmosphere compartments. (C) Observation of confluent cultures with dedicated imaging systems. (D) Transfer of the cultures back to the incubator compartment.

is i. Not intended to be placed on the market; ii. Prepared on a non-routine basis; iii. Not within an industrialized manner; iv. Prepared as a custom-made product for an individual patient."[63] Unfortunately, the European directive may have multiple interpretations for what is considered "non-routine basis," "industrial process," or "custom-made," preventing the adoption of a consensus around hospital exemptions. In Switzerland, the situation is even more restrictive, because such exemptions are currently admitted under specific conditions for medicines, but are excluded for standardized transplants [Article 2 alinea 2 of the Therapeutic Products Ordinance (TPO), SR 812.212.21].[65]

Table 3. Possible regulatory pathways to maintain use of cell therapies in University Hospitals and Burn Centers for hospitalized patients

Regulatory Pathway	Discussion	Responsibility Bearing
ATMP-drug type dossier submission	Extremely costly and stringent regulatory requirements Requires subcontracting to CMO Mitigated interest by pharmaceutical industry	Clinician Manufacturer
Compassionate use (Helsinki declaration)	Ethically justified from a clinical point of view but brings legal exposure regarding local regulations	Clinician Institution (hospital)
Hospital exemptions	Restricted to products not intended to be marketed, prepared on a nonroutine basis, in a nonindustrial manner, and used as custom-made products for individual patients	Clinician Institution (hospital)
Orphan drugs	Produced for diagnosis, prevention, or treatment of a life-threatening disease or potential chronic disability, which affects less than 5 of 10,000 people at a given time	Clinician Manufacturer
Hospital Magistral Preparations	Products manufactured, on demand or serially, by an authorized pharmacy following a medical prescription and intended for the treatment of a determined patient or subset of patients	Clinician Pharmacist
Hospital officinal preparations	Products manufactured, on demand or serially, by an authorized pharmacy following a recognized formula or monograph and to be used for treatment of the institution's own patients	Clinician Pharmacist

ATMP, Advanced Therapy Medicinal Product; *CMO*, Contract Manufacturing Organization.

Compassionate Use

Article 37 of the Declaration of Helsinki specifies: "*In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, reestablishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available*".[67]

Therefore, in the absence of effective or available therapeutic alternatives, an unauthorized TEP could ethically be used by attending clinicians, albeit under their own extended responsibility and legal exposure, as the warranted interventions defined in the Declaration may conflict with superseding local legal bases. Applicability of compassionate use for CEAs is additionally undermined by the undeniability of gathered clinical proof and the routine manufacture during several decades. Despite the fact that compassionate use is not provided as such by the Swiss legislation, hospitals may be allowed to prescribe unauthorized TEPs under certain conditions, if great therapeutic benefit is expected for the concerned patients [Articles 35–37, Therapeutic Products Ordinance (TPO), SR 812.212.21].

Hospital Magistral Preparations and Officinal Preparations

HMPs may constitute an alternative option which may respect both existing regulatory frameworks and the dependency of severe burn patients to rapid access to innovative therapies.[60] As already mentioned, Switzerland foresees additional conditions for the HMP's authorization exemption, in particular that the Pharmacopeia or another recognized drug formulary mentions the active substance (Article 37 § 1 letter d, TPO). HMPs (ie, compounded prescription drug products in the United States) are defined as products prepared, on demand or serially, in the pharmacy under the supervision of an authorized pharmacist, following a medical prescription, for an individual patient or a determined group of patients, according to scientific standards and technical specifications of pharmaceutical art (European Directive 2001/83/EC, Article 3, also defined by Article 9 § 2 letter a, TPA).[61,64]

Officinal preparations are similar to magistral preparations, but require that the pharmacist follows a recognized formula or monograph. Therefore, in alignment with recent work on bacteriophages and definitions of novel Active Pharmaceutical Ingredients, it is of great current interest to establish general or specific ATMP monographs to be adequately approved and implemented in specific compendia, allowing standardized preparation of TEPs for specific clinical indications and under the responsibility of the pharmacist and the prescriber. These have to be considered under GMP requirements, following a medical prescription and for a specific patient of the institution.[60]

In addition, with the adopted regulatory classifications and for the particular case of severe burn victims in need of salutary therapeutic interventions, appropriate clinical trials for cell therapies should be integrated with recruitment of patients that are not in life-threatening situations (ie, implemented for lower TBSA burns). This concerns potential commercial product development around autologous or allogenic cellular therapies, whereas an actual final product is fully developed for a specific clinical indication.

CONCLUSIONS

A growing synergistic collaboration of various professionals gravitating around burn care is of paramount importance, as it bears significant impact on morbidity, mortality, and optimized health capital restoration. Nevertheless, specific considerations for risk and cost management are crucial for

sustainability in burn care. These comprise specific choices of infrastructure and organization, technical and scientific aspects of cell therapy production, and clinical integration in modern regulatory frameworks.

Due to the naturally fluctuating burn patient admission rates, Burn Centers are pressured to optimize the use of their resources. Thus, an open-space design may be a good option to optimize the allocation of space and personnel. Collaboration agreements with rehabilitation centers ensure a continuum of postburn care and further reduce the costs of hospitalizations. In-house GMP manufacturing can also be designed unconventionally and cost-effectively within closed-system installations instead of the traditional open-system infrastructures, thereby allowing for control simplifications, effective risk mitigation, and reduced overall manufacturing costs. The cost-effectiveness of wound coverage products is multifactorial, as improved clinical outcomes may shorten hospital stays and reduce overall costs, despite the relatively high individual product prices.

Continuous optimization and standardization of cellular therapy protocols contribute in simplifying methods of manufacturing and delivery to the patient, while reducing overall healthcare costs. To this day, the highest modifiable risk to vulnerable burn patients resides in the regulatory turmoil introduced by literal interpretations of European legislations by local regulators, thus in a market where public hospitals are being regarded as commercial pharmaceutical industries. Compromise should clearly not be made with regard to quality standards for clinical product manufacture. However, current medical reality and the dire need of severe burn patients should prompt consensual establishment of a *modus vivendi* within public healthcare structures regarding historically used cell therapy interventions. Therein, appropriate product classification solutions should be implemented, guaranteeing compliance with the national and international regulatory landscape.

ACKNOWLEDGEMENTS

Philippe Abdel-Sayed and Lee Ann Applegate acknowledge funding from the Marie Sklodowska-Curie Action (N°833594—PHAS).

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