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Review article

Manufacturing processes

A management model in blood, tissue and cell establishments to ensure rapid and sustainable patient access to advanced therapy medicinal products in Europe

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ABSTRACT

Blood, tissue and cell establishments (BTCs) stand out in the management of donor selection, procurement and processing of all types of substances of human origin (SoHO). In the last decades, the framework created around BTCs, including hospitals and national health system networks, and their links to research, development and innovation organizations and agencies have spurred their involvement in the study of groundbreaking advanced therapy medicinal products (ATMP). To further improve strategic synergies in the development of ATMPs, it will be required to promote intra- and inter-European collaborations by creating an international network involving BTCs and major stakeholders (i.e., research organizations, hospitals, universities, patient associations, public agencies). This vision is already shared with the European Blood Alliance, the association of non-profit blood establishments, with 26 member states throughout the European Union and European Free Trade Association states. Herein we present and analyze the “BTC for ATMP Development And Manufacture” (BADAM) model, an ethically responsible business model based on the values and missions of BTCs and their commitment to health equity, patient access and education (based on voluntary donation of SoHO to address unmet clinical needs, while contributing to training professionals and scientific literacy of our Society).

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Blood, Tissue and Cell Establishments in Context

Cell, gene and tissue (CGT)-based therapies emerged out of revolutionizing (i) traditional cell therapies (namely, blood transfusion and hematopoietic stem cell transplantation), typically conducted in hospitals and elaborated in blood, tissue and cell establishments

(BTCs), and (ii) biological drug and vaccine development, largely conducted by the biotechnology and pharmaceutical industry. Although BTCs were primarily established to provide high-quality blood and its components for clinical use in therapy and diagnostics, they have gradually expanded operations to processing and banking all types of substances of human origin (SoHO) as well as complex products resulting from their manipulation (e.g., hematopoietic stem cells; advanced therapy medicinal products [ATMPs]) [1]. In all cases, voluntary donors are on the foundation of BTCs, providing SoHO as starting materials for clinical purposes and also offering human biological reagents for high-quality research & development & innovation (RDI)

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activities in cell biology, process engineering, diagnostics, pharmaceutical manufacturing and medical practice [2,3]. Due to the nature of their services, BTCs hold a key position connecting donors and patients, understanding perfectly the entire value chain from donor selection and SoHO procurement up to product release and patient treatment. Given the variety of SoHO, the spectrum and capacity of BTCs for conducting RDI and manufacturing activities are vast. Initially, CGT-based therapies were predominantly developed in academic hospital environments, in the autologous setting, with high production costs, poor clinical trial design and concerns regarding serious side effects, which largely discouraged the biopharmaceutical industry from entering the ATMP development field in its early stages [4–6]. Remarkably, a gradually greater understanding of the biology of these living drugs, the implementation of quality standards (European Directorate for the Quality of Medicines and HealthCare; good pharmaceutical practices [GxP]) and a growing body of evidence of efficacy and safety at longer follow-up times of patients receiving the first ATMPs have persuaded all the stakeholders involved (including regulators, clinicians, patients and funders) of the actual benefits of these developments, although at the cost of tremendous upheaval in bioprocessing and quality management [7,8].

The expertise of BTCs in mapping donor-to-donor variability, processing SoHO in compliance with strict quality standards and their active participation in the research, development and clinical-grade manufacturing of the first generation of ATMPs are key to offering revolutionary treatments targeting rare diseases and conditions lacking effective treatment [9,10]. As an illustrative example, chimeric antigen receptor (CAR) T-cell-based immune therapy (in whose development, manufacturing and/or distribution BTCs have been actively involved) has achieved unprecedented success as a life-saving technology for hematologic malignancies [11].

Therefore, BTCs are strategically positioned to bring innovative therapies to patients while adapting the existing framework in blood, cell and tissue procurement and processing, therefore adding value to voluntary SoHO donation. We are marching toward an age in which blood will be the safest it has ever been. Similarly, BTCs are committed to deliver advanced CGT-based therapies with same accuracy, efficiency and reliability.

Role of BTCs in ATMP Development and Manufacturing

The centralized procedure for the authorization of medicines applies to ATMP and involves a single application, a single evaluation and a single authorization throughout the EU. Three additional regulatory pathways exempt ATMPs from the centralized authorization pathway, namely (i) hospital exemption (HE), (ii) named patient use and (iii) compassionate use, which are all authorized on a national level. Named patient use and compassionate use pathways facilitate early access to investigational medicinal products for individual patients in life-threatening unmet medical need who are not enrolled in a clinical trial [12–15], in accordance with the specifications and under the direct responsibility of the medical practitioner (Directive 2001/83/EC, Article 5).

HE is described in Article 28(2) of the Regulation (EU) 1394/2007 and applies only to custom-made ATMPs, prepared locally on a “non-routine basis,” used in a hospital setting, under the responsibility of a treating physician, for a specific patient. In addition, a competent authority must authorize HE for use limited to the same Member State where it was developed, and the product must comply with the same national requirements concerning quality, traceability and pharmacovigilance that apply to authorized medicinal products. As a general rule, a risk–benefit approach and safety reporting are strictly required regardless of how the HE has been implemented [15]. The obvious advantage of the exemption is that patients can receive ATMP treatments under controlled conditions, particularly in areas of unmet medical need, where no authorized ATMP is available.

Additionally, it facilitates RDI in advanced therapies by non-profit organizations, such as academia, BTCs and hospitals.

There is a broad consensus in the field on both the necessity and limitations of HE; however, the harmonization of criteria and more guidance for its use across the EU are much needed [16]. Divergent interpretation and implementation of Article 28(2) could have a negative impact on patient access to treatments and ATMP development, and it also hampers transnational collaboration in HE-ATMPs [17]. Therefore, easily accessible, public EU-wide registries or databases, of the HE applications and approvals in the EU would help distinguishing between ATMPs that are or are not commercially viable, reduce patient risks, facilitate industry awareness of business opportunities and boost progressive entry of ATMPs into the therapeutic repertoire of health systems in a complementary fashion to commercial development [14,15,18]. In this context, developers need more practical assistance with regulatory, manufacturing and pharmacovigilance activities, which are indeed the areas of expertise of BTCs that could be further realized with the creation of centralized platforms for training and guidance via pan-European BTCs networks [16,19].

Due to the lack of clear registries, it is difficult to estimate the magnitude of the use of HE [20]. Available information points out that these ATMPs have close proximity to clinical practice, and manufacturing is primarily motivated by clinical needs and clinical experience. Regulatory aspects motivated or limited HE utilization, whereas financial resources generally limited HE use [14]. Most countries apply the definition of “non-routine” on a case-by-case basis per product, and there are differences in the individual details required for HE approval [21]. Some countries require extensive documentation and authorize specific products whereas others authorize establishments based on manufacturing licenses for ATMP product types. Interestingly, Spain seems to be the only EU country having approval for a CAR-T granted under HE. In February 2021, the CAR-T product ARI-0001, developed at Hospital Clínic de Barcelona, received authorization under the HE approval pathway for the treatment of patients relapsed/refractory acute lymphoblastic leukemia. This was an important landmark, given that it is the first CAR developed from bench to bedside in the EU and the first to receive the authorization of a governmental drug agency outside the centralized MA pathway [22].

The “Academic Niche” for Manufacturing ATMPs

The availability of ATMPs is greatly influenced by the huge costs associated with both their development and production, which makes the return on investment challenging for pharmaceutical companies, especially when considering the often-small patient population sizes, even under “orphan designation” incentives [23,24]. Nonetheless, industry has (i) succeeded in conducting clinical trials with ATMPs; (ii) brought the first products to marketing authorization (MA) and (iii) defined novel modes of interaction with academia. However, some of the ATMPs with granted MAs have been, not surprisingly, withdrawn from the market for “commercial reasons,” in some cases due to lack of reimbursement [20,25], therefore limiting patient access to potentially beneficial treatments.

Clearly, non-profit institutions are major contributors to the development of ATMPs but typically lack either the capacity or the interest to pursue the full developmental pathway to MA and are somehow risk-averse. They respond to clinical needs and foster therapeutic innovation in an environment that is not industrial. European investigator-initiated multicenter trials of ATMPs critically depend on academic Good Manufacturing Practice (GMP) facilities, as will the future delivery of many of the new medicines even after commercialization [25]. Initiatives such as the pre-GMP facility created in the Karolinska Institute University Hospital (Stockholm, Sweden) contribute to support process development and accelerate the transfer of cell product manufacturing from research to clinical GMP-grade and,

ultimately, to the clinic [26]. Similarly, a cooperation between Helsinki University Central Hospital (HUCH), the Finnish Red Cross Blood Service (FRCBS) and the University of Helsinki was signed to promote experimental treatments and clinical trials using cell therapy products as part of the treatment of patients in HUCH. In this context, the manufacturing capacity and regulatory expertise of FRCBS, in particular (or BTCs in general), can be effectively employed to advance in new developments. Moreover, HE has provided the regulatory niche for local manufacturing of ATMPs within an academic institution, including public facilities and non-profit organizations such as hospitals and BTCs. According to Priesner and Hildebrandt [25], the position of academia has changed substantially, being now at the front and at the end of the path of clinical development. Indeed, BTCs provide the appropriate environment needed for 360° product development and manufacturing: procurement of starting materials, patient recruitment, storage or final-stage preparation of products tested in late-phase, industry-sponsored trials and for authorized products [24,27]. BTCs also have extensive experience with donor recruitment, apheresis collection and timely issue of cells. This requires knowledge of trans-national and trans-continental SoHO import and export regulations and requirements. Specifically, the collaboration of BTC with experienced hospital and clinical research facilities is required for the provision of on-site point-of-care ATMP treatment. In contrast, Iancu *et al.* [28] pointed out that hospital-based GMP facilities have supported primarily investigator-initiated clinical trials but are increasingly involved in interactions with industry. Several academic hospitals have built their own personalized patient treatment programs and within those their own in-house manufacturing capacity (i.e., tumor-infiltrating lymphocyte therapy) [28,29].

As suggested by Priesner and Hildebrandt [25], regional ATMP “competence centers” could manufacture and provide for ATMPs locally, in a highly skilled environment and in the structural and regulatory framework needed, as an alternative to centralized manufacturing. In this context, BTCs could play a major role to provide broader access to innovative therapies as regional ATMP “competence centers,” therefore filling the gap between industry, regulatory authorities, and health care providers by the provision of technical, personnel, and infrastructure resources.

BTCs, Facilitators of Patient Access to ATMPs

Considering that major reasons for ATMP failure are likely related to high cost of development, quality control, regulatory requirements, starting material and donor-related aspects, qualified personnel, infrastructure and logistic limitations, we propose that BTCs would fit perfectly into the idea of sustainable regional GxP/ATMP “competence centers” and act as local manufacturers for ATMPs. BTCs are non-profit but can typically invest to a reasonable extent in RDI activities and collaborate closely with clinicians and the industry. BTCs hold a central position between donors and patients and manage the entire value chain from donor selection, testing and donation to pharmaceutical quality-assured manufacturing and logistics to hospitals. Novel cell therapies fit perfectly in the product portfolio of BTCs, and ATMPs are nowadays a central part of strategic plans of European BTCs, with investments in infrastructure, such as clean rooms and adequately trained personnel, which most academic research institutes cannot do. Besides infrastructure and logistics, BTCs have the capacity to understand the regulatory aspects and implement GxP in the work routines, as demonstrated by their active participation in the developments, such as the illustrative examples listed in Table 1 [30–34].

Commercial ATMP, especially autologous gene and cell therapy products such as CAR-T cells but also modified hematopoietic stem cells, require formidable logistics, including long air transports coupled with dedicated vans [35]. With the foreseen extension of ATMP to other, more frequent, indications, such logistic arrangements will not be viable. This is because of unbearable costs and incompatibility with the transition to a climate-neutral economy. It is possible that a decentralized system will become necessary, where the private sector provide the reagents and marketing authorization whereas BTCs handle the SoHO to produce the ATMPs.

Educational and Training Initiatives

The fast-growing field of ATMPs may potentially offer novel therapeutic approaches for a variety of pathologies; therefore, basic and advanced education (from regulatory to scientific and technical

Table 1
Illustrative examples of developments by BTCs.

BTC	ATMP	Stage	Role of BTC	Model	Ref
BST	TEP composed of MSC,WJ loaded into third-party pericardial matrix (BST +IGTP)	Phase 1/2	Regulatory development and GMP production	Public co-development (IGTP:BST) funded by the PERIS Program (Health Department, Government of Catalonia, Spain)	[30]
Sanquin	TIL therapy melanoma	Phase 3	Local production at different partners	public finance by the European Commission within Horizon2020 Framework Programme	[31]
BST	Transfer of Adenovirus, Cytomegalovirus and Epstein-Barr virus-specific T cells (TRACE)	Phase 3	Local production for partner clinical groups, therefore expanding capacity to reach larger population of patients to successfully complete Phase III studies	Public/private consortium funded by the European Commission within Horizon2020 Framework Programme	ClinicalTrials.gov Id. NCT04832607
CHUL	MSCs	CU	Local production for own hospital and other partners in Belgium	Public funding within the NHS	[32]
FRCBS	BM-MSC, autologous keratinocytes	HE	Local production under HE to Finnish hospitals	Public co-development	[33]
BST, CHUL, CHUM	Commercial CAR-T	Marketed products	Procurement of starting material (apheresis), QC, logistics and administration into patients.	Public/private agreement between BTCs and Pharma companies	[34]

Different types of ATMP (somatic, gene and tissue engineering products) are considered in this list of representative initiatives developed by BTCs, which comprise different stages of development (phase 1/2/3I, compassionate, HE, commercial) from public and/or private collaborations. BTCs listed include BST (Banc de Sang i Teixits, Spain); CHUL (Centre Hospitalier Universitaire Liege, Belgium); CHUM (University Hospital of Montpellier); and FRCBS (Finnish Red Cross Blood Service, Finland). ATMP, advanced therapy medicinal product; BM, bone marrow; BTC, blood, tissue and cell establishment; CAR-T, chimeric antigen receptor-T cell; CU, compassionate use; HE, hospital exemption; IGTP, Institut de Recerca Germans Trias i Pujol; MSC, mesenchymal stromal cells; NHS, national health system; TEP, tissue-engineered product; TIL, tumor-infiltrating lymphocyte; WJ, Wharton's jelly.

aspects) is a must for all professionals involved [36]. However, the new and emerging nature of the ATMP sector means that those currently working in BTCs may not have had the opportunity to professionally train in ATMP bioprocessing during their initial undergraduate and postgraduate education. Technicians and pharmacists trained for ATMP development and production are particularly needed, including in the private sector. Consequently, evolving the current ATMP educational opportunities to align with established strengths of BTCs will be a key component to expanding the capabilities within these establishments as well as adapting other professional profiles to the characteristics of the CGT field, given that the manufacturing and management of ATMP developments is interdisciplinary and complex. Compliance with tissue and cells, blood and ATMP legislation is crucial throughout the coordination of the multiple facilities required to ensure these therapies are available to a broad number of patients [37,38].

An effort is needed to understand the educational requirements surrounding the various ways in which BTCs may support ATMPs, including everything related to SoHO donation and processing of starting materials, their storage, distribution, quality assessment, safety and regulatory requirements. At present, there are several postgraduate opportunities in Advanced Therapies across Europe. Universities have evolved their courses to offering to include ATMP postgraduate education (e.g., Universidad de Granada, in Spain; Universities of Manchester and Sheffield, in the UK; University of Galway, in Ireland; Katholieke Universiteit Leuven, in Belgium). Training professionals on the particular needs of the CGT field is key to maintain a specialized workforce in the numbers required, albeit the global shortage of labor force. Such precise combination of concepts and skills is best understood and taught by BTCs and, consequently, it makes sense their involvement in educational and training initiatives. In this context, leading BTCs (namely, Sanquin in the Netherlands and Banc de Sang i Teixits in Spain) support a joint Master's Degree in Transfusion Medicine and Cellular and Tissue Therapies co-ordinated by Universitat Autònoma de Barcelona (UAB) and Leiden University Medical Centre (LUMC), which is a clear example of higher educational initiatives to train a new generation of professionals in the context of SoHO donation and processing, including ATMP development and manufacturing. Moreover, short courses and workshops are also organized by universities, scientific and professional societies and consultants covering key areas of the entire ATMP value chain, from early discovery to post-marketing monitoring.

The UK-based "Advanced Therapy Manufacturing Industry Consortium" (ATOMIC) is working with academic institutions to improve student preparedness for the ATMP industry [39]. Catapult provides educational platforms for translational facilities to progress research products to the commercial market and regulatory advice for marketing authorizations. Furthermore, the United Kingdom's National Health Service (NHS) Blood and Transplant (NHSBT) in collaboration with the Advanced Therapy Treatment Centre (ATTC) have created modules for staff in cell and gene therapy, procurement of starting materials, distribution, handling practices and traceability. In Ireland, the Cell and Gene Therapy and Vaccine Manufacturing Forum aims to address key barriers to ATMPs, including those in education and training. In October 2022, an ATMP-focused website called "ATMP Ireland" was launched to connect parties working in the sector. Launched in June 2023, the initiative "Bio'Occ" involves the Universities of Montpellier and Toulouse, and the Blood bank of Toulouse and the Cell Processing Facility of the University Hospital of Montpellier BTC, aim at attract and train the talents and actors of tomorrow in the field of bioproductions including ATMPs in response to the significant development of this sector of activity and at the request of manufacturers who are already facing recruitment difficulties, both quantitatively and qualitatively.

However, despite the emergence of new educational courses, as well as multiple national and international ATMP collaborations, the

role of the BTCs is rarely discussed and often omitted completely [39–41]. It is not possible to successfully address tailor-made ATMP educational needs of the new CGT workforce if the role of BTCs is not yet fully acknowledged, defined or understood. Although universities already play an important role in ATMP development, it could be made more prominent by improving interactions with support organizations [19,40], such as the European Blood Alliance (EBA). The EBA supports members to invest in new therapeutic fields by leveraging its members' experience with donors and blood product manufacturing. EBA is currently supporting ATMP development through facilitating collaborative networks and through the provision of information on new technologies and best practices pertaining to quality and safety of SoHOs [42]. Consultation with BTC on future ATMP educational strategies is crucial for ATMP experts, alongside BTC specialists, to provide guidance on the requirements for future undergraduate and postgraduate educational modules.

A Business Model for BTCs in ATMP

BTCs are a unique type of institution that emerged in the interphase of transfusion medicine, immunology, transplantation, stem cell biology and therapy [43]. The fact that CGT-based therapies are composed of living entities, rather than small molecules or biologicals, adds complexity to all segments of the value chain, from SoHO procurement to logistics of final product administration into patients. Typically, activities in BTCs comprise diverse clinical and laboratory-based services and are overseen by multiple regulatory agencies for mandatory and voluntary quality management systems geared toward patient safety. Figure 1 shows the assets of BTCs (including their own organizational model, specialized workforce, dedicated equipment and facilities, core services, integration with national health networks and expertise in the management of ethics, regulatory and quality aspects of SoHO) required to address medical needs and deliver personalized treatments by testing and processing SoHOs extracted either from third-party donors or from the same patient. Herein, we considered current models in European BTCs to increase competitiveness by their active participation in the value chain to help transform their national health systems and make them more sustainable while ensuring an ethically responsible use of SoHO. To define BADAM (BTC for ATMP Development And Manufacture), we borrowed concepts from Banda *et al.* [44] in their description of emerging business models in regenerative medicine, who identified six models: (i) materials and service provision business model; (ii) early-exit phase 1/2 business model; (iii) manufacturing and scale-up business model; (iv) translational services business model; (v) virtual business model and (vi) the integrated business model. BADAM is in fact a variant of the integrated business model in which co-operation with partner institutions from both public and private sectors is mutually reinforced according to the different requirements of each partner at given stages of ATMP development (e.g., SoHO procurement, regulatory non-clinical development, clinical development or support to marketed ATMPs), also considering the UK point-of-care model [45]. Two illustrative examples of the application of BADAM are (i) the co-development of PeriCord [30] and (ii) the hub-and-spoke model for CAR-T cell therapies [34] (Table 1). For the first example, PeriCord is a bioimplant composed of decellularized pericardium loaded with multipotent mesenchymal stromal cells derived from the Wharton's jelly of the umbilical cord [46]. The pharmaceutical formulation of PeriCord was adapted to current GMP from previous research and existing know-how in the consortium. We performed two parallel developments: (i) the establishment of a procedure for decellularization of human cadaveric pericardium, which is acting as a cell supportive material (scaffold) for surgical implantation and (ii) the design and validation of methods for a combined "matrix:cell" bioimplant in compliance with GMP. Data resulting from validations of methods for manufacture and characterization of

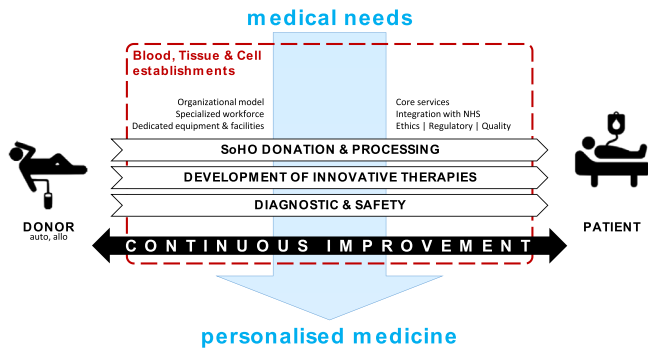


Figure 1. A management model in BTC establishments to ensure rapid and sustainable patient access to advanced therapy medicinal products in Europe. The management model of BTCs for emerging uses of SoHO is characterized by its central role in the value chain. BTCs are strategically positioned between SoHO procurement (used as starting materials in the manufacture of advanced therapy medicinal products) and patients in partner hospitals through synergies with their respective national health systems. The schematic shows the assets of BTCs and the three main lines of activity, namely SoHO donation and processing, development of innovative therapies and diagnostic and safety testing.

PeriCord allowed us the authorization for its production for a first-in-human clinical trial (ClinicalTrials.gov Id. NCT03798353) [30].

To fully realize BADAM in an international level, synergistic collaborations among BTCs are needed in almost all, if not all, segments of the value chain. In Figure 2, we show the impact of SoHO testing and processing and the different roles played by BTCs in two dimensions, namely “treatment dimension” (focused on patients) and “product dimensions” (focused on bioprocessing), which are defined based on the steps required in the development of ATMP from non-clinical to clinical and post-approval follow-up.

Ideally, a BTC network should be backed by stakeholders involved in the CGT field, including scientific societies and professional networks. Existing initiatives at the national level include ATMP Ireland, ATMP Sweden, Red Española de Terapias Avanzadas (TERAV/TerCel)

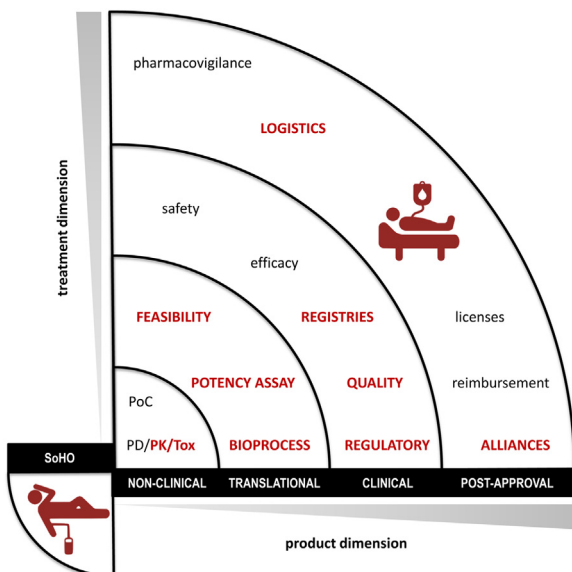


Figure 2. Value added by BTCs in the development of innovative therapies. Potential participation of BTCs at the different stages of product development are highlighted in red. Impact on either the treatment or the product dimensions have also been considered by placing the different contributions above or under the diagonal of the graph, respectively. PD, pharmacodynamics; PK, pharmacokinetics; PoC, proof of concept; Tox, toxicology.

in Spain [47] or the Advanced Therapy Manufacturing Industry Consortium (AToMIC) in the United Kingdom. Moreover, the EBA has taken a strategic stand for supporting members’ efforts to invest in new therapeutic fields, leveraging on the members’ experience with donors and blood product manufacturing and facilitating the creation of a network for ATMP development and production.

Final Remarks

The synergistic goal between all the stakeholders in the field, whether academic, non-profit, industrial, clinical, regulatory, patient advocacy or policy making representative, should be to develop a landscape toward effective clinical translation to produce better (that is, improved safety and efficacy) and affordable medicines that will eventually support health equity and facilitate patient access to ATMPs, compatible with sustainable development goals. The HE could provide a regulatory framework for the local manufacturing of ATMPs but needs better harmonization between Member State and guidance in its use. Transparency is an important part to be developed from of public EU-wide databases, also to promote transnational collaboration. The expertise of BTCs in processing ATMPs in compliance with quality standards as well as having infrastructure, logistics and close collaboration to clinics in place, makes them logical candidates for acting as regional “ATMP competence centers” and providers of these new treatments, qualified for a decentralized private sector ATMP use. Examples like PeriCord highlights the practical value of (i) access to voluntary donated SoHO from all sorts; (ii) compliance with strict regulations and pharmaceutical quality standards; (iii) strengthening collaboration between BTCs and (iv) active involvement in RDI consortia with national and international laboratories and societies, qualify cell and tissue banks like ours to become key players in the design, production and testing of the new generation of living medicines.

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Author Contributions

Conception and design of the study: JD and JV. Acquisition of data: JD, AW, EvdA, EK, CL, EB, JDV and JV. Analysis and interpretation of data: JD, AW, EvdA, EK, CL, EB, JDV and JV. Drafting or revising the manuscript: JD, AW, EvdA, EK, CL, EB, NG, JDV and JV. All authors have approved the final article.

Declaration of Competing Interest

All authors are employees of either non-profit Blood, Tissue and Cell Establishments or academic hospitals, whose role in the development, manufacturing and distribution of advanced therapies are the main topic of this manuscript. AW is member of the European Blood Alliance Donor Studies working group.

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