




Plumping up a Cushion of Human Biowaste in Regenerative Medicine: Novel Insights into a State-of-the-Art Reserve Arsenal

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Abstract

Major breakthroughs and disruptive methods in disease treatment today owe their thanks to our inch by inch developing conception of the infinitive aspects of medicine since the very beginning, among which, the role of the regenerative medicine can on no account be denied, a branch of medicine dedicated to either repairing or replacing the injured or diseased cells, organs, and tissues. A novel means to accomplish such a quest is what is being called “medical biowaste”, a large assortment of biological samples produced during a surgery session or as a result of physiological conditions and biological activities. The current paper accentuating several of a number of promising sources of biowaste together with their plausible applications in routine clinical practices and the confronting challenges aims at inspiring research on the existing gap between clinical and basic science to further extend our knowledge and understanding concerning the potential applications of medical biowaste.

Keywords Medical biowaste · Regenerative medicine · Benign tumours · Menstrual blood · Placenta

Abbreviations

AM	Amniotic membrane
APS	Anti-phospholipid syndrome
BD-MSCs	Burn-derived mesenchymal stem cells
Bmi1	B cell-specific Moloney murine leukaemia virus integration site 1
cGMP	Current good manufacturing practices
DePDL	Periodontal ligament of deciduous teeth

DFPC	Dental follicle progenitor cell
DFPC	Dental follicle progenitor cell
DMSC	Dental-derived mesenchymal stem cell
ECM	Extracellular matrix
eMSCs	Endometrial stroma-resident MSCs
ENS	Empty nose syndrome
ESC	Embryonic stem cell
FGF	Fibroblast growth factor
FMT	Faecal microbiota transplantation
GMSC	Gingival mesenchymal stem cell
GvHD	Graft versus host disease
HA/TCP	Hydroxyapatite/tricalcium phosphate
hAFMSC	Human amniotic fluid mesenchymal stem cell
HFSC	Hair follicle stem cell
HGF	Hepatic growth factor
HIV	Human immunodeficiency virus
hPCy-MS	Human periapical cyst mesenchymal stem cell
HSC	Haematopoietic stem cell
ICH	Intracerebral haemorrhage
IGF	Insulin-like growth factor
iPSC	Induced pluripotent stem cell
ISCs	Intestinal stem cells
IUF	Intrauterine transfusion
IUFD	intrauterine foetal demise

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LA	Lethal anomaly
Lgr5	Leucine-rich-repeat-containing G-protein-coupled receptor 5
MCAM	Melanoma cell adhesion molecule
MSC	Mesenchymal stem cell
MT	microbiota transplantation
NK	natural killer
OLFM4	olfactomedin 4
PAD	peripheral artery disease
PBS	peripheral blood serum
PBS	phosphate-buffered saline
PDGF	platelet-derived growth factor
PDGFR β	platelet-derived growth factor receptor- β
PDLSC	periodontal ligament-derived stem cell
rCDI	recurrent <i>Clostridium difficile</i> infection
RPEC	retinal pigment epithelium cell
SCAP	stem cells from apical papilla
SUSD2	sushi domain-containing 2
UCBC	umbilical cord blood cell
UCBS	umbilical cord blood serum
USCs	urine-derived stem cells
USSC	unrestricted somatic stem cell
VEC	vascular endothelial cell
VEGF	vascular endothelial growth factor
WHO	World Health Organisation
WIT	warm ischemia time

Introduction

Human has long sought plausible means to feed their voracious appetite for immortality. Throughout history, humankind has dreamed of circumventing death in various ways, a dream confronted by fatal challenges, such as acts of God and pandemics duelling for living. Recently, scientists relying on regenerative medicine have accentuated strategies to save and restore the damaged organs [1], a field of study fundamentally involved with cells, scaffolds, extracellular matrix (ECM), and biochemical molecules [2]. A mass of research has been undertaken to investigate the conceivably positive effects of cell therapy in preclinical and clinical trials; however, many obstacles to regard these strategies as a reliable treatment option need to be taken care of.

Current limitations in the autologous organ or cell transplantation leave no choice but to devise alternative options, such that autologous cell transplantation in the elderly proves barely efficient for several reasons like low quality, high cost, and patience-trying window of cell expansion [3]. In this sense, utilising allograft and further xenograft tissues in the clinic has struck promising in recent times [4]. Therefore, providing and administering tissue stocks seems a promising approach and a new horizon in medicine.

Nowadays, many clinics bring xenograft tissues into practice, such as porcine heart valves for patients with heart failure. However, since nothing is perfect, using xenograft tissues come with inevitable disadvantages, including immunological mismatch, ethical concerns, and even religious beliefs [5]. It is noteworthy that the human body is a rich store of biological tissues. The term “Biowaste” refers to all tissues that could be potentially removed from the human body and used in restoring the damaged organs. The human embryo and foetus are perceived as extraordinarily well-supplied sources of cells and tissues of high repair capability, including inner cell mass, a valuable embryonic stem cell depot, placenta, amniotic membrane, amniotic fluid, umbilical cord, cord blood, and aborted embryo or foetus [6]. Add to this urine, stool, oral cavity components, surgical residues, benign tumours, semen, and menstrual blood. Furthermore, deceased donation constitutes the most common multipurpose source of massive biowaste in regenerative medicine. In the present review, we are to introduce the plausible sources of human body biowaste and spotlight their potential application in reconstructing, restoring, or repairing the damaged tissues, firmly believing that introducing novel supplies and their regenerative potential could help healthcare decision-makers as a prospective choice of treatment.

Urine-derived Stem Cells (USCs)

Roughly one million nephrons in each kidney collectively secrete 0.96–1.8 L of urine per day into the urinary tract, consisting of a heterogeneous population of 2000–7000 cells [7]. Aside from the toxic metabolites, blood cells [8], and epithelial cells [9], such as dead squamous cells, renal tubular epithelial cells, and transitional epithelial cells of zero potencies [10, 11], voided human urine as a biological waste could also constitute a beneficial source of stem-like multipotent progenitor cells distinct from MSCs, known as urine-derived stem cells (USCs) [12, 13]. The biological properties of USCs, far from expressing haematopoietic markers, such as immune response trigger HLA-DR, CD14, CD31, CD34, CD45, and CD184 [14, 15], include self-renewability, paracrine effects, tissue regeneration [16], immunoregulation [17], immunomodulation [18], low levels of senescence-associated proteins [19], and adhesion to plastic surfaces, and multi-lineage differentiation into ectodermal, endodermal, and mesodermal cell lines [20], such as adipogenic, chondrogenic, osteogenic [17], beta-cell, uroepithelial [18], urothelial, smooth/skeletal myogenic [21], endothelial [22], endodermal hepatic [23], interstitial [24], renal tubular epithelial, podocyte, and neuronal lineages [25]. Also, having a competitive advantage over MSCs, the isolation and amplification of USCs are facile, safe, cost-effective, painless, free

of the need for digestive enzymes [20], and free of the risk of potential complications caused by invasive procedures [26], such as skin incision during liposuction [27]. Furthermore, USCs having a higher telomerase activity (USCs-TA⁺) and longer telomerase compared to BMSCs allows a higher indefinite proliferative property [28], chromosomal stability over long passages, telomere length maintenance [29], and absence of teratomas/tumour formation or renal abnormalities [30]. USCs exert paracrine effects by secreting multiple nutrient factors and trophic factors [22], including but not limited to cytokines, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), and hepatic growth factor (HGF), which explains the USCs-associated angiogenesis during tissue regeneration [31].

Aside from the urine, USCs could also be obtained from the upper urinary tract (tubules of the nephron, renal pelvis, and ureters), the morphology, cell growth pattern, and differentiation potential of which resemble those of bladder and urethra origins [18]. The main isolation protocol of USCs involves collecting 100–300 mL of voided midstream urine from healthy and ill donors in sterilised containers [32], centrifuging, washing out the sediment with phosphate-buffered saline (PBS), resuspending cell pellets in a medium, and culturing in gelatine-coated plates of 24 wells [12]. It is noteworthy that the donor age, isolation procedure, and culture media techniques would affect the quantity, proliferation rates, senescence tendency [33], and differentiation quality of USCs [34]. In this sense, urothelial-differentiated USCs are positive for corresponding markers like uroplakins (Ia, III), cytokeratin-7 (CK7), and CK13 [24], such that urine cells of urinary tract origin and renal system origin express the urothelial cell marker CK7 [35] and the renal epithelial marker carbonic anhydrase (CA) [36], respectively. In addition, renal system-derived urine cells of an individual are categorised under two subpopulations, exhibiting a couple of distinct morphologies, including (1) dome-forming cobblestone-like type I cells of smooth-edged contours and nephron tubule origin (Bowman's capsule to the distal convoluted tubule) with a tendency to differentiate into osteogenic and adipogenic lineages [10] and (2) randomly arranged spindle-like type II cells of renal mesenchyme origin (thin descending limb of the loop of Henle and the distal convoluted tubule) with higher proliferative capacity, lesser frequency, and greater motility, which are highly drawn to form chondrogenic lineage [10]. Thus, type I cells seem to be more promising for uroepithelium remodelling, whereas type II cells benefit bone tissue reconstruction. USCs regarding their differentiation capability and surface markers have been illustrated in Fig. 1.

Exercising USCs in clinic is still in its infancy, demanding more comprehensive studies for better drawing a sound conclusion regarding their limitations and addressing the

related issues. Table 1 depicts several preclinical and clinical studies using USCs for treating pathological conditions [23, 37–45]. In this context, current limitations highlighted in several experiments are well worth discussing, allowing for (1) despite the fact that USCs could be collected from individuals of any gender and age, viral/bacterial urinary tract infection, urinary tract malignancies [46], and anuria fail the procedure [47], (2) floor-derived microorganism contamination and the highly effective solution to eliminate multidrug resistant bacteria contamination in cell cultures is to add the broad-spectrum antibacterial reagent normocure [48], (3) low reprogramming, long-term manipulation, and tumorigenicity of USC-iPSCs, which could be overcome by replacing with USC-iNSCs [49], (4) the variety of genetic background and disease associated mutations [50] from person to person, which affects the lineage-specific differentiation efficiency of genome-edited wild-type USC-iPSCs under the same culture condition and the key is genome editing technology like CRISPR-Cas9 system, which helps correct genetic abnormalities, create disease mutation or deletion in USC-iPSCs and the healthy control USC-iPSCs of the same person, compare the two patterns of isogenic cell pairs [51], and cast light on the disease mechanism with genetic origins [52], and (5) various patterns of epigenetic memory in USC-iPSCs of different somatic origins, which means leading the differentiation into donor cell type-related lineage [53], which can be resolved by proper DNA methylation and histone acetylation in somatic cell genome followed by putting vitamin C or histone deacetylase inhibitor valproic acid (VPA) in the culture medium [54].

Gut Microbiota

For quite a time, microbiota transplantation (MT), which by definition is utilising microbial communities of commensal, symbiotic, and pathogenic microorganisms in various human body sites, has been subject to thorough investigations concerning their safety, efficacy, and potential therapeutic administration in a variety of infections like the recurrent *Clostridium difficile* infection (rCDI), especially in the case of multiple courses of antibiotic treatment [55, 56], such as vancomycin or fidaxomicin [57, 58]. Of the very first experiments conducted by Bohnhoff et al. on the susceptibility of streptomycin-fed mice to induced *Salmonella* infection, it was found that exposure to antibiotics is a contributing risk factor, highlighting that resident gut microbiota act out the role of an eradicator of invading pathogens [59]. Further studies carried out point out the connection between gut microbiota composition and gastrointestinal (GI) tract inflammatory diseases, such as ulcerative colitis, Crohn's disease, graft versus host disease (GvHD), metabolic syndrome, hepatic disease, and mental disorders [60]. In this

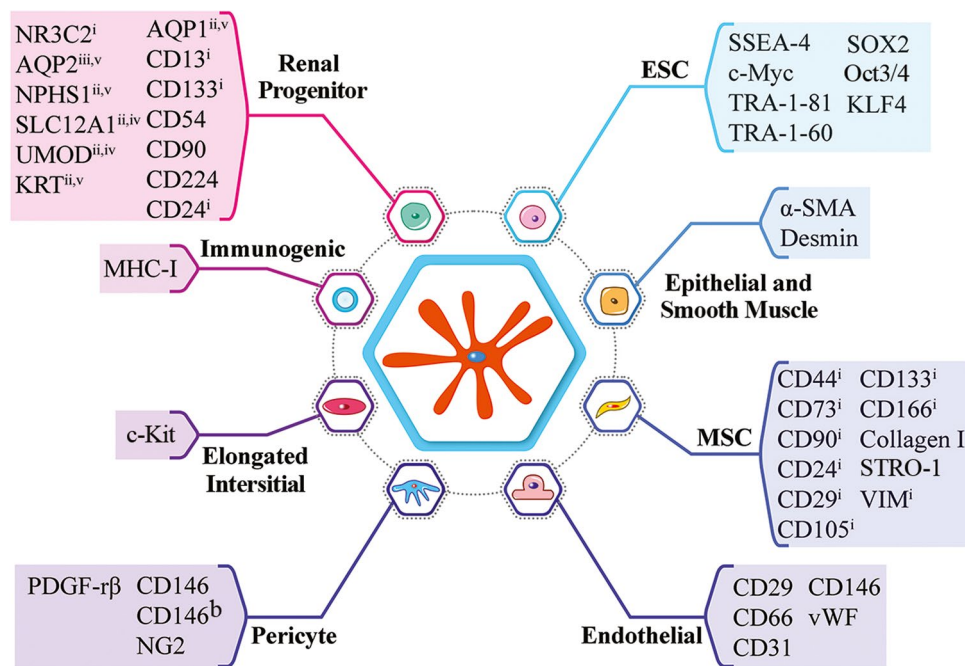


Fig. 1 Shows the characterisation of USC. It has been demonstrated that AQP1 in proximal tubules forms a highly permeable water-specific channel. KRT18 is a critical element of epithelial intermediate filament. USCs lack tumorigenesis phenotype due to the lack of teratoma formation when injected into immunodeficient *in vivo* models. Type I USCs partially express AQP1, NPHS1, SLC12A1, UMOD, and KRT18 and few are positive for AQP2. Type II USCs barely express SLC12A1 and UMOD and are negative for the other renal markers. ⁱ expressed both in type I USCs and type II USCs, ⁱⁱ expressed partially in type I USCs, ⁱⁱⁱ negative in type I USCs, ^{iv}

expressed partially in type II USCs, ^v negative in type II USCs. AQP1; protein aquaporin-1, AQP2; protein aquaporin-2, KLF4; Krüppel-like factor 4, KRT18; major histocompatibility complex I, NG2; neural/glia antigen 2, NR3C2; nuclear receptor subfamily 3 group C member 2, Oct3/4; octamer-binding transcription factor 3/4, PDGF-r β ; platelet-derived growth factor receptor beta, SLC12A1; solute carrier family 12 member 1, SOX2; SRY-box transcription factor 2, SSEA-4; stage-specific embryonic antigen 4, UMOD; uromodulin, Vim; vimentin, vWF; von Willebrand factor, α -SMA; α -smooth muscle actin

sense, stool, a heterogeneous complex consortium of highly variable and specialised microorganisms [61], as well as human tissue cells like bacteriophages, bile acids [62], mucus, water, diet-derived metabolites, and undigested food materials, would be taken into account as a transplant product equivalent to blood products [63]. The origins of this approach can be traced back to the ancient world, such as Tibetan, Korean, Dai, Yao, Tujia, Nu, Mongolian, and Chinese ethnic medicine. In this framework, traditional Chinese medicine, known as the most representative traditional medical system in China, exemplifies a reliable and efficacious therapeutic administration of animal- or human-derived dry faeces, processed faeces, or fresh faecal suspension (yellow soup) for centuries in the long-term nervous system, GI, skin, ophthalmic, or gynaecological disease prevention and treatment [64], such as heat toxins, high fever-caused unconsciousness, food poisoning, diarrhoea [65], rheumatism, jaundice, fever [66], dyspepsia, gastric ulcer [67], blood stasis, swelling, and trauma pain [68]. Every known drug among different ethnic medicines is attributed a different therapeutic application, for instance, Wu-Ling-Zhi, dry faeces of *Trogopterus xanthipes*, is a common medicine

for promoting blood circulation in blood stasis, engendering pain relief in the chest and hypochondrium [69]. Other therapeutic applications include dysmenorrhea, amenorrhea, post-traumatic swelling and aching, snake bites, gout, itching, whooping cough, and fever. Of note, as drying and processing are accompanied by the eradication of living microorganisms, various routes of faeces administration may follow a distinct molecular pathway [64].

Faecal Microbiota Transplantation (FMT)

Nowadays, faecal microbiota transplantation (FMT) following donor screening and stool regulation is a potentially life-saving therapeutic strategy and one of the recommended resources by clinical practice guidelines [70] aimed at modulating the altered gut microbiome [71], ensuring the safety of healthcare products, and restoring the gut microbiota community to a level analogous to that of a healthy individual [61]. A healthy gut microbiome is involved in enhancing metabolism, resisting inflammation and infection, preventing cancer and autoimmune diseases, and acting on the namely

Table 1 Summary of the preclinical studies administering USCs

Animal model	Animal groups	Conditions	Administration	Result	Reference
1	Rat	cisplatin-induced AKI	2×10^6 USCs suspended in 0.2 mL PBS injected into the tail vein	-Improved histological damage -Improved renal function -Increased proliferation of renal tubular epithelial cells -decreased inflammatory and apoptosis markers	Su et al (S. B et al., 2019)
2	Rat	Ischemia reperfusion-induced AKI	1×10^5 USCs in combination with 50 μ L sucrose solution, 50 μ L hydrogel, and 100 μ L PBS injected into the upper, middle and lower cortex	-decreased serum creatinine and blood urea nitrogen at day 1 -decreased histological tubular injury score and apoptosis at days 7 and 14	Tian et al (SF et al., 2017)
3	Rat	Ischemia reperfusion injury and gentamicin injection (dual-injury chronic kidney disease)	5×10^6 USCs suspended in 100 μ L PBS injected into renal parenchyma	-Improved renal function -decreased degree of glomerular sclerosis and atrophic renal tubules -decreased fibrosis, and monocyte infiltration -elevated SOD-1 expression levels	Zhang et al (Z. C et al., 2020) [152]
4	Mouse	Busulfan-induced NOA	USCs and exosomes injected and transplanted into the interstitial space in the testes	-Upregulation of Pou5f1, SYCP3, and Prm1 genes -promoted restoration of exogenous spermatogenesis in the testes	Deng et al (D. C et al., 2019)
5	Mouse	-36 chronic liver injury -36 acute liver injury group	2×10^6 HPCs or USCs suspended in 0.2 mL PBS injected into the tail vein or splenic vein of acute liver injury - 2×10^6 USCs or hypoxia-pretreated USCs suspended in 0.2 mL PBS injected into the tail vein of chronic liver injury twice a week for 2 weeks	-Improved hepatocyte degeneration and resolved liver fibrosis substantially in the hypoxia-pretreated USC-transplanted group -Improved abnormal liver function partially -Induced autophagy and promoted cell proliferation, migration, and colony formation followed by USC-elicited liver tissue recovery in hypoxia pretreatment -No significant difference in ALT and AST levels between the two groups	Hu et al (H. C et al., 2020)

Table 1 (continued)

Animal model	Animal groups	Conditions	Administration	Result	Reference
6 Mouse	-6 female control -10 female PBS group -10 female USC _S ^{Con shRNA} -Exos group -10 USC _S ^{shDMBT1 #1} -Exos group	Streptozotocin-induced diabetes intraperitoneally	-citrate buffer -100 μ L PBS injected subcutaneously at 4 injection site -200 μ g USC _S ^{Con shRNA} -Exos in 100 μ L PBS injected subcutaneously at 4 injection site -200 μ g USC _S ^{shDMBT1 #1} -Exos in 100 μ L PBS injected subcutaneously at 4 injection site	-enhanced proliferation and migration of wound healing-related cells including keratinocytes, fibroblasts, and vascular endothelial cells -angiogenic tube formation of endothelial cells	Chen et al (CY et al., 2018)
7 Rabbit	-10 experimental white rabbits -10 control white rabbits	cyclosporine A-induced immunosuppression at a dose of 5 mg/Kg per day	drain transferred between the two layers of the omentum of the rabbit through a ventral midline incision and fixed on the omentum by three interrupted 4/0 prolene sutures	-formed a tissue-engineered graft from multilayered urothelium -organised smooth muscle tissue after ureteral reconstruction	Zhao et al (Z et al., 2019)
8 Rat	-20 control SUI rats 20- experimental SUI rats	intravaginal balloon inflation-induced stress urinary incontinence (SUI)	-1 mL of 0.9% physiological saline injected locally in and around the pubococcygeus muscle -1 \times 10 ¹⁰ particles/mL injected locally in and around the pubococcygeus muscle	-improve urodynamic parameters (MBV, ALPP) -promoted activation, proliferation, and differentiation of SCs -enhanced phosphorylation of extracellular-regulated protein kinases (ERK) -repaired the injured pubococcygeus muscle	Wu et al (W. R et al., 2019)
9 Rodent	-20 sham control female Sprague-Dawley (SD) rats -20 IC alone female Sprague-Dawley (SD) rats -20 IC + USC _S female Sprague-Dawley (SD) rats	protamine/lipopolysaccharide (PS/LPS)-induced interstitial cystitis	-saline instillation - 10 mg/mL PS in the urinary bladder; 2 mg/mL LPS 30 min later, and the experimental conditions 45 min later -1.2 \times 10 ⁶ USC _S suspended in 0.2 mL PBS injected intravenously	-suppressed oxidative stress, inflammatory reaction, and apoptosis -ameliorated urinary bladder environmental condition	Li et al (L. J et al., 2017)

Table 1 (continued)

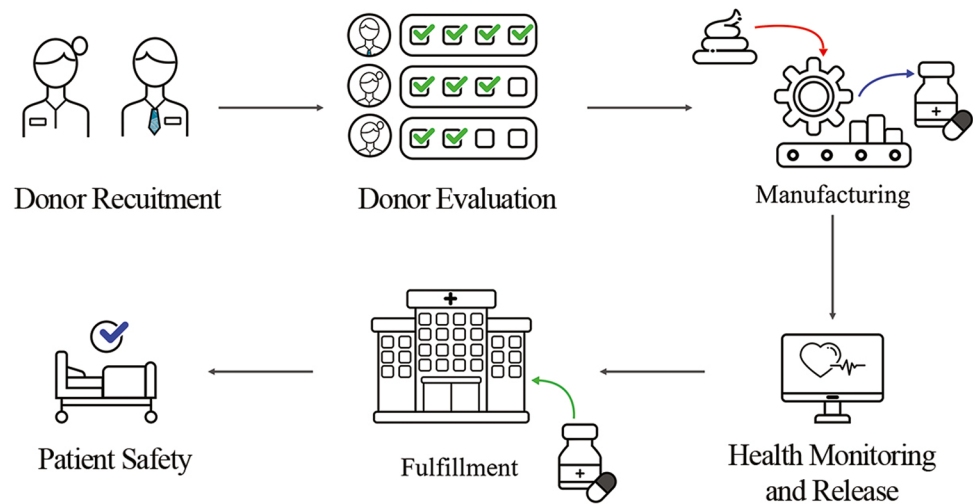
Animal model	Animal groups	Conditions	Administration	Result	Reference
10 Rat	-24 normal control SD rats -24 T2D SD rats -24 T2D + USC's SD rats	streptozocin-induced type 2 diabetes	-standard diet - high-fat diet of 44.3 kJ/Kg caloric value consisted of 22% fat + 48% carbohydrate + 20% protein; 35 mg/Kg streptozotocin injected intraperitoneally twice to the T2D SD rats -high-fat diet of 44.3 kJ/Kg caloric value consisted of 22% fat + 48% carbohydrate + 20% protein; 2 × 10 ⁶ USC's suspended in 0.2 mL PBS for six times every other week injected into tail vein of T2D + USC's SD rats	-alleviated histological destruction and functional decline of pancreatic islet, left ventricle, glomerulus, and bladder micturition -inhibited fibrosis and apoptosis of myocardium, glomerulus, and detrusor -nsignificant decrease of fasting blood glucose	Dong et al (D. X et al., 2016)

brain-gut axis [72, 73]. In this context, adult-derived wet stool contains 10¹¹ prokaryotes, 10⁷ colonocytes, and 10⁸ archaea and viruses per gram [74]. To sum up, albeit no universally agreed-upon definition exists for FMT, Hoffmann et al. [75] would regard this as transferring biologic material of minimally manipulated microbial communities of commensal, symbiotic, and pathogenic microorganisms from a human donor to a human recipient to affect the recipient's microbiota or also define it as transplanting pre-screened and regulated stool into the gastrointestinal tract (GI) system [71].

Stool Provision and FMT Regulation

Stool provision for FMT material preparation might be carried out through a couple of scenarios [76]. Overall, the core of both scenarios is ideally all about conducting a screening assay to examine whether a stool contains the minimum infective dose of a known pathogen and at the same time, not restrict access unduly to FMT material [77]. One scenario is the patient-selected donor through which the patient introduces an exclusive donor and further stool screening is done by physicians while the other proposed scenario is the stool banking, a seemingly cost-effective approach offering pre-screened frozen stool of more consistent and stringent manufacturing quality and safety criteria as well as an overnight supply of efficiently screened [78, 79]. Once stool is provided, the stool regulation follows phase-appropriate current good manufacturing practices (cGMP) and intends to supply clinicians with FMT materials [80]. For instance, Fig. 2 depicts the procedures conducted according to cGMP standards at the OpenBiome stool bank. The very first step is to call for stool donors aged 18–50 years old through conventional press or social media campaigns. The second step is to conduct an on-site screening and fill in an in-depth donor questionnaire, which is carried out until providing informed consent and a signed affidavit attesting that the health information is reliable. After reviewing the questionnaire by a staff member, applicants then have to pass through an in-person assessment. Eligible candidates are further asked a three-part laboratory screening, including nasal swab, blood, and stool to assess the probable presence of infectious risk factors and microbiota-mediated conditions. Once screening is successfully accomplished, stool samples are passed on-site in stool collection kits. Samples meeting the inclusion criteria are then homogenised using a sterile 330 µm filter bag to separate fibrous material from microorganisms, small molecules, and water. The product is further processed into two liquids and a capsule preparation, stored at –80°C, as well as a safety aliquot of 30 mL volume for safety testing. The liquid material of 250 mL volume, 22.7 g stool, and 1:10 dilution is administered through colonoscopy, sigmoidoscopy, or enema while the other one of

Fig. 2 Current standard six-part methodology conducted by stool banks. (A) Call for stool donors (B) Conduct an on-site screening and fill in an in-depth donor questionnaire (C) Manufacturing (D) random health status and vital signs checks (E) Fulfillment and (F) FMT material quality and efficacy and patient safety



30 mL volume, 8.6 g stool, and 5:2 dilution is administered through esophagogastroduodenoscopy or nasoenteric tube. Prepared FMT materials in the next step are shipped for research purposes or enforcement discretion procedures conducted by infectious disease physicians and gastroenterologists to treat non-responsive recurrent *Clostridium difficile* infection (rCDI) to standard therapy. Last but not least is to assess FMT material quality and efficacy.

Stillbirth, Neonatal Biowaste, and Embryo

Stillbirth

Stillbirth, also less commonly known as intrauterine foetal demise (IUID), is by definition either foetal death since 20 weeks' gestation or a birth weight of at least 350 g [81]. Over 2.6 million gestations worldwide are probed to culminate with third-trimester stillbirth, which in other words equals 18.4/1000 of total births [82]. Although there are controversies about whether or not stillbirth could be included as death or not, stillborn could be practised for medical purposes like organ donation in transplantation or research objectives. The following provides an intriguing window into the plausible therapeutic approaches to stillborn foetus within the currently existing framework of practice.

Resurrection following death stands the primary route for organs to depart their host and live on in another one. Though astounding, precious few could come across the radar in the research literature. Of the very first papers regarding the issue is a study conducted by De Paepe et al. [83], with the objective of providing rat models with alveolar epithelial progenitor cells of second-trimester stillborn foetus origins and examining their regenerative capacity, suggesting that foetal tissues, compared to those of adult, stand to benefit from higher proliferation and lower

immunogenicity. The grafts were obtained from the stillborn at 13–22 weeks' gestation, cultured for a short time, and grafted to the renal subcapsular space of immunosuppressed rats, culminating with foetal the lung tissues regaining their inherent high regenerative potential regardless of the presence of any inflammation or chorioamnionitis. Among the other stillborn foetus organs, heart transplantation might draw intriguing, as it is harvested merely from the brain-dead donors, limiting the accessible heart number. However, the possibility of exercising stillborn foetus' heart seems impractical since the procedure is facing a shortage of time. That is to say, it requires monitoring the exact timing of heartbeat stop in the uterus and thus running caesarean and harvesting heart for resuscitation for as long as a matching donor from the waiting list heaves into sight. Still, there is hope since the advancing breakthrough allows restoring the heartbeat five minutes after donor death by means of a console, connected up with blood to provide the heart with sufficient oxygen along with a special preservation solution to encourage the resistance to hypoxia-induced damage [84]. In a nutshell, despite the fact that stillborn donor could prove a game-changing breakthrough for potential regenerative exercise, questions rage as to the ethics and safety concerns succinctly addressed below.

Neonatal Biowaste

In consonance with the World Health Organisation (WHO), the first 28 days of a new-born's life is recognised as the neonatal period, during which the risk of death comparatively reaches its peak. In this sense, statistics reveal that developing countries with low access to health care hold the highest number of neonatal mortality cases [85]. Notwithstanding the grief and sorrow coming with this tragedy, recent advances provide an sunny window by drawing the gaze to exercising neonatal organ/tissue, such as the heart,

kidney, intestine, pancreas, lung, thymus, skin, bone marrow, and eye [86] for multiple transplantation purposes or research objectives at once revolving around both determining the causal agents associated with severe conditions, including neurological disorders, trauma, fatal anomalies, chromosomal abnormalities like Edwards' syndrome, congenital malformations like anencephaly being the major reason, and congenital deformations together with treating diseases, such as methicillin-resistant *Staphylococcus aureus* (MRSA) infection, diabetes, autism, rheumatoid arthritis, chronic diseases, cancer, infertility [87, 88], along with neurologic, gastrointestinal, pulmonary, vision, and genitourinary disorders [89]. One such instance could be Amalya Nathaniel, the boy who survived for 80 min and in the light of his mother's request to donate his organs/tissues, researchers could study the casual factors of type I diabetes, investigate cell generation, and pursue FDA clearance for a medical device specialised for rapid paediatric resuscitation [90, 91]. So much for the benefits of neonatal organ/tissue donation. The following lines will be giving a brief insight into the ethical aspects.

Ethicolegal considerations and procedures

As exercising neonatal organs/tissues in the field of research becomes mainstream, debates occur to draw upon comprehensive, simplified, and transparent standards and guidelines with reference to ethicolegal issues. In this regard, scholars have contributed to adopting policies and algorithms centred on at-term delivered neonates suffering from a lethal anomaly (LA), pre-term delivered neonates with an LA, and dead neonates with no LA by the agency of screening potential neonate donors for transplantation or research. This would also benefit family members of the deceased neonates as authorising the decision brings comfort and consolation [92, 93]. However, donating neonatal organs/tissues for transplantation stands to occur infrequently due to the fact that the number of recipients with matching sizes appears negligible [94]. On the other end, allocating neonatal organs/tissues to research has failed to elicit ample attention as neither family members are aware of this choice nor researchers seek this very option, which could be attributed to several reasons, encompassing limited access, highly specified organ/tissue donor acceptance criteria for a wide assortment of existing research types, uninformed healthcare staff about screening the eligible neonates for donation, or untrained transplant surgeons in organ recovery for research, rather than for transplant [95]. In order to promote neonatal organ/tissue donation, families experiencing a case of LA diagnosis need to carry the foetus to term and deliver a live birth since LA conditions perfectly justify the administration of the medical neglect, that is to say, withholding or withdrawing aggressive reviving treatment from the neonates

[96]. Also, pre-term delivery and abortion-obtained donated organ/tissue fail to commend themselves to ethicolegal principles. Once the delivery session takes place, neonates manage to survive for minutes to days and following the loss of their neonates, families will be confronted with a choice about which organs/tissues are to be donated and what the purpose of the donation will be in terms of transplantation and/or research. Of note, in the meanwhile of drawing on some time with their deceased neonate, organ recovery surgery has to be timed accordingly to address the concerns regarding the warm ischemia time (WIT) effect [87].

Placenta

Human foetal placenta of disk-like shape, 16–20 cm diameter, and roughly 470 g weight [97] acts as a peculiar and unprecedented coordinator between both the maternal and foetal organs, giving rise to the 55–60 cm chorioallantoic umbilical cord [98] and nourishing foetal-wise organs to champion their growth and development through providing abundant nutrients and oxygen, sweeping away toxic and hazardous metabolites, averting immune rejection [99], and relatively eliminating any chance of microbial infection [100], all of which happen to occur in the presence of umbilical cord. In a deeper dive into the foetal growth and development, trophoblasts play a conspicuous role by contributing vital gestational hormones, such as estradiol, progesterone, and chorionic gonadotropin [101]. Consequently, in the light of the exceptionally conducted research, foetus could safely be perceived as a semi-allograft, letting out ample room for a wide range of discrepancies between the attributed genotypes to mother and foetus [102]. In reference to the ways and means of placental cells remaining intact from the maternal immune response, research reveals that a series of factors suffice to justify the immunomodulatory face of the placenta as follows: (1) the presence of decidual stromal cells (DSCs), which guarantee immune tolerance by interacting with decidua-infiltrated immunocytes [103], (2) secretion of a whole range of hormones, cytokines, and growth factors like progesterone, which contribute to Th₂ upshift and Th₁ downshift, involved in secreting anti-inflammatory and pro-inflammatory cytokines, respectively [102], (3) induction of apoptosis in immunocompetent cells in a tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-Fas ligand (FasL)-dependent manner [104], (4) expression of MHCs in highly negligible levels, and last but not least, (5) expression of trophoblast-exclusive immunomodulatory non-classic MHC, encompassing HLA-G, HLA-F, and HLA-E [105].

Given the background, the above-mentioned critical functions and multiple cells in abundance characterise the non-invasively generated mature placenta, i.e. third-trimester placenta, as a potentially feasible post-delivery organ for

therapeutic application in the fast-approaching horizon of regenerative medicine and cell therapy [106]. This matter has assumed significant importance in literature since the past century and solidified its position with the absence of ethical hindrances and the advent of tissue banking, enabling access to a rich source of various cells at will [97], which mainly comprises MSCs, trophoblasts, and vascular endothelial cells (VECs). In a deeper dig, harvested postpartum placenta consists of maternal and foetal constituents. Foetal membranes of thin transparent amnion and chorion, with the former rising from a monolayer epithelium and the avascular connective tissue mesenchyme and the latter encompassing amnion and springing up from the fibroblastic and trophoblastic populations make up the foetal constituents along with the 50–70 cm long umbilical cord, which is composed of a triad of vessels, including two arteries and a vein encircled by Wharton's jelly and serves as a connecting wire between the foetus and the placenta [107, 108]. Coming to the maternal constituents, immune cells like natural killer (NK) cells and macrophages exist within a boundary of lacunae of decidual endometrial origin [109]. Having the detailed placental composition outlined, countless clinical endeavours have been conducted administering various components, including extracts and lyophilisates, umbilical cord blood serum (UCBS), umbilical cord blood cell (UCBC), tissue fragments, and foetal membranes in various amounts [110]; various forms of native, milked, chemically or thermally processed, cryopreserved, and sublimated; and various routes of intravenous (IV), intramuscular (IM), subcutaneous (SC), intraoperative (IO), or oral [111–113]

Placental Extracts and Lyophilisates

Aqueous placental extracts are, in actual fact, lysates enriched with essential macromolecules like proteins, minerals like trace elements, natural metabolites, and biomolecules, all of which enable this specific placental product to possess anti-oxidant, anti-inflammatory [113], endocrine [114], immunomodulatory [115], and regenerative characteristics [116]. Studies unveil that placental extracts best function when delivered at the mid-gestation and late gestation [117]. Evidence suggests α -fetoprotein (AFP) concentrations might be behind the anti-oxidant and cytoprotective conduct against the oxidative stress [118], thereby dwindling the oxidative stress-induced cellular harm away to negligible levels in vitro. Turning our attention from anti-oxidant and anti-inflammatory properties, another facet of placental extracts will be activating Th₂ cells, stimulating IgG and IgM secretion, and altering the levels of pro-inflammatory cytokines, such as TNF, interferon γ (IFN γ), and IL-6 [119]. Consequently, placental extracts hold an advantage over chemotherapeutics and anti-biotics regarding the corresponding angiogenic and anti-microbial properties [120].

Plus, placental trophoblast-derived TNFs and IFNs pave the way for exerting impairing forces on RNA and DNA virus replication [121], such that type I IFNs are known to regulate systemic infections while type III IFNs regulate the local ones by trophoblasts [122]. In addition, having the participation of inflammatory cytokines in instigating allergic responses and fatigue in mind, it could be assumed that placental extracts labour hormonal and anti-allergic properties [123]. Coming to tissue regeneration, purified placental extracts are found to be involved in infiltration debilitation, cellular biosynthesis, and epithelial regeneration by supporting the turnover of collagen and upregulating the expression of epithelialisation factors [124], such as transforming growth factor β (TGF β), VEGF, and FGF [125], thereby shortlisted as an upcoming commonplace option of treating surgical wounds, burns, and leprotic/diabetic ulcers. According to Chandanwale et al. [126], topically administered purified extract (PE) following orthopaedic surgeries exhibit analogous wound healing outcomes with that of povidone-iodine (PI). This regeneration property is not only limited to epithelial cells but also stretches horizons to osteocytes and neurons [119] since it induces growth-associated protein 43 (GAP43) and human glioma proliferation-associated CDC2 expression [127]. Be that as it may, one by far a significant drawback to consider after all the mentioned benefits would surround the biosafety issues, that is to say, early gestation-associated foetotoxic observations in vivo, but not in adult animal models or cell cultures [128]. All in all, placental extracts may be counted as a treatment option in the light of conducting investigations to address the biosafety concerns.

UCBS

A large body of evidence suggests that umbilical cord blood surpasses peripheral blood since a plentiful supply of cell-deficient supernatant serum could be collected when clotting occurs, which signifies best in patients suffering from blood dyscrasias like anaemia, and by far most importantly, UCBS, unlike the peripheral blood serum (PBS) is absent of any autoantibodies and proinflammatory cytokines [129]. The obtained serum harbours growth factors and active components in high concentrations [130], including epidermal growth factor (EGF), FGF, human growth hormone (hGH), nerve growth factor (NGF), insulin-like growth factor 1 (IGF-1), and fibronectin [131]. This further enables the topical eye drops application for treating ocular anterior segment disorders (ASDs), encompassing corneal epithelial defects, neurotrophic keratitis, dry eye syndrome, and persistent epithelial defects. Treatment results indicate accelerated epithelial recovery, refined symptoms, upshifted corneal sensitivity, and raised goblet cell density [131, 132]. Also, Mirazi et al. [133] found the beneficial facet of UCBS in alleviating gentamycin-induced liver necrosis and

inflammation when injected intraperitoneally in Wistar rat models. The results indicated a dramatic fall in the level of liver enzymes and inflammatory cytokines. In reference to obstetric anti-phospholipid syndrome (APS), Trifonov et al. [134] reported that UCBS flourished to drop the levels of anti-phospholipid antibodies.

UCBC

Empirical evidence for placental cells of foetal membrane, chorionic villi, and umbilical cord origins spotlights the capability of placental cells to differentiate into cardiomyocytes [135], hepatocytes [136], and endothelium [137]. In this sense, accumulating literature cast light on the fact that 50–100 mL of human umbilical cord blood (hUCB) could be obtained by means of hyaluronidase or explant technique [107], offering a stockpile laden with haematopoietic stem cells (HSCs) coinciding with that of bone marrow [138], as well as unrestricted somatic stem cells (USSCs) and mesenchymal stem cells (MSCs), with the former analogous with pluripotent embryonic stem cells (ESCs) as to the differentiation potential into ectodermal, mesodermal, and endodermal cell lines and the latter capable of proliferation, multi-lineage differentiation, CK7 and CD200 expression, and chorionic gonadotropin synthesis [139, 140], insofar as placental MSCs, including those acquired from the umbilical cord blood, have proven more immunomodulatory and proliferative compared to their fellows obtained from other sources [141]. Allogeneic transplantation of placental HSCs has proved efficacious in treating various benign and malignant haematological diseases along with ocular pathologies [142]. The very first attempt was to treat a 5-year-old patient suffering from Fanconi anaemia-caused aplastic anaemia by transplanting cryopreserved cells once undergoing thawing, culminating in complete haematological reconstitution after 22 days with no subsequent signs of GvHD [143]. In the light of this research, further endeavours by Huang et al. [144] details the efficacy of hUCB-derived MSCs in refining gross motor as well as comprehensive functions of an infant suffering from cerebral palsy (CP) after IV administration of four fixed doses. In addition, Bahk et al. [145] revealed that umbilical cord-derived SCs could benefit treating diabetes mellitus-engendered erectile dysfunction when transplanted intracavernously. Also, hUCB-MSCs had shown ameliorating effects in knee osteoarthritis patients. Expanding frontiers of research to address today's concerns, hUCB-MSCs relying on their immunomodulatory characteristics regarding inflammation suppression alleviate COVID-19 symptoms [146, 147]. Plus, Koh et al. [148] investigated the effectiveness of hUCB-MSCs differentiated into retinal pigment epithelium cells (RPECs), best reputed for promoting photoreceptor cell survival. The study involved a functionally

MERTK-deficient rat model with retinal degeneration and subretinal transplantation of PRECs was observed to retain retinal synaptic connectivity and save visual function. In fact, further in vivo experiments on animal models build up hopes for treating colitis [149], acute kidney injury [150], ischemia [151], GvHD [152], intracerebral haemorrhage (ICH) [153], and liver injuries [154]. Other than SCs, DSCs are observed to contribute towards treating haemorrhagic cystitis, a severe complication of HSCs transplantation [155]. Aside from the SCs and DSCs, add in the efficacy of foetal haemoglobin, known for its comparatively higher content and oxygen affinity than adult haemoglobin in hastening the recovery of premature newborn and delivering blood to an Rh⁺ foetus through intrauterine transfusion (IUF) [156]. Be that as it may, Khodabux and colleagues [157] contradicted this claim earlier based on the failure of hUCB-derived autologous RBCs in replacing at least 50% of allogeneic transfusions in premature infants.

Foetal Membranes

To briefly make mention of what is discussed earlier, foetal membranes, comprising the innermost amniotic membrane (AM) and the overlying chorionic membrane (CM) are all about encircling the foetus with the aim of shielding against trauma, infectious and toxic agents, and retaining health [158]. Harvesting AM follows screening for hepatitis B virus (HBV), HCV, human immunodeficiency virus (HIV), and syphilis to address the concerns over transmissible infections and occurs in no time post-caesarean delivery. Once blood clots are washed off, AM has to be detached from CM, rinsed with anti-biotic-containing saline solution, cut into pieces, laid smoothly with the epithelial face supine onto sterilised nitrocellulose papers, and preserved in vials of eighty degrees of frost for a year's time [159]. In parenthesis to add, cryopreservation is a proposed alternative to extend the lifespan to a couple of years more, but then again, the ability of growth factors and anti-inflammatory agents to elude the frigid temperature demands further unveiling [159]. Besides, foetal membrane-derived cells like human amniotic fluid stem cells (hAFSCs) and human amniotic fluid MSCs (hAFMSCs) could be harvested drawing upon collagenase, trypsin, or dispase [107]. Application of AM and CM are comparatively commonplace in clinical approaches through two monolayer and multilayer techniques due mostly to the extracellular matrix (ECM)-raised unprecedented properties [160], inclusive of crystalline clarity, immunomodulatory characteristics, anti-inflammatory and anti-microbial qualities, anti-angiogenic and pro-apoptotic features, stem cell migration and proliferation induction, and non-tumourigenic epithelial cell growth [161–164]. In an attempt to further illustrate the AM composition, Cooper et al. detail that amniotic membrane ECM from the bottom to the apex consists

of collagen fibrils-harboured stroma, fine fibrils-containing basal lamina, and the electron-dense lamina densa with abundant masses of heparan sulphate constituting the proteoglycan perlecan, along with the comparatively highest concentration of adhesive glycoproteins fibronectin and laminin of multiple binding sites for the underlying lamina densa and the overlying cells [165]. With this in mind, the very first attempt at utilising foetal membrane was the closure of dermal defects. In the light of this, foetal membranes drawing the interests of the future literature subsequently became of widespread use as a surgical plastic material in performing recurrence-free pterygium surgery, vaginal rejuvenation, and pelvic peritoneum reconstruction [166] and later on in treating inflammatory disorders [167], bone pathology, severe burns [168] and non-healing ulcers [168], such as persistent ocular inflammation, persistent corneal epithelial defects (PEDs), and keratitis [169–171].

Amniotic fluid

So much for whole foetal membranes. The amniotic fluid (AF) could be harvested during amniocentesis from the embryo or the inner face of the foetal amniotic sac by the agency of therapeutic purposes, foetal maturity evaluation, and foetal abnormality diagnosis [172]. AF, characterised as antimicrobial properties and foetal development-dependant dynamicity regarding the composition (coinciding with foetal plasma) and volume (25 mL–400 mL during the weeks 10–20) throughout various stages of pregnancy [173], harbours a widely heterogeneous cell population from the three germ layers along with nutrients, growth factors, hormones, electrolytes, enzymes, hyaluronic acid stimulating activator (HASA), amino acids like taurine, and biomolecules like carbohydrates, lipids, and proteins all suspended in water [174]. In this sense, aside from epithelioid and fibroblastic cells, a couple of other amniocytes of treatment-wise significance include hAFSCs and hAFMSCs of both embryonic and adult SC markers, which could be isolated on specific culture media and further stimulated to give rise to several germ layer-associated lineages [175], inclusive of osteogenic, adipogenic, myogenic, hepatic, endothelial, and neuronal [176]. On this subject, De Coppi and colleagues [177] revealed that CD117⁺ (c-Kit⁺) AFSCs constitute 1% of the amniocyte population and exhibit pluripotent features analogous with pluripotent ESCs or induced pluripotent stem cells (iPSCs), which in other words means the feasibility of reprogramming AFSCs towards pluripotency in a genetic manipulation-free manner [178]. Added to this the absence of ethical hindrances and tumorigenesis potential, along with the ability to give rise to keratinocyte precursors and pluristratified epithelium in vitro [179], altogether providing ample reasoning to safely recognise AFSCs as an autologous source of stem cells in the field of regenerative medicine like

dermal tissue engineering. This assumes inevitably critical significance since the current skin repair methods that of treating burns, encompassing autologous, allogeneic, and heterologous skin grafting are strongly argued due to the insufficient number of skin donors and high risk of immune rejection or secondary infection [180]. One such instance could be B7-H4⁺ AFSCs differentiating into keratinocyte precursors in vitro, regenerating the pluristratified epithelium in tissue culture, and suppressing inflammation contribute to wound repair [179]. In addition to CD117⁺ and B7-H4⁺ AFSCs, Liu et al. [181] acted to examine the efficacy of CD44⁺/CD105⁺ hAFMSCs on a mouse model of cyclophosphamide-induced premature ovarian failure (POF), ascertaining that the administered seed cells exhibit durable customary cell proliferation and self-renewal cycles, which nominate them an ideal prospective treatment option. Figure 3 illustrates the embryo- or neonate-derived biowastes.

Oral Cavity

The oral cavity of high reparability strikes plausible as another source of MSCs provision from both physiological and pathological aspects, according to maxillofacial specialists. To date, a widely heterogeneous population of MSCs from various oral cavity components, including dental pulp (DPSCs) [182], human exfoliated deciduous/primary teeth (SHED) [183], periodontal ligament (PDLSCs), periodontal ligament of deciduous teeth (DePDL) [184], dental follicle progenitor cells (DFPCs) [185], apical papilla (SCAP), and gingiva [186], all of which fall under the

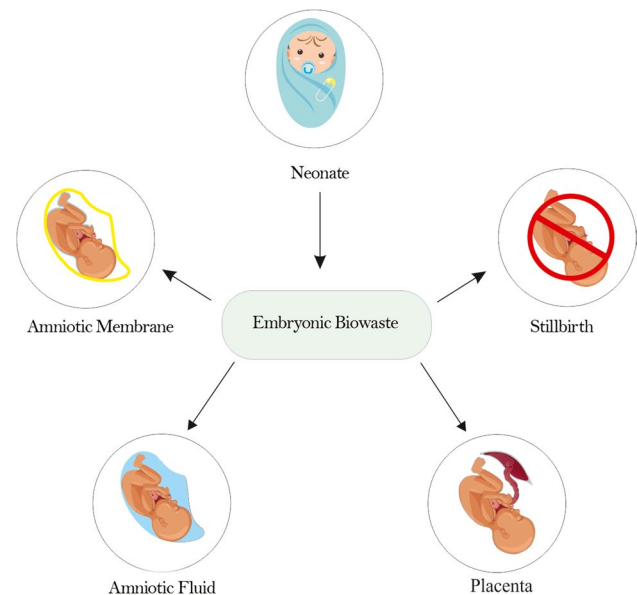


Fig. 3 Shows the embryonic-derived biowaste, including placenta, amniotic membrane, and amniotic fluid

umbrella term “dental-derived MSCs (DMSCs)”, have been harvested (Fig. 4). Throughout the recent years, conceptions concerning the structural development of teeth like dentin and pulp place emphasis on these structures arising from a couple of embryonic tissues, which include the ectodermal epithelium and the ectomesenchymal neural crests [187]. DMSCs hold a competitive edge over their fellow MSCs of other sources due to the fact that the extracted or exfoliated teeth are drawn from in a low-risk manner, rather than through invasive procedures, thus are safely recognised as a biowaste of dental procedures [188], but then again like any that has gone before, DMSCs too have to undergo a sound examination for their properties and feasibility in tissue regeneration endeavours. It is noted that the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy mentions that DMSCs show the characteristics of mesenchymal stem cells clonogenicity, plastic adhesion ability, multi-lineage differentiation potency, and specific surface markers. The following provides an insight into succinct conciseness with regard to DMSCs and the corresponding outlook. Table 2 shows the surface markers of different oral cavity- derived MSCs.

Dental Pulp-derived Stem Cells (DPSCs)

Dental pulp holds a reputation for highly critical importance in retaining teeth homeostasis and thus offering a longer lifespan. This property owes its thanks to the corresponding vascular system, contributing to oxygen and nutrition supply and waste material outtake, as well as the nerve fibres drawn into angiogenesis, neurogenesis, and immunisation [189]. Given the background, pulp-resident stem cells too benefit from this effective provision system. Of all the previously mentioned DMSCs, dental pulp-derived

stem cells (DPSCs) are the very first to be isolated from the permanent third molars in 2000 by Gronthos et al. [190] and have been subject to studies in minute detail since then. The story unfolds that the total unfractionated SC population expresses CD markers of CD105, CD133, CD24, MHCI, and MHCII [189]. Further revelation relates that in apposite of BMSCs, DPSCs are more proliferative and less mineral deposits-forming in vitro [190]. As for the differentiation potentials, these cells are observed to differentiate into adipogenic lineage in the presence of the necessary supplements [191]. According to in vivo literature, DPSC colonies either give rise to aligned odontoblast-like cells (OLCs) and subsequently dentin-like structures [190] or directly generate reparative dentin-like tissue on the dentin surface [192].

Stem cells from Human Exfoliated Deciduous teeth (SHED)

Bearing in mind that throughout an at least seven-year transition period, which dynamically involves replacing twenty deciduous teeth by means of dissolving the deciduous roots and developing permanent roots [193], the time comes to cast light on a comparatively unprecedented population of stem cells of multipotency. These stem cells, which stand to be of remnant pulp in origin, were first harvested in 2003 [184]. Recent compiling evidence in vitro indicates that SHED surpass BM-MSCs in terms of proliferation and are capable of giving rise to osteoblasts, adipocytes, and neural cells [194]. Contrarily, this differentiation ability of SHED into osteogenic lineage is cast doubt by Miura and colleagues [183], detailing that SHED is only characterised as an osteoinductive agent in vivo. Further corresponding in vivo studies on immunocompromised mice model by this group suggest that no more than 25% of the

Fig. 4 Illustrates the stem cells derived from the oral cavity

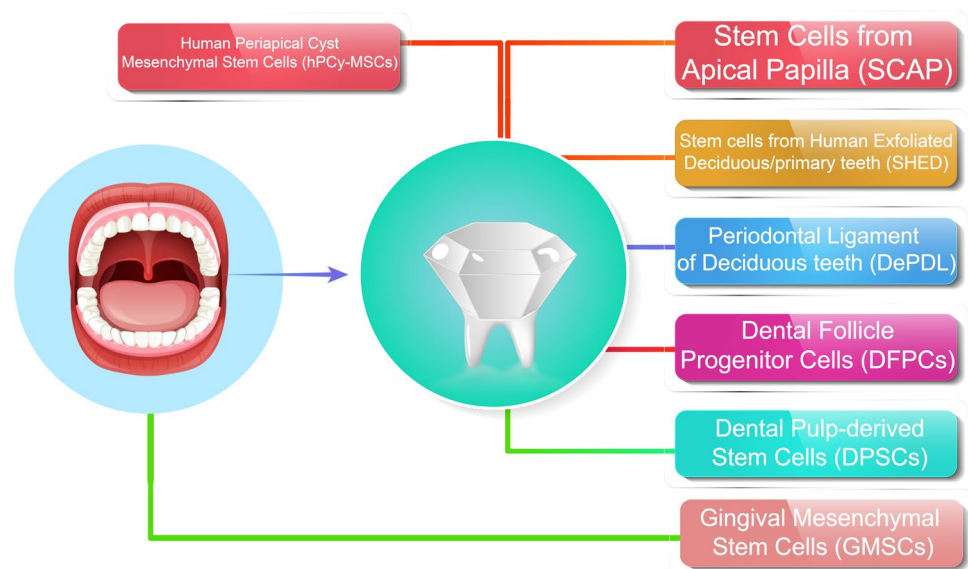


Table 2 shows the surface markers of oral cavity stem cells

Marker	DPSCs	SHED	PDLSCs	SCAP	DFPCs	GMSCs	DePDL
Embryonic Stem cell marker							
Oct-4	+	+	+	+	–	+	+
Nanog	+	+	–	–	–	+	NA
Mesenchymal markers							
CD106	–	–	–	+	–	+	NA
CD166	+	+	+	+	+	–	+
Stem cell marker							
SSEA-4	+	+	–	+	+	+	NA
CD9	+	–	+	+	+	+	NA
CD13	+	–	+	+	+	+	NA
Nestin	+	+	+	+	+	–	NA
Notch-1	+	–	–	–	+	+	NA
CD24	–	–	–	+	+	+	NA
CD29	+	–	+	+	+	+	NA
Haematopoietic marker							
CD80	–	–	–	+	–	–	NA
CD86	–	–	–	+	–	–	NA
Multipotency							
Chondro	+	+	+	–	+	+	NA
Myo	+	+	–	–	–	–	NA
Odonto	+	+	–	+	–	–	NA
Cardiomyo	+	–	–	–	–	–	NA
Hepatocyte-like cell	+	–	–	+	+	–	NA
Melanocyte	+	–	–	–	–	–	NA
Endothelial	–	+	–	–	–	–	NA
Cemento	–	–	+	–	+	–	NA
Endodermal	–	–	–	–	–	+	NA

12 single-colony-derived SHED clones acted parallel with multicolony-derived ones by forming ectopic dentin-like tissue on the scaffold hydroxyapatite/tricalcium phosphate (HA/TCP) carrier. Analogous observation is reported when administering SHED-seeded tooth slides to the mice model [195].

Periodontal Ligament-derived Stem Cells (PDLSCs)

Periodontal Ligament exists as an anchoring network of connective tissue fibres, which function to keep the root cementum of teeth attached to the alveolar bone [196]. It is noted that a novel population of MSCs is harvested from a heterogeneous population of various cellular subsets that was reported in 2004 by Seo et al., which inhabit the perivascular region of the periodontium [197] and live to differentiate into fibroblasts and osteoblasts/cementoblasts [198]. Interestingly, these MSCs are positive for the tendon-specific transcription factor scleraxis (Scx) [198]. Compared to BM-MSCs, PDLSCs are of higher proliferation ability [199]. In addition, PDLSCs taking their source of origin into account, are unsurprisingly capable of mineralising and

thereby differentiating into cementoblasts [200]. However, the number of nodules has never outnumbered that of BM-MSCs in vitro [198].

Periodontal Ligament of Deciduous teeth (DePDL)

A decade following the isolation of the first MSCs from the dental pulp, this time MSCs were detected in DePDL with the conception of harvesting MSCs from PDLSCs. Accumulating evidence in vitro signifies that DePDL favour adipocytes over osteoblasts, unlike their counterparts, and prove to be more active in proliferation [201].

Dental Follicle Progenitor Cells (DFPCs)

The dental follicle harbours a triad of periodontium-forming cells around the early-stage tooth germ [202]. The periodontium is a connective tissue of gingival tissue, alveolar bone, periodontal ligament (PDL), and cementum [203]. According to Patil et al., DFPCs, isolated first in 2005 by Morsczeck et al., tend to be more proliferative compared to DPSCs and SCAP of the same donor. When addressing the number of

the mineralised nodules in vitro, DPSCs and DFPCs surpass SCAP. Plus, DFPCs hold an advantage over the other two cell sources due to the expression of the chondrogenic-specific markers type I collagen, type III collagen, and aggrecan, rather than solely expressing the aggrecan marker [191].

Stem Cells from Apical Papilla (SCAP)

Apical papilla harbours MSCs in charge of root formation and thereby lies at the apex of the root [204]. Stimulating a developing tooth condition in a culture medium, in 2006, Sonoyama and colleagues ascertained that these cells could generate osteoblasts, odontoblasts, and adipocytes, but fail to form the dentin-like structure on a scaffold HA/TCP in vivo. Further in-depth investigation into the cDNA microarray profile brought down the curtain on whether or not these cells are the same as DPSCs and the results unveiled that SCAP proved to act more efficiently regarding the proliferation, migration, and telomerase activity [205].

Human Periapical Cyst Mesenchymal Stem Cells (hPCy-MSCs)

In 2013 Marrelli et al. [206] managed to add a new population of MSCs harvested from periapical cyst to the list of oral cavity-derived SCs. [207]. MSCs stood eyewitness suspects as a newly formed bone came to report in the light of surgical removal of periapical cyst. Antecedents to this conception could be traced in the observations credited to Maeda and subsequently Patel, assuming that a population of MSCs of osteogenic lineage commitment inhabit the periapical granulation tissue [208, 209]. [210]. Fibroblast-like design and SC-like properties, including proliferation, self-renewability, and multi-lineage differentiation into neurogenic, adipogenic, chondrogenic, and osteogenic cell lines characterise the isolated cells [206, 211]. Corresponding to their fellow DMSCs, hPCy-MSCs resemble no haematopoietic markers and importantly comprise two subpopulations with respect to the expression of CD146, with the CD146-low expressing subpopulation exhibiting a comparatively higher proliferative, clonogenic, and osteogenic capabilities from that of CD146-high expressing one [212]. When cultured in osteogenic medium within a three weeks' window, hPCy-MSCs and DPSCs reportedly orient towards osteogenesis and dentinogenesis, respectively [213].

Gingival Mesenchymal Stem Cells (GMSCs)

The stratified squamous gingival epithelium composed of the underlying basal cell bed [214], mucous membrane-encompassed vascular fibrous tissue [215], and the

submucosal connective tissue lamina propria constitutes of swift wound healing characteristic. In addition to the immune cells, as the neural crest and the mesenchyme are asserted to give rise to the gingiva, it is recognised as the most readily available and expandable depot of MSCs through minimally invasive interventions compared to the previously-mentioned oral cavity components [216, 217], such that GMSCs are obtained from the inflamed gum either directly through periodontal therapy like gingivectomy and gingiva incision during flap debridement or indirectly through preconditioning in a proinflammatory cytokine-supplemented milieu, which functionally in terms of differentiation capacity, colony formation, and cell surface marker expression, but not proliferation, coincide with those of healthy gum origins attained during dental therapies like crown lengthening and removing the third molars [218–220]. As described by Kim et al. [221], fibroblast-like spindle GMSCs corresponding to their fellow MSCs are positive for a series of known cell surface markers like CD73, CD105, CD90, STRO-1, and SSEA-4, but not the haematopoietic surface markers [222], and exhibit multipotent differentiation characteristics into osteogenic, adipogenic, and neurogenic lineages [223]. On a closer examination, GMSCs were proved to be a tough act to follow in terms of greater proliferation potential and shorter doubling time than BMSCs and hUCB-SCs [224, 225]. This goes on to an extent that IL-1 β - and/or TNF- α -treated GMSCs demonstrate augmented proliferation, migration, and motility capacity compared to those of no exposure to the proinflammatory cytokines and also remain alteration-exempt as to the viability, morphology, and functionality [226, 227]; however, these GMSCs together with their periodontal ligament counterparts (PDLSC) were observed to form fewer mineralised nodules, exert less alkaline phosphatase (ALP) activity, and express reduced titres of osteogenic surface markers osteocalcin (Ocn), type 1 collagen (COL1), and runt-related transcription factor 2 (RUNX2; CBF-alpha-1) in a corresponding differentiation induction medium [228]. The clinical application of DPSCs has been summarised in Table 3.

Surgical Biowastes

Surgery is counted as one of the most commonly performed medical procedures worldwide, the interventional nature of which allows the flow of biowaste in surplus depending on the fields of specialisation, encompassing dermal and mucosal irritations, abdominal diseases, thoracic disorders, trauma, herniation, and peripheral artery

Table 3 Summary of the registered clinical trials in www.ClinicalTrials.gov in regard with the administration of DMSCs

Clinical trial identifier	The number of participants	Status	Study Title	Conditions	Interventions	Study Type	Phase	Study Design	Locations
1 NCT03386877	First Posted: December 29, 2017 Actual Enrollment: 29 participants	Completed	Periodontal Regeneration Using Dental Pulp Stem Cells (DPSCs)	Periodontal Diseases	Procedure: periodontal regeneration	Interventional	Not Applicable	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment	CIR dental school Torino, Piedmont, Italy CIR Dental school Turin University Turin, Piedmont, Italy
2 NCT04641533	First Posted: November 24, 2020 Actual Enrollment: 13 participants	Completed	Effect of Dental Pulp Stem Cells and L-PRF After Impacted Third Molar Extraction	Stem Cell Third Molar Periodontal Pocket	Procedure: L-PRF + DPSC Procedure: L-PRF	Interventional	Not Applicable	Allocation: Randomized Intervention Model: Crossover Assignment Intervention Model Description: Prospective within person randomized split-mouth study. Left and right surgical sites for each participant were randomized using an online generated list to determine test and positive control LM3. (http://www.randomization.com). LM2s and LM3 extraction sockets were divided into two groups: a test group (extraction sockets filled with L-PRF membranes + DPSCs) and a control group (extraction sockets filled with L-PRF membranes) Masking: Double (Investigator, Outcomes Assessor) Masking Description: The random allocation list was generated by a periodontist (EEA), a clinical staff enrolled patients according to their reference date. The first allocation on the list was assigned to the right mandibular molar for each patient by the oral surgeon (SC) Primary Purpose: Prevention	Baskent University Ankara, Turkey
3 NCT02523651	First Posted: August 14, 2015 Estimated Enrollment: 40 participants	Unknown	Periodontal Regeneration of Chronic Periodontal Disease Patients Receiving Stem Cells Injection Therapy	Periodontal Diseases	Genetic: DPSC injection Other: Placebo	Interventional	Phase 1 Phase 2	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Capital Medical University School of Stomatology Beijing, Beijing, China

Table 3 (continued)

Clinical trial identifier	The number of participants	Status	Study Title	Conditions	Interventions	Study Type	Phase	Study Design	Locations
4 NCT03957655	First Posted: May 21, 2019 Estimated Enrollment: 40 participants	Not yet recruiting	Safety and Efficacy of SHED for Decompensated Liver Cirrhosis	Liver Cirrhosis	Biological: SHED group	Interventional	Early Phase 1	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor) Masking Description: Outcome assessors will be blind to the randomization results of the participants Primary Purpose: Treatment	Changhai Hospital Shanghai, Shanghai, China
5 NCT01814436	First Posted: March 20, 2013 Estimated Enrollment: 80 participants	Unknown	Revitalisation of Immature Permanent Teeth With Necrotic Pulp Using SHED Cells	Dental Pulp Necrosis Permanent Incisor Avulsed by Trauma	Device: scaffold-free SHED-derived pellet	Interventional	Not Applicable	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	School of Stomatology, Fourth Military Medical University Xi'an, Shaanxi, China
6 NCT01357785	First Posted: May 23, 2011 Estimated Enrollment: 35 participants	Unknown	Periodontal Tissue Regeneration Using Autologous Periodontal Ligament Stem Cells (PDLSC)	Periodontal Pocket	Procedure: Cell therapy	Interventional	Phase 1	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	School of Stomatology, Fourth Military Medical University Xi'an, Shaanxi, China
7 NCT01082822	First Posted: March 9, 2010 Estimated Enrollment: 35 participants	Unknown	Periodontal Ligament Stem Cell Implantation in the Treatment of Periodontitis	Chronic Periodontitis	Biological: cell sheet pellets and cell sheet fragment	Interventional	Phase 1 Phase 2	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Research and Develop Center for Tissue Engineering, Fourth Military Medical University Xi'an, Shaanxi, China

disease (PAD). On this basis, the following will be accentuating various means of biorecycling.

Liposuction and Lipoaspirates

Liposuction is defined as pulling out and disposing of the uninvited adipose tissue enveloping the ADSCs in a low-risk and safe manner [229, 230]. In this sense, liposuction-derived lipoaspirates today serve as an efficient way of harvesting ADSCs, also addressed as processed lipoaspirate cells (PLACs), the phenotypic characteristics of which are analogous to their fellows of bone marrow and skeletal muscle origins [231, 232] and resemble BMSCs in terms of differentiation into mesodermal lineages, inclusive of adipogenic, chondrogenic, and myogenic cell lines [233] along with antioxidant-induced ectodermal lineages *in vitro* like neurogenic cell lines [234]. Considering the aforementioned, ADSCs are right to be assumed of undeniable significance in aesthetic plastic surgery and reconstructive plastic surgery on account of remodelling the adipose tissue and refining the malpositioned subcutaneous fat and also in the regenerative medicine on account of serving as an alternative to BMSCs [235]. Simply put, one gram of adipose tissue equals 70,000 ADSCs following a 24-h culturing window, which could be continued for up to two weeks *in vitro* [236]. Once that is done, the extracted ADSCs are to form adipose tissue *in vivo* in the presence of biomaterials like alginate and poly(lactic-co-glycolic acid) (PLGA) [237]. To cut a long story short, characterising, analysing, and manipulating ADSCs would prove beneficial for supplying autologous adipose graft and thus treating anatomical defects caused by either pathological conditions, such as lipodystrophy, trauma, and injury or excision like breast-conserving surgery, also known as lumpectomy. This becomes mainstream since the current techniques drawn upon in reconstructive plastic surgery like shifting the mature adipocytes fail to meet the expectations in many cases [238, 239]. Aside from the aforementioned fields of interest, ADSCs could also serve to fulfil the insatiable demand for abundant sources of adipose tissue in body sculpting [240] as well as stromal vascular fraction (SVF), composed of MSCs, endothelial cells, adipocytes, immune cells and ECM, the reparative potency of which, allowing for angiogenesis, immunomodulation, and anti-inflammation renders SVF an invaluable therapeutic candidate for treating diabetic foot ulcer (DFU), cardiac diseases, cerebral ischemia, and facial deformities [241].

Hysterectomy

Hysterectomy, as another source of biowaste provision, involves the surgical excision of the uterus (ureterectomy) and the surrounding organs, such as the uterine cervix (trachelectomy), ovaries (oophorectomy), and the fallopian tubes (salpingectomy). The answer to the question arising concerning the benefits of hysterectomy to the regenerative medicine lies in the presence of

endometrial stroma-resident MSCs (eMSCs), which resembling their fellows of bone marrow origin [242] and expressing several surface markers, inclusive of melanoma cell adhesion molecule (MCAM; CD146), platelet-derived growth factor receptor- β (PDGFR β ; CD140b), and sushi domain-containing 2 (SUSD2) are postulated to inhabit the perivascular compartment and thus could be acquired from the endometrial biopsy samples [243]. Given a rudimentary background, eMSCs are theoretically able to give rise to the progesterone-mediated decidualised stroma *in vivo* and the observations unfold these cells not only commit to adipogenic, osteogenic, chondrogenic, myogenic, and endothelial lineages [244, 245], but also take part in the formation of vascular renal parenchyma in the superimmunodeficient NSGTM mice and endometrial stroma *in vivo* [246]. In this context, decellularising and recellularising the uterus of the fauna, especially sheep and pigs can prove beneficial in fabricating ECM-based uterine scaffolds and thus reconstructing and repairing the female genital tract. This matter gains even more significance as the number of people undergoing hysterectomy rapidly continues to rise [247–249].

Small Intestine

The small bowel, the 6–7 m long nutrient absorption hub made up of the duodenum, jejunum, and ileum could be deemed to be another feasible source of biowaste on account of the deep in the crypts-resident intestinal stem cells (ISCs), marked by the exclusive expression of leucine-rich-repeat-containing G-protein-coupled receptor 5 (Lgr5; GPR49) [250], olfactomedin 4 (OLFM4), and B cell-specific Moloney murine leukaemia virus integration site 1 (Bmi1) surface markers [251] and constitute critical components in frequently renewing the intestinal epithelium regarding the absorptive or secretory lineages [252] and retaining its homeostasis [253]. Of note, Lgr5⁺ cells represent a distinct population from the Bmi1⁺ cells, appointed a conspicuous role in physiological and pathological conditions, respectively [254]. Having the aforementioned in mind, ISCs have been widely taken advantage of in organoplasty, several cases of which are recapitulated moving forward. Trombetta et al. [255] attempted to evaluate the efficacy of longitudinal detubularisation and transverse retubularisation of ileo-neovagina in treating vaginal stenosis. The formation of the neovagina, abiding by the Monti channel principle, involved the isolation and exploitation of a modified ECM-rich ileal segment intestine, the advantages of which include low morbidity and treatment satisfaction. In addition to the ileum, the free vascular jejunal flap-derived neovagina too could act as an alternative to that derived from the ileal segments for vaginoplasty, the long-term safety and treatment objective achievement of which was confirmed by Akar et al. [256]. Aside from the vaginoplasty, the small intestine may benefit ureteroplasty following functional defects, the typical culprits of which encompass iatrogenic trauma or perforation, tumours, radiation therapy, stricture, and tuberculosis [257]. Another example would be the

empty nose syndrome (ENS) and administrating porcine small intestine submucosa (SIS) xenograft could produce statistically positive effects on reconstructing the inferior turbinate, refining the serial SNOT-25 scores as well as the quality of life (QOL) metrics [258]. Bladder diseases would be the last instance here among the many plausible applications of small bowel for organ reconstruction, such that augmentation cystoplasty is believed to lift the total bladder capacity along with QOL [259].

Post-Burn Scars

Post-burn scars, together with scar contractures, can by no means be avoided even with treatment at its best in that they heavily rely on the degree of burn and the severity of the immune response. In other words, disregarding the first-degree burn, also called the superficial burn, all other types of burns, allowing for the 2nd–4th degree burns culminate with tissue destruction and scar formation due to the post-burn hyperinflammatory response [260, 261]. The standard of care for burn management on an aesthetic basis involves early excision, debridement, and autologous skin grafting [262, 263]. Of the alternative means to address would be the keratinocyte-derived epidermal transplantation [264], physical therapy, and plastic surgery mentioned earlier; however, these procedures only offer a partial, but not complete, recovery from the scars [265]. For further elaboration, it is not until the surgical release of the contracture that a chronic ulcer or an unstable scar would heal. For this reason, burn-derived mesenchymal stem cells (BD-MSCs) discarded during debridement and exempt from ethical hindrances and risk of immune rejection could be perceived a robust and novel treatment option. BD-MSCs are characterised by the expression of CD73 and CD105, but not CD34 and CD45, and are able to give rise to chondrocytes, osteocytes, and adipocytes [266]. This distinct population of MSCs, when administered to the porcine and murine models [267] through decellularised tissue extracts, hydrogel formulation, and premade porous scaffolds, were reported to intensify wound closure, hasten epithelialisation, and counter tissue granulation [268]. Taking the above-mentioned into thorough account, properly processed cutaneous scar tissues could constitute a promising source of biowaste provision for skin grafting and organoplasty [269]. Nevertheless, to date, no clinical trials have been conducted to assess and evaluate the feasibility, therapeutic effects, and probable complications. Therefore, there is an urgent call for designing *in vitro* and *in vivo* clinical studies to ascertain the efficacy of such a theory.

Benign Tumours

Tumours, particularly benign tumours, strike as a promising source of biowaste for supplying ECM along with various cell types like stem cells, which could be harvested, induced,

or frozen for therapeutic purposes. Below further elaborates on a couple of benign tumours highlighting their applicability to regenerative medicine.

Cholesteatoma

Cholesteatoma, a likely lethal and noncancerous inflammation of the tympanic cavity engendered by the abnormal hyperkeratinisation of the squamous epithelium together with the erosion of the middle ear bone. In this context, Nagel et al., [270] detected a unique population of Nestin⁺S100B⁺ middle ear cholesteatoma-derived SCs (ME-CSCs) of self-renewal, neurosphere formation, and differentiation capacities into the mesodermal and ectodermal cell lines, which effectively contribute to the cholesteatoma progression, formation, or both. This finding assumes significance for providing precious and novel insights into the cholesteatoma pathogenesis and therefore unveiling specified treatment options. Given that cholesteatoma is of high incidence rate, it could be deemed an invaluable source of SCs and consequently biowaste.

Nasal Polyps

Nasal polyp, a sort of chronic rhinosinusitis, involves the paranasal sinus mucous membrane, the causal agents of which incorporate allergens along with microorganisms like bacteria, viruses, and fungi [271]. The noncancerous nature of nasal polyps, much like cholesteatoma, nominates them as a potentially nifty biowaste laden with various types of SCs, such as the progenitor cells and MSCs, namely the nasal polyps-derived MSCs (NPO-MSCs), which resemble the basic characterisation frame of reference of their bone marrow fellows [272], including plastic adherence, multilineage differentiation *in vitro* into the osteogenic, adipogenic, chondrogenic, and neurogenic cell lines, and expression of CD73, CD90, CD105, CD133 [273], neuroepithelial stem cell protein (Nestin), BMI-1 [274], Nanog, octamer-binding transcription factor 4 (Oct-4), SOX2, Kruppel-like factor 4 (KLF4), c-Myc, ATP-binding cassette super-family G member 2 (ABCG2), but not MHC-II, CD11b, CD14, CD34, or CD45 [275]. The above features consequently qualify NPO-MSCs as a suitable option to better investigate the molecular mechanisms associated with chronic rhinosinusitis with nasal polyposis (CRSwNP) *in vitro* and *in vivo*. Also, the immunomodulatory features attributed to PO-MSCs render them a potentially novel treatment option.

Menstrual Blood

Menstruation refers to the rhythmic discharge of menstrual fluid from the uterine endometrium all the way through the vagina. The menstrual fluid, also generally known as menstrual blood [276], consists of the peripheral blood, endometrial tissue, cervical mucosa, and vaginal secretions, which comprises variable percentages of proteins and electrolytes, such as sodium, calcium, phosphate, iron, and chloride [277]. Aside from the above

components, menstrual blood-derived MSCs (MenMSCs) originating from the endometrium play a crucial role in initiating the menstrual cycle of regeneration, differentiation, and finally shedding [278]. MenMSCs of endometrial stroma-resident fibroblast morphology and doubling time (T_d) of 18–36 h [279] exhibit at least 1.5-fold population doubling and thereby proliferate more rapidly compared to BMSCs [280], rendering this population of SCs conspicuous in preclinical *in vivo* experimental studies as well as in regenerative and restorative medicine, such that MenSCs are observed to exert protective and restorative effects on various organs including liver, lung, ovaries, and skin. It has been found that MenSCs drawing down the plasma levels of liver enzymes and metabolites could migrate to the fibrous area, lower the collagen fibre deposition together with macrophage and T-cell infiltration to consequently stop the inflammation and correspondingly refine the hepatic functions in acute liver injury. Furthermore, MenSCs, when administered intravenously, settle in the injury site and exert anti-inflammatory and restorative effects by modulating Interleukins. In addition, MenSCs were observed to migrate to the ovarian stroma in a POF model and prevent the granulosa cell apoptosis along with the ovarian stroma fibrosis, leading to elevated numbers of follicles, improved ovarian functions, and reinstated estrogen and progesterone plasma levels. As for the skin, the intradermal administration of MenSCs to rat models suffering from unresponsive wounds was reported to be accompanied by upregulated expression of angiogenic factors IL-8 and VEGF and thus enhanced angiogenesis and wound healing [281].

Semen

Predominantly remaining unnoticed, semen would be another invaluable supply of mitochondrial biowaste in that comparatively tremendous numbers of mitochondria of analogous functions with those in somatic cells are contained within the midpiece region of human sperm in an end to end arrangement [282]. This would conclusively promote mitochondria transplantation and further popularise novel therapeutic approaches towards mitochondrial dysfunctions [283–286].

Nail

Nails as the hyperkeratinised skin appendages [287] house nail stem cells (NSCs) in the nail matrix and the proximal fold, characterised by the rapid and slow proliferation rate, respectively [288] and the expression of keratin 19 (K19), K15, K14, CD29, and CD34 surface markers [289]. Nowadays, NSCs continue to assume widespread interest not only in treating nail-associated injuries and healing scars but also in curing other diseases in regenerative medicine,

owing a great debt of gratitude to a number of reasons, such as unlimited accessibility, relatively non-invasive collection procedure, transformation into corneocytes in the stratum corneum, and adhesion to fibrous scaffold *in vitro* [290]. Furthermore, transplanting cultured NSCs into a rat model of non-regenerative nail injury was reported to culminate with complete healing within four weeks window [291].

Hair

Hair is a protein rising from a follicle lying deep within the dermis. The origins of follicles could be traced back to the embryonic stage, developing a plate-like structure and maturing as a result of embedded stem cell proliferation. Given the background, hair follicles remaining in the dermis during alopecia marks plentiful stem cells for regenerative medicine objectives [292]. Hair follicle stem cells (HFSCs) are characterised by the expression of CD34, p63, and Ki-67, which are recognised as the major corresponding markers [293]. According to *in vivo* analysis, HFSCs, when implanted into a murine model of non-regenerative hair, had triggered hair regeneration [294]. Consistently, HFSCs had effectively alleviated the complications associated with radiation-induced acute alopecia *in vivo* [295]. Additionally, *in vitro* observations fabricating a similar microenvironment confirm this ability of HFSCs [296], which would be naïve to assume limited to hair regrowth, such that cultured HFSCs had proved to exhibit bladder-regenerative properties *in vivo* [293]. Add to this the ability of this population of stem cells to hasten wound healing [297]. These results demonstrate that HFSCs relying on their unique characteristics to support tissue regeneration could find a robust stem cell-based therapy method for treating alopecia, skin complications [298], neurodegenerative disorders [286], as well as bone-related diseases since HFSCs own osteogenic differentiation abilities [299].

Conclusion

As the days and nights are drawing on and the borders of science and knowledge keep stretching, we come to realise that we have been blind to matters beyond measure, which we address here as human biowaste, an unending supply of precious gifts that own the potential to bring us a step closer to what we as researchers have sworn to fulfil, that is the quest for voraciously making life more convenient and removing any obstacles confronting us in our way. In this paper, we have put a great deal of effort into making mention of a number of sources among the ceaseless list of biowaste, holding an overly optimistic view that this would

increasingly draw the attention and interest from scholars and therefore bring novel insights into our perception concerning the disease treatment.

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