Stem Cell Reviews and Reports (2019) 15:166–175
https://doi.org/10.1007/s12015-018-9866-1

Biological Products: Cellular Therapy and FDA Approved Products

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Published online: 9 January 2019

Abstract
The pace of advances in the world of science have created new opportunities and insights that give us new and more understanding of our nature and environment. Among the different fields of science, new medical sciences have drawn a great deal of attention among medical science researchers and the society. The hope for finding treatments for incurable diseases and further improvement of man's health is growing thanks to new medical technologies. Among the novel medical fields that have been extensively covered by medical and academic societies are cell therapy and gene therapy that are categorized under regenerative medicine. The present paper is an attempt to introduce the prospect of a curative cell-based therapy and new cellular and gene therapy drugs that have been recently approved by FDA (food and drug administration). Cellular and gene therapy are two very close fields of regenerative medicine and sciences which their targets and applications can be discussed together. What adds to the importance of this new field of science is the possibility to translate the hope for treatment of incurable diseases into actual treatments. What follows delves deeper into this new field of science and the drugs.

Keywords Approved drugs · Applications · Cellular therapy · Gene therapy · Stem cell

Introduction

Cell therapy, by definition, is to use cells to regenerate the function of non/miss-functional tissues or cells. The definition has become more comprehensive over time and now covers modern treatments like cell-based treatment including regenerative drugs. The process includes replacing or regenerating cells, tissues, or limbs to restore natural function of the body. In general, the foundations of qualitative systems in blood bank/transfusion centers and cell therapy are the same; although, there are differences in details [1]. Accreditation of cell therapy labs is done by FACT (Foundation of Accreditation of Cellular Therapies), AABB,[1] CAP (college of American pathologists), and other non-state organizations that are mostly USA-based. These organizations are recognized at international level. FDA deals with cell therapy under CFR 21 section 1271, which contains cGTP[2] and IND (investigational new drug) regulations. Cell therapy is performed in three ways of autologous (cell source is the patient), syngeneic (cell source is an identical twine), and allogeneic (other cell sources). It is used for homologous and non-homologous purposes. Homologous cellular products are used for repair, reconstruct, replace, or supplement cells or tissues of a patient that perform the same function(s) in the recipient as in the donor. An example is bone marrow implantation that is performed to replace hematopoietic progenitor cells (HPC) with hematopoietic stem cells (HSC). In the case of non-homologous cellular products, the cells generate a different function in the recipient from that in the donor. For example, HPCs are used to repair myocardium [2]. Among the key objectives of using cellular products for therapeutic purposes, three are notable; 1-To produce an ideal cell population; 2- To use the golden time to supply the cell; and 3- To find the most efficient method for supplying the cells [3]. Cell therapy is a novel method to cure different diseases and hard to cure diseases in particular. Researchers work to find the most effective ways of using cell therapy and make

[1] A key organization to set standards, facilitate accreditation, and educational activities in the USA.

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[2] A set of regulations concerning human-tissue cells or cell products based on tissue that are designed for human usages.

it available for all patients. Cellular and Gene therapy are two very close fields of regenerative medicine and sciences of which the targets and applications overlap. Despite the important advances in regenerative medicine and cell therapy, still and due to some limitations, cell and gene therapy have not been widely used for entire therapeutic applications [4]. Some of the most remarkable advancements in cell-based therapy are discussed here. The paper focuses on the cell therapy applications and its products and gene therapy fields as well. Moreover, some of the most remarkable advancements in cell-based therapy are discussed.

Candidate Diseases for Cellular Therapy

Cell therapy is recognized as an important field in the treatment of incurable human diseases; thereby, experimental studies on stem cell therapy hold great promises for new types of treatment. This includes treatments for untreatable disorders with available pharmaceuticals and/or incurable diseases categorized in groups like cancer and immunotherapies [5, 6], infectious diseases [7], cardiovascular diseases [8, 9], immunologic deficiency syndromes [10, 11], musculoskeletal diseases [12, 13], blood cell disorders [14, 15], neurodegenerative and movement disorders [16, 17], respiratory diseases [18], and skin diseases [4, 19] (Table 1). Theoretically, there is no limit to the types of diseases that could be treated with cell-based therapy. There are three sources of cells for therapeutic purposes including autologous, allogeneic, and xenogeneic. The xenogeneic source is presently set aside due to a variety of scientific and ethical concerns. The two other sources have their potential benefits and unique challenges. However, there are numerous sources of stem cells, progenitor cells, and engineered cells, and many of them are currently used for cell therapies at preclinical investigation or in clinical trials phases. Based on the nature of the disease and target tissues, cell therapy needs special tools and manipulations. This is where cellular gene engineering [20] and cell delivery systems [21] come to help for more efficient treatment (Fig. 1). All of these new possibilities make cell-based therapy a promising solution for a vast range of diseases and tissue injuries. However, when the cell manufacturing process is considered by the FDA as "more than minimal manipulation," the cells as biological and cellular products require a Biologics License Approval that includes compliance with Good Manufacturing Practices (GMP) for both drugs and biological products. It is

Table 1 Summary of source of cells for treatment of main candidate cell therapy diseases

Cell sources	Advantages & disadvantages	Main candidate diseases
Autologous	Advantages • No HLA matching is required • No need to immune-suppressive drug therapy • Low risk of other diseases Disadvantages • Expensive • Time consuming • The possibility of cells' function and efficacy attenuation	Heart disease: myocardial infarction Peripheral arterial disease: Critical limb ischemia Neurogenerative Diseases: Parkinson, Alzheimer, Multiple sclerosis Skin diseases: Vitiligo, Alopecia, Partial and/or full-thickness burns Blood diseases: sickle cell disease
Allogeneic	Advantages • Available for immediate delivery from cell bank • Elimination of any co-morbidities associated with the recipient • Cell source from young healthy donors • Scalable from a manufacturing perspective and its standardized procedures • production under GMP Disadvantages • Donors and sources restrictions • Viability reduction after infusion • Immunity reaction and rejection	Heart disease: myocardial infarction, chronic ischemic cardiomyopathy Circulatory system diseases: sickle cell disease, graft versus host disease (GVHD), congenital erythropoietic porphyria Cancers: non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma and leukemia Eye diseases: glaucoma, macular degeneration, Stargardt disease Metabolic diseases: lysosomal and peroxysmal metabolic diseases Skin diseases: Vitiligo, Alopecia, Partial and/or full-thickness burns
Genetic engineering	Advantages • Diverse opportunities to treat many different diseases • Using autologous and/or allogenic cell sources Disadvantages • Genome editing and manipulation problems • Immune system response	Infectious diseases: HIV, Hepatitis B virus, Herpes simplex virus Immunotherapy: T-cell immunotherapy, Circulatory system diseases: X-SCID, ADA-SCID, RS-SCID, Sickle cell disease and β-thalassemia Liver targeted diseases: Hemophilia, Enzyme replacement, Tyrosinemia, α-1-antitrypsin deficiency Neuromuscular disorders: Duchenne muscular dystrophy Skin diseases: Epidermolysis bullosa Ocular disorders: Leber's Congenital Amaurosis

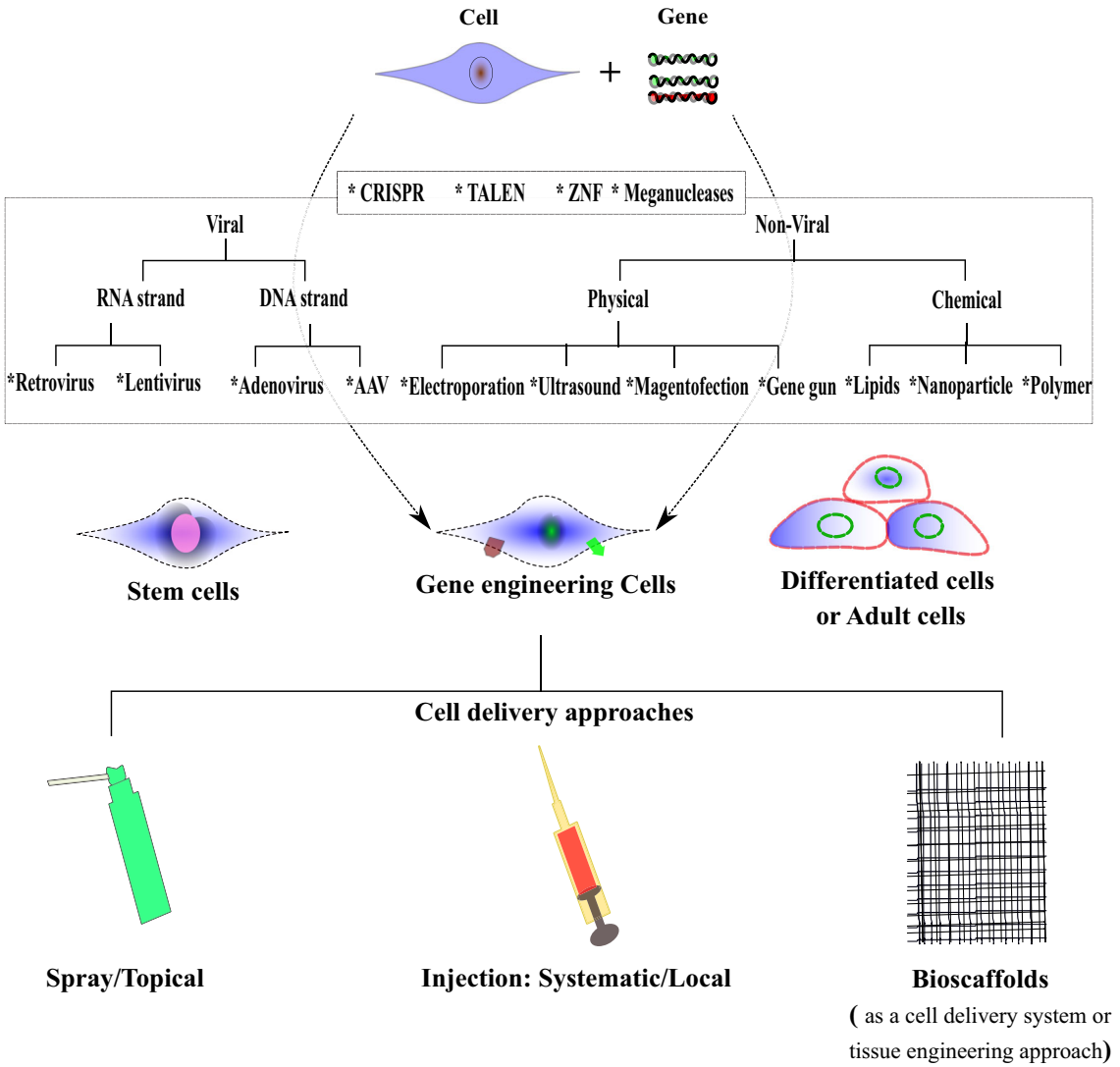

Fig. 1 Summary of the plot cellular and gene therapy in the regenerative medicine

notable that the number of candidate patients for cell therapy is growing day by day.

Cellular Drugs Approved for Medical Purposes

FDA is the authority in charge of preserving and improving public health in the USA. It regulates and supervises safety of foods and drugs, food supplements, vaccines, blood products, biologic products, medical devices, electromagnetic ray emitter devices (ERED), veterinary products, and beauty products. FDA license is recognized as an international license and producers of food, drug, and medical products all around the world can apply for such license. According to information categorization of FDA and its website, cellular and gene products and drugs are categorized under vaccine, blood, and biologic materials. Furthermore, cell therapy drugs and products are sub-categorized as cellular-gene products and tissue products. The subcategory of tissue products consists of body specimens like bone, skin, cornea, ligament, tendon, dura mater, heart valves, stem cells, HPC extracted from the mother's peripheral blood, umbilical cord, egg cell, etc. To the best of our knowledge, there is no cellular product approved by FDA. Center for Biologics Evaluation and Research (CBER) is in charge of codifying the regulations concerning human cellular and genetic drugs and also the devices used for cell/gene therapy. However, Cell-based therapy has been extensively tested in clinical trial studies and have led to promising outcomes in treating of different diseases (Fig. 2). As mentioned, accepting FDA approval for cellular and gene therapy products have an expensive, time-consuming, critical and crucial process.

Generally, the legal framework for approving biological products covers somatic cell therapy medicinal products, tissue-engineered products, stem cell products, and any genetic material that modify or manipulate the living cells of both autologous and allogeneic cells. The following section

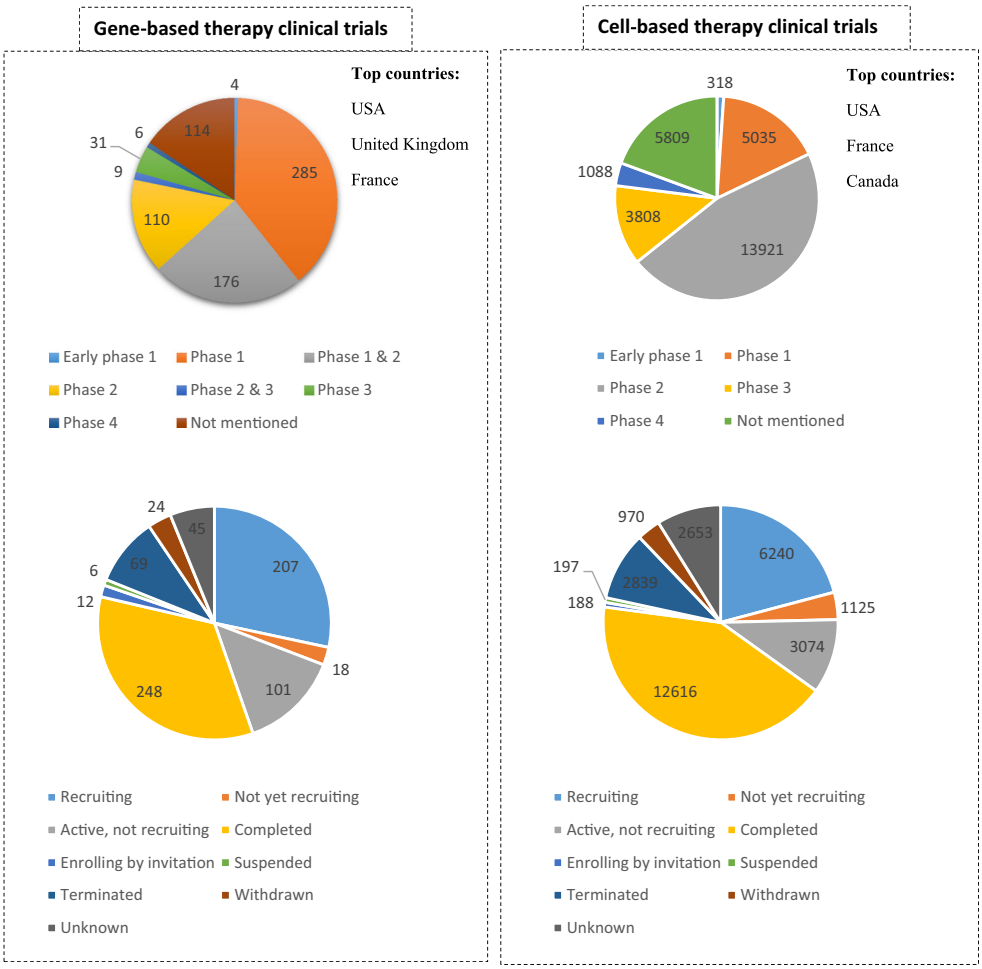

Fig. 2 Chart of clinical trials of cell and gene therapy. A search of the database of clinical trials (https://clinicaltrials.gov/ct2/home) for registered studies containing the term "Gene therapy" and "Cell therapy". Pie chare of trials by clinical phase and Pie chart of the status of studies have been shown

is a review of FDA approved products (16 approved products) in three classifications including stem cell-based products, somatic cell-based products, and gene therapy products (Table 2).

Cell-Gene Products Approved by FDA for Clinical Applications

Stem Cell-Based Products

Stem cell therapy is defined as direct or indirect (derivation) use of different types stem cells from different sources for therapeutic purposes. Stem cells are used for their indefinite cell division potential and transdifferention into other cell types or their paracrine effects through the release of cytokines and regulation functions. For instance, MSCs are used for therapeutic purposes because of their immune/inflammatory regulatory responses alongside their other stemness properties. There are several stem cells from a different source each with special advantages. Among these, some are more attractive due to applied therapeutic properties such as availability, low immunogenicity, and non-teratogenicity [22, 23]. In the following, we briefly introduce FDA approved stem cell-based products all from umbilical cord blood stem cells.

Umbilical Cord Blood Stem Cells (UCB-SC) and its Derived FDA Approved Products

Among different stem cell sources, umbilical cord blood (UCB) is one of the excellent sources of stem cells that its obtained stem cells are a standard treatment for hematopoietic stem cell transplantation in hematologic malignancies diseases include many types of leukemia's, lymphomas, myelodysplasias, and as well as different non-hematological diseases [24]. Recently UCB-SC banking due to its therapeutic potentials and emerging markets has been established in different countries [24, 25]. UCB-SC have a special importance between different stem cell sources so that several of its derivatives have succeeded to approve FDA insofar. Approved cellular therapy products derived from UCB-SC include Hemacord, Allocord, Clevecord, Ducord, and five products without of the trade name. These products have designed to prescribe in unrelated donor hematopoietic

Table 2 FDA approved cellular and gene therapy products

	Proper name	Trade name	Manufacturer	Indication/ details
Protein therapy	Coagulation factor Xa (recombinant), inactivated-zhzo	Andexxa	Portola Pharmaceuticals, Inc	Uncontrolled bleeding
Adult cell therapy	Laviv	Azficel-T	Fibrocell Technologies, Inc	Aesthetic therapy
	Autologous Cultured Chondrocytes on a Porcine Collagen Membrane	Maci	Vericel Corporation	Full-thickness cartilage defects of the knee
	Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen	Gintuit	Organogenesis Incorporated	Wounds of the oral soft tissue defects
Stem cell therapy	HPC, Cord Blood	Clevecord	Cleveland Cord Blood Center	Disorders affecting the hematopoietic system
	HEMACORD (HPC, Cord Blood)	Hemacord	New York Blood Center, Inc	Disorders affecting the hematopoietic system
	HPC, Cord Blood	Ducord	Duke University School of Medicine	Disorders affecting the hematopoietic system
	HPC, Cord Blood	None	Clinimmune Labs, University of Colorado Cord Blood Bank	Disorders affecting the hematopoietic system
	HPC, Cord Blood	None	LifeSouth Community Blood Centers, Inc	Disorders affecting the hematopoietic system
	HPC, Cord Blood	None	Bloodworks	Disorders affecting the hematopoietic system
	HPC, Cord Blood	None	MD Anderson Cord Blood Bank	Disorders affecting the hematopoietic system
	HPC, Cord Blood	Allocord	SSM Cardinal Glennon Children's Medical Center	Disorders affecting the hematopoietic system
Immuno-cell therapy	Tisagenlecleucel	Kymriah	Novartis Pharmaceuticals Corporation	B-cell precursor acute lymphoblastic leukemia (ALL)
	Axicabtagene ciloleucel	Yescarta	Kite Pharma, Incorporated	B-cell lymphoma
	Autologous Cellular Immunotherapy	Provenge	Dendreon Corporation	Prostate cancer
Virotherapy	Talimogene laherparepvec	Imlygic	Amgen Inc.	Melanoma
	Voretigene neparvovec-rzyl	Luxturna	Spark Therapeutics, Inc	Inherited retinal dystrophy
Devices	Plasma Cryoprecipitate (For Further Manufacturing Use	Plasma Cryoprecipitate	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H	N/A
	Sterile Cord Blood Collection Unit with Anticoagulant Citrate Phosphate Dextrose Solution USP (CPD)	None	MacoProductions S.A.S.	Cord blood samples conveyance

stem/progenitor cell transplantation approaches in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. UCB-SCs prepare by drawing blood from the umbilical cord or placenta of a newly born infant and then obtained cells have purified, concentrated and frozen for future applications. Once transplanted into an allogeneic recipient, these stem/progenitor cells migrate to the empty bone marrow, which has been depleted of endogenous cells by radiotherapy. These stem/ hematopoietic progenitor cells are then positioned in bone marrow cells niche to mature and eventually transferred to the blood flow. There they can reconstruct mature blood cells and immune system completely or almost completely [26]. Like other approaches to bone marrow implantation, HLA blood tests are necessary [27]. Hemacord (stem cells/HPC extracted from human cord blood) was approved by FDA in 2011 as the first ever cellular drug approved [26]. With a little interval time, Allocord and other products was approved by FDA [28].

Somatic Cell-Based Products

A somatic cell is defined as any biological cell that forms the body of an organism exclusive of undifferentiated stem cells. Somatic cells are often used with somatic cell nuclear transfer (SCNT) and gene therapy [29–31] for cell therapy purposes; however, in RG somatic cell therapy is one of the main interesting and product-centric topics. Currently, somatic cell therapy is focused on cell-based therapy for relatively simple

tissues such as skin and cartilage tissue. However, somatic cell therapy-related researches and developments are growing fast all around the world; while some of the products are at clinical trial studies.

LAVIV® (Azficel-T): After 10 years of work on producing autologous cellular products, FDA approved LAVIV® (Azficel-T) as the first cellular therapy autologous drug on June 2011 [32]. After the report of no side effects for the injection of skin fibroblasts cultivated in medium supplemented with human serum, studies were focused to produce new biological drugs in aesthetic therapy [33, 34]. Azficel-T is used to improve the appearance of wrinkles that are seen from the sides of the nose to the corners of the mouth that called "smile lines". This product is made from the autologous source of skin fibroblast cells placed in a mixture of water and salts [32]. The specimen, then, is cultured for 90 days and the cultured cells are then injected intra dermal (ID) through a specific therapeutic protocol. The data provided by Azficel-T was enough to secure an FDA approval; however, since it is a new drug, the approval entailed wide range monitoring in the market in terms of immunity and skin cancer side effects. Effectiveness of Azficel-T over 6 months is not confirmed [35]. Use Azficel-T to valid the appearance of aging and skin rejuvenation by replacing lost dermal cells and/or constituents show that autologous cellular therapy can denote the beginning of a new phase in aesthetic therapy [36]. However, Azficel-T has been reported as the first in class personalized cell therapy to skin rejuvenation and removal of fine wrinkles.

MACI® (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane) is a cellulose scaffold that is used in adults for repairing single or multiple full-thickness knee cartilaginous damages with average dimension of 2–10 cm^2 and with/without bone being inflicted. MACI® is an advanced product and relies on 3D scaffolds for chondrocyte cells cultures – a common practice in European countries, Australia, and the USA [37, 38]. Usually, cartilaginous damages larger than 3–4 cm^2 with bone damages are treated with MACI® along with autologous bone implant [39]. Short and mid-term follows up in the patients who used MACI® have confirmed clinical, radiography, and functional improvement and restoration of normal and complete activities [40]. Effectiveness of the drug on the joints other than the knees in individuals older than 55 years is not confirmed.

APLIGRAF® Apligraf® is a tissue-engineered biological wound dressing mat that was approved by FDA in 1998 as the first cell contained and matrix composite tissue analog for chronic wound management especially Venous leg ulcers (VLU) and diabetic foot ulcers (DFU). It is made from a bilayer structure containing a monolayer of protective keratinocytes at the outer layer and an inner layer of fibroblast cells within a bovine type I collagen matrix. It is notable that the Apligraf that has been used for several cases is actually produced out of 12 skin specimens [41]. As a living cell therapy, Apligraf is proven to be a valuable and cost-effective treatment for a variety of wounds especially chronic non-healing VLU and DFU. Apligraf® delivers the proteins produced by the cells and collagen, which are important for the healing process of the wounded area. It is used like other dressings and antibacterial treatments and it is designed to repair an injury via the body healing capability and treatment interposition. Apligraf® can play an active and dynamic role in the wound healing process.

GINTUIT® is a fibroblast and keratinocyte-containing sheet, as a combination product (containing cells and devices components) that is the first FDA approved cell therapy product for treatment of wounds in the oral soft tissue defects [42, 43]. In general, and to deal with tooth decay, dentists have to perform gum surgery, which is a painful operation in some cases and the result might be unsatisfactory. GINTUIT® is a new option for gum reconstruction treatment. In fact, it is the sister product of Apligraf for wound healing. Technology platform of GINTUIT® is similar to Apligraf and both products are obtained through an identical process on circumcision scare skin that undergoes and enzyme digestion process [44].

The obtained cells are disaggregated into keratinocytes and fibroblasts through centrifuge and kept in separate cell banks for further culture, proliferation, and storage [43]. These two cells are positions next to each other in a porous structure of polycarbonate. Keratinocytes improve structural strength of the product and fibroblasts provide the growth factors and the cytokine secretion effective on wound healing through a bovine collagen matrix structure. GINTUIT® is an allogeneic product for gum surgery that it is recommended for 0.75–7.5 mm wound on the gum [43].

Gene Therapy Products

Gene therapy is defined as introducing genetic material into living cells to compensate abnormal genes or to make a beneficial protein for treating or preventing a disease. Human gene therapy includes administration of genetic materials that modify or manipulate the expression of a gene product or alter the biological properties of human living cells for therapeutic purposes. Gene therapy can be classified into two types including somatic cell gene therapy and germline gene therapy. However, maybe the most attracting thing in gene therapy topics is chimeric antigen receptor T-cells (CAR-T), as the first gene therapy approved by FDA, for special cancers of the haematopoietic system [45]. Although in most gene therapy projects, a normal gene is inserted into the genome to replace an abnormal disease-causing gene, there are many studies on proceeding a genetically-mediated therapy by other methods for prevention of some diseases.

PROVENGE® (Sipuleucel-T) is the first autologous cell therapy cancer vaccine approved by FDA for advanced prostate cancer treatment. The therapeutic protocol is focused on generating dendritic cells (antigen-presenting cells) in a procedure called leukapheresis that enables the cells for identifying and killing cancerous cells that express PAP (prostate acid phosphatase) [46, 47]. Long-term viability of a group of men with resistive metastatic prostate cancer who received Sipuleucel-T was on average 4.1 months longer than a group that used placebo. In 3 years, the number of survived patients in the vaccine group was 50% higher than the control group [48]. Sipuleucel-T is designed to make the immune system responsive to PAP so that the immune system is activated to spot and fight cancerous cells. There are no other solutions with the same effects on increasing viability rate of the patients without side effect except for docetaxel, which is usually the last choice for many patients and physicians due to its intrinsic toxicity. Direct strategies to improve effectiveness of Sipuleucel-T might lead to better results [49].

LUXTURNA® is a therapeutic gene based on vector adenovirus virus that is designed for the patients with untreated *RPE65*-mediated inherited retinal dystrophy. The patients probably have cornea cells with viability capability; however, gene disorder leads to specific types of Leber's congenital amaurosis (LCA) and retinitis pigmentosa (RP) [50]. Over time, these patients lose the ability to detect light of any intensity. This product is the first gene replacement drug in the USA that is designed to target inherited retinal dystrophy by a gene therapy approach. However, it has been emphasized that genetic screening can identify these patients who might benefit from this, other genetic products and future gene therapies [51]. For more information about the related clinical trial can be visit ClinicalTrials.gov, number NCT00999609.

KYMRIAH® (tisagenlecleucel) is an autologous synthetic bio-immune product of anti-CD19 chimeric antigen receptor (CAR) T cells, which is prescribed for acute lymphoblastic leukemia (ALL) patients younger than 25 years with resistive or recurrent B cell [52, 53]. Since many leukemia's and lymphomas express CD19 as a surface antigen, this drug can be assumed as a turning point in treatment of B-ALL patients. Standard treatment for B-ALL patients are featured with high failure rates, which makes developing new treatment a necessity. The results of clinical trials indicate that KYMRIAH® can achieve a high response rate in B-ALL patients. Still, coincident toxicity like cytokine release syndrome and CART T encephalopathy syndrome might induce severe or even lethal side-effects; therefore, it is essential to control such toxicities [54, 55]. In general CAR T cell therapy has revolutionized cancer therapy by providing up to 90% complete response and hopes for treatment of other cancers has been increased.

YESCARTA® as the second gene/cell therapy product approved in the FDA, is a CD19-directed immunotherapy consisted of gene engineered autologous T cells that have been transduced with a retroviral vector encoding an anti-CD19 [56]. It is prescribed for adult's patients with diffuse large B cells lymphoma (DLBCL), primary mediastinal large B cells lymphoma, high grade B-cell lymphoma, and DLBCL caused by follicular lymphoma. Eye-catching effectiveness of the drug have been covered by the media extensively [57]. It is not recommended for the patients with early lymphoma of central nervous system due to considerable side effects including death. Still the long-term side effects need further studies. At the present time KYMRIAH® (produced by Novrtis with a price tag of US$475,000) and YESCARTA® (produced by Gilead Pharmaceuticals with a price tag of US$373,000,) are two CAR-T cell therapy which the cost of both are high [58]. However, advances in the processes of producing genetically modified T cells may lead to better version of T cell based treatments even for diseases other than cancer. For instance, they can be effective on infectious and autoimmunity diseases.

IMLYGIC® (Talimogene Laherparepvec) is a genetically modified oncolytic virus treatment that is designed for topical treatment of cutaneous and sub-cutaneous conditions in the patients with frequent melanoma after the primary surgery. The drug is the first oncolytic viral therapy approved for treatment of locally advanced melanoma in October 2015 and a primary viral immunotherapy that is obtained from simplex herpes virus (I) and used genetically to improve the rate of diagnosing tumor and stimulate immunity response to tumor [59]. Clinical trial phase III studies have indicated that the drug is more effective than natural factors of the body like GM-CGF[3] and improves viability rate [60]. It is notable that the effectiveness of IMLYGIC® on general viability or splanchnic metastases is not proved.

ANDEXXA® is a Xa coagulation factor (FXa) (recombinant protein) and the newest drug categorized as cell/gene therapeutic drugs. It is a human modified protein and prescribed for patients under FXa suppressor drugs like Rivaroxaban and Apixaban and it is used through vein injection. However, approving further usage entails further studies to confirm effectiveness of the drug on hemostasis [61, 62]. Continued approval for this indication may be contingent upon the results of studies to demonstrate an improvement in hemostasis in patients.

Outlook

Although, presently clinical trials utilizing gene and cell-based therapies are sparse, these developments are expected to substantially broaden the scope of regenerative medicine in the near future. Current cancer treatments focus on finding strategies to improve the prospect of survival and quality of cancerous patients' lives. Hence cell based therapy has drawn a

[3] Granulocyte-macrophage colony-stimulating factor

great deal of attentions. In recent years, cell-based therapies have been designed for the prominent disorders, including cancer (myeloma), cardiovascular (heart failure, peripheral arterial diseases), neurological (Parkinson's disease, stroke, spinal cord injury), autoimmune (Type 1 diabetes, multiple sclerosis, Crohn's disease), ophthalmologic (glaucoma, macular degeneration, Stargardt disease), renal, liver, skeletal (osteoarthritis), and infectious (HIV) diseases and wound healing. To this aim, Multiple cell sources have been utilized, including autologous (Adult cells, stem cells from different adult tissue, iPS), allogeneic (Adult cells, stem cells from bone marrow, adipose tissue, embryonic stem cells, umbilical cord and cord blood stem cells) and genetic engineering cells. In addition, and to facilitate cell-based therapeutic applications, high purity, low cost, and large scale cellular sources are needed. There are promising reports by different in vitro and in vivo studies indicating the potential success of using cell-based therapy in therapeutic applications. In addition to offering novel treatments for different incurable diseases, cellular and gene therapies give us deeper insights into how different cells of target tissues interact with one another in health and disease.

Author Contributions A.G. conceptualized the outline and contents of the article. All authors contributed to writing and editing the manuscript.

Compliance with Ethical Standards

Conflict of Interest Authors do not have conflict of interest.

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References

1. Petricciani, J., Hayakawa, T., Stacey, G., Trouvin, J.-H., & Knezevic, I. (2017). Scientific considerations for the regulatory evaluation of cell therapy products. *Biologicals, 50*, 20–26. https://doi.org/10.1016/J.BIOLOGICALS.2017.08.011.
2. Shaz, B., Hillyer, C. D., Abrams, C. S., & Roshal, M. (2013). *Transfusion medicine and hemostasis : Clinical and laboratory aspects* (3rd ed.). Elsevier. Retrieved from https://www.sciencedirect.com/science/book/9780123971647.
3. Kuraitis, D., Giordano, C., Suuronen, E. J., & Ruel, M. (2014). Cell therapy to regenerate the ischemic heart. In *Cardiac regeneration and repair* (pp. 118–137). Elsevier. https://doi.org/10.1533/9780857096708.2.118.
4. Golchin, A., Hosseinzadeh, S., & Ardeshirylajimi, A. (2018). The exosomes released from different cell types and their effects in wound healing. *Journal of Cellular Biochemistry, 119*(7), 5043–5052. https://doi.org/10.1002/jcb.26706.
5. Mehta, R. S., Randolph, B., Daher, M., & Rezvani, K. (2018). NK cell therapy for hematologic malignancies. *International Journal of Hematology, 107*(3), 262–270. https://doi.org/10.1007/s12185-018-2407-5.
6. June, C. H., O'Connor, R. S., Kawalekar, O. U., Ghassemi, S., & Milone, M. C. (2018). CAR T cell immunotherapy for human cancer. *Science, 359*(6382), 1361–1365. https://doi.org/10.1126/science.aar6711.
7. Zumla, A., Rao, M., Wallis, R. S., Kaufmann, S. H. E., Rustomjee, R., Mwaba, P., … Host-Directed Therapies Network consortium. (2016). Host-directed therapies for infectious diseases: current status, recent progress, and future prospects. *The Lancet Infectious Diseases, 16*(4), e47–e63. https://doi.org/10.1016/S1473-3099(16)00078-5.
8. Tsilimigras, D. I., Oikonomou, E. K., Moris, D., Schizas, D., Economopoulos, K. P., & Mylonas, K. S. (2017). Stem cell therapy for congenital heart disease. *Circulation, 136*(24), 2373–2385. https://doi.org/10.1161/CIRCULATIONAHA.117.029607.
9. Roura, S., Gálvez-Montón, C., Mirabel, C., Vives, J., & Bayes-Genis, A. (2017). Mesenchymal stem cells for cardiac repair: are the actors ready for the clinical scenario? *Stem Cell Research & Therapy, 8*(1), 238. https://doi.org/10.1186/s13287-017-0695-y.
10. Arnold, D. E., & Heimall, J. R. (2017). A review of chronic granulomatous disease. *Advances in Therapy, 34*(12), 2543–2557. https://doi.org/10.1007/s12325-017-0636-2.
11. Schlabe, S., & Rockstroh, J. K. (2018). Advances in the treatment of HIV/HCV coinfection in adults. *Expert Opinion on Pharmacotherapy, 19*(1), 49–64. https://doi.org/10.1080/14656566.2017.1419185.
12. Bajek, A., Porowinska, D., Kloskowski, T., Brzoska, E., Ciemerych, M. A., & Drewa, T. (2015). Cell therapy in Duchenne muscular dystrophy treatment: Clinical trials overview. *Critical Reviews in Eukaryotic Gene Expression, 25*(1), 1–11. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25955813.
13. Negroni, E., Bigot, A., Butler-Browne, G. S., Trollet, C., & Mouly, V. (2016). Cellular therapies for muscular dystrophies: frustrations and clinical successes. *Human Gene Therapy, 27*(2), 117–126. https://doi.org/10.1089/hum.2015.139.
14. Kumar, R., Bonfim, C., & George, B. (2017). Hematopoietic cell transplantation for aplastic anemia. *Current Opinion in Hematology, 24*(6), 509–514. https://doi.org/10.1097/MOH.0000000000000382.
15. Dong, A. C., & Rivella, S. (2017). Gene addition strategies for β-thalassemia and sickle cell anemia. *Advances in Experimental Medicine and Biology, 1013*, 155–176. https://doi.org/10.1007/978-1-4939-7299-9_6.
16. Lunn, J. S., Sakowski, S. A., Hur, J., & Feldman, E. L. (2011). Stem cell technology for neurodegenerative diseases. *Annals of Neurology, 70*(3), 353–361. https://doi.org/10.1002/ana.22487.
17. Sakthiswary, R., & Raymond, A. A. (2012). Stem cell therapy in neurodegenerative diseases: From principles to practice. *Neural Regeneration Research, 7*(23), 1822–1831. https://doi.org/10.3969/j.issn.1673-5374.2012.23.009.
18. Geiger, S., Hirsch, D., & Hermann, F. G. (2017). Cell therapy for lung disease. *European Respiratory Review, 26*(144), 170044. https://doi.org/10.1183/16000617.0044-2017.
19. Shin, T.-H., Kim, H.-S., Choi, S. W., & Kang, K.-S. (2017). Mesenchymal stem cell therapy for inflammatory skin diseases: clinical potential and mode of action. *International Journal of Molecular Sciences, 18*(2), 244. https://doi.org/10.3390/ijms18020244.
20. Maeder, M. L., & Gersbach, C. A. (2016). Genome-editing technologies for gene and cell therapy. *Molecular Therapy, 24*(3), 430–446. https://doi.org/10.1038/mt.2016.10.
21. Golchin, A., Hosseinzadeh, S., & Roshangar, L. (2017). The role of nanomaterials in cell delivery systems. *Medical Molecular Morphology, 51*(1), 1–12. https://doi.org/10.1007/s00795-017-0173-8.
22. Zhang, J., Huang, X., Wang, H., Liu, X., Zhang, T., Wang, Y., & Hu, D. (2015). The challenges and promises of allogeneic mesenchymal stem cells for use as a cell-based therapy. *Stem Cell Research & Therapy, 6*(1), 234. https://doi.org/10.1186/s13287-015-0240-9.

23. Golchin, A., Rekabgardan, M., Taheri, R. A., & Nourani, M. R. (2018). *Promotion of cell-based therapy: special focus on the co-operation of mesenchymal stem cell therapy and gene therapy for clinical trial studies* (pp. 1–16). New York: Springer. https://doi.org/10.1007/5584_2018_256.
24. Matsumoto, M. M., & Matthews, K. R. W. (2015). A need for renewed and cohesive US policy on cord blood banking. *Stem Cell Reviews, 11*(6), 789–797. https://doi.org/10.1007/s12015-015-9613-9.
25. Matsumoto, M. M., Dajani, R., & Matthews, K. R. W. (2015). Cord blood banking in the Arab world: current status and future developments. *Biology of Blood and Marrow Transplantation, 21*(7), 1188–1194. https://doi.org/10.1016/j.bbmt.2015.01.012.
26. Allison, M. (2012). Hemacord approval may foreshadow regulatory creep for HSC therapies. *Nature Biotechnology, 30*(4), 304–304. https://doi.org/10.1038/nbt0412-304.
27. Research, C. for B. E. and. (2018). Cellular & gene therapy products. Retrieved from https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/default.htm.
28. Dessels, C., Alessandrini, M., & Pepper, M. S. (2018). Factors influencing the umbilical cord blood stem cell industry: an evolving treatment landscape. *Stem Cells Translational Medicine*. https://doi.org/10.1002/sctm.17-0244.
29. Siripattarapravat, K., & Cibelli, J. B. (2011). Method for somatic cell nuclear transfer in zebrafish. *Methods in Cell Biology, 104*, 209–217. https://doi.org/10.1016/B978-0-12-374814-0.00012-4.
30. Trounson, A. (2014). Nuclear transfer for stem cells. In *Principles of cloning* (pp. 313–316). https://doi.org/10.1016/B978-0-12-386541-0.00024-2.
31. Brenner, M. K. (2018). Current gene marking and gene therapy protocols for human bone marrow transplantation. In *Somatic gene therapy* (pp. 225–242). CRC Press. https://doi.org/10.1201/9781351076760-13.
32. Schmidt, C. (2011). FDA approves first cell therapy for wrinkle-free visage. *Nature Biotechnology, 29*(8), 674–675. https://doi.org/10.1038/nbt0811-674.
33. Piñero Eça, L., Galdino Pinto, D., Murari Soares de Pinho, A., Paulo Vaccari Mazzetti, M., & Emiko Yagima Odo, M. (2012). Autologous fibroblast culture in the repair of aging skin. *Dermatologic Surgery, 38*(2 Part 1), 180–184. https://doi.org/10.1111/j.1524-4725.2011.02192.x.
34. Mehrabani, D., & Manafi, N. (2013). Role of cultured skin fibroblasts in aesthetic and plastic surgery. *World Journal of Plastic Surgery, 2*(1), 2–5. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25489497.
35. McArdle, A., Senarath-Yapa, K., Walmsley, G. G., Hu, M., Atashroo, D. A., Tevlin, R., … Longaker, M. T. (2014). The role of stem cells in aesthetic surgery. *Plastic and Reconstructive Surgery, 134*(2), 193–200. https://doi.org/10.1097/PRS.0000000000000404.
36. Smith, S. R., Munavalli, G., Weiss, R., Maslowski, J. M., Hennegan, K. P., & Novak, J. M. (2012). A multicenter, double-blind, placebo-controlled trial of autologous fibroblast therapy for the treatment of nasolabial fold wrinkles. *Dermatologic Surgery, 38*(7pt2), 1234–1243. https://doi.org/10.1111/j.1524-4725.2012.02349.x.
37. Dunkin, B. S., & Lattermann, C. (2013). New and emerging techniques in cartilage repair: MACI. *Operative Techniques in Sports Medicine, 21*(2), 100–107. https://doi.org/10.1053/j.otsm.2013.03.003.
38. Gobbi, A., Kon, E., Berruto, M., Francisco, R., Filardo, G., & Marcacci, M. (2006). Patellofemoral full-thickness chondral defects treated with Hyalograft-C. *The American Journal of Sports Medicine, 34*(11), 1763–1773. https://doi.org/10.1177/0363546506288853.
39. Ochs, B. G., Müller-Horvat, C., Albrecht, D., Schewe, B., Weise, K., Aicher, W. K., & Rolauffs, B. (2011). Remodeling of articular cartilage and subchondral bone after bone grafting and matrix-associated autologous chondrocyte implantation for osteochondritis Dissecans of the knee. *The American Journal of Sports Medicine, 39*(4), 764–773. https://doi.org/10.1177/0363546510388896.
40. Dekker, T. J., Erickson, B., Adams, S. B., & Gross, C. E. (2017). Topical review: MACI as an emerging technology for the treatment of Talar osteochondral lesions. *Foot & Ankle International, 38*(9), 1045–1048. https://doi.org/10.1177/1071100717711482.
41. Zaulyanov, L., & Kirsner, R. S. (2007). A review of a bi-layered living cell treatment (Apligraf) in the treatment of venous leg ulcers and diabetic foot ulcers. *Clinical Interventions in Aging, 2*(1), 93–98. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18044080.
42. Falanga, V., Faria, K., & Bollenbach, T. (2014). Bioengineered skin constructs. In *Principles of tissue engineering* (pp. 1619–1643). https://doi.org/10.1016/B978-0-12-398358-9.00077-X.
43. Schmidt, C. (2012). Gintuit cell therapy approval signals shift at US regulator. *Nature Biotechnology, 30*(6), 479–479. https://doi.org/10.1038/nbt0612-479.
44. McGuire, M. K., Scheyer, E. T., Nunn, M. E., & Lavin, P. T. (2008). A pilot study to evaluate a tissue-engineered bilayered cell therapy as an alternative to tissue from the palate. *Journal of Periodontology, 79*(10), 1847–1856. https://doi.org/10.1902/jop.2008.080017.
45. Yáñez-Muñoz, R. J., & Grupp, S. A. (2018). CAR-T in the clinic: drive with care. *Gene Therapy, 25*(3), 157–161. https://doi.org/10.1038/s41434-018-0023-x.
46. Jarosławski, S., & Toumi, M. (2015). Sipuleucel-T (Provenge®)—Autopsy of an innovative paradigm change in cancer treatment: why a single-product biotech company failed to capitalize on its breakthrough invention. *BioDrugs, 29*(5), 301–307. https://doi.org/10.1007/s40259-015-0140-7.
47. Vasani, D., Josephson, D. Y., Carmichael, C., Sartor, O., & Pal, S. K. (2011). Recent advances in the therapy of castration-resistant prostate cancer: The price of progress. *Maturitas, 70*(2), 194–196. https://doi.org/10.1016/j.maturitas.2011.07.018.
48. Cheever, M. A., & Higano, C. S. (2011). PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine. *Clinical Cancer Research, 17*(11), 3520–3526. https://doi.org/10.1158/1078-0432.CCR-10-3126.
49. Zheng, P.-P., Kros, J. M., & Li, J. (2018). Approved CAR T cell therapies: ice bucket challenges on glaring safety risks and long-term impacts. *Drug Discovery Today, 23*(6), 1175–1182. https://doi.org/10.1016/j.drudis.2018.02.012.
50. Dias, M. F., Joo, K., Kemp, J. A., Fialho, S. L., da Silva Cunha, A., Woo, S. J., & Kwon, Y. J. (2018). Molecular genetics and emerging therapies for retinitis pigmentosa: basic research and clinical perspectives. *Progress in Retinal and Eye Research, 63*, 107–131. https://doi.org/10.1016/j.preteyeres.2017.10.004.
51. Russell, S., Bennett, J., Wellman, J. A., Chung, D. C., Yu, Z.-F., Tillman, A., … Maguire, A. M. (2017). Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65 -mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *The Lancet, 390*(10097), 849–860. https://doi.org/10.1016/S0140-6736(17)31868-8.
52. Prasad, V. (2017). Immunotherapy: tisagenlecleucel — the first approved CAR-T-cell therapy: implications for payers and policy makers. *Nature Reviews Clinical Oncology, 15*(1), 11–12. https://doi.org/10.1038/nrclinonc.2017.156.
53. Bach, P. B., Giralt, S. A., & Saltz, L. B. (2017). FDA approval of tisagenlecleucel. *JAMA, 318*(19), 1861. https://doi.org/10.1001/jama.2017.15218.
54. Liu, Y., Chen, X., Han, W., & Zhang, Y. (2017). Tisagenlecleucel, an approved anti-CD19 chimeric antigen receptor T-cell therapy for

the treatment of leukemia. *Drugs of Today, 53*(11), 597. https://doi.org/10.1358/dot.2017.53.11.2725754.

55. Iyer, R. K., Bowles, P. A., Kim, H., & Dulgar-Tulloch, A. (2018). Industrializing autologous adoptive immunotherapies: manufacturing advances and challenges. *Frontiers in Medicine, 5*, 150. https://doi.org/10.3389/fmed.2018.00150.
56. Salmikangas, P., Kinsella, N., & Chamberlain, P. (2018). Chimeric antigen receptor T-cells (CAR T-cells) for cancer immunotherapy – moving target for industry? *Pharmaceutical Research, 35*(8), 152. https://doi.org/10.1007/s11095-018-2436-z.
57. Commissioner, O. of the. (2017). Press Announcements - FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma. *U.S. Food & Drugs Administration*. Retrieved from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm
58. de Lima Lopes, G., & Nahas, G. R. (2018). Chimeric antigen receptor T cells, a savior with a high price. *Chinese Clinical Oncology, 7*(2), 21–21. https://doi.org/10.21037/cco.2018.04.02.
59. Collichio, F., Burke, L., Proctor, A., Wallack, D., Collichio, A., Long, P. K., & Ollila, D. W. (2018). Implementing a program of talimogene laherparepvec. *Annals of Surgical Oncology, 25*(7), 1828–1835. https://doi.org/10.1245/s10434-018-6361-5.
60. Chesney, J., Awasthi, S., Curti, B., Hutchins, L., Linette, G., Triozzi, P., … Amatruda, T. (2018). Phase IIIb safety results from an expanded-access protocol of talimogene laherparepvec for patients with unresected, stage IIIB–IVM1c melanoma. *Melanoma Research, 28*(1), 44–51. https://doi.org/10.1097/CMR.0000000000000399.
61. Ghadimi, K., Dombrowski, K. E., Levy, J. H., & Welsby, I. J. (2016). Andexanet alfa for the reversal of factor Xa inhibitor related anticoagulation. *Expert Review of Hematology, 9*(2), 115–122. https://doi.org/10.1586/17474086.2016.1135046.
62. (2018). Andexxa–an antidote for apixaban and rivaroxaban. *The Medical Letter on Drugs and Therapeutics, 60*(1549), 99–101. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29913471.