The Outlook for Novel Pharmaceutics

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Abstract

Recent advances in treatment and prevention using novel approaches are opening the door for a seismic shift in healthcare. In this chapter, we report advances in four key areas of personalised medicine: tissue engineering, regenerative medicine, gene therapy, and nanomedicine. We include examples of products currently in the market, barriers to translating these novel therapies to the clinic, and the outlook for emerging therapies.

1 Introduction

Every year, regulatory bodies around the world approve hundreds of new medications. Most of these are variations of existing products that include new dosages for already approved drugs or cost-saving generics. These products aim to improve the quality of care, provide greater access to medication, and create a competitive marketplace in order to improve both affordability and public health. However, a small number of novel drugs are being approved that provide innovative approaches that are advancing clinical care to a new level.

The pharmaceutical industry is going through a paradigm shift that is catalysed by new and disruptive technologies (such as nanotechnology, additive manufacturing, and artificial intelligence (AI)) that facilitate the development of groundbreak-

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ing new therapies. These new therapies include innovative solutions involving cell and gene therapies, tissue-engineered products, and nanomedicine. It is expected that these novel therapies will bring important benefits to future healthcare and revolutionise the treatment of diseases such as neurological disorders or cancers. In addition, these therapies, which are often targeted and specific, will offer tailored solutions based on the needs of individual patients that will pave the way for more personalised therapies.

In this chapter, we will review some of the novel approaches that are expected to be adopted in the future, including examples from several clinically approved treatments. We will also discuss the challenges associated with the translation of these novel therapies to the clinic.

2 Personalised Medicine

Personalised medicine is the concept of tailoring healthcare based on a patient's genetics, phenotype, lifestyle, and environment. This strategy could influence the outcome of therapies by enhancing efficacy and increasing the safety of drugs whilst improving patient compliance and reducing costs. Personalised medicine is often intertwined with 'precision medicine', which is the use of data and genomics to tailor interventions to specific patient groups. Precision medicine relies heavily on data, analytics, and information. Rapid advancements in genomic technologies have provided a deeper understanding of pathology and the progression of diseases. This knowledge coupled with emerging methodologies for monitoring treatment responses drives more personalised approaches to the management and treatment of diseases.

The 'one-size-fits-all' model for delivering medicine is a thing of the past, and there is an urgent need to target specific medication to specific patient populations at the best dose and the right time. The introduction of government initiatives has pushed the fields of precision and personalised medicine forward. The '100,000 Genomes Project' in the United Kingdom was completed in 2018. The project aimed to combine genomic sequencing data with National Health Service medical records to sequence 100,000 genomes from around 85,000 patients affected by cancer or rare diseases (Wilson & Nicholls, 2015). The launch of the Precision Medicine Initiative in the United States in 2015 (Sankar & Parker, 2017) to create a centralised database of medical records from a diverse cohort of one million volunteers is another example of government support for developing personalised medicine.

2.1 Personalised Medicine in the Market

Oncology is the field that has been most impacted by the developments in precision medicine. However, personalised therapies in other therapeutic areas, including rare genetic disorders and diseases of the central nervous system, are slowly catching up. Although many of the approved precision treatments for cancer fall short of being

tailored to a specific individual, they allow for more detailed stratification of patients based on the oncogenic mutation of their tumours. Some common mutations are the human epidermal growth factor receptor 2 (HER2) in certain breast and stomach cancers and the epidermal growth factor receptor (EGFR) in lung cancer.

Advances in 'omic' technologies have led to the discovery of a variety of molecular-based targeted therapies. Monoclonal antibodies (mAbs), proteins with the ability to bind to a specific molecular target, are promising therapeutic candidates for cancer that offer low toxicity. Therapies based on monoclonal antibodies are the fastest-growing precision medicine. There are currently more than 20 Food and Drug Administration (FDA)-approved mAbs-based drugs in oncology alone (Lu et al., 2020). Some examples are Herceptin (trastuzumab) for HER-2, BRAF inhibitor Zelboraf (vemurafenib) (Plexxikon/Genentech), and EGFR inhibitor Tagrisso (osimertinib) (AstraZeneca Pharmaceuticals) (Schilsky, 2010). Monoclonal antibodies are also used in the treatment of autoimmune diseases (e.g., daclizumab for the treatment of multiple sclerosis or ustekinumab for psoriasis), infections (ibalizumab for HIV), bone loss (denosumab to treat osteoporosis), inflammatory diseases (adalimumab for rheumatoid arthritis), and haematological disorders (eculizumab for the treatment of paroxysmal nocturnal haemoglobinuria).

Next-generation sequencing technologies at the single-cell level have generated more precise information about novel drug targets and have resulted in the development of more personalised approaches. Regulators such as the FDA and the European Medicines Agency (EMA) have approved 'tumour-agonistic' treatments. The first and most famous example is Keytruda (pembrolizumab) (Merck) (Emancipator, 2020), which targets a genetic signature (a biomarker expressed in non-small-cell lung cancer) regardless of the tumour location.

More recently, genetically engineered chimeric antigen receptor (CAR) T-cell therapies have emerged as a promising step towards individualised cancer immunotherapy. The FDA has approved treatments such as Kymriah (Novartis) for children with acute lymphoblastic leukaemia and Yescarta (Kite Pharma) for adults with advanced lymphomas. In these treatment strategies, T cells are removed from the patient's blood and are modified to target tumour cell antigens before they are infused back into the bloodstream (Abreu et al., 2020). CAR T-cell therapies exemplify customised and personalised approaches to treat patients with relapse from malignancies that are resistant to treatment. So far, CAR T-cell therapies have demonstrated more successful responses to treatment compared with conventional therapies.

2.2 The Outlook for Personalised Medicine

The success of personalised medicine will depend on the integrity of data and a high level of understanding of the diseases and individual patients' needs. Data collection and analytics will play a big part in this process. Advances in genomics, diagnostic or predictive AI, genetic sequencing, and imaging data will be essential to gain more insight into disease processes. However, there will be many challenges to protect

the integrity of data due to its large volume and complexity. This also includes the transformation of the data that is another hurdle to overcome.

Another barrier in translating personalised therapies in the clinic is the high cost associated with the lengthy procedures of finding and validating specific biomarkers and analysis of vast amounts of data. Innovative trial designs and complex manufacturing processes (e.g., cell and gene therapies) are also very expensive. Promising innovations in CAR T manufacturing and potential 'off-the-shelf' T-cell production methods could help bring down the cost of these therapies in years to come and make them more accessible to a larger population of patients.

Uncertainty about regulation is another key factor that is hindering the translation of personalised medicine. Personalised medicine requires innovative clinical trial design with smaller sample sizes. This leads to difficulties with providing sufficient evidence of safety and efficacy, which limits eligibility for regulatory approval.

Addressing these barriers to personalised medicine, in combination with scientific advances in related fields such as digital health and artificial intelligence, will enable personalised therapies to reach their promised potential and reform the model of healthcare systems globally.

3 Gene Therapy

In the last two decades, cell and gene therapy has come of age, from theoretical conceptual approaches to patient-focused clinical practice. Cell therapy involves the treatment of diseases by modifying certain sets of cells or by transferring cells (either autologous or allogeneic) with a relevant function into the patient's body. Gene therapy involves the treatment of diseases by adding or replacing genes in cells or inactivating genes in cells. In gene therapy, the genetic material is transferred in a carrier or vector into the appropriate cells of the patient's body. Unlike traditional therapeutics, gene therapy assisted by emerging technologies, functional genomics screens, AI, machine learning, and human genetic locus associations can effectively introduce novel recombinant genetic material to increase the capability of cells and the immune system to fight or ameliorate infectious diseases, various types of cancer, and genetic disorders (Lostalé-Seijo & Montenegro, 2018).

Exogenous genetic material can replicate with the cell, and new cells can contain the same genetic material as the parent cell. The genetic material is transfected or transduced into cells via the negatively charged cell membrane. The genetic material may consist of negatively charged nuclei acids such as plasmid DNA to introduce protein expression, short-regulatory RNA or RNA interference to silence or knockout genes, messenger RNA (mRNA) to regulate protein expression, and antisense oligonucleotides to modulate gene expression (Tijsterman et al., 2002).

3.1 Gene Therapy and Gene Delivery

Gene therapy can be classified into two main categories depending on which types of cells are treated: somatic gene therapy, which does not pass the genetic change to the next generations, and germline gene therapy, which does pass the genetic change to the next generations (Tachibana et al., 2013). Although germline gene therapy may have great potential, it is accompanied by many bioethical considerations and its adoption has received criticism from the scientific community (Brokowski & Adli, 2020). At the time of writing, germline gene editing (for reproduction) is not allowed. Although many types of gene therapy are in clinical trials, the main therapeutic strategies that are used to treat several diseases and target specific populations of somatic cells are gene correction, gene addition, and gene silencing (Sung & Kim, 2019). Gene correction involves modifying part of a gene using gene editing technologies (e.g., CRISPR/Cas9) to replace a faulty region of DNA and produce a protein that functions properly. Gene addition can be achieved when a new copy of a gene is carried into the cells by an adeno-associated virus (AAV) to produce a protein. Gene silencing is a mechanism that regulates or prevents the production of a specific protein by degrading mRNA (Manjunath et al., 2013).

Depending on the type of the disease and the cells involved, genetic material can be administered either directly, i.e., in vivo, to the target cells that remain in the body of the patient or indirectly, i.e., ex vivo, where the cells are removed from the body of the patient and genetic material is delivered to the cells in vitro and are then introduced back to the patient (Hernandez-Alcoceba et al., 2016). Selecting the correct gene delivery system is important for the success of the gene therapy and requires an understanding of intracellular delivery, the target mechanism, and the long-term expression between the delivery system and the target cells. Although different types of gene delivery systems (vectors) that can be applied in gene therapy have been developed, all of them have certain limitations and side effects.

Most commonly, gene delivery systems are categorised as viral based, non-viral based, and hybrid (Cevher et al., 2012). Viral vectors have been successfully used over the last 50 years although these systems involve certain shortcomings such as cytotoxicity, immunogenicity, carcinogenicity, large-scale production limitations, and limited carrying capacity. The viruses involved are nonreplicating, meaning that they can induce host immune responses but cannot replicate in normal cells. The most frequently employed forms of viral vectors are retrovirus vectors, adenoviral vectors, lentivirus vectors, AAV vectors, herpes simplex virus vectors, and poxvirus vectors (Nayerossadat et al., 2012). It is worth mentioning that the success of virus vector-based gene therapies has a broader impact on the approval of new therapies that are constantly being proposed and investigated. Most recently, in response to the COVID-19 pandemic, AstraZeneca and Johnson and Johnson developed vaccines that use adenovirus vectors to carry double-stranded DNA to cells for transient spike protein expression (Moore, 2021).

Two gene therapies based on AAV vectors, Luxturna (Spark Therapeutics) (2017) and Zolgensma (Novartis) (2019), have been used to treat retinal dystrophy and

spinal muscular atrophy, respectively (Bulaklak & Gersbach, 2020). In Luxturna, a functional copy of the gene RPE65 (which is responsible for producing an enzyme that is necessary for the normal function of retinal cells) is administered in the subretinal space by injecting an AAV vector solution. Zolgensma utilises the novel AAV technology platform NAV AAV9 to deliver functional copies of the *SMN1* gene (which is responsible for producing a protein that is necessary for the normal functioning of the nerves that control muscle movement to neurons). Another example is Strimvelis (GlaxoSmithKline), which is approved in the EU. Strimvelis is indicated for the treatment of patients with adenosine deaminase deficiency and acts by transducing CD34+ cells with a retroviral vector to restore gene function and introducing them back to the patients.

Non-viral vectors have become a realistic alternative to viral vectors since they can effectively improve transfection and exhibit low host immunogenicity. In addition, they can lower the cost of large-scale production. Non-viral systems can be categorised into chemical and physical systems based on the method used to facilitate their uptake into the target cells. Chemical methods, which are more widely used than physical ones, include carriers prepared from natural or synthetic compounds that deliver the genetic material into the cells. This can often be facilitated through nanoparticle delivery using liposomes or cationic polymer complexes. We discuss these delivery systems and present examples of approved non-viral gene delivery products in more detail in the following section.

3.2 The Outlook for Gene Therapy

There are still many technical challenges that surround the global progress of cell and gene therapies as a mainstream clinical application. The primary obstacle to broader application of these therapies is the immune response to gene delivery vectors and transgenic products. It is necessary to further improve gene delivery methods to increase the efficiency and reduce the toxicity before their clinical implications can be realised.

Another challenge in the translation of gene therapy is the difficulty of evaluating these products. Regulatory agencies are still not fully on pace with their rapid development and the associated risks for the assessment of these products. Finally, most protocols developed for cell and gene therapies are specialised and require sophisticated facilities to prepare and administer gene therapies, which hinders their progress. There is an urgent need to review existing protocols with the goal of making cell and gene therapies more accessible to patients.

There will be a genuine attempt to bring curative cell and gene therapies to the market in the next decades. Most notably, the US National Institutes of Health and the Bill and Melinda Gates Foundation have recently committed to invest £160 million on research for advanced gene-based strategies for sickle cell disease and HIV. Using cell- and gene-based therapies to inactivate viruses, eliminate cancers, and treat inherited diseases is more likely than ever to be feasible in the long term.

4 Nanomedicine

Nanomedicine, as the name suggests, is a branch of medicine that uses nanotechnology to diagnose, prevent, and treat diseases. Nanomedicine uses a variety of structures, often referred to as nanocarriers, nanomaterials, nanoparticles, nanodrugs, or nanotherapeutics, that have at least one dimension in nanoscale. By leveraging the unique properties of materials in nanoscale, nanomedicine is offers new platforms in diagnostics and therapy through innovative routes such as targeted nanodrug delivery systems, nanorobots, and biocompatible nanoparticles for diagnosis, sensing, delivery, and actuation in living cells and organs.

Numerous materials compose the nanocarriers that deliver small-molecule drugs and biologics such as lipids, proteins, metals, or polymers. Depending on parameters such as composition, morphology, size, and surface charge, nanomedicine can be broadly categorised into (i) nanoparticles (e.g., lipid, polymeric, or inorganic nanoparticles and liposomes, where the active molecule is physically encapsulated in the delivery system), (ii) nanocrystals (where the active agent is shaped into crystalline nanoparticles in the presence of stabilisers for enhanced solubility and bioavailability of the drug), (iii) drug conjugates (where the active agent is chemically conjugated to the carrier system such as polymer-drug or antibody-drug conjugates), and (iv) polymer-protein conjugates.

Nanoparticles are ideal candidates for detecting and treating many diseases. They have the potential to act as vectors for gene therapy, carriers of multiple drugs, and tracking agents, for example. It has been reported that nanoparticles can improve the solubility and pharmacokinetic profile of drugs and enhance efficacy and reduce toxicity whilst providing enhanced selectivity and delivering lower dosages of drugs. Nanoparticles can also preserve the bioactivity of unstable biomolecules.

4.1 Nanomedicine in the Market

Nanomedicine is at the forefront of future healthcare. More than 50 nanomedicine formulations have been approved, and there is clear evidence of the potential for even more novel therapeutic approaches that can overcome unmet clinical needs, including the treatment of cancer and neurodegenerative and cardiovascular diseases.

Doxil (Padagis), a PEGylated liposome encapsulating doxorubicin (a potent chemotherapy agent), was the first marketed nanomedicine. The FDA approved it in 1995 for the treatment of several cancer types such as metastatic breast cancer and ovarian cancer. This was considered to be the dawn of the application of nanotechnology in medicine. It was followed by the development of other drug nanocarriers such as Myocet (Zeneus), Eligard (Tolmar Pharmaceuticals), Abraxane (Bristol Myers Squibb), and Genexol PM (Samyang Biopharm) (Anselmo & Mitragotri, 2016).

Eligard, which was approved in 2002, is a novel sustained released depot formulation of leuprolide acetate for hormonal therapy in prostate cancer. The formulation consists of a controlled-release (Atrigel: Reckitt Benckiser Pharmaceuticals) drug delivery system that consists of a biodegradable polymer polylactic-*co*-glycolic acid (PLGA) and *N*-methyl-2-pyrrolidone as a biocompatible solvent. It has been reported that this delivery system provides two times higher release rates of the drug than conventional depot formulations (Tombal & Berges, 2006). Abraxane is the first FDA-approved formulation to use nanoparticle-albumin-bound platform technology. Abraxane, a protein-based nanoformulation of paclitaxel, received its initial FDA approval for breast cancer therapy in 2005 (Wagner et al., 2006).

Nanoparticles with layered structures can provide the capacity to incorporate further components to enhance the nanoparticles' viability with different therapeutics and antibodies, including gene delivery systems. Nanoparticles with compartmentalised structures have emerged as an effective strategy for successful delivery of anticancer drugs due to the advantages of high surface area, high fluid permeation, and separation of incompatible drugs into physically distinct environments and the ability to tune drug-release rates via incorporation into controlled release polymers.

In 2017, the FDA approved a liposomal nanomedicine, Vyxeos (Jazz Pharmaceuticals), for the treatment of acute myeloid leukaemia. Vyxeos combines two chemotherapy drugs, cytarabine and daunorubicin, into a single nanoformulation at a synergistic ratio of 5:1 for enhanced efficacy whilst lowering the cumulative dose (Germain et al., 2020). The nanosystem allows for simultaneous and controlled delivery of two drugs with variable pharmacodynamic and biodistribution profiles at an optimal ratio that could not be reached if the two drugs were administered by any other method. It is anticipated that the success of this innovative approach will be reproduced with a variety of other combination therapies. Encapsulation of multiple drugs in nanocarriers could open more avenues in novel treatment for all ages and groups of patients, improve the performance of medicinal therapies already in the market, and reduce overall healthcare costs.

Nanomaterials in the form of nanocrystals can have therapeutic properties on their own without a delivery system. A recent example, Hasinfy, is a crystalline hafnium oxide nanoparticle that is functionalised with negatively charged phosphate coating. Hasinfy, which the FDA approved in 2019, is a new class of radiation-enhancing nanoparticles that represent the next generation of nanotherapeutics that complement and provide synergistic benefits to standard radiotherapy (Anselmo & Mitragotri, 2019).

4.2 Nanomedicine beyond Cancer

Most of the nanomedicine in the market has been approved for cancer treatment. This is due to the favourable passive targeting capability and the accumulation of nanoparticles through the enhanced permeability and retention effect at malignant tumours. However, a variety of other treatments have benefited from recent advancements in the field such as treatments for fungal infections and macular degeneration,

iron-replacement therapies, and the treatment of rare genetic diseases (Gadekar et al., 2021).

An early example is AmBisome (Gilead Sciences), a liposomal nanoformulation of amphotericin B for the treatment of fungal infection, which the EMA approved in 1997. In 2000 the FDA and the EMA approved another liposomal nanoformulation for treatment of neovascularisation from age-related macular degeneration, Visudyne (Novartis), encapsulating verteporfin through photodynamic therapy (Bressler & Bressler, 2000).

Onpattro (Alnylam Pharmaceuticals) is the first lipid nanoparticle formulation that contains small interfering ribonucleic acid (siRNA), which the FDA approved in 2018. Onpattro is prescribed for the treatment of a rare disease, hereditary transthyretin amyloidosis-induced polyneuropathy. The approval of this nanoformulation as the first platform technology for delivering nucleic acids is a great accomplishment in the field of nanomedicine for non-viral vector gene therapy (Adams et al., 2018). This nanoformulation and similar approaches could make gene-based therapies readily available to patients if the challenges with their delivery can be addressed.

As mentioned previously, genes and nucleotide-based drugs have great potential in future advanced medicinal therapies. However, they still pose specific limitations in delivery through systemic routes. They rapidly degrade in vivo and cannot reach the target site, whilst their uptake into cells is electrostatically hampered as they are often negatively charged. Hence, they require both protection and stealth carriers in order to enter organs and cells. Onpattro was designed to efficiently encapsulate siRNA in a lipid nanoparticle. Onpattro also prevents in vivo degradation of siRNA and enables it to escape endosomal clearance and delivers it within the cell cytoplasm.

Following the success of the approved nanoformulations currently in the market and the high number of ongoing clinical trials in nucleic acid-based nanomedicine, including mRNAs, it is expected that several new products will reach the market in the coming years. In fact, the COVID-19 pandemic unleashed new possibilities for nanomedicine therapies to be taken more seriously by the pharmaceutical industry and regulatory bodies. Vaccines developed by Moderna and Pfizer-BioNTech using lipid-based nanoparticles as delivery vehicles were given to millions of people around the world as a preventative measure against the infectious SARS-CoV-2 virus (Balkrishna et al., 2021). The development of mRNA-based vaccines at an extraordinary speed highlights the importance of mRNA-based nanomedicine for delivering solutions in a variety of other fields such as regenerative medicine, gene therapy for genetic disorders, cancer vaccines, and protein-replacement therapies.

Nanomedicine is not limited to the delivery of drugs and genes. Many nanomedicine products have been approved and are being developed for early-stage disease diagnosis and imaging. One clinically approved imaging nanomedicine is Magtrace (Mammotome|Danaher Corporation), a non-radioactive magnetic tracer that contains superparamagnetic iron oxide nanoparticles for sentinel lymph node biopsies in breast cancer (Hersi et al., 2019). Other examples for diagnostics such as iron oxide nanoparticles for PET/MRI scans (Thomas et al., 2019) or

liposome/nanoparticles containing radiomarkers (e.g., ^{99}Tc and ^{111}In) for single-photon emission computed tomography (SPECT) and PET analysis (Thomas et al., 2019) are currently in clinical trials. It is anticipated that nanomedicine will be a key player in future disease diagnostics.

The landscape of nanomedicine is undergoing a radical change. With more than 30% of the clinical trials under investigation focusing on applications other than cancer, it will not be very long until new nanomedicine products emerge for other diseases such as genetic disorders, central nervous system diseases, and infectious diseases.

The application of nanotechnology in medicine goes beyond therapeutic interventions. The unique properties of nanomaterials (mechanical, electrical, optical, and acoustic) offer cross-disciplinary solutions in healthcare. For instance, nanosensors are currently being developed and approved for diagnosing and controlling diseases (Munawar et al., 2019). Nanosensors have great potential for accurately detecting biomarkers in cancer and infectious diseases (e.g., Zika, Ebola, and COVID-19).

4.3 The Outlook for Nanomedicine

Despite the advances in the field and the recent emergence of nanomedicine products in the market, the uptake of nanomedicine is very slow. This is attributed to many challenges, including safety, regulatory hurdles, cost, reproducibility, and issues with scaling up that need to be resolved before nanomedicine can enter the market on a larger scale.

Synthesizing multifunctional nanoparticles requires several steps that pose challenges for large-scale good manufacturing practice (GMP) production that lead to an increase in the cost of manufacture. Current technologies that process nanoparticles are not automated, and the various stages of the synthesis cannot be isolated. Conventional small-scale batch reactors are utilised for the synthesis of nanoparticles. These reactors are poorly controllable and are not well characterised and suffer from insufficient mixing and low heat and mass transfer rates. This can lead to low reproduction efficiency, upscaling issues, and inability to decouple the manufacturing stages in real time.

The lack of regulatory and safety guidelines is another major hurdle for the translation of nanomedicine. Even though nanomedicine products have been in the market for two decades, the regulations that are used to ensure their quality, safety, and efficacy in clinical use are no longer appropriate. The development of standard protocols for testing complex formulations and a suitable regulatory framework for evaluation are necessary before nanomedicine can be translated to the clinic.

The shorter or alternative treatment schedules, better outcomes, and lower toxicity that nanomedicine offers would have a major impact on the accessibility and delivery of therapy and outcomes. The potentially curative nature of nanomedicine and the breakthroughs in new targeting treatments require the pharmaceutical

industry to recalibrate its model for developing therapies and to push the boundaries beyond traditional therapeutic approaches.

5 Tissue Engineering and Regenerative Medicine

One of the global healthcare challenges is improving the quality of life for a diseased and aging population. This can be done through innovative solutions such as tissue engineering and regenerative medicine. Regenerative medicine is an emerging field of medicine aimed at restoring and establishing structure and function of lost or damaged organs and tissues. Current transplantation therapies suffer from lack of donor supplies and from severe immune complications post-transplantation. Regenerative medicine is the next frontier in minimising the risks of organ rejection and accelerating patients' recovery post-transplant.

Regenerative medicine owes its success to the advances in tissue engineering that have led to the discovery of novel biomaterials that can support cell transplantation and proliferation. Tissue-engineered biomaterials combined with cells can mimic the native extracellular matrix of tissues and the in vivo environment of cells, making enhanced cell proliferation and improved differentiation possible. Tissue engineering assembles cells, scaffolds, and biologically active molecules (e.g., growth factors) to regenerate or replace damaged/diseased tissues.

Regenerative medicine combines tissue engineering with other approaches such as immunomodulation, nanomedicine, and gene- and cell-based therapy to induce restoration. It involves interventions that use cells as the central units of reconstruction. The cells used in regenerative medicine are typically differentiated cells that maintain proliferation capacity and are classified as autologous (the patient's own cells) or allogeneic (donor cells). Whilst both therapies use the same common technologies to promote cell growth, the scale is different. Autologous cells are custom products derived from harvested tissue of the patient, and the treatment is often delayed by the cell culture expansion process. Personalised medicine can easily be adapted to this type of cell therapy. Allogeneic cell sources, on the other hand, can be obtained 'off the shelf' and can be mass-produced to treat many patients (Mao & Mooney, 2015). Sufficient amount of time is available to quality control these products prior to administration, and therefore, the risk of an adverse immune reaction is diminished with allogeneic therapies.

5.1 Regenerative Therapies in the Market

Various factors are driving the growth of the regenerative medicine market. The widespread use of organ transplantation and the prevalence of chronic diseases and genetic disorders as well as an increase in the size of a geriatric population with musculoskeletal, dermatological, oncological, and cardiovascular diseases are contributing to the expansion of the market for regenerative medicine.

Carticel (Vericel Corporation) is the first biologic product the FDA has approved in the orthopaedic field. It uses autologous cultured chondrocytes to treat focal articular cartilage defects. The autologous chondrocytes are derived from in vitro expansion of the cells harvested from the patient's normal femoral cartilage. The expanded cells are then implanted at the site of injury, resulting in recovery of tissue that is comparable to results from conventional techniques. This technology was followed by the FDA approval of Maci (Vericel Corporation) in 2016, for the repair of symptomatic cartilage defects of the knee. Maci is the first approved product that utilises tissue-engineering scaffolds to grow cells from healthy cartilage tissue from the patient's own knee. Autologous cultured chondrocytes are implanted on a matrix from biodegradable porcine membrane (Vinatier & Guicheux, 2016).

Apligraf (Organogenesis) is another example of a commercially available advanced tissue-engineering composite. Apligraf is a bioengineered skin substitute for treating chronic wounds, including diabetic foot ulcers and venous leg ulcers. The tissue-engineering graft consists of allogeneic cells and contains a dermal layer of neonatal fibroblasts in a bovine type I collagen lattice and an epidermal layer containing human keratinocytes (Zaulyanov & Kirsner, 2007).

The first FDA approval for regenerative medicine in dental care was Gintuit (Organogenesis). Similar to Apligraf, Gintuit is an allogeneic cellular biodegradable scaffold containing fibroblast/keratinocyte therapy derived from neonatal foreskin that artificially creates a vascular wound bed to treat mucogingival conditions. Clinical data demonstrated that Gintuit regenerates 2 millimetres of gum tissue although the mechanism of action is not clear (Schmidt, 2012).

Benefiting from a 5-year regulatory 'free-for-all' in regenerative medicine in Japan, HeartSheet (Terumo) was conditionally approved in 2015 (McCabe & Sipp, 2016). HeartSheet is an autologous skeletal myoblast product that uses cell sheet technology and has been authorised for use in patients with serious heart failure. HeartSheet was one of the three treatments that received approval under the Pharmaceutical and Medical Devices Act that was introduced in Japan in 2014. The law allows for conditional approval of treatments that have gone through some (limited) clinical testing (Sipp, 2015). This provides the opportunity to market the product nationally under the condition that extra data should be collected over a 7-year time frame.

5.2 The Outlook for Regenerative Medicine

Even though there are various attempts globally to develop stem cell therapies for conditions like heart failure and other chronic diseases (e.g., Parkinson's), no approved therapies for these conditions have garnered widespread adoption. Despite the large research and development funding opportunities and initiatives that governments (e.g., Japan's Pharmaceutical and Medical Devices Act) have introduced that are more lenient towards accelerated regulatory approval, very few products are available to patients. The lack of regenerative medicine products in the

market and clinics is a major drawback that is primarily caused by scarcity of data on treatment outcomes and strict regulatory controls by health authorities.

Tissue engineering and regenerative medicine are still in their infancy, and there are numerous fundamental aspects to be addressed such as the selection of cell sources, assembly of complex organs, design of tissue-specific materials, and the development of specialised bioreactors. In addition, manufacturing regenerative medicine products involves multiple challenges that include the high cost of product development, complex and inefficient operations, and difficulty maintaining uniform cell quality. Finally, the mechanisms for forming new tissues or organs with tissue-engineered materials in vivo are still poorly understood. Tissue-engineered materials could reach their full potential in clinical applications if these limitations can be overcome.

The expansion of tissue engineering and the regenerative medicine field can be further supported by combining different disciplinary approaches, including stem cell biology, functional biomaterials, nanotechnology, and, most recently, additive manufacturing (e.g., 3D bioprinting) and by the use of AI. A better understanding of the patient's disease state, age, and microbiome that includes data supported by precision medicine will likely help with the advancement of the field. Finally, 3D cell culture and tissue models of disease and novel organ-on-chip technologies will allow more realistic preclinical testing of regenerative medicine approaches and facilitate the translation of promising approaches to the clinic (Han et al., 2020). Regenerative medicine offers revolutionary therapeutic approaches to treating devastating diseases in cases where a cure is not offered by conventional treatments. Innovations in this field could potentially address chronic diseases and eliminate the ongoing drug therapy demands.

6 Conclusions

Novel therapies such as tissue-engineering products, gene and cell therapies, and nanomedicine are growing rapidly. Targeted therapies and personalised medicine have paved the way for new clinical trial methodologies. Even though these innovative advanced therapy products are still in the early stages of development, it is highly likely that they will reach the market earlier than anticipated. Due to their complex nature, there is a need for extensive and complex preclinical and clinical developments. Regulatory uncertainty, complicated manufacturing processes, and the high cost of manufacture are common barriers for these products reaching the market. However, as these novel interventions offer the potential to cure severe chronic conditions and currently incurable diseases, the processes involved in their translation into the market are also changing and the industry and regulatory bodies are keen to adopt new strategies for their approval. Therefore, it is possible that patients could have access to these alternatives in the near future.

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