



Tissue Engineering and Photodynamic Therapy: A New Frontier of Science for Clinical Application -An Up-To-Date Review

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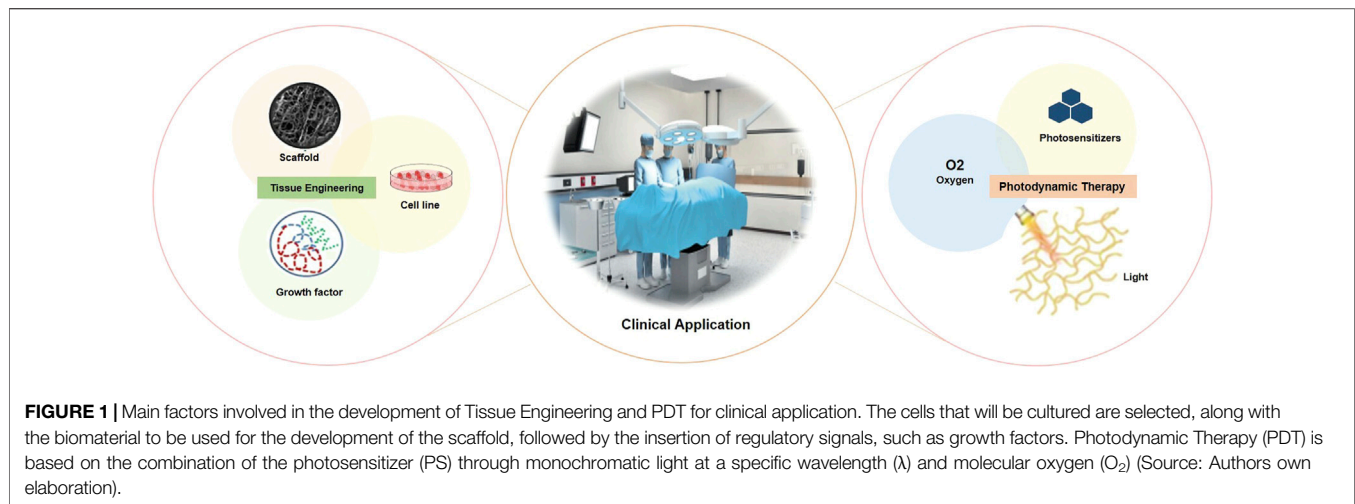
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Tissue engineering (TE) connects principles of life sciences and engineering to develop biomaterials as alternatives to biological systems and substitutes that can improve and restore tissue function. The principle of TE is the incorporation of cells through a 3D matrix support (scaffold) or using scaffold-free organoid cultures to reproduce the 3D structure. In addition, 3D models developed can be used for different purposes, from studies mimicking healthy tissues and organs as well as to simulate and study different pathologies. Photodynamic therapy (PDT) is a non-invasive therapeutic modality when compared to conventional therapies. Therefore, PDT has great acceptance among patients and proves to be quite efficient due to its selectivity, versatility and therapeutic simplicity. The PDT mechanism consists of the use of three components: a molecule with higher molar extinction coefficient at UV-visible spectra denominated photosensitizer (PS), a monochromatic light source (LASER or LED) and molecular oxygen present in the microenvironment. The association of these components leads to a series of photoreactions and production of ultra-reactive singlet oxygen and reactive oxygen species (ROS). These species in contact with the pathogenic cell, leads to its target death based on necrotic and apoptosis ways. The initial objective of PDT is the production of high concentrations of ROS in order to provoke cellular damage by necrosis or apoptosis. However, recent studies have shown that by decreasing the energy density and consequently reducing the production of ROS, it enabled a specific cell response to photostimulation, tissues and/or organs. Thus, in the present review we highlight the main 3D models involved in TE and PS most used in PDT, as well as the applications, future perspectives and limitations that accompany the techniques aimed at clinical use.

Keywords: tissue engineering, bioprinting, skin model, photodynamic therapy, photobiostimulation

INTRODUCTION

Tissue engineering (TE) is an interdisciplinary field, integrating engineering and medicine, that purpose to develop biological substitutes that will replace, repair or improve tissues and organs (Hasan et al., 2018). In 1970s was the first time that the concept of tissue engineering was introduced, by a pediatric orthopedic surgeon at Boston Children's Hospital, W. T. Green, who performed several



experiments aimed to generate cartilage from chondrocytes seeded in bone spicules (Melville et al., 2019). Twenty years later, TE was described by Robert Langer and Joseph Vacanti as “an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function” (Melville et al., 2019). In 2003, the Tissue Engineering Regenerative Medicine International Society was created, representing a huge milestone for the field, uniting scientists from all over the world to share and collaborate on their research, resulting in significant improvements (Melville et al., 2019).

TE is a field that is growing rapidly, providing new tools to manage complex diseases, and is a promising alternative to tissue harvesting, artificial tissues, and prostheses, since there are still high levels of graft rejection, low availability or unavailability of organ donation (Bodnar et al., 2018; Blum et al., 2021). In **Figure 1** is shown the three factors that are essential for successful tissue regeneration, a combination of scaffolds or a framework, cell signaling and cells (Melville et al., 2019). To create a microenvironment of the human body, an extracellular matrix (EMC) is required, forming the basis of all organs and tissues ((Maheshwari et al., 2019).

In this scenario, 3D cell culture creates a microenvironment that can simulate the EMC found in the human body, taking into account morphological, biochemical, and mechanical factors (Fitzgerald et al., 2015; Asadi et al., 2020).

3D cell culture method enables *in vivo* conditions can be mimicked (Shao et al., 2021). For this, 3D cell culture using scaffolds has been improved in order to simulate the complexity of tumors *in vivo* (Shao et al., 2021). Therefore, the 3D models developed provide soluble gradients and allow the distribution of adhesions in all three spatial dimensions without polarity (Herrerros-Pomares et al., 2021; Shao et al., 2021).

There are several types of platforms for 3D culture such as cell biology-based models (spheroids and organoids) and engineering-based models (scaffold and microfluidic platforms), cell biology-based have the advantage of having a greater similarity in the early details of cell development *in vivo*, while engineering-based models have better organization and

composition of materials to develop ideal conditions important in tissue reconstruction (Zhuang et al., 2018). The methods approached through TE are limited mainly by the lack of appropriate techniques to develop physiological architectures that can mimic the EMC, in addition to the lack of control of cellular functions and their numerous properties (Hasan et al., 2018).

Photodynamic Therapy (PDT) is a minimally invasive therapeutic modality used for the treatment of several diseases, including cancer and non-malignant lesions (Mohammad-Hadi et al., 2018). Raab and von Tappeiner first introduced the term “photodynamic effect” into the literature through studies that showed that certain classes of dyes can sensitize microorganisms when exposed to sunlight, leading to cell death (Kessel, 2019). The advances were even greater when a group of physicians from the Mayo Clinic demonstrated that by employing a hematoporphyrin derivative, the fluorescence in the tumor tissues tended to increase, and the acronym “HPD” was used to refer to the material (Kessel, 2019). After numerous advances in the field, the terminology “Photodynamic Therapy” was introduced, based on the words used by von Tappeiner (Kessel, 2019).

The mechanism used by PDT consists in the interaction between a photosensitizer (PS) and a specific wavelength (**Figure 1**) of light in the presence of oxygen. The interaction leads to the formation of reactive oxygen species (ROS) and free radicals, such as singlet oxygen (1O_2), that lead to the destruction of the target cells or tissue (Qidwai et al., 2020; Sun et al., 2020). Generally, studies using PDT is performed in monolayer, in other words, two-dimensional (2D) *in vitro* models, with advantages related to simplicity of application and reliability (Wu et al., 2020a; Demir Duman et al., 2020). However, the use of these models ultimately misses the cellular interactions with the EMC and does not reproduce the microenvironment correctly (Demir Duman et al., 2020). The use of animal studies also has limitations, such as the cost and the time of the experiment, which are usually long. In order to circumvent these factors in both techniques, more and more investment is being made in 3D culture models, where the microenvironment is optimally

reproduced (Demir Duman et al., 2020). A direct advantage related to the use of PDT and his dependence on oxygen, is that the use of 3D models can incorporate the hypoxia that occurs in several tissues, like cancerous tissue (Demir Duman et al., 2020).

The present article seeks to provide a broad review of Tissue Engineering and Photodynamic Therapy, highlighting the main 3D models involved in TE and the most commonly used photosensitizers in PDT, as well as the applications, future prospects, and limitations that accompany both techniques.

TISSUE ENGINEERING

Background

The advent of tissue engineering (TE) represents the intersection of a distinct areas, including clinical medicine, engineering and science, for the development of biological models that can be applied to improve, maintain or restore of tissue structures that were deteriorated or lost due to diseases such as cancer or trauma (Langer and Vacanti, 1993).

In this context, one of the first publications found in PubMed referring to the term tissue engineering was described Bell and colleagues in 1981, they designed a tissue-engineered 3D human skin equivalent composed by dermal and epidermal layers (Bell et al., 1981). In 1984, the accidental development of an endothelium-equivalent membrane under the surface of a long-established synthetic ophthalmologic prosthesis was described (Wolter and Meyer, 1985).

After understanding the concept of tissue engineering, it is necessary to show how the 3D based models are composed. In this sense, the basic components of Tissue Engineering are: cell sources and management, development of scaffolds and substances that induce cell growth and differentiation (Guiro and Arinzeh, 2015; Hapach et al., 2019).

Components of Tissue Engineering

The cell sources (not necessarily stem cells) used in TE that include autologous (differentiated cells), allogeneic (differentiated cells), adult stem cells/progenitors, embryonic stem cells (Al-HimDani et al., 2017).

There are several established techniques for developing TE-based 3d models to mimic current *in vivo* conditions. The models can be divided into cells cultivated as multicellular aggregates (spheroids) and cells incorporated in supports of natural or synthetic origin (scaffolds) (Guiro and Arinzeh, 2015; Naahidi et al., 2017; Brancato et al., 2020). The choice of scaffold must be carefully evaluated. The ideal scaffold should provide an architecture that allows for the attachment, migration, proliferation and differentiation of cells while enabling cell reorganization into a functional 3d network (Ceylan and Bölgen, 2016; Lanza et al., 2020).

Scaffolds of natural origin have the advantage of having better biocompatibility, less toxicity and can be prepared from natural polymeric materials, such as collagen, chitosan, glycosaminoglycans, fibroin, agarose, alginate and starch (Colley et al., 2011; Lv et al., 2017; Pal et al., 2019). While

scaffolds of synthetic origin have greater versatility, ease of reproduction and therefore can be processed more easily than those of natural origin, and can be formed from polyglycolic acid, polylactic acid, polyorthoester and their copolymers or blends, as well as the aliphatic polyester polycaprolactone (Colley et al., 2011; Lv et al., 2017; Pal et al., 2019). There are also scaffolds based on ECM: allogeneic, xenogenic acellular dermis and others (Colley et al., 2011; Lv et al., 2017; Pal et al., 2019).

There are several advantages of scaffold-free 3D cell cultivation, such as the possibility of co-culture; low cost and high throughput screening approach. On the other hand, the absence of a scaffold makes it impossible for the cell-cell and cell-ECM interactions to be mimicked *in vitro*, as well as the control over the size of the spheroids/organoids obtained (Brancato et al., 2020). On the other hand, scaffolds can overcome some of these limitations, as it is possible to be cultivated in co-culture, there is a wide variety of materials, as well as a decellularized matrix, possibility of customization and the commercial availability of scaffolds. Despite all the advantages of scaffolds it must be considered that depending on the manufacturing technique the cost can be high, cell removal can be difficult in the case of scaffolds based on MEC, and the high-throughput screening options limited (Guiro and Arinzeh, 2015; Naahidi et al., 2017; Pal et al., 2019; Brancato et al., 2020).

Approaches and Methods Available for Designing 3D Culture Models

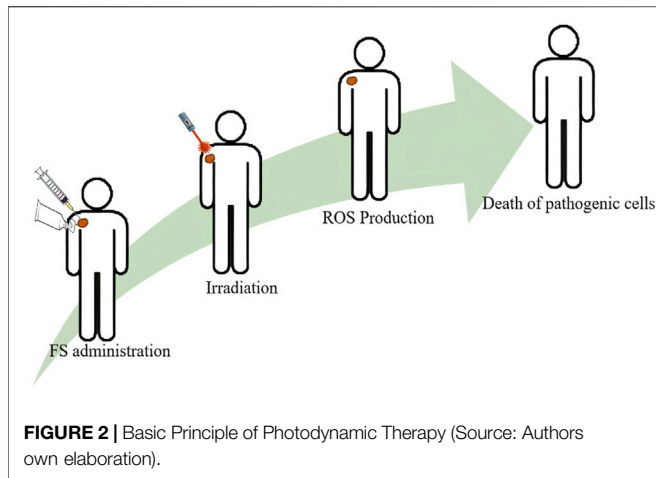
The *in vitro* study models are mostly based on cell culture in two dimensions (2D), since the investigation in these models is more accessible and can be easily reproduced (Ceylan and Bölgen, 2016). However, 2D systems have several limitations, as they do not have the necessary complexity in their structural organization, in addition to the absence of connective tissue, essential factors to mimic the model/target organ (Song et al., 2014). In addition, 2D model studies often show false-positive responses, so it is necessary to use *in vivo* models to confirm the result. However, the use of animals has ethical dilemmas and costly procedures (Alemany-Ribes et al., 2013; Doke and Dhawale, 2015).

In this sense, the search for advanced models for alternative biological tests becomes indispensable. The developed models can be used for various purposes, from studies mimicking healthy tissues and organs as well as to simulate and study different pathologies (Guiro and Arinzeh, 2015).

In this sense, the search for advanced models for alternative biological tests becomes indispensable. The developed 3D models can be used for various purposes, such as studies mimicking healthy tissues and organs, simulation and study of different pathologies, as well as drug delivery assessment (Groeber et al., 2016; Magdeldin et al., 2017; Bourland et al., 2018; Nishiguchi et al., 2018; Grifno et al., 2019; Pal et al., 2019; Woappi et al., 2020).

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is a therapeutic method that has been used in the treatment of several diseases, either as a single



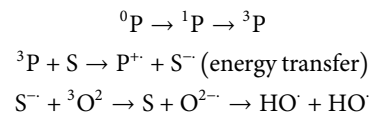
therapy or as a complement to conventional therapeutic protocols. This therapy is widely accepted by patients because it is less invasive than conventional ones, in addition to having few side effects and pain reduction. In addition, due to its therapeutic simplicity, it allows application in an outpatient setting, without the need for surgery (Li et al., 2017; Luo et al., 2017). The PDT mechanism is based on the correct combination of three components: photosensitizer (PS), monochromatic light at a specific wavelength (λ) and molecular oxygen (O_2) dissolved in a biological medium, PS is administered systemically, topical or oral, followed by exposure to visible light, resulting in a series of reactions that result in the death of target pathogenic cells (Figure 2), the three components do not show toxicity when separated (Calixto et al., 2016). After the internalization of the PS in the cells, irradiation is performed with a laser or LED at the wavelength where PS has greater energy absorption, the PS absorbs this energy and is excited to the singlet and triplet excited states, followed by an energy transfer to O_2 , which leads to the production of reactive oxygen species defined as ROS that attack specific centers within cell systems, triggering the

death of these tissues by processes of cell necrosis and/or apoptosis (Dai et al., 2012).

After the absorption of a photon of light, PS leaves the lower energy ground state (S^0) and passes to the higher energy singlet state (S^1-S^n), PS tends to return to the lower energy state, with this, part of the absorbed energy is used to return to the S_0 state, through the physical relaxation process known as internal conversion or by radiative processes such as fluorescence emission (Figure 3) (Benov, 2015). However, part of the energy can be transferred by the Intersystem conversion mechanism, where the PS passes from the excited states S^1/S^n and occupies the triplet excited state (T^1) of lower energy which can also be returned directly to S_0 by the internal conversion process or through the radiative process of emission of phosphorescence, or triggering a series of photochemical interactions that give rise to two known photodynamic mechanisms (Type I and II) (Foot, 1991; Kwiatkowski et al., 2018).

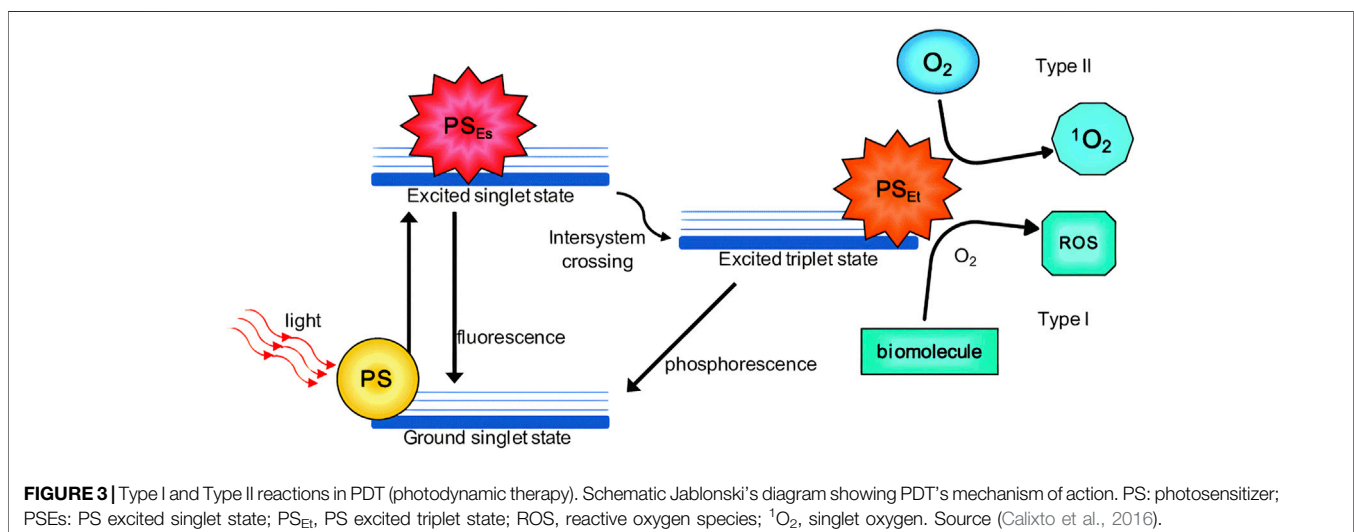
In the Type I mechanism, PS is in the T_1 state, there is a transfer of energy to the biomolecules or the abstraction of a hydrogen atom can also occur, in both cases these reactions result in the formation of free radicals or radical ions, in turn, these reduced species can transfer electrons to molecular oxygen diffused in the medium (which is in its triplet state), which leads to the generation of reactive oxygen species (ROS), hydrogen peroxides, anion superoxides. These reactions are outlined below (Benov, 2015).

Type I mechanism–Redox reactions with biomolecules



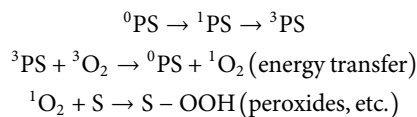
P = photosensitizer; S = organic substrate; + = cation and - = anion.

In the Type II mechanism PS in the T^1 state can transfer energy directly to molecular oxygen. This is possible due to the fact that molecular oxygen is also found in the T^1 conformation in



its ground state, thus forming the reactive species in the singlet state, which has strong oxidizing properties, outlined below (Benov, 2015; Tedesco et al., 2017).

Type II Mechanism—Mediated by the production of $^1\text{O}_2$, as an example, lipid peroxidation.



PS = photosensitizer and S = organic substrate.

In both mechanisms, a series of product responses are initiated, causing different effects and biological responses, such as oxidative stress to pathological tissue, and cell damage followed by death (Foot, 1991; Tedesco and Jesus, 2017).

General Approach to Photosensitizers

PS are one of the three crucial elements of PDT, PS are natural or synthetic molecules capable of absorbing energy and transferring this energy to neighboring molecules (Tedesco et al., 2017). PS have been used to treat disease for over 4,000 years ago. The ancient Egyptians used plants and solar light for vitiligo treatment. However, the advancement of PDT came with the emergence of first-generation PS, the derivatives of hematoporphyrin, its commercial forms called Photofrin, Photosan, Photogen and Photocarcinorin (Sternberg et al., 1998). Although these PS have been widely used in experimental clinical studies, they have some disadvantages, such as low solubility in aqueous media, low selectivity for pathogenic tissues, difficulty in purifying molecules and skin sensitivity (Dobson et al., 2018; Imberti et al., 2020).

These limitations of the PS stimulated the development of the second generation of PS with greater efficiency in ROS generation. The main characteristics of good PS are: high selectivity for pathogenic tissue, high production of singlet oxygen and free radicals, absence of dark toxicity and high absorption in the 600–800 nm wavelength region (Zhang et al., 2018). The second generation PS group is currently composed of hematoporphyrin derivatives, synthetic SF such as 5-aminolevulinic acid, benzoporphyrin derivatives, texaphyrins, thiopurine derivatives, chlorin and phthalocyanines (Agostinis et al., 2011). The 5-aminolevulinic acid (ALA) a precursor of protoporphyrin IX and which works as a pro-drug has become an important discovery for PDT. ALA becomes a PS only after its transformation into protoporphyrin, so this pro-drug can be used in various administration routes such as topical or oral (De Rosa and Bentley, 2000; Morton, 2002). Second-generation PS overcame the disadvantages of first-generation PS, such as greater chemical purity, greater tissue permeation, greater singlet oxygen production, decreased side effects, thus increasing selectivity for pathogenic tissues and faster elimination of PS from the body, however, the main disadvantage of these new PS is their low solubility in aqueous media, which becomes a very limiting factor regarding the administration of these PS, which requires the use of new methods for the delivery of this PS (Kwiatkowski et al., 2018).

The third generation photosensitizer emerged with the interest to improve the selectivity of therapy, this new generation is based on the

organic synthesis of new molecules with greater affinity to the pathogenic tissue, in addition to having the objective of expanding the administration routes of these photosensitizers (Kwiatkowski et al., 2018; Quina and Silva, 2021). Has been carried out by combining second-generation photosensitizers with receptor molecules to the desired target, such as proteins or lipoproteins that are used by pathogenic cells for their proliferation, monoclonal antibodies targeting a specific antigen of the target cell, surface markers such as, growth factors, hormones, or transferrin receptors (Muehlmann et al., 2014; Zhang et al., 2018). These strategies allow greater delivery of the photosensitizer to the target tissue, that is, greater selectivity, which improves the effectiveness of PDT, in addition to decreasing the doses needed for desired therapeutic responses (Calixto et al., 2016; Zhou et al., 2021).

TISSUE ENGINEERING AND PDT APPLICATIONS

PDT has mainly emerged as a new alternative treatment to conventional anti-cancer therapies that cause various side effects (Zhang et al., 2018). In the last 3 decades, several types of PS have been applied in pre-clinical and clinical studies (Table 1). In addition to some of these molecules reaching the market and showing great efficacy in the treatment of different types of cancer (Zhang et al., 2018).

Although the initial focus of the use of PDT was the treatment of several types of cancer, PDT can also be used in the treatment of many other diseases (Yoo et al., 2021). Table 2 presents a summary of some clinical and preclinical studies for non-cancer diseases that use PDT as a treatment.

There is a lot of effort to use PDT for the treatment of different types of diseases (Yoo et al., 2021). For that reason, it is extremely important to know the PS that has currently been employed in order to verify if there is potential for a new therapeutic application (Kou et al., 2017).

TE is an area in constant expansion and its use in association with PDT has shown promising results in some studies, especially in studies involving antitumor therapy (Table 3).

In the study by Cramer et al. (2019) a 3D model of malignant pleural mesothelioma (MPM) was developed to assess the effect of PDT using a 1st generation PS, Photofrin. First, they tested different combinations of scaffolds for cell growth: 1) agarose; 2) agarose-collagen type I; 3) agarose overlay preceded by hanging-drop; 4) GFR-matrigel. They observed that the combination containing collagen provided cell growth on the 7th day. However, some of the cell lines used did not grow under these conditions. The opposite was observed in GFR-Matrigel, cell growth was more efficient and consistent than the other combinations. Therefore, a 3D model containing Matrigel and type I collagen was used to evaluate the effect of PDT-Photofrin. For this, the protocol involved the use of erlotinib, an inhibitor of epidermal growth factor (EGFR) in order to confirm the hypothesis that this inhibition could improve the outcome of PDT. They concluded that the 3D model obtained can be used for future studies, allowing the analysis that the use of erlotinib was able to improve the cytotoxicity of PDT-Photofrin (Cramer et al., 2019).

TABLE 1 | Photosensitizers investigated in clinical trial for cancer treatment^a (Chen et al., 2001; Pogue et al., 2001; Cramers et al., 2003; Agostinis et al., 2011, 2012; Lamberti et al., 2014; Bacellar et al., 2015; Spring et al., 2016; Banerjee et al., 2017; Kwiatkowski et al., 2018; Dos Santos et al., 2019).

| Photosensitizer | Chemical family | Cancer type |
|---|---------------------|---|
| Porfimer sodium, HPD: hematoporphyrin derivative (Photofrin) | Porphyrin | Lung, Esophagus, Bile Duct, Bladder, Brain, Ovarian, Breast Skin Metastases |
| 5-ALA: 5-aminolevulinic acid (Levulan) | Porphyrin Precursor | Skin, Bladder, Brain, Esophagus |
| MAL: methyl-aminolevulinate (Metvix) | Porphyrin Precursor | Skin |
| h-ALA: hexylaminolevulinate (Hexvix) | Porphyrin Precursor | Basal Cell |
| Veteporfin, BDP: benzoporphyrin derivative (Visudyne) | Porphyrin | Pancreas, Breast, Ophthalmic, Skin |
| Palladium bacteriopheophorbide, padeliporfin, WST-11 (Tookad) | Porphyrin | Esophagus, Prostate |
| Temoporfin, mTHPC: meso-tetrahydroxyphenylchlorine (Foscan) | Chlorin | Head And Neck, Lung, Brain, Bile Duct, Pancreas Skin, Breast |
| Talaporfin, mono-L-aspartyl chlorin e6, NPe6, LS11 (Laserphyrin) | Chlorin | Liver, Colon, Brain, Lung, Breast Skin Metastases |
| HPPH: 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a (Photochlor) | Chlorin | Head And Neck, Esophagus, Lung |
| Rostaporfin, SnEt2: tin ethyl etiopurpurin I, or (Purlytin) | Chlorin | Skin, Breast |
| Fimaporfin, disulfonated tetraphenyl chlorin, TPCS2a (Amphinex) | Chlorin | Superficial Cancers, Cholon |
| Motexafin lutetium (Lutex) | Texaphyrin | Breast |
| Foscan (mTHPC) | Chlorine | Head And Neck, Lung, Brain, Skin, Bile Duct |
| Purlytin (SnEt2) | Chlorin | Skin, Breast |
| Taloporfin, LS11, MACE, Npe6 | Chlorin | Liver, Colon, Brain |
| Fotolon (PVP-Ce6), Radachlorin, Photodithazine | Chlorin | Nasopharyngeal, Sarcoma, Brain |
| Silicon phthalocyanine (PC4) | Phthalocyanine | Cutaneous T Cell Lymphoma |
| Padoporfin (TOOKAD) | Bacteriochlorin | Prostate |

^aAdapted from (Agostinis et al., 2012; Dos Santos et al., 2019).

TABLE 2 | Photosensitizers investigated in clinical and preclinical trials for non-cancer diseases treatment.

| Applications | Diseases | Photosensitizer | References |
|--------------------------|--|--|--|
| Dermatologic Disease | acnes, warts, photoaging, psoriasis, vascular malformations, cutaneous leishmaniasis, onychomycosis, hirsutism, keloids, alopecia areata | 5-Aminolaevulinic acid (ALA) | Orenstein et al. (1990); Stender et al. (2000); Goldberg, (2008); Jerjes et al. (2011); Calzavara-Pinton et al. (2013); Yang et al. (2013); Almutawa et al. (2015); Zhang et al. (2015); Shin et al. (2015); Zhao et al. (2016); Giorgio et al. (2020); Morton et al. (2020) |
| Ophthalmologic Disease | Central Serous Chorioretinopathy, Age-Related Macular Degeneration, Corneal Neovascularization | Verteporfin, Indocyanine Green | Díaz-Dávalos et al. (2016); Gao et al. (2018); van Dijk et al. (2018); Boon et al. (2019) |
| Cardiovascular Disease | Atherosclerosis, Esophageal Varix | 5-Aminolaevulinic acid (ALA), Indocyanine Green, Porphirin, Motexafin Lutetium, Chlorine(e6) | Rockson et al. (2000); Tawakol et al. (2006); Li et al. (2009); Qiu et al. (2012); Patel et al. (2013); Houthoofd et al. (2020) |
| Dental Disease | Periodontitis, Oral Lichen Planus | Curcumin, Indocyanine Green, Phenothiazine, Methylene Blue | De Oliveira et al. (2007); Lavanya et al. (2011); Sadaksharam et al. (2012); Cosgarea et al. (2020); Joshi et al. (2020); Botelho et al. (2021); Pérez-Pacheco et al. (2021) |
| Neurologic Disease | Alzheimer's Disease, Prion Disease | Rose Bengal, Methylene Blue, Porphyrin, Phthalocyanine | Murphy, (2002); Cobb and Surewicz, (2009); White and Mallucci, (2009); Benilova et al. (2012); Lee et al. (2015); Lee et al. (2017); Kostelanska et al. (2019) |
| Skeletal Disease | Rheumatoid Arthritis, Synovitis | Chloroquine, 5-Aminolaevulinic acid (ALA), Phthalocyanine | Hendrich and Siebert, (1997); Kirdaite et al. (2002); Dietze and Berg, (2005); Gallardo-Villagrán et al. (2019) |
| Gastrointestinal Disease | Crohn's Disease, Bacteria-Mediated Gastritis or Colitis | 5-Aminolaevulinic acid (ALA), Porphirin, Methylene Blue | Cassidy et al. (2011); Baccani et al. (2019) |
| Respiratory Disease | Ventilator-Associated Pneumonia, COVID-19 | Methylene Blue, Curcumin | Almeida et al. (2020); Gendrot et al. (2020); Moghissi et al. (2020); Zangirolami et al. (2020) |

Second-generation PS has been well described in the literature for clinical studies (Tables 1, 2). In this context, Aggarwal et al. (2015) reported in their work the development of a 3D model of inflammatory breast cancer (IBC MAME) for application in PDT. The IBC MAME model was obtained from reconstituted basement membrane (rBM) and different

breast cancer cell lines. After 7 days the formation of structures occurred. Subsequently, experiments involving PDT were conducted using two protocols. In the first protocol, the photosensitizer derived from benzoporphyrin monoacid A (BPD) was used with a light dose ranging from 45 to 540 mJ/cm². For the second protocol, they combined BPD

TABLE 3 | Overview of studies involving 3D tissue engineering model for application in Photodynamic Therapy.

| 3D model | Photosensitizer (s) | Photodynamic therapy parameters | Main conclusions | References |
|-----------------------------------|---|--|--|----------------------------|
| Inflammatory breast cancer | Benzoporphyrin derivative monoacid A (BPD) and N-aspartyl chlorin e6 (NPe6) | BPD-PDT: 1.5 μM (BPD) for 60 min Wavelength: 690 \pm 10 nm Post-irradiation: 37°C (18 and 24 h) BPD- NPe6—PDT: 1.5 μM (BPD) and 40 μM (NPe6) for 60 min Light dose: 45–540 mJ/cm^2 Wavelength: 690 and 660 nm Light Source: Halogen light (1.5 mW/cm^2) Post-irradiation: 37°C (24 and 48 h) | MAME model of IBC were killed at a 45 mJ/cm^2 BPD–PDT dose. When the light dose was increased, there was a progressive decrease in cell viability The combination of BPD and NPe6 generated photokilling of IBC MAME structures by apoptosis. This could be seen through the activation of caspase-3 and changes in nuclear morphology | Aggarwal et al. (2015) |
| Micrometastatic pancreatic cancer | Benzoporphyrin derivative (BPD, verteporfin) | BPD-PDT: 0.25 μM (BPD) for 90 min Light dose: 1–50 J/cm^2 Wavelength: 690 nm Light Source: Halogen light (50 mW/cm^2) Post-irradiation: 37°C (24 and 48 h) | The use of 3D models with computational analysis of treatment results allows testing a large number of combinations, which are necessary to establish the most effective set of treatment conditions. PDT can be employed as a postoperative procedure to prevent peritoneal carcinomatosis after surgery, for which the current study provides promising preclinical evidence | Broekgaarden et al. (2019) |
| Mesothelioma | Photofrin | Photofrin-erlotinib-PDT: 4 mM (erlotinib solution) and 10 $\mu\text{g}/\text{ml}$ (Photofrin) overnight Light dose: 4 J/cm^2 Wavelength: 632 nm Light Source: Red light (light emitting diodes) Post-irradiation: 37°C (24 h) | A new 3D cell culture method for malignant pleural mesothelioma (MPM) was developed. Erlotinib increases the direct cytotoxicity of Photofrin-mediated PDT without altering Photofrin uptake. The 3D model is suitable for further analysis such as flow cytometry. Potential use of receptor tyrosine kinase inhibitors to improve clinical PDT response | Cramer et al. (2019) |
| Squamous cell carcinoma | 5,10,15,20-tetrakis (1-methyl 4-pyridinio) porphyrin tetra (p-toluenesulfonate) (TMPyP) | TMPyP-PDT with or without gold nanorods (Au NRs): 20 $\mu\text{g}/\text{mL}^1$ and 1,08 $\mu\text{g}/\text{mL}^1$ for 7 and 20min. Light Source: blue LumiSource [®] flatbed lamp, peak emission at 420 nm and 7 mW/cm^2 output. Post-irradiation: 37°C (24 h) | The loading of TMPyP to Au NRs enhances the absorbance and emission intensity of the PS and improves the ROS generation by light irradiation under <i>in vitro</i> cell culture conditions. For short-term illumination, showed significantly higher phototoxicity compared to free PS at equivalent concentrations. Au NRs loaded with TMPyP are promising agents for photodynamic therapy and fluorescence imaging of HNSCC. | Demir Duman et al. (2020) |
| Cervical carcinoma | 5,10,15,20-tetra (m-hydroxyphenyl) chlorin (m-THPC - Foscan [®]) | m-THPC-PDT: 0,05, 0,25, 0,1, 0,5 e 2 $\mu\text{g}/\text{ml}$ for 3 and 24 h Light source: different LED sources (exposure time (t)) of 30, 20, 15, 8, 4, 2, 1 and 0.5 min) A: Emitting range (nm): 390–415; Irradiance ($\mu\text{W}/\text{cm}^2$): 12.41; Illuminance (lux; lm/m^2): 11.37; Photon flux (cm^2): 7.0. B: Emitting range (nm): 440–470; Irradiance ($\mu\text{W}/\text{cm}^2$): 12.92; Illuminance (lux; lm/m^2): 234,1; Photon flux (cm^2): 17.5. C: Emitting range (nm): 620–645; Irradiance ($\mu\text{W}/\text{cm}^2$): 12.24; Illuminance (lux; lm/m^2): 467.0; | Viability data indicate that the most effective light source is LED A (violet), followed by LED D (deep red). It is important to emphasize that the results in the present work support the utilization of violet LED light to treat the early stages of neoplastic cervical diseases | Etcheverry et al. (2020) |

(Continued on following page)

TABLE 3 | (Continued) Overview of studies involving 3D tissue engineering model for application in Photodynamic Therapy.

| 3D model | Photosensitizer (s) | Photodynamic therapy parameters | Main conclusions | References |
|--|---|--|--|------------------------|
| | | Photon flux (cm ²): 12.0. D: Emitting range (nm): 640–670; Irradiance (μW/cm ²): 12.89; Illuminance (lux; lm/m ²): 173,5; Photon flux (cm ²): 14.0. Post-irradiation: 37°C (6 and 24 h) | | |
| Pancreatic Cancer | Benzoporphyrin derivative (BPD, verteporfin) | BPD-PDT: 250 nmol/L for 1 h Light source: Laser Wavelength: 690 nm Light Dose: 5–20 J/cm Post-irradiation: 37°C (24 h) | Coculture with fibroblasts in this case enhanced the PDT response. The high sensitivity of the stromal compartment itself points to the potential of PDT as an adjuvant therapy for stromal depletion, not only priming the tumor for increased death response, as seen here, but also potentially enhanced permeability of the notoriously dense Pancreatic ductal adenocarcinoma (PDAC) stroma to subsequent drug delivery | Karimnia et al. (2021) |
| Spheroidal cell models of colorectal cancer | Hypericin | Hypericin-PDT: 0–200 nM for 16 h. Light source: LED; Wavelength: 594 nm; Dose light: 1 J/cm ² ; Light treatment: 72 min and 28 s at 0.23 mW/cm ² . The 3D models were incubated with 10 μM Ko143 at 37 °C/5% CO ₂ /95% for 90 min followed by the addition of increasing doses of Hypericin (0–200 nM) for an additional 16 h | Hypericin-PDT has reduced efficacy in colorectal cancer spheroids as compared to 2D cultures, which may be attributable through upregulation in ABCG2. The clinical efficacy of Hypericin-PDT may be enhanced by ABCG2 inhibition | Khot et al. (2018) |
| Nasopharyngeal carcinoma | Liposomal formulations of Temoporfin (m-THPC) [3,3',3''-(2,3-dihydroporphyrin-5,10,15,20-tetrayl) tetraphenol] (m-THPC- Fospeg [®]) | FosPeg [®] -PDT: 0.001 μg/ml to 5 μg/ml for 24 h Light source: Laser, Wavelength: 652 nm Light dose: 5–20 J/cm ² | 3D spheroids, especially the method with agarose base (MCL) spheroids, are more suitable for <i>in vitro</i> evaluation of FosPeg [®] mediated PDT effect on nasopharyngeal carcinoma cells. Further study on other photosensitizers are needed to prove the generality of the 3D models developed in this study | Wu et al. (2020a) |
| Multicellular tumor spheroids of head and neck squamous cell carcinoma | Temoporfin (mTHPC), Chlorin e6 (Ce6) and Indocyanine green (ICG) | mTHPC-Ce6-ICG-PDT: 4,5 and 40 μM Light source: Red light, 652 nm Light dose: 20 J/cm ² | They demonstrated that the presence of stroma influences the behavior of photoactive drugs in different ways: 1) No effect on Indocyanine Green distribution; 2) lower accumulation of Chlorin e6; 3) better penetration and PDT efficiency of Temoporfin. The developed stroma-rich spheroids enlarge the arsenal of <i>in vitro</i> pre-clinical models for high-throughput screening of anti-cancer drugs | Yakavets et al. (2019) |

and with PS N-aspartyl chlorin e6 (NPe6) (NPe6/BPD), which were incubated for 60 min and activated sequentially. They observed that the NPe6/BPD-PDT protocol was more efficient in the photo death of tumor cells compared to the first protocol. In addition, the light dose required to obtain death above 90% for the NPe6/BPD-PDT protocol was 45 mJ/cm². Obtaining this same death rate for BPD-PDT required an 8-fold higher light dose (Aggarwal et al., 2015).

Broekgaarden et al. (2019) evaluated the efficiency of PDT using BPD alone and in combination with the chemotherapy drug oxyplatin in a 3D culture model of metastatic pancreatic cancer. 3D culture models were established from different pancreatic cancer cell lines on matrigel scaffolds, which were kept in culture for 18 days. After the eighth day, the PDT assay was conducted. They used in the PDT protocol 0.25 μM of BPD, incubation for 1.5 h, laser light of 690 nm, irradiance of 50 mW/cm² and light dose of 1–50 J/cm², the effects of the treatment were

evaluated in the days 9, 11 and 18 post-treatment. For the chemotherapy protocol, oxyplatin was used for 72 h and the treatment effects were analyzed on day 11 and 18. The authors observed through the results that PDT combined with oxyplatin was more efficient than monotherapy. In addition, they noted that the effectiveness of the treatment was time-dependent. They concluded that PDT can prevent peritoneal carcinomatosis after surgery, which for the present study provides promising preclinical evidence (Broekgaarden et al., 2019).

Another study involving a 3D model of the pancreas was developed by Karimnia et al. (2021). The 3D model used presented in its composition co-culture of pancreatic cancer tumor cells and human fibroblasts and matrigel as a scaffold. After 7 days that the model was obtained, treatment with PDT was performed. The protocol involved the use of PS verteporfin (benzoporphyrin derivative monoacid ring A, BPD), incubation for 1 h, irradiation with a laser source of 690 nm, light dose variation from 5 to 20 J/cm² with irradiation of 100 mW/cm². They treated the 3D model with chemotherapeutic agents (gemcitabine and oxyplatin) in order to compare it with the response obtained by PDT after 24 h of treatment. They noted that the presence of fibroblasts in the 3D model promoted chemoresistance. In contrast, the response was increased to PDT when compared to monoculture. They concluded that PDT may be an efficient strategy to overcome tumor-promoting stromal interactions associated with poor therapeutic response in pancreatic cancer (Karimnia et al., 2021).

The generation of spheroids is frequently reported in the literature as an approach for evaluating the efficacy of drugs *in vitro*. This 3D model has advantages such as being relatively inexpensive with the possibility of co-culture (Gong et al., 2015; Khot et al., 2018; Yakavets et al., 2019; Brancato et al., 2020).

In this context, the surface of the culture plate used to obtain the spheroid plays an important role, mainly in the orientation of cellular behavior (Brancato et al., 2020). Therefore, some authors described in their work the use of agarose coated plate to obtain spheroids (Khot et al., 2018; Cramer et al., 2019; Yakavets et al., 2019).

Multicellular colorectal cancer spheroids to verify the effect of PDT-Hypericin compared to monolayer model was investigated by Khot et al. (2018). The authors concluded that the PDT-Hypericin effect was greater in the 2D culture than in the spheroids. However, using an ABCG2 protein inhibitor caused an increase in the effect of PDT-Hypericin (Khot et al., 2018). Yakavets et al. (2019) produced multicellular head and neck squamous cell carcinoma spheroids in co-culture. As in the work by Khot et al. (2018), the plate pre-coated with agarose to obtain the spheroid was used (Yakavets et al. (2019).

The PDT protocol employed by Yakavets et al. (2019) was based on the use of three second-generation PS, indocyanine green (ICG), temoporphylin (mTHPC), and Chlorin e6 (Ce6) in co-culture spheroids compared to homospheroids. The authors concluded that tumor stromal components may limit the antitumor activity of anticancer therapies. In the case of the PS used, they observed that Ce6 had less accumulation in the co-culture spheroids, unlike mTHPC, whereas ICG accumulated equally in the two spheroid models compared (Yakavets et al., 2019).

In the data presented in **Table 1**, it was possible to observe that in the clinical trials for the treatment of cancer most of the PS used belong to the first and second generation. Therefore, 3D model studies involving 3rd generation PS for PDT are essential to enable the expansion of its clinical use (Chen et al., 2001; Pogue et al., 2001; Cramer et al., 2019; Agostinis et al., 2011, 2012; Lamberti et al., 2014; Bacellar et al., 2015; Spring et al., 2016; Banerjee et al., 2017; Kwiatkowski et al., 2018; Dos Santos et al. al., 2019).

In the studies by Demir Duman et al. (2020), Etcheverry et al. (2020) and Wu et al. (2020) the effects of PDT with different third-generation PS on different 3D tumor models were studied. These being 1) nanocomposites of gold nanorods (Au NRs) with the cationic porphyrin TMPyP (5,10,15,20-tetrakis (1-methyl 4-pyridinium)porphyrin tetra (p-toluenesulfonate)); 2) m-THPC and 3) pegylated liposomes containing mTHPC, respectively. Results and protocols were varied. There was a consensus that PDT was efficient and further studies on other photosensitizers are needed to prove the generality of the 3D models developed in the studies described (Demir Duman et al., 2020; Etcheverry et al., 2020; Wu et al. (2020).

CONCLUSION

Therefore, the association of Tissue Engineering and Photodynamic Therapy protocols resulted in great advances for the understanding of therapeutic processes based on the interest in the interaction of monochromatic light with biological tissues. Tissue Engineering is a field of science in full expansion and would also contribute to a better understanding of photodynamic mechanisms. This scientific review article can directly contribute to the organization of what is considered a state of the art in this field of knowledge. Updating and presenting important information for the direction of works that wish to use these advanced protocols. There is no doubt about the great potential for using these combined concepts, which are at the Frontier of knowledge and can help in the development of new biological assays available for application in various clinical treatments and chronic pathologies such as antitumor, anticancer and chronic psoriasis.

CHALLENGES AND FUTURE PERSPECTIVES

The development of tissue engineering has been described in the literature for many decades. In recent years it has gained evidence mainly through the appeal to use alternatives to animal testing. Until now, the studies have involved non-systemic evaluation of drug behavior in human cells/tissues, replacement of damaged parts of the body, cosmetic testing, among others (Langer and Vacanti, 1993; Morales, 2008; Doke and Dhawale, 2015).

However, the biggest challenge related to this technology is to obtain models that faithfully emulate all the characteristics of the human biological structure. In addition, the pathophysiology of certain diseases often has different expressions between species, which becomes another limitation for reproducing the

methodologies (Guiro and Arinzeh, 2015; Hapach et al., 2019). Other possible obstacles to the development and application of 3D models mainly involve cell types, as it is necessary to use at least 2 cell types to be able to recreate the original structure and production costs (Langer and Vacanti, 2016).

Despite the challenges, the production of 3D Cell Culture Models is an excellent tool to assess the possibility of transposing data directly to humans (Ravi et al., 2015; Ceylan and Bölgen, 2016). In this context, there are several types of photosensitizing agents available for use in PDT that require biological models to be tested (Desmet et al., 2018; Yakavets et al., 2019; Etcheverry et al., 2020). However, the challenges associated with the structural characteristics of PS need to be overcome for application in PDT and, consequently, make its clinical use unfeasible. They are usually molecules of high molecular weight and lipophilicity, such as porphyrins, which lead to low permeability and make it difficult to incorporate it into conventional pharmaceutical forms (Webber, 2016).

Another factor to be considered for the application of PDT includes the low selectivity of PS action. Therefore, this contributes to the use of nanotechnology (Sharma et al., 2017). Therefore, a strategy to overcome these limitations associated with PS would be the use of delivery systems such as polymeric nanoparticles and liposomes (Sharma et al., 2017).

Therefore, the evolution of TE is related to the possibility of obtaining new tools such as the implantation of biofabricated tissues, elaboration of synthetic scaffolds capable of simulating the tissue's microenvironment, production of mini-organs, valves, cartilages, among others from 3D bioprinting (Nguyen

and Pentoney, 2017; W et al., 2017; Tarassoli et al., 2018). And more recently, the concepts of organ-in-a-chip and human body-on-chip were introduced, which are small three-dimensional biomimetic systems that aim to mimic characteristics of the organs they represent (Low et al.; Chen et al., 2021). In addition to being interconnected to form larger systems with different types of cells on which physical forces act, they have several applications such as analysis of pharmacokinetic, pharmacodynamic and toxicological properties of drugs, organ-organ interaction (Low et al., 2021; Chen et al., 2021).

AUTHOR CONTRIBUTIONS

MA-F and CA contributed to the conception and design of the manuscript. MA-F and CA wrote the first draft of the manuscript. MA-F, CA, and SdA wrote sections of the manuscript. MA-F designed the table and performed the formatting of the manuscript. FP performed the main corrections and revised the manuscript. All the authors contributed to manuscript revision, read, and approved the submitted version.

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