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# Promising Nanotechnology-Based Strategies for Melanoma Treatment

**Letícia Sias-Fonseca [1,2], Paulo C. Costa [1,2], Lucília Saraiva [3], Ana Alves [1,2] and Maria Helena Amaral [1,2,*]**

[1] UCIBIO—Applied Molecular Biosciences Unit, MedTech—Laboratory of Pharmaceutical Technology, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal; sias.leticia@gmail.com (L.S.-F.); pccosta@ff.up.pt (P.C.C.); adcoutinhoalves@gmail.com (A.A.)
[2] Associate Laboratory i4HB—Institute for Health and Bioeconomy, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal
[3] LAQV/REQUIMTE, Microbiology Laboratory, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal; lucilia.saraiva@ff.up.pt
* Correspondence: hamaral@ff.up.pt; Tel.: +351-220-428-500

## Abstract

Melanoma is a type of skin cancer with high lethality and increasing incidence. Current treatments typically involve surgery as the first step, followed by adjuvant treatments, which are necessary in most cases. These adjuvant treatments may include radiotherapy, phototherapy, chemotherapy, immunotherapy, and combined therapies. However, patients with melanoma still face great difficulties, such as the inefficiency of therapies and serious side effects, in addition to uncomfortable scars. Most of these problems are related to limitations of antitumor therapies, such as the low bioavailability of drugs, degradation in biological fluids, rapid clearance, difficulty in reaching the tumors, the low capacity for accumulation and infiltration in tumor cells, toxicity to healthy cells, and systemic action. Thus, antitumor therapy for melanoma remains a challenge. In this line, nanotechnology has brought new perspectives and has been the subject of intensive research on the use of nanoparticles (liposomes, lipid nanoparticles, polymeric nanoparticles, inorganic nanoparticles, carbon nanotubes, dendrimers, nanogels, and biomimetic nanoparticles, among others) as carriers for the controlled release of drugs and tumor diagnosis. This work outlines the main limitations of current melanoma therapies and explores how nanoparticle-based drug delivery systems can overcome these challenges, highlighting recent research and clinical developments.

**Keywords:** nanotechnology; melanoma; drug targeting

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## 1. Introduction

Melanoma is the most dangerous skin cancer, and although it represents about 5% of all skin cancers, it is responsible for most deaths [1–4]. The depth of cutaneous melanoma is much more important than its extent, as it is proportional to the chances of metastases occurring by transporting tumor cells through blood and/or lymphatic vessels [5]. Patients with metastatic melanoma have a median survival time between 8 and 9 months, and an overall 3-year survival rate of less than 15% [6]. The incidence of melanoma is increasing all over the world, gradually and worryingly [7,8].

The main current treatment for melanoma is surgery, considered a risky incisive intervention that leaves uncomfortable scars, usually in visible areas, since the highest

incidence is in exposed areas [1]. In most cases, adjuvant treatments are also needed, such as radiotherapy, phototherapy, chemotherapy, immunotherapy, combined therapies, and others [9,10]. However, despite all available treatments, this disease remains unresolved, as even the most recent alternatives have limitations in terms of curative and even palliative effects, in addition to serious side events [11,12]. Some of the challenges to be overcome are low bioavailability, degradation by organic fluids, fast clearance, low selectivity for tumor cells, small accumulation and infiltration in tumors, chemoresistance, immunoresistance, and others that result in insufficient efficiency of treatments and serious adverse effects [9–12].

To overcome these important challenges of antitumor therapies for melanoma, there is an urgent need to develop new technologies that can be combined with current therapies to improve clinical management. In this sense, the use of nanoparticulate systems as drug carriers has been the target of an extensive investigation, showing very satisfactory results [9–13]. There are several types of nanoparticles, namely liposomes, lipid nanoparticles, polymeric nanoparticles, inorganic nanoparticles, dendrimers, nanogels, carbon nanotubes, biomimetic nanoparticles, and others [10–12,14–17]. The characteristics of nanoparticles (shape, size, and interface) can be optimized to overcome each of the barriers of current therapies and fill their gaps [10–12,14–21].

Thus, the objective of this review is to provide a current overview of melanoma, the most widely used therapies and their challenges, the main types of nanoparticles and how these carriers can contribute to the treatment of this disease, their advantages and disadvantages, and the reasons they have been considered a promising strategy in the treatment of melanoma, improving clinical outcomes and reducing side effects.

## 2. Melanoma: Definition, Causes, Occurrence, and Evaluation

Melanoma is potentially the most fatal skin cancer, is caused by the transformation of melanocytes, and is characterized by malignant proliferation, high metastasis, rapid recurrence, and a low survival rate [11].

Although melanoma accounts for over 5% of all skin cancers, it causes most of the deaths [1–4]. The incidence of melanoma is dramatically rising around the world. Since the 1960s, the incidence of cutaneous melanoma has increased gradually and continuously [7,8].

Melanoma is more prevalent in people with skin type I to IV (Fritzpatick Scale) [22], with light hair and eyes, who have had extensive exposure to the sun, and in elderly people [23]. However, it is becoming one of the most common cancers in young adults [1]. Currently, it is predicted that 2.94% of males (1 in 34) and 1.89% of women (1 in 53) will be diagnosed with melanoma [24,25].

Melanoma is found mainly on the face, neck, and hands, but it can occur in other parts of the body, including the eyeball and nails. If localized in the neck and head regions, it will present a prognosis about 20% worse than in other locations [26]. The first exam for evaluation in suspected cases is commonly called the ABCDE of melanoma. It is characterized by observations of the following cutaneous spots: asymmetry (A), border (B), color (C), diameter (D), and evolution (E) [1]. More important than the extent of melanoma on the skin's surface is the depth it reaches. The depth is assessed during the biopsy and is measured in millimeters (mm), according to the Breslow score [1]. The deeper it is, the greater the likelihood of metastasis occurring through the transport of cancer cells via the sanguineous and/or lymphatic vessels, which may reach lymph nodes or organs that are more distant (Figure 1) [23]. Metastatic melanoma patients present a median survival time between 8 and 9 months, and a 3-year survival rate lower than 15% [6]. Brain metastases are present in more than 60% of patients with melanoma [27].

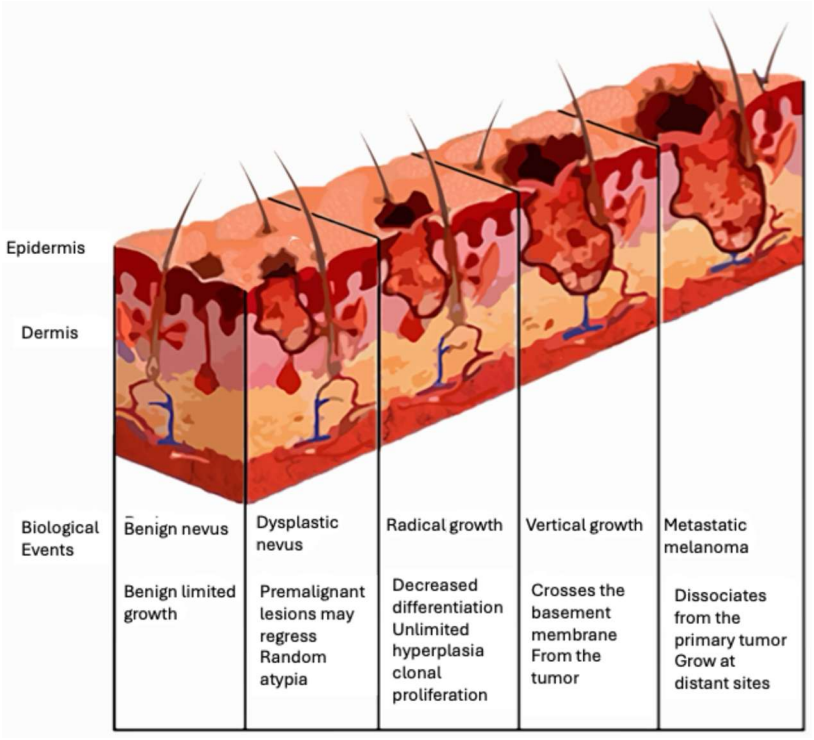



**Figure 1.** A representation of the skin layers and depth of melanoma and its relationship with severity and prognosis (adapted from [23]).

The highly heterogeneous malignancy of melanoma results from the interaction of genetic, host, and environmental factors [28]. The mutations of oncogenes and tumor suppressors, considered major drivers of melanomagenesis, include B-Raf proto-oncogene (BRAF) (~50% mutation frequency), neuroblastoma RAS viral oncogene homolog (NRAS) (~30%), tyrosine kinase (KIT) (~1%), cytoplasmic protein of molecular mass 53 (p53) (~5%), and phosphatase and tension homolog (PTEN) (~50%), among others [28]. Furthermore, the higher somatic mutation load in melanoma compared to in other cancer types is believed to be attributable to the preponderance of cytosine-to-thymine nucleotide substitutions because of ultraviolet (UV) radiation exposure [29]. Also, melanoma is one of the most immunogenic tumors, in which immune evasion and suppression have an important role [30].

## 3. Current Treatments for Melanoma, Their Limitations, and Promising Nanotechnology Contributions

Although several therapeutic options are available for melanoma, this disease remains practically unresolved, as even the most recent therapeutic alternatives have limitations in terms of curative and even palliative effects, in addition to undesirable toxic events in healthy cells (Table 1). One of the most important challenges to overcome in the treatment of melanoma is drug resistance. Possible causes for drugs resistance are their interaction with biological fluids and membranes, as well as heterogeneous tumor immunology and vasculature [31,32]. Additionally, poor bioavailability, chemical and/or biological degradation, and rapid clearance result in an insufficient and ineffective amount of drug reaching tumor cells. There is also systemic toxicity, which restricts the drug dosage [10–12].

The advent of drug carriers based on nanoparticles capable of protecting and releasing drugs in a controlled and selective way to tumor tissues is a promising strategy to overcome the limits of current treatments. The characteristics of nanomaterials (design, size, and interface) can be modified to overcome barriers and fill gaps. However, few effective systems have been developed for loading and releasing drugs driven by nan-

otechnology [10,33,34]. Some of these widely studied nanoparticles (NPs), which will be discussed in this work, are liposomes (LSs), lipid nanoparticles (LNPs), polymeric nanoparticles (PNPs), nanogels (NGs), carbon nanotubes (CNTs), inorganic nanoparticles (INPs), dendrimers (DMs), biomimetic nanoparticles (BNPs), and others (Figure 2).

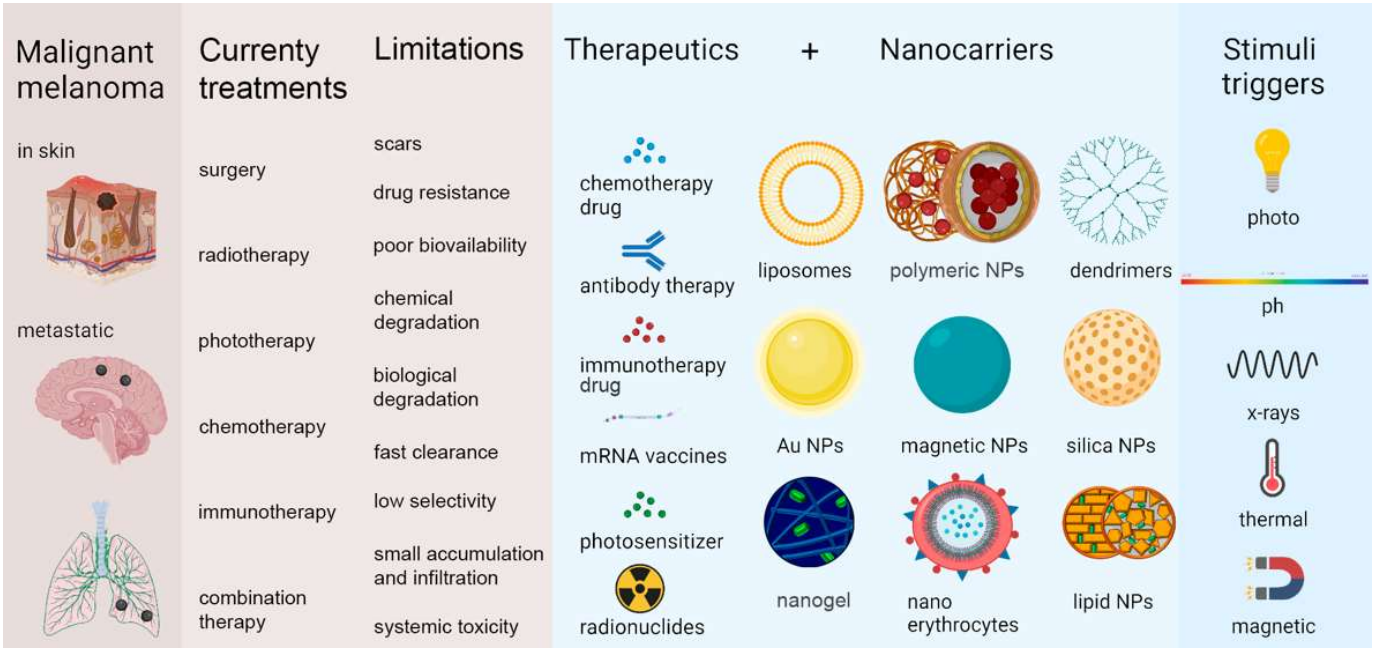



**Figure 2.** Factors to be considered in a sensible design strategy, such as the stage of melanoma to be treated or diagnosed, the type of therapies, the various possibilities of NP types, abd the alternatives in terms of triggers (adapted from [11]).

In recent years, new strategies for the treatment of melanoma have emerged, which involve combining immunotherapy with other treatments, such as chemotherapy and radiotherapy. Additionally, due to the melanoma pigment, the use of phototherapy is suggested. Currently, photodynamic therapy (PDT) and photothermal therapy (PTT) also have clear clinical applications. Currently, many studies use stimulus response and other methods to combine PDT/PTT and chemotherapy or immunotherapy. Therefore, the development of multifunctional nanocomposites with a high loading capacity for different therapeutic agents could further improve the effectiveness of melanoma treatments [35–42].

Current treatments, limitations, challenges, and promising nanotechnologies applied to the treatment of melanoma are summarized in Table 1.

**Table 1.** General aspects of current treatments, limitations, and challenges of current treatments and promising nanotechnology contributions.

| Current Treatments | General Aspects | Limitations | Promising Nanotechnology Contributions |
| --- | --- | --- | --- |
| Surgery | Consists of the removal of affected skin tissue with a safety margin of 5 cm around the lesion, including deep fascia, for tumors in the limbs and trunk and 2.5 cm for tumors in the face [1]. | It is considered a risky intervention, especially in elderly patients who generally have other health problems that can hamper healing, such as diabetes. Discomfort with the scar, considering that the highest incidence of melanoma is on the face and other regions generally exposed [1]. | Selective accumulation of nanoparticles (NPs) at disease sites enables early tumor visualization, improving diagnosis and reducing toxic side effects on healthy tissues [43–45]. |
| Radiotherapy (RT) | RT is an adjuvant treatment that supports cure or palliation and enhances immunotherapy effects [10,46,47]. | RT alone does not improve survival, limited by factors like poor tumor vascularization, hypoxia, and radiation absorption [48].<br>Cutaneous melanoma is considered relatively radioresistant [47,49,50]. | Metallic inorganic nanoparticles, such as gold (AuNP) and platinum (PtNP), act as radiosensitizers that enhance X-ray absorption, improving radiotherapy effectiveness against melanoma [48]. |
| Phototherapy (PT) | PT is a specific, localized outpatient treatment with low side effects. It includes photothermal therapy, which uses near-infrared light to heat and kill tumor cells, and photodynamic therapy, which activates photosensitizers to produce reactive oxygen species or heat, causing tumor death [51–55]. | PT alone has limited tumor ablation due to shallow light penetration, especially in melanin-rich melanoma cells that block radiation. Therefore, PDT requires photosensitizers like Indocyanine Green (ICG), which absorbs longer wavelengths for better effectiveness [56–59]. | Nanocarriers improve ICG stability and concentration in target tissues. Developing new nanomaterials for combined PTT and PDT allows for precise, controlled drug release using light-responsive nanoparticles, modulated by light intensity, wavelength, and exposure time [60–62]. |
| Chemotherapy (CT) | Chemotherapeutic drugs are toxic compounds that inhibit the rapid proliferation of cancer cells [63]. | CT causes side effects by affecting healthy fast-growing cells, and its drugs often have poor pharmacokinetics and wide distribution, reducing treatment efficiency [12,64].<br>Multidrug resistance is habitual, caused by internal factors, including mutations [65,66], gene amplification [67,68], deletions [69,70], and chromosomal rearrangements [71,72], or external factors, such as pH [73], hypoxia [74], and paracrine signaling interactions with stromal cells [11,75,76]. | LPs loaded with vemurafenib improve skin drug delivery and reduce toxicity [77].<br>SLNs loaded with temozolomide and SLNs loaded with paclitaxel show strong antimelanoma effects without toxicity [78,79].<br>PNPs loaded with flavone apigenin loaded with apigenin and functionalized with DMSA enhance drug release, bioavailability, lung targeting, and efficacy against melanoma metastases [80]. |

**Table 1.** *Cont.*

| Current Treatments | General Aspects | Limitations | Promising Nanotechnology Contributions |
| --- | --- | --- | --- |
| Immunotherapy (IT) | It aims to modulate the systemic immune system so that it defends itself against cancer, focusing on the body's defence system, not on the cancer cells themselves, as chemotherapy [81]. | It has great challenges, such as drug resistance from immune control point inhibitors, low immunogenicity of therapeutic vaccines [82], significant immunological adverse events (iRAE), off-target side effects and drug resistance [83]. The results of vaccines, cytokines, and cell therapies are only significant in a very small portion of patients with metastatic melanoma (MM), partially due to melanoma-induced immunosuppression [11,84–86]. | NLC loaded with LEM2 improved drug release and its solubility and bioavailability problems and does not interfere with molecular action, due to the adhesion and occlusion properties of NLC [87]. A polyethyleneimine-CpG PNP (CpG @ PEI) was tested as an in situ vaccine to enhance anti-cancer immunity, increasing cell stability and CpG internalization, improving innate and adaptive immunity, increasing NK cell numbers and infiltrating T cells in the tumor as well as the expression of CD80 on dendritic cells (DCs) and therefore effectively inhibiting the growth of murine B16F10 melanoma [88]. Dosta et al. developed dendrimers containing an interferon gene stimulator (STING) in the cytosol and concluded that NPs were advantageous in the delivery of gene-based immunomodulators [89]. Nanogels that selectively release IL-2 in response to activation of T cell receptors after T cell antigen recognition on tumor cells have been developed, showing improved efficiency and reduced severity of side effects [90]. |
| Chemoimmunotherapy | Chemotherapeutic drugs can induce immunomodulation, mainly by increasing the intrinsic immunogenicity of tumor cells [91], regulating the suppressive influence of T cells [92] and impacting the function of other cells, such as myeloid-derived suppressor cells (MDSC) [93] and dendritic cells (DC) [94], positively regulating the expression of tumor antigens [95] and the main class I histocompatibility complex (MHC-I) [96], inducing the expression of co-stimulatory molecules [97]. Chemotherapeutics can also act by negatively regulating the immunological checkpoint molecules expressed on the surface of the tumor cell [98], inducing the death of the tumor cell by secretion of adenosine triphosphate (ATP) or expression of calreticulin [91] and others [99,100]. | Chemoimmunotherapy has shown remarkable clinical results, however, there are also worrying effects, such as an inadequate T-cell response, a large discrepancy in the curative effect among patients, in addition to the fact that many patients do not present a satisfactory response [101]. Thus, developments in the use of chemoimmunotherapy are still needed to increase the effects of the immune response [102]. When there is a combination of drugs, as in chemoimmunotherapy, it is necessary to guarantee the ideal synergistic antitumor efficacy, considering the different pharmacokinetics and insufficient in vivo distribution of both agents, drug specificity for tumor cells and insufficient accumulation of drugs in the tumor and severe systemic side effects [103]. | The use of NP as drug carriers can improve pharmacokinetic behaviours in vivo, increase the stability and perform a controlled release of drugs and even targeted them to tumor cells, being, therefore, a promising tool for chemoimmunotherapy [104] |

## 4. Nanoparticles and Melanoma Treatment

### 4.1. Drug Targeting Through Nanoparticles

NPs have been extensively studied for use in the administration of drugs for melanoma treatment. NPs have shown promising results in terms of their ability to increase drug bioavailability, delivering them directly to tumor cells, without harming healthy cells [10,33,34,105–110].

The targeted delivery of different drugs used in the treatment of melanoma with nanotechnology helps in the accumulation of drugs inside tumor cells at high concentrations, increases the uptake and internalization of drug-loaded NPs by target tumors, and avoids side effects caused by drug delivery in healthy cells. Thus, the incorporation of chemotherapeutic drugs, proteins, nucleic acids, vaccines, or other therapeutic agents can create an ideal delivery system for the treatment of metastatic melanoma [17], resulting in greater efficacy and lower side effects [33,34,105,111].

Basically, drug targeting to tumor cells can be achieved in different ways: passive or active targeting, responsive to different internal or external stimuli, which will be discussed below.

### 4.2. Passive Targeting

Tumors have different characteristics from healthy tissues, for example, leakage of the vasculature and deficient lymphatic drainage. At cancer sites, the blood vessels are discontinuous, resembling tubes with nanosized holes and poor lymphatic filtration inside the tumors that facilitates the accumulation of drugs [31]. This particularity of the tumor areas causes enhanced permeability and retention (EPR), the characteristics on which passive targeting is based [112]. Thus, nanoparticulate carriers may be able to cross this tumor leakage vasculature and accumulate there, due to low lymphatic drainage, and release the drug in the target tissue. As healthy tissues do not have blood vessels with these large fenestrations and the NPs cannot leave the bloodstream and go into healthy tissues, they do not suffer unwanted toxic effects [31,113,114].

Still, the EPR effect acts only at the level of the NP distribution pattern but does not improve the targeting of the NPs to the intended target. In other words, the capacity of uptake of NPs by tumor cells and the increase in the intracellular concentration of the drug carried are not improved. According to clinical results of therapies using NPs, this EPR effect may not be as significant as previously assumed [17].

### 4.3. Active Targeting

Tumor cells also differ from healthy cells in the number of specific receptors, which can be overexpressed. Knowing this characteristic of the cells of a specific target tumor, drug-carrying NPs can have their surface modified with a specific ligand based on nucleic acid or other molecules that specifically bind to overexpressed receptors on the local target [115]. In this way, the modified NPs can recognize the surface receptors in specific targeted cells and bind effectively to the receptor site, increasing drug specificity [10].

Active targeting refers to specific interactions between modified carriers and targeted tumors. So, active targeting allows for a better interaction between NPs and tumor lesions and greater internalization of drugs through specific receptor-mediated endocytosis [17].

Therefore, specific ligand–receptor interactions with active targeting can fill the gap presented by passive targeting, because in addition to increasing the affinity between nanotransporters and tumor cells, they can also facilitate the absorption of NPs by tumor cells via receptor-mediated endocytosis [17,44].

Stimuli-responsive delivery systems are other targeted drug delivery systems that aim to maximize the release of a drug at tumor pathological sites. According to this system,

NPs are designed to react to certain stimuli, internal or external, which trigger the release of encapsulated drugs [17]. Some unique features of tumors in comparison to normal tissues, such as the more acidic intratumoral microenvironment and the greater sensitivity to hyperthermia, can act as an internal stimuli and lead to the release of the drug at the tumor site [116]. Meanwhile, when bio-responsive NPs are exposed to certain external stimuli, such as ultrasound or light, the time and spatial control of drug release can be achieved at the exposed location [117].

## 5. Types of Nanoparticles, Their Advantages and Disadvantages, and Improvements in Tumor Treatments

Drug-loaded NPs were used to treat cancer and showed excellent properties, such as targeted delivery, response to the tumor microenvironment, and specific site drug release. Several drug-loaded nanocarriers have been approved and have shown significant improvement in therapeutic efficiency compared to conventional formulations. Some of them are liposomes (Doxil®—doxorubicin, Lipusu®—paclitaxel), biomimetic nanoparticles (Abraxane®—albumin linked to paclitaxel) and polymeric NPs (Genexol-PM®—paclitaxel) [118].

In addition, several other types of nanocarriers have been studied extensively for the treatment of melanoma and other types of cancers. Some examples and research related to these types of drug-loaded NPs will be presented below and can also be observed in Figures 2 and 3.

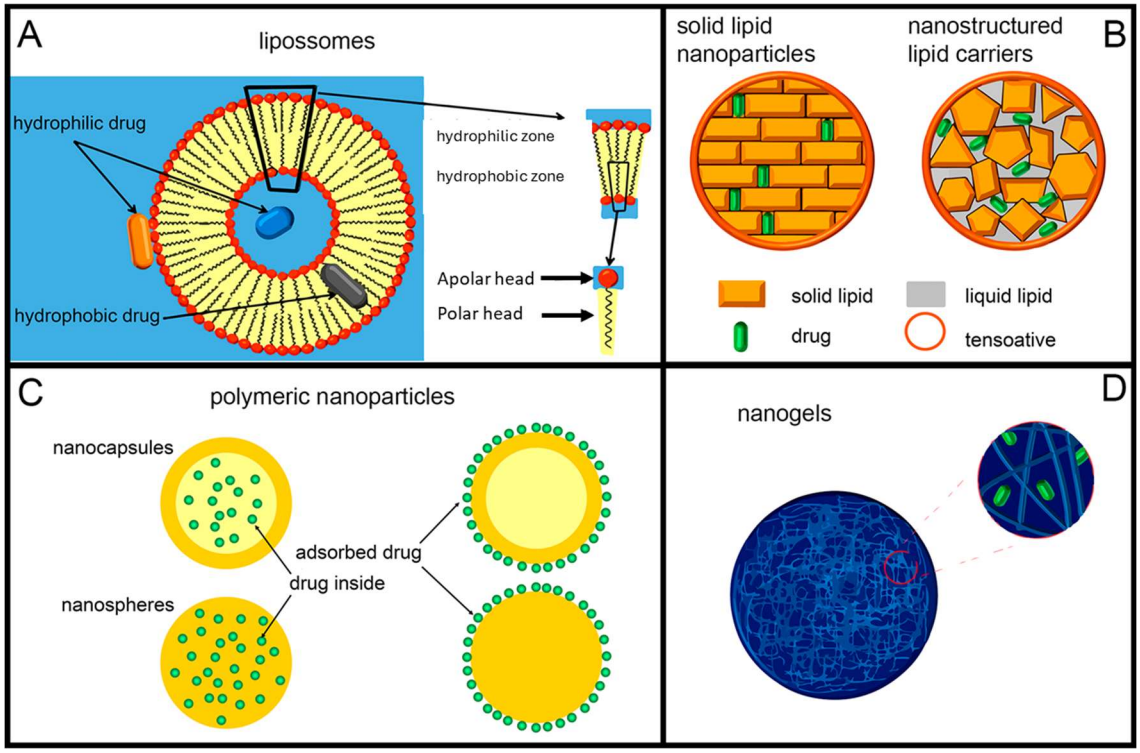



**Figure 3.** A structural representation of (**A**) a liposome loaded with a hydrophilic drug and a lipophilic drug, in their respective positions, (**B**) the two types of solids at room temperature and lipid NPs (LNPs): solid lipid nanoparticles and nanostructured lipid carriers (NLCs); (**C**) the two types of NPs: nanospheres (NSs), which are matrix polymeric particles, and nanocapsules (NCs), which have an oily core and polymeric walls, and (**D**) the external and internal composition of a nanogel (NG).

Depending on the type of NP, there are advantages and disadvantages inherent to the characteristics of each one.

Liposomes (LPs) are composed of a hydrophobic phospholipid bilayer structure, forming a central aqueous compartment (Figure 3A) [33]. Nanostructured liposomal systems can transport hydrophilic drugs/lipophilic drugs [33,119]. They have a lot of advantages, such as being non-toxic, flexible, and non-immunogenic carriers, reducing drug toxicity and enabling passive targeting or selective active targeting through surface modification [18,20,33,34,44,45,116–130]. These nanoparticles also show some disadvantages, such as drug leakage and fusion from phospholipid degradation, limited encapsulation efficiency, and a short half-life due to chemical and physical instability [33,34,44,45,116–118,120–127,130]. Promising improvements in tumor treatments have been made as small hydrophilic drugs are encapsulated in the liposome's aqueous core, while lipophilic agents like immunotherapeutics can attach to the phospholipid bilayer [33,124,125]. LPs fuse with cell membranes for efficient delivery. Adjusting size (<100 nm) or carrying out functionalization (e.g., PEGylation) extends circulation time by evading immune detection. Tumor-targeting ligands or pH-sensitive release (tumor pH ~6.5) enhance efficacy, as shown by pH-sensitive liposomes co-delivering paclitaxel and siRNA to inhibit melanoma proliferation [45,126].

Lipid nanoparticles (LNPs) are solid at body temperature and can be solid lipid nanoparticles (SLNs), composed of one or more solid lipids, or nanostructured lipid carriers (NLCs), consisting of a mixture of solid and liquid lipids, thus forming an imperfect matrix structure that avoids the possibility of rearrangement and uncontrolled release of drugs during storage, which occurs with SLNs (Figure 3B) [15,131–139]. These delivery systems based on lipids enhance the bioavailability of entrapped drugs or compounds and provide chemical protection for labile incorporated substances while allowing for easy, large-scale production [15,19,77,78,123,131–151]. However, they have limitations such as limited drug loading capacity, structural degradation during storage, and premature drug release [15,19,77,78,123,131–151]. These lipid-based nanoparticles hold great promise for the diagnosis and treatment of melanoma, as they can bypass the reticuloendothelial system, thereby improving blood circulation time and increasing drug uptake by tumor cells [151].

Inorganic nanoparticles (INPs), including graphene oxide-based INPs [152], mesoporous silica nanoparticles [153–155], black phosphorus [156], gold nanoparticles (AuNPs) (Figure 2), silver-derived nanoparticles (AgNPs), and others [157,158], are employed in the treatment and diagnosis of several diseases. They offer high drug loading capacity, and their surfaces can be modified by various chemical species [80,88,152–171]. However, metals can be toxic and INPs often have low stability during storage [80,88,152–171]. Gold, platinum, and silver INPs have applications in melanoma diagnosis and treatment. AuNPs are notable for their versatility in size, shape, surface chemistry, synthetic accessibility, high biocompatibility and stability, and surface plasmon resonance [160]. Consequently, AuNPs have been explored as (1) drug and siRNA carriers; (2) therapeutic agents; (3) photodynamic and photothermal agents; and (4) active delivery systems, as they can be conjugated to antibodies targeting cancer biomarkers [161].

Polymeric nanoparticles (PNPs) are thermodynamically stable colloidal dispersions formed by the self-assembly of blocks of amphiphilic copolymers (Figure 3C) [172–174]. Various types of PNPs can be synthesized depending on the properties of the polymer and its applications [172,175,176]. PNPs are called nanocapsules (NCs) when they contain a polymeric wall and an internal oil core, or nanospheres (NSs) when they are formed of a polymeric matrix stabilized by surfactants [12,172,177–182]. They have several advantages such as high structural stability, which prevents the degradation and metabolism of the loaded drug, the ability to load a large amount of drug, and sustained release, which increases the water solubility of loaded hydrophobic drugs and allows the surface to be modified by var-

ious chemical species [12,43,44,79,87,105,172–195]. However, these particles present some limitations, including the possibility of side effects due to the increased drug circulation period, industrial production complexity, difficulties in gaining approval by regulatory authorities, and the use of organic solvents [12,43,44,79,87,172–175,177–193]. PNPs can transport lipophilic molecules dissolved in their internal oil core, and hydrophilic molecules can be transported through physical interactions or chemical conjugation with the polymeric walls or the stabilizing surfactants. Thus, PNPs may allow for the use of a single delivery device combining two types of drugs and combination therapy [12,172,177–182]. A ligand that can be used to promote the specificity of NPs to melanoma cells, with low effects on healthy cells, is the α-melanocyte-stimulating hormone (MSH) peptide. MSH binds to melanocortin receptors that are overexpressed by melanoma cells [43]. The selective accumulation of NPs at the disease site would permit the visualization of tumors in the early stages, allowing for better diagnostic possibilities and contributing to the reduction in toxic side effects on normal tissues [43,44].

Dendrimers (DMs) are synthetic three-dimensional polymers with a branched tree-like structure (Figure 2). Structurally, dendrimers consist of a central core to which multiple branched arms and peripheral groups are progressively attached [15,196,197]. They offer precise control over molecular structure and monodispersity, and their small size enables them to cross biological barriers. Their end groups can carry positive, negative, or neutral charges [15,196–202]. However, the three-dimensional structure and design of dendrimers are not fully understood, and their nonspecific interactions with various cells can cause toxic effects [15,196–202]. The dendrimer structure allows for the introduction of multiple functionalities at different sites within a single molecule—on the surface, core, branch points, or even encapsulated between branches [196]. This versatility makes dendrimers promising candidates for controlled drug delivery systems, potentially enabling combination therapies by carrying two types of drugs in one delivery platform [196].

In addition to the above-mentioned types of NPs, others have been the subject of many studies, such as nanogels, niosomes [203,204], and biomimetic nanoparticles. Nanogels (NGs) are considered very promising for use as biocompatible carriers for controlled release of drugs due to their internal constitution of a hydrogel, which has a high water content (Figure 3D). This makes them highly compatible with various therapeutic agents such as small molecules or even bio-macromolecules [83]. Like other nanocarriers, nanogels can be functionalized with targeted ligands, responsive functional bonds, and others, resulting in multifunctional drug delivery systems [44,205–210].

The use of NPs as drug-carrying systems has several challenges, including the potential for immune system capture and early removal. To evade the immune system, increase circulation time, and improve targeting, NPs have been functionalized with biological cells, organisms, or natural structures such as erythrocytes, immune cells, cancer cells, platelets, viruses, and others (Figure 2). In this way, NPs (e.g., LP, PNP, or INP) inherit the biological functions of the natural system of origin. These NPs are called biomimetics (BNPs), as they have the morphology, size, and surface properties of natural structures. In addition to the advantages already mentioned, these characteristics improve biocompatibility, reducing side effects and increasing the effectiveness of the treatment [12,53,61,211–213].

To overcome the limitations commonly presented by treatment with immunotherapeutics, such as natural biological barriers, low immunogenicity, and a highly immunosuppressive tumor microenvironment, Luo et al. developed a BNP functionalized with folate-modified red blood cells (RBCs), which was loaded with the chemotherapeutic paclitaxel and an indoleamine 2,3-dioxygenase (IDO) inhibitor (immunotherapy) [213]. The results showed that this BNP had prolonged blood circulation and specific absorption in B16F10 melanoma cells. Furthermore, rapid drug release can be triggered by the conversion

of a negative to a positive charge in response to the acidic environment in lysosomes. An increase in the efficiency of the combined antitumor treatment and a reduction in side effects were observed in a mouse melanoma model [213].

## 6. Summary of Recent Studies Applying NPs to Melanoma Treatment

In the literature, preclinical studies describing the use of nanoparticles in the treatment of melanoma are much more abundant than clinical trials. Table 2 summarizes a set of studies published between 2018 and 2025 that applied different types of NPs in the treatment of melanoma. Among these 24 studies presented in Table 2, in the majority (13 studies), the route of administration is intravenous injection, while in only 1 the route of administration is topical [87].

**Table 2.** Summary of recent studies using NPs in melanoma treatment.

| | Functionalization | Therapy | Anticancer Agent(s) | Results | Ref. |
|---|---|---|---|---|---|
| Liposomes (LPs) | Stearyl chain (C18) fused pH-sensitive cell-penetrating peptide (TR) | Combination therapy | Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) Paclitaxel (PTX) | TRAIL-[Lip-PTX] C18-TR exhibited a tumor inhibition rate of 93.8%, improving TRAIL-based therapy. Moreover, this system showed a better IC50 in vitro compared to free drugs and liposomal drugs separately; therefore, synergism of the two types of drugs in a single system was observed. | [144] |
| | Tf-PEG-PE (Tf = transferrin) | Combination therapy | Mitoxantrone (MIT) Anacardic acid and Ammonium ascorbate | This peptide-modified co-delivery system was effective for use with chemotherapeutics and natural bioactive substances, showing an enhanced active tumor-targeting effect and therapeutic efficacy, due to the increased level of apoptosis and cell death in melanoma cell lines, which was not verified in normal cells. | [145] |
| | T-cell receptor (TCR)-like antibody (scFv G8 and Hyb3) | Combination therapy | Doxorrubicin (DXR) | These LPs effectively and selectively target antigen-positive melanoma and coupled to anti-M1/-A1 scFv inflict a significant antitumor response. This NPs can be used for drug delivery, immunotherapy, potentially imaging, and diagnosis of melanoma. | [45] |
| | | Immunotherapy | Interleukin (IL)−2 Agonistic anti-CD137 | This immunoliposome delivery system achieved antitumor activity in multiple tumor models like both free drugs, but overcame the important challenge of IL-2/anti-CD137 toxicity. | [123] |
| Solid lipid nanoparticles (SLN) | Biological-inspired peptide TD (ACSSSPSKHCG) | Chemotherapy | Vemurafenib | The effective antitumor ability of the drug carrier delivered via the skin was better than that of oral and intravenous administrations; in terms of toxicity in the liver, kidney, and lungs, it was negligible and antitumor efficacy was increased. Moreover, surface modification with the peptide TD significantly enhanced the transdermal delivery of the drug. | [77] |
| | | Chemotherapy | Temozolomide | The drug-loaded LP showed better inhibitory effects on cell proliferation, neoangiogenesis, growth, and vascularization of melanoma when compared to the free drug, with no apparent toxic effect. | [78] |
| | | Immunotherapy | Programmed cell death siRNA-1 (PD-1) | PD-1 siRNA-SLN significantly decreased PD-1 expression in cultured macrophages and tumor tissues, as well as tumor growth in vivo, compared to negative control. | [143] |

**Table 2.** *Cont.*

| | Functionalization | Therapy | Anticancer Agent(s) | Results | Ref. |
|---|---|---|---|---|---|
| Nanostructured lipid carriers (NLC) | Tyr-3-octreotide | Chemotherapy | Paclitaxel (PTX) | Compared to dacarbazine (DTIC), the carrier system exerted more apoptotic and anti-invasive effects in vitro; in addition, an interesting immune modulation was observed, resulting in effective reduction in tumor volume in vivo. Furthermore, a reduction in the number of nodule formations of pulmonary metastases was observed. | [79] |
| | | Immunotherapy | LEM2 | NLC improved LEM2 delivery and bioavailability issues and did not interfere with the drug's molecular mechanism of action, as it showed greater cytotoxicity against the A375 melanoma cell line than uncharged NLCs, probably due to the adhesion and occlusive properties of NLC in the stratum corneum. | [87] |
| | | Chemotherapy | Bupivacaine Lavender or Melaleuca essential oils | According to cytotoxicity tests, IC50 values of encapsulated bupivacaine decreased, relative to the free drug, in mice and human melanoma cells by ~80% and 62% (containing lavender oil) and 80% and 25% (containing melaleuca oil), respectively. In addition, anesthesia time doubled. | [188] |
| Polymeric nanoparticles (PNP) | Acid folic | Combination therapy | Metformin Doxorubicin | This drug carrier was developed with a new pH-sensitive homopolymer, based on the conjugation of sodium alginate, cholesterol, and folic acid, where metformin and doxorubicin were encapsulated. This system proved to be promising for effective combined drug delivery, increasing the antimelanoma effects. | [187] |
| | | Immunotherapy | siRNA | A nano-carrier developed for siRNA inhibited proliferation of B16F10 cells and significantly inhibited the growth and metastasis of melanoma in vivo. | [159] |
| | | Immunotherapy | CpG oligodeoxynucleotides | The nanocomplex effectively inhibited the growth of melanoma, the effect of which was attributed to the activation of both the innate and adaptive immune response. | [88] |
| Inorganic nanoparticles (INP) | meso-2,3-dimercaptosuccinic acid (DMSA) | Chemotherapy | Apigenin | The formulation of NP loaded with flavone apigenin and conjugated with DMSA improved bioavailability, increased antitumor and antimetastatic efficacy. | [80] |
| | | Radiotherapy | Iode-131 ($^{131}$I) | Combining grafted hybrid polymer (poly(methacrylic acid) NPs (PMAA-AuNPs) for systemic radioiodine therapy showed the effectiveness of a clinically relevant approach; therefore, this system is promising for use as a radiosensitizer in the field of RT internal radioisotopes. | [170] |
| | | Photothermal | | Carbon xerogel NPs converted NIR light to heat efficiently and within a duration of 10 min, successfully induced cell death, reduced necrosis by 70%, and resulted in significant reductions in tumors. | [214] |
| | MSH | Radiotherapy | Lutetium-177 ($^{177}$Lu) | Surface modification of the developed targeted ultra-small radiotherapeutic silica NPs, modified to have favorable pharmacokinetic properties, increased efficacy and survival. | [215] |

**Table 2.** *Cont.*

| | Functionalization | Therapy | Anticancer Agent(s) | Results | Ref. |
|---|---|---|---|---|---|
| Dendrimers (DM) | Arginine or mixture of arginine/lysine cationic polypeptides | Immunotherapy | Stimulator of interferon genes agonist | Arginine-modified dendrimer formulations were efficiently internalized into THP-1 cells, activating IRF3 and NF-κB, and showed less toxicity than unmodified dendrimers. The combination of the polypeptide-modified dendrimer-based system with anti-PD-1 induced large tumor regression. | [89] |
| Nanogels (NGs) | Methoxy polyethylene glycol (mPEG) | Immunotherapy | siRNA | Functionalized Au DENPs were able to deliver siPD-L1, resulting in a knock down of PD-L1 in tumors with an efficiency of 59%, thus mediating tumor immunotherapy (based on immune checkpoint blockade) and immune responses. | [216] |
| | | Combination therapy | Doxorrubicin (DXR) cytosine–phosphate–guanine (CpG) | The use of gel prolonged the action time of DOX-CpG NPs and allowed for sustained release of DOX and CpG NP, increasing the bioavailability of drugs and adjuvants. DOX-induced tumor cell damage provided tumor-associated antigens that promoted the immune system response, followed by the CpG NP effect, further improving the immune response and tumor inhibition. | [206] |
| | | Immunotherapy | Interleukin-2 (IL-2) | The designed system expanded the transferred tumor-reactive T cells 80 times more than free IL-2/Fc and showed no effects on tumor infiltration regulatory T cell expansion, with no overt toxicity. | [90] |
| Biomimetic nanoparticles (BNP) | | Chemotherapy | Doxorubicin (DXR) | Leukosomes, biomimetic NPs generated by combining lipids with membrane proteins derived from lipopolysaccharide-stimulated macrophages, showed more potent anticancer activity than LPs, reducing tumor volume and increasing survival, due to significantly greater accumulation in B16 tumors in vivo. This can be explained by the interaction of leukosome membrane proteins and tumor-associated vasculature. | [212] |
| | Folate modified red blood cell membrane | Combination therapy | Paclitaxel (PTX) indoleamine 2,3-dioxygenase (IDO) | The nanoplatform prolonged blood circulation and improved accumulation in tumor tissues, efficiently increasing uptake by specific cells (B16F10 and type M2 tumor-associated macrophages (TAM2)) and drug release. | [213] |
| | Antigenic peptide, a toll-like receptor 9 agonist and galactose-inserted erythrocyte membrane | Immunotherapy | Baicaina | PLGA biomimetic NPs reverted TAM phenotype M2 to M1 transition, resulting in effective T cell activation and induction of cytotoxic T cell responses and, consequently, significant suppression of melanoma tumor growth in vivo. | [217] |

## 7. Clinical Trials

Prior to clinical trials, it is essential to carry out an in-depth study of the pharmacokinetics, pharmacodynamics, and long-term toxic effects of nanosystems. In preclinical studies, the focus is essentially on the effectiveness of nanosystems; however, the control of adverse effects is not always adequately assessed. For this reason, when translated into clinical trials, nanoparticle-based medicines are often rejected due to their inadequate toxicological profiles. In fact, only fourteen clinical trials have been carried out regarding the application of nanosystems in melanoma therapy, a small number when compared to the preclinical studies carried out in recent years.

Data regarding clinical trials involving NPs for the treatment and/or detection of melanoma were obtained using the key words “nanoparticles” and “melanoma”, searched on the ClinicalTrials.gov platform [218]. From the clinical studies found, one has been suspended and one refers to the study of a sunscreen. Regarding the phases of clinical studies, three were phase 1, six were phase 2, and one was phase 1 and 2. Additionally, in eight

clinical studies, NPs were administered intravenously (IV) and they were administered locally, by peritumoral and intratumoral injection, in only two studies. All studies recruited patients of both sexes and older than 18 years. Some examples of these clinical trials are described below.

The effectiveness of ABI-007 (a Cremophor®-free, protein-stabilized, nanoparticle Paclitaxel) in treating patients with locally recurrent or metastatic melanoma that is inoperable (unresectable) was investigated in a phase II trial. Drugs like temozolomide, carboplatin, and a paclitaxel albumin-stabilized nanoparticle formulation (ABI-007) function in multiple ways to stop tumor cells from growing, either by killing the cells or preventing them from dividing. To treat patients with stage IV malignant melanoma that cannot be removed surgically, a randomized phase II trial was also carried out to examine the side effects of administering temozolomide in combination with bevacizumab as well as how it performs in comparison to administering bevacizumab in combination with carboplatin and ABI-007.

In another randomized phase II trial, nab-paclitaxel (paclitaxel albumin-stabilized nanoparticle formulation) and bevacizumab or ipilimumab are being used as first-line therapy in treating patients with stage IV melanoma that cannot be removed by surgery. Bevacizumab may stop the growth of tumor cells by binding to vascular endothelial growth factor and by preventing the growth of new blood vessels. Ipilimumab blocks a substance called cytotoxic T-lymphocyte-associated antigen-4 on the surface of T cells and may help the immune system kill tumor cells. This study will allow us to evaluate whether nab-paclitaxel and bevacizumab are more effective than ipilimumab in treating melanoma.

In another clinical trial, CALAA-01, a nanocomplex formulation designed to inhibit tumor growth and/or reduce tumor size, has as its active ingredient a small interfering RNA (siRNA), which inhibits tumor growth via RNA interference to reduce expression of the M2 subunit of ribonucleotide reductase (R2). The complete nanocomplex formulation consists of four components: a duplex of synthetic, non-chemically modified siRNA (C05C); a cyclodextrin-containing polymer (CAL101); a stabilizing agent (AD-PEG); and a targeting agent (AD-PEG-Tf) that contains the human transferrin protein (Tf). The cationic polymer and anionic siRNA interact electrostatically to form nanocomplexes that are less than 100 nm in diameter and protect the siRNA from serum nuclease degradation. The cells that overexpress the transferrin receptor (TfR) are the target of the siRNA-containing nanocomplex. The siRNA-containing nanocomplex enters the target cell via endocytosis after transferrin attaches to TfRs on the cell surface.

Gold nanorods (GNRs) injected via the intratumoral route and activated by Near-Infrared Spectroscopy (NIR) light generate localized heat through a process called targeted hyperthermia therapy (THT), which allows us to selectively target tumor cells while minimizing damage to surrounding healthy tissues. A new phase I/II device clinical trial is investigating the safety and efficacy of GNR-mediated THT in patients with stage 3C/3D/4M1 cutaneous metastatic melanoma unresponsive to systemic immunotherapy or in patients who have contraindications to systemic immunotherapy. This trial, which is not yet recruiting, aims to establish a safe, effective dose of GNRs for THT for cutaneous metastatic melanoma treatment and explore the potential for its localized tumor destruction.

Despite the many advantages associated with the use of nanoparticles, it is important to emphasize that non-biodegradable nanoparticles (e.g., gold, silica, dendrimers) can persist in organs for long periods and accumulate in the liver, spleen, and other reticuloendothelial system tissues. This raises concerns about chronic organ toxicity, inflammation, or unknown long-term effects because they are not broken down and cleared like biodegradable carriers [219].

Table 3 also summarizes information from some relevant clinical trials involving NPs and melanoma patients listed on ClinicalTrials.gov [218].

**Table 3.** Summary information from some relevant clinical trials involving NPs and melanoma patients listed on ClinicalTrials.gov [218].

| Title | Status | Study Results | Conditions | Interventions | Outcome Measures | Phase |
|---|---|---|---|---|---|---|
| Sunscreen Based on Bioadhesive Nanoparticles | Completed | No Results Available | Melanoma and UV Ray Skin Damage | Drug: standard sunscreen (padimate O (7%) and oxybenzone (3%)) Device: bioadesive nanoparticles | Skin reaction | Phase 1 (13 enrolled) |
| Novel RNA-Nanoparticle Vaccine for the Treatment of Early Melanoma Recurrence Following Adjuvant Anti-PD-1 Antibody Therapy | Suspended | No Results Available | Melanoma | Biological: Autologous total tumor mRNA-loaded DOTAP liposome vaccine | Skin reaction | Phase 1 (18 enrolled) |
| Targeted Silica Nanoparticles for Real-Time Image-Guided Intraoperative Mapping of Nodal Metastases | Active, not recruiting | No Results Available | Head and Neck Melanoma | Drug: fluorescent dye-labeled particle (cRGDY-PEG-Cy5.5-C dots) | Feasibility of conducting pre-operative SLN mapping | Phase 1 Phase 2 (86 enrolled) |
| Bevacizumab and Temozolomide or Bevacizumab and Paclitaxel Albumin-Stabilized Nanoparticle Formulation and Carboplatin in Treating Patients With Stage IV Malignant Melanoma That Cannot Be Removed by Surgery | Completed | Has Results | Melanoma (Skin) | Biological: bevacizumab \| Drug: carboplatin Drug: paclitaxel albumin-stabilized nanoparticle formulation Drug: temozolomide | Progression-free survival at 6 months; tumor response rate, calculated as a percentage along With its 95% confidence interval; overall survival | Phase 2 (95 enrolled) |
| Paclitaxel Albumin-Stabilized Nanoparticle Formulation in Treating Patients With Metastatic Melanoma of the Eye That Cannot Be Removed By Surgery | Completed | Has Results | Intraocular Melanoma | Drug: nab-paclitaxel (paclitaxel albumin-stabilized nanoparticle formulation) | Overall response rate; progression-free survival; overall survival | Phase 2 (4 enrolled) |
| ABI-007 in Treating Patients With Inoperable Locally Recurrent or Metastatic Melanoma | Completed | No Results Available | Melanoma (Skin) | Drug: paclitaxel albumin-stabilized nanoparticle formulation | Not included | Phase 2 |
| Carboplatin and ABI-007 in Treating Patients With Stage IV Melanoma That Cannot Be Removed By Surgery | Completed | Has Results | Melanoma (Skin) | Drug: carboplatin Drug: paclitaxel albumin-stabilized nanoparticle formulation | Tumor response sate, as measured by RECIST criteria; survival time; time to disease progression; duration of response; number of treatment cycles administered | Phase 2 (76 enrolled) |
| MR Lymphography and Magnetic Sentinel Lymph Node Biopsy in Melanoma Patients Measured With DiffMag | Unknown status | No Results Available | Melanoma (Skin) | Device: magnetic (super paramagnetic iron oxide (SPIO) nanoparticles) sentinel lymph node (SLN) biopsy by means of Magtrace®, in combination with SentiMag® and DiffMag | True positive/false negative rate for magnetic SLN detection measured via the DiffMag system and the Sentimag system compared to radioactive detection. True positive/false negative rate for metastatic SLN using ex vivo MRI. True positive/false negative rate for metastatic SLN using in vivo MRI. | Not Applicable (20 enrolled) |

**Table 3.** *Cont.*

| Title | Status | Study Results | Conditions | Interventions | Outcome Measures | Phase |
|---|---|---|---|---|---|---|
| Stereotactic Brain-Directed Radiation With or Without Aguix Gadolinium-Based Nanoparticles in Brain Metastases | Recruiting | No Results Available | Brain Cancer, Brain Metastases, Melanoma, Lung Cancer, Breast Cancer, HER2-positive Breast Cancer, Colorectal Cancer, Gastrointestinal Cancer, SRS, SRT, Whole-Brain Radiation, Stereotactic Radiation, AGuIX Nanoparticles, Cystic Brain Tumor | Radiation: stereotactic radiation<br>Drug: AGuIX gadolinium-based nanoparticles<br>Other: placebo | Key clinical endpoints include local recurrence, overall survival (OS), progression-free survival (PFS), time to progression (TTP), neurologic-related death, performance status, daily living activities, and incidence/timing of new brain metastases, radiation necrosis, leptomeningeal disease, intracranial progression, salvage craniotomy, additional radiotherapy, seizures, and steroid use. Neurocognitive functions assessed cover verbal learning and memory, visual attention and task switching, verbal fluency, and overall cognitive impairment. | Phase 2<br>(112 enrolled) |
| Nab-Paclitaxel and Bevacizumab or Ipilimumab as First-Line Therapy in Treating Patients With Stage IV Melanoma That Cannot Be Removed by Surgery | Completed | Has Results | Metastatic Melanoma, Mucosal Melanoma, Stage IV Cutaneous Melanoma AJCC v6 and v7, Stage IV Uveal Melanoma AJCC v7, Unresectable Melanoma | Biological: bevacizumab<br>Biological: ipilimumab<br>Other: laboratory biomarker analysis<br>Drug: nab-paclitaxel (paclitaxel albumin-stabilized nanoparticle formulation) | Progression-free survival (PFS); overall survival (OS); number of patients with tumor response; number of patients who experienced toxicity | Phase 2<br>(24 enrolled) |
| A Study of BIND-014 Given to Patients With Advanced or Metastatic Cancer | Completed | No Results Available | Metastatic Cancer, Cancer, Solid Tumors | Drug: BIND-014 (docetaxel nanoparticles for injectable suspension) | To assess the dose-limiting toxicities (DLTs) of BIND-014 when given on day 1 of a 21-day cycle or when given on day 1, 8, and 15 of a 28-day cycle. To characterize the pharmacokinetics of BIND-014 following an IV infusion. To assess any preliminary evidence of antitumor activity observed with BIND-014. To assess changes in serum tumor markers when appropriate. | Phase 1<br>(58 enrolled) |

**Table 3.** *Cont.*

| Title | Status | Study Results | Conditions | Interventions | Outcome Measures | Phase |
|---|---|---|---|---|---|---|
| Dose Escalation Study of mRNA-2752 for Intratumoral Injection to Participants With Advanced Malignancies | Active, not recruiting | No Results Available | Dose Escalation: Relapsed, Refractory Solid Tumor Malignancies, or Lymphoma<br>Dose Expansion: Triple-Negative Breast Cancer, HNSCC, Non-Hodgkins, Urothelial Cancer, Immune Checkpoint Refractory Melanoma, and NSCLC Lymphoma | Biological: mRNA-2752<br>Biological: durvalumab<br>Device: lipid nanoparticle | Number of participants with dose-limiting toxicities (DLTs). Number of participants with adverse events (AEs). Arm B: overall response rate (ORR): percentage of participants with tumor response (partial or complete) based on response evaluation criteria in solid tumors version 1.1 in cutaneous melanoma. ORR: percentage of participants with tumor response (partial or complete) based on RECIST v1.1 and modified RECIST (iRECIST), and Cheson and lymphoma response to immunomodulatory therapy criteria (LYRIC) for participants with lymphoma. Pharmacokinetics: maximum observed concentration (Cmax) | Phase I<br>(264 enrolled) |
| Nab-Paclitaxel and Bevacizumab in Treating Patients With Unresectable Stage IV Melanoma or Gynecological Cancers | Suspended | No Results Available | Stage IV Unresectable Melanoma, Cancer of the Cervix, Endometrium, Ovary, Fallopian Tube, or Peritoneal Cavity | Biological: bevacizumab laboratory biomarker analysis<br>Drug: nab-paclitaxel (paclitaxel albumin-stabilized nanoparticle formulation)<br>Pharmacological study | Maximum tolerated dose; tumor response; progression-free survival (PFS); overall survival (OS); incidence of adverse events (soft tissue expansion cohort) | Phase 1<br>(73 enrolled) |
| Safety Study of CALAA-01 to Treat Solid Tumor Cancers | Terminated | No Results Available | Cancer, Solid Tumor | Drug: CALAA-01 (a small interfering RNA (siRNA)) protected from nuclease degradation within a stabilized nanoparticle targeted to tumor cells | Objectives include assessing the tolerability, safety, and maximum tolerated dose (MTD) of intravenous CALAA-01; characterizing its pharmacokinetics (PK); evaluating preliminary tumor response for efficacy; recommending a dose for future studies; and measuring immune response by antibody, cytokine levels, and complement effects. | Phase 1<br>(24 enrolled) |

## 8. Conclusions

In this work, we addressed the use of NPs to improve melanoma treatment, focusing on targeting, concepts, recent studies, and more relevant research. Furthermore, the advantages and disadvantages of the most widely studied and used types of NPs, such as LSs, LNPs, PNPs, DMs, and INPs, were highlighted.

The advantages of NPs for melanoma patients include the increase in the effectiveness of chemotherapy, immunotherapy, radiotherapy, and phototherapy. Furthermore, all these advantages also contribute to a reduction in side effects. However, there are still some difficulties, especially regarding the industrial-scale production of drug delivery systems based on nanotechnology. Still, we can already find on the market some examples of drugs for the treatment of various tumors which provide patients with benefits resulting from the use of nanocarriers. In addition, several clinical trials with nanoparticulate systems have been carried out. This shows that many efforts have been made to overcome barriers and make more effective medicines containing NPs as an alternative for the treatment of patients with melanoma.

Altogether, the use of NPs is a very promising therapeutic strategy, as they can greatly improve survival and quality of life among melanoma patients.

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## References

1. Orzan, O.A.; Șandru, A.; Jecan, C.R. Controversies in the diagnosis and treatment of early cutaneous melanoma. *J. Med. Life* **2015**, *8*, 132–141.
2. Cullen, J.K.; Simmons, J.L.; Parsons, P.G.; Boyle, G.M. Topical treatments for skin cancer. *Adv. Drug Deliv. Rev.* **2020**, *153*, 54–64. [CrossRef]
3. Miller, K.D.; Fidler-Benaoudia, M.; Keegan, T.H.; Hipp, H.S.; Jemal, A.; Siegel, R.L. Cancer statistics for adolescents and young adults, 2020. *CA A Cancer J. Clin.* **2020**, *70*, 443–459. [CrossRef]
4. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. *CA A Cancer J. Clin.* **2021**, *71*, 7–33. [CrossRef]
5. Sacchetto, L.; Zanetti, R.; Comber, H.; Bouchardy, C.; Brewster, D.H.; Broganelli, P.; Chirlaque, M.D.; Coza, D.; Galceran, J.; Gavin, A.; et al. Trends in incidence of thick, thin and in situ melanoma in Europe. *Eur. J. Cancer* **2018**, *92*, 108–118. [CrossRef] [PubMed]
6. Balch, C.M.; Gershenwald, J.E.; Soong, S.-J.; Thompson, J.F.; Atkins, M.B.; Byrd, D.R.; Buzaid, A.C.; Cochran, A.J.; Coit, D.G.; Ding, S.; et al. Final version of 2009 AJCC melanoma staging and classification. *J. Clin. Oncol.* **2009**, *27*, 6199–6206. [CrossRef] [PubMed]
7. Naik, P.P. Cutaneous Malignant Melanoma: A Review of Early Diagnosis and Management. *World J. Oncol.* **2021**, *12*, 7–19. [CrossRef] [PubMed]
8. Miller, K.D.; Nogueira, L.; Mariotto, A.B.; Rowland, J.H.; Yabroff, K.R.; Alfano, C.M.; Jemal, A.; Kramer, J.L.; Siegel, R.L. Cancer treatment and survivorship statistics, 2019. *CA Cancer J. Clin.* **2019**, *69*, 363–385. [CrossRef]
9. Lopes, J.; Rodrigues, C.M.; Gaspar, M.M.; Reis, C.P. Melanoma management: From epidemiology to treatment and latest advances. *Cancers* **2022**, *14*, 4652. [CrossRef]
10. Beiu, C.; Giurcaneanu, C.; Grumezescu, A.M.; Holban, A.M.; Popa, L.G.; Mihai, M.M. Nanosystems for improved targeted therapies in melanoma. *J. Clin. Med.* **2020**, *9*, 318. [CrossRef]
11. Song, M.; Liu, C.; Chen, S.; Zhang, W. Nanocarrier-Based Drug Delivery for Melanoma Therapeutics. *Int. J. Mol. Sci.* **2021**, *22*, 1873. [CrossRef]

12. Mu, W.; Chu, Q.; Liu, Y.; Zhang, N. A review on nano-based drug delivery system for cancer chemoimmunotherapy. *Nano-Micro Lett.* **2020**, *12*, 142. [CrossRef] [PubMed]
13. López-Estévez, A.M.; Lapuhs, P.; Pineiro-Alonso, L.; Alonso, M.J. Personalized cancer nanomedicine: Overcoming biological barriers for intracellular delivery of biopharmaceuticals. *Adv. Mater.* **2024**, *36*, e2309355. [CrossRef] [PubMed]
14. Bombelli, F.B.; Webster, C.A.; Moncrieff, M.; Sherwood, V. The scope of nanoparticle therapies for future metastatic melanoma treatment. *Lancet Oncol.* **2014**, *15*, e22–e32. [CrossRef] [PubMed]
15. Cassano, R.; Cuconato, M.; Calviello, G.; Serini, S.; Trombino, S. Recent advances in nanotechnology for the treatment of melanoma. *Molecules* **2021**, *26*, 785. [CrossRef]
16. Prow, T.W.; Grice, J.E.; Lin, L.L.; Faye, R.; Butler, M.; Becker, W.; Wurm, E.M.; Yoong, C.; Robertson, T.A.; Soyer, H.P. Nanopar-ticles and microparticles for skin drug delivery. *Adv. Drug Deliv. Rev.* **2011**, *63*, 470–491. [CrossRef]
17. Li, J.; Wang, Y.; Liang, R.; An, X.; Wang, K.; Shen, G.; Tu, Y.; Zhu, J.; Tao, J. Recent advances in targeted nanoparticles drug delivery to melanoma. *Nanomed. Nanotechnol. Biol. Med.* **2015**, *11*, 769–794. [CrossRef]
18. Manconi, M.; Sinico, C.; Caddeo, C.; Vila, A.O.; Valenti, D.; Fadda, A.M. Penetration enhancer containing vesicles as carriers for dermal delivery of tretinoin. *Int. J. Pharm.* **2011**, *412*, 37–46. [CrossRef]
19. Pardeike, J.; Hommoss, A.; Müller, R.H. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. *Int. J. Pharm.* **2009**, *366*, 170–184. [CrossRef]
20. Sinico, C.; Fadda, A.M. Vesicular carriers for dermal drug delivery. *Expert Opin. Drug Deliv.* **2009**, *6*, 813–825. [CrossRef]
21. Feng, S.; Zhang, Z.; Almotairy, A.; Repka, M.A. Development and evaluation of polymeric mixed micelles prepared using hotmelt extrusion for extended delivery of poorly water-soluble drugs. *J. Pharm. Sci.* **2023**, *112*, 2869–2878. [CrossRef]
22. Fitzpatrick, T.B. The Validity and Practicality of Sun-Reactive Skin Types I Through VI. *Arch. Dermatol.* **1988**, *124*, 869–871. [CrossRef]
23. Miller, A.J.; Mihm, C.M., Jr. Melanoma. *N. Engl. J. Med.* **2006**, *355*, 51–65. [CrossRef]
24. Burns, D.; George, J.; Aucoin, D.; Bower, J.; Burrell, S.; Gilbert, R.; Bower, N. The pathogenesis and clinical management of cutaneous melanoma: An evidence-based review. *J. Med. Imaging Radiat. Sci.* **2019**, *50*, 460–469.e1. [CrossRef]
25. Smith, A.J.; Lambert, P.C.; Rutherford, M.J. Understanding the impact of sex and stage differences on melanoma cancer patient survival: A SEER-based study. *Br. J. Cancer* **2021**, *124*, 671–677. [CrossRef] [PubMed]
26. Lesage, C.; Barbe, C.; Le Clainche, A.; Lesage, F.-X.; Bernard, P.; Grange, F. Sex-related location of head and neck melanoma strongly argues for a major role of sun exposure in cars and photoprotection by hair. *J. Investig. Dermatol.* **2013**, *133*, 1205–1211. [CrossRef] [PubMed]
27. Hamid, O.; Molinero, L.; Bolen, C.R.; Sosman, J.A.; Muñoz-Couselo, E.; Kluger, H.M.; McDermott, D.F.; Powderly, J.D.; Sarkar, I.; Ballinger, M.; et al. Safety, clinical activity, and biological correlates of response in patients with metastatic melanoma: Results from a phase I trial of atezolizumab. *Clin. Cancer Res.* **2019**, *25*, 6061–6072. [CrossRef] [PubMed]
28. Flaherty, K.T.; Hodi, F.S.; Fisher, D.E. From genes to drugs: Targeted strategies for melanoma. *Nat. Rev. Cancer* **2012**, *12*, 349–361. [CrossRef]
29. Hill, V.K.; Gartner, J.J.; Samuels, Y.; Goldstein, A.M. The genetics of melanoma: Recent advances. *Annu. Rev. Genom. Hum. Genet.* **2013**, *14*, 257–279. [CrossRef]
30. Jacobs, J.F.; Nierkens, S.; Figdor, C.G.; de Vries, I.J.M.; Adema, G.J. Regulatory T cells in melanoma: The final hurdle towards effective immunotherapy? *Lancet Oncol.* **2012**, *13*, e32–e42. [CrossRef]
31. Pautu, V.; Leonetti, D.; Lepeltier, E.; Clere, N.; Passirani, C. Nanomedicine as a potent strategy in melanoma tumor microenviron-ment. *Pharmacol. Res.* **2017**, *126*, 31–53. [CrossRef]
32. Popescu, M.; Munteanu, A.; Isvoranu, G.; Suciu, L.; Pavel, B.; Marinescu, B.; Zagrean, L. Dynamics of endothelial progenitor cells following sevoflurane preconditioning. *Roum. Arch. Microbiol. Immunol.* **2011**, *70*, 109–113.
33. Mihai, M.M.; Holban, A.M.; Călugăreanu, A.; Orzan, O.A. Recent advances in diagnosis and therapy of skin cancers through nanotechnological approaches. In *Nanostructures for Cancer Therapy*; Elsevier: Amsterdam, The Netherlands, 2017; pp. 285–306.
34. Mihai, M.M.; Dima, M.B.; Dima, B.; Holban, A.M. Nanomaterials for wound healing and infection control. *Materials* **2019**, *12*, 2176. [CrossRef]
35. Adnane, F.; El-Zayat, E.; Fahmy, H.M. The combinational application of photodynamic therapy and nanotechnology in skin cancer treatment: A review. *Tissue Cell* **2022**, *77*, 101856. [CrossRef] [PubMed]
36. Bahreyni, A.; Mohamud, Y.; Luo, H. Recent advancements in immunotherapy of melanoma using nanotechnology-based strategies. *Biomed. Pharmacother.* **2023**, *159*, 114243. [CrossRef] [PubMed]
37. Wang, Z.; Yu, Y.; Wang, C.; Li, J.; Pang, Y. Advances in the Application of Nanomaterials to the Treatment of Melanoma. *Pharmaceutics* **2022**, *14*, 2090. [CrossRef] [PubMed]
38. Zhang, P.; Han, T.; Xia, H.; Dong, L.; Chen, L.; Lei, L. Advances in Photodynamic Therapy Based on Nanotechnology and Its Application in Skin Cancer. *Front. Oncol.* **2022**, *12*, 836397. [CrossRef]

39. Pereira, T.A.; Ramos, D.N.; Sobral, L.M.; Martins, Y.A.; Petrilli, R.; Fantini, M.d.A.C.; Leopoldino, A.M.; Lopez, R.F.V. Liquid crystalline nanogel targets skin cancer via low-frequency ultrasound treatment. *Int. J. Pharm.* **2023**, *646*, 123431. [CrossRef]
40. e Silva, S.A.M.; de Souza, J.G.; Melo, P.S.; Moreno, I.A.M.; Alencar, S.M.; Lopez, R.F.V.; Leonardi, G.R. Target action of antioxidants using iontophoresis. *J. Cosmet. Dermatol.* **2021**, *20*, 664–676. [CrossRef]
41. Vale, D.L.; Martinez, R.M.; Medeiros, D.C.; da Rocha, C.; Sfeir, N.; Lopez, R.F.V.; Vicentini, F.T.M.C.; Verri, W.A.; Georgetti, S.R.; Baracat, M.M.; et al. A topical formulation containing quercetin-loaded microcapsules protects against oxidative and inflammatory skin alterations triggered by UVB irradiation: Enhancement of activity by microencapsulation. *J. Drug Target.* **2021**, *29*, 983–997. [CrossRef]
42. Martin, B.A.; Dalmolin, L.F.; Lemos, C.N.; Vaidergorn, M.d.M.; Emery, F.d.S.; Vargas-Rechia, C.G.; Ramos, A.P.; Lopez, R.F.V. Electrostimulable polymeric films with hyaluronic acid and lipid nanoparticles for simultaneous topical delivery of macromolecules and lipophilic drugs. *Drug Deliv. Transl. Res.* **2024**, *14*, 2499–2519. [CrossRef]
43. Ceci, P.; Vannucci, L.; Falvo, E.; Fornara, M.; Micco, D.; Benada, O.; Krizan, J.; Svoboda, J.; Capkova, H.; Morea, V.; et al. Selective targeting of melanoma by PEG-masked protein-based multifunctional nanoparticles. *Int. J. Nanomed.* **2012**, *7*, 1489–1509. [CrossRef]
44. Marques, A.C.; Costa, P.J.; Velho, S.; Amaral, M.H. Functionalizing nanoparticles with cancer-targeting antibodies: A comparison of strategies. *J. Control. Release* **2020**, *320*, 180–200. [CrossRef]
45. Saeed, M.; Zalba, S.; Seynhaeve, A.L.; Debets, R.; Hagen, T.L.M.T. Liposomes targeted to MHC-restricted antigen improve drug delivery and antimelanoma response. *Int. J. Nanomed.* **2019**, *14*, 2069–2089. [CrossRef]
46. Wang, Y.; Yang, T.; Wang, X.; Dai, W.; Wang, J.; Zhang, X.; Li, Z.; Zhang, Q. Materializing sequential killing of tumor vasculature and tumor cells via targeted polymeric micelle system. *J. Control. Release* **2011**, *149*, 299–306. [CrossRef]
47. Dossgg, L.L.; Memula, N. The radioresponsiveness of melanoma. *Int. J. Radiat. Oncol. Biol. Phys.* **1982**, *8*, 1131–1134. [CrossRef]
48. Daneshvar, F.; Salehi, F.; Karimi, M.; Vais, R.D.; Mosleh-Shirazi, M.; Sattarahmady, N. Combined X-ray radiotherapy and laser photothermal therapy of melanoma cancer cells using dual-sensitization of platinum nanoparticles. *J. Photochem. Photobiol. B Biol.* **2020**, *203*, 111737. [CrossRef] [PubMed]
49. Testori, A.; Rutkowski, P.; Marsden, J.; Bastholt, L.; Chiarion-Sileni, V.; Hauschild, A.; Eggermont, A.M.M. Surgery and radiotherapy in the treatment of cutaneous melanoma. *Ann. Oncol.* **2009**, *20*, vi22–vi29. [CrossRef] [PubMed]
50. Espenel, S.; Vallard, A.; Rancoule, C.; Garcia, M.-A.; Guy, J.-B.; Chargari, C.; Deutsch, E.; Magné, N. Melanoma: Last call for radiotherapy. *Crit. Rev. Oncol. Hematol.* **2017**, *110*, 13–19. [CrossRef] [PubMed]
51. Shi, L.; Luo, M.; Zhang, F.; Zhang, L.; Wang, B.; Liu, P.; Zhang, Y.; Zhang, H.; Yang, D.; Zhang, G.; et al. Photothermal therapy enhanced the effectiveness of imiquimod against refractory cutaneous warts through boosting immune responses. *J. Biophotonics* **2019**, *12*, e201800149. [CrossRef]
52. Zhang, Z.; Wang, J.; Nie, X.; Wen, T.; Ji, Y.; Wu, X.; Zhao, Y.; Chen, C. Near infrared laser-induced targeted cancer therapy using thermoresponsive polymer encapsulated gold nanorods. *J. Am. Chem. Soc.* **2014**, *136*, 7317–7326. [CrossRef] [PubMed]
53. Ouyang, X.; Wang, X.; Kraatz, H.-B.; Ahmadi, S.; Gao, J.; Lv, Y.; Sun, X.; Huang, Y. A Trojan horse biomimetic delivery strategy using mesenchymal stem cells for PDT/PTT therapy against lung melanoma metastasis. *Biomater. Sci.* **2020**, *8*, 1160–1170. [CrossRef]
54. Wang, X.; Ouyang, X.; Chen, J.; Hu, Y.; Sun, X.; Yu, Z. Nanoparticulate photosensitizer decorated with hyaluronic acid for photodynamic/photothermal cancer targeting therapy. *Nanomedicine* **2019**, *14*, 151–167. [CrossRef] [PubMed]
55. Zhu, H.; Fang, Y.; Miao, Q.; Qi, X.; Ding, D.; Chen, P.; Pu, K. Regulating near-infrared photodynamic properties of semiconducting polymer nanotheranostics for optimized cancer therapy. *ACS Nano* **2017**, *11*, 8998–9009. [CrossRef] [PubMed]
56. Han, Y.-H.; Kankala, R.K.; Wang, S.-B.; Chen, A.-Z. Leveraging engineering of indocyanine green-encapsulated polymeric nanocomposites for biomedical applications. *Nanomaterials* **2018**, *8*, 360. [CrossRef]
57. Zhang, Y.; Yang, D.; Chen, H.; Lim, W.Q.; Phua, F.S.Z.; An, G.; Yang, P.; Zhao, Y. Reduction-sensitive fluorescence enhanced polymeric prodrug nanoparticles for combinational photothermal-chemotherapy. *Biomaterials* **2018**, *163*, 14–24. [CrossRef]
58. You, Q.; Sun, Q.; Wang, J.; Tan, X.; Pang, X.; Liu, L.; Yu, M.; Tan, F.; Li, N. A single-light triggered and dual-imaging guided multifunctional platform for combined photothermal and photodynamic therapy based on TD-controlled and ICG-loaded CuS@$mSiO_2$. *Nanoscale* **2017**, *9*, 3784–3796. [CrossRef]
59. Yang, R.; Hou, M.; Gao, Y.; Lu, S.; Zhang, L.; Xu, Z.; Li, C.M.; Kang, Y.; Xue, P. Biomineralization-inspired crystallization of manganese oxide on silk fibroin nanoparticles for in vivo Mr/fluorescence imaging-assisted tri-modal therapy of cancer. *Theranostics* **2019**, *9*, 6314–6333. [CrossRef]
60. Chen, J.; Li, X.; Liu, X.; Yan, H.; Xie, Z.; Sheng, Z.; Gong, X.; Wang, L.; Liu, X.; Zhang, P.; et al. Hybrid $MoSe_2$–indocyanine green nanosheets as a highly efficient phototheranostic agent for photoacoustic imaging guided photothermal cancer therapy. *Biomater. Sci.* **2018**, *6*, 1503–1516. [CrossRef]
61. Wen, L.; Hyoju, R.; Wang, P.; Shi, L.; Li, C.; Li, M.; Wang, X. Hydrogen-Peroxide-Responsive Protein Biomimetic Nanoparticles for Photothermal-Photodynamic Combination Therapy of Melanoma. *Lasers Surg. Med.* **2021**, *53*, 390–399. [CrossRef]

62. Kil Song, C.; Lee, J.-H.; Jahn, A.; Choi, M.J.; Namgoong, S.K.; Hong, S.-S.; Chong, S.; Shim, C.-K.; Chung, S.-J.; Kim, D.-D. In vitro and in vivo evaluation of N,N,N-trimethylphytosphingosine-iodide (TMP) in liposomes for the treatment of angiogenesis and metastasis. *Int. J. Pharm.* **2012**, *434*, 191–198. [CrossRef]
63. Qin, S.-Y.; Cheng, Y.-J.; Lei, Q.; Zhang, A.-Q.; Zhang, X.-Z. Combinational strategy for high-performance cancer chemotherapy. *Biomaterials* **2018**, *171*, 178–197. [CrossRef]
64. Zhang, M.; Liu, E.; Cui, Y.; Huang, Y. Nanotechnology-based combination therapy for overcoming multidrug-resistant cancer. *Cancer Biol. Med.* **2017**, *14*, 212–227. [CrossRef]
65. Raaijmakers, M.I.G.; Widmer, D.S.; Narechania, A.; Eichhoff, O.; Freiberger, S.N.; Wenzina, J.; Cheng, P.F.; Mihic-Probst, D.; Desalle, R.; Dummer, R.; et al. Co-existence of *BRAF* and *NRAS* driver mutations in the same melanoma cells results in heterogeneity of targeted therapy resistance. *Oncotarget* **2016**, *7*, 77163–77174. [CrossRef] [PubMed]
66. Zaretsky, J.M.; Garcia-Diaz, A.; Shin, D.S.; Escuin-Ordinas, H.; Hugo, W.; Hu-Lieskovan, S.; Torrejon, D.Y.; Abril-Rodriguez, G.; Sandoval, S.; Barthly, L.; et al. Mutations associated with acquired resistance to PD-1 blockade in melanoma. *N. Engl. J. Med.* **2016**, *375*, 819–829. [CrossRef] [PubMed]
67. Vergani, E.; Vallacchi, V.; Frigerio, S.; Deho, P.; Mondellini, P.; Perego, P.; Cassinelli, G.; Lanzi, C.; Testi, M.A.; Rivoltini, L.; et al. Identification of MET and SRC activation in melanoma cell lines showing primary resistance to PLX4032. *Neoplasia* **2011**, *13*, 1132–1142. [CrossRef] [PubMed]
68. Villanueva, J.; Infante, J.R.; Krepler, C.; Reyes-Uribe, P.; Samanta, M.; Chen, H.-Y.; Li, B.; Swoboda, R.K.; Wilson, M.; Vultur, A.; et al. Concurrent MEK2 mutation and BRAF amplification confer resistance to BRAF and MEK inhibitors in melanoma. *Cell Rep.* **2013**, *4*, 1090–1099. [CrossRef]
69. Ablain, J.; Xu, M.; Rothschild, H.; Jordan, R.C.; Mito, J.K.; Daniels, B.H.; Bell, C.F.; Joseph, N.M.; Wu, H.; Bastian, B.C.; et al. Human tumor genomics and zebrafish modeling identify *SPRED1* loss as a driver of mucosal melanoma. *Science* **2018**, *362*, 1055–1060. [CrossRef]
70. Horn, S.; Leonardelli, S.; Sucker, A.; Schadendorf, D.; Griewank, K.G.; Paschen, A. Tumor CDKN2A-associated JAK2 loss and susceptibility to immunotherapy resistance. *JNCI J. Natl. Cancer Inst.* **2018**, *110*, 677–681. [CrossRef]
71. Davis, E.; Teng, H.; Bilican, B.; Parker, I.M.; Liu, B.; Carriera, S.; Goding, C.R.; Prince, S. Ectopic Tbx2 expression results in polyploidy and cisplatin resistance. *Oncogene* **2008**, *27*, 976–984. [CrossRef]
72. Pakneshan, S.; Salajegheh, A.; Smith, R.A.; Lam, A.K.-Y. Clinicopathological relevance of BRAF mutations in human cancer. *Pathology* **2013**, *45*, 346–356. [CrossRef]
73. Ruzzolini, J.; Peppicelli, S.; Andreucci, E.; Bianchini, F.; Margheri, F.; Laurenzana, A.; Fibbi, G.; Pimpinelli, N.; Calorini, L. Everolimus selectively targets vemurafenib resistant BRAFV600E melanoma cells adapted to low pH. *Cancer Lett.* **2017**, *408*, 43–54. [CrossRef]
74. Walbrecq, G.; Lecha, O.; Gaigneaux, A.; Fougeras, M.R.; Philippidou, D.; Margue, C.; Nomigni, M.T.; Bernardin, F.; Dittmar, G.; Behrmann, I.; et al. Hypoxia-induced adaptations of miRNomes and proteomes in melanoma cells and their secreted extracellular vesicles. *Cancers* **2020**, *12*, 692. [CrossRef]
75. Patel, D.; Gao, Y.; Son, K.; Siltanen, C.; Neve, R.M.; Ferrara, K.; Revzin, A. Microfluidic co-cultures with hydrogel-based ligand trap to study paracrine signals giving rise to cancer drug resistance. *Lab A Chip* **2015**, *15*, 4614–4624. [CrossRef] [PubMed]
76. Wilson, B.J.; Saab, K.R.; Ma, J.; Schatton, T.; Pütz, P.; Zhan, Q.; Murphy, G.F.; Gasser, M.; Waaga-Gasser, A.M.; Frank, N.Y.; et al. ABCB5 maintains melanoma-initiating cells through a proinflammatory cytokine signaling circuit. *Cancer Res.* **2014**, *74*, 4196–4207. [CrossRef]
77. Zou, L.; Ding, W.; Zhang, Y.; Cheng, S.; Li, F.; Ruan, R.; Wei, P.; Qiu, B. Peptide-modified vemurafenib-loaded liposomes for targeted inhibition of melanoma via the skin. *Biomaterials* **2018**, *182*, 1–12. [CrossRef] [PubMed]
78. Clemente, N.; Ferrara, B.; Gigliotti, C.L.; Boggio, E.; Capucchio, M.T.; Biasibetti, E.; Schiffer, D.; Mellai, M.; Annovazzi, L.; Cangemi, L.; et al. Solid lipid nanoparticles carrying temozolomide for melanoma treatment. Preliminary in vitro and in vivo studies. *Int. J. Mol. Sci.* **2018**, *19*, 255. [CrossRef] [PubMed]
79. Banerjee, I.; De, M.; Dey, G.; Bharti, R.; Chattopadhyay, S.; Ali, N.; Chakrabarti, P.; Reis, R.L.; Kundu, S.C.; Mandal, M. A peptide-modified solid lipid nanoparticle formulation of paclitaxel modulates immunity and outperforms dacarbazine in a murine melanoma model. *Biomater. Sci.* **2019**, *7*, 1161–1178. [CrossRef]
80. Sen, R.; Ganguly, S.; Ganguly, S.; Debnath, M.C.; Chakraborty, S.; Mukherjee, B.; Chattopadhyay, D. Apigenin-Loaded PL-GADMSA Nanoparticles: A Novel Strategy to Treat Melanoma Lung Metastasis. *Mol. Pharm.* **2021**, *18*, 1920–1938. [CrossRef]
81. Esfahani, K.; Roudaia, L.; Buhlaiga, N.; Del Rincon, S.V.; Papneja, N.; Miller, W.H., Jr. A review of cancer immunotherapy: From the past, to the present, to the future. *Curr. Oncol.* **2020**, *27*, S87–S97. [CrossRef]
82. Fan, Y.; Moon, J.J. Nanoparticle drug delivery systems designed to improve cancer vaccines and immunotherapy. *Vaccines* **2015**, *3*, 662–685. [CrossRef]
83. Francis, D.M.; Thomas, S.N. Progress and opportunities for enhancing the delivery and efficacy of checkpoint inhibitors for cancer immunotherapy. *Adv. Drug Deliv. Rev.* **2017**, *114*, 33–42. [CrossRef]

84. Lu, L.; Sun, Y.; Wan, C.; Hu, Y.; Lo, P.-C.; Lovell, J.F.; Yang, K.; Jin, H. Role of intravital imaging in nanomedicine-assisted anti-cancer therapy. *Curr. Opin. Biotechnol.* **2021**, *69*, 153–161. [CrossRef] [PubMed]
85. Sengupta, S. Cancer Nanomedicine: Lessons for Immuno-Oncology. *Trends Cancer* **2017**, *3*, 551–560. [CrossRef] [PubMed]
86. Van Der Meel, R.; Sulheim, E.; Shi, Y.; Kiessling, F.; Mulder, W.J.M.; Lammers, T. Smart cancer nanomedicine. *Nat. Nanotechnol.* **2019**, *14*, 1007–1017. [CrossRef] [PubMed]
87. Malta, R.; Loureiro, J.B.; Costa, P.; Sousa, E.; Pinto, M.; Saraiva, L.; Amaral, M.H. Development of lipid nanoparticles containing the xanthone LEM2 for topical treatment of melanoma. *J. Drug Deliv. Sci. Technol.* **2021**, *61*, 102226. [CrossRef]
88. Xu, Y.; Ma, S.; Si, X.; Zhao, J.; Yu, H.; Ma, L.; Song, W.; Tang, Z. Polyethyleneimine-CpG Nanocomplex as an In Situ Vaccine for Boosting Anticancer Immunity in Melanoma. *Macromol. Biosci.* **2021**, *21*, e2000207. [CrossRef]
89. Dosta, P.; Cryer, A.M.; Prado, M.; Dion, M.Z.; Ferber, S.; Kalash, S.; Artzi, N. Delivery of Stimulator of Interferon Genes (STING) Agonist Using Polypeptide-Modified Dendrimer Nanoparticles in the Treatment of Melanoma. *Adv. NanoBiomed Res.* **2021**, *1*, 2100006. [CrossRef]
90. Xie, Y.-Q.; Arik, H.; Wei, L.; Zheng, Y.; Suh, H.; Irvine, D.J.; Tang, L. Redox-responsive interleukin-2 nanogel specifically and safely promotes the proliferation and memory precursor differentiation of tumor-reactive T-cells. *Biomater. Sci.* **2019**, *7*, 1345–1357. [CrossRef]
91. Michaud, M.; Martins, I.; Sukkurwala, A.Q.; Adjemian, S.; Ma, Y.; Pellegatti, P.; Shen, S.; Kepp, O.; Scoazec, M.; Mignot, G. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. *Science* **2011**, *334*, 1573–1577. [CrossRef]
92. Berthold, D.R.; Pond, G.R.; Roessner, M.; de Wit, R.; Eisenberger, M.; Tannock, I.F. Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: Relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. *Clin. Cancer Res.* **2008**, *14*, 2763–2767. [CrossRef]
93. Kodumudi, K.N.; Woan, K.; Gilvary, D.L.; Sahakian, E.; Wei, S.; Djeu, J.Y. A novel chemoimmunomodulating property of docetaxel: Suppression of myeloid-derived suppressor cells in tumor bearers. *Clin. Cancer Res.* **2010**, *16*, 4583–4594. [CrossRef]
94. Eralp, Y.; Wang, X.; Wang, J.-P.; Maughan, M.F.; Polo, J.M.; Lachman, L.B. Doxorubicin and paclitaxel enhance the antitumor efficacy of vaccines directed against HER 2/neu in a murine mammary carcinoma model. *Breast Cancer Res.* **2004**, *6*, R275-83. [CrossRef]
95. Haggerty, T.J.; Dunn, I.S.; Rose, L.B.; Newton, E.E.; Martin, S.; Riley, J.L.; Kurnick, J.T. Topoisomerase inhibitors modulate expression of melanocytic antigens and enhance T cell recognition of tumor cells. *Cancer Immunol. Immunother.* **2011**, *60*, 133–144. [CrossRef] [PubMed]
96. Hodge, J.W.; Garnett, C.T.; Farsaci, B.; Palena, C.; Tsang, K.; Ferrone, S.; Gameiro, S.R. Chemotherapy-induced immunogenic modulation of tumor cells enhances killing by cytotoxic T lymphocytes and is distinct from immunogenic cell death. *Int. J. Cancer* **2013**, *133*, 624–636. [CrossRef] [PubMed]
97. Ghebeh, H.; Lehe, C.; Barhoush, E.; Al-Romaih, K.; Tulbah, A.; Al-Alwan, M.; Hendrayani, S.-F.; Manogaran, P.; Alaiya, A.; Al-Tweigeri, T.; et al. Doxorubicin downregulates cell surface B7-H1 expression and upregulates its nuclear expression in breast cancer cells: Role of B7-H1 as an anti-apoptotic molecule. *Breast Cancer Res.* **2010**, *12*, R48. [CrossRef] [PubMed]
98. Lesterhuis, W.J.; Punt, C.J.; Hato, S.V.; Eleveld-Trancikova, D.; Jansen, B.J.; Nierkens, S.; Schreibelt, G.; de Boer, A.; Van Herpen, C.M.; Kaanders, J.H.; et al. Platinum-based drugs disrupt STAT6-mediated suppression of immune responses against cancer in humans and mice. *J. Clin. Investig.* **2011**, *121*, 3100–3108. [CrossRef]
99. Lynch, T.J.; Bondarenko, I.; Luft, A.; Serwatowski, P.; Barlesi, F.; Chacko, R.; Sebastian, M.; Neal, J.; Lu, H.; Cuillerot, J.-M. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non–small-cell lung cancer: Re-sults from a randomized, double-blind, multicenter phase II study. *J. Clin. Oncol.* **2012**, *30*, 2046–2054. [CrossRef]
100. Ramakrishnan, R.; Assudani, D.; Nagaraj, S.; Hunter, T.; Cho, H.-I.; Antonia, S.; Altiok, S.; Celis, E.; Gabrilovich, D.I. Chemotherapy enhances tumor cell susceptibility to CTL-mediated killing during cancer mmunotherapy in mice. *J. Clin. Investig.* **2010**, *120*, 1111–1124. [CrossRef]
101. Smyth, M.J.; Ngiow, S.F.; Ribas, A.; Teng, M.W.L. Combination cancer immunotherapies tailored to the tumour microenvironment. *Nat. Rev. Clin. Oncol.* **2016**, *13*, 143–158. [CrossRef]
102. Middleton, G.; Silcocks, P.; Cox, T.; Valle, J.; Wadsley, J.; Propper, D.; Coxon, F.; Ross, P.; Madhusudan, S.; Roques, T.; et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer (TeloVac): An open-label, randomised, phase 3 trial. *Lancet Oncol.* **2014**, *15*, 829–840. [CrossRef]
103. He, C.; Tang, Z.; Tian, H.; Chen, X. Co-delivery of chemotherapeutics and proteins for synergistic therapy. *Adv. Drug Deliv. Rev.* **2016**, *98*, 64–76. [CrossRef] [PubMed]
104. Da Silva, C.; Rueda, F.; Löwik, C.; Ossendorp, F.; Cruz, L.J. Combinatorial prospects of nano-targeted chemoimmunotherapy. *Biomaterials* **2016**, *83*, 308–320. [CrossRef] [PubMed]

105. Meewan, J.; Somani, S.; Almowalad, J.; Laskar, P.; Mullin, M.; MacKenzie, G.; Khadke, S.; Perrie, Y.; Dufès, C. Preparation of zein-based nanoparticles: Nanoprecipitation versus microfluidic-assisted manufacture, effects of PEGylation on nanoparticle characteristics and cellular uptake by melanoma cells. *Int. J. Nanomed.* **2022**, *17*, 2809–2822. [CrossRef] [PubMed]
106. Wahlich, J.; Desai, A.; Greco, F.; Hill, K.; Jones, A.T.; Mrsny, R.J.; Pasut, G.; Perrie, Y.; Seib, F.P.; Seymour, L.W. Nanomedicines for the Delivery of Biologics. *Pharmaceutics* **2019**, *11*, 210. [CrossRef]
107. Neubert, R.H. Mechanisms of penetration and diffusion of drugs and cosmetic actives across the human Stratum corneum. *Eur. J. Pharm. Biopharm.* **2024**, *202*, 114394. [CrossRef]
108. Adem, A.A.; Belete, A.; Lai, K.K.; Hage, C.; Neubert, R.H.; Gebre-Mariam, T. Nanoemulgel formulation for topical delivery of plant glucosylceramide: Characterization and optimization. *J. Drug Deliv. Sci. Technol.* **2023**, *79*, 104056. [CrossRef]
109. Neubert, R.H. Potentials of new nanocarriers for dermal and transdermal drug delivery. *Eur. J. Pharm. Biopharm.* **2011**, *77*, 1–2. [CrossRef]
110. Siepmann, J.; Siepmann, F. Modeling of diffusion controlled drug delivery. *J. Control. Release* **2012**, *161*, 351–362. [CrossRef]
111. Marwah, M.; Perrie, Y.; Badhan, R.K.S.; Lowry, D. Intracellular uptake of EGCG-loaded deformable controlled release liposomes for skin cancer. *J. Liposome Res.* **2020**, *30*, 136–149. [CrossRef]
112. Matsumura, Y.; Maeda, H. A new concept for macromolecular therapeutics in cancer chemotherapy: Mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer Res.* **1986**, *46*, 6387–6392.
113. Iyer, A.K.; Khaled, G.; Fang, J.; Maeda, H. Exploiting the enhanced permeability and retention effect for tumor targeting. *Drug Discov. Today* **2006**, *11*, 812–818. [CrossRef] [PubMed]
114. Maeda, H. Toward a full understanding of the EPR effect in primary and metastatic tumors as well as issues related to its heterogeneity. *Adv. Drug Deliv. Rev.* **2015**, *91*, 3–6. [CrossRef] [PubMed]
115. Yu, B.; Tai, H.C.; Xue, W.; Lee, L.J.; Lee, R.J. Receptor-targeted nanocarriers for therapeutic delivery to cancer. *Mol. Membr. Biol.* **2010**, *27*, 286–298. [CrossRef] [PubMed]
116. Almeida, H.; Amaral, M.H.; Lobão, P. Temperature and pH stimuli-responsive polymers and their applications in controlled and self-regulated drug delivery. *J. Appl. Pharm. Sci.* **2012**, *2*, 01–10.
117. Fleige, E.; Quadir, M.A.; Haag, R. Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: Concepts and applications. *Adv. Drug Deliv. Rev.* **2012**, *64*, 866–884. [CrossRef]
118. Sundarraj, K.; Raghunath, A.; Perumal, E. A review on the chemotherapeutic potential of fisetin: In vitro evidences. *Biomed. Pharmacother.* **2018**, *97*, 928–940. [CrossRef]
119. Jaudoin, C.; Gehrke, M.M.; Grillo, I.; Cousin, F.; Ouldali, M.; Arteni, A.-A.; Ferrary, E.; Siepmann, F.; Siepmann, J.; Simelière, F.; et al. Release of liposomes from hyaluronic acid-based hybrid systems: Effects of liposome surface and size. *Int. J. Pharm.* **2023**, *648*, 123560. [CrossRef]
120. Laouini, A.; Jaafar-Maalej, C.; Limayem-Blouza, I.; Sfar, S.; Charcosset, C.; Fessi, H. Preparation, characterization and applica-tions of liposomes: State of the art. *J. Colloid Sci. Biotechnol.* **2012**, *1*, 147–168. [CrossRef]
121. Bawarski, W.E.; Chidlowsky, E.; Bharali, D.J.; Mousa, S.A. Emerging nanopharmaceuticals. *Nanomed. Nanotechnol. Biol. Med.* **2008**, *4*, 273–282. [CrossRef]
122. Mei, K.-C.; Liao, Y.-P.; Jiang, J.; Chiang, M.; Khazaieli, M.; Liu, X.; Wang, X.; Liu, Q.; Chang, C.H.; Zhang, X.; et al. Liposomal delivery of mitoxantrone and a cholesteryl indoximod prodrug provides effective chemo-immunotherapy in multiple solid tumors. *ACS Nano* **2020**, *14*, 13343–13366. [CrossRef] [PubMed]
123. Xiao, W.; Zhang, W.; Huang, H.; Xie, Y.; Zhang, Y.; Guo, X.; Jin, C.; Liao, X.; Yao, S.; Chen, G.; et al. Cancer targeted gene therapy for inhibition of melanoma lung metastasis with eiF3i shRNA loaded liposomes. *Mol. Pharm.* **2019**, *17*, 229–238. [CrossRef] [PubMed]
124. Pattni, B.S.; Chupin, V.V.; Torchilin, V.P. New developments in liposomal drug delivery. *Chem. Rev.* **2015**, *115*, 10938–10966. [CrossRef]
125. Gu, Z.; Wang, Q.; Shi, Y.; Huang, Y.; Zhang, J.; Zhang, X.; Lin, G. Nanotechnology-mediated immunochemotherapy combined with docetaxel and PD-L1 antibody increase therapeutic effects and decrease systemic toxicity. *J. Control. Release* **2018**, *286*, 369–380. [CrossRef]
126. Reddy, T.L.; Garikapati, K.R.; Reddy, S.G.; Reddy, B.V.S.; Yadav, J.S.; Bhadra, U.; Bhadra, M.P. Simultaneous delivery of Paclitaxel and Bcl-2 siRNA via pH-Sensitive liposomal nanocarrier for the synergistic treatment of melanoma. *Sci. Rep.* **2016**, *6*, 35223. [CrossRef]
127. Zhang, Y.; Li, N.; Suh, H.; Irvine, D.J. Nanoparticle anchoring targets immune agonists to tumors enabling anti-cancer immunity without systemic toxicity. *Nat. Commun.* **2018**, *9*, 6. [CrossRef]
128. Sinico, C.; Manconi, M.; Peppi, M.; Lai, F.; Valenti, D.; Fadda, A.M. Liposomes as carriers for dermal delivery of tretinoin: In vitro evaluation of drug permeation and vesicle–skin interaction. *J. Control. Release* **2005**, *103*, 123–136. [CrossRef]

129. Caddeo, C.; Nacher, A.; Vassallo, A.; Armentano, M.F.; Pons, R.; Fernàndez-Busquets, X.; Carbone, C.; Valenti, D.; Fadda, A.M.; Manconi, M. Effect of quercetin and resveratrol co-incorporated in liposomes against inflammatory/oxidative response associated with skin cancer. *Int. J. Pharm.* **2016**, *513*, 153–163. [CrossRef]
130. Tzanova, M.M.; Nguyen, L.; Moretti, F.; Grassi, M.; Magnano, G.C.; Voinovich, D.; Stein, P.C.; Hiorth, M.; di Cagno, M.P. Interpreting permeability as a function of free drug fraction: The case studies of cyclodextrins and liposomes. *Eur. J. Pharm. Sci.* **2023**, *189*, 106559. [CrossRef]
131. Muller, R.H.; Runge, S.A. Solid lipid nanoparticles (SLN) for controlled drug delivery. In *Submicron Emulsions N Drug Targeting and Delivery*; CRC Press: Boca Raton, FL, USA, 1998; Volume 22, pp. 219–234.
132. Estanqueiro, M.; Amaral, M.H.; Conceição, J.; Lobo, J.M.S. Nanotechnological carriers for cancer chemotherapy: The state of the art. *Colloids Surfaces B Biointerfaces* **2015**, *126*, 631–648. [CrossRef]
133. Geszke-Moritz, M.; Moritz, M. Solid lipid nanoparticles as attractive drug vehicles: Composition, properties and therapeutic strategies. *Mater. Sci. Eng. C* **2016**, *68*, 982–994. [CrossRef]
134. Müller, R.H.; Radtke, M.; Wissing, S.A. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv. Drug Deliv. Rev.* **2002**, *54*, S131–S155. [CrossRef]
135. Kasongo, W.; Pardeike, J.; Müller, R.H.; Walker, R.B. Selection and characterization of suitable lipid excipients for use in the manufacture of didanosine-loaded solid lipid nanoparticles and nanostructured lipid carriers. *J. Pharm. Sci.* **2011**, *100*, 5185–5196. [CrossRef]
136. Souto, E.; Wissing, S.; Barbosa, C.; Müller, R. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. *Int. J. Pharm.* **2004**, *278*, 71–77. [CrossRef] [PubMed]
137. Pouton, C.W. Lipid formulations for oral administration of drugs: Non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. *Eur. J. Pharm. Sci.* **2000**, *11*, S93–S98. [CrossRef] [PubMed]
138. Jores, K.; Mehnert, W.; Drechsler, M.; Bunjes, H.; Johann, C.; Mäder, K. Investigations on the structure of solid lipid nanoparticles (SLN) and oil-loaded solid lipid nanoparticles by photon correlation spectroscopy, field-flow fractionation and transmission electron microscopy. *J. Control. Release* **2004**, *95*, 217–227. [CrossRef]
139. Jores, K.; Haberland, A.; Wartewig, S.; Mäder, K.; Mehnert, W. Solid lipid nanoparticles (SLN) and oil-loaded sln studied by spectrofluorometry and Raman spectroscopy. *Pharm. Res.* **2005**, *22*, 1887–1897. [CrossRef] [PubMed]
140. Mussi, S.V.; Torchilin, V.P. Recent trends in the use of lipidic nanoparticles as pharmaceutical carriers for cancer therapy and diagnostics. *J. Mater. Chem. B* **2013**, *1*, 5201–5209. [CrossRef]
141. Lim, E.-K.; Jang, E.; Lee, K.; Haam, S.; Huh, Y.-M. Delivery of cancer therapeutics using nanotechnology. *Pharmaceutics* **2013**, *5*, 294–317. [CrossRef]
142. Salehzadeh, R.; Abdullah, R. Solid lipid nanoparticles as new drug delivery system. *Int. J. Biotechnol. Mol. Biol. Res.* **2011**, *2*, 252–261.
143. Hanafy, M.S.; Hufnagel, S.; Trementozzi, A.N.; Sakran, W.; Stachowiak, J.C.; Koleng, J.J.; Cui, Z. PD-1 siRNA-Encapsulated Solid Lipid Nanoparticles Downregulate PD-1 Expression by Macrophages and Inhibit Tumor Growth. *AAPS PharmSciTech* **2021**, *22*, 60. [CrossRef]
144. Huang, S.; Zhang, Y.; Wang, L.; Liu, W.; Xiao, L.; Lin, Q.; Gong, T.; Sun, X.; He, Q.; Zhang, Z.; et al. Improved melanoma suppression with target-delivered TRAIL and Paclitaxel by a multifunctional nanocarrier. *J. Control. Release* **2020**, *325*, 10–24. [CrossRef] [PubMed]
145. Filipczak, N.; Jaromin, A.; Piwoni, A.; Mahmud, M.; Sarisozen, C.; Torchilin, V.; Gubernator, J. A Triple Co-Delivery Liposomal Carrier That Enhances Apoptosis via an Intrinsic Pathway in Melanoma Cells. *Cancers* **2019**, *11*, 1982. [CrossRef] [PubMed]
146. Teeranachaideekul, V.; Souto, E.B.; Junyaprasert, V.B.; Müller, R.H. Cetyl palmitate-based NLC for topical delivery of Coen-zyme Q10–Development, physicochemical characterization and in vitro release studies. *Eur. J. Pharm. Biopharm.* **2007**, *67*, 141–148. [CrossRef]
147. Garcês, A.; Amaral, M.; Lobo, J.S.; Silva, A. Formulations based on solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for cutaneous use: A review. *Eur. J. Pharm. Sci.* **2018**, *112*, 159–167. [CrossRef]
148. Almeida, H.; Amaral, M.H.; Lobão, P.; Silva, A.C.; Loboa, J.M.S. Applications of polymeric and lipid nanoparticles in ophthalmic pharmaceutical formulations: Present and future considerations. *J. Pharm. Pharm. Sci.* **2014**, *17*, 278–293. [CrossRef]
149. Cunha, S.; Amaral, M.H.; Lobo, J.M.S.; Silva, A.C. Lipid nanoparticles for nasal/intranasal drug delivery. *Crit. Rev. Ther. Drug Carr. Syst.* **2017**, *34*, 257–282. [CrossRef]
150. Tichota, D.M.; Silva, A.C.; Lobo, J.M.S.; Amaral, M.H. Design, characterization, and clinical evaluation of argan oil nanostruc-tured lipid carriers to improve skin hydration. *Int. J. Nanomed.* **2014**, *9*, 3855.
151. Kurakula, M.; Chen, L.; Tiwari, A.K.; Srinivas, N.R.; Dash, R.P.; Panizzi, P.R.; Arnold, R.D.; Babu, R.J. Recent Advances in Li-pid-Based Nanovesicular Delivery Systems for Melanoma Therapy. *Crit. Rev. Ther. Drug Carr. Syst.* **2021**, *38*, 1–38. [CrossRef]
152. Jiang, T.; Sun, W.; Zhu, Q.; Burns, N.A.; Khan, S.A.; Mo, R.; Gu, Z. Furin-mediated sequential delivery of anticancer cytokine and small-molecule drug shuttled by graphene. *Adv. Mater.* **2015**, *27*, 1021–1028. [CrossRef]

153. Hu, X.; Wang, Y.; Peng, B. Chitosan-capped mesoporous silica nanoparticles as pH-responsive nanocarriers for controlled drug release. *Chem.—Asian J.* **2014**, *9*, 319–327. [CrossRef]
154. Slowing, I.I.; Vivero-Escoto, J.L.; Wu, C.-W.; Lin, V.S.-Y. Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. *Adv. Drug Deliv. Rev.* **2008**, *60*, 1278–1288. [CrossRef]
155. Zheng, D.-W.; Chen, J.-L.; Zhu, J.-Y.; Rong, L.; Li, B.; Lei, Q.; Fan, J.-X.; Zou, M.-Z.; Li, C.; Cheng, S.-X.; et al. Highly integrated nano-platform for breaking the barrier between chemotherapy and immunotherapy. *Nano Lett.* **2016**, *16*, 4341–4347. [CrossRef]
156. Ou, W.; Byeon, J.H.; Thapa, R.K.; Ku, S.K.; Yong, C.S.; Kim, J.O. Plug-and-Play nanorization of coarse black phosphorus for targeted chemo-photoimmunotherapy of colorectal cancer. *ACS Nano* **2018**, *12*, 10061–10074. [CrossRef]
157. Bobo, D.; Robinson, K.J.; Islam, J.; Thurecht, K.J.; Corrie, S.R. Nanoparticle-based medicines: A review of FDA-approved materials and clinical trials to date. *Pharm. Res.* **2016**, *33*, 2373–2387. [CrossRef] [PubMed]
158. Liang, X.; Ye, X.; Wang, C.; Xing, C.; Miao, Q.; Xie, Z.; Chen, X.; Zhang, X.; Zhang, H.; Mei, L. Photothermal cancer immunotherapy by erythrocyte membrane-coated black phosphorus formulation. *J. Control. Release* **2019**, *296*, 150–161. [CrossRef] [PubMed]
159. Liu, X.; Chen, L.; Zhang, Y.; Xin, X.; Qi, L.; Jin, M.; Guan, Y.; Gao, Z.; Huang, W. Enhancing anti-melanoma outcomes in mice using novel chitooligosaccharide nanoparticles loaded with therapeutic survivin-targeted siRNA. *Eur. J. Pharm. Sci.* **2021**, *158*, 105641. [CrossRef]
160. Li, B.; Lane, L.A. Probing the biological obstacles of nanomedicine with gold nanoparticles. *WIREs Nanomed. Nanobiotechnol.* **2019**, *11*, e1542. [CrossRef] [PubMed]
161. Choi, B.B.R.; Choi, J.H.; Hong, J.W.; Song, K.W.; Lee, H.J.; Kim, U.K.; Kim, G.C. Selective killing of melanoma cells with non-thermal atmospheric pressure plasma and p-FAK antibody conjugated gold nanoparticles. *Int. J. Med Sci.* **2017**, *14*, 1101–1109. [CrossRef]
162. Lomelí-Marroquín, D.; Cruz, D.M.; Nieto-Argüello, A.; Crua, A.V.; Chen, J.; Torres-Castro, A.; Webster, T.J.; Cholula-Díaz, J.L. Starch-mediated synthesis of mono- and bimetallic silver/gold nanoparticles as antimicrobial and anticancer agents. *Int. J. Nanomed.* **2019**, *14*, 2171–2190. [CrossRef]
163. Zhang, X.; Teodoro, J.G.; Nadeau, J.L. Intratumoral gold-doxorubicin is effective in treating melanoma in mice. *Nanomed. Nanotechnol. Biol. Med.* **2015**, *11*, 1365–1375. [CrossRef]
164. Tawagi, E.; Massmann, C.; Chibli, H.; Nadeau, J.L. Differential toxicity of gold-doxorubicin in cancer cells vs. cardiomyocytes as measured by real-time growth assays and fluorescence lifetime imaging microscopy (FLIM). *Analyst* **2015**, *140*, 5732–5741. [CrossRef]
165. Labala, S.; Jose, A.; Chawla, S.R.; Khan, M.S.; Bhatnagar, S.; Kulkarni, O.P.; Venuganti, V.V.K. Effective melanoma cancer suppression by iontophoretic co-delivery of STAT3 siRNA and imatinib using gold nanoparticles. *Int. J. Pharm.* **2017**, *525*, 407–417. [CrossRef] [PubMed]
166. Labala, S.; Jose, A.; Venuganti, V.V.K. Transcutaneous iontophoretic delivery of STAT3 siRNA using layer-by-layer chitosan coated gold nanoparticles to treat melanoma. *Colloids Surfaces B Biointerfaces* **2016**, *146*, 188–197. [CrossRef] [PubMed]
167. Vankayala, R.; Lin, C.-C.; Kalluru, P.; Chiang, C.-S.; Hwang, K.C. Gold nanoshells-mediated bimodal photodynamic and photothermal cancer treatment using ultra-low doses of near infra-red light. *Biomaterials* **2014**, *35*, 5527–5538. [CrossRef]
168. Camerin, M.; Moreno, M.; Marín, M.J.; Schofield, C.L.; Chambrier, I.; Cook, M.J.; Coppellotti, O.; Jori, G.; Russell, D.A. Delivery of a hydrophobic phthalocyanine photosensitizer using PEGylated gold nanoparticle conjugates for the in vivo photodynamic therapy of amelanotic melanoma. *Photochem. Photobiol. Sci.* **2016**, *15*, 618–625. [CrossRef]
169. Mohammadi, Z.; Sazgarnia, A.; Rajabi, O.; Toosi, M.S. Comparative study of X-ray treatment and photodynamic therapy by using 5-aminolevulinic acid conjugated gold nanoparticles in a melanoma cell line. *Artif. Cells Nanomed. Biotechnol.* **2017**, *45*, 467–473. [CrossRef]
170. Le Goas, M.; Paquet, M.; Paquirissamy, A.; Guglielmi, J.; Compin, C.; Thariat, J.; Vassaux, G.; Geertsen, V.; Humbert, O.; Renault, J.-P.; et al. Improving 131I radioiodine therapy by hybrid polymer-grafted gold nanoparticles. *Int. J. Nanomed.* **2019**, *14*, 7933–7946. [CrossRef]
171. Li, Z.; Tan, S.; Li, S.; Shen, Q.; Wang, K. Cancer drug delivery in the nano era: An overview and perspectives. *Oncol. Rep.* **2017**, *38*, 611–624. [CrossRef]
172. Fessi, H.; Puisieux, F.; Devissaguet, J.P.; Ammoury, N.; Benita, S. Nanocapsule formation by interfacial polymer deposition following solvent displacement. *Int. J. Pharm.* **1989**, *55*, R1–R4. [CrossRef]
173. Vlasceanu, G.M.; Victor, L.; Maricica, H.; Raluca, T.; Vlad, O.; Gheorghe, I.; Bolocan, A.; Grumezescu, A.M.; Holban, A.M. Nanostructures for cancer therapy: From targeting to selective toxicology. In *Nanostructures for Cancer Therapy*; Elsevier: Amsterdam, The Netherlands, 2017; pp. 831–847.
174. O'REilly, R.K.; Hawker, C.J.; Wooley, K.L. Cross-linked block copolymer micelles: Functional nanostructures of great potential and versatility. *Chem. Soc. Rev.* **2006**, *35*, 1068–1083. [CrossRef]
175. Knop, K.; Hoogenboom, R.; Fischer, D.; Schubert, U.S. Poly (ethylene glycol) in drug delivery: Pros and cons as well as potential alternatives. *Angew. Chem. Int. Ed.* **2010**, *49*, 6288–6308. [CrossRef] [PubMed]

176. Jonassen, H.; Kjøniksen, A.-L.; Hiorth, M. Stability of chitosan nanoparticles cross-linked with tripolyphosphate. *Biomacromolecules* **2012**, *13*, 3747–3756. [CrossRef] [PubMed]
177. Pohlmann, A.R.; Cruz, L.; Mezzalira, G.; Soares, L.U.; Da Silveira, N.P.; Guterres, S.S. Structural model of polymeric nanospheres containing indomethacin ethyl ester and in vivo antiedematogenic activity. *Int. J. Nanotechnol.* **2007**, *4*, 454. [CrossRef]
178. da Fonseca, L.S.; Silveira, R.P.; Deboni, A.M.; Benvenutti, E.V.; Costa, T.M.; Guterres, S.S.; Pohlmann, A.R. Nanocapsule@ xerogel microparticles containing sodium diclofenac: A new strategy to control the release of drugs. *Int. J. Pharm.* **2008**, *358*, 292–295. [CrossRef]
179. Feng, C.; Yuan, X.; Chu, K.; Zhang, H.; Ji, W.; Rui, M. Preparation and optimization of poly (lactic acid) nanoparticles loaded with fisetin to improve anti-cancer therapy. *Int. J. Biol. Macromol.* **2019**, *125*, 700–710. [CrossRef]
180. Kataoka, K.; Harada, A.; Nagasaki, Y. Block copolymer micelles for drug delivery: Design, characterization and biological significance. *Adv. Drug Deliv. Rev.* **2012**, *64*, 37–48. [CrossRef]
181. Escrivani, O.D.; Lopes, M.V.; Poletto, F.; Ferrarini, S.R.; Sousa-Batista, A.J.; Steel, P.G.; Guterres, S.S.; Pohlmann, A.R.; Rossi-Bergmann, B. Encapsulation in lipid-core nanocapsules improves topical treatment with the potent antileishmanial compound CH8. *Nanomed. Nanotechnol. Biol. Med.* **2020**, *24*, 102121. [CrossRef]
182. Jäger, A.; Stefani, V.; Guterres, S.S.; Pohlmann, A.R. Physico-chemical characterization of nanocapsule polymeric wall using fluorescent benzazole probes. *Int. J. Pharm.* **2007**, *338*, 297–305. [CrossRef]
183. Cho, H.; Lai, T.C.; Tomoda, K.; Kwon, G.S. Polymeric micelles for multi-drug delivery in cancer. *AAPS PharmSciTech* **2015**, *16*, 10–20. [CrossRef]
184. Kumar, R.; Kulkarni, A.; Nagesha, D.K.; Sridhar, S. In vitro evaluation of theranostic polymeric micelles for imaging and drug delivery in cancer. *Theranostics* **2012**, *2*, 714–722. [CrossRef]
185. Torchilin, V.P. Micellar nanocarriers: Pharmaceutical perspectives. *Pharm. Res.* **2007**, *24*, 1–16. [CrossRef] [PubMed]
186. Mohan, P.; Rapoport, N. Doxorubicin as a molecular nanotheranostic agent: Effect of doxorubicin encapsulation in micelles or nanoemulsions on the ultrasound-mediated intracellular delivery and nuclear trafficking. *Mol. Pharm.* **2010**, *7*, 1959–1973. [CrossRef] [PubMed]
187. Song, M.; Xia, W.; Tao, Z.; Zhu, B.; Zhang, W.; Liu, C.; Chen, S. Self-assembled polymeric nanocarrier-mediated co-delivery of metformin and doxorubicin for melanoma therapy. *Drug Deliv.* **2021**, *28*, 594–606. [CrossRef] [PubMed]
188. Geronimo, G.; da Silva, G.H.R.; de Moura, L.D.; Ribeiro, L.N.; Guilherme, V.A.; Mendonça, T.C.; Castro, S.R.; Breitkreitz, M.C.; de Paula, E. Development of S 75: R 25 bupivacaine-loaded lipid nanoparticles functionalized with essential oils for treating melanoma. *J. Chem. Technol. Biotechnol.* **2021**, *96*, 8.
189. Herai, H.; Gratieri, T.; Thomazine, J.A.; Bentley, M.V.L.B.; Lopez, R.F.V. Doxorubicin skin penetration from monoolein-containing propylene glycol formulations. *Int. J. Pharm.* **2007**, *329*, 88–93. [CrossRef]
190. Makadia, H.K.; Siegel, S.J. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers* **2011**, *3*, 1377–1397. [CrossRef]
191. Gref, R.; Minamitake, Y.; Peracchia, M.T.; Trubetskoy, V.; Torchilin, V.; Langer, R. Biodegradable long-circulating polymeric nanospheres. *Science* **1994**, *263*, 1600–1603. [CrossRef]
192. Luu, Y.; Kim, K.; Hsiao, B.; Chu, B.; Hadjiargyrou, M. Development of a nanostructured DNA delivery scaffold via electrospinning of PLGA and PLA–PEG block copolymers. *J. Control. Release* **2003**, *89*, 341–353. [CrossRef]
193. Su, Z.; Xiao, Z.; Wang, Y.; Huang, J.; An, Y.; Wang, X.; Shuai, X. Codelivery of anti-PD-1 antibody and paclitaxel with matrix metalloproteinase and pH dual-sensitive micelles for enhanced tumor chemoimmunotherapy. *Small* **2020**, *16*, e1906832. [CrossRef]
194. McCoubrey, L.E.; Ferraro, F.; Seegobin, N.; Verin, J.; Alfassam, H.A.; Awad, A.; Marzorati, M.; Verstrepen, L.; Ghyselinck, J.; De Munck, J.; et al. Poly(D,l-lactide-co-glycolide) particles are metabolised by the gut microbiome and elevate short chain fatty acids. *J. Control. Release* **2024**, *369*, 163–178. [CrossRef]
195. Siepmann, J.; Siepmann, F. Stability of aqueous polymeric controlled release film coatings. *Int. J. Pharm.* **2013**, *457*, 437–445. [CrossRef] [PubMed]
196. Palmerston Mendes, L.; Pan, J.; Torchilin, V.P. Dendrimers as nanocarriers for nucleic acid and drug delivery in cancer therapy. *Molecules* **2017**, *22*, 1401. [CrossRef] [PubMed]
197. Tomalia, D.A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. A new class of polymers: Starburst-dendritic macromolecules. *Polym. J.* **1985**, *17*, 117–132. [CrossRef]
198. STripathy; Das, M.K. Dendrimers and their applications as novel drug delivery carriers. *J. Appl. Pharm. Sci.* **2013**, *3*, 142–149.
199. Kesharwani, P.; Jain, K.; Jain, N.K. Dendrimer as nanocarrier for drug delivery. *Prog. Polym. Sci.* **2014**, *39*, 268–307. [CrossRef]
200. Degim, I.T.; Burgess, D.J.; Papadimitrakopoulos, F. Carbon nanotubes for transdermal drug delivery. *J. Microencapsul.* **2010**, *27*, 669–681. [CrossRef]
201. Siu, K.S.; Chen, D.; Zheng, X.; Zhang, X.; Johnston, N.; Liu, Y.; Yuan, K.; Koropatnick, J.; Gillies, E.R.; Min, W.-P. Non-covalently functionalized single-walled carbon nanotube for topical siRNA delivery into melanoma. *Biomaterials* **2014**, *35*, 3435–3442. [CrossRef]

202. Bajpai, V.K.; Khan, I.; Shukla, S.; Kang, S.-M.; Aziz, F.; Tripathi, K.M.; Saini, D.; Cho, H.-J.; Heo, N.S.; Sonkar, S.K. Multifunctional NP-doped carbon dots for regulation of apoptosis and autophagy in B16F10 melanoma cancer cells and in vitro imaging applications. *Theranostics* **2020**, *10*, 7841. [CrossRef]
203. Manca, M.L.; Manconi, M.; Nacher, A.; Carbone, C.; Valenti, D.; Maccioni, A.M.; Sinico, C.; Fadda, A.M. Development of novel diolein–niosomes for cutaneous delivery of tretinoin: Influence of formulation and in vitro assessment. *Int. J. Pharm.* **2014**, *477*, 176–186. [CrossRef]
204. Manconi, M.; Sinico, C.; Valenti, D.; Lai, F.; Fadda, A.M. Niosomes as carriers for tretinoin: III. A study nto the in vitro cutaneous delivery of vesicle-incorporated tretinoin. *Int. J. Pharm.* **2006**, *311*, 11–19. [CrossRef]
205. Wu, X.; Wu, Y.; Ye, H.; Yu, S.; He, C.; Chen, X. Interleukin-15 and cisplatin co-encapsulated thermosensitive polypeptide hydrogels for combined immuno-chemotherapy. *J. Control. Release* **2017**, *255*, 81–93. [CrossRef]
206. Dong, X.; Yang, A.; Bai, Y.; Kong, D.; Lv, F. Dual fluorescence imaging-guided programmed delivery of doxorubicin and CpG nanoparticles to modulate tumor microenvironment for effective chemo-immunotherapy. *Biomaterials* **2020**, *230*, 119659. [CrossRef]
207. Li, Y.; Fang, M.; Zhang, J.; Wang, J.; Song, Y.; Shi, J.; Li, W.; Wu, G.; Ren, J.; Wang, Z.; et al. Hydrogel dual delivered celecoxib and anti-PD-1 synergistically improve antitumor immunity. *OncoImmunology* **2016**, *5*, e1074374. [CrossRef] [PubMed]
208. Qiao, H.; Chen, X.; Chen, E.; Zhang, J.; Huang, D.; Yang, D.; Ding, Y.; Qian, H.; Feijen, J.; Chen, W. Folated pH-degradable nanogels for the simultaneous delivery of docetaxel and an IDO1-inhibitor in enhancing cancer chemo-immunotherapy. *Biomater. Sci.* **2019**, *7*, 2749–2758. [CrossRef] [PubMed]
209. Lefol, L.; Bawuah, P.; Zeitler, J.; Verin, J.; Danede, F.; Willart, J.; Siepmann, F.; Siepmann, J. Drug release from PLGA microparticles can be slowed down by a surrounding hydrogel. *Int. J. Pharm. X* **2023**, *6*, 100220. [CrossRef]
210. Ilochonwu, B.C.; van der Lugt, S.A.; Annala, A.; Di Marco, G.; Sampon, T.; Siepmann, J.; Siepmann, F.; Hennink, W.E.; Vermonden, T. Thermo-responsive Diels-Alder stabilized hydrogels for ocular drug delivery of a corticosteroid and an anti-VEGF fab fragment. *J. Control. Release* **2023**, *361*, 334–349. [CrossRef]
211. Wang, H.; Liu, Y.; He, R.; Xu, D.; Zang, J.; Weeranoppanant, N.; Dong, H.; Li, Y. Cell membrane biomimetic nanoparticles for inflammation and cancer targeting in drug delivery. *Biomater. Sci.* **2020**, *8*, 552–568. [CrossRef]
212. Molinaro, R.; Martinez, J.O.; Zinger, A.; De Vita, A.; Storci, G.; Arrighetti, N.; De Rosa, E.; Hartman, K.A.; Basu, N.; Taghipour, N.; et al. Leukocyte-mimicking nanovesicles for effective doxorubicin delivery to treat breast cancer and melanoma. *Biomater. Sci.* **2020**, *8*, 333–341. [CrossRef]
213. Luo, K.; Lian, Y.; Zhang, M.; Yu, H.; Wang, G.; Li, J. Charge convertible biomimetic micellar nanoparticles for enhanced melanoma-targeted therapy through tumor cells and tumor-associated macrophages dual chemotherapy with IDO immunotherapy. *Chem. Eng. J.* **2021**, *412*, 128659. [CrossRef]
214. Gorgizadeh, M.; Azarpira, N.; Veis, R.D.; Sattarahmady, N. Repression of melanoma tumor in vitro and in vivo by photothermal effect of carbon xerogel nanoparticles. *Colloids Surfaces B Biointerfaces* **2019**, *176*, 449–455. [CrossRef]
215. Zhang, X.; Chen, F.; Turker, M.Z.; Ma, K.; Zanzonico, P.; Gallazzi, F.; Shah, M.A.; Prater, A.R.; Wiesner, U.; Bradbury, M.S.; et al. Targeted melanoma radiotherapy using ultrasmall 177Lu-labeled α-melanocyte stimulating hormone-functionalized core-shell silica nanoparticles. *Biomaterials* **2020**, *241*, 119858. [CrossRef]
216. Xue, X.; Li, J.; Fan, Y.; Shen, M.; Shi, X. Gene silencing-mediated immune checkpoint blockade for tumor therapy boosted by dendrimer-entrapped gold nanoparticles. *Sci. China Mater.* **2021**, *64*, 2045–2055. [CrossRef]
217. Han, S.; Wang, W.; Wang, S.; Wang, S.; Ju, R.; Pan, Z.; Yang, T.; Zhang, G.; Wang, H.; Wang, L. Multifunctional biomimetic nanoparticles loading baicalin for polarizing tumor-associated macrophages. *Nanoscale* **2019**, *11*, 20206–20220. [CrossRef]
218. U.S. National Library of Medicine. *ClinicalTrials.gov.*. Available online: https://clinicaltrials.gov/search?cond=Melanoma,%20Skin&term=nanoparticles (accessed on 8 August 2025).
219. Moni, S.S.; Moshi, J.M.; Matou-Nasri, S.; Alotaibi, S.; Hawsawi, Y.M.; Elmobark, M.E.; Hakami, A.M.S.; Jeraiby, M.A.; Sulayli, A.A.; Moafa, H.N. Advances in Materials Science for Precision Melanoma Therapy: Nanotechnology-Enhanced Drug Delivery Systems. *Pharmaceutics* **2025**, *17*, 296. [CrossRef]


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