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Nanoparticle Delivery Systems for Skin-Localized Chemotherapy in Non-Melanoma Skin Cancers

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Abstract

Nanoparticle delivery systems are innovative platforms for skin-localized chemotherapy in the treatment of non-melanoma skin cancers (NMSCs), including basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC). These common cancers often require localized treatment approaches to minimize systemic toxicity and preserve healthy skin. Nanoparticles, engineered at the nanoscale, offer unique advantages in delivering chemotherapeutic agents directly to tumor sites through enhanced skin penetration, sustained drug release, and selective targeting of cancer cells. Liposomes, polymeric nanoparticles, solid lipid nanoparticles, and dendrimers have demonstrated high efficacy in encapsulating drugs such as 5-fluorouracil, doxorubicin, and cisplatin, improving their bioavailability and therapeutic outcomes. Nanoparticle-based systems leverage passive targeting through enhanced permeability and retention (EPR) effects and can be further functionalized with ligands to achieve active targeting of overexpressed receptors on NMSC cells. These systems have shown potential in reducing off-target effects, minimizing drug degradation, and improving patient compliance compared to traditional topical or systemic therapies. Preclinical studies have highlighted the ability of nanoparticles to penetrate the stratum corneum and accumulate in tumor tissue without significant systemic absorption, emphasizing their role in localized treatment. Furthermore, the integration of nanoparticles with photodynamic and immunotherapy agents offers synergistic effects, enhancing tumor eradication and

immune activation. Through utilizing localized drug delivery in NMSCs, nanoparticle-based therapies represent a promising avenue for effective, targeted treatment while minimizing adverse effects, ultimately improving outcomes for patients with these skin cancers.

Keywords

Nanoparticle Drug Delivery, Non-Melanoma Skin Cancer, Basal Cell Carcinoma, Cutaneous Squamous Cell Carcinoma, Targeted Chemotherapy, Photodynamic Therapy, Cancer Nanomedicine

1. Introduction

Skin cancers are among the most prevalent malignancies worldwide, with a steadily increasing incidence attributed to prolonged sun exposure, geographic factors, and individual predispositions. Non-melanoma skin cancers (NMSCs), which encompass basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), represent a significant public health burden, accounting for 30% of all cancer diagnoses [1]. According to recent global data, in 2018, NMSCs accounted for approximately 1.4 million new diagnoses and 65,155 related deaths [2]. Overall mortality remains low, with men exhibiting a mortality rate three times higher than women, at 1.3 for men compared to 0.3 for women. Nationwide, the mortality for NMSC increased from 0.7 to 0.8. Notably, the incidence of NMSCs in males is double that of women at 1021 out of 100,000, compared to 603 in women [3]. Although generally not fatal, these cancers can cause substantial physical, emotional, and psychological distress, particularly given their high occurrence in cosmetically sensitive areas such as the face and neck [4]. The rising incidence, coupled with the diverse clinical presentations of these malignancies, poses considerable challenges for healthcare providers in both diagnosis and management [5]. A comprehensive assessment of the patient's mental well-being, physical expectations, and overall health is essential for developing an appropriate and individualized treatment plan.

BCC is the most common form of skin cancer, predominantly occurring on the head and neck. It is largely driven by mutations in the Hedgehog (HH) signaling pathway, with 90% of BCCs exhibiting alterations in this pathway, particularly loss-of-function mutations in the *smoothened oncogene* (*SMO*) [6]. BCC can be classified into several subtypes, including nodular, superficial, fibroepithelial, morpheaform, micronodular, mucinous, basosquamous, and infiltrative, each with distinct histological and clinical features [2]. Histologic differences and gross appearance are the primary methods used to identify and differentiate each subtype. Nodular is the most common variant, accounting for 50% - 79% of BCC's. The most common appearance is a central depression of a papule or pearly nodule that is frequently bleeding. Histologically, it shows islands of tumor cells characterized by a cribriform pattern [6]. Superficial is the second most common subtype and

appears as a macula or atrophic plaque that is well-defined, pink, and can be scaly. Fibroepithelial mostly involves the trunk and occurs as a pink-colored plaque or papular lesion that does or does not include a pigment. Morpheaform is a rare variant that accounts for 5% - 10% of BCCs and is characterized by an elevated or depressed pinkish cream plaque that can include telangiectasias. It is also highly aggressive and can locally invade and metastasize. Histologically, it shows malignant cells surrounded by sclerotic stroma with collagen. Infiltrative is very similar to Morpheaform in that it can invade the subcutis. It shows stromal fibrosis and dense collagen bundles and forms a large irregular nodule. Micronodular deeply extends into the dermis and subcutis with stromal proliferation. Lastly, Basosquamous is differentiated by its infiltrating jagged clumps or tumor cells that demonstrate basaloid morphology and cytoplasmic keratinization [6]. Understanding and differentiating each subtype is paramount to correctly diagnosing BCC and choosing the most beneficial treatment.

In contrast, cSCC is primarily induced by ultraviolet radiation (UVR) and is characterized by genetic alterations in key tumor suppressor genes such as *TP*53*, CDKN*2*A*, and *NOTCH*1 [2]. The majority of activating mutations affected genes in the RAS-RAF-MEK-ERK and PI3K/AKT pathways [7]. This carcinoma often presents as a hyperkeratotic plaque or papule, frequently with pigmentation. It is the second most common skin cancer, and it occurs more commonly in Caucasian subjects exposed to environmental factors. The mortality is correlated with the number of malignant cells and their metastasis to distant sites, as well as age, male gender, and location [6]. There is no accepted classification; however, superficial SCC is widely considered the most common subtype, and it typically develops from actinic keratosis or Bowen disease. SCC is mostly classified by the gene affected and the mutation that ensues. Over 31 SCC-related genes have been identified, and multiple mutation types have been found for each gene. SCC is also linked to several hereditary conditions, including xeroderma pigmentosum, oculocutaneous albinism, and Lynch syndrome [6]. The broad spectrum of clinical presentations in cSCC can complicate diagnosis, necessitating a comprehensive patient history to accurately inform the workup and treatment strategy.

The treatment of BCC and cSCC is fraught with challenges, which are influenced by factors such as tumor location, size, metastasis, and patient comorbidities. Surgical excision remains the cornerstone of therapy, particularly for localized tumors, due to its ability to provide clear histological margins and minimize recurrence [8]. However, when surgery is not feasible due to anatomical constraints or advanced disease, alternative treatments such as radiotherapy, cryosurgery, and electrode section are employed. These options, while effective, are not without drawbacks, including potential systemic toxicity and scarring, which can be particularly problematic when tumors occur in visible or sensitive areas [9]. Furthermore, the development of resistance to systemic therapies in BCC through mutations in *SMO* and downstream genes like *glioma-associated oncogene* (*GLI*2) adds another layer of complexity [6]. Consequently, there is a pressing need for more targeted,

localized therapies that minimize adverse effects while maintaining therapeutic efficacy.

Nanotechnology, defined as the design and application of materials ranging from 1 to 100 nm in size, has emerged as a promising solution to the limitations of traditional therapies for NMSCs [4]. Specifically, nanoparticle-based delivery systems offer a targeted approach to drug delivery, enabling drugs to be concentrated at the site of the tumor while minimizing systemic exposure and toxicity. These systems, including lipid-based carriers, have been designed to penetrate the skin's deeper layers, improving drug stability and enhancing tumor cell death [9]. Nanoparticles also allow for site-specific targeting, enabling the delivery of lower doses with greater therapeutic effectiveness, which may reduce the side effects commonly associated with conventional treatments.

Emerging studies have shown promising results in the application of nanoparticle-based therapies for NMSCs. For instance, pH-sensitive nanoparticles, such as those loaded with gemcitabine or doxorubicin, have demonstrated superior cytotoxicity compared to traditional therapies by exploiting the acidic microenvironment of cancer cells [9]. Additionally, formulations such as 5-fluorouracil-loaded nanogels have shown efficacy in reducing tumor size, particularly in animal models of aggressive BCC [10]. Furthermore, imiquimod-loaded nanoparticles have proven more effective than standard formulations, enhancing tumor regression while reducing local inflammation and scarring [8]. These advancements underscore the potential of nanoparticle-based systems to revolutionize the treatment landscape for NMSCs by offering more effective, less invasive alternatives to current therapies. This review aims to evaluate the mechanisms, advantages, and current status of nanoparticle-based therapies in the treatment of NMSCs, focusing on their role in improving treatment outcomes while minimizing cosmetic and systemic side effects. Additionally, we will identify existing gaps in research and propose future directions for the development and clinical application of these innovative delivery systems.

2. Mechanisms of Nanoparticle Delivery System

Nanoparticle delivery systems have emerged as a groundbreaking platform in modern therapeutics, offering precise control over drug delivery and improved therapeutic outcomes. Central to their design is the ability to engineer nanoparticles with specific features, including size, shape, surface charge, and biocompatibility [11]. These parameters are not only fundamental to their stability and biodistribution but also play a key role in determining their interaction with biological barriers. For instance, nanoparticles typically range from 1 to 100 nanometers in size, allowing them to navigate capillaries and penetrate target tissues effectively [12]. Surface modifications, such as polyethylene glycol (PEG) coatings [13], enhance circulation time by evading immune recognition, while functional groups or ligands on the surface facilitate targeted delivery. While these modifications have been extensively studied, there remains variability in the effectiveness of different

nanoparticle formulations, particularly concerning their long-term stability and immune response evasion. Some studies suggest that repeated administration of PEGylated nanoparticles may trigger an anti-PEG immune response, potentially reducing their efficacy over time [14]. Future research should continue to focus on optimizing surface modifications to ensure sustained therapeutic benefit without eliciting unintended immunogenicity.

A critical aspect of nanoparticle-based drug delivery lies in its ability to employ both passive and active targeting strategies. Passive targeting capitalizes on the enhanced permeability and retention (EPR) effect, a phenomenon observed in pathological tissues such as tumors [15] [16]. Tumor vasculature is characterized by irregular endothelial gaps and poor lymphatic drainage, which allow nanoparticles to accumulate selectively within the tumor microenvironment. While numerous preclinical studies support the EPR effect, recent evidence suggests that its efficacy varies significantly between tumor types and even among patients due to differences in vascular architecture and microenvironmental factors [17]. This variability highlights the need for further exploration into patient-specific nanoparticle delivery approaches that account for tumor heterogeneity.

Active targeting, on the other hand, involves the functionalization of nanoparticles with ligands, peptides, or antibodies that bind specifically to receptors overexpressed on the surface of target cells [18]. This receptor-mediated mechanism facilitates precise cellular uptake, further enhancing therapeutic efficacy. However, the success of active targeting is contingent upon several factors, including receptor expression levels, endocytosis pathways, and intracellular trafficking efficiency. Some studies indicate that receptor saturation and rapid lysosomal degradation can limit the effectiveness of ligand-functionalized nanoparticles [18]. Comparative analyses of different targeting ligands have shown variability in uptake efficiency and intracellular fate, underscoring the importance of selecting optimal targeting moieties based on tumor biology.

The ability of nanoparticles to penetrate biological barriers and accumulate in target tissues is equally critical to their success. For topical applications, nanoparticles can traverse the stratum corneum, the skin's outermost barrier, through intercellular diffusion, follicular pathways, and transient disruption of tight junctions [19]-[21]. This capability makes them particularly promising for delivering drugs in dermatological conditions such as psoriasis and skin cancers. However, the efficiency of penetration is highly dependent on nanoparticle composition, size, and surface properties. Some studies have reported inconsistent penetration depth across different formulations, suggesting that further standardization in nanoparticle design is necessary for achieving predictable therapeutic outcomes [22]. To address these challenges, ongoing research is focusing on optimizing nanoparticle surface chemistry, incorporating stimuli-responsive mechanisms, and exploring hybrid delivery systems that enhance penetration efficiency while minimizing adverse effects. Such refinements will be essential in ensuring that nanoparticle-based topical treatments consistently achieve therapeutic efficacy across

diverse patient populations.

Nanoparticle delivery systems represent a convergence of nanoscale engineering, precision targeting, and advanced therapeutic strategies. Their ability to enhance drug bioavailability, achieve tissue-specific accumulation, and minimize adverse effects has positioned them as a cornerstone of modern drug delivery research. While significant advancements have been made, ongoing studies continue to refine nanoparticle design and expand their clinical applications. However, discrepancies in preclinical and clinical findings emphasize the necessity for more rigorous comparative studies evaluating different nanoparticle formulations under standardized conditions. Among these, the treatment of NMSC has emerged as a particularly promising area, where the unique properties of nanoparticles are being leveraged to improve the delivery of chemotherapeutic agents, photodynamic therapy compounds, and immune-modulating therapies. Exploring the types of nanoparticles utilized in NMSC treatment highlights the versatility of this platform and underscores the potential for further innovation in addressing this prevalent and challenging condition.

3. Types of Nanoparticles in NMSC Treatment

Liposomes are lipid-soluble vesicles with an aqueous core encapsulated by concentric phospholipid bilayers. The hydrophilic heads and hydrophobic tails enable the bilayer's amphiphilic properties to interact with polar and nonpolar substances, enhancing their potential as drug delivery systems [23]. By encapsulating bioactive molecules of varying polarities, liposomes allow the gradual release of therapeutic compounds as the bilayer degrades into the bloodstream. This targeted delivery to the pathological site reduces systemic toxicity, as drugs remain inactive until they reach the target tissue [24]. Additionally, liposomes can be tailored for specific drug delivery needs by modifying their size, charge, or lipid composition. Engineering neutral, small-sized liposomes can improve steric stability, reduce protein corona formation, and prolong circulation time by avoiding phagocytic recognition [25]. By reducing this recognition, these modified liposomes exhibit prolonged circulation times, enhancing their ability to reach specific tissues and cells with greater efficiency. In treating solid tumors affecting the skin, the stratum corneum, composed of densely packed corneocytes and intercellular lipids, presents a significant challenge by acting as a barrier to topical anti-cancer treatments, impeding their effectiveness. A study by Luiziana Crisóstomo *et al.* addressed ways to overcome these barriers by investigating the use of liposomal formulations of 5-Fluorouracil (5-FU) in combination with the penetration enhancer sorbitan monolaurate (span 20) [26]. 5-FU, a widely utilized hydrophilic antineoplastic agent, is commonly formulated for topical use in the management of BCC and cSCC. The *in vitro* studies demonstrated this formulation significantly enhanced the penetration of 5-FU [27]. These findings were corroborated through flow cytometry and microscopy, which revealed a markedly higher uptake of 5-FU in the treated regions. This evidence illustrates promising revelations

of how these innovative delivery systems can enhance the efficacy of topical anticancer therapies.

The success of liposomal systems in enhancing drug delivery has encouraged the development of other nanotechnology-based vehicles, such as polymeric nanoparticles. Nanoparticles, particularly those made from polylactic acid (PLA), polyglycolic acid (PGA), and polylactic-co-glycolide (PLGA), offer another innovative avenue for drug delivery due to their biocompatibility and low toxicity [27]. Unlike liposomes, which are easily suitable for drugs that vary in water solubility, polymeric nanoparticles more efficiently encapsulate hydrophobic drugs and require additional modifications for hydrophilic drugs. Furthermore, PLGA-based polymeric nanoparticles are thought to provide more structural stability, especially with hydrophobic drugs. Depending on how the drug is engineered, these types can be classified as nanocapsules or nanospheres. In nanocapsules, drugs dissolve in the oily core, with controlled release governed by a polymeric shell, demonstrating zero-order kinetics *in vitro*. Conversely, nanospheres feature a polymeric network where drugs are retained on the surface or within the matrix, showing first-order kinetics. This distinction arises from the fluidity of nanocapsules versus the rigidity of nanospheres. Xiaojie Wang *et al.* conducted a study that investigated PLGA nanoparticles for delivering aminolevulinic acid (ALA) in topical photodynamic therapy (PDT) for cSCC [28]. Compared to ALA alone, ALA-loaded PLGA nanoparticles significantly increased protoporphyrin IX (PpIX) fluorescence intensity, peaking at 6 hours and demonstrating higher selectivity for cSCC cells through fluorescence imaging [28]. These results highlight the adaptability of nanoparticles in optimizing therapeutic delivery and targeting complex diseases.

Solid lipid nanoparticles (SLNs) emerge as a novel lipid-based carrier subclass that addresses several limitations of traditional polymeric systems. To address the scarcity of safe polymers when addressing the limitations of polymeric nanoparticle engineering, SLNs have a novel subset of lipid-based drug carriers that utilize biodegradable, water-based technology [29]. Their solid lipid core ensures controlled and targeted drug release, enhancing stability and extending drug shelf life. Similarly to the liposomal method of drug delivery, SLNs exhibit high encapsulation efficiency for lipophilic and hydrophilic drugs, making them versatile across therapeutic applications. Jain *et al.*'s study demonstrated SLN efficacy in transdermal delivery of flurbiprofen, a nonsteroidal anti-inflammatory drug (NSAID). Optimized SLN formulations achieved 92.7% drug entrapment efficiency, with *in vitro* studies showing sustained drug release over 24 hours [30]. Skin permeation experiments confirmed that SLN formulations enhanced drug penetration and retention compared to conventional systems, shedding light on their potential in topical therapies [30]. As SLNs continue to demonstrate significant improvements in drug stability and controlled delivery, researchers are also exploring other nanostructures, such as dendrimers, which offer distinct structural and functional advantages for targeted drug delivery.

Dendrimers are hyperbranched polymers with a central hollow core and tendrils branching outward, offering structural diversity and adaptability. Their hydrophobic core and hydrophilic periphery mimic unimolecular micelles, encapsulating hydrophobic drugs. This nanoparticle offers higher drug-loading capacity because of the large internal cavities and high surface binding. In the field of oncology, conjugating hyaluronic acid to polyamidoamine (PAMAM) dendrimers leverages hyaluronic acid's affinity for CD44 receptors, highly expressed in tumor cells, for enhanced drug targeting [31]. To investigate this concept from a dermatological perspective, David Ybarra *et al.*'s study explores PAMAM dendrimers loaded with Vismodegib (VDG) for BCC treatment [32]. As illustrated via epifluorescence microscopy, amine-terminated (DG4.0) and carboxy-terminated (DG4.5), dendrimers penetrated the stratum corneum and reached the viable epidermis. However, reverse-phase high-performance liquid chromatography (RT-HPLC) revealed that DG4.5 maintained greater stability, confining VDG to its internal pockets for controlled release [32]. These findings demonstrate dendrimers' unique ability to enhance precision and effectiveness in drug delivery while overcoming biological barriers, making them valuable nanoparticles in advancing therapeutic strategies. However, it is critical to consider that their large size may pose challenges with tissue accumulation and cytotoxicity. This consideration may be crucial to determining whether to choose an approach like the dendrimer or SLNs, which are biodegradable and at lower risk for toxicity.

Given the growing interest in nanoparticle-based therapies for NMSCs, further research is needed to optimize their efficacy and long-term safety. Liposomes have demonstrated improved drug penetration, but more studies should evaluate their efficiency in deeper BCC tumors and hyperkeratotic lesions of SCC, where deep penetration may be challenged by structural complexity. Similarly, polymeric nanoparticles show promise for sustained drug release and enhanced PDT, yet comparative studies are necessary to determine whether they outperform liposomes or SLNs in delivering chemotherapeutic agents. Regarding the concerns about the dendrimers' safety profile, they warrant further safety investigations. More specifically, assessing potential candidates for eligibility in this delivery system and identifying any medical conditions that may be contraindicated due to the risk of cytotoxicity. Comparative clinical trials with various tailored nanoparticle formulations may be essential when evaluating a patient's clinical presentation, past medical history, and response to previous regimens. This patient-centered approach may further enhance therapeutic outcomes while minimizing side effects. By integrating the advantages of diverse nanocarrier systems, modern drug delivery continues to evolve, offering more precise, efficient, and safer therapeutic options.

4. Advantages of Nanoparticle-Based Therapies

4.1. Enhanced Efficacy

Modern drug delivery systems significantly enhance the therapeutic effectiveness

of medications through innovative mechanisms that improve solubility, bioavailability, and targeted release. Poorly water-soluble compounds benefit from increased absorption rates, ensuring they reach therapeutic targets more effectively [33]. By optimizing bioavailability, these systems make active drugs more accessible in the bloodstream or target tissues, leading to faster and more consistent therapeutic effects. Recent advancements in nanoparticle technology have introduced AI-driven nanoparticle design, enabling precise drug formulation and improving treatment efficacy. Nanoparticle-based therapies further address solubility challenges by enabling sustained and localized drug release, maintaining therapeutic concentrations at the target site while minimizing fluctuations in drug levels [34] [35]. Controlled release reduces the need for frequent dosing and minimizes the risk of sub-therapeutic effects or overdosing [34]. Additionally, site-specific delivery focuses the drug's action directly on affected areas, improving outcomes for localized conditions such as cancer, infections, and inflammation. In advanced modalities like PDT, nanoparticles play a crucial role in delivering drugs with precision, ensuring effective tumor cell eradication through controlled distribution and retention [33]. Stimuli-responsive nanoparticles, which release drugs in response to specific environmental triggers such as pH, temperature, or enzymatic activity, are emerging as a promising innovation in NMSC treatment. These advancements collectively maximize the potency, safety, and reliability of treatments, ensuring improved health outcomes for patients.

The last ten years have witnessed the rapid growth of nanomedicine, with unparalleled achievements in diagnosis and disease therapy [36]. There are approved nanomedicines, and this has displayed the potential value of bringing bench-to-bedside translated nanotechnology-altered medications. Nanotechnology developments, particularly in personalized therapy, have pushed the specificity and effectiveness of therapy even further. The application of artificial intelligence (AI) in the development of nanotechnology-based products can transform the healthcare sector by enabling the gathering and analysis of big data and the tailoring of precision nanomedicines for cancer therapy [36] [37]. AI-nanotechnology is likely to make patient diagnosis accuracy better through precision in molecular profiling and early diagnosis of patients, optimize the design pipeline of nanomedicines by customizing their properties, achieve effective synergy of drugs, and minimize nanotoxicity. These advancements promote enhanced biocompatibility, greater bioavailability, and longer circulation times, leading to improved patient outcomes.

4.2. Reduced Toxicity

Modern drug delivery systems significantly reduce toxicity by minimizing systemic absorption and off-target effects, addressing a key limitation of conventional therapies like chemotherapy [33] [34]. By targeting medications specifically to tumor sites, nanoparticles decrease exposure to healthy tissues, lowering the risk of systemic toxicity and adverse effects [38]. This selectivity enhances patient

safety and widens the therapeutic window of otherwise toxic agents. Innovative delivery methods further improve safety by limiting the presence of drugs in the bloodstream, thereby reducing interactions with healthy organs and tissues. Targeted approaches also decrease the likelihood of side effects, which is particularly critical in treatments involving potent medications [11]. For example, delivering chemotherapy drugs directly to tumors reduces damage to healthy cells, resulting in fewer adverse effects such as immunosuppression or nausea. Controlled drug release mechanisms additionally prevent sudden spikes in drug concentration, reducing the risk of overdosing and associated toxicity. These advancements are especially beneficial for patients with comorbidities or those prone to adverse reactions. By prioritizing precision, modern drug delivery systems ensure safer and more effective treatments tailored to patient needs.

Anticipating interactions among nanocarriers and encapsulated drugs, biological mediators, or cell membranes, drug encapsulation efficiency prediction, and drug release kinetics modeling from nanocarriers through AI algorithms can accelerate nanopharmaceutical formulations for enhancing the transport and targeting of nanomedicines [37]. AI-driven approaches also facilitate the selection of drug combinations and combination therapy global optimization to achieve drug synergism with reduced toxicity, ultimately enhancing clinical outcomes. Furthermore, machine learning algorithms coupled with nanoscale biosensors can facilitate the identification of new biomarkers and therapeutic targets, classify diseased patients from healthy individuals, and forecast disease outbreaks or recurrence [37] [39]. Such AI-augmented features are transforming more effective, less invasive, and highly personalized cancer therapies.

4.3. Improved Patient Compliance

Advanced drug delivery systems significantly improve patient compliance by making therapies more convenient and less burdensome. Non-invasive methods, such as transdermal patches, oral dissolving films, or intranasal sprays, simplify drug administration and eliminate the need for injections or complex regimens [40]. These innovations are particularly beneficial for individuals with chronic conditions who might otherwise struggle with adherence due to treatment complexity or discomfort [41]. Sustained-release mechanisms further enhance compliance by reducing the frequency of dosing, allowing patients to maintain consistent regimens without the stress of multiple daily administrations [41] [42]. Additionally, nanoparticle-based therapies provide targeted delivery and fewer side effects, improving tolerability and encouraging patients to complete their prescribed treatments effectively [11]. This is especially important for pediatric and elderly populations, where ease of use and minimal discomfort are critical for adherence. By addressing both the physical and psychological barriers to treatment, these systems ensure that patients remain engaged in their care plans, leading to improved therapeutic outcomes and overall quality of life.

5. Integration with Synergistic Modalities

Preclinical studies have demonstrated remarkable synergy between nanoparticle delivery systems and immune-based therapies in dermatology, particularly in enhancing the efficacy of photodynamic and immunotherapy combinations. PDT, with its unique combination of non-invasiveness and specificity, has become a promising tool in the management of dermatological conditions, particularly skin cancers. The treatment relies on the activation of photosensitizers by light, which generates reactive oxygen species (ROS) to selectively destroy cancerous cells [43] [44]. Nanoparticles, as delivery systems, have further enhanced the efficacy of PDT in dermatology by addressing key limitations of traditional therapies, such as poor solubility and off-target effects of photosensitizers. For example, polymeric and lipid-based nanocarriers have been shown to improve skin permeability and enable deeper penetration of photosensitizers into the skin layers, overcoming the barrier posed by the stratum corneum [45] [46]. Additionally, mesoporous silica nanoparticles have been investigated for their capacity to co-deliver photothermal agents and cytokines, synergizing localized tumor destruction with systemic immune activation [47]. Such approaches not only amplify the therapeutic impact but also demonstrate the potential for long-term tumor remission through immunological memory.

In dermatology, the application of PDT extends beyond cancer treatment, offering therapeutic potential for conditions such as psoriasis, acne, and photoaging [48] [49]. The introduction of nanotechnology has also facilitated the use of PDT for early-stage cancer detection, as nanoparticles can be engineered with imaging functionalities to aid in diagnostic precision. Moreover, studies have demonstrated the ability of metallic nanoparticles, such as gold and silver, to amplify light absorption, enhancing ROS generation and improving therapeutic outcomes [50] [51]. These developments are particularly relevant for addressing aesthetic concerns in dermatology, as the selective targeting and minimal damage to surrounding healthy tissue preserve the skin's appearance. Future research aimed at optimizing the biocompatibility and multifunctionality of nanoparticles in PDT holds promise for expanding its applications to other dermatological conditions while also addressing critical knowledge gaps in long-term safety and efficacy.

PDT has emerged as a reliable, non-invasive treatment modality for NMSCs and other dermatologic conditions. However, its geographic and financial accessibility remains a significant barrier to widespread adoption. A retrospective analysis of U.S. Medicare reimbursement data from 2012 to 2017 highlighted these disparities, revealing that PDT was available in 41.6% of metropolitan counties but only 5.4% of nonmetropolitan counties [52]. Given the high prevalence of NMSCs in both elderly and rural populations, this discrepancy suggests a critical gap in care that warrants targeted interventions. Several strategies may mitigate this disparity, including enhanced provider training in PDT, the development of mobile dermatologic units and telemedicine programs, and collaborative partnerships between rural providers and metropolitan dermatology centers to improve

resource allocation. In addition to geographic limitations, treatment logistics pose another significant challenge, particularly in underserved areas. PDT requires a photosensitizer incubation period prior to light activation, which may exacerbate barriers to care in rural settings where patients face extended travel times and limited specialist availability. The Food and Drug Administration (FDA) mandates a three-hour incubation period for ALA-PDT in actinic keratosis, a precursor lesion to SCC. Although clinical evidence suggests that shortened incubation periods (1 - 1.5 hours) may yield comparable efficacy, such practices remain off-label [53]. The inconvenience of prolonged incubation may deter patients from pursuing PDT, further compounding accessibility challenges.

To address this issue, ongoing clinical trials are evaluating the efficacy of alternative incubation protocols, including no incubation and reduced incubation times (1-hour and 2-hour regimens) in actinic keratosis. These findings may inform future guideline modifications, enhancing both treatment efficiency and patient adherence. Ultimately, improving the accessibility of PDT across geographic, economic, and systemic barriers is imperative for ensuring that advancements in dermatologic oncology translate into meaningful clinical outcomes for diverse patient populations.

6. Challenges, Limitations, and Future Directions

Although nanoparticle-based delivery systems show great promise for treating NMSCs, their transition from preclinical research to clinical practice remains challenging. A primary obstacle is the disparity between animal models and human physiology, which often results in variable outcomes. For example, the differences in nanoparticle penetration across the stratum corneum between murine and human skin significantly affect therapeutic efficacy and drug absorption [54]. This emphasizes the need for more representative models, such as three-dimensional organotypic skin constructs and patient-derived xenografts, to better simulate human skin architecture and tumor microenvironments. These models provide an opportunity to refine nanoparticle formulations for enhanced clinical success [55]. Additionally, the absence of longitudinal clinical studies on nanoparticle-based systems, particularly for applications requiring prolonged use, creates a gap in understanding their long-term safety and effectiveness [56]. Addressing these challenges is essential to advancing the clinical reliability of these therapies.

Technological and economic barriers further impede the scalability and accessibility of nanoparticle-based treatments. Maintaining critical properties such as particle size, surface charge, and drug encapsulation efficiency during large-scale production is a persistent issue, often resulting in batch-to-batch variability [57]. Moreover, the infrastructure required for nanoparticle manufacturing, including cleanrooms and specialized equipment, increases costs, which are particularly prohibitive in resource-limited settings. These economic constraints are concerning given the rising prevalence of NMSCs in developing regions [58]. Innovations such as microfluidics and continuous manufacturing processes hold promise for

improving scalability and cost efficiency, enabling consistent production quality [11]. In addition, public-private partnerships and tiered pricing strategies can promote equitable access, ensuring these therapies are available to underserved populations. Addressing these systemic barriers is vital to bridging the gap between technological advances and real-world accessibility.

The regulatory landscape presents another significant challenge. Nanoparticles often possess unique physicochemical properties and mechanisms of action that do not fit neatly into existing regulatory frameworks. This leads to delays in approval and clinical adoption. Furthermore, concerns about the long-term safety of nanoparticles, including their potential to accumulate in non-target tissues and induce immunogenicity, underscore the need for robust evaluation protocols [59]. Clear regulatory guidelines tailored to nanoparticles, including their nanoscale behavior and interaction with biological systems, are essential to streamline the approval process. Comprehensive post-marketing surveillance and longitudinal safety studies will also be necessary to address public concerns and ensure trust in these therapies [60]. Establishing such regulatory frameworks will facilitate the safe and timely integration of nanoparticle-based systems into clinical practice.

Emerging technologies offer promising avenues for overcoming these limitations. AI can optimize nanoparticle design by predicting ideal physicochemical properties, identifying effective drug combinations, and simulating biological interactions [61]. For example, AI-based algorithms can enhance the development of stimuli-responsive nanoparticles and ligand-functionalized systems, improving targeting precision and therapeutic outcomes. Additionally, wearable biosensors integrated with nanoparticle therapies can enable real-time monitoring of drug delivery and patient responses, enhancing treatment personalization. Advances in controlled-release mechanisms and novel targeting strategies further expand the therapeutic potential of nanoparticles, minimizing systemic exposure and off-target effects [62]. These innovations not only address current challenges but also position nanoparticle-based therapies as transformative tools in the treatment of NMSCs.

7. Conclusion

Nanoparticle-based delivery systems offer significant potential for improving NMSC treatment outcomes. By enhancing drug bioavailability, achieving targeted delivery, and minimizing systemic toxicity, these systems address critical limitations of conventional therapies. Various nanoparticle types, including liposomes, polymeric nanoparticles, and dendrimers, exhibit unique properties that can be exploited for effective drug delivery. These systems improve the penetration of therapeutic agents through the skin, enhance drug retention within the tumor microenvironment, and enable controlled release, thereby maximizing therapeutic efficacy and minimizing side effects. The advancements in nanoparticle-based therapies hold immense promise for revolutionizing NMSC treatment. By enhancing drug delivery and minimizing side effects, these technologies can signifi-

cantly improve patient quality of life and contribute to better treatment outcomes. Collaboration among clinicians, engineers, researchers, and stakeholders is essential for the future development of NMSC nanoparticle delivery systems. By fostering interdisciplinary collaboration, we can bring these systems from research labs to a patient's bedside and improve NMSC outcomes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Shalhout, S.Z., Emerick, K.S., Kaufman, H.L. and Miller, D.M. (2021) Immunotherapy for Non-Melanoma Skin Cancer. *Current Oncology Reports*, **23**, Article No. 125. https://doi.org/10.1007/s11912-021-01120-z

[2] Kim, J.Y.S., Kozlow, J.H., Mittal, B., Moyer, J., Olencki, T., Rodgers, P., *et al.* (2018) Guidelines of Care for the Management of Basal Cell Carcinoma. *Journal of the American Academy of Dermatology*, **78**, 540-559. https://doi.org/10.1016/j.jaad.2017.10.006

[3] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., *et al.* (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[4] Hasan, N., Nadaf, A., Imran, M., Jiba, U., Sheikh, A., Almalki, W.H., *et al.* (2023) Skin Cancer: Understanding the Journey of Transformation from Conventional to Advanced Treatment Approaches. *Molecular Cancer*, **22**, Article No. 168. https://doi.org/10.1186/s12943-023-01854-3

[5] Carroll, R.P., Ramsay, H.M., Fryer, A.A., Hawley, C.M., Nicol, D.L. and Harden, P.N. (2003) Incidence and Prediction of Nonmelanoma Skin Cancer Post-Renal Transplantation: A Prospective Study in Queensland, Australia. *American Journal of Kidney Diseases*, **41**, 676-683. https://doi.org/10.1053/ajkd.2003.50130

[6] Cives, M., Mannavola, F., Lospalluti, L., Sergi, M.C., Cazzato, G., Filoni, E., *et al.* (2020) Non-Melanoma Skin Cancers: Biological and Clinical Features. *International Journal of Molecular Sciences*, **21**, Article 5394. https://doi.org/10.3390/ijms21155394

[7] Li, Y.Y., Hanna, G.J., Laga, A.C., Haddad, R.I., Lorch, J.H. and Hammerman, P.S. (2015) Genomic Analysis of Metastatic Cutaneous Squamous Cell Carcinoma. *Clinical Cancer Research*, **21**, 1447-1456. https://doi.org/10.1158/1078-0432.ccr-14-1773

[8] Dias, M.F., de Figueiredo, B.C.P., Teixeira-Neto, J., Guerra, M.C.A., Fialho, S.L. and Silva Cunha, A. (2018) *In Vivo* Evaluation of Antitumoral and Antiangiogenic Effect of Imiquimod-Loaded Polymeric Nanoparticles. *Biomedicine & Pharmacotherapy*, **103**, 1107-1114. https://doi.org/10.1016/j.biopha.2018.04.079

[9] Souto, E.B., da Ana, R., Vieira, V., Fangueiro, J.F., Dias-Ferreira, J., Cano, A., *et al.* (2022) Non-Melanoma Skin Cancers: Physio-Pathology and Role of Lipid Delivery Systems in New Chemotherapeutic Treatments. *Neoplasia*, **30**, Article 100810. https://doi.org/10.1016/j.neo.2022.100810

[10] Sahu, P., Kashaw, S.K., Sau, S., Kushwah, V., Jain, S., Agrawal, R.K., *et al.* (2019) PH Responsive 5-Fluorouracil Loaded Biocompatible Nanogels for Topical Chemotherapy of Aggressive Melanoma. *Colloids and Surfaces B*: *Biointerfaces*, **174**, 232-245.

https://doi.org/10.1016/j.colsurfb.2018.11.018

[11] Mitchell, M.J., Billingsley, M.M., Haley, R.M., Wechsler, M.E., Peppas, N.A. and Langer, R. (2020) Engineering Precision Nanoparticles for Drug Delivery. *Nature Reviews Drug Discovery*, **20**, 101-124. https://doi.org/10.1038/s41573-020-0090-8

[12] Singh, R. and Lillard, J.W. (2009) Nanoparticle-Based Targeted Drug Delivery. *Experimental and Molecular Pathology*, **86**, 215-223. https://doi.org/10.1016/j.yexmp.2008.12.004

[13] Suk, J.S., Xu, Q., Kim, N., Hanes, J. and Ensign, L.M. (2016) Pegylation as a Strategy for Improving Nanoparticle-Based Drug and Gene Delivery. *Advanced Drug Delivery Reviews*, **99**, 28-51. https://doi.org/10.1016/j.addr.2015.09.012

[14] Yang, Q. and Lai, S.K. (2015) Anti-PEG Immunity: Emergence, Characteristics, and Unaddressed Questions. *WIREs Nanomedicine and Nanobiotechnology*, **7**, 655-677. https://doi.org/10.1002/wnan.1339

[15] Maeda, H. and Matsumura, Y. (1989) Tumoritropic and Lymphotropic Principles of Macromolecular Drugs. *Critical Reviews in Therapeutic Drug Carrier Systems*, **6**, 193-210.

[16] Matsumura, Y. and Maeda, H. (1986) A New Concept for Macromolecular Therapeutics in Cancer Chemotherapy: Mechanism of Tumoritropic Accumulation of Proteins and the Antitumor Agent Smancs. *Cancer Research*, **46**, 6387-6392.

[17] Maeda, H., Bharate, G.Y. and Daruwalla, J. (2009) Polymeric Drugs for Efficient Tumor-Targeted Drug Delivery Based on EPR-Effect. *European Journal of Pharmaceutics and Biopharmaceutics*, **71**, 409-419. https://doi.org/10.1016/j.ejpb.2008.11.010

[18] Shi, P., Cheng, Z., Zhao, K., Chen, Y., Zhang, A., Gan, W., *et al.* (2023) Active Targeting Schemes for Nano-Drug Delivery Systems in Osteosarcoma Therapeutics. *Journal of Nanobiotechnology*, **21**, Article No. 103. https://doi.org/10.1186/s12951-023-01826-1

[19] Lademann, J., Richter, H., Teichmann, A., Otberg, N., Blume-Peytavi, U., Luengo, J., *et al.* (2007) Nanoparticles—An Efficient Carrier for Drug Delivery into the Hair Follicles. *European Journal of Pharmaceutics and Biopharmaceutics*, **66**, 159-164. https://doi.org/10.1016/j.ejpb.2006.10.019

[20] Baroli, B., Ennas, M.G., Loffredo, F., Isola, M., Pinna, R. and Arturo López-Quintela, M. (2007) Penetration of Metallic Nanoparticles in Human Full-Thickness Skin. *Journal of Investigative Dermatology*, **127**, 1701-1712. https://doi.org/10.1038/sj.jid.5700733

[21] Desai, P., Patlolla, R.R. and Singh, M. (2010) Interaction of Nanoparticles and Cell-Penetrating Peptides with Skin for Transdermal Drug Delivery. *Molecular Membrane Biology*, **27**, 247-259. https://doi.org/10.3109/09687688.2010.522203

[22] Chehelgerdi, M., Chehelgerdi, M., Allela, O.Q.B., Pecho, R.D.C., Jayasankar, N., Rao, D.P., *et al.* (2023) Progressing Nanotechnology to Improve Targeted Cancer Treatment: Overcoming Hurdles in Its Clinical Implementation. *Molecular Cancer*, **22**, Article No. 169. https://doi.org/10.1186/s12943-023-01865-0

[23] Nsairat, H., Khater, D., Sayed, U., Odeh, F., Al Bawab, A. and Alshaer, W. (2022) Liposomes: Structure, Composition, Types, and Clinical Applications. *Heliyon*, **8**, e09394. https://doi.org/10.1016/j.heliyon.2022.e09394

[24] Nisini, R., Poerio, N., Mariotti, S., De Santis, F. and Fraziano, M. (2018) The Multirole of Liposomes in Therapy and Prevention of Infectious Diseases. *Frontiers in Immunology*, **9**, Article 155. https://doi.org/10.3389/fimmu.2018.00155

[25] Maitz, M.F. (2015) Applications of Synthetic Polymers in Clinical Medicine. *Biosur-*

face and Biotribology, **1**, 161-176. https://doi.org/10.1016/j.bsbt.2015.08.002

[26] Crisóstomo, L.C.C.F., Carvalho, G.S.G., Leal, L.K.A.M., de Araújo, T.G., Nogueira, K.A.B., da Silva, D.A., *et al.* (2022) Sorbitan Monolaurate—Containing Liposomes Enhance Skin Cancer Cell Cytotoxicity and in Association with Microneedling Increase the Skin Penetration of 5-Fluorouracil. *AAPS PharmSciTech*, **23**, Article No. 212. https://doi.org/10.1208/s12249-022-02356-z

[27] Zielińska, A., Carreiró, F., Oliveira, A.M., Neves, A., Pires, B., Venkatesh, D.N., *et al.* (2020) Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology. *Molecules*, **25**, Article 3731. https://doi.org/10.3390/molecules25163731

[28] Shi, L., Wang, X., Tu, Q., Wang, H., Zhang, H., Wang, P., *et al.* (2015) Treating Cutaneous Squamous Cell Carcinoma Using 5-Aminolevulinic Acid Polylactic-Co-Glycolic Acid Nanoparticle-Mediated Photodynamic Therapy in a Mouse Model. *International Journal of Nanomedicine*, **10**, 347-355. https://doi.org/10.2147/ijn.s71245

[29] Mukherjee, S., Ray, S. and Thakur, R. (2009) Solid Lipid Nanoparticles: A Modern Formulation Approach in Drug Delivery System. *Indian Journal of Pharmaceutical Sciences*, **71**, 349-358. https://doi.org/10.4103/0250-474x.57282

[30] Jain, S.K., Chourasia, M.K., Masuriha, R., Soni, V., Jain, A., Jain, N.K., *et al.* (2005) Solid Lipid Nanoparticles Bearing Flurbiprofen for Transdermal Delivery. *Drug Delivery*, **12**, 207-215. https://doi.org/10.1080/10717540590952591

[31] Wang, J., Li, B., Qiu, L., Qiao, X. and Yang, H. (2022) Dendrimer-Based Drug Delivery Systems: History, Challenges, and Latest Developments. *Journal of Biological Engineering*, **16**, Article No. 18. https://doi.org/10.1186/s13036-022-00298-5

[32] Ybarra, D.E., Calienni, M.N., Ramirez, L.F.B., Frias, E.T.A., Lillo, C., Alonso, S.d.V., *et al.* (2022) Vismodegib in PAMAM-Dendrimers for Potential Theragnosis in Skin Cancer. *OpenNano*, **7**, Article 100053. https://doi.org/10.1016/j.onano.2022.100053

[33] Zhuo, Y., Zhao, Y. and Zhang, Y. (2024) Enhancing Drug Solubility, Bioavailability, and Targeted Therapeutic Applications through Magnetic Nanoparticles. *Molecules*, **29**, Article 4854. https://doi.org/10.3390/molecules29204854

[34] Menilli, L., Milani, C., Reddi, E. and Moret, F. (2022) Overview of Nanoparticle-Based Approaches for the Combination of Photodynamic Therapy (PDT) and Chemotherapy at the Preclinical Stage. *Cancers*, **14**, Article 4462. https://doi.org/10.3390/cancers14184462

[35] Aghebati-Maleki, A., Dolati, S., Ahmadi, M., Baghbanzhadeh, A., Asadi, M., Fotouhi, A., *et al.* (2020) Nanoparticles and Cancer Therapy: Perspectives for Application of Nanoparticles in the Treatment of Cancers. *Journal of Cellular Physiology*, **235**, 1962-1972. https://doi.org/10.1002/jcp.29126

[36] Tan, P., Chen, X., Zhang, H., Wei, Q. and Luo, K. (2023) Artificial Intelligence Aids in Development of Nanomedicines for Cancer Management. *Seminars in Cancer Biology*, **89**, 61-75. https://doi.org/10.1016/j.semcancer.2023.01.005

[37] Mazumdar, H., Khondakar, K.R., Das, S., Halder, A. and Kaushik, A. (2025) Artificial Intelligence for Personalized Nanomedicine; from Material Selection to Patient Outcomes. *Expert Opinion on Drug Delivery*, **22**, 85-108. https://doi.org/10.1080/17425247.2024.2440618

[38] Torchilin, V.P. (2005) Recent Advances with Liposomes as Pharmaceutical Carriers. *Nature Reviews Drug Discovery*, **4**, 145-160. https://doi.org/10.1038/nrd1632

[39] Zhang, Y., Li, J. and Pu, K. (2022) Recent Advances in Dual- and Multi-Responsive Nanomedicines for Precision Cancer Therapy. *Biomaterials*, **291**, Article 121906. https://doi.org/10.1016/j.biomaterials.2022.121906

[40] Tran, N. and Webster, T.J. (2010) Magnetic Nanoparticles: Biomedical Applications and Challenges. *Journal of Materials Chemistry*, **20**, 8760-8767. https://doi.org/10.1039/c0jm00994f

[41] Baryakova, T.H., Pogostin, B.H., Langer, R. and McHugh, K.J. (2023) Overcoming Barriers to Patient Adherence: The Case for Developing Innovative Drug Delivery Systems. *Nature Reviews Drug Discovery*, **22**, 387-409. https://doi.org/10.1038/s41573-023-00670-0

[42] Ezike, T.C., Okpala, U.S., Onoja, U.L., Nwike, C.P., Ezeako, E.C., Okpara, O.J., *et al.* (2023) Advances in Drug Delivery Systems, Challenges and Future Directions. *Heliyon*, **9**, e17488. https://doi.org/10.1016/j.heliyon.2023.e17488

[43] Li, X., Lovell, J.F., Yoon, J. and Chen, X. (2020) Clinical Development and Potential of Photothermal and Photodynamic Therapies for Cancer. *Nature Reviews Clinical Oncology*, **17**, 657-674. https://doi.org/10.1038/s41571-020-0410-2

[44] Ming, L., Cheng, K., Chen, Y., Yang, R. and Chen, D. (2021) Enhancement of Tumor Lethality of ROS in Photodynamic Therapy. *Cancer Medicine*, **10**, 257-268. https://doi.org/10.1002/cam4.3592

[45] Borzęcka, W., Domiński, A. and Kowalczuk, M. (2021) Recent Progress in Phthalocyanine-Polymeric Nanoparticle Delivery Systems for Cancer Photodynamic Therapy. *Nanomaterials*, **11**, Article 2426. https://doi.org/10.3390/nano11092426

[46] Mello, V.C., Araújo, V.H.S., de Paiva, K.L.R., Simões, M.M., Marques, D.C., da Silva Costa, N.R., *et al.* (2022) Development of New Natural Lipid-Based Nanoparticles Loaded with Aluminum-Phthalocyanine for Photodynamic Therapy against Melanoma. *Nanomaterials*, **12**, Article 3547. https://doi.org/10.3390/nano12203547

[47] Aljabali, A.A.A., Obeid, M.A., Gammoh, O., El-Tanani, M., Mishra, V., Mishra, Y., *et al.* (2024) Nanomaterial-Driven Precision Immunomodulation: A New Paradigm in Therapeutic Interventions. *Cancers*, **16**, Article 2030. https://doi.org/10.3390/cancers16112030

[48] Makuch, S., Dróżdż, M., Makarec, A., Ziółkowski, P. and Woźniak, M. (2022) An Update on Photodynamic Therapy of Psoriasis—Current Strategies and Nanotechnology as a Future Perspective. *International Journal of Molecular Sciences*, **23**, Article 9845. https://doi.org/10.3390/ijms23179845

[49] Philipp-Dormston, W.G. (2018) Photodynamic Therapy for Aesthetic-Cosmetic Indications. *Giornale Italiano di Dermatologia e Venereologia*, **153**, 817-826. https://doi.org/10.23736/s0392-0488.18.05982-5

[50] Lucky, S.S., Soo, K.C. and Zhang, Y. (2015) Nanoparticles in Photodynamic Therapy. *Chemical Reviews*, **115**, 1990-2042. https://doi.org/10.1021/cr5004198

[51] Cheng, S. and Lo, L. (2011) Inorganic Nanoparticles for Enhanced Photodynamic Cancer Therapy. *Current Drug Discovery Technologies*, **8**, 269-276. https://doi.org/10.2174/157016311796798982

[52] Cheraghlou, S., Feng, H. and Cohen, J.M. (2020) Trends in the Access and Cost of Photodynamic Therapy among Medicare Beneficiaries in the United States, 2012-2017. *JAMA Dermatology*, **156**, 1021-1022. https://doi.org/10.1001/jamadermatol.2020.2427

[53] Zeitouni, N.C., Bhatia, N., Ceilley, R.I., Cohen, J.L., Del Rosso, J.Q., Moore, A.Y., Munavalli, G., Pariser, D.M., Schlesinger, T., Siegel, D.M., Willey, A. and Goldman, M.P. (2021) Photodynamic Therapy with 5-Aminolevulinic Acid 10% Gel and Red Light for the Treatment of Actinic Keratosis, Nonmelanoma Skin Cancers, and Acne: Current Evidence and Best Practices. *The Journal of Clinical and Aesthetic Dermatology*, **14**, E53-E65.

[54] Wacker, M. (2013) Nanocarriers for Intravenous Injection—The Long Hard Road to the Market. *International Journal of Pharmaceutics*, **457**, 50-62. https://doi.org/10.1016/j.ijpharm.2013.08.079

[55] Tay, C.Y., Muthu, M.S., Chia, S.L., Nguyen, K.T., Feng, S. and Leong, D.T. (2016) Reality Check for Nanomaterial-Mediated Therapy with 3D Biomimetic Culture Systems. *Advanced Functional Materials*, **26**, 4046-4065. https://doi.org/10.1002/adfm.201600476

[56] Tran, S., DeGiovanni, P., Piel, B. and Rai, P. (2017) Cancer Nanomedicine: A Review of Recent Success in Drug Delivery. *Clinical and Translational Medicine*, **6**, e44. https://doi.org/10.1186/s40169-017-0175-0

[57] Desai, N. (2012) Challenges in Development of Nanoparticle-Based Therapeutics. *The AAPS Journal*, **14**, 282-295. https://doi.org/10.1208/s12248-012-9339-4

[58] Hu, W., Fang, L., Ni, R., Zhang, H. and Pan, G. (2022) Changing Trends in the Disease Burden of Non-Melanoma Skin Cancer Globally from 1990 to 2019 and Its Predicted Level in 25 Years. *BMC Cancer*, **22**, Article No. 836. https://doi.org/10.1186/s12885-022-09940-3

[59] Etheridge, M.L., Campbell, S.A., Erdman, A.G., Haynes, C.L., McCullough, J. and Wolf, S.M. (2013) The Big Picture on Nanomedicine: The State of Investigational and Approved Nanomedicine Products. *Nanomedicine*: *Nanotechnology*, *Biology and Medicine*, **9**, 1-14. https://doi.org/10.1016/j.nano.2012.05.013

[60] Raschi, E. (2015) Drug- and Herb-Induced Liver Injury: Progress, Current Challenges and Emerging Signals of Post-Marketing Risk. *World Journal of Hepatology*, **7**, 1761-1771. https://doi.org/10.4254/wjh.v7.i13.1761

[61] Serov, N. and Vinogradov, V. (2022) Artificial Intelligence to Bring Nanomedicine to Life. *Advanced Drug Delivery Reviews*, **184**, Article 114194. https://doi.org/10.1016/j.addr.2022.114194

[62] Kumari, P., Ghosh, B. and Biswas, S. (2016) Nanocarriers for Cancer-Targeted Drug Delivery. *Journal of Drug Targeting*, **24**, 179-191. https://doi.org/10.3109/1061186x.2015.1051049