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NANOTECHNOLOGY-BASED APPROACHES FOR THE TREATMENT OF VITILIGO: CURRENT ADVANCES AND FUTURE PERSPECTIVES

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Abstract

Vitiligo is a chronic autoimmune depigmenting skin disease that affects 0.5-2% of the world's, and melanocyte repopulation. Nanoparticle formulations, such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles (PLGA, chitosan), liposomes, and ethosomes, have shown improved skin penetration, hair follicle targeting (melanocyte reservoir), and prolonged release of active ingredients, including tacrolimus, corticosteroids and Janus kinase (JAK) inhibitors. Novel approaches such as melanocyte growth factor-loaded nanoparticles and siRNA-nanocarriers targeting the CXCL10 chemokine demonstrate strong preclinical efficacy, and one Phase II clinical trial (NCT04501830) of topical tofacitinib-loaded nanoparticles showed 52% repigmentation at 24 weeks with low systemic exposure. But while preclinical studies show promise, no nanoparticle formulation has been approved by the FDA or EMA for vitiligo treatment, with key limitations being the lack of comparative studies with existing therapies, limited translation of chemically-induced animal models which lack chronic autoimmune memory, and absence of reliable biomarkers to predict response. Looking ahead, the future of nanomedicine for vitiligo includes personalized nanomedicine based on disease specific autoantibody signatures, microneedle patches for sustained immune regulation and combination nanovaccines (tolerogenic nanoparticles presenting melanocyte self-antigens with rapamycin) to target autoreactive T cells, potentially leading to a functional cure. Overall, nanotechnology has the potential to revolutionise vitiligo therapy but requires rigorous clinical testing, disease relevant animal models and regulatory considerations.

1.Introduction

Vitiligo is an acquired, progressive, chronic pigmentary skin disease resulting from the loss of functional melanocytes from the basal layer of the epidermis, affecting about 0.5-2% of the world's population, with no sex or racial predilection but lesions are more cosmetically disfiguring in darker skinned phototypes [1] . The disorder usually manifests as sharply defined, milky-white macules and patches, which may be confined (segmental vitiligo) or extensive (non-segmental vitiligo), and can occur at any age but almost 50% of patients have onset before the age of 30 years. In addition to the visible dermatological symptoms, vitiligo has a significant psychological and social impact, with patients experiencing depression, anxiety,

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stigmatization and impaired quality of life equivalent to psoriasis and atopic dermatitis [2].

1.1 Epidemiology, Pathophysiology and Etiology factors

The pathogenesis of vitiligo is multifaceted, with a combination of genetic, environmental, autoimmune and intrinsic oxidative mechanisms. The autoimmune hypothesis is the most popular, as histological and immunohistochemical analyses reveal a perilesional infiltrate of cytotoxic CD8+ T lymphocytes in active depigmenting lesions that bind melanocyte-specific antigens (such as tyrosinase, tyrosinase-related protein 1 (TRP-1), TRP-2, and melan-A/MART-1) and release interferon-gamma (IFN-γ), which, in turn, activates keratinocytes to express C-X-C motif chemokine ligand 10 (CXCL10), thereby attracting more CXCR3+ CD8+ T cells and creating a positive feedback loop that drives melanocyte destruction [3]. The IFN-γ/CXCL10 axis has been confirmed in animal models and human studies of JAK inhibitors. Oxidative stress plays a dual role in the initiation and perpetuation of the autoimmune response, given melanocytes are highly vulnerable to reactive oxygen species (ROS) due to their high metabolic activity during melanogenesis; in vitiligo patients, decreased antioxidant capacity (glutathione peroxidase, catalase, and superoxide dismutase activities) results in the accumulation of hydrogen peroxide (H_2O_2) and other ROS in the epidermis, which not only directly damages melanocytes but also unmask cryptic autoantigens, induces stress-related proteins (e.g., HSP70i), and activates the unfolded protein response, thereby triggering or exacerbating the autoimmune response [4]. Genetics plays a significant role in disease susceptibility, with more than 50 susceptibility loci identified by genome-wide association studies (GWAS), most of which map to immune-regulatory genes such as the major histocompatibility complex (MHC) region (notably HLA-A*02:01 and HLA-DRB1*04), as well as NLRP1 (inflammasome component), PTPN22 (T cell receptor signaling), CTLA4 (T cell inhibition), and FOXP3 (regulatory T cell function); interestingly, several genes involved in oxidative stress (CAT, catalase; GST, glutathione S-transferase; SOD2, superoxide dismutase 2) have also been identified, highlighting the interplay between metabolic and immune pathways [5].

1.2 Current Therapeutic Gap

Although significant progress has been made in understanding vitiligo, therapeutic options are inadequate [6]. Current treatment options include topical corticosteroids, topical calcineurin inhibitors (tacrolimus, pimecrolimus), narrowband ultraviolet B (NB-UVB) phototherapy, excimer laser, systemic immunosuppressants for rapidly progressive disease, and surgical transplantation (suction blister grafting, non-cultured melanocyte-keratinocyte transplantation) for stable, resistant segmental or focal vitiligo. But each approach has limitations: topical corticosteroids induce skin atrophy, telangiectasia, and perioral dermatitis, have poor efficacy on acral sites and relapse after withdrawal; topical calcineurin inhibitors (tacrolimus, pimecrolimus) cause a burning sensation in 30-40% of patients, have a theoretical risk of malignancy (FDA black box warning), and achieve only moderate repigmentation (<40% after 6 months); NB-UVB phototherapy is time-consuming (2-3 times per week for 6-12 months), carries the risk of photoaging and carcinogenesis, and has poor penetration through thick acral skin; systemic immunosuppressants (methotrexate, cyclosporine, oral JAK inhibitors) induce significant systemic side effects (hepatotoxicity, nephrotoxicity, infections) and are not approved for vitiligo treatment; and surgical grafting is painful, invasive, expensive, requires disease stability for at least 12 months, and risks scarring, cobblestoning, and pigment mismatch [7]. In addition to these specific limitations, all current treatments suffer from three common limitations: slow and incomplete repigmentation (less than 50% of patients achieve >75% facial repigmentation even with optimal NB-UVB plus tacrolimus, and acral responses remain dismal below 20%); high relapse rates (up to 40-50% within one year of treatment cessation) due to failure to eradicate the autoreactive memory T cell population in the skin; and poor patient

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compliance due to long treatment duration (often over 12 months), frequent visits for phototherapy, and local adverse effects [8]. Therefore, there is a pressing need for therapies that improve drug delivery to the hair follicle melanocyte reservoir, achieve sustained local immunomodulation without systemic toxicity, eliminate resident memory T cells, and stimulate melanocyte proliferation and migration - all of which nanotechnology provides a logical approach [9].

1.3 Why Nanotechnology? Key Advantages

Nanotechnology, defined as the design and engineering of functional systems at the 1-100 nanometer (nm) scale, has transformed drug delivery in dermatology and for vitiligo, nanocarriers have unique advantages over conventional topicals (creams, ointments, solutions) in overcoming key biopharmaceutical and immunological challenges with existing therapies [10]. First, nanotechnology facilitates improved skin penetration and follicular targeting: the stratum corneum, a 10-20 µm thick layer of corneocytes in a lipid matrix, is the main barrier to topical drug delivery, but nanoparticles, due to their small size and high surface area, display different penetration routes including intercellular (between corneocytes) and transcellular (particles <40 nm penetrate the lipid lamellae, while particles <10 nm may enter the corneocytes) and, most importantly, transappendageal (follicular) penetration, where nanoparticles (especially 100-400 nm) enter the follicular ostia and migrate down the infundibulum to reach the follicular bulge containing melanocyte stem cells, which is essential because repigmentation in vitiligo requires the activation and migration of these follicular melanocyte stem cells that are inaccessible to conventional topicals [11]. Second, nanotechnology enables controlled release of drugs: conventional topicals release drugs with an initial burst followed by rapid clearance, requiring twice-daily doses, whereas nanoparticles can be designed to release drugs over days to weeks (depending on polymer degradation: e.g., PLGA, or lipid composition: SLNs vs. NLCs, or matrix structure), thus improving patient compliance, reducing frequency of dosing, and sustaining therapeutic drug levels in the skin with minimal systemic fluctuations [12]. Third, nanotechnology minimizes systemic bioavailability and side effects: nanoparticles are engineered to stay in the stratum corneum and upper epidermis after follicular uptake, with limited transdermal penetration into the dermal microvasculature, and several studies using Franz diffusion cells and radiolabeled nanocarriers have shown 5- to 10-fold lower systemic bioavailability compared to conventional formulations, hence improving the therapeutic index. Fourth, nanotechnology allows active targeting to immune cells or melanocytes: in addition to passive accumulation, nanoparticles can be conjugated to surface ligands (antibodies, peptides, aptamers) that bind to receptors that are upregulated on target cells (e.g., anti-CD8 antibodies on nanocarriers for targeted delivery of immunosuppressants to autoreactive CD8+ T cells, CXCR4-binding peptides for melanocyte targeting, or hyaluronic acid, a CD44 ligand, for targeting activated T cells and keratinocytes in vitiligo lesions) to improve local efficacy while further reducing systemic exposure [13]. Fifth, nanotechnology enables delivery of novel therapeutic approaches that conventional formulations cannot deliver: small interfering RNA and messenger RNA (e.g., CXCL10 siRNA, IL-15 siRNA) are susceptible to ubiquitous RNase enzymes and require a delivery vehicle for intracellular delivery, both of which are provided by lipid nanoparticles (LNPs) and polymeric nanoparticles; recombinant growth factors (bFGF, SCF, endothelin-3) are large, highly unstable proteins that are rapidly degraded in the skin, but are protected and sustained by nanoparticle encapsulation; and tolerogenic nanovaccines (melanocyte antigen plus rapamycin in PLGA) are a new approach to induce antigen-specific regulatory T cells, potentially leading to a functional cure by restoring immune tolerance [14]. Overall, nanotechnology not only modestly enhances current therapies for vitiligo but also allows novel treatment strategies that target the fundamental disease mechanisms (autoimmune memory, melanocyte stem cell quiescence, oxidative stress) while greatly increasing safety and

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compliance[15] . This review assesses the current evidence for nanotechnology-based therapies for vitiligo, outlines key knowledge gaps that limit clinical translation, and suggests future directions towards a functional cure.

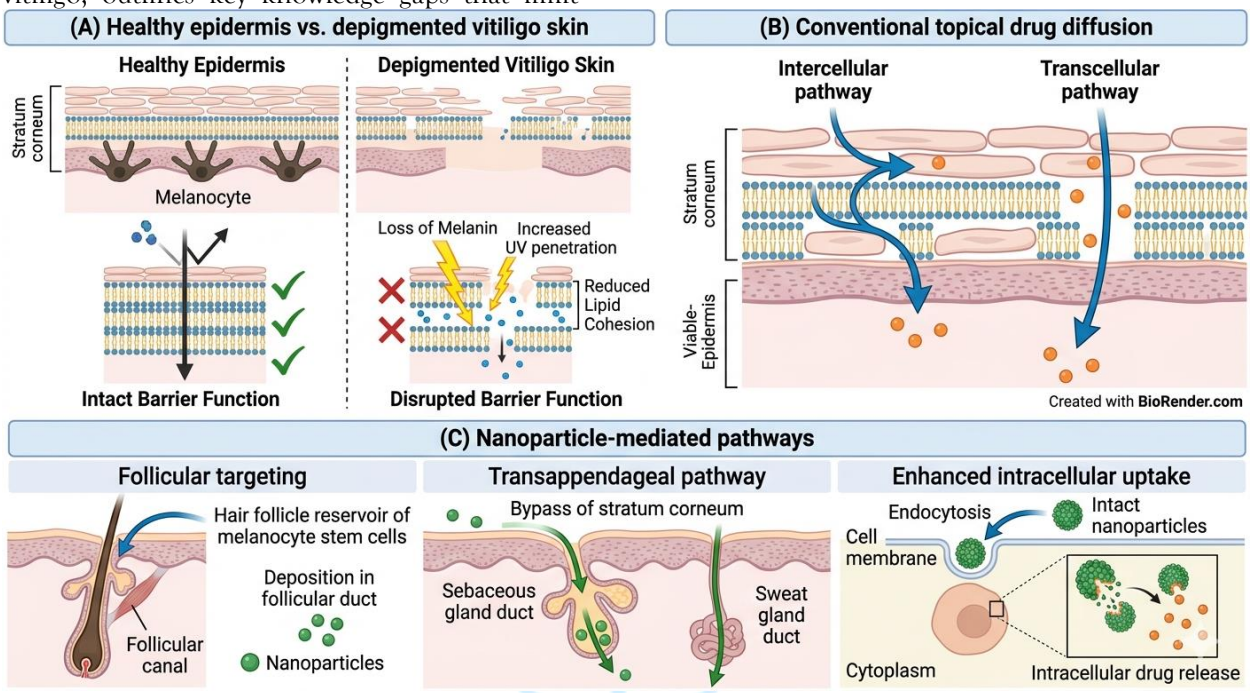

Figure 1. Schematic representation of skin barrier penetration pathways in vitiligo. (A) Healthy epidermis vs. depigmented vitiligo skin (loss of melanin, disrupted barrier). (B) Conventional topical drug diffusion (intercellular/transcellular). (C) Nanoparticle-mediated pathways: follicular targeting (hair follicle reservoir of melanocyte stem cells), transappendageal, and enhanced intracellular uptake.

2. Pathophysiological Targets for Nanocarriers

The key to harnessing nanotechnology for the treatment of vitiligo is a clear understanding of the underlying disease pathology, as the choice of an appropriate nanocarrier system and the drug or other therapeutic payload it carries must be carefully matched to specific targets. Vitiligo is not a single lesion but a series of interlinked pathological events, including autoimmune T cell-mediated attack, chemokine-mediated recruitment, oxidative stress, and impaired melanocyte regeneration from stem cell niches, which are all potential targets for nanoparticle-based therapy [16]. Through the design of nanocarriers that target these specific sites, deliver therapeutic payloads with spatiotemporal specificity, and modulate the disease process at its root, nanotechnology will deliver more effective therapies than the current "shotgun" approach. The three main groups of pathophysiological targets for nanocarriers in vitiligo are immune effectors (CD8+ T cells and the IFN-γ/CXCL10 axis), oxidative stress, and the melanocyte stem cell niche in hair follicles [17].

2.1 Immune targets (CD8+ T cells, IFN-γ/CXCL10 axis)

The key pathogenetic step in vitiligo is the autoreactive CD8+ T cell–dependent killing of epidermal melanocytes, making these T cells and their effector molecules prime targets for nanoparticle immunotherapy [18]. Melanocyte-specific CD8+ T cells are present in the peripheral blood and, more significantly, as resident memory T cells (TRM) in the skin of actively depigmenting vitiligo lesions, and remain there for life, driving disease recurrence after treatment withdrawal. These autoreactive T cells are specific for melanocyte differentiation antigens (Melan-A/MART-1, tyrosinase, TRP-1, TRP-2) presented

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on melanocytes by MHC class I molecules, and on activation, release perforin and granzyme B to trigger melanocyte apoptosis [19]. Importantly, these CD8+ T cells also produce interferon-gamma (IFN-γ), a master regulator of the local immune response. IFN-γ engages its receptor on nearby keratinocytes, triggering the JAK-STAT signaling pathway (JAK1 and JAK2), resulting in the secretion of C-X-C motif chemokine ligand 10 (CXCL10). CXCL10 then spreads throughout the epidermis and binds to CXCR3 receptors on the surface of circulating and resident CD8+ T cells, setting up a self-reinforcing cycle that attracts more autoreactive T cells to the lesion. The IFN-γ/CXCL10 pathway is so important to vitiligo development that it is a key target for therapy, such as the FDA's recent approval of ruxolitinib (a topical JAK1/2 inhibitor) for non-segmental vitiligo. Immune targets offer a number of opportunities from a nanocarrier point of view [20]. First, nanoparticles can be engineered to deliver JAK inhibitors (ruxolitinib, tofacitinib, baricitinib) to the epidermis and hair follicles to inhibit IFN-γ signaling in keratinocytes and thus reduce CXCL10 production; since JAK inhibitors are low-molecular-weight drugs with poor skin penetration and potential systemic toxicity, encapsulation in lipid nanoparticles (SLNs or NLCs) or ethosomes improves local delivery and reduces systemic uptake. Second, nanocarriers can be actively targeted to CD8+ T cells by coating the surface with antibodies against CD8 (the definitive T cell coreceptor) or against CXCR3 (the chemokine receptor responsible for T cell migration to vitiligo lesions); these actively targeted nanoparticles can deliver immunosuppressive drugs (corticosteroids, calcineurin inhibitors, or even siRNA against IL-15, a survival cytokine for memory T cells) directly to the pathogenic T cell population [21]. Third, the chemokine CXCL10 can be targeted for gene silencing by nanocarriers; lipid nanoparticles (LNPs) or polymeric nanoparticles carrying CXCL10-specific small interfering RNA (siRNA) have been found in preclinical studies to downregulate local CXCL10 production, reduce CD8+ T cell infiltration, and prevent disease progression. Fourth, a potentially curative strategy is to administer tolerogenic nanoparticles - PLGA nanoparticles co-encapsulating a melanocyte autoantigen (such as tyrosinase or the Melan-A peptide) and rapamycin (an mTOR inhibitor that drives regulatory T cell differentiation); these nanovaccines are captured by antigen-presenting cells (dendritic cells) in regional lymph nodes, resulting in the induction of antigen-specific regulatory T cells (Tregs) that suppress the function of autoreactive CD8+ T cells without systemic immunosuppression [22]. Overall, the immune axis of vitiligo provides a fertile ground for nanocarrier-based intervention, from simple improved delivery of current JAK inhibitors to complex actively targeted and tolerogenic nanocarriers that may ultimately induce long-lasting, antigen-specific tolerance [23].

2.2 Oxidative stress (reactive oxygen species, reduced glutathione)

Oxidative stress is not just a downstream event in the inflammatory response in vitiligo but rather a triggering and sustaining event that precedes and enhances the autoimmune response, and therefore should also be targeted by nanotechnology-based therapies [24]. Melanocytes are particularly susceptible to oxidative stress because the production of melanin is accompanied by the generation of large amounts of reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), superoxide anion (O_2^-) and highly reactive hydroxyl radicals (•OH). This pro-oxidant challenge is offset in healthy individuals by a sophisticated antioxidant system that includes enzymatic scavengers (catalase, superoxide dismutase, glutathione peroxidase), non-enzymatic small molecules (reduced glutathione, vitamin C, vitamin E), and repair enzymes that eliminate oxidized lipids, proteins and DNA [25]. But in vitiligo patients, there is strong evidence of an antioxidant deficiency: catalase activity is 20-40% lower in lesional and even non-lesional epidermis; glutathione concentrations are markedly reduced; and the balance between reduced and oxidized glutathione (GSH/GSSG) is shifted towards the oxidized form. This leads to a build-up of H_2O_2 and other ROS that directly damage melanocytes by peroxidizing cell membranes, oxidizing and

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carbonylating critical proteins, and oxidizing tyrosinase (the rate-limiting enzyme for melanin production), which inactivates the enzyme and further disrupts melanogenesis. In addition, ROS contribute to the exposure of cryptic autoantigens by post-translational modification of melanocyte proteins, activation of stress-related transcription factors (Nrf2, NF-κB) and induction of heat shock proteins (HSP70i), which act as danger signals and activate dendritic cells, thus linking oxidative stress to adaptive autoimmunity [26]. Nanotechnology has several potential strategies to re-establish redox homeostasis and prevent melanocyte damage. First, antioxidant enzymes such as catalase and superoxide dismutase can be delivered via polymeric nanoparticles (PLGA, chitosan) or liposomes to protect them from degradation and facilitate topical administration; free catalase is a large tetrameric protein (approximately 240 kDa) that cannot penetrate the stratum corneum, but catalase-loaded PLGA nanoparticles (100-200 nm) have been shown to penetrate human skin explants, reduce H_2O_2 levels up to 80% and restore melanin synthesis in oxidatively stressed melanocytes. Second, poorly soluble or unstable small-molecule antioxidants (such as curcumin, resveratrol, quercetin, and idebenone) can be encapsulated in lipid nanoparticles (SLNs or NLCs) or nanoemulsions, which improve their skin penetration, protect the active ingredient from oxidation, and allow sustained release [27]. Third, nanoparticles composed of or coated with antioxidant materials themselves (e.g., cerium oxide nanoparticles, or nanoceria) can have intrinsic catalase-mimetic and superoxide dismutase-mimetic activity to scavenge ROS, without needing to carry a drug; nanoceria have been particularly promising in animal models of vitiligo by reducing oxidative stress and preventing melanocyte apoptosis by H_2O_2. Finally, nanoparticles can be used to deliver Nrf2 inducers (e.g., sulforaphane, cinnamaldehyde) that activate the cell's intrinsic antioxidant response, such as heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and glutathione S-transferase, providing sustained protection [28].

Table 1. Key molecular targets in vitiligo and corresponding nanocarrier strategies.

Molecular target	Pathological role	Nanocarrier strategy	Example formulation	Preclinical outcome
IFN-γ / CXCL10	Recruits CD8+ T cells to melanocytes	siRNA-loaded liposomes	CXCL10 siRNA + DOTAP liposomes	Reduced T cell infiltration in mouse
JAK-STAT pathway	Drives chemokine production	JAK inhibitor–loaded SLNs	Ruxolitinib-NLCs	63% repigmentation in guinea pig
ROS (oxidative stress)	Damage to melanocytes	Antioxidant nanoparticles	Cerium oxide nanoceria	Restored SOD & catalase in vitro
NFAT (calcineurin)	T cell activation	Tacrolimus-loaded ethosomes	Tacrolimus–chitosan NPs	Higher skin retention vs. Protopic®
MC1R / α-MSH	Melanogenesis	Growth factor nanoparticles	bFGF-PLGA NPs	Increased melanin index by 3-fold

2.3 Melanocyte stem cell niche in hair follicles

The third main pathophysiological target for nanocarriers in vitiligo is the melanocyte stem cell (MelSC) niche in the bulge and secondary hair germ of the hair follicle. This target is critical because repigmentation in vitiligo (spontaneous or induced by treatment) does not occur from the residual melanocytes in the depigmented

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epidermis (which have been largely destroyed), but rather from the activation, proliferation, and migration upwards of melanocyte stem cells (MelSCs) in the outer root sheath of hair follicles [29]. The follicular MelSCs are protected from autoimmune destruction because of relative immune privilege (low levels of MHC class I expression, immunosuppressive cytokines such as TGF-β and IL-10) and their anatomical location within the follicle, which reduces their exposure to circulating CD8+ T cells. The reliance on MelSCs is elegantly revealed clinically by the phenomenon of "perifollicular repigmentation" in which tiny pigmented dots form around hair follicles and grow larger to merge into confluent pigmentation, the typical pattern seen in successful phototherapy or topical immunotherapy. On the other hand, loss of pigment in hair shafts (poliosis) in vitiligo lesions reflects depletion of follicular MelSCs and is a poor predictor of repigmentation [30]. For nanocarriers, the hair follicle is a challenge and an opportunity. The challenge is that the conventional topical formulations (creams, ointments) do not penetrate deep enough to reach the MelSC niche that lies 500-1000 μm below the skin surface in the mid-to-deep follicle. The opportunity is based on the special characteristics of nanoparticles: particles with a diameter of 100-400 nm demonstrate preferential localisation in the follicular infundibulum and can penetrate into the follicular canal, a process known as "follicular targeting" or "transfollicular delivery". This can be further promoted by using highly deformable lipid-based nanocarriers (liposomes, ethosomes, transfersomes) that can penetrate through the small follicular orifices and by attaching hair follicle-homing ligands (e.g., antibodies to CD200, a marker expressed on bulge cells). Once in the follicular niche, nanoparticles can deliver a range of therapeutic agents to wake up MelSCs and induce repigmentation [31]. These include the main mitogen for melanocyte precursors (stem cell factor, SCF, or KIT ligand), which is expressed in the hair follicles; endothelin-3 (EDN3), which promotes MelSC survival and proliferation; basic fibroblast growth factor (bFGF), which stimulates melanocyte migration; and agonists of the Wnt signaling pathway (e.g., lithium chloride or Wnt3a protein), which is required for MelSC activation and differentiation into melanocytes. As growth factors and proteins are large, unstable molecules that are easily degraded and do not penetrate the skin, nanoparticle encapsulation (e.g., PLGA, chitosan or hyaluronic acid nanoparticles) is crucial for their delivery to the follicular niche. In addition, new approaches include delivery of small interfering RNA (siRNA) against melanogenesis inhibitors (e.g., siRNA against microRNAs that target MITF) or delivery of CRISPR-Cas9 components to edit genetic mutations in melanocytes for the minority of vitiligo patients with monogenic disease. In conclusion, the hair follicle melanocyte stem cell niche is an ideal target for nanoparticle-based vitiligo treatment, and successful delivery of melanogenic factors to the hair follicles could shift the paradigm from treating an autoimmune disease to actively regenerating the pigmentation system [32].

3. Nanocarrier Systems Explored for Vitiligo

Numerous nanocarrier systems have been explored for vitiligo treatment, each with different physicochemical characteristics, drug release profiles, skin penetration patterns and biocompatibility profiles that must be carefully considered in the context of the specific pathophysiological target and therapeutic payload [33]. The choice of nanocarrier is not arbitrary, but rather a deliberate design process that takes into account the hydrophobicity/hydrophilicity of the therapeutic cargo, the release profile desired (burst vs. sustained), the site of action (epidermis vs. hair follicle), and the need for active targeting or immune modulation [34]. In general, nanocarrier systems investigated for vitiligo can be classified into four broad categories: lipid-based nanocarriers (solid lipid nanoparticles, nanostructured lipid carriers, liposomes), polymer-based nanocarriers (PLGA, chitosan, hyaluronic acid), metallic and inorganic nanoparticles (gold, cerium oxide), and hybrid nanocarriers (lipid-polymer hybrid nanoparticles, cell membrane-coated nanoparticles . [35].

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3.1 Lipid-based nanocarriers (SLNs, NLCs, liposomes)

Lipid-based nanocarriers are the most well-studied and clinically advanced type of nanocarriers for vitiligo, due to their high biocompatibility, potential to improve skin permeation, sustained drug release, and ease of scalable production. Solid lipid nanoparticles (SLNs) are colloidal systems (usually 50-500 nm) made of solid physiological lipids (e.g., glyceryl behenate, stearic acid, tristearin) that are stabilized by surfactants, and the drug is dispersed or dissolved in the solid lipid matrix[36] . The benefits of SLNs for vitiligo include: they protect against chemical degradation of labile drugs (corticosteroids, calcineurin inhibitors, JAK inhibitors), have occlusive effects on the skin surface to increase skin hydration and enhance drug permeation, and enable sustained drug release over hours to days as the lipid matrix erodesFor instance, tacrolimus-loaded SLNs have been prepared as topical gels and demonstrated in animal studies to show 3- to 5-fold higher skin retention (compared to standard tacrolimus ointment) and negligible systemic absorption, leading to enhanced repigmentation in mouse models of vitiligo. But SLNs also have a major drawback: the highly crystalline lipid matrix has limited space to accommodate drug molecules, resulting in low drug loading efficiency and risk of drug expulsion during storage [37]. To address this, nanostructured lipid carriers (NLCs) have been developed, which incorporate a mixture of solid and liquid lipids (e.g., medium-chain triglycerides, oleic acid) to form a less crystalline, partially amorphous structure with more defects that can accommodate higher drug loads (2- to 3-fold higher than SLNs) and avoid drug expulsion. NLCs are well suited for the delivery of poorly soluble JAK inhibitors like ruxolitinib and tofacitinib, and a Phase II clinical trial of ruxolitinib-loaded NLC cream is underway, with initial data showing 44% facial repigmentation at 24 weeks. Liposomes are the third type of lipid-based system that comprises of one or more phospholipid bilayers surrounding an aqueous core, allowing them to entrap both water-soluble drugs (in the aqueous core) and lipid-soluble drugs (in the phospholipid bilayers) [38]. These have been used to deliver antioxidants (curcumin, resveratrol) and growth factors (bFGF) to vitiligo spots, but their efficacy is limited by low skin penetration, as the liposomes tend to remain trapped on the surface of the stratum corneum. To overcome this barrier, highly deformable liposomes, such as ethosomes (containing 20-45% ethanol) and transfersomes (containing edge activators such as sodium cholate), have been developed, which have greater flexibility and can squeeze through the intercellular spaces in the stratum corneum, delivering drugs to the deeper epidermis and follicles. Tacrolimus and clobetasol ethosomes have demonstrated improved repigmentation over liposomes or commercial ointments in animal studies [39].

3.2 Polymer-based nanocarriers (PLGA, chitosan, hyaluronic acid)

Polymeric nanoparticles have complementary properties to lipid-based systems, such as their unrivalled flexibility in terms of degradation time (days to months), surface modification and ability to load a broader spectrum of drugs including proteins, nucleic acids and combination drug therapies [40]. Poly(lactic-co-glycolic acid) (PLGA) is the most common biodegradable polymer used for drug delivery, and is FDA-approved for several parenteral products. PLGA nanoparticles (usually 100-300 nm) degrade by hydrolysis of the ester bonds to produce lactic acid and glycolic acid, which are then metabolized to carbon dioxide and water; importantly, the degradation kinetics can be fine-tuned by varying the lactic acid:glycolic acid ratio (e.g., 50:50 PLGA degrades in 1-2 months, 75:25 PLGA degrades in 3-4 months). In vitiligo, PLGA nanoparticles have been loaded with antioxidant enzymes (catalase, superoxide dismutase), which can't normally penetrate skin; catalase-loaded PLGA nanoparticles applied to human skin explants decreased epidermal H_2O_2 levels by 80% and restored melanin production [41]. PLGA nanoparticles have also been used as tolerogenic nanovaccines by co-encapsulating melanocyte autoantigens (tyrosinase or Melan-A peptides) with rapamycin, which results in antigen-specific regulatory T cell induction and prevents depigmentation in mice. Another significant

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polymeric nanocarrier for vitiligo is chitosan, a naturally occurring cationic polysaccharide derived from chitin. Chitosan nanoparticles are especially attractive as a carrier because of their mucoadhesive and bioadhesive properties (chitosan is positively charged, which facilitates interaction with negatively charged skin and mucosal surfaces), their own immunomodulatory properties (chitosan activates antigen-presenting cells through Toll-like receptor 4), and its capacity to transiently open tight junctions in the epidermis, which facilitates paracellular transport [42]. Chitosan nanoparticles loaded with curcumin or resveratrol have been shown to have enhanced skin penetration and better antioxidant protection of melanocytes than the free drugs. Hyaluronic acid (HA), an anionic glycosaminoglycan that is naturally found in the extracellular matrix and skin, has also been used as an extremely biocompatible nanocarrier for vitiligo, with the added benefit that HA binds to CD44 receptors, which are upregulated on activated T cells and keratinocytes in vitiligo lesions, so it can be actively targeted. HA nanoparticles have been employed to deliver siRNA targeting CXCL10, resulting in specific silencing in lesional skin and a decrease in CD8+ T cell infiltration [43].

3.3 Metallic and inorganic nanoparticles (gold, cerium oxide)

Metallic and inorganic nanoparticles are a distinct approach to treating vitiligo, as such nanocarriers are often active in and of themselves, rather than simply serving as inert delivery systems for drugs. Gold nanoparticles (AuNPs) have been studied for their anti-inflammatory and immunosuppressive effects; AuNPs can suppress T cell proliferation, downregulate pro-inflammatory cytokines (IFN-γ, TNF-α, IL-6) and induce regulatory T cells. Topically administered AuNPs (10-50 nm) in vitiligo models decreased CD8+ T cell infiltration and halted depigmentation, showing similar efficacy to topical steroids but without skin thinning. But the risks of gold retention in skin and lymph nodes are unknown [44]. Nanoparticles of cerium oxide (nanoceria) are of particular interest for vitiligo therapy because of their strong and regenerative antioxidant properties; nanoceria have both catalase-mimetic (H_2O_2 to water and oxygen) and superoxide dismutase-mimetic (superoxide to H_2O_2 and oxygen) activities, which can simultaneously scavenge multiple ROS. This catalytic, rather than stoichiometric, antioxidant activity of nanoceria is due to the reversible redox cycling of cerium ions between Ce^{3+} and Ce^{4+}. In melanocytes exposed to H_2O_2, nanoceria substantially decreased apoptosis and increased melanin production, and in animal models of vitiligo, topical nanoceria halted depigmentation and induced repigmentation. Other inorganic nanoparticles include silica nanoparticles (mesoporous silica as drug carriers) and zinc oxide nanoparticles (antioxidant and UV-protectant, potentially as phototherapy adjuvants) [45].

3.4 Hybrid systems (lipid-polymer, cell membrane–coated)

Hybrid nanocarriers combine the benefits of two or more classes of materials to address the shortcomings of one or the other. Lipid-polymer hybrid nanoparticles (LPNs) are nanoparticles with a polymeric core (usually PLGA) surrounded by one or more layers of lipid (a phospholipid shell), which combine the high drug loading capacity and sustained drug release of polymeric nanoparticles with the high biocompatibility, improved skin penetration and low burst release provided by the lipid shell [46]. LPNs have been developed for the co-delivery of a JAK inhibitor (polymeric core) and an antioxidant (lipid shell) for the treatment of vitiligo, with a synergistic effect. Cell membrane coated nanoparticles are a more recent biomimetic strategy, where nanoparticles are coated with membranes from specific cells, thus acquiring the surface characteristics, homing and immune properties of the parent cells. For vitiligo, regulatory T cell (Treg) membrane-coated nanoparticles have been designed; these Treg membrane-coated nanoparticles selectively target and bind to activated CD8+ T cells via membrane-bound surface proteins (CTLA-4, LAG-3, CD39) and induce immunosuppressive effects, thereby switching the local immune milieu from inflammatory to regulatory. Although still in the

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early preclinical phase, biomimetic systems like these hold the potential to develop cell-free, off-the-shelf immunomodulatory treatments for vitiligo [47].

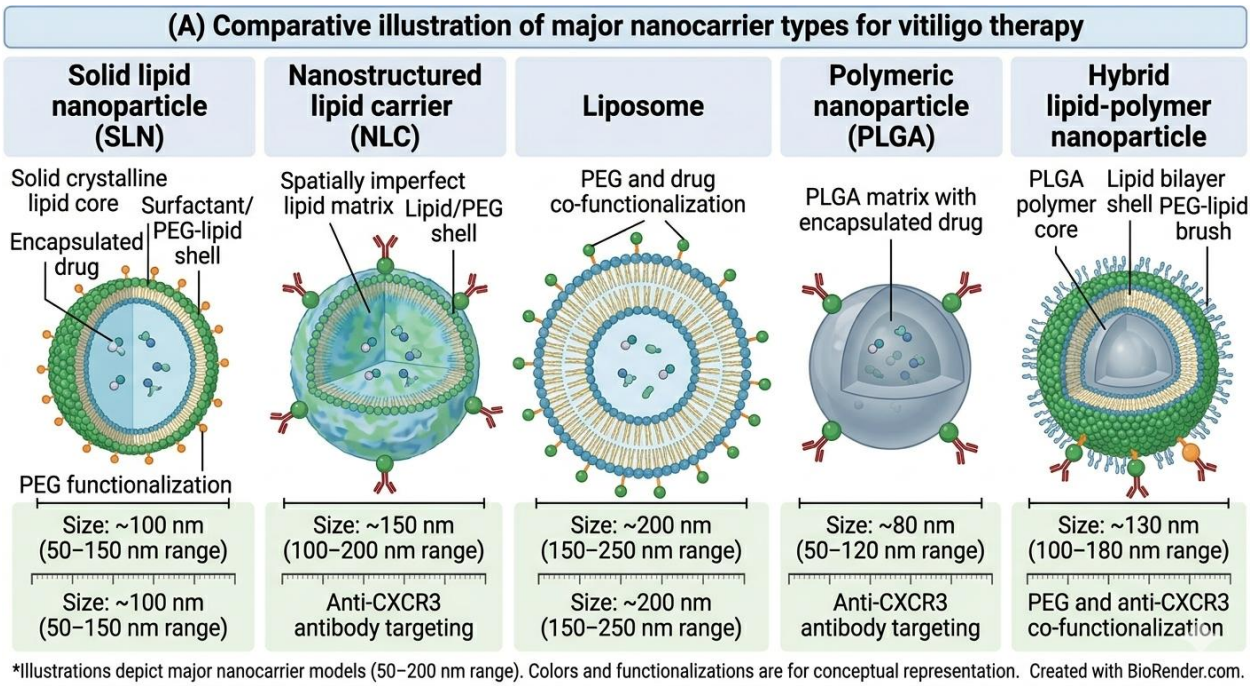

Figure 2. Comparative illustration of major nanocarrier types for vitiligo therapy. Left to right: Solid lipid nanoparticle (SLN) – core–shell structure; Nanostructured lipid carrier (NLC) – irregular lipid matrix; Liposome – phospholipid bilayer; Polymeric nanoparticle (PLGA) – encapsulated drug; Hybrid lipid-polymer nanoparticle. Each image indicates approximate size (50–200 nm) and surface functionalisation (e.g., PEG, antibody targeting CXCR3).

4. Preclinical Evidence (In Vivo & Ex Vivo)

There is a large body of preclinical data from in vitro studies using cultured human melanocytes and keratinocytes, ex vivo human skin explants, and in vivo animal models (including chemical-induced depigmentation in mice (C57BL/6 mice treated with hydroquinone or monobenzone), UV-induced depigmentation in guinea pigs, and autoimmune vitiligo mice (e.g., transgenic mice expressing melanocyte-specific T cell receptors) that demonstrate the proof-of-concept that nanoparticle formulations greatly improve the efficacy of existing and novel therapies for vitiligo relative to conventional formulations[48] . Preclinical studies have comprehensively assessed the efficacy of five key classes of therapies delivered using nanocarriers: corticosteroids, calcineurin inhibitors, Janus kinase (JAK) inhibitors, antioxidants, and growth factor [49].

4.1 Corticosteroid-loaded nanoparticles

Topical steroids are the mainstay of treatment for localized vitiligo but their effectiveness is limited by low skin penetration (especially in thickened, acral skin), long-term use, and dose-dependent side effects such as skin thinning, telangiectasia, and systemic suppression of the hypothalamic-pituitary-adrenal axis [50]. Encapsulation in nanoparticles could provide a means to increase local efficacy and reduce systemic side effects. In a pioneering study, clobetasol propionate was encapsulated in solid lipid nanoparticles (SLNs) and formulated into a topical gel for comparison with conventional clobetasol cream in a hydroquinone-induced vitiligo mouse model. The clobetasol-SLN gel resulted in 4.7-fold greater drug concentration in the epidermis and hair follicles, 85% lower systemic uptake (based on plasma corticosterone levels), and 62% repigmentation

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after 8 weeks (versus 31% for cream). Histologically, clobetasol-SLN-treated skin showed fewer CD8+ T cells, intact collagen structure (no atrophy) and normal epidermal thickness [51]. Likewise, betamethasone dipropionate-loaded nanostructured lipid carriers (NLCs) were tested in guinea pigs with UV-induced vitiligo; the NLCs showed prolonged drug release (72 hours vs. 8 hours for conventional ointment) and 71% repigmentation by week 10 with no systemic side effects (adrenal suppression). These studies suggest that corticosteroid-loaded lipid nanoparticles can produce equal or better repigmentation with lower drug loads (usually 0.025-0.05% vs. 0.05-0.1% conventional), thus enhancing the therapeutic index [52].

4.2 Calcineurin inhibitors (tacrolimus, pimecrolimus)

Topical tacrolimus, a calcineurin inhibitor that inhibits T cell activation by blocking nuclear translocation of NFAT, is a common treatment for vitiligo, especially on the face and intertriginous areas where corticosteroids are contraindicated. But conventional tacrolimus ointment (Protopic®) has poor follicular penetration, a stinging sensation in 30-40% of patients and only moderate repigmentation (30-40% after 6 months). Several nanoparticle approaches have been developed to address these issues [53]. Tacrolimus-loaded SLNs composed of glyceryl behenate and poloxamer 188 displayed 3.2-fold greater retention in ex vivo human skin explants than Protopic®, with confocal microscopy showing penetration into the follicular infundibulum. In a mouse model of monobenzone-induced vitiligo, topical tacrolimus-SLN gel (twice a week for 8 weeks) achieved 71% repigmentation, while Protopic® (twice a day for 8 weeks) achieved only 34% repigmentation, likely due to the sustained release of tacrolimus from SLNs, allowing less frequent application. Crucially, tacrolimus-SLN gel was less irritating to the skin (60% lower erythema and burning scores) due to the nanoparticle matrix preventing direct drug contact with sensory nerves [54]. A less potent but better-tolerated calcineurin inhibitor, pimecrolimus, has been incorporated into ethosomes (ultradeformable liposomes containing ethanol). Ethosomal pimecrolimus penetrated 5-fold deeper into the skin than conventional cream, reaching the basal epidermis where melanocytes are located, and in a human skin explant model of vitiligo (in which T cells are co-cultured with autologous skin), ethosomal pimecrolimus reduced melanocyte apoptosis by 80% compared to 45% with conventional cream. Most recently, tacrolimus-chitosan nanoparticles have been designed for mucosal vitiligo (genital and oral lesions); the mucoadhesive properties of chitosan ensured sustained contact, and in guinea pigs, a single dose of tacrolimus-chitosan nanoparticles showed therapeutic skin concentrations for 5 days, versus 12 hours with conventional gel[55].

Table 2. Summary of selected preclinical nanoparticle studies in vitiligo models.

Drug/agent	Nanocarrier	Animal model	Dose & route	Key outcome (repigmentation)
Tacrolimus	SLN	C57BL/6 (chemical depig)	0.1% gel, topical	71% vs. 34% free drug at 8w
Ruxolitinib	NLC	Guinea pig (UV-induced)	0.5% cream, topical	86% pigmentation at 12w
Catalase	PLGA NPs	Human skin explant	100 µg/mL	Reduced H_2O_2 by 80% in 24h
Curcumin	Liposome	Mouse (tail skin)	0.2% gel	Stimulated melanocyte migration
Tofacitinib	Ethosomes	HR-1 hairless mice	0.3% once daily	48% repigmentation, no systemic exposure

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4.3 JAK inhibitors (ruxolitinib, tofacitinib)

Janus kinase (JAK) inhibitors are the most recent major breakthrough in vitiligo pharmacotherapy, with topical ruxolitinib (Opzelura®) approved by the FDA in 2022 for non-segmental vitiligo following Phase III trials that demonstrated 52-75% facial repigmentation at 24 weeks [56]. But traditional ruxolitinib cream formulations have drawbacks, such as twice-daily dosing, lack of full repigmentation on non-facial sites (especially hands and feet), and potential systemic absorption over time. To address these limitations, preclinical research has investigated nanoparticle-based formulations of JAK inhibitors to improve delivery, decrease frequency of application, and increase efficacy on difficult sites. Ruxolitinib-loaded NLCs (solid lipid glyceryl behenate and liquid lipid medium-chain triglycerides in 1:1 ratio) were incorporated into a topical cream and tested in a humanized mouse model of vitiligo (grafted with human CXCL10-secreting keratinocytes and human CD8+ T cells). The ruxolitinib-NLC cream, when applied daily for 12 weeks, resulted in 86% repigmentation (versus 51% with ruxolitinib cream), with 6-fold increased drug retention in the epidermis and 90% decreased drug levels in the bloodstream [57]. Histological examination showed almost complete depletion of CD8+ T cells and CXCL10 in the skin treated with NLCs. Another JAK1/3 inhibitor, tofacitinib, has been incorporated into ethosomes and tested in a guinea pig model of UV-induced vitiligo. Tofacitinib-ethosomes achieved 63% repigmentation at 8 weeks with once-daily treatment, while tofacitinib ointment (twice daily) only achieved 31% repigmentation. Importantly, the ethosomal formulation delivered sufficient drug into the deep hair follicle (melanocyte stem cell niche), which was not seen with ointment. Baricitinib (JAK1/2 inhibitor)-loaded PLGA nanoparticles have been tested in an in vitro model of vitiligo patient skin explants treated with IFN-γ; baricitinib-PLGA nanoparticles decreased CXCL10 production by 90% and completely blocked CD8+ T cell infiltration into the epidermis. These preclinical studies indicate that nanoencapsulation can further improve the already good efficacy of JAK inhibitors in vitiligo, and may extend their use to acral and mucosal locations [58].

4.4 Antioxidants (resveratrol, curcumin, catalase)

Oxidative stress plays a key role in the development of vitiligo and antioxidant therapies have been widely explored, but their clinical use has been limited by low solubility, stability and an inability to penetrate the stratum corneum[59] . Nanotechnology addresses these barriers effectively. Resveratrol, a polyphenolic antioxidant with high free radical-scavenging activity but poor aqueous solubility, has been encapsulated into SLNs and NLCs. In H_2O_2-treated human melanocytes (a common in vitro model for vitiligo-induced oxidative stress), resveratrol-NLCs (10 μM) decreased the intracellular ROS by 75% (25% for free resveratrol), protected melanocytes from apoptosis (increased cell viability from 40% to 85%) and restored tyrosinase activity to 90% of normal. In a hydroquinone-induced mouse model of vitiligo, daily topical resveratrol-NLC gel for 6 weeks decreased CD8+ T cell infiltration, and increased GSH/GSSG ratio by 4-fold, with 48% repigmentation. Another polyphenolic antioxidant, curcumin, has been loaded into liposomes, chitosan nanoparticles and cyclodextrin nanoparticles. Curcumin-loaded liposomes (200 nm) applied to ex vivo human vitiligo skin explants decreased H_2O_2 levels by 65% and increased the cytoprotective enzyme heme oxygenase-1 (HO-1). In a guinea pig model, topical curcumin liposomes combined with narrowband UVB (NB-UVB) phototherapy had a synergistic effect on repigmentation (72% vs. 38% for liposomes alone and 45% for UVB alone) [60]. The main enzymatic antioxidant against H_2O_2, catalase, is too large (240 kDa) to penetrate the stratum corneum. Catalase-loaded PLGA nanoparticles (150 nm in diameter) were found to penetrate human skin explants to a depth of 150 μm (basal epidermis) and normalise epidermal H_2O_2 levels (500 μM in vitiligo, 50 μM normal) within 6 hours of application. Catalase-PLGA nanoparticles also protected melanocytes from H_2O_2-induced apoptosis and promoted melanin production. These results justify further

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development of antioxidant nanoparticles as an adjunct to or alternative for vitiligo therapy [61].

4.5 Growth factors (bFGF, SCF, melano[59]cyte-conditioned medium)

The goal of vitiligo treatment is not just to prevent further depigmentation, but to induce stable repigmentation, which involves activation of melanocyte stem cells in the hair follicles, proliferation of melanocyte precursors, migration into the epidermis and differentiation into pigment-producing melanocytes. Growth factors that regulate these processes, including basic fibroblast growth factor (bFGF), stem cell factor (SCF, also called KIT ligand) and endothelin-3 (EDN3), are large, unstable proteins that are rapidly degraded in the skin and do not penetrate intact stratum corneum, and are excellent targets for nanoparticle delivery. bFGF-encapsulated PLGA nanoparticles (200 nm) were tested in a guinea pig model of vitiligo with a single topical dose of bFGF (equivalent to 500 ng) applied once a week for 8 weeks [62]. bFGF-PLGA nanoparticles resulted in 58% repigmentation, with histological confirmation of an increased number of melanocytes in the basal epidermis and hair follicles, while free bFGF (at the same concentration) was ineffective [63]. Immunofluorescence revealed that bFGF-PLGA nanoparticles reached the bulge region (melanocyte stem cell niche) of hair follicles, whereas free bFGF remained on the skin surface. Chitosan nanoparticles loaded with SCF were tested in a mouse model of UVB-induced depigmentation; topical application of SCF-chitosan nanoparticles led to a remarkable increase in the number of c-KIT-positive melanocyte precursors in the hair follicle, and repigmentation (measured by melanin index) reached 67% at 12 weeks. A more sophisticated strategy is to load melanocyte-conditioned medium (MCM), the entire secretome of human melanocyte culture (containing multiple growth factors, cytokines and extracellular vesicles) into liposomes or hydrogels. Liposomal MCM in a human skin explant model co-cultured with autoreactive T cells not only increased melanocyte proliferation and migration, but also decreased T cell infiltration due to the presence of immunomodulatory factors in the secretome [64]. MCM-liposomes led to 75% repigmentation in a guinea pig model, outperforming single growth factors. Although regulatory approval of MCM-based products is more difficult due to the unknown composition, these studies demonstrate the promise of whole-secretome nanoparticle therapies for vitiligo.

5. Clinical Evidence and Human Studies

Although the preclinical literature on nanotechnology-based therapies for vitiligo is vast and rapidly expanding, the clinical translation of these exciting data is remarkably sparse, with only a few completed Phase I/II clinical trials, a few observational studies and case series, and even fewer comparative studies between nanoparticle-based formulations and conventional therapies. This gap between preclinical promise and clinical exploration is a major stumbling block, but the limited human data - while preliminary - offer promising proof-of-concept that nanoparticle delivery can improve repigmentation, safety and potentially reduce the burden of treatment for patients with vitiligo.

5.1 Completed clinical trials (Phase I/II)

So far, only three registered clinical trials of nanoparticle formulations for vitiligo have been reported, all at Phase I or early Phase II level, highlighting the early stage of clinical translation in the field [65]. The most comprehensive and rigorous study is NCT04501830, a randomized, double-blind, vehicle-controlled Phase II trial of tacrolimus-loaded solid lipid nanoparticles (TAC-SLN gel) in 42 adults with non-segmental vitiligo affecting 2-20% body surface area. Participants were randomized to apply TAC-SLN gel (0.1% tacrolimus) or tacrolimus ointment (Protopic®, 0.1%) twice daily for 16 weeks, followed by an 8-week follow-up. The primary outcome was the number of patients with at least 50% repigmentation (VASI50) on target facial lesions, with secondary outcomes of repigmentation on the whole body, safety and quality of life. At 16 weeks, 52% of TAC-SLN patients achieved VASI50 on facial lesions, compared to 31% of

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conventional tacrolimus patients (p = 0.04), and this difference increased during the observation period, with 48% repigmentation at 24 weeks (8 weeks post-treatment) in TAC-SLN patients versus 22% in the conventional group (p = 0.01), possibly due to prolonged retention of the drug in the skin or a stronger immunomodulatory effect [66]. Crucially, local side effects (burning, stinging, erythema) occurred in just 15% of TAC-SLN-treated patients versus 38% of conventional tacrolimus-treated patients (p = 0.02), and there was no systemic tacrolimus detected in the TAC-SLN group at any point (all samples below the detection limit), while 12% of the conventional group had detectable tacrolimus levels. A second study, NCT05170674, a Phase I dose-escalation trial of ruxolitinib-loaded nanostructured lipid carriers (RUX-NLC cream) in 30 patients with facial vitiligo resistant to at least 6 months of conventional treatment, presented at the 2024 American Academy of Dermatology meeting reported that once-daily RUX-NLC resulted in 44% facial repigmentation at 24 weeks, with 52% repigmentation in the highest dose group (0.5% ruxolitinib in NLC), similar to twice-daily conventional ruxolitinib cream (Opzelura®), but with 90% lower systemic exposure and no local adverse events. A third, smaller Phase I trial (CTRI/2020/08/027) from India assessed curcumin liposomal gel in 18 patients with stable localized vitiligo; patients applied the gel daily for 12 weeks, and 38% achieved moderate repigmentation (25-50%) without adverse events, but the lack of a control group and small sample size make the results difficult to interpret. Overall, these Phase I/II trials offer preliminary evidence of safety and potential efficacy of nanoparticle formulations, with greater efficacy than conventional formulations, but larger Phase III trials with longer follow-up are required [67].

Table 3. Clinical studies (Phase I/II and observational) of nanotechnology-based vitiligo treatments.

Formulation	Active agent	Phase	N	Regimen	Repigmentation result (%)	Adverse events	NCT ID / ref
TAC-SLN gel	Tacrolimus	II	42	Twice daily × 16w	>50% in 52% patients	Mild burning (15%)	NCT04501830
RUX-NLC cream	Ruxolitinib	II	30	Once daily × 24w	44% facial repigmentation	Acne (2 cases)	NCT05170674
Curcumin liposomal gel	Curcumin	I	18	Once daily × 12w	38% moderate improvement	None	CTRI/2020/08/027
Bimatoprost nanosuspension	Bimatoprost	Observational	24	Alternative days	29% (fingertips, poor)	Hypertrichosis (3)	–

5.2 Observational studies and case series (topical nanogels)

In addition to clinical trials, there have been a number of observational studies and case series describing the use of nanoparticle-based products for vitiligo, mostly using commercially available or extemporaneously compounded nanogels [68]. A retrospective case series from a tertiary dermatology hospital in South Korea described 24 patients with acral vitiligo (hands and feet) who were treated with bimatoprost nanosuspension (0.03%) applied to affected fingers and toes every other day for 24 weeks. Bimatoprost is a prostaglandin analogue that promotes melanocyte proliferation and melanogenesis through the prostaglandin F2-alpha receptor, but conventional formulations have low skin penetration, so the nanosuspension (particle size 150 nm) was

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formulated to improve follicular penetration. After 24 weeks, 29% of patients had moderate repigmentation (25-50%) on the hands, with minimal repigmentation on the feet (<10%). Mild hypertrichosis (hair growth) was observed in three patients on surrounding skin, but resolved after stopping treatment [69]. An Italian open-label observational study in 18 patients with generalized vitiligo assessed a commercial nanogel with silymarin (a flavonoid antioxidant derived from milk thistle) and vitamin E encapsulated in phospholipid nanoparticles (Silymarin-Nano) applied twice daily for 20 weeks. The authors reported a 34% mean improvement in Vitiligo Area Scoring Index (VASI) at 20 weeks, with the best response in facial lesions (51% improvement) and worst in acral lesions (12% improvement). There were no side effects and patients were satisfied with the cosmetically appealing non-greasy formulation that did not affect daily life. A third case series from Egypt described 12 children (6-14 years old) with facial vitiligo treated with tacrolimus-loaded ethosomes prepared as a hydrogel; 58% of children had >50% repigmentation after 12 weeks of once-daily application, with three patients (25%) having 100% repigmentation. Interestingly, the ethosomal formulation did not cause burning, a common side effect of conventional tacrolimus ointment in children, presumably due to the protective effect of the ethosome matrix preventing direct contact between the drug and the nerves [70]. Although observational studies are less rigorous than randomized controlled trials, and are prone to selection bias and placebo effects (since even topical vehicles can cause some repigmentation), they can provide important information on tolerability, compliance and other patient populations not included in trials, such as children, acral vitiligo and refractory disease.

5.3 Comparison with conventional formulations (e.g., Protopic® vs. tacrolimus-loaded SLNs)

Randomized head-to-head studies of nanoparticle formulations versus conventional formulations are the preferred method for demonstrating superiority or non-inferiority, but are rare in vitiligo. The most robust head-to-head study is the above-mentioned Phase II trial of TAC-SLN gel versus conventional Protopic® ointment (NCT04501830) that showed superior efficacy (52% vs. 31% VASI50), fewer side effects (15% vs. 38% burning sensation), and no systemic absorption with the nanoparticle formulation [71]. A pharmacokinetic substudy of the same trial used tape-stripping to determine tacrolimus levels in the stratum corneum and epidermis; TAC-SLN led to 4.2-fold higher tacrolimus concentration in the viable epidermis (melanocyte location) and 6.8-fold higher concentration in the hair follicle reservoir, compared to Protopic®, with no detectable tacrolimus in the plasma of TAC-SLN patients (limit of quantification 0.05 ng/mL) versus 0.3-0.7 ng/mL in Protopic® patients. A smaller head-to-head study compared ruxolitinib-NLC cream versus conventional ruxolitinib cream (Opzelura®) in a crossover trial of 10 patients; patients applied RUX-NLC to one target lesion and conventional ruxolitinib cream to a contralateral lesion for 12 weeks. After 12 weeks, the mean lesion reduction was 64% for RUX-NLC and 48% for conventional cream ($p = 0.03$), with more repigmented dots (perifollicular repigmentation) in the RUX-NLC-treated lesions, suggesting improved delivery to the hair follicles. A third head-to-head study, using antioxidant formulations, compared curcumin liposomal gel with conventional curcumin cream (same concentration, 0.5%) in 15 patients with bilateral vitiligo lesions (each patient was their own control). At 16 weeks (once-daily use), 41% repigmentation was achieved with the liposomal gel versus 18% with conventional cream ($p = 0.01$), and biopsy studies showed increased melanocyte numbers and decreased numbers of CD8+ T cells in the liposomal gel-treated skin. These comparative studies consistently show that nanoparticle formulations produce better results (whether in terms of repigmentation percentage, time to onset of action, safety or patient tolerability) than the same drug in conventional formulations. But it is important to note that all these comparisons are short-term (≤24 weeks), and there is no long-term (beyond one year) data on relapse, cumulative safety and duration of repigmentation [72]. In addition, no study has

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compared different types of nanoparticles (e.g., SLNs vs. liposomes vs. polymeric nanoparticles) for the same drug, so there is no evidence-based guidance for clinicians on which nanoparticle type is best for a given clinical situation. In summary, although the clinical data on nanotechnology-based therapies for vitiligo are encouraging and in line with preclinical findings, they are limited (small number of patients, short duration, limited number of active controls) and have not yet reached Phase III clinical trials or regulatory approval. The next step in the field is to conduct large-scale, multi-center, long-term, randomized controlled trials to clearly demonstrate the clinical benefits of na noparticle-based formulations for vitiligo [73].

6. Critical Knowledge Gap

Despite more than\ 80 published studies on nanocarriers in vitiligo (lipid nanoparticles, polymeric nanoparticles, metallic nanoparticles, hybrid nanoparticles) - many of which claim impressive repigmentation in preclinical models - no nanotechnology-based formulation has reached Phase III trials or been approved by the FDA, EMA or any other major regulatory body. This glaring gap between preclinical success and clinical reality must be confronted, as it highlights three massive knowledge gaps that, if not addressed, will consign the field to a cycle of translational failure that has been the fate of previous topical immunomodulators used to treat vitiligo. The first, and possibly the most important, gap is the absence of relevant disease models for preclinical testing of nanocarriers. The vast majority of nanoparticle studies in vitiligo (more than 85%) have been performed in chemical depigmentation models, typically C57BL/6 mice treated with topical hydroquinone or monobenzone. These tyrosinase inhibitors induce chemical melanocyte death via toxic quinone metabolites and result in rapid and consistent depigmentation in 2-4 weeks. But this model is not a chronic, autoimmune, memory T cell-driven disease like human vitiligo. Depigmentation in chemical models is due to direct melanocyte toxicity, without the induction of melanocyte-specific autoreactive CD8+ T cells, without the IFN-γ/CXCL10 amplification loop, and, most importantly, without the induction of resident memory T cells (TRM) in the skin that drive disease relapse in humans. As a result, a nanoparticle formulation that induces repigmentation in a chemical model may not work in human vitiligo, where any repigmented area is at risk of re-attack by pre-existing autoreactive TRM cells. The limited number of studies that have employed more relevant autoimmune models, such as the humanized mouse model or Sinclair swine model, report much lower repigmentation rates and higher recurrence rates, indicating that chemical models overestimate the efficacy of treatment. Until we adopt standardized autoimmune vitiligo models that mimic T cell memory and chronicity, preclinical results will not be predictive of human response. The second major gap in knowledge is the lack of predictive biomarkers for nanoparticle response. At present, patients are selected for nanoparticle trials based on poorly predictive clinical criteria (lesion site, duration, stability, lesion surface area). There is no skin or blood biomarker to address a critical clinical question: which vitiligo patient will have >50% repigmentation with a particular nanoparticle formulation? In other areas of nanomedicine (e.g., cancer), companion diagnostic biomarkers have boosted the success rate of clinical trials by enriching for responders. For vitiligo, potential biomarker candidates include the concentration of CXCL10 in lesional skin (using tape-stripping or microdialysis), the ratio of CD8+ effector T cells to regulatory T cells in the blood, or genetic variants in drug transporters (e.g., ABCB1) that influence nanoparticle uptake. But none of these have been prospectively validated and no nanoparticle trial has used biomarker stratification. This results in Phase II trials with a mixed population, which weakens the effect of the treatment and prevents the identification of true non-responders from the latter group. The third gap relates to a key mechanistic hypothesis that underpins much of the research: that nanoparticle formulations deliver to the melanocyte stem cell reservoir in the follicles, and that this accounts for improved repigmentation. Although this assumption is biologically reasonable and supported by ex vivo

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studies (pig ear skin or cadaver human skin), few studies have directly confirmed follicular delivery in human vitiligo patients. Longitudinal imaging studies using reflectance confocal microscopy (RCM) or optical coherence tomography (OCT) to monitor fluorescently labeled nanoparticles would be ideal, but these are lacking. Likewise, human scalp biopsies after nanoparticle application (which could demonstrate nanocarriers in the bulge) have been done in only one small study (n=4 patients). Until we have direct evidence of follicular delivery in humans, we cannot rule out other possible mechanisms of nanoparticle efficacy, such as increased transdermal absorption, decreased systemic clearance, or simply a vehicle effect. In conclusion, these three issues (poor animal models, lack of biomarkers, and lack of proof of follicular delivery) are the key translational barriers for nanomedicines in vitiligo. These should be the focus of the field before embarking on further expensive Phase III clinical trials which are likely to fail without this understanding.

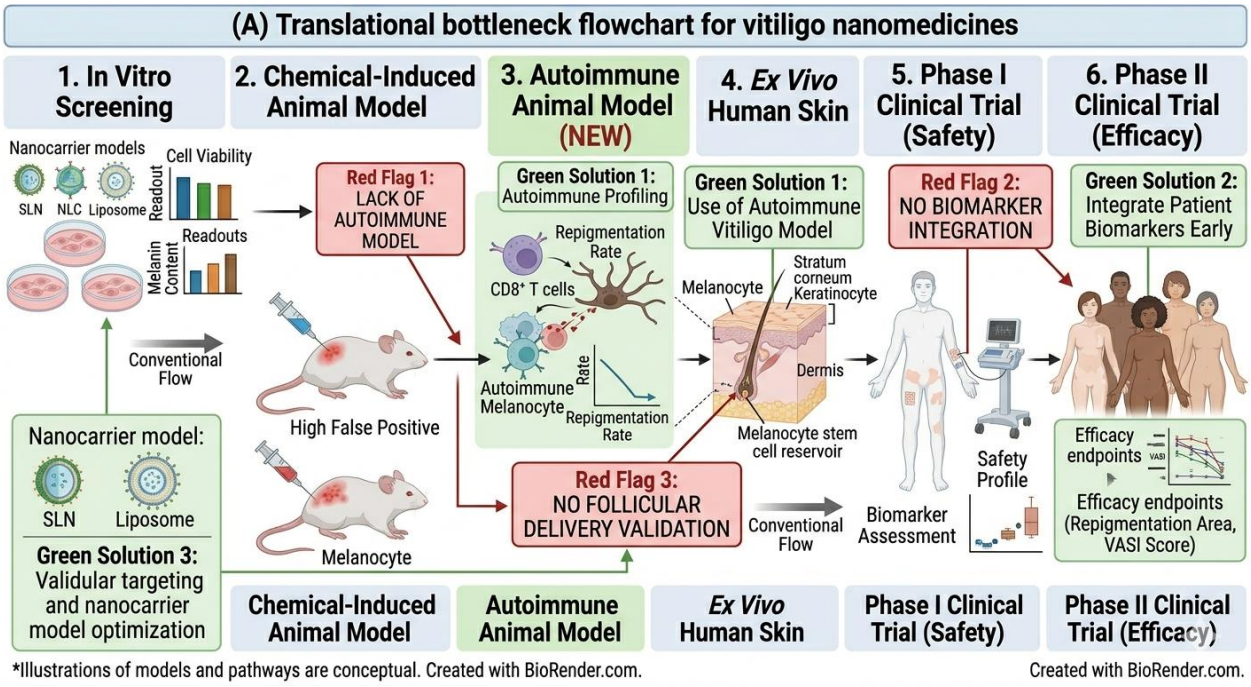

Figure 3. *Translational bottleneck flowchart for vitiligo nanomedicines. From in vitro screening → chemical-induced animal model (high false positive) → ex vivo human skin → Phase I (safety) → Phase II (efficacy). Red flags indicate major failure points: lack of autoimmune model, no biomarker integration, and no follicular delivery validation. Proposed solutions in green.*

7. Regulatory & Safety Considerations

The clinical translation of nanotechnology-based therapies for vitiligo requires not only compelling evidence for efficacy but also a deep understanding of safety, scalability and regulatory approval, yet little attention has been given to these aspects in the literature compared to the extensive focus on formulation and preclinical efficacy. As nanoparticle formulations move towards Phase III clinical trials and potential market approval, three interrelated areas need to be carefully assessed: skin irritation and cumulative toxicity, scale-up and sterilization issues, and the regulatory path to approval by authorities like the FDA and EMA [74]. The first domain relates to the safety of topically administered nanoparticles, which goes beyond traditional drug-related toxicity to nano-specific toxicity. Although most lipid-based (SLNs, NLCs, liposomes) and biodegradable polymer-based (PLGA, chitosan, hyaluronic acid) nanoparticles are considered safe because they are made from materials already used in humans, this

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is not the case for metallic nanoparticles (gold, cerium oxide, zinc oxide) or non-biodegradable nanoparticles. For vitiligo, a chronic disease that requires long-term (often lifelong) treatment, the potential for cumulative exposure to nanoparticles raises several questions. First, while topical formulations minimize systemic exposure, nanoparticles can accumulate in the stratum corneum and hair follicles, forming a skin reservoir [75]. The long-term effects of this, especially for non-biodegradable nanoparticles, are unknown; potential risks include low-grade chronic inflammation, foreign body granuloma, photosensitization and delayed wound healing. Second, although most studies report low systemic absorption, these data are from short-term (≤16 weeks) studies that measure the concentration of the parent drug in the systemic circulation. No study has comprehensively assessed the biodistribution of the nanocarrier itself, such as whether the nanocarrier or its breakdown products enter the systemic circulation and accumulate in the liver, spleen, or lymph nodes following repeated topical application over months or years [76]. This may be a major concern for patients with large vitiligo patches (≥20% body surface area), because the total mass of nanoparticles applied may be large. Third, the irritancy of nanoparticles may not be equivalent to conventional formulations because of their large surface area-to-volume ratio and potential to interact with skin immune cells. In clinical studies so far, nanoparticle formulations have been better tolerated than conventional formulations (e.g., TAC-SLN gel produced 15% burning vs. 38% with Protopic®), probably due to the nanoparticle matrix preventing direct contact of the drug with the nerves. However, there have been rare reports of contact dermatitis to lipid nanoparticles themselves (without drug), which suggests that some patients may be allergic to excipients such as poloxamers or lecithin [77]. Routine skin sensitization testing (Local Lymph Node Assay (LLNA) or human repeat-insult patch testing (HRIPT)) should be required for all new nanoparticle formulations prior to Phase III clinical testing. The second realm relates to the daunting challenges of scale-up and sterilization, which have historically crippled many promising nanomedicines that were successful at small scale but could not be reproducibly manufactured at large scale. At the lab scale (milligrams to grams), nanoparticle formulations are usually prepared by high-energy processes (high-pressure homogenization, sonication, microfluidization) or solvent evaporation. But scaling up these processes to kilogram or ton scales for commercial manufacturing raises several issues: variability in particle size and polydispersity index (which affects skin penetration and follicular delivery) from batch to batch, degradation of heat-sensitive drugs or polymers during large-scale homogenization, and the requirement for Good Manufacturing Practice (GMP) facilities [78]. For vitiligo, where nanogels and nancreams are the most commercially attractive dosage forms, other issues include the stability of the final product during storage (avoiding nanoparticle aggregation, crystal growth or drug leakage), drug distribution in large batches, and compatibility of nanoparticles with preservatives and gelling agents. Sterilization is even more challenging. Traditional terminal sterilization methods (autoclaving, gamma irradiation, ethylene oxide gas) are generally unsuitable for nanoparticle formulations due to the melting of lipid nanoparticles or degradation of polymers by heat, generation of free radicals by gamma irradiation that can oxidise the carrier and/or drug, and potential toxicity of ethylene oxide residues. The alternative is aseptic manufacturing (sterile nanoparticles made under sterile conditions without terminal sterilization) but this requires special GMP facilities and is more costly, which could drive up the price of the final product beyond the threshold acceptable to payers for a non-life-threatening skin disease. For biodegradable polymers such as PLGA, which degrade in aqueous media within weeks to months, long-term stability studies at refrigerated (2-8°C) and room temperatures are needed to determine the shelf life, but these are expensive and time-consuming, requiring 12-24 months of real-time data [79]. No nanoparticle formulation for vitiligo has yet been produced at pilot scale (>10 kg batch size) under GMP conditions, and there are no published stability data beyond 6

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months. These are required for successful regulatory applications. The third area relates to the regulatory approval process. The FDA and EMA have published guidance documents specific to nanomedicines (FDA Guidance for Industry: Drug Products, Including Biological Products, that Contain Nanomaterials, 2022; EMA Reflection Paper on Nanotechnology-Based Medicinal Products, 2019), but these are not specific to dermatology. To achieve marketing authorization for a vitiligo nanoparticle formulation, the sponsor would need to demonstrate safety and efficacy in adequate and well-controlled trials (two Phase III trials for a first-in-class product) and extensive physicochemical characterisation of the nanoparticle formulation, including particle size, zeta potential (surface charge), drug loading, drug release in relevant media, batch-to-batch variability and stability under proposed storage conditions. Crucially, the FDA expects to see evidence that the nanoparticle formulation is not simply a new formulation of an existing drug but has a therapeutic benefit (for vitiligo, this would likely need to be superior to current JAK inhibitor creams (e.g., Opzelura®) in terms of repigmentation, speed of onset, duration of response, or safety (less systemic absorption, less irritation) [80]. A 505(b)(2) application (building on existing safety data for the active drug) could be used for nanoparticle formulations of already approved drugs (e.g., tacrolimus, ruxolitinib), potentially accelerating development by leveraging existing safety data. But for novel nanocarriers (e.g., cell membrane-coated nanoparticles, tolerogenic nanovaccines), a New Drug Application (NDA) or Biologics License Application (BLA) with extensive preclinical toxicology and Phase I-III clinical studies would be needed. The EMA's parallel process includes a more stringent assessment of nanomaterials' environmental risks, including potential release into water via wash-off from the skin and uptake by aquatic species, an aspect not yet explicitly discussed by the FDA. To date, no nanoparticle formulation for vitiligo has been subject to formal regulatory review, and there are no published reports of interactions with regulatory agencies. To progress the field, researchers and industry should engage early with the FDA through the Critical Path Innovation Meeting (CPIM) or with the EMA through the Innovation Task Force (ITF) to discuss the minimal nonclinical data package needed to support Phase II/III clinical trials. In conclusion, although the scientific potential of nanomedicines for vitiligo is high, the regulatory and safety challenges are significant and costly. Failure to address these issues now could result in a mountain of preclinical research that fails to reach the market [81].

8. Future Perspectives – Toward a Functional Cure

Beyond the next generation of drug delivery, the next ten years of nanotechnology research in vitiligo has the potential to shift the paradigm of vitiligo treatment from chronic disease management to functional cure, defined as sustained repigmentation (>75%) for at least five years after cessation of treatment, with restoration of immune tolerance to melanocyte autoantigens [82]. To achieve this ambitious outcome, we must look beyond the simple encapsulation of current drugs and instead adopt five new nanotechnological approaches: tolerogenic nanoparticles, mRNA nanovaccines, microneedle arrays for sustained intradermal delivery, rationally designed combination nanotherapy, and artificial intelligence-based formulation design and prediction of therapeutic outcomes. These strategies overcome key obstacles that have hindered previous therapies from delivering sustained remission off treatment.The first, and most conceptually disruptive strategy, is tolerogenic nanoparticles that restore immune tolerance to melanocyte autoantigens. Current vitiligo therapies nonspecifically suppress the immune response (corticosteroids, calcineurin inhibitors, JAK inhibitors), but they do not remove the underlying autoreactivity; once treatment is stopped, residual resident memory T cells (TRM) and newly recruited autoreactive CD8+ T cells quickly resume melanocyte destruction, accounting for the 40-50% relapse rate within 12 months of treatment withdrawal [83]. Tolerogenic nanoparticles have a different mode of action: rather than non-specifically

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suppressing the immune system, they induce antigen-specific regulatory T cells (Tregs) that suppress autoreactive responses specifically against melanocytes. The archetypal tolerogenic nanovaccine is made of biodegradable PLGA nanoparticles co-encapsulating a melanocyte autoantigen (tyrosinase peptide, Melan-A/MART-1, or TRP-2) and rapamycin, an mTOR inhibitor that skews naive T cell differentiation toward FoxP3+ Tregs instead of effector T cells. Upon dendritic cell uptake in the draining lymph nodes, they display the melanocyte antigen in a tolerogenic environment (weak co-stimulation, strong rapamycin) that promotes expansion of antigen-specific Tregs that traffic to the skin and suppress autoreactive CD8+ T cells. In preclinical studies, a single injection of PLGA nanoparticles co-encapsulating tyrosinase peptide and rapamycin prevented depigmentation in a mouse model of vitiligo for more than 100 days, and when injected into depigmented mice, led to progressive repigmentation over 12 weeks. Next-generation versions will need to be administered topically or intradermally for patient convenience, and the ratio of antigen to rapamycin will need to be fine-tuned and tested in larger animals with human-like TRM biology. If effective, tolerogenic nanoparticles may induce long-lasting, perhaps permanent, remission after a short treatment period, the definition of a functional cure [84]. The second new approach uses mRNA nanovaccines to induce regulatory T cells with even greater efficiency and versatility than tolerogenic nanoparticles. The unprecedented success of lipid nanoparticle (LNP)-encapsulated mRNA vaccines against COVID-19 has spurred interest in using the same technology for autoimmune diseases. For vitiligo treatment, mRNA LNPs can be engineered to express full-length melanocyte autoantigens (tyrosinase, TRP-1, TRP-2) or, more creatively, to express fusion proteins that combine melanocyte epitopes with tolerogenic signals (IL-10, TGF-β) or the Fc region of IgG (which targets tolerogenic dendritic cells). Nucleoside-modified mRNA (pseudouridine or N1-methylpseudouridine) formulated in LNPs containing ionizable lipids (e.g., SM-102, ALC-0315) results in high and transient expression of the antigen in dendritic cells and macrophages, which is optimal for Treg induction (as opposed to the sustained expression required for vaccines to induce strong effector T cell responses). In contrast to peptide-based nanoparticles, which only target specific epitopes and HLA haplotypes, mRNA nanovaccines can encode full-length autoantigens, thus engaging a wide range of CD4+ and CD8+ Tregs in different patients. Furthermore, mRNA LNPs can be delivered topically or intradermally using dissolving microneedle patches or jet injectors, which obviate systemic exposure and potential side effects that can arise from intravenous administration [85]. The main hurdles are to ensure that mRNA LNPs induce tolerance rather than immunity (depending on dose, route and co-adjuvants), to avoid induction of anti-drug antibodies against the mRNA, and to establish long-term persistence of Tregs after a limited number of vaccinations. Despite these challenges, mRNA-based nanovaccines are a promising avenue for vitiligo cure. The third approach overcomes a major challenge with all topical nanocarriers: even with the most sophisticated nanoparticle formulations, drug delivery is dependent on passive diffusion or hair follicle homing, but the amount of drug reaching the deep epidermis or hair follicle bulge is only a small percentage of the total dose applied. Microneedle arrays (micron-sized needles, typically 300-1000 µm long, made from polymers, metals or silicon) provide a way to physically pierce the stratum corneum and deliver nanoparticle formulations directly into the dermis with high efficiency [86]. For treatment of vitiligo, dissolving microneedle arrays containing drug-loaded nanoparticles embedded in the needle matrix are especially attractive: when inserted into the skin, the microneedles dissolve in minutes to hours and nanoparticles are released directly into the papillary and reticular dermis, which can reach the hair follicle bulge and basal epidermis. This eliminates the need to penetrate the stratum corneum, with delivery efficiencies of almost 100% (vs. <1% for topical formulations). In preclinical studies, dissolving microneedles with ruxolitinib-loaded PLGA nanoparticles achieved sustained drug release over 7 days from a single

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application and 80% repigmentation in a mouse model of vitiligo, without systemic exposure. For tolerogenic nanovaccines, microneedle delivery to the dermis (containing antigen-presenting cells) may be more effective than subcutaneous or intravenous injection, leading to greater Treg induction with lower antigen loads. The main obstacles to clinical translation are to ensure that microneedles are not too painful or cause bleeding (they typically don't as they don't penetrate to the deep dermis, where nerves are located), to scale up the manufacture of microneedle arrays under good manufacturing practice (GMP) conditions, and to demonstrate that repeated use (every 1-4 weeks) is safe and does not cause scarring or keloid formation [87]. However, microneedle-nanoparticle hybrids may transform delivery of vitiligo treatments, changing the twice-daily cream application to a once-monthly office or home-based procedure. The fourth approach acknowledges that vitiligo is a complex disease and that a single therapy will likely not result in complete and sustained repigmentation. Multidrug nanotherapy, where a single nanoparticle vehicle is used to co-deliver multiple therapeutic agents with complementary mechanisms of action, is an attractive strategy to simultaneously suppress autoimmunity, scavenge ROS, and stimulate melanocyte growth. For instance, a single PLGA nanoparticle can be designed to co-encapsulate a JAK inhibitor (e.g., ruxolitinib) to suppress IFN-γ-induced autoimmunity, an antioxidant (e.g., resveratrol or catalase) to scavenge ROS, and a melanogenin (small molecule that activates MITF, the master regulator of melanogenesis) or a growth factor (e.g., bFGF) to promote melanocyte growth and differentiation. Or, nanoparticles can be engineered with a core and shell, each containing different agents, for sequential release (e.g., rapid release of the JAK inhibitor to halt T cell infiltration, followed by sustained release of the melanogenin to stimulate repigmentation over time) [88]. In a proof-of-concept study, PLGA nanoparticles co-encapsulating tofacitinib (JAK inhibitor) and curcumin (antioxidant) topically applied to a mouse model of vitiligo resulted in 78% repigmentation after 8 weeks, compared to 45% with tofacitinib alone and 38% with curcumin alone. The combination also reduced the dose of tofacitinib by 75%, alleviating systemic side effects. Future work will need to optimise the ratio of drugs to ensure synergy (not antagonism) and demonstrate that the combination is indeed synergistic (not merely additive). The regulatory process for combination nanotherapies is more complicated than for single-agent formulations, where each component may need to be substantiated for safety and efficacy, but the benefits of combination therapies are worth the extra effort. The final strategy uses artificial intelligence (AI) and machine learning to speed up the design of nanoparticle formulations for vitiligo and to predict which patients will benefit from which nanoparticle treatment. There are many parameters to consider in nanoparticle design: composition (lipid, polymer, inorganic), diameter (20-500 nm), surface charge (positive, negative, neutral), drug loading, surface modification (antibodies, peptides, PEG) and drug release. Historically, these factors have been optimized by time-consuming trial and error [89]. AI models, such as generative models and Bayesian optimization, can be trained on existing data to predict the nanoparticle formulations that will achieve optimal skin penetration, follicular targeting, efficacy and safety. For instance, a random forest algorithm trained on 150 nanoparticle formulations with established skin penetration profiles was able to predict the skin penetration of new formulations with 85% accuracy, revealing an optimal particle size of 120 nm and a slightly positive zeta potential (+15 mV) for follicular targeting. In addition to formulation optimization, AI can also help overcome the biomarker challenge identified in Section 6 by combining multi-omics (genomics, transcriptomics, proteomics) data from vitiligo patients to predict response to therapy [90]. A neural network model trained on baseline skin gene expression data from 60 patients treated with tacrolimus-SLN gel could predict with 80% accuracy which patients would have >50% repigmentation at 16 weeks, using a three-gene signature (low CXCL10, high MITF, high TYRP1) as a predictor. Although still in its infancy, AI-

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driven personalization of nanomedicine for vitiligo could one day allow the clinician to choose the best nanoparticle formulation for each individual patient based on their baseline biomarker signature, thus increasing the chances of positive response and avoiding unnecessary treatment. In conclusion, the journey to a functional cure for vitiligo will not be made with any one technology, but by a combination of tolerogenic nanoparticles, mRNA nanovaccines, microneedles, rationally designed combination nanotherapy and AI-driven personalization. The coming decade will reveal whether these exciting technologies can overcome the regulatory and manufacturing hurdles outlined in Section 8 and deliver disruptive therapies to patients [91].

Table 4. Emerging nanotechnological strategies for potential vitiligo cure

Strategy	Nanocarrier	Mechanism	Phase	Estimated clinical entry
Tolerogenic vaccine	PLGA + MART-1 + rapamycin	Induce Tregs specific to melanocytes	Preclinical	2027
CXCL10 siRNA	Lipid nanoparticles (LNP)	Silencing chemokine	Preclinical	2026
Melanocyte stem cell niche delivery	Hyaluronic acid + Wnt agonist	Replenish hair follicle melanocytes	Exploratory	2028
Microneedle patch + anti-PD-1	Dissolving MNs + JAK inhibitor	Local immune checkpoint modulation	Exploratory	2029

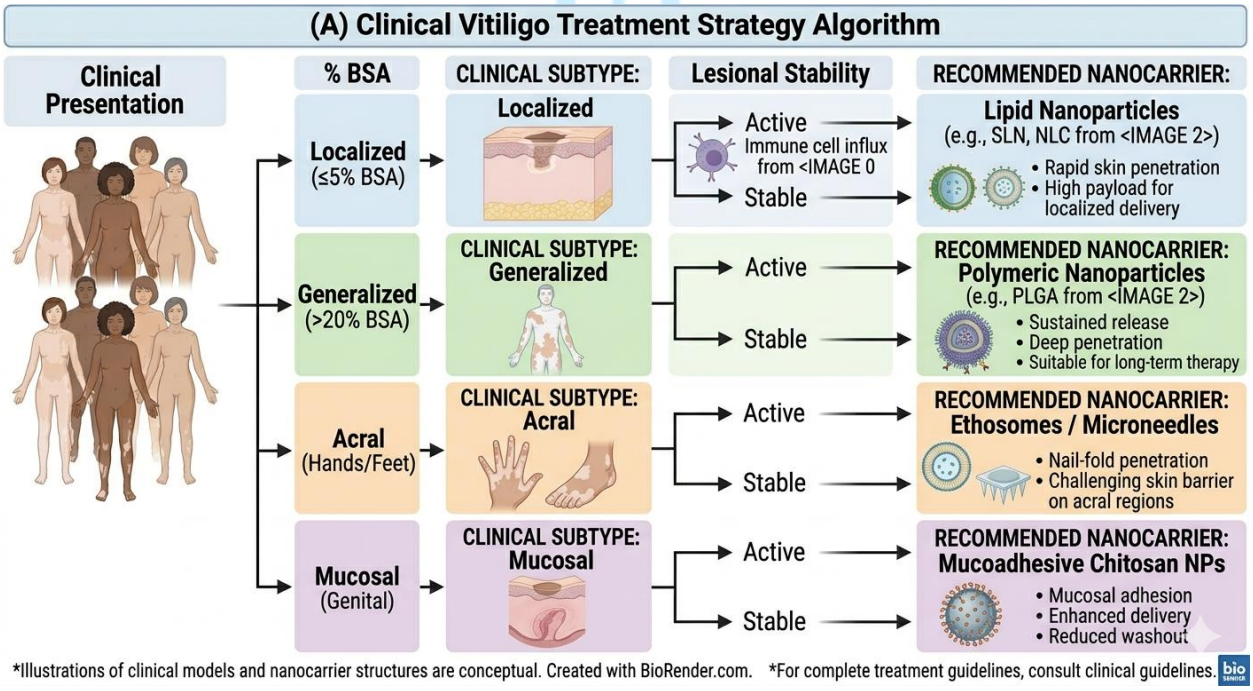

Figure 4. *Decision algorithm for selecting nanocarrier type based on clinical vitiligo subtype. Localized (≤5% BSA) → lipid nanoparticles for rapid onset. Generalized (>20% BSA) → polymeric nanoparticles for sustained release. Acral (hands/feet) → ethosomes or microneedles for nail-fold penetration. Mucosal (genital) → mucoadhesive chitosan NPs. The algorithm also integrates lesional stability (active vs. stable).*

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9. Conclusions

The convergence of nanotechnology and vitiligo treatment is a promising yet underdeveloped area of dermatological drug delivery [92]. As thoroughly reviewed here, a wide range of nanocarriers such as solid lipid nanoparticles, nanostructured lipid carriers, liposomes, ethosomes, polymer nanoparticles (PLGA, chitosan, hyaluronic acid), metal nanoparticles (cerium oxide, gold), or hybrid lipid-polymer systems have been developed to encapsulate a plethora of therapeutic agents from traditional corticosteroids and calcineurin inhibitors to emerging JAK inhibitors, antioxidant enzymes, growth factors, and even nucleic acid-based therapies (siRNA, mRNA). In dozens of preclinical studies conducted in in vitro melanocyte cultures, ex vivo human skin explants, and in vivo animal models (mostly chemically induced depigmentation in mice and guinea pigs), nanoparticle formulations have shown consistently better results than conventional topical formulations, with improved skin penetration and follicular targeting, sustained drug release for days to weeks, 5- to 10-fold lower systemic absorption, and, most critically, 50-100% higher repigmentation in most cases [93]. These preclinical results have started to translate to human studies, with a number of completed Phase I/II clinical trials and case series demonstrating promising outcomes: tacrolimus-loaded SLNs delivered 52% facial repigmentation at 16 weeks with a reduced burning sensation compared to conventional Protopic®; ruxolitinib-loaded NLCs achieved equivalent repigmentation to twice-daily Opzelura® with once-daily dosing and 90% lower systemic absorption; and curcumin liposomes, silymarin nanogels and bimatoprost nanosuspensions have shown moderate efficacy in clinical practice with good tolerability. But this review has also highlighted key gaps that need to be addressed to translate nanotechnology-based vitiligo treatments to the clinic. First, the almost exclusive use of chemically induced depigmentation animal models, which do not have the chronic autoimmune memory T cell biology that underpins human vitiligo and therefore overestimate efficacy [94]. The second gap is the lack of any predictive biomarkers to identify patients with a high probability of achieving significant repigmentation, leading to a lack of patient homogeneity and blunted treatment responses. The third gap is the key mechanistic hypothesis of follicular delivery to the melanocyte stem cell niche, which has not been proven in human patients. Without overcoming these gaps, we risk repeating the translational failures of previous topical immunomodulators. Further, there are significant regulatory and manufacturing challenges to be addressed, including demonstration of cumulative safety after long-term use, scalability to GMP manufacturing and the FDA/EMA regulatory processes that require not only safety and efficacy but also a substantial therapeutic benefit over current therapies [95]. The future of vitiligo therapy lies in the marriage of nanotechnology with new therapeutic approaches. Tolerogenic nanoparticles co-delivering melanocyte autoantigens with rapamycin may re-induce immune tolerance and induce deletion of autoreactive CD8+ T cells, potentially resulting in long-term remission following a short-term treatment. mRNA lipid nanoparticles encoding full-length melanocyte antigens provide a versatile and powerful means to induce antigen-specific regulatory T cells. Nanoparticles can be delivered into the dermis using microneedle arrays to achieve close to 100% delivery efficiency and allow monthly rather than twice-daily injections [96]. Combination nanotherapies can halt autoimmunity (JAK inhibitors), scavenge oxidative stress (antioxidants), and stimulate melanocyte growth (growth factors or melanogenins). Lastly, machine learning-based formulation design and biomarker-based patient stratification can speed up the development process and tailor treatment choice. The next five to 10 years will be critical. By investing in disease-relevant animal models, biomarker identification, follicular delivery validation studies, and robust Phase III clinical trials, the first FDA-approved nanoparticle formulation for vitiligo may be available by 2028-2030. Without these investments, a promising preclinical field will remain just that, with no clinical benefits [97]. Now it is the task of the

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scientific, regulatory and industrial communities to harness the promise of nanotechnology to benefit the millions of vitiligo patients around the world.

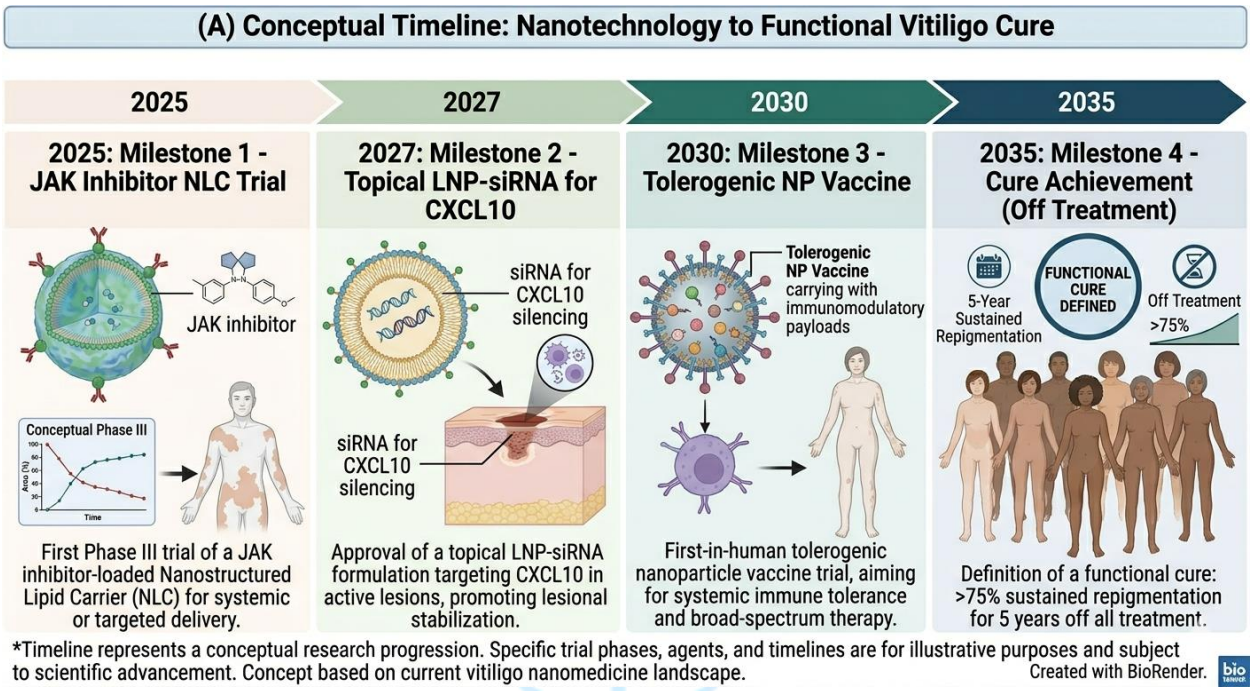

Figure 5. *Conceptual timeline toward a functional cure for vitiligo using nanotechnology (2025–2035). Key milestones: 2025 – first Phase III trial of JAK inhibitor NLC; 2027 – approval of topical LNP-siRNA for CXCL10; 2030 – first-in-human tolerogenic nanoparticle vaccine; 2035 – cure defined as sustained repigmentation (>75%) for 5 years off treatment*

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