

REVIEW ARTICLE

Gold nanoparticle-enhanced hydrogel skin patches for cutaneous T-cell lymphoma treatment: A review

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Abstract

Cutaneous T-cell lymphoma (CTCL) is a rare type of cancer, and its prevalence has been increasing in recent years. The lack of curative treatments makes this cancer critical in terms of diagnosis and treatment. The two main types of treatment are skin-directed and systemic therapies, with limitations related to adverse effects. Accordingly, there is a need for localized, non-invasive approaches that reduce systemic toxicity. To achieve this, nanotechnology has been explored to deliver safe, appropriate diagnosis and treatment. Gold nanoparticles (AuNPs) and transdermal patches containing AuNPs have shown great promise in the treatment of CTCL with a high safety profile. In this review, the pathophysiology of CTCL and its treatment modalities using AuNPs and transdermal patches are presented from both materials science and clinical perspectives.

Keywords: Cutaneous T-cell lymphoma; Hydrogel patches; Gold nanoparticles; Skin cancer; Cancer therapies

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1. Introduction

Advances in nanotechnology have transformed the methods used to diagnose and treat cancer, paving the way for more localized, non-invasive treatments in rare cancers, such as cutaneous T-cell lymphoma (CTCL). CTCL affects about 1 in 200,000 people annually. Although it is considered a rare type of cancer, the incidence of CTCL is increasing, and there is a lack of curative treatments, making it especially critical for diagnosis and treatment.^{1,2}

Cutaneous T-cell lymphoma is a type of skin cancer and an extranodal non-Hodgkin lymphoma that affects T-lymphocytes.^{2,3} In healthy individuals, these cells aid the body's immune system. However, in patients with CTCL, these cells can no longer aid the immune system; instead, they begin to infiltrate and accumulate in the patient's skin, driving inflammatory and neoplastic changes. As a result, dermal infiltration occurs, leading to rashes in the form of scales. This, in the long term, leads to tumor development (Figure 1).³ A combination of clinical data and histopathological findings is essential for diagnosing CTCL.

Current therapies for CTCL are limited. Treatment options depend on the stage and type of CTCL. There are two main types of therapies: (i) skin-directed, and (ii) systemic. Skin-directed therapy options include topical creams and steroids or phototherapy. Systemic therapies include chemotherapy and monoclonal antibodies. These, however, are non-curative. The only curative option available is an allogeneic hematopoietic stem cell transplant.⁴ Nevertheless, even with current management strategies, patients with this type of cancer have a reduced quality of life.⁵

Localized treatments, such as topical agents, treat symptoms rather than the disease. Hence, there is a need for localized, non-invasive treatments for CTCL with minimal side effects. To address this, recent advances in nanotechnology and biomaterials have been explored as strategies for localized, non-invasive treatment. In particular, gold nanoparticles (AuNPs) and AuNP-containing patches have shown promising therapeutic benefits with minimal side effects in the treatment of CTCL.^{6–8} These materials have become indispensable in cancer treatment due to their ability to transport therapeutic drugs to specific sites with minimal adverse effects. The adaptability and functionalization enable concurrent drug administration, making them advantageous for precious medicines and combination therapy strategies in CTCL. Physicochemical properties specific to the nanoscale, such as high surface area and remarkable electronic and optical properties, make AuNPs and their composites promising candidates for the treatment and management of various types of cancer. Although AuNPs have great potential for cancer treatment, several limitations should be addressed. In the long run, issues related to toxicity, concentration, and conjugation with other materials need to be addressed.⁸ This study presents a comprehensive review of the pathophysiology of CTCL and its treatment with AuNPs and polymer patches.

2. Pathophysiology of cutaneous T-cell lymphoma

Cutaneous T-cell lymphomas are a heterogeneous group of extranodal non-Hodgkin lymphomas derived from mature, skin-tropic T-cells and involve lymph nodes and peripheral blood in more advanced stages.⁹ They mainly include mycosis fungoides (MF) and Sézary syndrome (SS), malignancies driven by epidermotropic CD4⁺ T cells that localize and proliferate in the skin.¹⁰ These malignant cells express skin-homing adhesion molecules, such as cutaneous lymphocyte antigen (CLA) and chemokine receptors (C-C chemokine receptor [CCR] 4 and CCR10), which enable them to adhere

to the skin microenvironment.¹¹ CLA mainly binds to endothelial E-selectin to tether malignant T cells to dermal postcapillary venules, while CCR4 interacts with key skin-derived chemokines, such as CCL17 and CCL22, produced by epidermal cells.¹²

An understanding of skin homing and epidermotropism is important for the management of CTCL, as malignant T cells are highly restricted to the skin. This allows early-stage interventions, including topical medications, phototherapy, or localized radiation, to directly target the disease with minimal systemic exposure and toxicity.¹⁰ Moreover, these mechanisms form the foundation for advanced localized delivery systems. In addition, CTCL cells evade immune clearance by upregulating immune checkpoint molecules, such as programmed death-ligand 1/programmed cell death 1, and downregulating major histocompatibility complex class I, thereby reducing cytotoxic T-cell recognition and allowing the tumor to proliferate in the skin microenvironment.¹³

2.1. Classification of hematolymphoid tumors

In the World Health Organization (WHO) Classification of Hematolymphoid Tumors,⁹ primary cutaneous T-cell lymphomas are categorized into nine distinct entities. These include common types such as MFs and SS, as well as less common forms such as CD30-positive lymphoproliferative disorders, subcutaneous panniculitis-like T-cell lymphoma, and several rare subtypes that were previously grouped under “cutaneous peripheral T-cell lymphoma.”

2.1.1. Mycosis fungoides

Mycosis fungoides accounts for 65% of all CTCL cases, with an overall five-year survival rate of 75% to 98%. Most cases are CD4⁺ T-cell derived, though less than 5% are CD8⁺ variants. It includes various clinical forms such as classic MF, folliculotropic MF, and pagetoid reticulosis, all of which have similar disease progression patterns.⁹ A full breakdown of the WHO-European Organisation for Research and Treatment of Cancer (EORTC) classification of cutaneous T-cell lymphomas, including subtype, frequency, and five-year disease-specific survival, is shown in Table 1.

The classic type of MF, Alibert–Bazin, generally follows a slow, multistage progression with the following stages: (i) the patch stage: appearance of erythematous or brownish slightly atrophic scaly patches on mainly sun protected regions of the torso and extremities, (ii) the plaque stage: these lesions may turn to erythematous infiltrated plaques with clear demarcated borders with a foveolar, semi annular,

Table 1. World Health Organization-European Organisation for Research and Treatment of Cancer Classification of cutaneous T-cell lymphomas

World Health Organization-European Organisation for Research and Treatment of Cancer Classification ¹⁴	Frequency (%)	Five-year DSS
Mycosis fungoides (MF)	39	88
Folliculotropic MF	5	75
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
Sézary syndrome	2	36
Adult T-cell leukemia/lymphoma	<1	NDA
Primary cutaneous CD30-positive lymphoproliferative disorders		
Primary cutaneous anaplastic large cell lymphoma	8	95
Lymphomatoid papulosis	12	99
Subcutaneous panniculitis-like T-cell lymphoma	1	87
Extranodal NK/T-cell lymphoma, nasal type	<1	16
Chronic active EBV infection	<1	NDA
Primary cutaneous peripheral T-cell lymphoma, rare subtypes		
Primary cutaneous g/d T-cell lymphoma	<1	11
Primary cutaneous aggressive epidermotropic CD8 ⁺ T-cell lymphoma (provisional)	<1	31
Primary cutaneous CD4 ⁺ small/medium T-cell LPD (provisional)	6	100
Primary cutaneous acral CD8 ⁺ T-cell lymphoma (provisional)	<1	100
Primary cutaneous peripheral T-cell lymphoma NOS	2	15

Abbreviations: DSS: Disease-specific survival; EBV: Epstein–Barr virus; LPD: Lymphoproliferative disorder; NDA: No data available; NK: Natural killer; NOS: Not otherwise specified.

and serpiginous appearance, and (iii) the tumor stage, characterized by creation of one or more tumor nodules that are mainly deep red.¹⁵ Unusual presentations include folliculotropic MF (hair follicle involvement and alopecia), erythrodermic MF (widespread redness with scaling and lymphadenopathy), and other localized variants, such as pagetoid reticulosis.¹⁶ The various stages of progression are illustrated in [Figure 1](#).

2.1.2. Sézary syndrome

Sézary syndrome is a leukemic variant of CTCL recognized as a distinct entity within the WHO/EORTC classification. It is defined by the presence of erythroderma and generalized lymphadenopathy.^{15,18} SS is characterized by a triad of erythroderma, lymphadenopathy, and the presence of malignant T-cells (Sézary cells) in the peripheral blood. The cutaneous symptoms include widespread redness in the form of a rash covering 80% or more of the body surface, with severe pruritus. Non-scarring alopecia, which mainly affects the eyebrows, along with nail dystrophy and palmoplantar keratoderma, is also observed. Lymphadenopathy is usually generalized and can often be the first sign of systemic involvement. Unlike MF, SS is leukemic from onset, with circulating Sézary cells that show

cerebriform nuclei and distinct immunophenotypes.^{18,19} The main stages of SS are illustrated in [Figure 2](#).

2.2. Immunopathogenesis of cutaneous T-cell lymphoma

Cutaneous T-cell lymphoma typically stays localized to the skin during the early stages of MF. However, in approximately 30% of patients, the disease progresses to more advanced stages, which involve lymph nodes, peripheral blood, or visceral organs.²⁰ SS also involves cell transformation characterized by the presence of malignant T cells that are at least four times larger than normal lymphocytes. This transformation is linked to a more aggressive clinical state with a significant decrease in survival rates.²¹

2.2.1. Disease progression from skin localization to systemic spreading

Progression of CTCL results from the accumulation of genetic and epigenetic mutations. These mutations are associated with increased aggressiveness and disease spread, especially *TP53* mutations and deletions that affect DNA repair mechanisms.²² Additionally, activation of the Janus



Figure 1. The main stages of mycosis fungoides (MF). Image adapted from He *et al.*¹⁷
Abbreviations: CCR: C-C chemokine receptor; CLA: Cutaneous lymphocyte antigen; IL: Interleukin.



Figure 2. Main stages of Sézary syndrome (SS). Image adapted from He *et al.*¹⁷
Abbreviations: CCR: C-C chemokine receptor; IL: Interleukin.

kinase/signal transducer and activator of transcription (STAT) pathway (STAT3 and STAT5B), which enables cell survival, along with mutations in DNA methyltransferase 3 alpha, phosphoinositide 3-kinase, mitogen-activated protein kinase, and chromatin regulators, contributes to genomic instability. With visceral involvement, the median survival time drops to below 1.5 years.²³ These molecular findings emphasize the importance of early detection and monitoring of these markers.

2.2.2. Tumor-promoting inflammatory loop in the skin microenvironment

In CTCL, malignant CD4⁺ T cells produce Th2 cytokines, including interleukin (IL)-4 and IL-13. These cytokines activate skin cells, such as keratinocytes and fibroblasts, leading to the production of pro-inflammatory mediators, such as IL-25 and periostin. These molecules further promote T-cell proliferation through the STAT5/STAT6 pathway, creating a self-amplifying loop that favors tumor survival and inhibits the immune response.^{24–27} This interaction between tumor cells and the skin's microenvironment is fundamental to disease progression, as illustrated in Figure 3.²⁷

Figure 4 shows a patient with increasing skin involvement and inflammation from early-stage disease (Figure 4A), with limited patches and plaques, to more aggressive clinical stages involving more than 10% of body surface area (Figure 4B,C).²⁸

2.2.3. Treatment modalities for cutaneous T-cell lymphoma

Cutaneous T-cell lymphomas require treatment strategies tailored to their stage to manage the disease with a high safety profile. Management goals are different at each stage. The early stage requires lesion removal, and the late stage requires systemic spread control.

2.2.4. Skin-directed therapies

In early-stage CTCL (IA–IIA), skin-directed therapies are the main treatment approaches. These therapies primarily target cancerous T cells in the skin. A few important treatment approaches include:

- (i) Topical nitrogen mustard: Mechlorethamine is a topical alkylating agent most frequently used in the treatment of early MF. Although the precise mechanism of action in CTCL remains largely

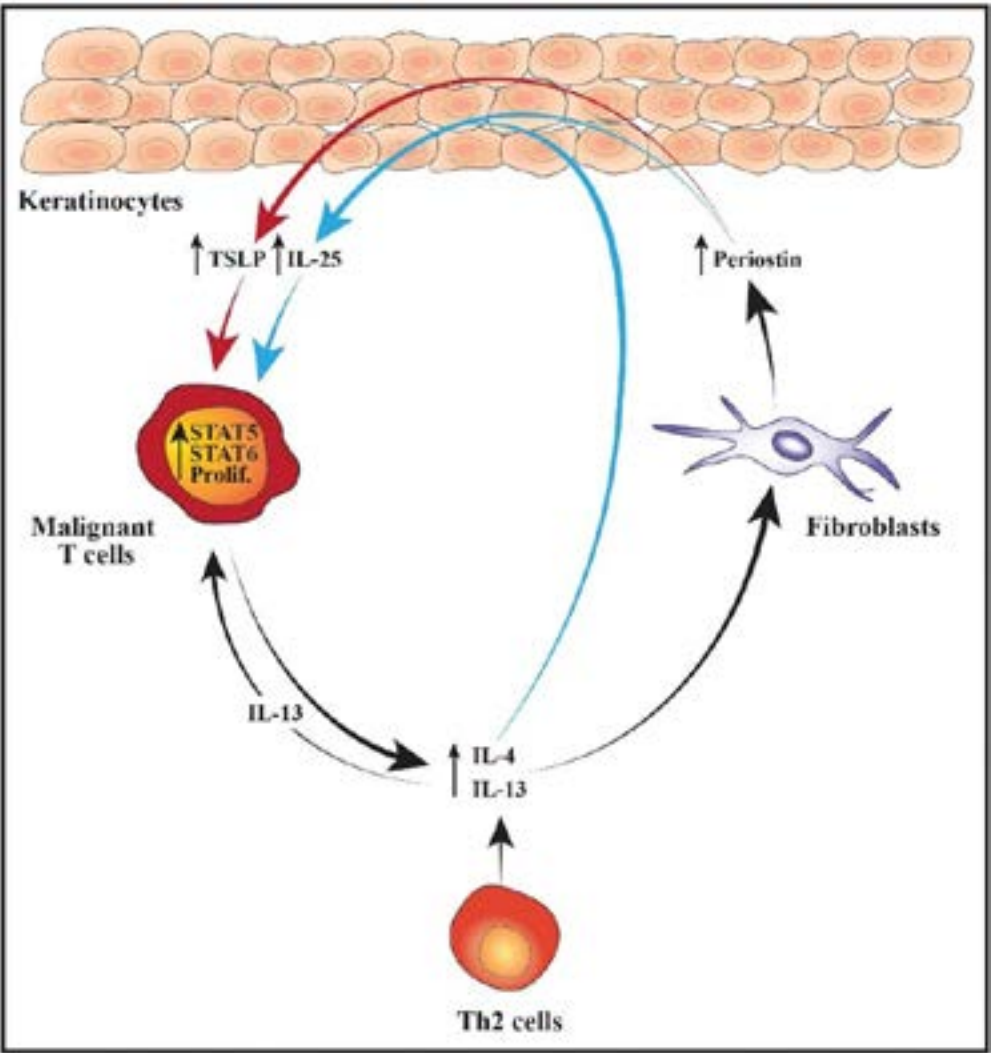


Figure 3. Cytokine-mediated inflammatory loop in cutaneous T-cell lymphoma. Image adapted from Stoleranco *et al.*¹⁸
Abbreviations: IL: Interleukin; STAT: Signal transducer and activator of transcription; TSLP: Thymic stromal lymphopoietin.



Figure 4. Example of a patient with progressive mycosis fungoides. Image adapted from Krejsgaard *et al.*²⁸

unknown, mechlorethamine is believed to cause DNA crosslinks that interfere with the proliferation of malignant T cells. Due to its localized action and low systemic toxicity, mechlorethamine remains a key therapeutic agent in the treatment of early-stage MF, especially in stages IA and IB.²⁹ Despite its effectiveness, several limitations are associated with mechlorethamine, and the most common is contact dermatitis with hypopigmentation, pruritus, and skin irritation.^{30,31}

- (ii) Topical corticosteroids: Topical corticosteroids play a crucial role in treating early-stage MF, particularly for T1–T2 lesions. They bind intracellular glucocorticoid receptors, which help regulate gene transcription and dampen inflammatory and immune responses.^{29,32} Further, about 10–20% of patients using class I steroids for three months or more experienced irritant dermatitis or purpura, skin atrophy, and striae. Reversible suppression of cortisol levels has also been reported with the use of topical steroids in CTCL.³³
- (iii) Phototherapy: Phototherapy is a well-known, non-invasive treatment for early-stage MF. Narrowband ultraviolet (UV)-B is effective for patch-stage disease³⁴, inducing apoptosis in epidermal T cells with minimal side effects. It is often the best choice due to its safety profile; however, relapse is a common drawback. In contrast, PUV-A therapy pairs psoralen (a photosensitizer) with UV-A radiation, making it more effective for thicker plaques. PUV-A penetrates deeper into the skin and causes apoptosis. However, PUV-A has side effects like nausea (due to psoralen), phototoxicity, hyperpigmentation, and, in the long term, susceptibility to non-melanoma skin cancer. Both therapies require multiple sessions (from weeks to months), which is time-consuming for the patients.³⁵

2.2.5. Systemic therapies

In the treatment of early-stage MF, especially in stages IA–IIA, skin-directed therapies are essential. However, for advanced cases of MF and SS, where the disease progresses beyond the skin or visceral organs, systemic treatments become essential. These include the following:

- (i) Bexarotene: For the first-line systemic treatments for CTCL, oral bexarotene, a synthetic retinoid X receptor agonist, has proven to be effective. However, dose-limiting side effects such as hyperlipidemia, hypercholesterolemia, and hypothyroidism have been reported.^{36,37}
- (ii) Targeted therapies for relapsed or refractory CTCL: Vorinostat, a histone deacetylase inhibitor, promotes apoptosis, arrests the cell cycle in malignant T cells,

and achieves an overall response rate of about 30%. Another histone deacetylase inhibitor, romidepsin, was also found to be similarly effective.³⁸

- (iii) Extracorporeal photopheresis: This is an approved immunomodulatory therapy for erythrodermic CTCL. The treatment involves leukapheresis, a process that separates mononuclear cells from peripheral blood.³⁹ These cells are then treated with 8-methoxypsoralen and UV-A irradiation before being reinfused into the patient. This process induces apoptosis in malignant T cells and enhances antigen presentation to dendritic cells, thereby boosting the body's anti-tumor immune response. While this method has a favorable safety profile, it has several limitations, including a delayed onset of action and the need for specialized equipment.⁴⁰

3. Role of nanoparticles in cancer therapy

The discovery of nanoparticles (organic and metallic) marked a major breakthrough in medicine, enabling early diagnosis and treatment of diseases. Nanoparticles typically range between 1 and 100 nm in size with various surface morphologies.^{41–43}

3.1. Organic nanoparticles

Organic nanoparticles are carbon-based. They are typically stabilized by non-covalent intermolecular interactions and exhibit high structural integrity. These materials possess unique thermal and heat-responsive properties. They are widely used in drug delivery, vaccines, and gene therapy applications. However, the applications of organic nanoparticles in medical applications are limited due to their relatively low physicochemical stability, limited functional versatility, and short shelf life.^{44,45}

3.2. Inorganic nanoparticles

Inorganic nanoparticles are generally metal-, metal oxide-, or mineral-based. They are often hydrophobic and demonstrate better physical, chemical, catalytic, and thermal properties. Their robust structural characteristics contribute to improved stability, enabling precise tissue targeting, advanced imaging applications, and more controlled therapeutic interventions.⁴¹ In drug delivery, inorganic nanoparticles are capable of achieving higher drug loading capacities compared to organic nanoparticles. A key advantage is their ability to be engineered and functionalized to target specific cell types or disease sites, offering a degree of customization not feasible with naturally derived organic nanoparticles. Among various metallic nanoparticles, AuNPs have been extensively studied for both therapeutic and diagnostic applications and are particularly well-established in preclinical and clinical oncology studies.^{45–47}

3.3. Delivery of nanoparticles in cancer therapy

There are two main routes for the delivery of nanoparticles in cancer therapy: (i) passive targeting, and (ii) active targeting.

- (i) **Passive targeting:** Passive targeting relies on the spontaneous accumulation of nanoparticles at the tumor site. For example, in cutaneous or solid tumors, nanoparticles can penetrate the skin or the vasculature and localize within the tumor microenvironment. Once inside, they can interfere with growth factors, such as vascular endothelial growth factor, thereby inhibiting angiogenesis and slowing tumor progression.⁴⁸ The efficiency of passive delivery is highly dependent on tumor physiology, and failure of nanoparticles to overcome biological barriers can limit therapeutic efficacy.
- (ii) **Active targeting:** A more advanced strategy is active targeting, which uses ligands that enable nanoparticles to selectively recognize and bind to tumor-associated receptors. This approach enhances drug accumulation at the tumor site and can reduce off-target exposure, thereby lowering systemic toxicity. Moreover, it can facilitate crossing biological barriers, unlike passive targeting. Common ligands include monoclonal antibodies, peptides, and folic acid, each selected based on the specific molecular profile of the tumor.^{49–51}

The efficiency of nanoparticle-mediated drug delivery depends on several critical factors, which ultimately determine whether passive or active targeting is preferred.

The size of nanoparticles plays a central role, as smaller particles more readily accumulate within tumors via the enhanced permeability and retention effect. Similarly, cellular uptake and intracellular trafficking dictate therapeutic efficacy, since insufficient uptake may necessitate active targeting strategies.

Other important considerations include nanoparticle surface charge, shape, tumor vascularization, and the composition of the tumor microenvironment, all of which significantly influence accumulation, penetration, and therapeutic outcomes. While passive targeting offers simplicity and a direct approach, active targeting provides a higher specificity, making it a cornerstone of next-generation nanomedicine.⁵² The barriers to the use of nanoparticles in drug delivery are illustrated in Figure 5.

Gold nanoparticles have recently emerged as promising enhancers of photodynamic therapy (PDT) due to their unique surface properties, including size, shape, and surface morphology.⁵³ These nanoparticles not only act as efficient photothermal agents but also as versatile carriers for photosensitizers, improving both stability and tumor selectivity. By facilitating controlled delivery and enhancing light absorption, AuNPs markedly improve the overall efficiency and specificity of PDT.^{53,54} Collectively, the integration of AuNPs into PDT provides a dual advantage: (i) it improves the pharmacokinetic profile of photosensitizers and (ii) amplifies therapeutic outcomes with reduced collateral toxicity.

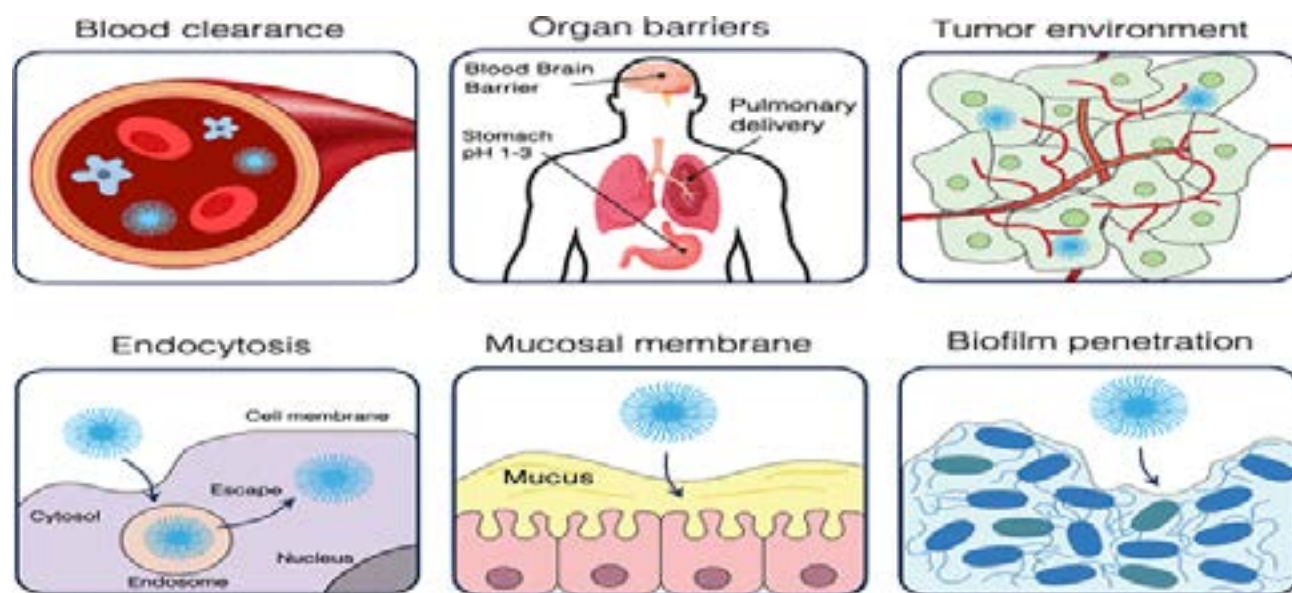


Figure 5. Illustration of various barriers in drug delivery using nanoparticles. Image adapted from Beach *et al.*⁵²

3.4. Properties and role of gold nanoparticles in cancer therapy

Gold nanoparticles are among the most extensively studied inorganic nanomaterials in biomedical research, with applications mainly in cancer therapy. Their widespread use originates from their unique characteristics, including high stability, tunable size and shape, biocompatibility, low toxicity, and the ability to convert light into energy. These properties make AuNPs particularly well-suited for advanced therapeutic modalities such as photothermal therapy (PTT) and PDT. Depending on the desired optical properties, AuNPs can be synthesized into nanospheres, nanorods, nanoshells, or nanostars. These structural variations directly influence their surface plasmon resonance (SPR) properties, enhancing light absorption and conversion efficiency and thereby improving treatment outcomes, particularly in PDT and PTT applications.^{55–58}

In addition to the shape, particle size plays a pivotal role in determining therapeutic efficiency. AuNPs can be synthesized with precise geometric control, enabling optimal drug-loading capacity and improved penetration into deep tissues. This precision design ensures that AuNPs reach tumor sites effectively and deliver therapeutic agents directly to malignant cells, thereby enhancing treatment efficacy while minimizing systemic toxicity. Their ability to navigate biological barriers and preferentially accumulate in tumors highlights their value as both drug carriers and therapeutic enhancers.⁵⁹

3.4.1. Biocompatibility and safety

A central consideration in nanomedicine is biocompatibility and minimal toxicity. AuNPs demonstrate excellent compatibility with human tissues and typically do not provoke adverse immune responses. Their chemical inertness further ensures stability when integrated with chemotherapeutic agents or photothermal systems, without generating harmful interactions. This combination of safety, stability, and functional versatility makes AuNPs highly reliable platforms for clinical translation in oncology.

3.4.2. Photothermal capabilities

Beyond their role in drug delivery, AuNPs exhibit exceptional efficiency in PTT. When irradiated with near-infrared light, they efficiently convert photon energy into localized heat, inducing apoptosis and necrosis in cancer cells. This localized hyperthermia slows tumor progression and improves therapeutic outcomes, especially when combined with chemotherapeutic drugs or immune modulators. The dual functionality of AuNPs—combining light-to-heat conversion with drug delivery—makes them among the most versatile nanoplatforms for precision cancer therapy.⁶⁰

3.4.3. Imaging applications

Gold nanoparticles are also emerging as powerful imaging agents due to their strong SPR effects, photostability, and low cytotoxicity relative to other nanomaterials. Specific morphologies such as nanorods and nanoshells have shown promise. Gold nanorods have demonstrated superior two-photon luminescence signals compared to natural tissue autofluorescence, enabling high-resolution deep-tissue imaging. Furthermore, AuNPs significantly enhance modalities such as photoacoustic tomography and optical coherence tomography, delivering high-contrast imaging through efficient infrared absorption and thermoelastic expansion. Their safety profile and multifunctionality highlight their potential as dual-purpose agents for both diagnosis and therapy, paving the way for more effective theranostic strategies in clinical oncology.

3.4.4. Applications in hematological malignancies and skin cancers

Gold nanoparticles have demonstrated remarkable potential in oncology due to their unique physicochemical properties, including tunable size and shape, excellent biocompatibility, and high photothermal conversion efficiency. These characteristics have opened new avenues for cancer diagnosis and treatment, addressing several limitations of conventional therapeutic strategies.⁶¹ Hematological malignancies are diagnosed by the abnormal production of blood cells. AuNPs have shown significant promise in both diagnostic and therapeutic applications. For instance, when conjugated to Ab2 antibodies, AuNPs enable highly sensitive detection of CD10, a critical biomarker in acute lymphoblastic leukemia and follicular center-cell lymphoma. Notably, this detection remains accurate even in complex mixtures containing CD10, CD19, and CD20, underscoring the robustness and specificity of the AuNP-based platform.^{62–64}

Beyond diagnostics, AuNPs are being investigated for their potential to overcome drug resistance, a major obstacle in leukemia therapy. Unlike conventional chemotherapeutics, AuNPs can directly penetrate malignant tissues, bypass cellular drug resistance mechanisms, and enhance cytotoxicity against tumor cells. This dual role as both diagnostic enhancers and therapeutic agents positions AuNPs as a transformative tool in the management of hematological malignancies. A recent study demonstrated promising results using AuNPs loaded with doxorubicin, AS14111, and an anti-miR-221 component. This led to increased drug accumulation in cancerous cells, thereby slowing the spread of leukemia. This approach was reported as novel, reflecting the rapid development of AuNPs in the field of anticancer therapies, especially for cancers with existing drug resistance.

Skin cancers represent another domain where AuNPs have gained momentum, largely due to the anatomical accessibility of these malignancies. Given that skin tumors are located at or near the surface, they are highly amenable to light-based therapies. This makes PTT with AuNPs especially effective, as light can efficiently penetrate the tumor site and activate nanoparticles.⁶⁵ Skin cancers are broadly divided into melanoma and non-melanoma subtypes:

- (i) Melanoma: The more aggressive and treatment-resistant form of skin cancer, melanoma often shows poor responsiveness to conventional chemotherapy. In this context, AuNPs provide advantages both diagnostically and therapeutically. Imaging modalities benefit from AuNPs' strong contrast and stability, which enhance the visualization of melanoma cells and enable earlier, more accurate diagnosis. Therapeutically, AuNP-mediated PTT has demonstrated superior efficacy compared to chemotherapy, particularly in chemoresistant melanoma, by inducing localized hyperthermia that drives apoptosis and necrosis of malignant cells.^{66,67}
- (ii) Non-melanoma skin cancers (Basal cell carcinoma, squamous cell carcinoma): These tumors are typically less aggressive and more responsive to treatment compared to melanoma. For these cancers, AuNPs serve as efficient drug delivery vehicles, capable of penetrating the stratum corneum and releasing therapeutic agents directly at the tumor site. Their small size and biocompatibility enable localized therapy with minimal systemic toxicity, improving patient outcomes while reducing adverse effects.^{68,69}

3.4.5. Limitations and safety considerations

Despite the promising and outstanding properties of AuNPs in PTT, several limitations must be addressed before achieving safe and effective clinical translation. One key concern is particle size; while smaller AuNPs enhance tissue penetration and therapeutic efficacy, they also tend to accumulate in the liver and spleen, potentially causing long-term toxicity. Furthermore, AuNPs can induce oxidative stress and inflammatory responses, potentially leading to permanent tissue damage. These risks are especially relevant for patients with pre-existing chronic conditions, such as liver disease, where vulnerability to adverse outcomes is heightened.^{70–72}

4. Hydrogel patches as transdermal drug delivery systems

Polymeric drug delivery systems based on hydrogels are an attractive approach for addressing the poor drug delivery at local sites. Hydrogels are three-dimensional crosslinked

polymer networks that can absorb large amounts of water or physiological fluids without being dissolved. This physical property is mainly due to their crosslinked structure and the large number of hydrophilic polymeric chains, which reduce their solubility. Depending on the type of crosslinking, they are classified either as physical or chemical hydrogels. These materials are developed using natural or synthetic polymers depending on their applications.⁷³ Hydrogels are known for their enhanced transdermal flux due to their hydrated, bioadhesive matrices, which ensure a close skin contact and attachment. CTCL is generally skin-limited at early stages; thus, guidelines prioritize localized skin-targeted therapies, and hydrogel patches can deliver treatment to lesions while avoiding systemic toxicity.^{73–75}

4.1. Properties and performance considerations for transdermal hydrogel patches

A set of structural and biological properties must be considered to ensure an effective hydrogel-based transdermal drug delivery system. Some key properties of hydrogels include water absorption, bioadhesion, biocompatibility, and mechanical properties.

4.1.1. Absorption and moisture retention

The ability of a hydrogel matrix to absorb and retain water can be mainly quantified by the swelling ratio and the equilibrium water content. This property is directly dependent on the osmotic pressure that drives water movement and on the hydrogel's ability to adjust its size and structure (overcoming the network's mechanical and elastic forces).^{76–79}

Multiple environmental and structural factors can significantly alter a hydrogel's swelling behavior. The density of crosslinking normally has an inverse relationship with the swelling ratio. This is due to increased elastic retractive forces and technical stiffening of the hydrogel network, which oppose water uptake. Additionally, both the pH and temperature of the hydrogel's environment are major factors affecting its swelling.^{80–90}

4.1.2. Bioadhesion

The bioadhesive properties of hydrogels allow the patch to form close contact with the stratum corneum, ensuring a stable diffusion gradient. The main intermolecular forces that maintain attachment to the skin are ionic pairing (electrostatic interactions), van der Waals forces, hydrogen bonds, and chain interpenetration. These interactions could be broadly classified into permanent covalent, dynamic covalent, and non-covalent bonds, each contributing differently to the hydrogel adhesion on biological surfaces (Table 2).⁹¹ Skin characteristics, such as softness, texture,

hydration, and sweat and sebum production, can reduce adhesion.^{92–94}

Cilurzo *et al.*⁹⁵ highlighted the main tests, such as peel tests, probe tack, and rheology, to assess skin-patch adhesion and the hydrogel's internal cohesion. Gutschke *et al.*⁹⁶ reported that the probe tack test is a useful tool for assessing the long-term adhesion of a patch to skin prior to *in vivo* wear studies.⁹⁶ In practice, a set of complementary metrics is used to quantify and profile the bioadhesion of a patch, such as initial tack, peel energy, shear hold, wear, and post-removal skin response.^{97–101}

4.1.3. Biocompatibility

The chemical composition of a hydrogel, including the types and amounts of polymers and crosslinkers, determines its biocompatibility. Water-rich, non-ionic (neutral) hydrogels made from polyvinyl alcohol, polyethylene glycol (PEG), hyaluronic acid, and alginate have been shown to promote re-epithelialization and to be cytocompatible with keratinocytes and fibroblasts. Hydrogels containing cationic polymers (e.g., polyethyleneimine) have been reported to exhibit cytotoxicity *in vitro* via plasma membrane disruption, unless the polymer's charge is reduced or adjusted. Photoinitiators are added to hydrogel networks to promote gelation on demand. Classic photoinitiator systems (e.g., Irgacure 2959) reduce cell viability and are associated with cytotoxicity.^{102–106}

Catechol-containing hydrogels have been developed to achieve strong adhesion on wet surfaces. However, the oxidation of catechol and its conversion to quinones can generate reactive oxygen species that produce protein adducts in tissue. Guyot *et al.*¹⁰⁷ showed that this adverse reaction is due to the release of quinones from the gel matrices. This can be controlled by incorporating antioxidants and lower concentrations of catechol compounds.¹⁰⁷ Additionally, de Groot *et al.*¹⁰⁸ emphasized the cautious use of isobornyl acrylate and other acrylate monomers in transdermal drug delivery systems, as they are associated with an increased risk of triggering allergic contact dermatitis.^{108,109} Considering these, precise control of formulations and production conditions is essential

to produce hydrogel skin patches with high cell viability, low inflammatory responses, and preserved skin barrier functions.¹¹⁰

4.1.4. Mechanical properties

Hydrogel-based transdermal drug patches must be soft and compliant enough to ensure their attachment to the skin and avoid margin lift. Conversely, they must be robust enough to withstand mechanical forces that can affect drug delivery. These characteristics are optimized by balancing water content, the amount of plasticizers, the density of crosslinking, double-network or nanocomposite designs, and other controllable factors. These formulation variables determine the mechanical properties of the hydrogel, such as elastic vs. viscous response (G'/G''), Young's modulus (overall stiffness), elongation at break, and fracture energy. Additionally, these variables also affect the release and diffusion of the drug from the patches.¹¹¹

Sun *et al.*¹¹² created a double-network hydrogel with high fracture energy and stretchability. The first brittle layer acts as an energy-dissipating network, and the second softer layer maintains integrity. Even though these hydrogels have a high water content of ~90%, they exhibit fracture energies of ~9,000 J/m² and can undergo more than 20-fold tensile extension.¹¹²

Sliding crosslinkers, such as polyrotaxanes, have been used to develop thermoresponsive hydrogels with good mechanical properties. The ring can roll over the polymer backbone when a mechanical strain is applied. This limits the hysteresis by redistributing the stress across the chains and preventing damage to the polymer network.^{113,114} Sun *et al.*¹¹⁵ developed polyampholyte physical hydrogels, in which ionic bonds are disrupted and reform, enabling the network to self-recover. Such hydrogels exhibit a high fracture energy of 4,000 J/m² and strains of 150–1,500%.^{115–117}

4.2. Benefits of transdermal patches in cutaneous oncology

Transdermal patches can achieve a localized cutaneous therapeutic effect while minimizing systemic delivery.

Table 2. Overview of representative physical and chemical bonds responsible for the bioadhesion of hydrogel patches on the skin

Types of bonds	Representative examples
Covalent (permanent)	Carbon–carbon, siloxane, amide, carbon–nitrogen, etc.
Covalent (dynamic)	Disulfide, imine, and boronate ester complexes
Non-covalent (physical)	Ionic interactions, hydrogen bonds, hydrophobic interactions, and van der Waals interactions

Minimal systemic exposure can reduce adverse effects associated with the therapeutics. This form of treatment maximizes local bioavailability by bypassing first-pass metabolism. Additionally, most advanced patches can deliver the drug at a steady, modifiable rate for extended periods (12–96 h).^{118,119} Patches use diffusion-controlled layers to deliver active agents, ensuring a uniform dose per unit area. The main characteristics of hydrogel patches are softness, high water content, and semi-occlusion, which ensure the hydration of the stratum corneum and significantly improve flux. In such patches, it is possible to maintain water–vapor transmission within a target range of 2,000 to 2,500 g/m² in 24 h, resulting in moisture control without maceration.^{120,121} Hydrogel skin patches can deliver therapeutics evenly over large areas. Furthermore, their ability to be co-loaded with multiple classes of anticancer drugs allows combination therapy (e.g., cytotoxic chemotherapy and immunotherapy).¹²²

Hydrogel-forming microneedle patches have been proposed for deep cutaneous delivery of therapeutics. The needles swell *in situ* by absorbing interstitial fluid, forming micro-reservoirs and conduits (channels), allowing the drug to diffuse from the storage to its target (Figure 6).¹²³ Some super-swelling designs have been introduced that can form large conduits and leave no needle residue in the skin.¹²⁴

4.3. Applications in cutaneous malignancies

Hydrogel skin patches have been increasingly used for the management of skin cancers due to their attractive features. Zhu *et al.*¹²⁵ highlighted that hydrogel microneedle systems are attractive therapeutic options for melanoma treatment. These hydrogel patches have compositions that mimic the extracellular matrix. They easily achieve effective bioavailability at lesions and minimize systemic toxicity.¹²⁵

Zhang *et al.*¹²⁶ designed a hydrogel microneedle system to combine therapeutics against melanoma. The constructed patches were evaluated for their effectiveness in sequential melanoma ablation and later for their ability to promote skin regeneration. It was demonstrated that the microneedle patch ablated melanoma via photothermal and photodynamic therapy.¹²⁶ He *et al.*¹²⁷ demonstrated the application of hydrogel needles to maximize immunotherapy drug retention and utility at tumor sites. Hydrogel-based patches have been studied for multiple skin cancers, including melanoma. However, not many systems have been reported for the treatment of CTCL.

5. Combining gold nanoparticles with hydrogels for cutaneous T-cell lymphoma patches

Combining AuNPs with hydrogels has a synergistic effect that facilitates regulated drug delivery, prolongs retention

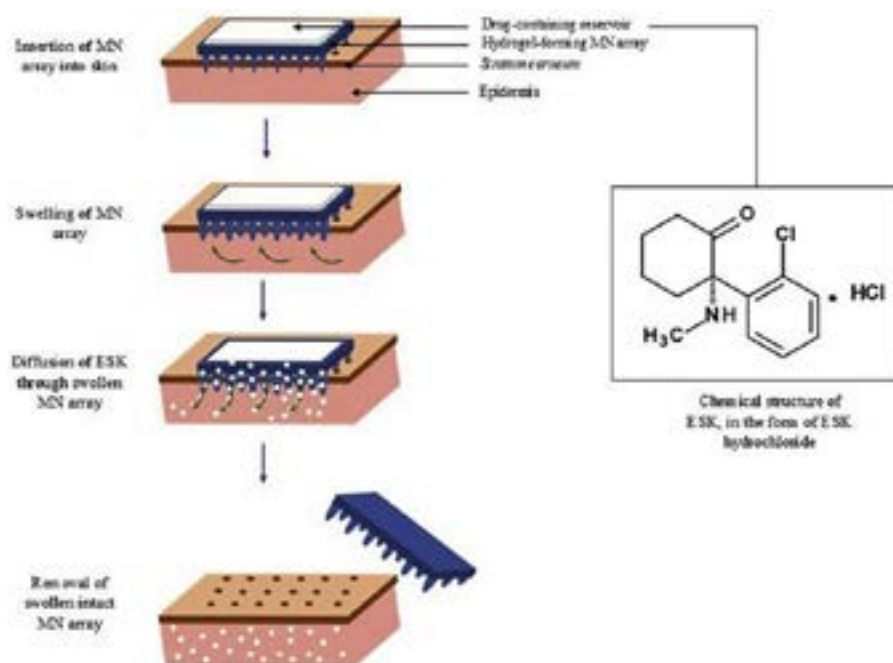


Figure 6. Schematic representation of the mechanism of action of an esketamine (ESK)-containing microneedle (MN) patch. ESK-containing MN patches consist of hydrogel-forming MN arrays and an ESK-containing reservoir. Hydrogel-forming MN arrays take up skin interstitial fluid, thereby inducing the diffusion of ESK from an ESK-containing reservoir through the swollen microprojections. Image adapted from Courtenay *et al.*¹²³

at CTCL lesion sites, and enables AuNP-mediated photothermal ablation to promote efficient treatment. The AuNP-hydrogel system serves as a multimodal platform for controlled drug release, localized photothermal effects, and targeted therapeutic action. The hydrogel network physically entraps the AuNPs and forms a hydration shell around them.^{128–132} The hydrogel matrix contributes to a gradual, controlled release of drugs, thereby anchoring the AuNPs at the lesion site.^{133,134} When near-infrared light is directed at AuNPs, the nanoparticles absorb the light and convert it to heat due to the photothermal effect, as illustrated in Figure 7.^{135–137}

Hyperthermia can directly disrupt the membranes of malignant T cells, leading to their destruction or increasing their sensitivity to chemotherapy drugs present in the hydrogel matrix.¹³⁸ The damaged tumor cells release tumor-associated antigens and damage-associated molecular patterns that activate the cytotoxic response of the immune system. This selectively recognizes and targets the remaining malignant cells.^{139–144} This targeted action results from the dual effect of AuNPs functionalized with antibodies that recognize markers on malignant T-cells.

In CTCL, the drug delivery or transportation of nanoparticles becomes increasingly difficult and inefficient due to the tumor microenvironment. The tumor microenvironment creates barriers due to dense, crosslinked collagen networks, increased stiffness, aligned fiber arrangement, and reduced pore size.¹⁴⁵ To overcome these obstacles, the surface of the nanoparticles was modified and functionalized. The incorporation of AuNPs in hydrogels for drug delivery in CTCL provides a mechanistic advantage for improved diffusion. This system creates a diffusion-regulated matrix for sustained drug delivery.^{146–149} AuNPs functionalized with PEG were effective in reducing the surface charge interactions

with the tumor microenvironment. The functionalized nanoparticles interacted with bone morphogenetic protein-2 and, under ultrasound irradiation, degraded the tumor effectively.^{150,151}

Gold nanoparticles in hydrogels can facilitate precise drug delivery through stimulus-response mechanisms, known as release triggers. There are various release triggers; the most commonly studied are pH, temperature, light, and glutathione. Many of these systems are composed of PEG, poly(*N*-isopropylacrylamide), chitosan, and hydroxypropyl methyl cellulose.^{152,153}

Nanoparticles are introduced into the hydrogel matrix through different methods. The five commonly used approaches are presented in Figure 8. These include (i) direct incorporation of polymers into nanoparticle suspension, (ii) incorporation of nanoparticles after hydrogel formation, (iii) direct formation of nanoparticles within the hydrogel, (iv) *in situ* formation of nanoparticles and *in situ* polymerization, and (v) one-pot synthesis of nanoparticles and hydrogel.^{154–157}

6. Preclinical and experimental evidence

The pathophysiology of CTCL remains complex and incompletely understood, and treatment options span from skin-directed therapies (e.g., topical agents, phototherapy, localized radiotherapy) to systemic approaches, chosen based on disease stage and the treatment goals. Despite these options, allogeneic stem cell transplantation is the only potentially curative therapy to date.¹⁵⁸ Hydrogels containing AuNPs have been explored as a promising platform for localized therapy. Lai et al developed a thermo-responsive gelatin–tannic acid hydrogel containing thiol-functionalized porous gold nanorods. Upon near-infrared irradiation at 750 nm, the hydrogel temperature exceeded 42 °C, triggering both photothermal heating and stimulus-

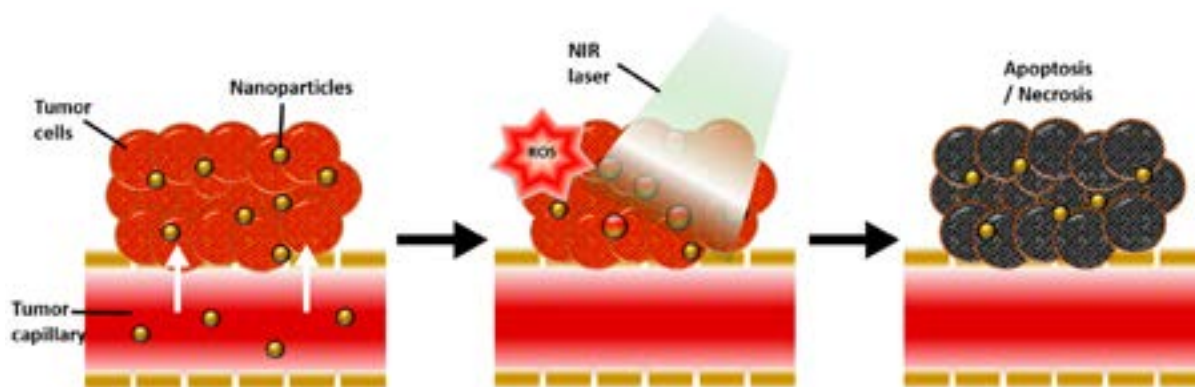


Figure 7. Photothermal effect of gold nanoparticles under near-infrared irradiation (NIR). Image adapted from Kim and Lee.¹³⁵

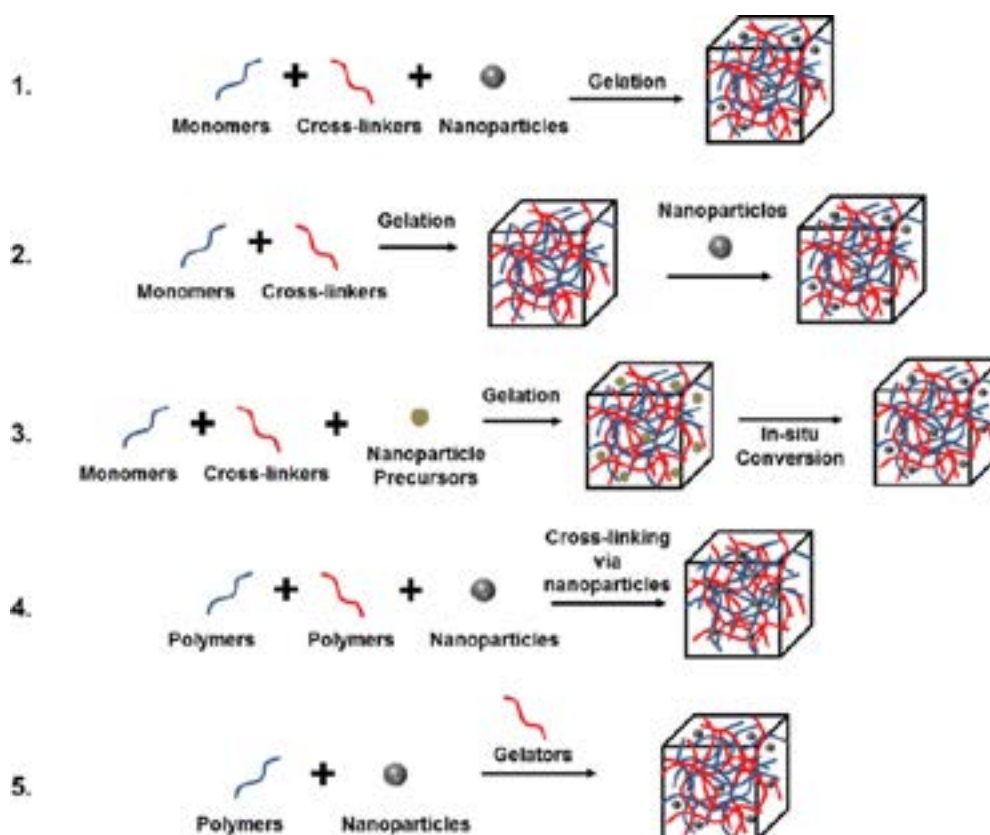


Figure 8. Configurations of gold nanoparticles in hydrogel. Image adapted from Thoniyot *et al.*¹⁵⁴

responsive release of the loaded doxorubicin, offering a combination of photothermal and chemotherapeutic effects *in vitro*.¹⁵⁹

El-Sayed *et al.*¹⁶⁰ fabricated dissolvable PEG-stabilized gold nanostar-loaded polyvinylpyrrolidone microneedles for the treatment of melanoma by PTT. This approach was developed to deliver therapeutics painlessly, avoiding systemic exposure.^{160–162} Hao *et al.* explored the use of gold nanorod-loaded hydrogel-forming microneedles for basal cell carcinoma, which showed excellent drug delivery with tissue preservation and minimal scarring. This system was developed from near-infrared-responsive hydrogel-forming long needles loaded with gold nanorods, serving as a potential plasmonic photothermal device for localized treatment of nodular basal cell carcinoma. In this approach, near-infrared-mediated heating was delivered via the device within subcutaneous lesions, resulting in rapid temperature rise and robust localized tumor regression.¹⁶³

Chen *et al.*¹⁶¹ reinforced the above concept by developing a hydrogel based on carrageenan containing poloxamer 407, silver, and AuNPs. Due to the superficial nature of CTCL lesions, which often manifest as plaques, patches, or tumors, patch-based therapeutic approaches are well-

suited for treating this disease. CTCL is readily accessible, making it easy to apply patches or microneedles, similar to basal cell carcinoma and melanoma, which are also likely to respond to localized photothermal and drug-delivery approaches. This reinforces the strong potential for adapting AuNPs with hydrogel systems or microneedles for CTCL treatment.^{164,165}

Fan *et al.* engineered on-demand active laser release of rituximab–AuNPs in B-cell models for lymphoma treatment. The plasmonic excitation contributed to membrane rupture, showing a dual mechanism for targeting malignant cells.¹⁶⁶ Additionally, Dreaden *et al.* developed targeted anti-CD30 AuNPs, which are a Hodgkin marker. In this work, selective photothermal ablation of lymphoma cells was achieved while sparing the healthy tissue. The study showed that lymphoma cells are indeed susceptible to AuNP-mediated PTT when nanoparticles are localized to the surface.¹⁶⁷

One possible limitation is the limited penetration depth of near-infrared radiation, which may reduce the drug's efficacy in thicker CTCL lesions. Henderson *et al.*¹⁶⁸ demonstrated that low-level near-infrared light does not penetrate beyond 2 mm of skin tissue, indicating

the limitation of PTT in thicker lesions. Another main concern is the long-term biodistribution and retention of AuNPs. While most studies propose minimal acute toxicity, the possibility of chronic accumulation in the skin or systemic tissue remains an important concern. To the best of our knowledge, no published preclinical study has yet investigated AuNP-PTT specifically for CTCL models. This emphasizes both the novelty of this strategy and the need for more robust evaluation in *in vitro* and *in vivo* systems before clinical translation.

7. Challenges and future perspectives

A complete evaluation of local and systemic safety is necessary when translating AuNP-loaded hydrogel patches for CTCL into clinical practice. The physicochemical properties of AuNPs, including their size, shape, surface ligands, surface charge, and exposure route, are the most significant factors affecting their toxicity. Studies have shown that topical treatments, such as skin patches, reduce systemic load by allowing fewer nanoparticles to enter the circulation than intravenous therapeutic agents. However, this may not be the case with CTCL, since the skin becomes inflamed and ulcerated, making it easier for extra particles to enter the circulation, increasing the toxicity potential.^{169–172} Nevertheless, cytotoxicity, genotoxicity, and inflammatory processes could be induced by this accessibility.¹⁷³ Li *et al.*¹⁷⁴ showed that AuNPs in the size range 42.5 nm to 61.2 nm mainly accumulated in the liver and spleen and were eliminated after 90 days. The smaller nanoparticles, ranging from 6.2 nm to 24.3 nm, spread faster across the organs and were cleared more quickly.¹⁷⁴

Furthermore, the shape of the nanoparticle is as significant as the size because various shapes, such as cubes, spheres, and rods, have distinct effects. In biomedical applications, the biodistribution effect of rod-shaped nanoparticles differs from that of spherical nanoparticles in influencing the toxicity and efficacy of the material.^{175–179} Nanoparticle-focused dermatological research has shown that surface charge and penetration paths, such as appendageal or intracellular, have a substantial impact on the site where nanoparticles cross the inflammatory CTCL tumors.

To manage the penetration of nanoparticles, the patch shape, dosage, and wear duration must be adjusted to prevent nanoparticle release beyond the lesion. Several *in vivo* investigations of AuNPs skin deposition reveal no increased toxicity at therapeutic exposures; however, these results vary depending on particle size and cannot be generalized for applications in CTCL therapy.¹⁸⁰ Furthermore, co-optimizing the chemistry of hydrogels and nanoparticles is critical to achieving the best outcome rather than validating them separately. Recent studies have

shown that crosslinkers, residual monomers, and pH/ionic changes affect the aggregation of AuNPs.¹⁷¹

In clinical practice, nanotoxicology guidelines should be followed to ensure the safety of CTCL patches and to balance the therapeutic benefits of AuNP-hydrogel patches. This includes: (i) dermal irritation/sensitization and photo-irritation testing on diseased skin models; (ii) percutaneous absorption and biodistribution under repeated-dose conditions; (iii) immunogenicity (anti-PEG/anti-ligand antibodies, complement); and (iv) organ histopathology with washout to document clearance.^{169,181–186} Even though AuNP-based hydrogel skin patches show promising results in the management of CTCL, there are challenges in their clinical translation.^{187–189}

Hydrogel patches are designed for localized delivery, and AuNPs' therapeutic effectiveness depends on their ability to penetrate malignant T cells within the skin lesion. However, nanoparticle internalization into tumor cells creates a barrier. As a result, insufficient nanoparticle uptake by tumor cells may necessitate higher doses, increasing toxicity to surrounding healthy keratinocytes and fibroblasts. To address this issue, surface modification of AuNPs to make them tumor-selective is a viable option.¹⁹⁰

Gold nanoparticle-enhanced hydrogel skin patches offer a multifaceted platform for application in personalized medicine. The major advantage of AuNPs-enhanced hydrogel is the adjustable characteristics, which can be tailored to specific patient needs. For instance, stimuli-responsive hydrogels containing AuNPs could be designed to deliver the therapeutic agent in a controlled manner in response to external stimuli. Recent innovations include DNA-based hydrogels that respond to external stimuli, enabling the accurate, on-demand release of therapeutics tailored to patient needs.^{191,192} Furthermore, hydrogels with specific markers such as CCR4 and CD30, and specific antibodies are expected to promote personalized therapeutic needs.¹⁹³

8. Conclusion

The incorporation of AuNPs in hydrogel-based systems (as patches) is considered a new and promising approach for improving therapeutic strategies in CTCL. The surface functionalization of the nanoparticles and the choice of hydrogel matrix provide effective and on-demand controlled delivery of therapeutics. Such systems offer patient-centered treatment strategies for targeted delivery of therapeutics to control and manage CTCL. Multiple safety considerations, including biodegradability and cytotoxicity, must be addressed before clinical translation and scale-up.

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Conflict of interest

The authors declare they have no competing interests.

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Writing–review & editing: All authors

Ethics approval and consent to participate

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