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REVIEW ARTICLE

Harnessing Artificial Intelligence for Microneedle-Mediated Transdermal Delivery of Stimulus-Responsive Nanocarriers: A New Frontier in Personalized Cancer Immunotherapy

Komang Dian Aditya PUTRA[*], Andayana Puspitasari GANI[**], Akhmad Kharis NUGROHO[***°]

Harnessing Artificial Intelligence for Microneedle-Mediated Transdermal Delivery of Stimulus-Responsive Nanocarriers: A New Frontier in Personalized Cancer Immunotherapy

SUMMARY

Microneedle (MN) patches integrated with nanocarriers that are responsive to the tumor microenvironment (TME) enable localized and minimally invasive cancer immunotherapy. However, designing these systems requires complex optimization. This complexity arises from nonlinear release kinetics and anatomical constraints. This review synthesizes the extant evidence on MN–nanocarrier hybrid systems. It critically examines the contribution of artificial intelligence (AI) and machine learning (ML) to predictive formulation, in silico pharmacokinetics, biodistribution, and patient-specific hardware–software co-design. The aim is to evaluate mechanical principles, therapeutic outcomes, and translational pathways. Preclinical findings show that MN-mediated delivery increases intralesional drug concentration and immune activation. The TME is responsive to stimuli such as pH, hypoxia, and enzymes, and the release mechanisms triggered by these stimuli reduce systemic toxicity. Mechanistic approaches include enzyme-sensitive feedback systems, photodynamic therapy–hypoxia-activated prodrug cascades, and core-shell MN architectures that localize biologics at the needle tip. The utilization of AI/ML models has been demonstrated to expedite nanoparticle and MN optimization. It enables closed-loop theranostic control and supports personalized therapy by correlating trigger chemistries with omics data. Nonetheless, several limitations persist. The drug's limited penetration restricts access to deep tumors. Furthermore, the heterogeneity of the TME leads to inconsistent release profiles. The clinical translation demands compliance with Good Manufacturing Practice standards, sterilization protocols that preserve bioactivity, and validated shelf-life studies. The predictions of AI/ML models remain constrained by data availability and await external validation. In conclusion, MN-based TME-responsive immunotherapeutic systems, supported by AI/ML, offer promising advances in precision, efficacy, and safety. Mechanism-driven design, image-guided therapy, and rigorous validation are pivotal for personalized cancer therapy.

Keywords: *Microneedles, artificial intelligence, tumor microenvironment, stimuli-responsive nanocarriers, cancer immunotherapy, theranostics.*

Uyarıcıya Duyarlı Nanotaşıyıcıların Mikroiğne Aracılı Teslimatı İçin Yapay Zekadan Yararlanılması: Kişiselleştirilmiş Kanser İmmünoterapisinde Yeni Bir Sınır

ÖZ

Tümör mikro ortamına (TME) yanıt veren nanotaşıyıcılarla entegre edilen mikroiğne (MN) yamaları, minimal invaziv lokal ve bölgesel kanser immünoterapisine olanak tanımaktadır. Ancak bu sistemin tasarlanması, doğrusal olmayan salım kinetiği ve anatomik kısıtlamalardan kaynaklanan karmaşık bir optimizasyon süreci gerektirmektedir. Bu derleme, MN-nanotaşıyıcı hibrit sistemlere ilişkin mevcut kanıtları sentezlemekte; yapay zekanın (YZ) ve makine öğrenmesinin (MÖ) öngörücü formülasyon geliştirmeye, in silico farmakokinetiğe, biyodağılım analizine ve hastaya özgü donanım-yazılım ortak tasarımına katkılarını eleştirel bir bakış açısıyla incelemektedir. Çalışmanın amacı, mekanik prensipleri, terapötik sonuçları ve translasyonel yolları kapsamlı biçimde değerlendirmektir. Preklinik bulgular, MN aracılı ilaç iletiminin intralezyonel ilaç konsantrasyonunu ve bağışıklık aktivasyonunu belirgin şekilde artırdığını ortaya koymaktadır. TME; pH, hipoksi ve enzimler gibi çevresel uyaranlara karşı duyarlıdır ve bu uyaranların tetiklediği salım mekanizması sistemik toksisiteyi azaltmaktadır. Mekanistik yaklaşımlar arasında enzim duyarlı geri besleme sistemleri, fotodinamik-hipoksi terapisiyle aktive edilen proilaç kaskadları ve iğne uçlarında biyolojik olarak lokalize edilmiş çekirdek-kabuk MN mimarileri yer almaktadır. YZ/MÖ modellerinin kullanımının nanopartiküllerin ve MN'lerin optimizasyon sürecini hızlandırdığı gösterilmiştir. Bu modeller kapalı döngü teranostik kontrolü sağlamakta ve tetikleyici kimyasını omik verilerle ilişkilendirerek kişiselleştirilmiş terapiyi desteklemektedir. Bununla birlikte bazı önemli sınırlamalar hâlâ mevcuttur. Yetersiz ilaç penetrasyonu derin tümörlere erişimi kısıtlamakta; TME'nin heterojen yapısı ise tutarsız salım profillerine yol açmaktadır. Klinik çeviri açısından İyi Üretim Uygulamaları (GMP) standartlarına uyum, biyoaktiviteyi koruyan sterilizasyon protokollerinin geliştirilmesi ve doğrulanmış raf ömrü çalışmalarının yürütülmesi zorunludur. Öte yandan YZ/MÖ model tahminleri, veri erişilebilirliğiyle sınırlı kalmakta ve harici doğrulama gerektirmektedir. Sonuç olarak, YZ/MÖ ile desteklenen MN tabanlı TME duyarlı immünoterapi sistemleri; hassasiyet, etkinlik ve güvenlik açısından umut verici gelişmeler sunmaktadır. Mekanizma tabanlı tasarım, görüntü rehberli terapi ve titiz doğrulama süreçleri, kişiselleştirilmiş kanser tedavisinin geleceği için vazgeçilmez unsurlar olmaya devam etmektedir.

Anahtar Kelimeler: *Mikro iğneler, yapay zeka, tümör mikroçevresi, uyarıcıya duyarlı nanotaşıyıcılar, kanser immünoterapisi, teranostik.*

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[*] ORCID: 0000-0003-1652-8339, Master in Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Gadjah Mada, Jl. Sekip Utara, Sleman, Yogyakarta, 55281, Indonesia
[**] ORCID: 0000-0002-0775-8127, Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia
[***] ORCID: 0000-0003-4277-5413, Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia

[°] Corresponding Author; Akhmad Kharis Nugroho
E-mail: a.k.nugroho@ugm.ac.id

INTRODUCTION

Immunotherapy has emerged as a leading-edge cancer treatment, with immune checkpoint inhibitors (ICIs), such as anti-PD-1/CTLA-4 antibodies, demonstrating remarkable clinical efficacy by enabling cytotoxic T cells to attack tumors (Wang, Ye, Hochu, Sadeghifar, & Gu, 2016). However, the systemic administration of ICIs is hampered by significant limitations, including severe immune-related adverse effects (irAEs) due to non-specific immune activation (Moreira et al., 2019) and suboptimal effectiveness, characterized by an objective response rate of only 20–33% in some advanced cancers (Lan et al., 2020). Poor pharmacokinetics is the leading cause of this limited effectiveness; less than 0.7% of systemically administered nanoparticle doses typically accumulate in tumors (Desai, Priya, Gorantla, & Singhvi, 2023).

In order to address the aforementioned challenges, a locally tailored delivery strategy is highly recommended. The use of transdermal delivery is a promising approach, but its application has historically been limited by significant inhibitions from the stratum corneum, which blocks the penetration of macromolecules such as antibodies (Chen et al., 2022). Microneedles (MNs) elegantly overcome this limitation. Microneedles, which are available in minimally invasive arrays measuring 50–1500 μm, have the capacity to create temporary microchannels for directly delivering a wide range of therapies—from small molecules to proteins and nanocarriers—to the immune cell-rich layers of skin (Desai et al., 2023; Moreira et al., 2019). This particular method of therapy administration offers significant advantages: increasing the concentration of local drugs at the tumor site, minimizing systemic exposure and irAEs, avoiding hepatic first-pass metabolism, and enabling patient-friendly self-administration to improve adherence (Moreira et al., 2019).

While MNs offer a superior delivery mechanism, their therapeutic effectiveness can be optimized by controlling drug release temporally and spatially. This can be achieved by integrating "smart" nanocarriers that are responsive to stimuli. These nanocarriers are engineered to undergo structural changes in response to exogenous triggers, such as light or ultrasound, or endogenous triggers typical of the tumor microenvironment (TME) (Hatakeyama, 2017). Pathological conditions of the TME—such as acidic pH, hypoxia, and excessive enzyme expression—provide an ideal trigger for releasing a specific drug payload at the tumor site (Li, Zhao, Su, & Shuai, 2020; Liu et al., 2025; Chen, Han, Du, Shi, & Zhou, 2023a). This mechanism enables the release of drugs restricted to the TME, thereby maximizing antitumor efficacy while minimizing systemic toxicity.

The convergence of MNs and stimulus-responsive nanocarriers presents advanced delivery systems (Permana, Mir, Utomo, & Donnelly, 2020). However, the complexity of their design—including MN geometry, polymer composition, and release kinetics—makes optimization through conventional experimental methodologies highly inefficient (Huanbutta et al., 2024; Yadav, Han, Olatunji, Pattanayek, & Das, 2020). The advent of artificial intelligence and machine learning (AI/ML) has ushered in a new paradigm for analyzing complex datasets to identify non-linear patterns that will enable predictive design approaches (Panchpuri, Painuli, & Kumar, 2025). In this context, AI/ML can be used to optimize formulations (Narayanan et al., 2021), predict the pharmacokinetics of hybrid systems *in silico* (Jia et al., 2025), and most transformatively, personalize therapies by integrating patient data to customize system design as well as predict treatment (Johnson et al., 2021).

The present review article aims to comprehensively analyze and synthesize the current state of this rapidly evolving field, in which the disciplines of drug delivery engineering, nanotechnology, immunology, and computational science converge. This review addresses four core research questions, focusing on the synergies between MN and TME-responsive nano-

carriers. It also outlines the role of AI in optimizing and personalizing these drug delivery systems. Additionally, it discusses the potential of multimodal theranostic platforms and critically evaluates the challenges hindering clinical translation. Ultimately, this article presents a vision for a future in which immunotherapy for cancer has evolved into a more potent, safer, and truly personalized approach, supported by the intelligent convergence of hardware (MNs and nanocarriers) and software (AI).

SYNERGY OF MICRONEEDLES AND TME-RESPONSIVE NANOCARRIERS FOR TARGETED CANCER THERAPY

Design principles and mechanisms of TME-responsive nanocarriers

The most common mechanism for pH-responsive nanocarriers involves chemical bonds that are stable at physiological pH but rapidly hydrolyze in the acidic TME. Bonds such as hydrazine, acetal, and ketal can attach drugs to polymers or hold together copolymer blocks in micelles or polymersomes. When the nanocarrier reaches the acidic TME, this bond is cleaved, leading to structural dissociation and drug payload release (Chu, Shi, Tian, & Gao, 2022; Liu et al., 2025). An alternative is to combine polymers with protonated groups, such as tertiary amines. At a neutral pH level, these polymers are hydrophobic and form a stable nanoparticle core. In acidic TMEs, amines become protonated and positively charged, leading to electrostatic repulsion, polymer swelling, and drug release (Gao, Chan, & Farokhzad, 2010; Hu et al., 2017).

A particularly relevant example is the development of a microneedle system that delivers pH-responsive lipid nanoparticles (NPs) targeted to tumors, loaded with cisplatin chemotherapy agents (CDDPs) and anti-PD-1 immunotherapy antibodies. In this system, anti-PD-1 is adsorbed to the NP surface via hydrophobic and electrostatic interactions. The pH-responsive lipid-coated cisplatin nanoparticles (LCC-NPs) release a higher amount of cisplatin in the tumor's acidic environment, achieving a drug loading efficiency of 80%. Microneedles enable nanoparticles to penetrate the stratum corneum for safe local delivery. This process enhances immune responses by targeting a substantial number of antigen-presenting cells (APCs) in the skin. The system has demonstrated a significant antitumor effect, with an apoptosis index of 73.2% observed in the anti-PD-1/CDDP@NP MN group, without systemic toxicity, nephrotoxicity, hepatotoxicity, or pulmonary toxicity (Lan et al., 2018, 2020).

Hypoxia-responsive nanocarriers often rely on bioreductive chemistry. Specific functional groups, such as nitroimidazole or azobenzene, are electronically stable under normoxic conditions. However, within hypoxic TMEs, these groups can be reduced by cellular enzymes (e.g., nitroreductase), which instigate chemical alterations. For example, the reduction of hydrophobic azobenzene to two hydrophilic aniline groups can lead to polymer micellar dissociation and drug release (Kulkarni, Haldar, You, Choi, & Mallik, 2016; Wang, Shang, Niu, Tian, & Xu, 2019; Zeng et al., 2018). A highly innovative strategy is to create temporal synergy, in which one therapy actively creates optimal conditions for the second. A pioneering study has developed a soluble MN-based cascade-activation nanoplatform for enhanced photodynamic therapy (PDT). The PDT is a treatment modality in which photosensitizers produce cytotoxic reactive oxygen species (ROS) following irradiation with light. However, the effectiveness of PDT is limited by pre-existing hypoxia in the TME and is further compromised by oxygen consumption during PDT (Kan et al., 2025). To address this, a micelle containing Ce6 and a hypoxia-activated prodrug, tirapazamine (TPZ), has been designed. The development of TPZ's cytotoxic properties is only observed under conditions of severe hypoxia. These micelles are then incorporated into MN hyaluronates, which are soluble in these micelles. When MNs are applied to a skin tumor and irradiated with a laser, the initial PDT consumes the remaining oxygen in the TME, creating a severe state of hypox-

ia. This therapy-induced state subsequently cascades to activate TPZ, eradicating hypoxic cancer cells that may exhibit resistance to early PDT. This approach has been demonstrated to convert the inherent weakness of PDT into a powerful trigger for a second therapy, yielding significant synergistic antitumor effects in models of melanoma and cutaneous squamous cell carcinoma (Ma et al., 2024).

Enzyme-responsive systems utilize the high biocatalytic activity of TME-specific enzymes. A standard design involves conjugating drugs to nanocarriers via peptide linkages that serve as substrates for target enzymes, such as matrix metalloproteinases (MMPs). When the nanocarrier reaches the TME, the MMP cleaves the peptide linker, releasing the active drug (Minehan & Del Borgo, 2022; Zhu, Kate, & Torchilin, 2012). A more sophisticated approach involves the development of a system capable of generating its own triggers through an enzymatic process at the right time. In an elegant study by Wang et al. (2016), a self-degradable MN patch for sustained delivery of anti-PD-1 was developed. The MN in question is composed of hyaluronic acid and has been integrated with pH-sensitive dextran nanoparticles. These nanoparticles encapsulate anti-PD-1 along with the enzyme glucose oxidase (GOx). When MN patches are applied to the skin, blood and interstitial fluid seep into the microneedle. Subsequently, GOx catalyzes the conversion of abundant glucose in body fluids into gluconic acid. This accumulation of gluconic acid locally lowers the pH in the MN microenvironment, triggering the gradual dissociation of dextran nanoparticles and sustained release of anti-PD-1 over several days. This intelligent enzymatic feedback system resulted in a significantly stronger antitumor immune response and higher survival rates in mouse melanoma models than free anti-PD-1 injections, demonstrating physiologically controlled local delivery power (Wang et al., 2016).

Mechanistically, MN arrays establish transient microchannels that bypass the SC and deliver responsive nanocarriers to immune-rich dermal strata, in which local TME cues actuate release (Chen et al., 2022; Waghule et al., 2019). In enzyme-coupled designs (e.g., GOx-loaded dextran NPs), glucose oxidation generates gluconic acid, which lowers the local pH level, accelerating NP disassembly and sustaining antibody release—linking substrate flux, enzymatic rate, and polymer pKa to a tunable, feedback-based kinetic profile (Wang et al., 2016). In temporal cascade platforms (e.g., PDT followed by hypoxia-activated TPZ), light-driven O_2 consumption intentionally deepens hypoxia to surpass TPZ activation thresholds, synchronizing spatiotemporal kill across normoxic and hypoxic niches (Ma et al., 2024). Core–shell MNs that tip-load fragile biologics concentrate payloads at the apex for efficient deposition and prolonged residence, which aligns with observed increases in local $CD8^+$ infiltration and tumor apoptosis versus systemic or intratumoral controls (Yang et al., 2020). Collectively, these mechanisms rationalize the reported *in vivo* outcomes (reduced tumor burden, higher ICD markers, enhanced antigen presentation) because the MN-mediated spatial precision and the TME-gated temporal control increase the intralesional effective dose while minimizing off-target exposure (Chen et al., 2020; Hu et al., 2025; Park, Seong, Han, Yang, & Hahn, 2021).

Comparative analysis: increased effectiveness and safety

As summarized in Table 1, microneedle- or MN-nanocarrier hybrid systems have demonstrated consistent superior therapeutic efficacy in comparison to conventional administration routes across various cancer models. In a squamous cell carcinoma homograft model, dissolving MNs co-delivering anti-programmed cell death protein 1 (anti-PD-1) and cisplatin resulted in the lowest tumor volume and weight among all treatment groups, with an apoptosis index of 73.2% and CD8+ T cell (a type of immune cell) infiltration reaching 75.95%. These outcomes were not achieved with systemic chemotherapy alone (Lan et al., 2020). In a murine model of breast cancer

(4T1), physiologically self-degradable MNs loaded with anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) and zinc phthalocyanine outperformed both photodynamic therapy and immunotherapy monotherapies, substantially increasing tumor-infiltrating T cells without inducing systemic immune impairment (Chen et al., 2020). In the colorectal xenograft model, dissolving MNs delivering imiquimod and cancer cell membrane proteins led to an 8-fold inhibition of tumor growth compared with the control at day 21, accompanied by significant increases in IFN-γ and TNF-α, and confirmed their *in vivo* biocompatibility (Park et al., 2021). In a metastatic lung melanoma model, polycarbonate MNs that release a plasmid ovalbumin (pOVA) DNA vaccine and polyinosinic:polycytidylic or poly(I:C), an immune stimulant, at a pH of 7.4 generated Anti-OVA IgG1 antibodies and CD8+ T cells at levels that were three times higher than those observed with soluble vaccine formulations, resulting in a 20% survival rate in the animal model after 60 days (Duong et al., 2018). Collectively, these findings indicate that the MN-nanocarrier format enhances immunotherapeutic responses by enabling spatially controlled, localized co-presentation of antigen and adjuvant to skin-resident antigen-presenting cells. Additionally, the transdermal route circumvents the systemic toxicity associated with parenteral immunotherapy delivery.

In addition to efficacy metrics, several studies in Table 1 introduced mechanistically distinct innovations that address limitations of conventional immunotherapy. Hu et al. (2025) reported that X-ray-responsive manganese zeolitic imidazolate framework-8 (Mn-ZIF-8) nanoparticles within dissolving MNs functioned as both a radiosensitizer (enhancer of radiotherapy) and stimulator of the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, promoting immunogenic cell death and enhancing innate immunity to achieve an abscopal effect in melanoma B16. This effect, wherein local treatment induces systemic tumor regression, is clinically significant. In a melanoma model incorporating cancer stem cells (CSCs), MNs composed of silk fibroin and mesoporous silica nanoparticles enabled heat-controlled, on-demand release of anti-PD-1 and ammonia borane over three days, eradicating the CD133+ CSC subpopulation and reversing immune evasion with minimal systemic toxicity (Yang et al., 2022). The core-shell MN (CSMN) design applied in melanoma B16 by Yang et al. (2020) addressed the limitations of conventional MNs in terms of drug loading by delivering protein to the tip, achieving retention times up to 48 hours, and CD3+/CD8+ T lymphocyte infiltration twice as high as with intratumoral injection at equivalent doses. This demonstrates that MN structural engineering is a significant efficacy variable. In murine prostate cancer (TRAMP-C1), MN-delivered RALA/pDNA nanoparticles induced IFN-γ secretion and cytotoxic lysis of TRAMP-C1 cells by splenocytes (immune cells from the spleen), representing the first platform for targeting endogenous prostate cancer antigens via transdermal DNA delivery and outperforming intramuscular injection of the same nanoparticle (Cole et al., 2019). These mechanistic advances demonstrate that MN-nanocarrier hybrids not only replicate but also surpass the immunological capabilities of conventional routes through stimulus-responsive release, prolonged local retention, and architectural optimization. Each of these features addresses a distinct aspect of the translational gap between the promise of preclinical

immunotherapy and clinical efficacy.

Table 1. Proof-of-concept study of microneedle-nanocarrier hybrid systems for *in vivo* cancer ımmunotherapy

Cancer model	Type of hybrid system	Drug loaded	Delivery Performance and Therapeutic Efficacy	Key findings	References
Squamous cell carcinoma with an immunocompetent murine tumor homograft	Dissolving MNs + pH-responsive lipid nanoparticles	Anti-PD-1 (immune checkpoint inhibitor) + Cisplatin (chemotherapy)	MN penetrated the mouse skin and dissolved within 20 minutes, releasing the drug. The antitumor effect produced the lowest tumor volume and weight, with an apoptosis index of 73.2%.	CD8+ T cell infiltration was highest (75.95%), and regulatory T cell suppression was observed in the TME. This observed system can overcome anti-PD-1 resistance and reduce toxicity compared to systemic chemotherapy.	(Lan et al., 2020)
Cutaneous melanoma B16	Dissolving MNs + x-ray sensitive Mn-ZIF-8	Anti-PD-1 (immune checkpoint inhibitor) + Mn-ZIF-8 (immunotherapy agonist, radiosensitizer)	MN successfully penetrates the skin to a depth of 300–340 μm, with a dissolution time of 8 minutes and drug retention in TME for 24 hours. This combination showed significant tumor growth control and suppression compared to other therapy groups.	X-ray-responsive Mn-ZIF-8 acts as a dual-functional radiosensitizer + cGAS-STING agonist. Promoted ICD and augmented innate immunity; Combined radio-immunotherapy achieved an abscopal effect.	(Hu et al., 2025)
Cutaneous melanoma B16	MN + hyaluronidase-sensitive core-shell structure	Anti-PD-L1 (immune checkpoint inhibitor) + 1-methyl-D,L-tryptophan (IDO inhibitor)	CSMN demonstrates superior transdermal delivery efficiency through a core-shell design that concentrates proteins at the needle tip, surpassing conventional MN. With a long retention time of up to 48 hours, antitumor efficacy is significantly better than with intratumoral injection at the same dose.	The core-shell structure overcomes the low drug-loading capacity of MN. The efficacy advantage of CSMN is also associated with the ability to recruit large numbers of T lymphocytes to the tumor site and with cytotoxic infiltration of T lymphocytes (CD3+, CD8+), 2 times more than in the control.	(Yang et al., 2020)
Melanoma with cancer stem cells	MN + silk fibroin + polycaprolactone + mesoporous silica nanoparticles	Anti-PD-1 + ammonia borane (prodrug resulting H2)	The system exhibits heat-controlled on-demand drug release, facilitating sustained release at the tumor site for up to 3 days, superior to intravenous injection. Synergistic hybrid systems produce highly potent sustained inhibitions with minimal systemic toxicity.	H2 therapy works to destroy the heterogeneity of CSCs and suppress their self-renewal. Significant therapeutic synergism eliminated the CSC population (CD133+) in tumors *in vivo* compared with the control group. CD8+ T cell infiltration is highest in tumors, signaling strong reverse immune evasion.	(Yang et al., 2022)

Colorectal carcinoma tumor xenograft	Dissolving MNs + polymeric nanoparticles	Imiquimod (R837) (TLR7 agonist) + Cancer cell membrane proteins (M)	The system demonstrated mechanical strength to penetrate the skin and dissolve (>90% in 60 s), resulting in the most significant tumor growth inhibition *in vivo* (8 times smaller than the control at day 21).	The system can stimulate immunity via M as a tumor-specific antigen and R837 as a TLR7 agonist adjuvant. This synergy is significant compared to monotherapy with either of the two. There is an increase in IFN-γ and TNF-α secretion. MN is proven to be biocompatible without *in vivo* toxicity	(Park et al., 2021)
Metastatic lung melanoma	Polycarbonate MNs + ultra-responsive pH + nanoengineered DNA	pOVA (DNA vaccine), Poly (I: C) (TLR3 agonist)	MN successfully penetrates the SC, a layer-by-layer system releasing >90% pOVA and Poly(I:C) at pH 7.4. The system showed suppression of lung metastatic tumor growth, with the highest survival rate (20% of animals survived up to 60 days).	MN vaccine outperforms soluble DNA vaccine formulations, producing Anti-OVA IgG1 antibodies and CD8+ T cells 3 times higher.	(Duong et al., 2018)
Murine prostate cancer TRAMP-C1	Dissolving MNs + cationic nanoparticles	RALA/pDNA	MN successfully delivers NPs into the skin, leading to local *in vivo* PSCA mRNA expression. The MN application significantly delays tumor formation and prolongs survival.	This study is the first to report on the use of a platform that targets endogenous prostate cancer antigens. There is an induction of IFN-γ and cytotoxic activity (lysis of TRAMP-C1 cells) by splenocytes. This system shows superior efficacy compared to intramuscular injection of the same NP.	(Cole et al., 2019)
Murine breast cancer 4T1	Physiologically self-degradable MNs + acetylated dextran nanoparticles	Anti-CTLA-4 (immunotherapy) + Zinc phthalocyanine (photosensitizer)	MN exhibits sufficient mechanical strength for skin penetration (~300 μm) and rapidly dissolves, releasing >80% of the drug in 10 minutes in a pH-responsive manner. The system showed the most significant and sustained tumor inhibition, outperforming PDT monotherapy (MNs + ZnPc + Laser) or immune monotherapy (MNs + aCTLA-4).	The synergy of PDT kills tumor cells (triggers antigen release) and then enhances the efficacy of subsequent aCTLA-4 immunotherapy. Combination therapy significantly increased tumor T cell infiltration and showed no systemic immune impairment (good safety profile).	(Chen et al., 2020)

Abbreviation: aCTLA-4 (Anti-Cytotoxic T-Lymphocyte-Associated Protein 4), Anti-PD-1 (Anti-Programmed Cell Death Protein 1), Anti-PD-L1 (Anti-Programmed Death-Ligand 1), IDO (Indoleamine 2,3-Dioxygenase), Mn-ZIF-8 (Manganese-Zeolitic Imidazolate Framework-8), pOVA (Plasmid Ovalbumin), TLR (Toll-Like Receptor), ZnPc (Zinc Phthalocyanine), ICD (immunogenic cell death), CSMN (core-shell microneedle), poly(I:C) (polyinosinic:polycytidylic acid), PSCA (prostate stem cell antigen), PDT (photodynamic therapy)

THE ROLE OF ARTIFICIAL INTELLIGENCE IN HYBRID SYSTEM OPTIMIZATION AND PERSONALIZATION

Designing and developing MN-nanocarrier hybrid systems is a highly complex multi-parameter undertaking. The success of the therapeutic intervention depends on the intricate interactions among MN geometry, material properties, nanocarrier chemistry, drug loading, and dynamic biological environments. Historically, such systems have been optimized through empirical approaches, characterized by low efficiency, high cost, and frequent inability to capture the nonlinear relationships that govern behavior *in vivo*. The advent of artificial intelligence (AI) and machine learning (ML) represents a paradigm shift from empirical design to predictive design, as evidenced in Table 2. These technologies empower scientists to engineer hybrid systems for optimal performance methodically and to personalize them for individual patients. The potential of AI to bridge the gap between the fundamental chemical properties of nanocomponents and their eventual fate and efficacy in complex biological systems is a transformative capability that traditional modeling has found difficult to achieve.

Table 2. The role of AI in the hybrid system development cycle

Development stage	AI technique used	Benefit
Nanoparticle design	Machine learning (ML), Generative Adversarial Networks (GANs)	Nanoparticle design optimization for drug delivery efficiency (Ali, Reza, Mandal, Chakraborty, Hossain, 2025), creating lipids with high encapsulation efficiency (Bhujel, Enkmann, Burgstaller, & Maharjan, 2025).
Microneedle optimization	Machine Learning (ML)	Optimization of microneedle design and fabrication methods (He et al., 2024), increased transdermal delivery efficiency (Yang et al., 2021).
Stimuli-responsive system development	AI-driven predictive models	Precision delivery through specific stimulus exposure (Tian, Xin, Wu, Guan, & Zhou, 2022), prediction of nanoparticle biodistribution (Bhujel et al., 2025).
Test and Validation	AI-powered analysis	Rapid analysis of the interaction of nanoparticles with immune cells (Ali et al., 2025), prediction of immune response to therapy (Seth, Ladbury, & Amini, 2025).
Personalized drug delivery	AI-enhanced drug delivery system	Development of drug delivery systems that are genetically and molecularly appropriate to patients (Sheikh & Jirvankar, 2024), identification of new T-cell targets and biomarkers (Seth et al., 2025).
Therapy Monitoring and Adjustment	Federated Learning Model, Quantum Machine Learning	Multi-institutional data sharing for therapy optimization and real-time prediction of formulation stability (Bhujel et al., 2025).

Machine learning in the optimization of nanocarrier and MN design

The application of ML algorithms to the synthesis of nanoparticles has enabled significant progress in the optimization of reaction conditions and the prediction of material properties. Random forests, Bayesian optimization, and deep neural networks have proven more effective than conventional methodologies, as evidenced by lower mean squared error (MSE) and higher R-squared values (Chakravarthi et al., 2024). Decision trees, random forest, and extreme gradient boosting (XGBoost) algorithms have been employed to determine the parameter space for advanced experiments, thereby improving model accuracy and synthesis results (Nathanael, Cheng, Kovalchuk, Arcucci, & Simmons, 2023). Bayesian optimization has been shown to navigate parameter spaces to identify optimal synthesis conditions efficiently (Chakravarthi et al., 2024; Wahl et al., 2021). Latin hypercube sampling, combined with in situ UV-Vis control, has enabled the systematic variation of reaction parameters and real-time monitoring of nanoparticle formation (Guda et al., 2023). Predictive models, such as Support Vector Regression (SVR), have demonstrated the ability to predict nanoparticle sizes in real-time applications accurately (Glänzer, Göpfert, Schmitz-Rode, &

Slabu, 2024). Regression algorithms have been shown to establish relationships between synthesis parameters and the desired endpoint, such as core size and its activity (Furxhi et al., 2024).

The integration of automation and ML has revolutionized process synthesis through a self-driving laboratory platform. Autonomous Fluidic Identification and Optimization of Nanochemistry (AFION) integrates microfluidic reactors with in-line spectroscopic and ML characterization to optimize plasmonic nanoparticle synthesis in closed-loop systems without human intervention (Wu et al., 2025). Self-driving laboratories, which are equipped with NMR spectroscopy, gel permeation chromatography, and dynamic light scattering, facilitate the exploration and optimization of the autonomous synthesis of polymer nanoparticles (Knox et al., 2025). This ML-based approach has been demonstrated to reduce optimization time by up to 30%, improve reproducibility, and support the development of scalable nanoparticles (Lafi et al., 2025). Its application has been extended to various nanoparticle types, including silver, gold, and magnetic nanoparticles, with the potential for expansion into more complex nanomaterials (Schletz, Breidung, & Fery, 2023; Tao et al., 2021; Xu et al., 2023).

One of the main goals in drug delivery is to ensure the efficient capture of the nanocarrier by the intended cell type while sparing healthy cells. ML has the potential to outline the design principles that govern these cell-specific interactions (Ritu et al., 2024; Panchpuri et al., 2025). Xu et al. (2024) tested the transfection efficiency of over 1,000 different lipid nanoparticle (LNP) formulations in various cell types. By applying ML models to these high-throughput datasets, meaningful relationships between LNP composition and efficacy were identified across various cell types. ML models have been shown to accurately predict the effectiveness of new LNP formulations. Furthermore, these models have been shown to lack quantitative design features that enable preferential gene delivery to specific cell types. These insights are invaluable for the design of nanocarriers that selectively target tumors or antigen-presenting cells within the skin (Chan et al., 2025; Mehradfar et al., 2025; Xu et al., 2024).

Safety is a fundamental consideration in the development of nanocarriers. The ML can be utilized to screen material candidates for potential toxicity during the early stages of the design process, conserving significant resources (Ahmadi, Ayyoubzadeh, & Ghorbani-Bidkorpeh, 2024; Cave et al., 2025; Hosni, Achour, Saadi, Chen, & Al Qaraghuli, 2025). A novel computational approach utilizes ML to predict the biocompatibility of metal-organic frameworks (MOFs) based on the chemical properties of their building blocks, namely metal centers and organic ligands. Menon & Fairen-Jimenez (2025) developed a tool capable of predicting the potential toxicity of MOF ligands with an accuracy of more than 80% by training classification models (e.g., Random Forests and gradient boosting machines) on an extensive database of known organic-molecule toxicity. Combining this with the metal's central toxicity database, they screened more than 86,000 known MOF structures to identify hundreds of promising candidates with minimal toxicity profiles. The employment of such predictive tools enables the rational design of safe nanocarriers from the outset.

Table 3 shows significant progress in integrating AI/ML algorithms into MN platforms. This progress spans many translational fields. In their study, Wang et al. (2026) used an artificial neural network coupled with an Internet of Things (ANN-IoT) system within a multi-material MN construct, which resulted in suppressed tumor burden and modulated the immune environment. The efficacy of the device was attributed to its ability to inhibit TNF-α and regulate reactive oxygen species, yielding strong preclinical therapeutic outcomes. Liu et al. (2026) built on the closed-loop approach, which employed extreme gradient boosting (XGBoost) and long short-term memory (LSTM) algorithms in a polypyrrole-based MN system to monitor inflammatory cytokines in real time and to ad-

just methotrexate release. This strategy yielded a ML classification area under the curve (AUC) of 0.787 and reduced inflammatory markers by at least 40%. Furthermore, it facilitated the development of a theranostic system suitable for tracking the TME. Albayati, Talluri, Dholaria, & Michniak-Kohn, (2025) optimized the formulation by using a deep neural network (DNN)-BioSIM-COMSOL pipeline. As a result, bioavailability was improved for several drug types, and a basis was established for individualized immunotherapy dosing within narrow therapeutic windows. In transdermal delivery for cancer, Suriyaamporn et al. (2025) employed random forests (RF), principal component analysis (PCA), support vector machines (SVM), and an ANN ensemble. They optimized a PEGylated liposome-hydroxypropyl-β-cyclodextrin (HPβCD) MN formulation for 5-fluorouracil delivery targeting non-melanoma skin cancer. Their method demonstrated 91.5% cancer cell apoptosis and 41.78% *ex vivo* permeation, indicating the potential of ensemble ML to address complex formulation challenges. In summary, the integration of AI within MN systems supports closed-loop sensing, adaptive release mechanisms, personalized multi-physics approaches, and ensemble optimization. The integration of AI and ML into microneedle platforms could establish a strong foundation for the development of next-generation microneedle platforms for cancer immunotherapy. However, none of these four studies have been validated in human clinical trials, suggesting the need for further *in vivo* research.

Table 3. AI/ML-integrated microneedle fabrication

Constituent Materials	Computational Methods Employed	Principal Objective	Target Agent / Sensing Analyte	Documented Outcomes	Identified Constraints	Prospective Directions	Reference
GelMA photo-crosslinked hydrogels, PLGA biodegradable microspheres, PVP matrices, composite metallic scaffolds, PEGDA networks, polydopamine coatings, graphene oxide, gold nanorods, black phosphorus, MOF particles	Artificial neural networks, logic-encoded adaptive control, IoT-coupled smart release actuators	Simultaneous multi-disease therapeutic delivery, real-time biosensing, and externally triggered drug release	Insulin, cytotoxic chemotherapeutics, reactive oxygen species modulators (ROS), TNF-α inhibitors, VEGF, nitric oxide (NO) donor	12-day continuous wound healing confirmed; tumor burden suppressed in preclinical models; strong multi-target therapeutic outcomes	Preclinical-only validation; absence of embedded AI algorithms; complex multi-component data acquisition infrastructure	Wireless AI-controlled MN microchips, full-wearable autonomous therapeutic platforms, and a clinical translation roadmap	(Wang et al., 2026)
Polypyrrole-functionalised MNs, PEGDA crosslinked matrix with conductive dopant incorporation	XGBoost gradient boosting classifier, LSTM temporal sequence learning	Autonomous closed-loop arthritis drug delivery with concurrent inflammatory biomarker surveillance	Methotrexate (MTX) — first-line DMARD; Rhodamine B as fluorescent release tracer	Paw edema reduction: ≥40%; pro-inflammatory cytokine suppression confirmed; ML classification AUC: 0.787	Classification accuracy ceiling at 76.74%; confined to rodent model; no multi-joint human data	Bidirectional closed-loop therapeutic platform, multiplexed cytokine panel sensing, progression to human clinical studies	(Liu et al., 2026)
Chitosan biopolymer, ethosomal lipid vesicles, phospholipid liposomes, PLA microparticles, hydrogel networks, metallic and biodegradable MN arrays	Deep neural networks (DNN), BioSIM pharmacokinetic simulator, COMSOL Multiphysics solver, K-nearest neighbours (KNN), support vector machine (SVM), ANN regression	Personalised transdermal pharmacotherapy with concurrent wearable physiological sensing	Acyclovir, SARS-CoV-2 vaccine antigen, insulin, lidocaine, fentanyl; wearable analytes: pH, skin temperature, hydration index	Reduced systemic adverse effects; adaptive dosing algorithm outperformed static regimens; enhanced transdermal bioavailability across drug classes	Training data biases; inconsistent benchmark standards; inter-individual skin variability; wearable system integration complexity	AI-nanoparticle synergistic platforms, real-time adaptive smart patches, IoT physiological feedback, AI-directed microfabrication workflows	(Albayati et al., 2025)
Photocrosslinked hydrogel MN patches incorporating PEGylated liposomes, hydroxypropyl-β-cyclodextrin complexes, and limonene as a permeation enhancer	Random forest regression, PCA feature selection, SVM classification, ANN predictive modeling	AI-directed topical chemotherapy delivery for non-melanoma cutaneous malignancies	5-Fluorouracil (5-FU) — a pyrimidine antimetabolite for basal and squamous cell carcinoma	Cancer cell apoptosis induction: 91.5%; *ex vivo* skin permeation: 41.78%; drug recovery efficiency: >90%	Limited to *in vitro*/*ex vivo* tissue models; manufacturing scale-up and batch-to-batch reproducibility are undemonstrated	Expanded oncological drug portfolio, continuous *in vivo* permeation monitoring, long-term stability, and shelf-life investigations	(Suriyaamporn et al., 2025)

AI-driven predictive modeling for pharmacokinetics and biodistribution in MN–nanocarrier hybrid systems

One of the most significant and costly challenges in drug development is predicting a candidate's *in vivo* behavior. The safety and efficacy of a drug are determined by its absorption, distribution, metabolism, excretion, and toxicity (ADME-Tox) profiles. The use of AI provides a suite of powerful tools for predicting these parameters early in the development process. By analyzing the structural and physicochemical features of the nanocarrier and its drug payload, the AI models can predict its pharmacokinetic and biodistribution profiles. These models are capable of estimating key metrics, including circulation half-life, accumulation in various organs (including off-target buildup in the liver and spleen), and potential toxicity (Makong Ekpan, Oluchi Ori, Sam Samuel, & Peter Egwuatu, 2024). This predictive ability significantly mitigates the necessity of conducting expensive, time-consuming, and often controversial animal studies. By tagging drug candidates with poor pharmacokinetic profiles or unacceptable toxicity at an early stage in the research process, the utilization of AI has the potential to expedite the development pipeline, conserve resources, and enable researchers to prioritize the most promising candidates (Ferreira & Carneiro, 2025).

Towards precision oncology: personalization of AI-based therapies

The most transformative application of AI lies in its ability to realize the promise of precision oncology. Rather than treating breast cancer, the goal is to treat specific patients' breast cancer, taking into account the unique molecular landscape of their tumors and their overall biology. Modern AI platforms can combine and analyze diverse datasets, including genomic data (Rahem & Al-Akayleh, 2024), transcriptomics, proteomics, radiological imaging (Fedorov et al., 2023), and electronic medical record data (e.g., treatment history, comorbidities) (Lin, 2024).

By identifying patterns in this multimodal data, ML algorithms can detect biomarkers that predict a patient's response to a particular therapy (Captier et al., 2025). A landmark study that analyzed data from over 78,000 cancer patients afflicted with 20 different types of cancer identified nearly 800 genetic alterations that directly influence survival outcomes. In light of these findings, Yuan, Feng, Ding, Yang, & Xu, (2025) developed an ML tool, the Random Survival Forest model, to predict how patients with advanced lung cancer will respond to immunotherapy based on their specific mutation profiles, including Kirsten rat sarcoma viral oncogene homolog (KRAS), neurofibromatosis type 1 (NF1), and tumor protein 53 (TP53).

The future of precision oncology goes beyond prediction of drug responses; the potential exists for the utilization of AI in the design of new, personalized therapies for each patient. The AI platforms have revolutionized CAR-T therapeutic design. These platforms have been instrumental in optimizing CAR construction, predicting patient responses and toxicities, and improving the stratification of patients afflicted with hematological malignancies and solid tumors. A process that previously required years can now be completed in weeks, a significant reduction in time that can be attributed to advancements in AI computing (Baena et al., 2025). The concept can be extended to MN-nanocarrier systems, where AI designs smart nanocarriers, such as stimulus-responsive nanoparticles, that adapt to TME characteristics, including acidity and hypoxia, ensuring on-target drug release while minimizing systemic toxicity (Masanam, Ramasamy, Vivekanandhan, & Narasimhan, 2026; Noury, Rahdar, Romanholo Ferreira, & Jamalpoor, 2025; Shirzad et al., 2025). This approach promises to improve efficacy and reduce side effects, but faces challenges in obtaining quality data, overcoming regulatory barriers, and addressing ethical issues related to data privacy and algorithmic bias (Marra et

al., 2025; Noury et al., 2025). The solution entails the development of Explainable AI (XAI) for transparency and regulatory trust (Bongurala, Save, & Virmani, 2025; Shirzad et al., 2025), and interdisciplinary collaborations of AI, nanotechnology, and oncology to realize the full potential of personalized cancer therapies (Bhoyar & Chandu, 2025; Noury et al., 2025).

Bridging the complexity of MN-nanocarrier design with AI

A critical gap in the current literature is the lack of synthesis between advanced hardware design and the computing potential of AI. The most innovative TME-responsive systems are not governed by simple Fickian diffusion; they are complex, nonlinear systems that traditional pharmacokinetic models cannot adequately predict. In such cases, AI plays an important role.

Case study 1 is a model of the kinetics of enzymatic feedback (Glucose Oxidase/GOx system). The GOx-based MN system developed by Wang et al. (2016) is one example of such a system. The system's release kinetics is a non-linear feedback system in which the release of anti-PD-1 (output) depends on a series of interrelated events: (a) the fluctuating rate of the patient's glucose diffusion (input); (b) the enzymatic reaction rate of GOx (which can be saturated); (c) the rate of gluconic acid production; (d) the pKa response curve of the dextran nanoparticles; and (e) the diffusion of the released anti-PD-1. The utilization of traditional PK models for predicting anti-PD-1 release is rendered almost infeasible. However, recurrent neural network (RNN) or similar deep learning models—which excel at time-series modeling—can be trained on both *in vitro* and *in vivo* data. Such a model can predict personalized *in vivo* anti-PD-1 release profiles obtained from patient data from a continuous glucose monitor.

Case study 2 focuses on optimizing temporal cascades (photodynamic therapy-tirapazamine/ TPZ system). The PDT-TPZ cascade by Ma et al. (2024) presents temporal optimization challenges. The success of PDT hinges on its capacity to consume oxygen efficiently, thereby inducing severe hypoxia that activates TPZ. There is a sweet spot: if the PDT is insufficient, hypoxia will not be achieved; if the PDT is excessive, TPZ may no longer be effective. The key parameters—light dose, photosensitizer concentration, O2 consumption rate, and pO2 threshold for TPZ activation—interact nonlinearly. ML models, such as those used to predict therapeutic responses, can be trained on *in vivo* hypoxia imaging data to predict optimal light dose regimens and drug concentrations. This ensures that cascades occur correctly, maximizing hypoxic and normoxic tumor cell killing.

Case study 3 pertains to the personalization of hardware design. As previously mentioned, AI has the capacity to personalize hardware selection. The Random Survival Forest model can be trained on both genomic data and proteomic data. For patients with elevated levels of matrix metalloproteinase-9 (MMP-9) as indicated by proteomic data, the AI model would recommend an MN-nanocarrier formulation with a peptide linker that can be cleaved by MMP-9. For patients with low MMP-9 tumors but highly acidic TMEs, the model would recommend pH-responsive particles. This represents a paradigm of smart pharmacy, in which AI does not merely optimize a single system but rather identifies the most suitable system for the specific patient.

While AI/ML models have demonstrated strong predictive utility for formulation performance and preliminary *in silico* PK/BD, most models remain contingent on the training domain and data quality. Consequently, external validation across laboratories, materials, and disease models is essential before clinical extrapolation. Accordingly, the statements herein should be interpreted as a synthesis of demonstrated capabilities in preclinical settings and forwardlooking perspectives rather than established clinical standards.

MULTIMODAL THERANOSTIC PLATFORM BASED ON MN-NANOCARRIER HYBRID SYSTEM

Theranostic concept

The theranostic platform represents a paradigmatic evolution in precision oncology through the integration of diagnostic and therapeutic capabilities. In contrast to the conventional approach of evaluating treatment effectiveness several weeks later, the theranostic platform provides real-time monitoring through the use of imaging techniques such as MRI, PET, and SPECT to visualize drug distribution and therapeutic response (Sharma, 2025). The employment of nanocarriers, which are equipped with imaging agents, allows healthcare workers to visualize biodistribution (Gupta, Sood, Fuhrer, Djanashvili, & Agrawal, 2022), ensure effective tumor accumulation, and dynamically optimize treatment strategies (Bauri et al., 2023). This integration enables personalized dosing at the optimum time, increasing efficacy while minimizing adverse effects. Local delivery via MN patches provides an added benefit for superficial tumors by ensuring a high concentration of therapeutic agents in the target area (Mendes, Lima, & Torchilin, 2018).

Application by nanocarrier type

Quantum dots (QDs) are semiconductor nanocrystals with outstanding optical properties (intense brightness and high photostability) (Babu & Paira, 2017). These properties render them superior fluorescent probes for bioimaging applications (Han et al., 2025). Therapeutically, QDs can act as photosensitizers in PDT, producing ROS (Uprety & Abrahamse, 2022), or convert light energy into heat for photothermal therapy (Han et al., 2025). Microneedle patches containing QDs deliver them with precision to the skin tumor via transdermal delivery, increasing penetration and therapeutic efficacy (Yin et al., 2025; Zhao, Duan, Liu, Xi, & Wu, 2023). External light penetration is most effective for enabling guided PDT imaging. Nonetheless, despite the encouraging outlook, challenges related to the toxicity of QDs, notably those containing heavy metals, along with the necessity for increased targeting specificity and regulatory approval for broad clinical adoption, must be addressed to fully actualize the potential of QD-based theranostic platforms.

Metal-organic frameworks (MOFs) are hybrid crystalline materials with a high degree of porosity, conferring them with an exceptional drug-loading capacity (Wang & Ding, 2020). Diagnostically, paramagnetic metal ions (e.g., Gd, Mn) can serve as nodes for converting MOFs into MRI contrast agents (Cai, Chu, Liu, & Wáng, 2015). Alternatively, porphyrin ligands can be used for PDT and fluorescence imaging (Shang et al., 2020). A study has reported that a dissolving microneedle patch that delivers a bimetallic MOF (Cu-Fe) nanosheet-based biocatalyst to the melanoma site, triggering a tiered catalytic reaction in the acidic TME to produce ROS, demonstrates the potential of MOFs in targeted catalytic therapy (Chen et al., 2023a). Notwithstanding their potential, the clinical translation of MOFs is encumbered by challenges related to scalability, stability, biocompatibility, and potential toxicity. These challenges require comprehensive investigations to ensure safety in biomedical applications (Kumar, Kumar, Jha, & Mathur, 2023) through *in silico* design.

Carbon nanotubes (CNTs) exhibit a significant degree of optical absorption in the near-infrared (NIR) region, a biological window through which light penetrates tissues with minimal absorption and scattering (Brito et al., 2024; Zhang et al., 2017). This property makes them excellent agents in photothermal therapy (PTT). The CNTs have been demonstrated to efficiently convert light energy into heat when exposed to NIR laser irradiation, resulting in a rapid local increase in temperature (Wang et al., 2018; Zhang et al., 2017). This localized hyperthermia has been shown to induce cancer cell death via protein denaturation and membrane damage (Zhang et al., 2017). Furthermore, their large surface area permits functionalization with

chemotherapeutic drugs, such as doxorubicin, and imaging probes, enabling synergistic chemo-photothermal therapy and real-time monitoring, thus establishing CNTs as versatile and potent theranostic platforms (Brito et al., 2024; Wang et al., 2018; Zhang et al., 2017).

Lipid nanoparticles (LNP) and Polymeric Nanoparticles (PNP) are the most established classes of nanocarriers, characterized by excellent biocompatibility (Kaur et al., 2024) and existing FDA/EMA approvals (Kaur et al., 2024). Despite their lack of intrinsic theranostic properties, they can be easily converted into theranostic agents through the encapsulation of therapeutic agents (drugs) and diagnostic agents (dyes, contrast agents) simultaneously (Maximilien, Beyazit, Rossi, Haupt, & Tse Sum Bui, 2016; Rezigue, 2020). However, clinical translations face significant challenges regarding morphological and biochemical changes in LNPs after *in vivo* administration that may affect stability and targeting (Kaur et al., 2024), the issue of entrapment efficiency and controlled release in PNPs (Baghel & Bhattacharya, 2022), as well as the need to address long-term biosafety, immunogenicity, and large-scale production issues to ensure a successful transition from laboratory research to clinical applications (Raka, Belemkar, & Bhattacharya, 2025; Raut et al., 2024).

Towards an AI-guided closed-loop system

The theranostic platform described facilitates both visualization and treatment. However, in practice, this process is often still human-mediated, entailing the doctor's observation (via imaging) and subsequent intervention (treatment). The true synthesis of this field lies in the merging of hardware (MNs and nanocarriers), software (AI), and sensors (theranostics) to create a truly autonomous smart patch. In this vision of the future, the system operates in a closed loop. A theranostic MN patch (e.g., one that uses an MRI-imageable metal-organic framework or quantum dot sensor) continuously senses real-time TME biomarkers (e.g., pH, oxygen levels, enzyme activity). The sensor data is fed directly to the embedded AI/ML model. The model analyzes the data, compares it with patient profiles, and determines in real time that an optimal drug-release regimen is required. The AI system then triggers the release of the appropriate drug dose from the stimulus-responsive nanocarrier on demand, likely via AI-controlled external triggers such as ultrasound or NIR irradiation. This closed-loop system exemplifies the pinnacle of smart pharmacy, transitioning from scheduled dosing to a truly dynamic and personalized administration that responds to tumor biology over time.

CLINICAL TRANSLATIONAL CHALLENGES AND COPING STRATEGIES

Systemic, regulatory, and manufacturing barriers to challenges for clinical translation

The translational journey of MN-nanocarrier hybrid systems from laboratory concepts to clinical applications faces complex regulatory, manufacturing, and safety challenges (Table 4.). From a regulatory perspective, these systems are classified as combination products requiring navigation through a complex approval framework, such as that set by the United States FDA. This classification requires the submission of integrated and comprehensive safety and efficacy data for all components (FDA, 2022). The primary strategy to address this issue is proactive, early engagement with regulatory bodies through pre-submission meetings to align expectations and data requirements, thereby preventing significant delays

Table 4. Clinical translational challenges and mitigation strategies

Domain	Barrier	Implications	Proactive strategies
Regulation	Classification of combination products, regulatory uncertainty for nanomedicines (Duvall, Wyatt, & Yeung, 2011)	Long and expensive approval pathways can cause potential delays in commercialization (Duvall et al., 2011)	Early engagement with regulators, case-by-case regulatory approach (Duvall et al., 2011; Kim et al., 2024)
Manufacturing GMP	Difficult sterilization processes, non-standard manufacturing processes (de Souza Cardoso Delfino et al., 2025).	Risk of batch failures (Zagalo, Silva, Silva, Simões, & Sousa, 2022), high production costs (de Souza Cardoso Delfino et al., 2025)	QbD and implementation of GMP standards (de Souza Cardoso Delfino et al., 2025; Zagalo et al., 2022)
Biocompatibility	Bioaccumulation of nanomaterials, long-term toxicity concerns (Khalid et al., 2025)	Potential regulatory hurdles (Khalid et al., 2025)	Safety-by-Design using AI (Elbagory, Marima, & Dlamini, 2021); surface modifications to enhance biocompatibility (Hulugalla et al., 2024)
Fabrication	Processing conditions that damage drug stability, scalability of production (Kim et al., 2017; Moradi et al., 2025)	Degradation of immunotherapeutics like antigens (Kim et al., 2017)	Use of biodegradable and non-toxic materials; Development of more efficient fabrication techniques (Kim et al., 2017; Moradi et al., 2025).
Characterization	Low encapsulation efficiency (Jose, Amra, Bhavsar, Momin, & Omri, 2018), suboptimal drug release profile (Yousaf, Ahmad, Mahmood, Khan, & Akhtar, 2025)	Inconsistent release hindering sustained immune activation (Yousaf et al., 2025)	Use of nanomaterials like graphene to improve performance and integrate MN with a nanocarrier for a better release profile (Moradi et al., 2025).
Stability	Low physical stability; Uneven drug release; Interactions with the immune system (Handa, Saini, Tripathi, Yadav, & Shukla, 2023)	Degradation during storage affects drug potency; Variable bioavailability in tumor microenvironments.	Use of fabrication techniques that reduce negative solvent interactions; Use of controlled release systems (Kim et al., 2017; Mohan, Nair, & Narayanasamy, 2025).

In manufacturing, the main challenge associated with microneedle-nanocarrier systems lies in the scalability of precision microneedle array production and compliance with Good Manufacturing Practice (GMP) standards, which guarantee batch-to-batch consistency (de Souza Cardoso Delfino et al., 2025; Gulcur, Whiteside, Fook, Rickens, & Riemer, 2019; Gülçür et al., 2021; Pahal et al., 2025). The complexity of the manufacturing process increases with the aseptic integration of the two components, in which the drug's stability, primarily biological in nature, must be preserved without compromising the integrity of the nanocarrier or the mechanical properties of the microneedle (Kheirieh, Abbasi, Malaekeh-Nikouei, Golmohammadzadeh, & Mousavi Shaegh, 2025; Pahal et al., 2025). In order to address these challenges, it is essential to implement a range of strategies. Firstly, the application of a quality-by-design (QbD) approach is required to identify and control critical parameters. Secondly, the adoption of sustainable manufacturing processes, such as micro-injection molding, is necessary (Gülçür et al., 2021). Thirdly, the use of gentler sterilization methods (López, Ravasio, González-Aramundiz,J. V, & Zacconi, 2023) and cutting-edge fabrication techniques, such as 3D printing, is essential to ensure product quality and reproducibility (Dabbagh et al., 2021; Han et al., 2024).

The long-term safety aspects and biocompatibility of nanomaterials are the most critical considerations in the development of theranostic platforms. The formation of corona proteins, which significantly alter the biodistribution, immune response, and nanopar-

ticle targeting efficiency (Hui et al., 2022; Z. Li, Wu, Zhang, & Gao, 2024), and the potential toxicity of degradation products, such as metal ions from QDs, CDs, or MOFs, require in-depth investigation (Sobhanan et al., 2020). A Safety-by-Design approach, which includes the selection of materials that are inherently biocompatible and biodegradable (Elbagory et al., 2021), as well as surface engineering using methods such as PEGylation to reduce protein adsorption, is considered key (Hulugalla et al., 2024). Furthermore, the utilization of AI/ML platforms to predict toxicity *in silico* based on precursor chemical properties can dramatically expedite the identification and rational design of safer nanocarriers (Huanbutta et al., 2024).

Practical and anatomical limitations of MN-mediated delivery

Despite the compelling preclinical evidence, MN-mediated cancer therapy faces several practical and anatomical limitations. The limited penetration depth, typically measuring only hundreds of micrometers, restricts direct access to deep-seated tumors (Zhang et al., 2025). Consequently, MNs are most effective for cutaneous or superficial lesions and for regional immunomodulation within skin-resident antigen-presenting cells (APCs), rather than for bulk delivery to visceral tumors (Shi, Yin, Zheng, & Cai, 2023). Moreover, the heterogeneity present within the TME, including spatial pH gradients, localized hypoxia, and variable matrix metalloproteinase (MMP) expression, can result in uneven trigger engagement and heterogeneous drug release across the lesion. Inter-patient differences in skin thickness, dermal composition, and local perfusion may further influence microchannel closure kinetics, residence time, and overall drug exposure (He et al., 2026; Simi, Pruthvi, Nagashree, Vishweshwaraiah, & Osmani, 2025). Addressing these challenges will likely require image-guided planning, such as mapping pH or oxygen partial pressure; adaptive dosing schedules; co-triggerable chemistries with broader tolerance windows; and standardized, regulator-aligned manufacturing controls.

From an engineering standpoint, the aforementioned limitations motivate the integration of imaging-informed placement (e.g., pH/pO_2 mapping), co-trigger chemistries (e.g., pH+enzyme or pH+NIR) with wider tolerance windows, and adaptive, image-guided dosing schedules. In parallel, regulator-aligned GMP workflows are necessary to ensure clinical suitability. These workflows cover aseptic integration of biologics with MN arrays, sterilization that preserves bioactivity, and validated shelf-life protocols without compromising nanocarrier integrity or MN mechanical strength. Collectively, these design-to-regulation linkages serve to reduce exposure variability and enhance the reliability of TME-restricted release.

CONCLUSION

Artificial intelligence (AI) is increasingly guiding the delivery of microneedle-mediated immunotherapy via stimulus-responsive nanocarriers. This development marks a rapid transition from theoretical speculation to active research, with the potential to transform cancer care by enabling localized delivery and responsiveness to the TME. In addition, the approach has been informed by computational design. The integration of nanotechnology, microneedles, and AI- or ML-driven predictive methods may enable more precise and personalized immunotherapy. Notwithstanding recent advancements, major translational challenges persist. These challenges include regulatory complexity, manufacturing scalability, and long-term biocompatibility of nanomaterials. Further challenges are posed by anatomical limitations on microneedle penetration and heterogeneity within the TME. Progress toward clinical adoption requires a collaborative effort among scientists, clinicians, engineers, and regulators operating within an integrated framework. The utilization of AI/ML models in preclinical settings has been shown to possess strong predictive utilities for formulation performance, pharmacokinetics, and biodistribution. However, the

majority of the models are highly dependent on the quality and domain specificity of their training data. Robust external validation by independent laboratories using diverse materials and disease models must be conducted prior to clinical implementation. The findings presented in this review represent a synthesis of current knowledge and future potential, rather than established clinical standards. Ongoing interdisciplinary collaboration and rigorous validation may enable the development of safer, more effective, and personalized cancer immunotherapy.

ABBREVIATIONS

aCTLA-4: anti–cytotoxic T-lymphocyte–associated protein-4 antibody; AI: artificial intelligence; AFION: Autonomous Fluidic Identification and Optimization of Nanochemistry; ANN: artificial neural network; APCs: antigen-presenting cells; aPD-1: anti–programmed cell death protein-1 antibody; aPD-L1: anti–programmed death-ligand-1 antibody; BD: biodistribution; BioSIM: biological systems pharmacokinetic simulator; CDDP: cis-diamminedichloridoplatinum(II)/cisplatin; $CD8^+$: cluster of differentiation 8–positive T lymphocyte; Ce6: chlorin e6 (photosensitizer); CSMN: core–shell microneedle(s); cGAS: cyclic GMP–AMP synthase; DMARD: disease-modifying antirheumatic drug; DNN: deep neural network; FDA: U.S. Food and Drug Administration; GANs: generative adversarial networks; GelMA: gelatin methacrylate; GMP: Good Manufacturing Practice; GOx: glucose oxidase; HPβCD: hydroxypropyl-**β**-cyclodextrin; ICD: immunogenic cell death; IFN-**γ**: interferon-gamma; IoT: Internet of Things; KRAS: Kirsten rat sarcoma viral oncogene homolog; LCC-NPs: lipid-coated cisplatin nanoparticles; LNP(s): lipid nanoparticle(s); LSTM: long short-term memory (recurrent neural network); ML: machine learning; MMP(s): matrix metalloproteinase(s); MN(s): microneedle(s); MOF(s): metal–organic framework(s); MRI: magnetic resonance imaging; NF1: neurofibromatosis type 1; NIR: near-infrared; NO: nitric oxide; NP(s): nanoparticle(s); NMR: nuclear magnetic resonance; OVA (pOVA): ovalbumin (plasmid ovalbumin for DNA vaccine); PCA: principal component analysis; PCL: polycaprolactone; PDT: photodynamic therapy; PEG: polyethylene glycol; PEGDA: poly(ethylene glycol) diacrylate; PK: pharmacokinetics; PK/BD: pharmacokinetics/biodistribution; PLA: polylactic acid; PLGA: poly(lactic-co-glycolic acid); PNP(s): polymeric nanoparticle(s); poly(I:C): polyinosinic:polycytidylic acid; PSCA: prostate stem cell antigen; PTT: photothermal therapy; PVP: polyvinylpyrrolidone; QbD: Quality-by-Design; QD(s): quantum dot(s); RF: random forest; ROS: reactive oxygen species; SC: stratum corneum; SVM: support vector machine; SVR: support vector regression; TME: tumor microenvironment; TNF-**α**: tumor necrosis factor-alpha; TP53: tumor protein 53; TPZ: tirapazamine; TLR(s): toll-like receptor(s); TLR3/TLR7: toll-like receptor-3 / toll-like receptor-7; UV–Vis: ultraviolet–visible spectroscopy; XGBoost: extreme gradient boosting; ZnPc: zinc phthalocyanine.

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AUTHOR CONTRIBUTION STATEMENT

KDAP: Conceptualization, investigation, resources, writing – original draft, writing – review & editing. APG: Conceptualization, writing – original draft, writing – review & editing. AKN: Conceptualization, supervision, writing – original draft, writing – review & editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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