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# 3D-Printed Microneedle-Based Localized Anti-PD-L1 Immunotherapy for Breast Cancer

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**Keywords**

Breast cancer, Triple-negative breast cancer, PD-1/PD-L1, Microneedles, 3D printing, Localized immunotherapy.

**Abstract**

Breast cancer especially triple-negative breast cancer is a significant clinical issue because of its aggressive nature, a lack of targeted therapy, high recurrence and metas rates. The use of immune checkpoint blockade with the programs of the PD-1/PD-L1 axis has proven to be a promising approach; nonetheless, systemic delivery has been linked with low response rates and immunologic adverse events. Local immunotherapy has thus received growing popularity as a tool to increase therapeutic efficacy at reduced systemic toxicity. This review will center on the recent use of 3D-printed platforms based on microneedles used on localized anti-PD-L1 immunotherapy in breast cancer. Microneedles provide an opportunity to deliver biologics into immunologically active skin strata with high concentrations of antigen-presenting cells and lymphatic networks in the least invasive way through the skin, which facilitates effective immune modulation. The development of new 3D printing technologies, such as stereolithography, digital light processing, and two-photon polymerization, has allowed a narrow control of the microneedle geometry, mechanical strength, and capacity to load drugs. These functions support long-term and localized rollout of immunological checkpoint restraints, enhance tumor reorganization, and raise the cytotoxic T-cell activities with lowered systemic exposure. The review is a critical treatise of the biological rationale, design, fabrication, immunological consequences and translational issues involved with 3D-printed 3D-microneedle-mediated anti-PD-L1 delivery. This article summarizes existing preclinical data and technological advances and identifies the promise of localized microneedle-based immunotherapy to address major shortcomings of traditional systemic therapies and to enable the development of more specific immuno-oncology of breast cancer.

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## 1. Introduction

Breast cancer is still amongst the most important health issues affecting the world as it is the most common cancer that is diagnosed in women and the most common cause of death related to cancer around the world. Although significant advances have been made in screening, molecular classification and multimodal approaches to treatment, cancer of the breast is on the increase especially in the low and middle income countries where access to early diagnosis and advanced care is limited. It is a very heterogeneous disease, which includes several molecular subtypes, each having different biological behaviours, different therapeutic vulnerabilities and different clinical outcomes [1]. Out of them, the most well-known and aggressive and difficult to treat subtype is triple-negative breast cancer (TNBC).

TNBC is characterized by lack of expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2, excluding the application of endocrine or HER2 based therapies. TNBC is often characterized by high speed of disease progression, early recurrence, high rates of distant metastasis and poor survival, which is why there is an urgent unmet need in new treatment methods that are not based on traditional chemotherapy [2].

Immunotherapy has taken a new direction in the treatment of cancer in recent years and has become a promising treatment method in cancer, especially in immunogenic types like TNBC. Evidence of Tumour-infiltrating lymphocytes, a comparatively high mutational load and enhanced expression of immune checkpoint molecules in TNBC give a potent biological justification of immune-based interventions. However, breast tumours have developed advanced ways of avoiding immune surveillance, which allows them to grow and metastasize over time despite the existence of an active immune system [3]. One of the most obvious immune evasion mechanisms utilized by cancer cells of the breast is the programmed cell death protein 1 (PD -1) and the programmed death ligand 1 (PD -L1) signalling axis. In the physiological conditions, the interactions between PD-1/PD-L1 serve as an immune checkpoint to ensure self-tolerance and inhibit hyper-immune responses. Aberrant overexpression of PD-L1 on tumour cells and tumour-associated immune cells negatively regulates cytotoxic T-cell activity, causes T-cell exhaustion, and inhibits antitumour immune responses facilitating immune escape in cancer [4], [5].

Immune checkpoint blockade PD-1/PD-L1 has been employed to treat cancer and its clinical translation has become a milestone in cancer treatment. PD-1 or PD-L1 mAbs have shown long-term response and survival rates in a variety of malignancies and have been included in the therapy of selected patients with breast cancer, especially those who have metastatic TNBC and express PD-L1. However, the general response rates are low and most of the patients do not experience long-term benefit. A number of reasons explain this small efficacy such as heterogeneity of tumours, immunosuppressive tumour microenvironment and poor drug accumulation in tumour tissues [6]. Furthermore, immune checkpoints inhibitors administered systemically are commonly linked to immune-related adverse events induced by immune activation on a global scale impacting the skin, gastrointestinal tract, liver, endocrine glands, and lungs. Not only do these toxicities impair the quality of life of a patient but also limit dosing and the therapeutic index of immune checkpoint blockade [7].

These issues have led to the growing interest in alternative delivery methods that can be used to improve the treatment efficacy and reduce the systemic toxicity. The localised immunotherapy has become of specific interest as one such technique because it attempts to localise immune-modulating agents to the tumour site or its immediate microenvironment, at which point immune suppression is most intense. Localised delivery can enhance the amount of antitumour immunity in the local tumour area and limit off-target immune responses by limiting exposure to drug to the tumor site [8]. This approach is particularly applicable to solid tumours like breast cancer where there might be no need to actively activate the immune system systemically to provide any significant therapeutic effect. Localised immune checkpoint blockade can re-model tumour microenvironment, trigger the infiltration and activation of effector immune cells, and result in long-term antitumour immunity using much lower doses of drugs [9], [10].

Microneedle-based systems have drawn much attention among other localised delivery platforms due to their special capability of linking transdermal drug delivery with immunomodulation. Microneedles are micron size projections that can be painlessly inserted into the stratum corneum and introduce therapeutic agents into the epidermal and dermal layers of the skin. Immune cells such as dendritic cells, macrophages and lymphatic vessels in large quantities are found in these layers of the skin, partaking vital roles in antigen presentation and immune activation [11]. Making use of this immunologically active environment, the microneedles are potentially applied as drug delivery systems, as well as immune-interfacing systems that promote both local and systemic antitumour immune responses. It has been demonstrated through preclinical research that microneedle-mediated delivery of immune checkpoint inhibitors has been able to provide sustained local release to drugs, improved immune activation, and antitumour efficacy over systemic delivery [12].

Micro-needle design which determines geometry, mechanical strength, material composition, and drug-loading capacity have a strong impact on the efficacy of microneedle-based immunotherapy. Early efforts in this direction have been enabled by traditional methods of making microneedles, including micromoulding, lithography and etching which are often limited by inflexible design requirements, multi-step manufacturing and lack scalability [13]. These limitations inhibit accurate regulation of microneedle architecture, which is essential to optimise skin penetration, drug delivery depth and release kinetics. In this regard, one can refer to the use of three-dimensional (3D) printing as a revolutionary technology in production of microneedles since it allows to control the geometry of the needles and their tips, their distance, and arrangement of the array, allowing to systematise the optimisation of mechanical and functional characteristics [14].

In addition to geometric accuracy, 3D printing is associated with a number of benefits compared to traditional fabrication, including rapid prototyping, high level of reproducibility, and the ability to work with a vast assortment of biodegradable and

biocompatible material. These properties are applications, the most important aspects of which are the maintenance of antibody bioactivity, controlled release, and patient safety. Besides, 3D printing also enables scalable manufacturing, as well as paves the way to the more personalised microneedle design to fit the tumour location, size and the anatomical characteristics unique to the patient [15]. Notwithstanding these benefits, the use of the 3D-printed microneedle systems to treat breast cancer with the use of localised immune checkpoint blockade is still a novel area, and an all-encompassing synthesis of the existing developments, challenges, and future prospects is yet to be performed [16].

There is a major gap in knowledge of the rational design of geometry-controlled, 3D-printed microneedle platforms, which are specifically designed to address localized anti-PD-L1 immunotherapy in breast carcinoma [17]. Although the feasibility of microneedle-based delivery of immune checkpoint inhibitors has been demonstrated in isolated studies, few have comprehensively studied the geometry of the microneedle, choice of material, and release kinetics to understand the effects of microneedle delivery on immune activation, tumor microenvironment regulation, and therapeutic response in breast cancer models. In addition, the translational capability of such systems such as manufacturing scalability, regulatory implications and clinical applicability have not been fully addressed [18].

The review aims at addressing these gaps to offer an integrated and critical review of 3D -printed, microneedle-based localized anti-PD-L1 immunotherapy in breast cancer. Through the analysis of biological rationale behind immune checkpoint blockade, limitations of systemic immunotherapy, and the emergence of micro-needle and additive manufacturing technologies, the article outlines the possibilities of the localized approach to delivery to transform breast cancer immunotherapy. By both summarizing existing data and elaborating on potential future opportunities, this review will provide information to guide the rational design and clinical implementation of the next generation, microneedle-based immunotherapeutic devices in breast cancer treatment [19].

## 2. Methodology for review

### 2.1. Literature Search Strategy

The literature search was conducted thoroughly and systematically to retrieve the research work that covers the topics of immune checkpoint blockade, microneedle-based drug delivery systems, and three-dimensional printing technologies in the context of breast cancer immunotherapy. To find peer-reviewed articles, reviews, and key reports, mainly of the last ten years or more, the primary biomedical databases such as PubMed, Web of Science, Scopus, and Google Scholar were interrogated. The search terms used included the following combinations of keywords and Boolean operators: the breast cancer, triple negative particularly useful in immunotherapeutic breast cancer, PD-1, PD-L1, immune checkpoint inhibitor, localized immunotherapy, microneedles, 3D printing. Moreover, hand-screening of reference lists of highly-cited and current review articles was done to identify any relevant publication that could have been missed by database retrieval.

### 2.2. Selection and Eligibility Criteria of the study

The inclusion and exclusion criteria were used to select the studies in line with the predefined inclusions and exclusions, to achieve relevance and scientific rigor. The included articles were original research articles, preclinical/translational studies, and high-quality review articles, which included at least one of the following aspects; PD-1/PD-L1-induced immune evasion in breast cancer, systemic versus localized immune checkpoint blockade, microneedle-based drug delivery platforms, or 3D printing technologies in biomedical applications. Special attention was given to articles with models of triple-negative breast cancer and local immunotherapeutic approaches. Articles that were not in English, abstracts of conferences that did not contain full text, editorials, and studies that did not provide adequate information on their methodology were sidelined. Even in studies where microneedle-based delivery was not explicitly assessed, clinical trial data regarding immune checkpoint inhibitors in breast cancer were included to place them in context.

### 2.3. Data Synthesis and Extraction

The relevant data were independently obtained based on the chosen articles in terms of the purpose of the studies, the model of the experiment, the techniques of delivery, the characteristics of the design of microneedles, the method of producing them, the immunological results, and the important conclusions. In case of studies with microneedle systems, one paid a particular focus to microneedle type, materials used, geometry, drug-loading methods, and release features. Details regarding immune responses, i.e., T-cell infiltration, cytokine secretion, and tumor growth inhibition were also systematically summarized. An alternative method adopted to do the quantitative meta-analysis was the qualitative and narration synthesis in place of the heterogeneity of designs of the studies, models of the experiment and the outcomes measures. This methodology made it easier to critically compare the studies and find the common tendencies, strengths, and weaknesses in the area.

### 2.4. Inclusion and Exclusion Criteria

Peer-reviewed original research articles, preclinical studies, translational studies, and authoritative review papers addressing PD-1/PD-L1-mediated immune evasion in breast cancer, immune checkpoint blockade approaches, microneedle-based drug delivery approaches, or 3D printing technologies to biomedical or immunotherapeutic use were included in this review. The priority was given to the studies on breast cancer and triple-negative breast cancer, as well as on localized or

transdermal immunotherapy. Clinical trial reports of cancer to give some translation. The exclusion criteria included publication not in English, abstract of a conference without full-text access, editorial, commentary and publications that did not provide adequate methodological details or were not relevant to immune checkpoint inhibition, microneedle-based applications, or breast-cancer-specific applications.

### 3. Immune Evasion in Breast Cancer

PD-1 and PD-L1 are programmed cell death protein 1 (PD-1) and its antigen which form a major immune checkpoint pathway that is key in controlling immune homeostasis in physiological setting. PD-1 is an inhibitory receptor that is found mainly on activated T cells, B cells, and natural killer cells, but PD-L1 is found on antigen-presenting cells and a host of non-hematopoietic tissues. Stimulation of PD-1 by PD-L1 conveys inhibitory messages which cut off the signaling of T-cell receptors, cytokine generation, and T-cell expansion [20], [21].

PD-L1 expression by breast cancer cells and tumor-associated stromal and immune cells may be increased by inflammatory factors within the tumor microenvironment, including interferon- G. This adaptive response increases enable tumors to resist antitumor immunity by causing T -cell exhaustion and functional impairment. Besides inhibiting the effector T-cell functions, the PD-1/PD-L1 signaling enhances expansion of regulatory T cells and facilitates an immunosuppressive tumor micro environment. [22].

PD-L1 may be expressed by tumor cells and by tumor immune cells, and is associated with significant clinical implications. Although PD-L1 positivity has PD-1/PD-L1 inhibitors were also relevant in breast mostly been linked to aggressive features of the disease, it is also a predictive biomarker of responsiveness to immune checkpoint inhibitors, which has determined a patient subset capable of being responsive to immunotherapy [23].

Figure 1 illustrates the mechanistic regulation of antitumor immunity through immune checkpoint interactions during both the priming and effector phases. In the priming phase, dendritic cells (DCs) present tumor-associated antigens to naïve T cells via major histocompatibility complex (MHC) molecules engaging the T-cell receptor (TCR). Effective T-cell activation requires co-stimulatory signaling, particularly the interaction between B7 on dendritic cells and CD28 on T cells [24]. However, inhibitory receptors such as CTLA-4 compete with CD28 for B7 binding, attenuating activation signals and limiting T-cell expansion. Thus, blockade of CTLA-4 restores activation and promotes clonal proliferation of tumor-specific T cells. In the effector phase, activated T cells recognize cancer cells through TCR–MHC interactions and mediate cytotoxic attack. Tumor cells frequently overexpress PD-L1, which binds PD-1 on T cells and induces functional exhaustion, reducing cytokine production and cytolytic activity. Blocking PD-1/PD-L1 signaling reverses this suppression, reinvigorating effector function and enhancing immune-mediated tumor destruction. Figure 1 therefore integrates checkpoint regulation at two critical stages of the immune response, highlighting how CTLA-4 and PD-1/PD-L1 blockade synergistically restore antitumor immunity and improve therapeutic outcomes in cancer immunotherapy [25], [26].

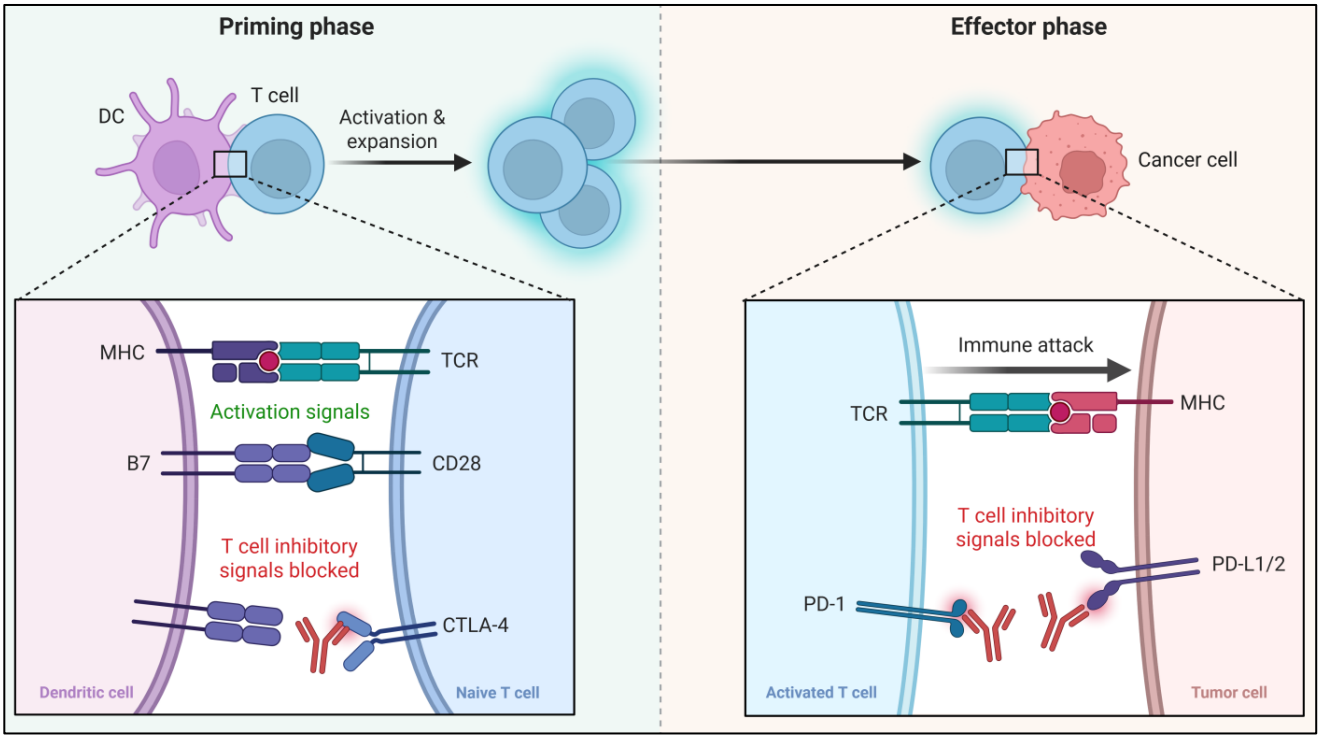


**Figure 1: Mechanistic overview of immune checkpoint regulation during the priming and effector phases of antitumor immunity;** CTLA-4 limits T-cell activation in priming, while PD-1/PD-L1 suppresses effector function; blockade restores antitumor immunity.

PD-1/PD-L1 axis is a very important way the breast cancer cells avoid the host immune surveillance system, which turns out to be the combination of antitumor immune responses suppression. PD -L1 is expressed not only in tumor cells but also in tumor-associated macrophages, dendritic cells, endothelial cells, and cancer-associated fibroblasts, as summarized in Table 1, which indicates how the immune checkpoint acts systemically in the tumor microenvironment [27]. The interaction of PD-1 with $CD8^+$ and $CD4^+$ T cells can cause functional exhaustion, decrease cytokine release, and dysfunctional cytotoxic ability, which allows tumors to survive immune infiltration. PD-L1 expression in aggressive subtypes like triple-negative breast cancer is also enhanced by inflammatory cytokines and hypoxic stress via PI3K/AKT, MAPK, and NF-b signaling pathways, which contributes to adaptive immune resistance [28]. Moreover, exosomal PD-L1 mediates long-range immune suppression which is further extended out of the primary tumor site. The combination of these various mechanisms forms an immunosuppressive niche that dominates tumor growth and resistance to therapy. Table 1 incorporates cellular, molecular, and microenvironmental factors in immune escape to provide a mechanistic model whose interplay with PD-1/PD-L1 signals has been linked to such clinical outcomes as poor prognosis and resistance to systemic immunotherapy. This holistic discussion highlights the importance of the need and focus of exploring the use of localized delivery approaches to interfere with immune suppression with minimal systemic toxicity [29].

**Table 1:** Role of the PD-1/PD-L1 Axis in Immune Evasion in Breast Cancer

| S. No. | Immune Component | PD-1/PD-L1 Mechanism | Cellular Location | Effect on T Cells | Impact on Tumor Microenvironment | Clinical Relevance | References |
|---|---|---|---|---|---|---|---|
| 1. | Tumor cells | PD-L1 overexpression | Tumor surface | Induces T-cell exhaustion | Promotes immune escape | Predictive biomarker | [30], [31] |
| 2. | $CD8^+$ T cells | PD-1 upregulation | Tumor infiltrate | Reduced cytotoxicity | Weakens tumor killing | Therapy response indicator | [32] |
| 3. | $CD4^+$ T cells | PD-1 signaling | Tumor stroma | Impaired helper function | Reduced immune coordination | Poor prognosis | [33] |
| 4. | Regulatory T cells (Tregs) | PD-1/PD-L1 activation | Tumor niche | Suppresses effector T cells | Enhances immunosuppression | Resistance mechanism | [34], [35] |
| 5. | Tumor-associated macrophages | PD-L1 expression | Tumor core | Inhibits T-cell activation | Maintains suppressive milieu | Target for combination therapy | [36], [37] |
| 6. | Dendritic cells | PD-L1 upregulation | Tumor-draining lymph nodes | Impaired antigen presentation | Weak immune priming | Limits immunotherapy | [38] |
| 7. | Myeloid-derived suppressor cells | PD-L1 secretion | Tumor vasculature | Blocks T-cell expansion | Sustains immune tolerance | Associated with metastasis | [39] |
| 8. | Interferon-γ | Induces PD-L1 | Tumor cells | Feedback inhibition | Adaptive immune resistance | Explains transient responses | [39], [40] |
| 9. | Hypoxia (HIF-1α) | Activates PD-L1 gene | Tumor core | Promotes T-cell dysfunction | Supports aggressive phenotype | Poor survival association | [41] |
| 10. | EMT signaling | Increases PD-L1 | Tumor margins | Immune escape | Enhances invasion | Metastatic progression | [42], [43] |
| 11. | PI3K/AKT pathway | Stabilizes PD-L1 | Tumor cytoplasm | Blocks immune killing | Promotes growth | Drug resistance link | [44] |
| 12. | MAPK signaling | Regulates PD-L1 | Tumor cells | Dampens immunity | Supports immune evasion | Therapeutic target | [45] |
| 13. | NF-κB pathway | Drives PD-L1 transcription | Tumor nucleus | Immune inhibition | Chronic inflammation | Predicts checkpoint | [46], [47] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | response | |
| 14. | Exosomal PD-L1 | Systemic PD-L1 delivery | Blood circulation | Systemic T-cell suppression | Distant immune evasion | Biomarker potential | [46] |
| 15. | Cancer-associated fibroblasts | PD-L1 secretion | Tumor stroma | Blocks infiltration | Physical immune barrier | Therapy resistance | [48], [49] |
| 16. | PD-L1 glycosylation | Enhances stability | Tumor membrane | Sustained T-cell inhibition | Persistent immune escape | Drug sensitivity modulator | [50] |
| 17. | Tumor vasculature | PD-L1 expression | Endothelium | Prevents T-cell trafficking | Immune exclusion | Limits infiltration | [51] |
| 18. | Cytokines (IL-10, TGF-β) | Induce PD-L1 | Tumor immune cells | Suppress immunity | Immunosuppressive niche | Predicts poor response | [52], [53] |
| 19. | TNBC subtype | High PD-L1 expression | Tumor/immune cells | Immune checkpoint dominance | Inflamed but suppressed | Best candidate for ICIs | [54] |
| 20. | Luminal breast cancer | Low PD-L1 expression | Tumor cells | Limited immune engagement | Cold microenvironment | Poor ICI response | [55] |
| 21. | PD-L1 gene amplification | Increases PD-L1 levels | Tumor genome | Strong immune inhibition | Aggressive behavior | Poor prognosis | [56], [57] |
| 22. | PD-1$^{+}$ exhausted T cells | Sustained PD-1 signaling | Tumor infiltrate | Dysfunctional immunity | Chronic immune failure | Target of therapy | [58] |
| 23. | Therapy-induced PD-L1 | Chemo/radiation induced | Residual tumor | Immune adaptation | Treatment resistance | Combination rationale | [59], [60] |

Despite the above rationale, the clinical efficacy of PD-1/PD-L1 inhibitors in breast cancer has been relatively small when compared to its use in other high immunogenicity malignant cancers including melanoma or non-small cell lung cancer. PD-L1-positive metastatic triple-negative breast cancer (TNBC) Pembrolizumab and atezolizumab (2010) Randomised controlled trial (RCTs) demonstrated statistically significant progression-free survival advantage of the two inhibitors with chemotherapy in PD-L1-positive metastatic disease, thus gaining regulatory approvals under specific clinical conditions. However, general response rates have been suboptimal and a significant percentage of patients fail to respond or acquire resistance. The factors that lead to these results include intratumoral heterogeneity of PD-L1 expression, small infiltration of functional cytotoxic T lymphocytes, and the stimulation of other immunosuppressive pathways in the tumour microenvironment [61], [62].

Moreover, the systemic delivery of PD-1/PD-L1 inhibitors is often accompanied by immune -adverse events, which are caused by systemic activation of the immune system and can limit the duration of treatment and its severity. The challenges highlight the need to consider new approaches that would help enhance the effectiveness of immune checkpoint blockade and reduce systemic toxicity. A deeper rationalization of PD -L1 -based immune escape the mechanisms of breast cancer, especially TNBC, is the basis of biological justification of the development of local and targeted delivery strategies to bypass the immune inhibition and achieve better therapeutic results [63].

## 4. Microneedle-Based Platforms for Cancer Immunotherapy

Microneedle based systems form a flexible category of transdermal delivery systems designed to enter the stratum corneum with no pain, and deliver therapeutic agents to viable epidermis and dermis. Micro needles can be categorized into solid, coated, dissolving and hydrogel forming according to their structural composition and material composition. The major functions of solid microneedles are to form transiently created microchannels through which drugs can then diffuse, and coated microneedles, which conveys drugs that have been adsorbed onto the microneedle surface. The design criteria of the microneedles such as length, tip sharpness, base width and array density are the key determinants on insertion efficiency, mechanical stability and drug delivery efficiency. These parameters can be accurately controlled to allow microneedle systems to be optimized to particular immunotherapeutic uses, such as local immune checkpoint blockade [64].

The skin is an immunologically active organ that is

abundant in professional antigen-presenting cells macrophages and a highly developed system of lymphatics. Such unique immunological environment makes the skin an interesting site of immunotherapeutic intervention. Micro needling of immune-modulating agents leads to direct contact with immune cells residing on the skin, and, consequently, antigen absorption, immune priming, and subsequent activation of systemic antitumour responses. Microneedle-mediated delivery in cancer immunotherapy: This immunological niche is exploited by capitalizing on controlled exposure to off-target tissues and is enhanced by immune activation to a maximum in this immunological niche [65]. The microneedles compared to conventional subcutaneous or intratumoral injections, offer a more uniform and reproducible interface of delivery and minimize tissue damage. This mode of delivery based on immunomodulation delivery is especially beneficial to immune checkpoint inhibitors, where localized immune signaling therapies in tumor proximate or tumor-draining lymphatics can be effective to reinvigorate exhausted T cells, as well as to remodel the tumor microenvironment without triggering a systemic immune response [66], [67].

Microneedle platforms have a number of benefits that make them potential promising agents of the cancer immunotherapy. They are less invasive and may be self-administered, which increases compliance with patients and decreases the burden of the repeated visits to clinics. Pharmacologically, microneedles enhance the high local drug concentrations and long retention at the site of delivery, which is critical in optimizing the effectiveness of immune checkpoints inhibitors. This is an efficient localized delivery method with the ability to significantly decrease the overall therapeutic dose, which acts to decrease systemic-toxicity and immune-adverse events that come with systemic immunotherapy [66]. Preclinical research has revealed that the immune checkpoint inhibitors, vaccines and immune adjuvants delivered using a microneedle method can induce powerful antitumor immunity, enhance cytotoxic T-cell invasion, and promote better tumor control compared to systemic delivery. Despite the fact that most research is at the preclinical phase, the overall evidence supports the hypothesis of the microneedle-based platforms to overcome the main limitations of traditional immunotherapy. With the development of the materials science and fabrication technologies, microneedle systems are increasingly being acknowledged as a revolutionary means of interface between drug delivery and cancer immunoengineering [68], [69].

## 5. 3D Printing Technologies for Microneedle Fabrication

### 5.1. Stereolithography

One of the oldest and most widely used additive manufacturing processes in the microneedles fabrication is called stereolithography (SLA), as it is highly resolution-based, reliable, and compatible with a large number of photo-curable polymers. In including Langerhans cells, dermal dendritic cells, SLA, a layer-by-layer polymerisation of liquid resin is selectively caused by a focused ultraviolet (UV) laser based on computer-aided design (CAD) models. The laser is used to irradiate the resin surface in pre-programmed patterns inducing localised photopolymerisation thereby allowing the creation of three-dimensional microstructures with well-defined geometries. In the case of microneedle fabrication, SLA is adequately resolution-rich enough to form sharp pointed tips, high aspect ratio features and mechanically robust arrays that are amenable to transdermal insertion [70].

The wide usage of SLA has enabled the production of solid and hollow microneedles with a well-defined height, base diameter, and inter-needle spacing. The common thickness of the layers (10 to 50 μm) allows reproducibly making microneedles that can pierce the stratum corneum without breaking. The method has specific benefits where a prototype can be created quickly with the design parameters that can be adapted and optimised repeatedly without the need of new moulds or templates. In addition, SLA allows fabricating microneedle arrays in batch with strong dimensional consistency, which is of high potential importance to translational studies [71].

However, SLA has its own weaknesses that are applicable in immunotherapeutic uses. Photopolymer resins regularly used in SLA can prove to be poor in biodegradability or biocompatibility and thus require careful selection of materials and post-processing. Also, the light scattering and the size of the laser spot can limit the sharpness of the tip that can be achieved compared to finer methods. Nevertheless, SLA still remains a feasible and scalable fabrication approach to micro-needle systems and is particularly appropriate to initial development and pre-clinical testing of localized immunotherapeutic platforms [72].

### 5.2. Digital Light Processing

Digital Light Processing (DLP) is a new technique of vat photopolymerisation which has received increasing attention to the microneedle fabrication due to its high printing rate, fine resolution, and excellent reproducibility. Unlike SLA that relies upon point-by-point laser scanning, DLP makes use of a digital micromirror element to expose an entire light pattern on the resin surface, which immediately cures a full layer. The technique demonstrates a significant shortening of the fabrication time with a fine resolution of features making DLP particularly attractive to scalable production of microneedles [73].

The DLP systems typically have a lateral resolution of 10 -30um, which enables the creation of micro needles with a sharp tip, a uniform geometry, and uniform arrays. These are reduced by synchronous treatment of every layer, which results in increased mechanical consistency and predictable skin-penetration behaviour. The properties are vital especially in immunotherapeutic microneedle

systems so that consistent insertion depths and the reproducible immune modulation. Additionally, the DLP technique can provide the accurate control of microneedle architecture, including height gradient, tapered tips, and complex base architecture [74], [75].

Translational On a translational perspective, DLP has better throughput and scalability in manufacturing as compared to SLA. The short print durations and reduced mechanical complexity make DLP quite adaptable in batching the microneedles patches of greater sizes. However, similarly to SLA, there is still an issue of selecting the material, because photocurable resins have to balance between printability and biocompatibility, as well as the stability of antibodies. Moreover, the inhibition of oxygen and depth of light penetration may influence the fidelity of curing of thicker structures. Overall, DLP is a powerful and scalable fabrication approach to the creation of geometry-controlled microneedle arrays that can be used to produce localized immune checkpoint blockade [76].

### 5.3. Two-Photon Polymerization

Two-photon Polymerisation (2PP) is an additive manufacturing method that uses laser as its light source to provide unmatched resolution and geometry precision in creating micro-needles. Unlike traditional photopolymerisation methods, 2PP takes advantage of the nonlinear absorption of femtosecond laser pulses in which case polymerisation only occurs at the focal point of the laser as a result of two photons being simultaneously absorbed. This three-dimensional confinement allows making three-dimensional micro- and nanoscaled structures with sub-micron precision, which is significantly more precise than SLA and DLP can achieve [77].

In microneedle production, 2PP gives an outstanding control of needle tip radius, surface roughness and complex internal structures. The microneedles manufactured using 2PP are able to achieve very sharp ends and high aspect ratios, which reduce insertion force as well as enhance efficiency of skin-penetration. The method can also be used to produce novel geometries of microneedles including hierarchical or porous ones that can be utilized to tune drug loading or release dynamics. These features make 2PP a useful instrument in the basic research of structure/function studies in microneedle-based immunotherapy [78].

manipulation of drug delivery are critical to

Although 2PP has technical advantages, the technology is limited by relatively slow fabrication rates, small build volumes, and high equipment prices, thus limiting it to research-level production at large scale production. Further, the range of permissible photopolymers is also limited, and post-processing can be required to ensure biocompatibility. Therefore, 2PP will not be a major manufacturing method to make clinical microneedle patches but it is essential in prototyping, precision optimisation, and development of the next-generation microneedles one-on-one cancer immunotherapy [79], [80].

The use of additive manufacturing to fabricate microneedle arrays is based on a wide variety of 3D printing technologies with each having different benefits related to resolution, material compatibility and scalability. As shown in Table 2, vat photopolymerisation techniques, such as stereolithography and digital light processing, dominate the modern microneedle production due to abilities to form a sharp tip, high-aspect-ratio structures, and an array of uniformly spaced components with precision of the micrometers. Further technologies like two-photon polymerisation offer sub-micron resolution of features which makes them useful in prototype development, as well as structure-function studies although their low throughput limits their usefulness in large volume production [81].

Extrusion based and inkjet processes allow biocompatible drug laden polymers to be incorporated, but have a tendency to compromise mechanical strength and sharpness of tips. The hybrid and multi-material printing approaches also allow greater flexibility of designs as they enable compartmentalised drug reservoirs and mechanical reinforced bottoms. More importantly, both technologies involve trade-offs between the speed of fabrication, cost and the geometric precision achievable. Table 2 clarifies the effect of printing modality on microneedle performance and translational abilities by carefully assessing the principles and material compatibility and relevance of the application. This discussion indicates that careful choice of method of fabrication is crucial in order to maximise drug loading, skin-penetration efficacy, and reproducibility, and so, move further to developing clinically viable microneedle-based immunotherapeutic delivery systems [82].

**Table 2:** 3D Printing Technologies for Microneedle Fabrication

| S. No. | Printing Technology | Working Principle | Typical Resolution | Compatible Materials | Key Advantages | Major Limitations | References |
|---|---|---|---|---|---|---|---|
| 1. | Stereolithography (SLA) | UV laser cures resin layer-by-layer | 10–50 μm | Photopolymers | High accuracy, smooth surface | Limited biopolymers | [83], [84] |
| 2. | Digital Light | Projected UV | 10–30 μm | Photocurable | Fast, | Resin | [85] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Processing (DLP) | image cures whole layer | | resins | uniform arrays | toxicity concerns | |
| 3. | Two-Photon Polymerization (2PP) | Femtosecond laser induces localized curing | <1 µm | Specialized resins | Ultra-high precision | Slow, costly | [86] |
| 4. | Fused Deposition Modeling (FDM) | Molten polymer extruded through nozzle | 50–200 µm | PLA, PCL, ABS | Low cost, accessible | Low tip sharpness | [87], [88] |
| 5. | Continuous Liquid Interface Production (CLIP) | Continuous resin curing | 10–50 µm | Photopolymers | Rapid printing, smooth | Expensive equipment | [89], [90] |
| 6. | MultiJet Printing (MJP) | Droplet-based photopolymer jetting | 16–32 µm | UV resins | High detail | Post-curing needed | [91] |
| 7. | Inkjet 3D Printing | Droplets deposited and cured | 20–50 µm | Polymer inks | Multi-material capability | Weak mechanical strength | [92] |
| 8. | Micro-Extrusion Printing | Pressure-based extrusion | 50–100 µm | Hydrogels, biopolymers | Biocompatible | Poor tip sharpness | [93], [94] |
| 9. | Projection Micro-Stereolithography (PµSL) | Mask-based UV projection | 5–10 µm | Photopolymers | High resolution, fast | Limited build size | [95], [96] |
| 10. | Laser Direct Writing | Focused laser polymerization | <10 µm | Photoresins | Precise control | Time-consuming | [97] |
| 11. | Selective Laser Sintering (SLS) | Laser fuses powder | 50–100 µm | Nylon, PCL | No support needed | Rough surface | [98] |
| 12. | Binder Jetting | Binder binds powder | 50–100 µm | Ceramic/polymer powders | Large builds | Weak strength | [99], [100] |
| 13. | Aerosol Jet Printing | Aerosolized ink deposition | 10–20 µm | Conductive inks | Functional coatings | Low mechanical strength | [101] |
| 14. | Volumetric Printing | Entire volume cured simultaneously | 50–100 µm | Photoresins | Extremely fast | Complex optics | [102] |
| 15. | Hybrid SLA–Extrusion | SLA + polymer extrusion | 10–50 µm | Mixed polymers | Structural + drug loading | Complex setup | [103] |
| 16. | Multi-Material DLP | Layer-wise multi-resin curing | 10–30 µm | Multiple photopolymers | Functional gradients | Resin switching issues | [104], [105] |
| 17. | Electrohydrodynamic Printing | Electric field-driven jet | <10 µm | Polymer solutions | Nano-precision | Complex control | [106] |
| 18. | Microfluidic-Assisted Printing | Microfluidic-controlled extrusion | 50 µm | Hydrogels | Drug encapsulation | Low rigidity | [107] |
| 19. | Resin Transfer Printing | Mold filled with resin | 10–50 µm | Biopolymers | High reproducibility | Mold dependent | [108] |
| 20. | Lithography-Based Printing | Masked UV curing | <5 µm | Photoresists | Extremely sharp tips | Multi-step process | [109], [110] |
| 21. | Cold-Extrusion Printing | Low-temp extrusion | 50–100 µm | Protein, sugars | Antibody safe | Weak mechanics | [111] |
| 22. | UV-Assisted Extrusion | UV crosslinking during extrusion | 50 µm | GelMA, PEGDA | Shape retention | UV damage risk | [112] |
| 23. | Drop-on-Demand | Controlled | 20–50 µm | Bioinks | Precise | Low | [113] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Printing | droplet deposition | | | dosing | structural strength | |
| 24. | Roll-to-Roll 3D Printing | Continuous fabrication | 50 μm | Photopolymers | Industrial scale | Low customizati on | [114] |
| 25. | AI-Assisted 3D Printing | Algorithm-optimized printing | Variable | Multiple | Optimized geometry | Needs data models | [115], [116] |

## 6. 3D-Printed Microneedles for Anti-PD-1/PD-L1 Delivery

### 6.1. Design and Engineering of 3D-Printed Microneedles

The build and engineering of 3D-printed microneedles make up important predeterminants of the mechanical functionality, drug-delivery effectiveness, and immunotherapeutic functionality of these tools. Microelectronic needles are manufactured by computer-aided design (CAD) using geometry parameters, such as height of the needle, base diameter, sharpness of tip and inter-needle spacing, which are fine-tuned by computer-aided design (CAD) to control the insertion force, depth of penetration, and stability when used. Under anti-PD-1/PD-L1 delivery, microneedles are designed to pierce through stratum corneum and target the epidermal and dermal layers that are richly endowed with immunological properties without causing pain or bleeding [117].

Some of the 3D -printing technologies that allow the production of high aspect ratio, reproducible, smooth-surface, microneedles are stereolithography (SLA) and digital light processing (DLP). The choice of the materials is also very important; biocompatible and biodegradable polymers including poly(lactic -co - glycolic acid) (PLGA), polyethylene glycol diacrylate (PEGDA), or methacrylated gelatin are usually used. These polymers have the advantage of enough mechanical strength to allow skin insertion and allow the safe degradation of the polymers after administration. Hollow or porous microneedle structures can also be engineered in engineering strategies to increase the capacity of antibodies loaded and diffusion pathways [118].

Moreover, the array architecture is customizable in order to maximize the local drug concentration and uniform tissue coverage. Close arrays enhance the aggregate delivered dose, and spacing expansion enhances mechanical stability and minimizes skin deformation. More complicated designs can also include swellable or dissolving matrices in order to release the antibodies gradually. On the whole, 3D printing enables the rational and geometry-controlled design of microneedles that can be customized to the localized immune checkpoint blockade bypassing the limitations of the traditional fabrication techniques of microneedles [119].

### 6.2. Antibody Loading and Controlled Release Strategies

Effective loading of antibodies and controlled discharge is a defining factor of success in anti PD 1 /PD L1 therapy mediated by the microneedles. Monoclonal antibodies are sensitive biomolecules and because of their size and structure they require incorporation techniques that do not destroy their biological qualities. The most frequent loading techniques are physical entrapment in dissolving microneedle matrices, coating of solid microneedles, and entrapment in polymeric or hydrogel forming needles. Melting of microneedles made of water-soluble polymers allow the release of antibodies into the skin directly after insertion and elimination of the means of device removal [120].

Controlled release is achieved through maximizing polymer composition, crosslinking density and pore structure of the microneedles. As an example, microneedles that form hydrogel swell when they come into contact with the interstitial fluid, and they create diffusion channels that enable the release of antibodies during a few hours or days. By also incorporating pH-sensitive or enzyme-responsive substances, the stimulus-precise release in tumour-associated microenvironment can be achieved. Spatial segregation of drug and structural components is possible through layer-by-layer fabrication which ensures mechanical stability without interference with payload stability [121], [122].

Another important thing is antibody stabilization during the printing process and storage. Denaturation and aggregation could be avoided by the addition of protective excipients like trehalose or serum albumin. Micro needle systems have an advantage as they minimize systemic exposure by forming high local antibody concentrations at the delivery site and provide long-lasting checkpoint inhibition. As a consequence, sustained local immunomodulation can be achieved on the basis of optimized loading and release plans, thus leading to better therapeutic index as compared to the traditional intravenous antibody delivery [123].

### 6.3. Localized Immune Modulation through PD-1 /PD-L1 Microneedle Delivery

PD-1/PD-L1 microneedle delivery is a localized immune modulation strategy that is a relative strategic change of systemic immune checkpoint blockade to site-specific immunotherapy. Direct administration of anti-PD-1 or anti-PD-L1 antibodies to skin tissue or tumour-proximal tissue concentrates the adaptive immune response in areas with high concentrations of antigen-presenting cells and lymphatic systems. This is a local exposure that facilitates the activation of cytotoxic T lymphocytes and reduces off-target immune activation in normal organs [124].

In the tumour site, PD 1/PD L1 blockade overturns T cell exhaustion and reinstates anti tumour immunity. the local microenvironment allowing a continuous checkpoint inhibition. The strategy has the potential to restructure tumour immune space by enhancing the entry of CD8+ T cells, depleting the total of regulatory T cells, and imitating the production of pro-inflammatory cytokines. Moreover, local immune reaction could induce a systemic anti-tumour immunity by the lymphatic drainage and traffic of immune-cells, and thus cause abscopal effects at remote tumor locations [125].

Localized microneedle delivery is significantly more effective in reducing the number of doses of drug to produce a therapeutic effect, which lowers the chance of immune-mediated adverse events such as colitis, dermatitis, and endocrinopathies than intravenous administration. Micro needles are also minimally invasive, which makes it easy to administer them repeatedly and by patients themselves, making them more adherent to treatment. In sum, PD -1/PD -L1 microneedle delivery allows spatial confinement of checkpoint blockade, which is a safer and more effective approach to augment anti-tumour immunity in breast cancer and other solid tumours [126], [127].

## 7. Immunological Outcomes of Microneedle-Mediated Anti-PD-L1 Therapy

### 7.1. Enhancement of Cytotoxic T-Cell Responses

Reinstatement and enhancement of the cytotoxic T lymphocyte (CTL) functions in the tumor microenvironment is one of the major immunological effects of anti-PD-L1 therapy by microneedle. Micro needle delivered antibodies block PDL1 signalling locally to suppress inhibitory signalling on the exhausted CD8+ T cells, stimulating their proliferation, cytokine release and ability to kill tumours. Localised delivery makes the antibodies remain in the treatment site and induce long-lasting checkpoint adherence and permanent immune stimulation. Increased infiltration of CD8 + T cells in tumour tissues through microneedle based immune checkpoint blockade has been demonstrated in preclinical studies associated with heightened interferon -7 and granzyme -B that are characteristic of an efficient antitumour immune response. These localised immunoreactivation results in better tumour control than systemic delivery with corresponding dosages or lower dosages. In addition, improved T-cell priming in skin-associated lymphoid tissues can also lead to extended immune response to tumour-associated antigens, which will strengthen the therapeutic effect of the checkpoint inhibition with the use of microneedles [128].

### 7.2. Tumour Microenvironment Modulation

Anti-PD-L1 therapy associated with the use of microneedles also causes a significant tumour microenvironment reorganization into an immunosuppressive to an immunostimulatory area. Local checkpoint blockade inhibits PD -L1mediated inhibition of effector immune cells and lessens the superiority of regulatory T cells and myeloid-derived This effect is reinforced by microneedle-based delivery that maintains the presence of antibodies in suppressor cells, which are major mediators of immune evasion. This means that the immune activation and tolerance balance in the tumour changes towards the activation side [129]. Inflammatory cytokines and chemokines increase recruitment of other immune cells such as natural killer cells and dendritic cells which further enhance antitumour responses. Microinjection of the microneedles into the locality of the tumour causes these alterations to be localised mainly to the tumour-proximal area to reduce systematic immune stimulation. Not only does this spatial restriction of immune modulation enhance the specificity of therapy but it also promotes the creation of an immune-permissive niche that is antitumour growth and metastasis-hostile. It is critical that such reprogramming of the tumour microenvironment is necessary to provide sustained responses to immune checkpoint blockade [130].

### 7.3. Stimulation of Systemic Antitumour Immunity and Immune Memory

Despite the fact that anti-PD-L1 therapy mediated by micron-needles is localised, it may induce systemic antitumour immunity by activating and trafficking of immune cells. Tumour antigens released during immune-mediated tumour cell death are absorbed by the antigen-presenting cells in the skin and tumour-draining lymph nodes and presented to the T cells, thus stimulating the growth of tumour-specific lymphocyte populations [131]. These activated T cells are able to disseminate and attack far tumour lesions, which cause abscopal effects. Besides that, the long-term local immune response to microneedle injection facilitates immunological memory. T cells which are developed during therapy as memory T cells allow the long-term monitoring of tumour recurrence and metastasis. This property is most useful in cancerous diseases that are aggressive like triple-negative breast cancer, as such diseases have a high rate of relapse. So, the delivery through microneedles does not just regulate the development of local tumours, but it also generates immunity systemically [132].

### 7.4. Minimization of Immune Related Adverse Events

The most important beneficial side effect of anti-PD-L1 therapy via microneedles is that immune-adverse events are less frequent than those when it is administered systemically. Micro needles delivery can focus immune checkpoint blockade on a localised area thereby restricting extensive immune activation that normally targets healthy organs. Reduced antibody doses in total are needed to get therapeutic effect and thus this reduces the chances of toxicities like dermatitis, colitis, hepatitis and endocrinopathies. This safety profile is better and increases the therapeutic window of immune checkpoint inhibitors and facilitates repeated or long-term therapy. Moreover, microneedle patch has a greater compliance and quality of life due to its low invasive and possibly self-administered nature. A combination of these results underscores the two-fold advantage of

microneedle-mediated anti-PD-L1 immunotherapy; strong antitumour immunity and less systemic toxicity [133].

**8. Clinical and Translational Issues.**

There are various aspects that should be taken into account when undertaking the clinical translation of 3D -printed microneedle systems to localised anti-PD-L1 immunotherapy, such as safety, manufacturability, regulatory approval, and patient usability. Even though preclinical trials have shown them to have a good antitumour effect and lower systemic toxicity, the success of their clinical implementation requires the scalability of fabrication, consistent product quality, and the establishment of effective clinical protocols [134].

As regards to safety, microneedle materials should be biocompatible, non-immunogenic and reliable in their mechanical capacity. The polymer to be used in making the microneedles must not cause inflammatory or allergic effects and must break down to non-toxic by-products. Especially, transdermal devices that are set to be used repeatedly require sterility assurance. Moreover, it is important to maintain the stability of antibodies during the manufacturing, storage and administration process so that they have therapeutic activity. Exposure to light or heat or conditions of photopolymerisation can cause destruction to monoclonal antibody structure, and processing parameters should therefore be optimised and stabilising excipients introduced [135], [136].

Scalability in manufacturing is a significant challenge in translation. As much as 3D printing provides a great deal of design flexibility and allows quick prototyping, when it comes to adapting the laboratory-scale fabrication process to large-scale production, the printing rate, repeatability, and cost-effectiveness of the technology has to be proven. Microneedle geometry and drug content consistency is required on batch to batch consistency in a clinical reliability manner. Optical inspection and mechanical testing are advanced quality control techniques that should be incorporated in production processes. Additionally, the regulatory authorities will demand that the standards of Good Manufacturing Practice are met and the fabrication procedures are well documented [137].

The problem of regulatory classification of immunotherapy systems based on the use of micro needle could be classified as a combination product, because they combine a medical device and a biological drug. Such a two-sided character makes it complicated to approve the pathways and requires the coordinated assessment of the device performance and pharmacological activity. Preclinical toxicology studies should not focus on systemic effects of immune but local tissue reactions on the point of application. Repeated-use safety, risk of infection and the possibility of chronic inflammation or fibrosis are to be determined by long-term studies. Further, pharmacokinetic and biodistribution studies will have to indicate that the localised delivery does not cause unintentional accumulation in the system [138].

Translational feasibility is also affected by patient-centered considerations. Microneedle patches have the benefits of painlessness, of administration ease and may be used by self-administration that can ease hospital visits and enhance compliance. Nevertheless, such practical problems as the adhesion of patches, consistent penetration of the patch into the skin, and the inconsistency of skin thickness in different individuals should be solved with the help of optimal design. The clinical guidelines should establish the proper sites of application, dosage, and therapy period. Combination with other current therapeutic or treatment options like chemotherapy or radiotherapy must be scheduled carefully to prevent the effects of immunosuppression or superimposition of toxicities [139], [140].

The other aspect of translational consideration is patient selection. The biomarkers that are apt to affect responsiveness to localized immune checkpoint blockade include PD-L1 expression, immune infiltration, and tumor mutational burden. These parameters can be used in stratifying patients to enhance clinical outcomes and prevent unwarranted treatment. Moreover, micro needle based delivery could also be especially applicable on tumors that can be accessed easily as well as post-surgery tumor beds, where local immune suppression can suppress recurrence [117].

Last but not least, there is economic and logistical factor to be considered. Though 3D printing can be customizable and on-demand, the implications of high-resolution printers, specialized materials, and quality control can make the prices of high-resolution printers, and 3D printing in resource-limited environments prohibitive. Micro needle designs and fabrication working processes should be made standardized and solitary to minimize the cost and to make it accessible to a wide range of clinical applications. In general, engineering, immunology, and clinical practice alignment will have to be carried out very carefully to implement microneedle-mediated anti-PD-L1 therapy out of the experimental bases and into the clinically feasible immunotherapeutic approaches [141], [142].

**9. Challenges and Limitations**

Although 3D-printed microneedle systems have a high potential in localized anti-PD-L1 immunotherapy, a number of scientific, technical, and translational barriers exist, which still need to be tackled before being used in a wide scale clinical setting. The main weakness is the low drug-loading capacity of microneedles in comparison to systemic delivery. Monoclonal antibodies are large biomolecules, which demand rather large doses to have an effect on checkpoint blockade and the volume of individual microneedles limits the overall amount of payload that can be delivered in a single application. This constraint might require re-dose or increased patch size which may impact on patient convenience and

adherence to treatment [143].

Another significant challenge is to maintain the stability of antibodies during fabrication, storage and use. During 3D printing, antibody structure and biological activity can be lost due to exposure to ultraviolet light, heat or reactive monomers. Protective excipients and after printing loading methods can help address these effects, however, it remains challenging to achieve uniform antibody integrity with each batch. Moreover, most microneedle-based immunotherapeutic formulations have not been established as being stable over the long term during different temperature and humidity regimes [144], [145]. Mechanically, it is not that easy to have consistent and reliable skin penetration in various populations of patients. The change in skin thickness, hydration, and elasticity may affect the efficiency of the insertion and drug release profiles. Partial insertion can cause lack of accuracy in dosing and erratic therapeutic results. Additionally, local irritation, micro-inflammation or disruptive skin barrier with repeated use at the same site can lead to an increased risk of infection or fibrosis with time [146].

PD-L1 localized blockade may not be strong enough to counteract elaborate immunosuppressive pathways in advanced or metastatic tumours, produced biologically. PD-1/PD-L1 is not the only pathway that can participate in tumor immune evasion, with other pathways including: CTLA-4 signaling, T-cell growth, and immunosuppressive cytokines. As a result, it is possible to assess that monotherapy using microneedles can be effective in some types of tumors or stages but requires a combination approach with vaccines, adjuvants, or chemotherapeutic options. Nevertheless, the use of more than one agent in a single platform of a microneedle complicated the formulations and regulatory requirements [147], [148].

There are also still translational barriers. The process of 3D printing is not easily standardized to produce products of clinical quality because of differences in the performance of the printers, the resin materials, and even the environmental factors. Combination products that are a combination of a drug and a delivery device are still complex and time consuming to get a regulatory approval. Additionally, there is no long-term clinical information available to determine chronic safety, immunogenicity, and sustainability of therapeutic responses. All these difficulties indicate the necessity of further interdisciplinary studies that combine materials science, immunology, and clinical oncology. The limitations and especially the fabrication methods will need to be overcome by applying better fabrication methods, optimized formulations, and rigorous preclinical and clinical development, to achieve the potential of microneedle-mediated immune checkpoint blockade [149], [150].

## 10. Future Perspectives and Emerging Opportunities

The future of delivery systems of localized anti-PD-1/PD-L1 immunotherapy by using microneedles makes of 3D-printing materials is to unite with the progress of materials science, immunoengineering, and precision medicine. Further development of 3D printing technologies should produce microneedles with a higher geometric accuracy, a higher mechanical stability, and an increased payload. The development of microneedle platforms with programmable and environment-responsive drug delivery can be assessed based on emerging printable biomaterials, such as stimuli-responsive polymers and organic-inorganic composite materials. These materials might drive the release of antibodies upon tumor-related signals like acidic pH, activity of enzymes, or inflammatory cytokines and so enhance location and time-dependent incentive of immune checkpoint blockade [151].

Another possible direction is the personalized microneedle design. Micro needles patches are designed to be targeted to tumor sites, depth, and immune status by using patient-specific data related to patient imaging and tumor profiling. The strategy is consistent with the larger shift towards precision oncology and can allow optimizing therapeutic value and reducing unwarranted immunogenicity. Moreover, recently developed multi-material 3D printing enables the creation of complicated and complex microneedle structures that incorporate structural parts, drug reservoirs and bioactive layers into a single device. This allows multifunctional microneedle systems to be created to deliver immune checkpoint inhibitors together with adjuvants, vaccines, or chemotherapeutic agents [152].

A particularly interesting emerging opportunity is combination immunotherapy that is administered through microneedles. Any of the above anti-PD-L1 antibodies combined with immune-stimulatory agents like toll-like receptor agonists, cytokines or tumor antigens might be used in combination to stimulate immunity and achieve overcoming resistance. Likewise, photodynamic therapies could be coordinated with spatiotemporal destruction of tumours by integration with photothermal or photodynamic therapies. Such mixtures of approaches may be applied in layered or compartmentalized designs of microneedles, with sequential or staged delivery of various agents [153].

In addition to breast cancer, it is also possible that microneedle-mediated immune checkpoint blockade will be useful in other solid tumors that are accessible or highly interact with the skin-associated immune networks (including melanoma, head and neck tumors, and cutaneous metastases). Tumor post-surgical beds are also good targets of localized immune modulation to avoid recurrence. Moreover, by including biosensing capabilities into microneedle interrogatives, real-time measurements of the local immune markers or drug delivery would be possible,

forming feedback-regulated therapeutic frameworks [154], [155].

Translational perspective Future activities should aim at developing standardized making guidelines, the to select the patients. The economic factors and accessibility should also be taken to the consideration to make sure that these advanced technologies can be implemented not only in specialized centers [156]. On the whole, microneedle platforms 3D-printed have a high potential as the next-generation immunotherapeutic interfaces to integrate localized delivery, immune modulation, and personalized design. The further development of them could reshape the way immune checkpoint blockers are conducted to become systemic forms of infusion rather than patient-friendly and highly targeted forms of cancer immunotherapy [157]. [158].

## Conclusion

Micro-needle based delivery systems constructed using 3-D printing can be a good and novel approach to local delivery of anti-PD-L1 immunotherapy in breast cancer. Microneedle platforms can serve as an alternative to this form of systemic immune checkpoint blockade, by overcoming the basic limitations of this approach, such as poor accumulation of tumor drugs and immune-adverse events in patients. The immune modulation environment of the immunologically active skin offers a perfect interface, allowing successful reactivation of the cytotoxic T cells, remodeling of the tumor microenvironment, and possible generation of systemic antitumor immunity and immune memory. The development of 3D printing technologies has demonstrated that design flexibility, precision, and reproducibility of the microneedle arrays can be greatly increased, which has provided the ability of controlling geometry, material composition, and release kinetics very fine. These properties are important to maximize the skin penetration, the stability of antibodies, and the prolonged localized drug delivery. Although there have been promising preclinical results, there are a number of difficulties before clinical translation is made possible. These are the lack of large drug loading capacity with large biologics, the capacity to maintain antibody stability in fabrication and storage, interpatient differences in long-term safety profile, and strong clinical evidence. In pre-clinical trials, it will be necessary to establish the best dosing levels, timelines and the criteria used

skin characteristics and regulatory complications that rely on combination products. Moreover, the localized administration of PD-L1 blockade could not be effective enough on its own to circumvent complex immunosuppressive interactions in advanced disease, suggesting the possibility of combining therapies. Future directions in research have been on the optimization of printable biomaterials, creation of stimuli-responsive and multi-agent microneedle devices, development of scalable manufacturing guidelines and creation of robust clinical evidence. On the whole, localized immunotherapy with 3D-printed microneedles has a high potential to transform the delivery of immune checkpoints, which is safer and more effective and personalized to manage breast cancer.

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## Author Contribution

**SP:** Conceptualization; **TMV:** Supervision; **PS:** Literature review; **TA:** Writing – original draft; **DS:** Data curation; **MSP:** Editing; **SA:** Visualization, Proofreading.

## Conflict of Interest

The authors declare no conflict of interest.

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## AI Declarations

The authors declare that no artificial intelligence (AI) language tools were used in the preparation of this manuscript. All writing, editing, and revisions were performed solely by the authors.

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