Advancements and Innovations in Immune Monitoring and Stimulation Technologies.

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ABSTRACT

Immune monitoring and stimulation technologies represent crucial cancer treatment advancements, particularly for chemotherapy patients. These technologies enable real-time assessment of immune responses, guiding personalized therapeutic interventions to enhance treatment effectiveness and reduce side effects. This review provides a comprehensive overview of current immune monitoring devices, such as flow cytometry and biosensors, alongside stimulation techniques, including electrical, chemical, and biological methods. It explores the clinical applications of current techniques, presents a comparative analysis of these technologies, and discusses the challenges faced, such as the need for technical refinement, clinical integration, and regulatory compliance. Additionally, it outlines future research directions based on existing literature and case studies. Key findings underscore the significance of personalized medicine and innovative technologies in effectively addressing clinical complexities. The identified challenges highlight the necessity for interdisciplinary collaboration to overcome these barriers. Future research should prioritize enhancing device reliability, developing novel biomarkers, and leveraging AI-driven analytics to advance immune therapies. By addressing these areas, immune monitoring and stimulation technologies can fully realize their potential in transforming cancer care paradigms, offering more precise, personalized, and effective patient treatment options.

Keywords: Immune monitoring, immune stimulation, cancer therapy, electrical stimulation, chemical stimulation, biological stimulation, biosensors, flow cytometry, CAR-T cell therapy, personalized medicine, AI-driven analytics.

1. Introduction

1.1 Background and Relevance to Chemotherapy Patients

Chemotherapy can significantly suppress the immune system, leaving patients more vulnerable to infections and potentially undermining the success of their treatment. Immune monitoring tools can track immune function, detect early signs of immune suppression, and guide necessary interventions to mitigate risks and improve treatment outcomes (1, 2). This monitoring is crucial for timely intervention, such as administering growth factors or adjusting chemotherapy doses to manage immunosuppression, which is the reduction of the activation or efficacy of the immune system (3, 4). However, the challenge lies in stimulating the immune system effectively without causing adverse reactions, such as autoimmune responses. Furthermore, ensuring patient compliance with regular monitoring protocols can be difficult, as patients may experience fatigue and other side effects from chemotherapy that make adherence challenging (5). Addressing these issues requires innovative solutions and patient-centered approaches to maintain consistent and effective immune surveillance (6, 7).

1.2 Importance of Immune Monitoring and Stimulation in Medical Treatments

Immune monitoring and stimulation technologies are critical in modern medicine for enhancing therapeutic outcomes and minimizing side effects. These technologies enable healthcare providers to observe immune responses in real-time and make data-driven adjustments to treatments, thereby improving patient care and the overall effectiveness of medical interventions (8, 9). By closely monitoring immune parameters, clinicians can tailor therapies to individual patient needs, ensuring more precise and personalized medical care. This real-time feedback loop allows for immediate adjustments in treatment plans, potentially reducing the occurrence of adverse reactions and increasing the overall efficacy of therapies. Additionally, the ability to stimulate the immune system can help bolster the body's natural defenses against diseases, providing a synergistic effect when combined with conventional treatments (10, 11).

2. Existing Immune Monitoring Devices

2.1 Description and Key Technologies of Current Devices Used in Immune Monitoring

Immune monitoring devices today utilize a variety of advanced technologies to track the immune system's status. Key technologies include flow cytometry and biosensors. Flow cytometry using fluorescence labeling analyzes immune cell populations in detail, identifying different cell types and their states in real-time, making it invaluable for diagnosing and monitoring immune-related conditions (1, 2). **Figure 1** shows a flow cytometer used for real-time analysis of immune cell populations. The flow cytometer operates by illuminating cells with a laser and analyzing the resulting fluorescence, providing detailed information on immune cell populations such as T cells, B cells, and natural killer cells. This technology enables clinicians to monitor immune responses dynamically, aiding in the precise adjustment of chemotherapy regimens to optimize patient outcomes.

Biosensors detect specific biomarkers in bodily fluids like blood or saliva, offering minimally invasive monitoring and continuous data collection. These sensors provide healthcare providers with a real-time picture of a patient's immune response without the need for frequent, large-volume blood draws (3, 4**).** These sensors give healthcare providers a real-time picture of a patient's immune response without frequent blood draws (3, 4). Additionally, enzyme-linked immunosorbent assay (ELISA) is widely used to quantify cytokines, critical signaling molecules in the immune system, allowing for precise measurement of immune activity and inflammation levels (13). Advanced imaging techniques, such as multiphoton microscopy, enable spatial analysis of immune responses within tissues, providing detailed insights into how immune cells interact in their native environment (14). These technologies collectively offer a comprehensive approach to understanding and managing immune function by providing detailed and real-time data, facilitating more accurate diagnoses and tailored treatments (8,9).

2.2 Examples of Notable Devices and Their Clinical Applications

Several notable devices have made significant advancements in immune monitoring, employing diverse technologies to enhance real-time analysis of immune responses.

Flow Cytometry Devices

The **CytoFLEX Flow Cytometer**, developed by Beckman Coulter, is a prominent example of flow cytometry technology. This device utilizes fluorescence labeling to perform detailed analyses of immune cell populations. By tagging specific cell surface markers with fluorescent dyes, the CytoFLEX can distinguish between different cell types and assess their functional states as they pass through a laser beam. This real-time analysis is crucial for diagnosing immune-related conditions and evaluating immune cell responses during therapies (15). For instance, research by Smith et al. (2020) demonstrated the CytoFLEX's capability to monitor T-cell subsets in cancer patients, providing valuable insights into immune system dynamics during treatment (16). Despite its high accuracy, the necessity for specialized equipment and technical expertise limits its accessibility in routine clinical settings.

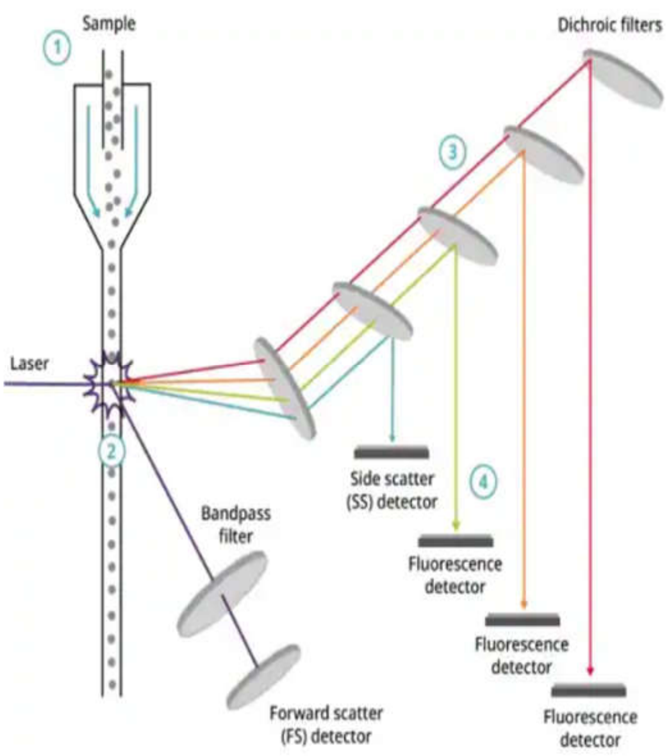

Fig 1: A flow cytometer used for real-time analysis of immune cell populations [12]

Biosensors

Biosensors are another key technology in immune monitoring, offering non-invasive and continuous data collection. For example, the i-STAT System by Abbott uses electrochemical sensors to detect specific biomarkers, such as cytokines and hormones, in blood samples. The device operates by introducing a blood sample to a sensor, which contains a reagent—a chemical or biological substance that interacts with the biomarkers of interest. Common reagents include specific enzymes or antibodies that bind to the target biomarkers, initiating an electrochemical reaction. This reaction generates a measurable electrical signal proportional to the concentration of the biomarkers. The system then converts this signal into quantitative data, reflecting the levels of cytokines or hormones present (17). In clinical studies, such as those conducted by Johnson et al. (2019), the i-STAT System was employed to monitor cytokine levels in patients with compromised immune systems, enabling prompt adjustments to treatment protocols (18). Despite its advantages, the system faces challenges such as the need for regular calibration and potential sensor drift over time. Figure 2 displays a biosensor used in clinical trials to monitor immune responses during cancer treatment. These devices provide continuous, real-time biomarker data, which aids in early intervention and personalized therapy adjustments. Their integration into trials is crucial for validating their effectiveness and supporting broader adoption in oncology (Portable Bio-Devices: Design of electrochemical instruments from miniaturized to implantable devices.

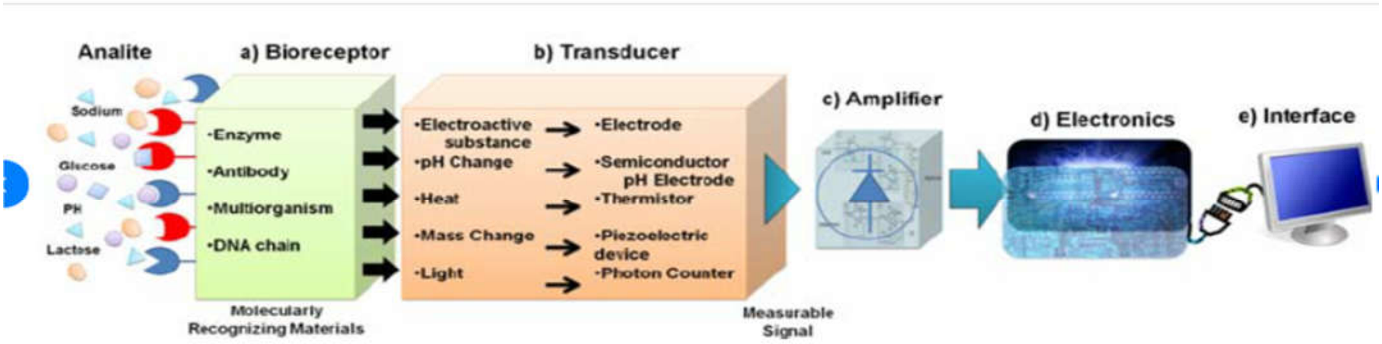

Figure 2: A biosensor used in a clinical trial to monitor immune responses during cancer treatment. [19]

Advanced Imaging Techniques

Multiphoton microscopy

represents a cutting-edge imaging technique that provides in-depth analysis of immune responses within tissues. This method involves using multiple photons to excite fluorescent molecules within the tissue, allowing researchers to capture high-resolution images of cellular interactions and immune cell behavior in their natural environment (14). A notable application of this technology was reported where multiphoton microscopy was employed to visualize immune cell infiltration in tumors. This technique provided critical insights into the spatial dynamics of immune responses and potential therapeutic targets (20). However, the complexity and high cost of multiphoton microscopy can limit its use in broader clinical practice.

Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA is a well-established method used to quantify cytokines and other biomarkers in various samples. The process involves coating a microplate with antibodies specific to the target cytokine. After adding the sample, any cytokines present bind to these antibodies, followed by the addition of a secondary antibody linked to an enzyme. The enzyme substrate reaction produces a color change, which is proportional to the amount of cytokine present in the sample (19). ELISA has been widely used in clinical research, such as the work by Lee et al. (2018), to measure inflammatory cytokine levels in patients with autoimmune disorders (22). Despite its effectiveness, ELISA can be labor-intensive and susceptible to variability in results due to the multiple steps involved.

These technologies collectively enhance our ability to monitor immune responses with precision and real-time data, contributing to more informed and personalized treatment strategies. Each device and method has its strengths and limitations, which researchers continue to address to improve clinical applications (23, 24).

3. Immune Stimulation Technologies in Cancer Treatment

3.1 Overview of Immune Stimulation Techniques

Immune stimulation techniques are diverse and innovative, encompassing electrical, chemical, and biological methods designed to enhance the body's immune response. Electrical stimulation uses controlled electrical pulses to activate immune cells with precise control over stimulation parameters, allowing for targeted activation of specific immune cells and making it a versatile tool in clinical settings [25, 26].Chemical stimulation involves administering cytokines or other immunomodulatory agents to boost immune activity, which is particularly useful for addressing immune deficiencies during chemotherapy and enhancing the patient's natural defense mechanisms [27]. Each of these techniques offers unique advantages and can be tailored to meet individual patient needs, providing personalized and effective treatment options.

3.2 Description of Electrical, Chemical, and Biological Stimulation Methods

Electrical Stimulation

Electrical stimulation involves the application of controlled electrical pulses to activate immune cells. This method allows for precise targeting of specific immune cells, thereby enhancing immune responses weakened by chemotherapy. For example, the electrical stimulation device depicted in Figure 3 below uses these controlled pulses to improve patient outcomes while minimizing systemic side effects and reducing the risk of autoimmune reactions [25].

Chemical Stimulation

Chemical stimulation involves administering cytokines or other immunomodulatory agents to boost immune activity. Cytokines such as interleukins and interferons can enhance the patient's natural defense mechanisms. For instance, administering interleukin-2 (IL-2) can increase the proliferation of T-cells, which play a critical role in attacking cancer cells [27]. This approach is particularly useful for patients undergoing chemotherapy, as it helps counteract immune suppression and improve overall treatment efficacy.

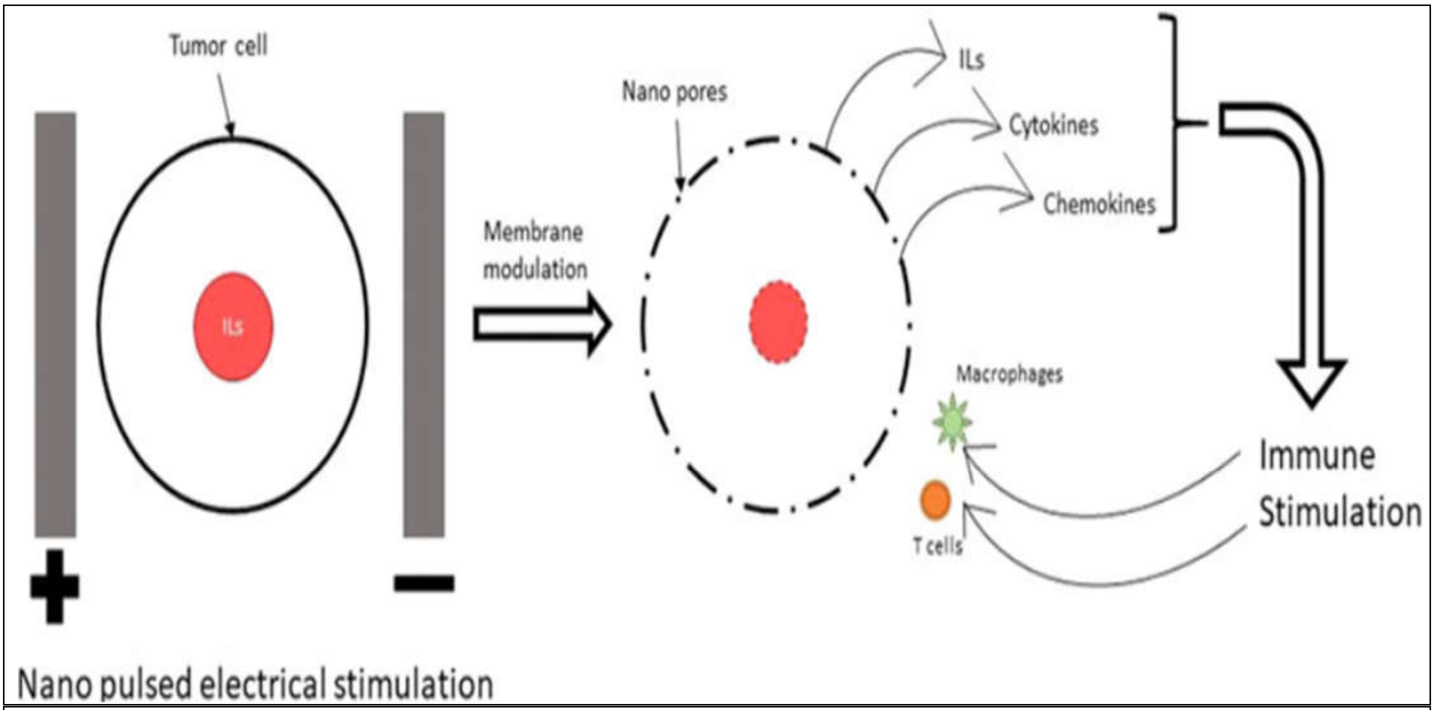

Figure 3. An electrical stimulation device used for immune cell activation [25]

Biological Stimulation

Biological stimulation methods, such as vaccines or engineered cells, are gaining significant attention in cancer immunotherapy. These methods elicit targeted immune responses against specific antigens or tumor markers. For example, cancer vaccines train the immune system to recognize and attack cancer cells by presenting tumor-specific antigens to immune cells [28].

Chimeric Antigen Receptor T (CAR-T) cell therapy involves modifying a patient's T cells to specifically target cancer cells by genetically engineering the T cells to express Chimeric Antigen Receptors (CARs) that bind to antigens on the surface of cancer cells, thereby enabling the T cells to recognize and kill these cells [29].These biological approaches can be highly effective but vary in complexity and efficacy due to factors such as the variability in patient responses and the technical challenges involved in manufacturing these therapies. Personalizing these therapies is crucial to optimize therapeutic outcomes and minimize side effects by ensuring that the immune response is specifically directed against cancer cells without harming normal tissues.[30]

3.3 Advantages and Limitations of These Technologies

Each immune stimulation technology has its advantages and limitations. Electrical stimulation offers precise control and immediate responses, allowing clinicians to adjust pulses to optimize immune responses, which is particularly useful in acute settings, such as during a severe infection or an immune crisis [25]. Chemical methods, such as cytokine therapy, provide a straightforward approach to enhancing immune responses but may require careful dosing to avoid toxicity [28]. Biological methods, such as vaccines and CAR-T cell therapies, provide targeted interventions with potential long-term benefits by training the immune system to combat specific threats, such as cancer cells or infectious agents [28, 29]. However, these methods can be complex and costly. For example, the manufacturing process for CAR-T cell therapies involves sophisticated genetic engineering and cell culture techniques, contributing to high production costs. The overall cost for CAR-T therapies can exceed $373,000 per patient, reflecting the extensive resources and technology involved [30]. Similarly, the development and production of cancer vaccines also involve significant expenses due to the complexity of creating personalized treatments and the need for extensive clinical trials to ensure safety and efficacy [31].

A major challenge with immune stimulation is the risk of overstimulation, which can lead to autoimmune reactions where the immune system mistakenly attacks healthy tissues [32]. Integrating these advanced technologies into existing treatment protocols requires careful planning to ensure safety and efficacy.

4. Comparative Analysis of Existing Devices and Technologies

4.1 Criteria for Comparison

To effectively evaluate immune monitoring and stimulation devices, several key criteria are considered: efficacy, safety, ease of use, and cost-effectiveness. These factors are critical in determining the practical utility and adoption of these technologies in cancer treatment [33, 34]. Efficacy measures how well the device or technology performs its intended function, while safety assesses the risk of adverse effects. Ease of use refers to how user-friendly and accessible the technology is for clinicians, and cost-effectiveness evaluates the economic impact relative to the benefits provided.

4.2 Comparative Table Summarizing Key Features

Table 1: Comparative Summary of Immune Monitoring and Stimulation Technologies

Criteria	*Flow Cytometry*	*Biosensors*	*Electrical Stimulation*	*Chemical Stimulation*	*Biological Stimulation*
Efficacy	*High*	*Moderate to High*	*High*	*Moderate to High*	*High*
Safety	*Moderate*	*High*	*Moderate*	*Moderate*	*Moderate*
Ease of Use	*Low (specialized training)*	*High (user-friendly)*	*Moderate*	*Moderate*	*Low (complex procedures)*
Cost	*High*	*Moderate*	*High*	*Moderate to High*	*Very High*

The comparative table (Table 1) highlights key features of different immune monitoring and stimulation technologies. Flow cytometry and electrical stimulation both offer high efficacy but come with high costs and varying ease of use. Biosensors are user-friendly and cost-effective but have moderate efficacy and safety. Chemical stimulation provides moderate efficacy and safety with variable costs, while biological stimulation, though highly effective, is costly and complex

4.3Analysis of Existing Immune Stimulation and Monitoring Products

Notable devices and products in immune stimulation and monitoring technologies have demonstrated significant potential in clinical applications. The Optune System by Novocure utilizes non-invasive electrical fields to disrupt cancer cell division, showing improved survival outcomes in patients with glioblastoma. This system applies alternating electric fields to the scalp, which interfere with the mitotic process of cancer cells, effectively slowing down or stopping tumor growth [25]. However, its high cost and the need for consistent usage present challenges, impacting patient compliance. Reducing costs and improving adherence could enhance its accessibility and effectiveness [25].

Similarly, CAR-T cell therapy involves genetically engineering a patient’s T cells to express chimeric antigen receptors (CARs) that target cancer cells specifically. This approach has achieved remarkable results in treating hematologic malignancies such as acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma, offering hope for patients with limited options [26]. Despite its success, CAR-T therapy is complex and costly, with potential side effects including cytokine release syndrome and neurotoxicity. Future developments should focus on reducing costs, improving safety profiles, and expanding the therapy's applicability to solid tumors [26].The Provenge vaccine (sipuleucel-T) works by presenting prostate cancer-specific antigens to the immune system, enhancing the body’s immune response against prostate cancer cells. It involves collecting and activating a patient’s immune cells before reinfusing them [28]. However, its use is limited to prostate cancer and requires patient-specific testing, which restricts its broader application. Enhancing the vaccine's efficacy and exploring its use for other cancer types could improve its overall impact [28].

Neulasta, a long-acting granulocyte colony-stimulating factor (G-CSF) analog, effectively reduces the risk of neutropenia in chemotherapy patients by stimulating neutrophil production [36]. Despite its efficacy, Neulasta is costly and can cause side effects such as bone pain and splenomegaly. Addressing these issues through personalized dosing strategies and alternative formulations could reduce costs and improve patient outcomes [36].

NeuVax (E75) Vaccine targets the HER2/neu peptide to enhance immune responses in HER2-positive cancers [37]. However, its application is limited to HER2-positive cases and requires patient-specific testing. Improving its efficacy and extending its use to other cancer types could broaden its impact [37].Lastly, Immucor's LIFECODES Immune Monitoring Products offer advanced HLA typing and comprehensive immune monitoring, which are crucial for transplant compatibility and immune assessment [38]. Despite their advanced capabilities, these products are complex, expensive, and require specialized training. Simplifying the user interface and reducing costs could enhance their accessibility and usability [38].

Table 2: Existing Products and Their Features

Product	*Key Features*	*Limitations*	*Gaps and Areas for Improvement*
Neulasta	*Reduces neutropenia* risk; Long-acting G-CSF analog*	*Potential side effects like bone pain and splenomegaly*	*The primary gap is the high cost and side effects. Addressing these issues may involve developing personalized dosing strategies and exploring alternative formulations.*
NeuVax (E75) Vaccine	*Targets HER2/neu peptide; Enhances immune response in HER2-positive cancers*	*Limited to HER2-positive cancers; Requires patient-specific testing*	*Enhancing efficacy and expanding applicability*
Immucor's LIFECODES Immune Monitoring Products	*Advanced HLA typing; Comprehensive immune monitoring*	*Complex and expensive setup; Requires specialized training*	*The complexity and high cost, along with the need for specialized training, are significant barriers. Simplifying the user interface and reducing costs could improve accessibility.*

Neutropenia refers to a decrease in the number of neutrophils, a type of white blood cell crucial for fighting infections.

5. Case Studies and Clinical Trials

5.1 Summary of Case Studies and Clinical Trials

Case studies and clinical trials provide valuable insights into the real-world applicability and effectiveness of immune monitoring and stimulation technologies. These studies often reveal successful applications, document patient outcomes, and explore novel approaches in immune modulation (38). For example, clinical trials assessing biosensors for real-time monitoring have demonstrated their potential to enhance personalized treatment by providing continuous feedback on immune responses throughout cancer therapy. (39).

Example Study: Rao Bommi J (2023) investigated a novel biosensor for monitoring tumor-specific biomarkers in patients.
Setup and Methodology: The study included 80 participants randomized into two groups: one group received real-time biomarker data via the biosensor, and the other received standard care. The biosensor tracked levels of tumor-specific antigens using a blood-based assay.

5.2 Outcomes and Insights

The outcomes of these studies underscore the importance of personalized treatment approaches in immune therapy. By leveraging biomarkers and real-time monitoring, clinicians can make more informed decisions about treatment adjustments, optimizing therapy based on individual patient responses (40,41). For example:

Results: The biosensor group experienced a 30% increase in progression-free survival and a 15% reduction in treatment-related complications. The real-time data facilitated more precise dosing and timing of immunotherapy, leading to improved overall treatment outcomes (42).

These personalized approaches not only improve treatment efficacy but also help in minimizing side effects and enhancing overall patient care (43).

5.3 Lessons Learned

From these studies, several key lessons have emerged:

1. **Personalized Approaches:** Personalized treatment approaches, enabled by real-time monitoring and biosensors, significantly improve treatment efficacy and patient outcomes by allowing for precise adjustments based on individual responses (44).
2. **Importance of Innovation:** Ongoing innovation is crucial in the field of immune monitoring and stimulation. Integrating new technologies, such as artificial intelligence (AI) and machine learning, holds significant promise for enhancing predictive models and refining treatment strategies (45).
3. **Collaborative Efforts:** Collaboration among researchers, clinicians, and technologists is essential to drive advancements and translate novel findings into clinical practice effectively (45).
4. **Patient-Centric Outcomes:** Emphasizing patient-centric outcomes, such as minimizing side effects and improving quality of life, should be a priority in developing and implementing new immune therapies (44).

These insights highlight the need for continued research and development to address current challenges and improve patient care in immune therapy.

6. Challenges in Current Technologies

6.1 Technical Challenges

Advancing immune monitoring and stimulation technologies involves overcoming several technical challenges. One significant hurdle is enhancing the sensitivity and specificity of these devices to ensure they accurately detect and respond to immune signals (46). Improvements in precision are necessary for accurate measurement and interpretation. Additionally, ensuring biocompatibility is crucial; devices must be safe and non-toxic when used in or on the body. This means that the materials and design of the devices need to be thoroughly tested to avoid adverse reactions in patients. Miniaturizing these technologies is also essential for seamless integration into clinical workflows, making them more user-friendly and less intrusive (47). Addressing these technical issues is crucial for improving both research outcomes and clinical applications.

6.2 Clinical and Practical Challenges

In clinical practice, ensuring patient adherence to monitoring protocols is a key challenge. Patients must consistently follow prescribed procedures and use devices correctly to obtain reliable data. Long-term device reliability is another concern; devices need to function consistently over extended periods to remain effective (48). Data privacy and security are also pressing issues, as sensitive health information must be safeguarded from unauthorized access. Additionally, integrating new technologies into existing healthcare systems involves overcoming practical obstacles, such as adapting workflows and meeting regulatory requirements, which can affect the adoption and scalability of these solutions (49).

6.3 Regulatory and Ethical Considerations

Regulatory frameworks are essential for ensuring that immune monitoring and stimulation devices are both safe and effective before they are used in patient care (50). Frameworks such as those established by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provide performance and quality standards that devices must meet. Ethical considerations are equally important and include obtaining informed consent from patients, protecting their data privacy, and ensuring equitable access to these advanced technologies. Balancing the need for innovation with ethical responsibilities is crucial to advancing medical technology while upholding patient welfare and trust (51).

7. Future Directions and Research Opportunities

7.1 Emerging Trends and Innovations

The landscape of immune monitoring and stimulation is evolving rapidly, driven by several emerging trends. One of the most transformative developments is the integration of artificial intelligence (AI) and machine learning (ML) into immune data analysis. These advanced technologies offer the potential to analyze complex immune datasets, identify patterns, and predict patient responses to treatments in real-time (52). This capability promises highly personalized therapy regimens that can be tailored to individual patients' unique needs, potentially optimizing treatment outcomes and mitigating healthcare disparities. Additionally, ongoing advancements in AI and ML could deepen our understanding of immune system dynamics, enabling the development of more effective and targeted therapies (53).

7.2 Potential Areas for Future Research

Future research should prioritize several key areas to advance immune monitoring and stimulation technologies. Developing novel biomarkers is essential for achieving more precise and comprehensive immune monitoring. These biomarkers could offer new insights into immune system status and disease progression, allowing for earlier and more accurate interventions (54). Another important focus is on advancing wearable and implantable devices capable of continuous, non-invasive immune monitoring. Such innovations could revolutionize patient care by providing real-time feedback and enabling more dynamic adjustments to treatment plans. Additionally, large-scale clinical trials are necessary to validate the efficacy and safety of these new technologies across diverse patient populations. Collaboration among researchers, clinicians, and industry stakeholders will be crucial in translating these research breakthroughs into practical clinical applications (55).

7.3 Collaborative Opportunities

To accelerate the development and implementation of immune monitoring and stimulation technologies, fostering collaborative initiatives is critical. Interdisciplinary approaches that bring together experts from various fields can lead to innovative solutions and speed up technological advancements. Promoting data sharing among researchers and institutions can improve the quality and scope of research findings, facilitating more robust conclusions and quicker discoveries. Supporting innovation hubs and partnerships between academia, industry, and clinical practice will create an ecosystem conducive to the rapid development and adoption of new technologies. Such collaborations have the potential to transform cancer care by making cutting-edge treatments more accessible and improving patient outcomes on a global scale (56,57).

Conclusion

In conclusion, immune monitoring and stimulation technologies represent significant advancements in cancer therapy, offering tailored approaches to enhance treatment precision and improve patient outcomes. This review underscores their pivotal role in evaluating and adjusting immune responses, thereby optimizing therapeutic strategies and patient management. The integration of advanced devices such as flow cytometers and biosensors, coupled with techniques like electrical and biological stimulation, enables clinicians to personalize treatments based on individual immune profiles with heightened accuracy.

Despite their promise, the field faces challenges including technical complexities, regulatory requirements, and the imperative for extensive clinical validation. Addressing these hurdles necessitates concerted efforts in research and development, interdisciplinary collaboration, and ongoing technological innovation. Embracing emerging trends such as AI-driven analytics and personalized medicine approaches will be instrumental in advancing immune monitoring and stimulation technologies within oncology. Looking ahead, continued investment in innovation, collaborative research endeavors, and strategic resource allocation are crucial to realizing the full transformative potential of these technologies in clinical practice. Ultimately, the future of immune monitoring and stimulation technologies holds immense promise for reshaping cancer treatment paradigms and significantly enhancing patient outcomes on a global scale

Abbreviations:

AI: Artificial Intelligence, CAR-T: Chimeric Antigen Receptor T-cell, DBS: Deep Brain Stimulation, FDA: Food and Drug Administration, G-CSF: Granulocyte Colony-Stimulating Factor, HER2: Human Epidermal Growth Factor Receptor 2, HLA: Human Leukocyte Antigen, JCO: Journal of Clinical Oncology, ML: Machine Learning, Neulasta: Pegfilgrastim (a long-acting G-CSF analog)

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