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Personalized Medicine in Aging: Strategies and Specific Needs of Older Adults

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Abstract:

Advanced Therapies has been held in high regard in geriatric care, especially as the world population continues to age and the question of management of diseases that are multi-morbid and chronic becomes more pronounced. Personalized medicine attempts to quantify this complexity by customizing medical intervention based on the individual specifics in order to maximize treatment efficacy and reduce side effects.

This review examines the recent growth of personalized medicine in the management of ageing populations and highlights the importance of patient individualized education plans to take into consideration age-associated physiological modifications, such as modified pharmacokinetics, diminished organ functioning, senescence of the immune system, as well as having transformed body composition. The impact of both genetic predispositions and the environment and lifestyle exposures on the course and response to treatment is also discussed.

In addition to pharmacological options, this review emphasizes the increasing role of modern therapies that include a new field of gene therapy and cell-based therapies, targeted biologics, and RNA-based therapeutics, which may be tailored with high specificity and minimal systemic side effects. These frontier treatments frequently informed by molecular and genomic profiling have the potential to revolutionize chronic-illness care in the elderly. Naturally, the review also describes major ethical, financial, and logistical impediments to implementation, data privacy, access, and monetary accessibility. Lastly, it gives recommendations on how to break these hindrances and ensure there is equitable delivery of personalized and advanced therapies in geriatric medicine.

Keywords: elderly care, pharmacogenomics, geriatric healthcare, individualized therapy, age-related diseases

Introduction

The scene of global demographics is changing dramatically as the percentage of people 65 years of age and above rises at unheard-of rates (1). Particularly as aging is strongly associated with an increased burden of chronic, non-communicative diseases, including cardiovascular diseases, type 2 diabetes, neurodegenerative conditions like Alzheimer's and Parkinson's disease, osteoporosis, and many types of cancer, this demographic change presents major

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public health challenges. Many times requiring advanced, long-term medical management, these chronic diseases demand more exact, individualized treatment plans than one-size-fits-all solutions (2).

Sometimes referred to as precision medicine, personalized medicine (PM) uses a paradigm change in healthcare to try to fit medical treatment to the unique traits of every patient (3). Personalized medicine can deal with issues related to do with genetic makeup, epigenetic changes, metabolomic changes, environmental exposures, and lifestyle, including diet, exercise, and social determinants of health. It is expected that by overcoming general therapeutic strategies, PM will help to enhance the effectiveness of treatment, reduce side effects, and ultimately improve clinical outcomes (4).

The use of personalized medicine has been shown to yield some considerable positive effects in oncology and with rare genetic conditions in young patients; however, its use has not been fully exploited yet among older patients (5). The issue with old patients is that they pose specific challenges that make the adoption of individualized medicine difficult. These include age-related physiological changes such as reduced renal and hepatic functioning, altered pharmacokinetics and pharmacodynamics, being more prone to adverse drug reactions, frequent polypharmacy and multimorbidity (6). Additionally, the processes of providing tailored care among this group are complicated by the following factors: social and functional determinants, such as frailty, cognitive decline, inaccessibility of healthcare technologies, and the question of digital literacy (7).

Given these complications, it is imperative to assess how tailored personalized medicine can be to satisfy the particular needs of the aging population. Regarding geriatric care, this review aims to present a whole picture of the present state of tailored medicine. In this paper, we will review current strategies, innovations, and the most critical impediments-scientific, clinical, and ethical-that need to be overcome to best implement PM in older adults (8). This paper also seeks to highlight chances for advancing inclusive and efficient precision health interventions that fit an aging society by pointing out gaps in research and clinical practice.

Physiological Changes in Aging and Their Impact on Medical Care

Changes in Organ Function

Aside from a spectrum of physiological changes, aging affects the pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics (drug action and efficacy) of drugs. Considering tailored medicine for senior citizens, these developments demand careful thought. Two of the most important organs in drug metabolism and clearance the kidneys and the liver—undergo functional decline with aging (9). Renal blood flow, lower glomerular filtration rate (GFR), and tubular function all help to progressively lower renal function. Among the drugs mostly eliminated by the kidneys whose excretion can be greatly lowered by these changes are digoxin, some antidiabetic medications, and aminoglycosides. In polypharmacy or dehydration, especially, poor renal clearance can lead to drug accumulation and increased nephrotoxicity risk (10). While less so than in renal function, hepatic function changes with age. Reduced liver mass, hepatic blood flow, and activity of metabolic enzymes especially those involved in phase I reactions e.g., cytochrome P450 enzymes can all lower lipophilic drug metabolic clearance. Extending the half-life of drugs and raising plasma drug concentrations will help to reduce toxicity and the risk of adverse drug reactions (ADRs) (11). Apart from pharmacokinetic considerations, aging changes pharmacodynamic reactions as well. Older people may show increased sensitivity to some drugs (e.g., benzodiazepines and opioids) while showing decreased responsiveness to some others (e.g., beta-adrenergic agonists). In order to be as safe and efficacious as possible, therapy should therefore be personalized to include personalized dosing, frequent evaluation, and consideration of age-related pharmacological parameters (12).

Beyond metabolism, aging produces immunosenescence a process whereby the immune system loses integrity. Taken together, these include compromised function of B cells, decreased production of naive T cells, and chronic low-grade inflammation (inflammaging), impairing the body's capacity to mount strong immune responses (13). The implications of these immune changes on the progression of infectious disease, the efficacy of vaccines and elderly control of chronic inflammatory disease are indeed strong. Personalized immunity may also be required by providing predesigned immunomodulators, adjuvanted vaccines, and personalized immunization schedules to enhance immunization protection to this vulnerable population (14).

Cognitive Decline

Another age-related determinant making the delivery of medical care to elderly people or sick individuals very difficult is cognitive deterioration. Older people are more prone to acquiring diseases, including mild cognitive impairment (MCI), Alzheimer's disease, and other dementias. The diseases are capable of significantly distorting the understanding, memory, and adherence capacity of a patient to complicated medical prescriptions (15). The ideas of personalized medicine hold that

cognitive decline calls for the application of unique treatments different from pharmacological drugs. Medication schedules could have to be streamlined to lower the cognitive load and the possibility of non-adherence. Care plans ask family members or caregivers to be involved in the decision-making process and incorporate digital health tools, pill organizers, or reminders (16). Furthermore affected by cognitive impairment could be a person's capacity to provide informed permission or to properly express symptoms. This presents major ethical questions regarding the autonomy and decisions taken by groups. Clinicians have to apply sensitive communication techniques; cognitive capacity has to be routinely assessed using reliable tools. By including neurocognitive profiles in tailored treatment plans, people can recognize those who are at risk and direct treatments meant to maintain cognitive capacity and improve general quality of life conditions (17). When all the elements are taken into account, cognitive and physiological changes experienced by senior citizens underline the need to customize medical treatment to the reality of the biological process of aging. A one-size-fits-all approach is inadequate to guarantee that treatments for the elderly population are both safe and effective. Functional assessments, geriatric syndromes, and comprehensive care planning have to be part of customized medicine (18).

Multi-Morbidity and Polypharmacy in Aging

Challenges of Multi-Morbidity

When people age, they often have Multi-morbidity, i.e. two or more chronic diseases, which complicates clinical care and increases the likelihood of poor outcomes. Older patients are more likely to have multimorbid conditions that include cardiovascular disease, diabetes, arthritis, neurodegenerative disease and chronic kidney disease, which adds to a more complex treatment situation (19). The complex management of these diseases often leads to polypharmacy, or taking multiple medications, which may lead to an increased rate of drug-drug/drug-disease interactions and adverse drug reactions and struggles with medication adherence. These risks are further increased by age, consisting of physiological changes such as impaired renal and hepatic function, changes therein affecting drug metabolism, and the residual physical reserve, all of which affect the responsiveness of the body to pharmacologic treatment (20). Guidelines of conventional treatment tend to be disease-specific and are usually based on the studies of younger or 1-disease patients, and they can be ineffective in older adults with multimorbidity. Personalized medicine brings a more appropriate or adapted solution in this regard. Personalized medicine overcomes these shortcomings of standardized care by designing treatment approaches on an individual basis, according to a person's genetic, clinical, and psychosocial characteristics (21). In personalized medicine, pharmacogenomics is a tool that helps clinicians select and dose drugs optimally using the genomic profile of a patient to achieve better therapeutic outcomes and minimize adverse effects. As an example, drug metabolism typically varies in individuals with genetic variants in cytochrome P450 genes or other drug transporters, and the identification of these variants can guide personalization of therapy and help inform the need to prescribe a drug. In addition, the ability to incorporate real world data, clinical decision support tools, and electronic health records enables active, patient-specific care planning where comorbidities and historic responses to treatment are considered (22). Despite these promising developments, barriers such as limited access to genetic testing, insufficient provider education, and ethical concerns regarding data privacy must be addressed to fully realize the benefits of personalized medicine in older adults. Finally, the fifth step of treatment multi-morbidity in elderly patients should be based on the removal of the disease-based model in favor of the patient-based model of precision medicine that can provide a better therapeutic outcome and patient well-being (23).

Pharmacogenomics and Aging

Included in the personalised medicine is pharmacogenomics, which deals with studying how genes interact with drugs to have a response in a person. In the elderly, pharmacogenomic data can be utilized to deduce how a patient is likely to catabolize particular medicines and limit the chances of adverse effects (24). As an example, genetic differences in other enzymes, such as cytochrome P450 (CYP450), can affect the way some medications, such as anticlotting medications and antidiabetic drugs, are broken down. Introduction of pharmacogenomic testing in clinical practice can enable healthcare providers to develop safer and more effective treatment regimens, which have many benefits for older adults (25).

Genomic and Environmental Factors in Aging

Genetic Influences on Aging and Disease

Genetic factors have a key role in the biological process of aging and also age-related diseases, and are involved in population variability in both health trajectories and longevity. Many genes have been discovered to regulate longevity, cellular senescence, and the predisposition to age-dependent diseases like cardiovascular, cancer, and neurodegenerative diseases (26). The recent developments in genomics have helped scientists to identify the genetic

variations that moderate inflammation, oxidative stress response, and DNA repair pathways, which have been consistently tied to changes in the age of physiological decline. In the midst of personalized medicine, these findings have a significant implication on the care of the elderly (27). Genetic screening is becoming more common to distinguish high-risk patients with a given disease in order to effectively find more personalized prevention methods. The example of the APOE ε4 single-nucleotide polymorphism is a well-described genetic risk factor in the development of Alzheimer's disease, and those who possess this particular variant are potential candidates to benefit through early cognitive screening, lifestyle changes and possible participation in clinical trials as subject to receive disease-modifying treatment (28). Similarly, hereditary cancer-related genes, e.g. BRCA1 and BRCA2, can considerably elevate the risk of breast, ovarian and other cancers over a lifetime, which necessitates genetic testing to inform decisions regarding following up the disease (increased surveillance), prophylactic surgery, or chemoprevention. Along with risk prediction, genetic data can enhance treatment personalization; polymorphisms in drug-metabolizing enzymes, so common in older individuals, can alter a person's response to common drugs used in older age groups, thereby personalizing drug selection and dosing (29). Ethical considerations, the psychological burden of genetic risk disclosure, and patient access disparities are some of the concerns that are relevant to genetic information implementation in clinical practice, although they are still considered to be great promises. Nonetheless, the trend towards the uses of genomic technologies in geriatrics will presumably lead to an increasingly preventive and remedial approach to the healthy aging process and increasing the healthy years of life (30).

Environmental and Lifestyle Factors

Environmental and lifestyle factors have a significant negative effect on the aging process and the condition of the development of chronic morbidity, which has a complementary relationship with genetic determinants. The factors that have a large influence on health and the pathway towards longevity include diet, physical activity, smoking, and alcohol consumption, sleep quality, as well as long-term exposure to environmental toxins (e.g. air pollution, heavy metals and endocrine-disrupting chemicals). The aggregate effects of these external influences are magnified as people age, resulting in oxidative stress, chronic inflammation, cell injury and accelerated aging (31).

Genetically personalized medicine will use individualized care approaches by incorporating these potentially variable factors, including lifestyle and the environment, that can interact with genetic susceptibilities in ways that can increase or eliminate disease risks (32). Another example is the individual with a genetic tendency to type 2 diabetes who can be helped by intense, individualized nutrition, coupled with routine workouts and weight control, and so prevent or at least postpone a disease development. Similarly, patients who have cardiovascular risk factors may be advised to make lifestyle modifications that would be tailored to their clinical phenotypes but also to their genomes, once personalized to interventions that relate to the reduction of sodium or increasing physical activity and smoking cessation (33).

With the rise of wearables, mobile healthcare software, and various forms of digital biomarkers, the real-time tracking of lifestyle-related factors is made possible, and the adaptation of health plans can be adjusted in real-time. Furthermore, the epigenetics studies have shown that the effects of environmental as well as behavioral factors can also manipulate the gene expression through the influencing of both methylation and modifications of histones and have proved that the aging process is not irreversible, but depending on the available interventions, the aging process can also be suspended or at least stopped partly by the effect of the interventions (34). The development of such things as wearable devices, mobile health applications, and digital biomarkers helps to introduce real-time tracking of lifestyle parameters, providing an opportunity to alter health plans, based on instant feedback (35). Epigenetic studies have been found to demonstrate that behavior and environmental factors can affect gene expression via processes like DNA methylation and histone regulation, and have also indicated that the aging process is not irreversible and could be reversed or at least slowed down through a series of interventions (36).

Integrating the role of the environment and lifestyle into the concept of personalized medicine, clinicians can create a more wholesome, preventive, and therapeutic strategy of care that would not be limited to symptom management by actively enhancing the resilience, functional independence, and overall well-being of aging people. Such a strategy not only results in a longer lifespan but also a healthier life, in the number of years free of disability and illness (37).

Emerging Technologies in Personalized Medicine for Older Adults

Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning (ML) have now become revolutionary in the field of personalized medicine as they provide sources to tackle the complexity of healthcare in aging populations (38). Since older adults typically have

a complex mixture of concerns (chronic conditions, cognitive decline, and functional limitations), AI-enabled tools can be indispensable in using a variety of data (genomic, clinical, imaging, behavioral and environmental data) and translating this information into useful feedback. Big and complicated data can be processed by these technologies, and correlations, patterns, and trends are detected that cannot be cognitively perceived by a human (39).

In geriatric practice, AI-driven algorithms are being used to assist in making more accurate diagnoses, making therapy choices, and keeping track of disease. As an example, the use of machine learning models has demonstrated potential in forecasting the onset and progression of diseases like Alzheimer's and Parkinson's based on longitudinal changes in biomarkers (e.g., in imaging, genetic risk factors, such as the APOE variants), cognitive tests, and potentially lifestyle behaviors (40). Such predictive models can also be used to help select interventions and the timing of those interventions to maximize the benefits and prolong the maintenance of cognitive function (41).

The use of IA also enables risk stratification of the older population to assess individuals who are susceptible to adverse drug reactions, readmission and functional decay. The integration of pharmacogenomic information would allow AI to guide clinicians in optimizing drug regimens in order to avoid complications related to polypharmacy, commonly faced by geriatric patients (42). Further, NLP tools can draw meaningful insights that might have otherwise been identified by aggregating unstructured EHRs to help healthcare providers develop comprehensive and personalized care plans. In addition to diagnostics and treatment planning, AI-assisted wearable devices and intelligent appliances provide 24/7 monitoring of vital signs, mobility trackers, sleep quality and drug compliance status (43). By allowing health deterioration to be identified early to assist in aging in place, these tools can help prevent hospitalizations. The use of AI enhances the decision support systems, which also empowers clinicians and caregivers who, through evidence-based recommendations, receive advice that considers the specific physiological and psychosocial situation of a patient among the elderly (44).

Nevertheless, the ethical, privacy, and equity consequences are issues of concern to the widespread use of AI and ML in geriatric personalized medicine, since even the most optimistic scenarios (45). Algorithmic transparency, overcoming biases in training data, and data security are crucial to prevent the absence of trust and promote fair and equitable provision of care. Even so, these technologies have the potential to transform the process of aging care by making personalized medicine more proactive, precise, and patient-centered as they continue to evolve (46).

Biomarkers and Personalized Diagnostics

Personalized diagnostics hinges on biomarkers as measurable indicators of bio-status or pathological processes, especially with age-related dimensions. With the swelling population of the aging people, there is a need for early, accurate and more individualized forms of disease detection and management. In geriatric medicine, biomarkers provide an effective means of predicting the onset of disease, tracking disease progression and even evaluating the effectiveness of treatment in many cases before the clinical pathology is noticed (47).

Age-related alterations at the molecular and cellular levels (e.g., chronic, low-grade inflammation, or inflammagin, oxidative stress, or cell senescence) are often mirrored by certain biomarker patterns. Discovering and confirming these biomarkers can be used in early diagnosis of disease conditions, especially cardiovascular disease, chronic kidney disease, diabetes type two, Osteoporosis and diseases of the nerve like Alzheimer's and Parkinson among others (48). As an example, cardiac biomarkers, e.g. high-sensitivity troponin and natriuretic peptides (e.g. NT-proBNP) can provide helpful information regarding the subclinical heart failure or strain in elderly individuals. Equally, biomarkers such as serum creatinine, cystatin C, and albumin-to-creatinine ratio kidney data allow clinicians to identify and treat early renal impairment that is prevalent in older individuals (49).

In the neurodegenerative disease field, the existing activity of the measurement of neural biological fluids (cerebral spinal fluid (CSF) and plasma) biomarkers has transformed early diagnosis of Alzheimer's disease, which includes measurements of 8-amyloid protein, frontotemporal dementia, total tau, and phosphorylated tau proteins. Such biomarkers can be used to stratify which individuals at risk of dementia can be treated years or even decades before their clinical onset, to the benefit of effective interventions to prevent the disease or even cure it (50).

Tailoring of diagnostics and interventions to the disease, as well as to the biological age of the patient (which often significantly differs from chronological age), is enabled by the personalization of diagnostics on the basis of a biomarker profile. This differentiation is vital because some people will undergo a faster rate of biological aging because of genetic tendencies, environmental exposures or lifestyle behaviors. Biomarker-aided interventions have the potential to tailor choices on whether, when, and how aggressively therapeutic interventions are initiated, and what the interventions should be in

patients with multimorbidity and many medications (51).

Additionally, personalized diagnostics can further be enhanced by incorporating biomarker evidence along with the evidence of genomic, proteomic, metabolomic, and microbiomic data sources, so-called multimics. This kind of merger makes it possible to understand the health status and disease development of an individual in its whole dimension, and it creates opportunities regarding the provision of preventive geriatric health care (52).

Nevertheless, there are still issues with validation and standardization of discovery and routine use of biomarkers in older adults. Too much variability due to comorbidities, use of medication, and other age-related physiological changes makes interpretation difficult. Hence, further research, universal longitudinal studies and age-specific reference ranges are mandatory to leverage the clinical usefulness of biomarkers in geriatric personalized medicine (53).

Barriers to Implementing Personalized Medicine in Geriatric Care

Economic Barriers

Besides financial barriers, economic barriers are also a major threat to the wider adoption of personalized medicine, especially in the care of the aged. Personalized medicine may run on very advanced technology, including genetic/genomic testing, enhanced biomarker analysis and high-resolution imaging systems, and tailored medication - all of which can advance much too costly to be affordable (54). A substantial financial burden can be imposed on healthcare systems by the costs of such relative diagnostic tools and individual treatment options, especially when budgets are already strained or costs are not covered in low- and middle-income countries (55).

In case of older adults, who more often than not need complex, long-term medical treatment of their chronic conditions and multimorbidity, the personalized interventions increase the cost of care even more (56). Genetic testing or precision therapies may be beyond the current means of many elderly patients, who base their income on fixed payments, pensions, or coverage with limited insurance plans. Such an economic inequality generates health inequalities in access to personalized medicine, constituting a possible way of worsening the current health inequalities in older populations (57).

Personalized medicine is variably covered by insurance across the world. Genetic screening, pharmacogenomic testing, and novel genetically targeted treatment have also not seen full recognition or reimbursement by health insurance policies or governmental health programs in many regions, with a resulting lack of access to individuals who could benefit the most. Without universal coverage, financial burdens are placed on patients and families, discouraging usage and reducing the potential value of personalized medicine to geriatrics in general (58).

Also, the support structure that would enable the implementation of personalized medicine (i.e., trained workforce, bioinformatics support, and genetic counseling services) would add further costs to the existing infrastructures that are not ready to take the load. The economic limitations can also act as a restrictive factor, leading to slower adoption of new innovative technologies into the mainstream of clinical practice, increasing the time lag between the technology options and their positive impact on older adults (59).

To overcome these economic impediments, it is important that policy makers, medical professionals, insurance companies and industry stakeholders act in sync with each other. Some of the most critical strategies that should be implemented are the development of cost-effectiveness analyses, support of policy changes to increase insurance coverage, investment in scalable and affordable diagnostic technology, and investment in resource distribution on an equal basis (60). Moreover, creative approaches such as public-private partnerships and novel funding mechanisms can be valuable in minimizing the cost of personalized medicine and thereby improving equitable accessibility so that the benefits of personalized medicine are available to all older adults, irrespective of their socioeconomic status (61).

Ethical and Social Considerations

The use of personalized medicine in aging populations has many ethical and social implications that are complex and must be carefully considered because the proper interpretations of the process must pursue fairness and responsible healthcare service. Among the central ethical issues, there is the concern over privacy and confidentiality of the genetic information (62). Genetic data is also very sensitive in nature as it holds deep personal and possibly predictive information concerning the health risks and predispositions in an individual. In the case of older adults, the security of this data being stored properly, where no one other than the owner can access it, is a key to the trust of healthcare systems. The disclosures of genetic privacy may give rise to stigmatization or abuse of the information, which presents patients with worries about who gets to see their record and can do with it (63).

The other major ethical concern is the prospect of genetic discrimination, especially in matters of insurance coverage, workplaces, and social relations. Older people may even be subject to prejudices or to being denied services if their genetic predisposition

towards specific diseases is revealed, irrespective of legislation in some nations intended to stop this form of discrimination. There are dangers that individuals fear discrimination due to the results of genetic tests, which makes them avoid genetic testing and the implementation of personalized medicine altogether (64).

Informed consent is another issue that is related to geriatric care, especially when the patient has cognitive decline or dementia. The correct procedure of consenting to genetic testing and other complex personalized interventions should be sensitively explained, and discussion with custodians or legal guardians should be conducted in order to make valid and informed consent. It is crucial that older adults be aware of the consequences, risks, and benefits of the testing to stay as autonomous and free citizens (65).

Personalization medicine in the older populations is significantly affected by social determinants of health as well. Genetic information can increase confusion around the mechanisms of health literacy, and some older adults have low health literacy due to a lack of access or ability to navigate the healthcare system and make informed health choices. Personalized medicine demands the absence of unclear education and support sensitivity to the level of understanding of the individual person to prevent the enhancement of the health disparities (66).

Another burning issue is accessibility. The socioeconomic status, the geographical location and the culture of an older person have been seen as having some role to play in terms of the accessibility of the older person to the customized diagnostic, treatments and post-testing measures. There also may be additional barriers to genetic counseling or new medical treatments among rural populations or marginalized groups, further widening health disparities (67).

To mitigate these ethical and social issues, the policies and healthcare practitioners should employ inclusive approaches that encourage transparency, education and equality. This encompasses drafting the laws of the genetic data protection, laws of anti-discrimination, culturally competent communication, health literacy programs in older aging, among others (68). Moreover, it is important to promote community involvement and help older adults make decisions to make this group of patients more empowered and able to enjoy personalized medicine delivered to them (69).

In short, ethical stewardship and social sensitivity should also become essential to realize the full promise of personalized medicine in aging populations by ensuring it adds value to each person, is reached in equitable and ethical ways, and addresses all in a way that respects their dignity, rights, and diverse backgrounds (70).

Logistical Challenges

The barriers that present challenges to older adults are usually in the form of dire logistical problems to access personalized medicine. Their lack of mobility, such as the ability to drive or indeed rely on others to take them to their medical appointments, as well as to specialized testing to receive specialized care, usually becomes their disability to attend regular medical care or indeed, testing so that they can receive specialized care (71). Cognitive dysfunctions that are common in an aging-growth community, like memory loss and impaired executive functioning, have the potential to make interaction with medical institutions, reading complex medical information, and adhering to medical prescriptions much more difficult. Communication barriers that can be augmented are sensory deprivation, such as loss of sight or hearing ability. Healthcare systems and providers must develop more adaptable models that are more patient-centric to deal with such issues (72). This can be in terms of offering transport assistance, application of telemedicine and home-based care comparisons, simplification of language usage or reducing the complexity of the language, and the involvement of caregivers in treatment modality. It can address these logistical challenges keenly, and by default, personalized medicine would become effective for older adults and ultimately give them good positive results in their health and other aspects of life (73).

Future Directions in Personalized Medicine for Aging Populations

The future of health is personalized medicine, and this has a fascinating potential for bettering the lives and the outcome in older adults. The future research directions in genomic medicine, AI, and even more personal approaches to diagnostics are predicted to enable us to predict, prevent, and treat age-related diseases and individualize the process (74). However, navigating the economic, ethical, and practical challenges would require the interaction of the healthcare providers with the researchers, policymakers, and above all, the aging population. It is necessary to incorporate personalized medicine into the everyday life of geriatrics in order to provide the elderly with the most beneficial level of care by taking into consideration their own needs (75).

DISCUSSION

This review emphasis the fact that although the conceptual requirement of personalized medicine has grown considerably during the last two decades, it is still in a nascent and fragmented stage as applied intermittently to geriatric medicine (76). The gap is not only technical but also epistemological: most studies on pharmacogenomic finding and

biomarker validation were studied in a younger or disease-specific group with limited extension into the physiological complexity of elderly populations (77). As such, there is a danger in overpromising the benefits, without providing adequate consideration to the altered pharmacokinetics, multimorbidity, and frailty for which this group is characterized (78).

One principal constraint from the current pool of evidence is a lack of robust, large, age-stratified clinical trials. Although a number of genetic variants and biomarkers have been associated with drug response in elderly subpopulations, reproducibility across different populations is inconsistent (79). The fact that surrogate endpoints are relied on instead of patient hard clinical outcomes, further undermines their immediate applicability in clinical decision-making. This underpins a critical need to refocus research priorities, past descriptive studies and towards pragmatic, geriatric-focused trials that can assess efficacy and tolerability in a real world multi-morbid context (80).

Technological innovations - especially artificial intelligence, machine learning and monitoring using wearable technology - have been touted as the solution to geriatric care's complexities (81). However, these approaches can hauntingly increase health inequities if digital literacy, socioeconomic disparities and cognitive decline are not explicitly considered in designing and implementing strategies. Algorithmic transparency and the removal of bias in training datasets are other imperatives if these toolsets are to be trusted by clinicians and patients (82).

Advanced therapies like gene and cell-based therapy mark the cutting edge of individualized treatment but have enormous translational hurdles. The high financial investment, the logistic challenges and inferentiability of ancillary clinical studies within the elderly population preclude, at this time, their general incorporation in routine practice (83). In contrast, strategies that are more immediately actionable-ones that can singly be described as pharmacogenomic-guided prescribing, dose optimization based on renal and hepatic function, and risk stratification by polypharmacy-found realistic opportunities for near-term impact (84). Policymakers and healthcare systems should therefore try to focus on scalable and cost-effective ways to take advantage of personalization while ensuring at the same time that regulatory and ethical structures are prepared to cope with the next-generation therapeutics (85).

In conclusion, the promise of personalized and advanced therapies for older adults is undeniable, but their successful implementation requires a paradigm shift in research, practice, and policy. Establishing geriatric centered clinical evidence, equitable access to digital and molecular innovations andcrafting the divide between technological enthusiasm and pragmatic delivery of health care will determine whether precision medicine will become a transformational tool or just an aspirational dream for aging societies at risk.

CONCLUSION

Personalized medicine is an innovative strategy in healthcare that can be used to change the way age-related conditions are treated in a far better way. Based on the individual physiological, genetic, and environmental conditions that age-related changes affect health in later years, personalized medicine would assist in streamlining the approach to treatment, minimizing adverse effects, and increasing the quality of life in general. The introduction of PM to geriatric care offers a variety of obstacles that need to be resolved to ensure a positive outcome, including economic, moral, and logistical challenges. Personalized medicine has a chance to become a landmark in the realm of aging-related healthcare with constant research and innovation to help people and provide them with what they need.

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REFERENCE

1. Noto, S., Perspectives on Aging and Quality of Life. Healthcare (Basel), 2023. 11(15).
2. Kopp, W., Aging and "Age-Related" Diseases - What Is the Relation? Aging Dis, 2024. 16(3): p. 1316-1346.
3. Stefanicka-Wojtas, D. and D. Kurpas, Personalised Medicine-Implementation to the Healthcare System in Europe (Focus Group Discussions). J Pers Med, 2023. 13(3).
4. Gupta, I., et al., Connecting the dots: investigating the link between environmental, genetic, and epigenetic influences in metabolomic alterations in oral squamous cell carcinoma. Journal of Experimental & Clinical Cancer Research, 2024. 43(1): p. 239.
5. Wang, R.C. and Z. Wang, Precision Medicine:

Disease Subtyping and Tailored Treatment. Cancers (Basel), 2023. 15(15).
6. Wang, R.C. and Z. Wang Precision Medicine: Disease Subtyping and Tailored Treatment. Cancers, 2023. 15, DOI: 10.3390/cancers15153837.
7. Reynolds, C.F., 3rd, et al., Mental health care for older adults: recent advances and new directions in clinical practice and research. World Psychiatry, 2022. 21(3): p. 336-363.
8. Edvardsson, M. and M.K. Heenkenda, Precision Medicine: Personalizing Healthcare by Bridging Aging, Genetics, and Global Diversity. Healthcare (Basel), 2025. 13(13).
9. Ngcobo, N.N., Influence of Ageing on the Pharmacodynamics and Pharmacokinetics of Chronically Administered Medicines in Geriatric Patients: A Review. Clin Pharmacokinet, 2025. 64(3): p. 335-367.
10. Reynolds 3rd, C.F., et al., Mental health care for older adults: recent advances and new directions in clinical practice and research. World Psychiatry, 2022. 21(3): p. 336-363.
11. Ruiz, A. and S. DiCristina, Absorption to Excretion: The Aging Body's Take on Drugs – A Review of Pharmacokinetic Changes and their Impact on Medication Management. Current Pharmacology Reports, 2025. 11(1): p. 42.
12. Gronich, N., Central Nervous System Medications: Pharmacokinetic and Pharmacodynamic Considerations for Older Adults. Drugs Aging, 2024. 41(6): p. 507-519.
13. Wang, Y., et al., Immunosenescence, aging and successful aging. Front Immunol, 2022. 13: p. 942796.
14. Müller, L. and S. Di Benedetto Immunosenescence and Cytomegalovirus: Exploring Their Connection in the Context of Aging, Health, and Disease. International Journal of Molecular Sciences, 2024. 25, DOI: 10.3390/ijms25020753.
15. Chen, L., J. Jiao, and Y. Zhang, Therapeutic approaches for improving cognitive function in the aging brain. Front Neurosci, 2022. 16: p. 1060556.
16. Haleem, A. and M. Javaid, Role of cognitive computing in enhancing innovative healthcare solutions. Advances in Biomarker Sciences and Technology, 2024. 6: p. 152-165.
17. David, M.C.B., et al., Considerations for legal, ethical, and effective practice in dementia research. Brain Commun, 2024. 6(4): p. fcae211.
18. Barbaccia, V., et al., Mature and Older Adults' Perception of Active Ageing and the Need for Supporting Services: Insights from a Qualitative Study. Int J Environ Res Public Health, 2022. 19(13).
19. Skou, S.T., et al., Multimorbidity. Nat Rev Dis Primers, 2022. 8(1): p. 48.
20. Sutanto, H., Tackling polypharmacy in geriatric patients: Is increasing physicians' awareness adequate? Archives of Gerontology and Geriatrics Plus, 2025. 2(3): p. 100185.
21. Rushforth, A. and T. Greenhalgh, Personalized Medicine, Disruptive Innovation, and "Trailblazer" Guidelines: Case Study and Theorization of an Unsuccessful Change Effort. The Milbank Quarterly, 2020. 98(2): p. 581-617.
22. Sadee, W., et al., Pharmacogenomics: Driving Personalized Medicine. Pharmacol Rev, 2023. 75(4): p. 789-814.
23. Erdmann, A., C. Rehmann-Sutter, and C. Bozzaro, Patients' and professionals' views related to ethical issues in precision medicine: a mixed research synthesis. BMC Med Ethics, 2021. 22(1): p. 116.
24. Auwerx, C., et al., From pharmacogenetics to pharmaco-omics: Milestones and future directions. HGG Adv, 2022. 3(2): p. 100100.
25. Zhang, Y., et al., CYP3A4 and CYP3A5: the crucial roles in clinical drug metabolism and the significant implications of genetic polymorphisms. PeerJ, 2024. 12: p. e18636.
26. Castruita, P.A., et al., Genetic, Social, and Lifestyle Drivers of Healthy Aging and Longevity. Curr Genet Med Rep, 2022. 10(3): p. 25-34.
27. Zhao, Y., et al., DNA damage and repair in age-related inflammation. Nat Rev Immunol, 2023. 23(2): p. 75-89.
28. Stocker, H., et al., Prediction of clinical diagnosis of Alzheimer's disease, vascular, mixed, and all-cause dementia by a polygenic risk score and APOE status in a community-based cohort prospectively followed over 17 years. Molecular Psychiatry, 2021. 26(10): p. 5812-5822.
29. McCarthy, A.M. and K. Armstrong, The role of testing for BRCA1 and BRCA2 mutations in cancer prevention. JAMA Intern Med, 2014. 174(7): p. 1023-4.
30. Jamal, L., W. Schupmann, and B.E. Berkman, An ethical framework for genetic counseling in the genomic era. J Genet Couns, 2020. 29(5): p. 718-727.
31. Argentieri, M.A., et al., Integrating the environmental and genetic architectures of aging and mortality. Nature Medicine, 2025. 31(3): p. 1016-1025.
32. Molla, G. and M. Bitew, Revolutionizing Personalized Medicine: Synergy with Multi-Omics Data Generation, Main Hurdles, and Future Perspectives. Biomedicines, 2024. 12(12).
33. Singh, S., et al., Deciphering the complex interplay of risk factors in type 2 diabetes mellitus: A comprehensive review. Metabolism Open, 2024. 22: p. 100287.
34. Thacharodi, A., et al., Revolutionizing healthcare and medicine: The impact of modern technologies for a healthier future-A comprehensive review.

Health Care Sci, 2024. 3(5): p. 329-349.
35.Ahmed, M.M., et al., Integrating Digital Health Innovations to Achieve Universal Health Coverage: Promoting Health Outcomes and Quality Through Global Public Health Equity. Healthcare (Basel), 2025. 13(9).
36.Smokovski, I., et al., Digital biomarkers: 3PM approach revolutionizing chronic disease management - EPMA 2024 position. Epma j, 2024. 15(2): p. 149-162.
37.Alzeer, J.J.J.o.P.H. and Emergency, Integrating medicine with lifestyle for personalized and holistic healthcare. 2023, 2023. 7.
38.Bajwa, J., et al., Artificial intelligence in healthcare: transforming the practice of medicine. Future Healthc J, 2021. 8(2): p. e188-e194.
39.Alowais, S.A., et al., Revolutionizing healthcare: the role of artificial intelligence in clinical practice. BMC Medical Education, 2023. 23(1): p. 689.
40.Wang, H., et al., Neurodegenerative disorders: A Holistic study of the explainable artificial intelligence applications. Engineering Applications of Artificial Intelligence, 2025. 153: p. 110752.
41.Alowais, S.A., et al., Revolutionizing healthcare: the role of artificial intelligence in clinical practice. BMC Med Educ, 2023. 23(1): p. 689.
42.Alsanosi, S.M. and S. Padmanabhan, Potential Applications of Artificial Intelligence (AI) in Managing Polypharmacy in Saudi Arabia: A Narrative Review. Healthcare (Basel), 2024. 12(7).
43.Baig, M.M., et al. Generative AI in Improving Personalized Patient Care Plans: Opportunities and Barriers Towards Its Wider Adoption. Applied Sciences, 2024. 14, DOI: 10.3390/app142310899.
44.Dailah, H.G., et al., Artificial Intelligence in Nursing: Technological Benefits to Nurse's Mental Health and Patient Care Quality. Healthcare (Basel), 2024. 12(24).
45.Farhud, D.D. and S. Zokaei, Ethical Issues of Artificial Intelligence in Medicine and Healthcare. Iran J Public Health, 2021. 50(11): p. i-v.
46.Williamson, S.M. and V. Prybutok Balancing Privacy and Progress: A Review of Privacy Challenges, Systemic Oversight, and Patient Perceptions in AI-Driven Healthcare. Applied Sciences, 2024. 14, DOI: 10.3390/app14020675.
47.Bodaghi, A., N. Fattahi, and A. Ramazani, Biomarkers: Promising and valuable tools towards diagnosis, prognosis and treatment of Covid-19 and other diseases. Heliyon, 2023. 9(2): p. e13323.
48.Rea, I.M., et al., Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. Front Immunol, 2018. 9: p. 586.
49.Vasan, S.K., et al., Utility of Cardiac Biomarkers (N-Terminal Pro-B-Type Natriuretic Peptide and Hs-Troponin-T) in Predicting Mortality, Cardiovascular, and Renal Outcomes in Patients with Chronic Kidney Disease. Am J Nephrol, 2025: p. 1-16.
50.Kang, J.H., et al., Alzheimer Disease Biomarkers: Moving from CSF to Plasma for Reliable Detection of Amyloid and tau Pathology. Clin Chem, 2023. 69(11): p. 1247-1259.
51.Tao, X., et al., Biomarkers of Aging and Relevant Evaluation Techniques: A Comprehensive Review. Aging Dis, 2024. 15(3): p. 977-1005.
52.Babu, M. and M. Snyder, Multi-Omics Profiling for Health. Mol Cell Proteomics, 2023. 22(6): p. 100561.
53.Loughlin, K.N.M., et al., Perspective: Biomarkers of Aging in Human Nutrition Research—A Focus on Applications, Challenges, and Opportunities. Advances in Nutrition, 2025: p. 100486.
54.Parekh, A.E., et al., Artificial intelligence (AI) in personalized medicine: AI-generated personalized therapy regimens based on genetic and medical history: short communication. Ann Med Surg (Lond), 2023. 85(11): p. 5831-5833.
55.Butt, M.D., et al., A systematic review of the economic burden of diabetes mellitus: contrasting perspectives from high and low middle-income countries. J Pharm Policy Pract, 2024. 17(1): p. 2322107.
56.Wu, J., et al., Healthcare for Older Adults with Multimorbidity: A Scoping Review of Reviews. Clin Interv Aging, 2023. 18: p. 1723-1735.
57.Barajas-Nava, L.A., et al., Models of comprehensive care for older persons with chronic diseases: a systematic review with a focus on effectiveness. BMJ Open, 2022. 12(8): p. e059606.
58.Koleva-Kolarova, R., et al., Financing and Reimbursement Models for Personalised Medicine: A Systematic Review to Identify Current Models and Future Options. Appl Health Econ Health Policy, 2022. 20(4): p. 501-524.
59.Borry, P., et al., The challenges of the expanded availability of genomic information: an agenda-setting paper. J Community Genet, 2018. 9(2): p. 103-116.
60.Fan, C., C. Li, and X. Song, The relationship between health insurance and economic performance: an empirical study based on meta-analysis. Front Public Health, 2024. 12: p. 1365877.
61.Hussain, A., et al., Exploring sustainable healthcare: Innovations in health economics, social policy, and management. Heliyon, 2024. 10(13): p. e33186.
62.Brothers, K.B. and M.A. Rothstein, Ethical, legal and social implications of incorporating personalized medicine into healthcare. Per Med, 2015. 12(1): p. 43-51.
63.Clayton, E.W., et al., The law of genetic privacy: applications, implications, and limitations. J Law Biosci, 2019. 6(1): p. 1-36.

64.Chapman, C.R., et al., Genetic discrimination: emerging ethical challenges in the context of advancing technology. J Law Biosci, 2020. 7(1): p. lsz016.
65.Diaz, A., et al., Informed consent in dementia research: how Public Involvement can contribute to addressing “old” and “new” challenges. 2025. Volume 4 - 2025.
66.Coughlin, S.S., et al., Health Literacy, Social Determinants of Health, and Disease Prevention and Control. J Environ Health Sci, 2020. 6(1).
67.Chen, L. and M. Cheng Exploring Older Adults’ Perceived Affordability and Accessibility of the Healthcare System: Empirical Evidence from the Chinese Social Survey 2021. Healthcare, 2023. 11, DOI: 10.3390/healthcare11131818.
68.Clayton, E.W., et al., The law of genetic privacy: applications, implications, and limitations. Journal of Law and the Biosciences, 2019. 6(1): p. 1-36.
69.Pham, T., Ethical and legal considerations in healthcare AI: innovation and policy for safe and fair use. R Soc Open Sci, 2025. 12(5): p. 241873.
70.Alodhialah, A.M., A.A. Almutairi, and M. Almutairi, Ethical and Legal Challenges in Caring for Older Adults with Multimorbidities: Best Practices for Nurses. Healthcare (Basel), 2024. 12(16).
71.Horvat, M., I. Eržen, and D. Vrbnjak Barriers and Facilitators to Medication Adherence among the Vulnerable Elderly: A Focus Group Study. Healthcare, 2024. 12, DOI: 10.3390/ healthcare12171723.
72.Kamatham, P.T., et al., Pathogenesis, diagnostics, and therapeutics for Alzheimer's disease: Breaking the memory barrier. Ageing Research Reviews, 2024. 101: p. 102481.
73.Haleem, A., et al., Telemedicine for healthcare: Capabilities, features, barriers, and applications. Sens Int, 2021. 2: p. 100117.
74.Johnson, K.B., et al., Precision Medicine, AI, and the Future of Personalized Health Care. Clin Transl Sci, 2021. 14(1): p. 86-93.
75.Jones, C.H. and M. Dolsten, Healthcare on the brink: navigating the challenges of an aging society in the United States. NPJ Aging, 2024. 10(1): p. 22.
76.Jørgensen, J.T., Twenty Years with Personalized Medicine: Past, Present, and Future of Individualized Pharmacotherapy. Oncologist, 2019. 24(7): p. e432-e440.
77.Lauschke, V.M. and M. Ingelman-Sundberg, Emerging strategies to bridge the gap between pharmacogenomic research and its clinical implementation. NPJ Genom Med, 2020. 5: p. 9.
78.Zazzara, M.B., et al., Adverse drug reactions in older adults: a narrative review of the literature. Eur Geriatr Med, 2021. 12(3): p. 463-473.
79.Furrer, R. and C. Handschin, Biomarkers of aging: from molecules and surrogates to physiology and function. 2025. 105(3): p. 1609-1694.
80.Christensen, R., et al., Surrogate endpoints: a key concept in clinical epidemiology. J Clin Epidemiol, 2024. 167: p. 111242.
81.Wang, W.-H. and W.-S. Hsu Integrating Artificial Intelligence and Wearable IoT System in Long-Term Care Environments. Sensors, 2023. 23, DOI: 10.3390/s23135913.
82.Joseph, J., Algorithmic bias in public health AI: a silent threat to equity in low-resource settings. Front Public Health, 2025. 13: p. 1643180.
83.Kohn, D.B., Y.Y. Chen, and M.J. Spencer, Successes and challenges in clinical gene therapy. Gene Ther, 2023. 30(10-11): p. 738-746.
84.Rollinson, V., R. Turner, and M. Pirmohamed, Pharmacogenomics for Primary Care: An Overview. Genes (Basel), 2020. 11(11).
85.Ștefan, A.-M., et al. Empowering Healthcare: A Comprehensive Guide to Implementing a Robust Medical Information System—Components, Benefits, Objectives, Evaluation Criteria, and Seamless Deployment Strategies. Applied System Innovation, 2024. 7, DOI: 10.3390/asi7030051.

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CAR-T Cell Therapy in Systemic Lupus Erythematosus: Mechanisms, Toxicities, and Management Strategies

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Abstract:

Chimeric Antigen Receptor T-cell (CAR-T) therapy has revolutionized cancer treatment, particularly in hematologic malignancies, by genetically modifying a patient's T cells to specifically target and eliminate tumor cells. This groundbreaking approach has led to remarkable clinical outcomes, especially in patients with refractory or relapsed cancers. Over the past few years, CAR-T cell therapy has also been explored for the treatment of autoimmune diseases, including systemic lupus erythematosus (SLE), a complex and chronic autoimmune condition characterized by widespread inflammation and tissue damage. While the potential for CAR-T therapy in autoimmune disorders is significant, its application is accompanied by a range of toxicities that can pose substantial risks to patients, complicating its clinical use. These toxicities arise due to the powerful immune activation induced by CAR-T cells, which can affect various organ systems and result in serious side effects. This paper reviews the mechanisms behind CAR-T therapy-related toxicities, focusing on key adverse events such as Cytokine Release Syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), hematologic and cellular toxicities, as well as concerns regarding immunogenicity and oncogenic risks. Understanding these toxicities is critical to maximizing the therapeutic benefit of CAR-T therapy while minimizing potential harm to patients.

Keywords: Systemic lupus erythematosus (SLE), CAR-T cell therapy toxicities, Cytokine Release Syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Introduction

Systemic Lupus Erythematosus (SLE) is a complex and debilitating autoimmune disease that affects approximately 5 million people worldwide. Characterized by immune system dysregulation, SLE leads to the production of autoantibodies, causing widespread inflammation and damage to various organs (1-3). The disease course is unpredictable, with periods of flare-ups and remissions, and it is often associated with high morbidity and mortality. Traditional treatments for SLE, including corticosteroids, immunosuppressive drugs, and

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biologics such as rituximab and belimumab, aim to control immune hyperactivity but often come with significant side effects like increased infection risk and reduced patient quality of life (4). As a result, there is a growing need for novel therapies that can more precisely target immune dysregulation while minimizing adverse effects (5).

CAR-T cell therapy, a promising approach originally developed for cancer treatment, is emerging as a potential therapeutic strategy for autoimmune diseases like SLE. This therapy involves modifying a patient's T cells to express a chimeric antigen receptor (6), which allows the T cells to specifically recognize and target autoantibody-producing B cells, a hallmark of SLE (7). Although still in its early stages, CAR-T therapy has shown promise in preclinical and early clinical studies.

The application of CAR-T therapy in the treatment of autoimmune diseases, particularly in conditions like SLE, represents a paradigm shift in how autoimmune disorders could be managed in the future. In SLE, B cells and their resultant autoantibodies play a critical role in disease pathogenesis (8). By engineering CAR-T cells to target specific markers on autoreactive B cells, such as CD19 or CD20, researchers aim to directly eliminate these pathogenic B cells, potentially offering a more targeted approach compared to traditional immunosuppressive therapies (9).

However, CAR-T therapy is not without its challenges. The engineering process, which involves ex vivo manipulation of T cells, can result in a range of toxicities. These toxicities are particularly concerning in autoimmune disease contexts, where immune dysregulation is already at play (10). Thus, understanding the mechanisms behind these adverse events is crucial for advancing the clinical application of CAR-T therapy and mitigating the risks associated with its use in autoimmune disorders (11).

In this paper, we explore the complexities of CAR-T therapy in the treatment of autoimmune diseases, focusing on its potential application in SLE. Specifically, we examine the mechanisms of toxicities like CRS, Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), and other adverse effects related to CAR-T therapy. We also delve into strategies to mitigate these risks, discuss recent clinical advancements, and explore ongoing research that holds promise for improving the safety and efficacy of CAR-T therapy in autoimmune diseases.

DISCUSSION

CAR-T Cell Therapy: Mechanisms and Development

The development of CAR-T therapy has undergone several phases, with key innovations improving the safety and efficacy of this treatment. Initially, the first generation of CARs utilized a simple extracellular single-chain variable fragment (scFv) to target tumor-associated antigens (12). Over time, more advanced designs known as second- and third-generation CARs have incorporated additional co-stimulatory domains, such as CD28, 4-1BB, and ICOS, which enhance T cell activation, persistence, and anti-tumor activity (13). The use of co-stimulatory molecules has been shown to increase CAR-T cell expansion and provide better long-term efficacy, although they can also contribute to toxicities like CRS.

The complexity of the immune system, particularly in autoimmune diseases like SLE, requires careful consideration when designing CAR-T therapies. In SLE, targeting B cells through CAR-T is one of the most promising strategies, as B cells contribute significantly to disease progression through the production of autoantibodies. By targeting surface proteins like CD19 or CD20 on these B cells, CAR-T therapy could offer a selective means to reduce autoreactive B cell populations and ameliorate the disease (14).

While the clinical efficacy of B cell-targeted CAR-T therapy in autoimmune diseases like SLE is still being evaluated, early preclinical and clinical studies have shown some promising results. This approach has the potential to reduce or even eliminate the need for systemic immunosuppressive drugs, which can cause long-term complications and increase the risk of infections and malignancies (15).

One of the challenges with CAR-T therapy in autoimmune diseases is the potential for off-target effects. Since many antigens expressed on B cells are also found on other immune cells or tissues, there is a risk that CAR-T cells could attack healthy tissues, leading to autoimmunity or exacerbation of existing disease. Researchers are working to identify more specific antigens or use a combination of CAR-T designs that can minimize off-target effects while maintaining therapeutic efficacy (16, 17).

Cytokine Release Syndrome (CRS)

Mechanism and Pathophysiology

Cytokine Release Syndrome (CRS) is a systemic inflammatory response triggered by the activation of CAR-T cells. Upon recognizing and binding to their target antigen, CAR-T cells become activated and release large quantities of cytokines—signaling molecules that mediate immune cell communication (18, 19). Key cytokines involved in CRS include Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), and Interferon-gamma (IFN-γ). These cytokines initiate a cascade of immune responses, leading to inflammation, endothelial damage, and increased vascular permeability. The resulting vascular leakage can cause tissue edema, hypotension, and, in severe cases, multi-organ failure (20).

The pathophysiology of CRS is complex and

multifactorial. In addition to direct CAR-T cell activation, antigen-presenting cells (APCs) such as dendritic cells are stimulated, leading to the release of further inflammatory cytokines and amplifying the immune response. In autoimmune diseases like SLE, the baseline immune activation is already heightened, which can exacerbate CRS and make management more challenging (21).

The incidence and severity of CRS are influenced by several factors, including the CAR-T cell dose, their persistence in circulation, the specific target antigen, and the patient's underlying immune profile (11). Patients with autoimmune diseases, particularly those with dysregulated immune responses like SLE, may be more prone to CRS, either due to an increased likelihood of immune activation or because their immune systems may already be primed for exaggerated responses. Therefore, careful patient selection, vigilant monitoring, and early intervention are crucial when administering CAR-T therapy in autoimmune disease populations (22).

Grading and Management of CRS

As discussed earlier, CRS is graded based on the severity of symptoms. The grading system typically ranges from Grade 1 (mild symptoms such as fever) to Grade 5 (fatal complications). Management of CRS is tailored to the severity of the symptoms, with supportive care being essential for all patients. For Grade 1 or 2 CRS, symptomatic treatment such as antipyretics and intravenous fluids may suffice. For more severe forms (Grade 3 or 4), aggressive interventions are required (23, 24).

The standard treatment for severe CRS includes the use of tocilizumab, an IL-6 receptor antagonist, which effectively blocks IL-6 signaling and curtails the cytokine storm. Other interventions may include corticosteroids, which suppress the immune response and reduce the inflammation caused by the release of cytokines. In cases where tocilizumab and corticosteroids are ineffective, additional therapies such as Janus kinase (JAK) inhibitors may be explored (25).

In autoimmune disease patients, the management strategy for CRS may need to be adjusted. For instance, SLE patients often have elevated baseline levels of immune activation, so their response to CRS-triggering CAR-T cells may be unpredictable. Moreover, the use of immunosuppressive drugs in these patients could complicate CRS management, requiring a more careful balancing of treatment to avoid exacerbating the autoimmune response or inducing relapse (26).

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Mechanisms and Pathophysiology

The pathophysiology of ICANS involves neuroinflammation, which is triggered by the release of pro-inflammatory cytokines and the infiltration of immune cells into the central nervous system (CNS). This phenomenon is particularly concerning in autoimmune diseases like SLE, as these patients already have a compromised blood-brain barrier (BBB), making it easier for immune cells to enter the CNS and cause damage. The endothelial cells that form the blood-brain barrier are often dysregulated in autoimmune diseases, potentially increasing the risk of ICANS (27).

Additionally, the activation of microglial cells resident immune cells of the CNS can further exacerbate neuroinflammation and contribute to neuronal injury. The exact mechanisms that lead to ICANS in the context of CAR-T therapy remain a subject of ongoing research, but it is clear that the systemic inflammatory response, combined with the immune dysregulation seen in autoimmune diseases like SLE, plays a significant role in triggering these adverse neurological effects (28).

ICANS can be further complicated by the presence of other comorbidities common in autoimmune diseases, such as vascular abnormalities, prior neurologic events, or the use of immunosuppressive drugs, which may predispose patients to neurological side effects (29). As CAR-T therapies continue to expand into autoimmune disease treatment, understanding the unique risks associated with ICANS in this patient population will be critical (6).

Diagnosis and Management of ICANS in CAR-T Therapy

Immune Effector Cell-Associated Neurotoxicity **S**yndrome (ICANS) is a well-documented complication of CAR-T cell therapy, characterized by neurological symptoms ranging from mild cognitive dysfunction to severe manifestations such as delirium, seizures, and coma (30). The pathophysiology of ICANS is not fully understood, but it is believed to involve cytokine release, T-cell activity, and inflammation in the central nervous system. These mechanisms may be further exacerbated in patients with autoimmune diseases like SLE, as SLE itself is associated with dysregulation of the immune system, which could influence the neuroinflammatory response triggered by CAR-T therapy (31). Diagnosing and managing ICANS requires a comprehensive approach, with special attention to underlying autoimmune conditions like SLE, which may alter the clinical presentation and response to treatment (32).

Diagnosis of ICANS

The diagnosis of ICANS requires a thorough

neurological evaluation, as symptoms can range from mild cognitive issues to life-threatening conditions like seizures and coma (33). A multidisciplinary approach is typically employed to rule out other potential causes of neurological symptoms, such as infection, stroke, or progression of underlying autoimmune disease. Common diagnostic methods include:

•**Magnetic Resonance Imaging (MRI)**: An MRI of the brain is commonly performed to assess any structural changes. In most cases of ICANS, MRI findings are often **normal.** However, in severe cases, subtle findings such as **edema** or **white matter lesions** may be seen. These findings may reflect areas of the brain affected by neuroinflammation, though they are not always diagnostic (34).

•**Electroencephalography (EEG)**: An EEG can be instrumental in detecting subclinical seizures, which may occur even in the absence of overt clinical seizures. Given that some ICANS patients may experience non-convulsive seizures, EEG is particularly useful for identifying neurological dysfunction that is not immediately obvious (35).

•**Cerebrospinal Fluid (CSF) Analysis**: While CSF analysis in ICANS is typically unremarkable; it can be used to rule out other potential causes of neurological symptoms, such as infection (e.g., meningitis or encephalitis) or malignancy (36). CSF may show mildly elevated protein levels or white blood cells, but these findings are not specific to ICANS and may be more indicative of other conditions (37).

In patients with SLE, the diagnosis of ICANS may be particularly challenging because SLE is often associated with central nervous system (CNS) involvement, such as lupus cerebritis. Symptoms of SLE-related CNS involvement (e.g., cognitive dysfunction, seizures, psychosis) overlap significantly with those of ICANS (38). Therefore, distinguishing between ICANS and worsening SLE manifestations is crucial. The inclusion of neurologic autoantibodies, such as anti-NMDA receptor antibodies or antiphospholipid antibodies, may be helpful in assessing the autoimmune contribution to neurological symptoms in SLE patients.

Management of ICANS

The management of ICANS is aimed at reducing neuroinflammation and supporting neurological function. As ICANS can range from mild to life-threatening, treatment strategies should be individualized based on the severity of symptoms. In patients with SLE, special attention is required to ensure that any immune-modulatory treatments used for ICANS do not exacerbate pre-existing autoimmune activity (39).

•**Corticosteroids**: The cornerstone of ICANS treatment is the use of corticosteroids, particularly dexamethasone. Dexamethasone is effective in reducing neuroinflammation and improving neurological symptoms. The dose and duration of corticosteroid therapy are typically adjusted based on the severity of symptoms. In cases where ICANS is severe or resistant to initial steroid treatment, corticosteroids may be escalated or given as high-dose therapy (40).

•**Intravenous Immunoglobulin (IVIg)**: In refractory cases of ICANS, IVIg is an option. IVIg has been shown to reduce inflammation and modulate immune responses. However, its role in ICANS remains investigational, and more research is needed to determine its effectiveness and optimal use in CAR-T-related neurotoxicity (41).

•**Plasmapheresis**: As another potential therapeutic option, plasmapheresis may be considered in severe cases of ICANS. This approach is aimed at removing circulating inflammatory mediators, autoantibodies, or other factors contributing to the neuroinflammatory response. Plasmapheresis is generally reserved for cases that do not respond to steroids or IVIg (42).

•**Symptomatic Management**: In patients with severe neurotoxicity, symptomatic management is critical. For patients experiencing seizures, antiepileptic drugs (AEDs) such as levetiracetam or phenytoin may be administered (43). Additionally, sedation may be necessary to ensure patient comfort and safety in cases of severe agitation or delirium. For patients with respiratory failure, mechanical ventilation may be required, particularly in those with compromised airway or breathing function (44).

•**Ongoing Neurological Monitoring**: Given that ICANS symptoms can evolve rapidly, continuous monitoring of neurological status is essential. Frequent neurological exams, including assessments of mental status, motor function, and seizure activity, should be conducted. The use of EEG may help monitor subclinical seizures, and periodic MRI scans can assess for worsening edema or structural changes (44).

For patients with SLE, it is essential to monitor for exacerbations of the underlying disease. Since SLE can also cause neuropsychiatric manifestations, distinguishing between SLE-related neurotoxicity and ICANS is crucial for tailoring therapy. If there is evidence of SLE-related CNS involvement (e.g., lupus cerebritis), additional treatments, such as immunosuppressive agents or hydroxychloroquine, may be considered, in conjunction with the management strategies for ICANS (45).

Prognosis

The prognosis of ICANS is largely dependent on the severity of symptoms and the timeliness of treatment. In mild cases, with prompt management, patients typically recover without long-term neurological

deficits (46). However, in severe cases, if left untreated or poorly managed, ICANS can result in significant morbidity or even death. Patients with underlying autoimmune conditions, like SLE, may face a more complicated course, as the interaction between CAR-T therapy-induced immune activation and pre-existing immune dysregulation can lead to an unpredictable clinical course (47).

Early detection, appropriate management, and long-term follow-up are essential to improving outcomes for patients with ICANS, particularly those with complex autoimmune diseases such as SLE.

Expansion of Clinical Trials Testing CAR-T in Autoimmunity

Building on successes in lupus, clinical investigations into CAR-T therapies for autoimmune diseases have expanded significantly. As of November 2023, 29 ongoing trials were listed on ClinicalTrials.gov. Among these, 17 focus on lupus, while others explore vasculitis, neurological autoimmune diseases, and pemphigus vulgaris. The concentration on lupus reflects the challenges of treating the disease with existing therapies, unlike vasculitis, which often responds well to current anti-B cell strategies. This growing body of research underscores the widespread interest in CAR-T as a groundbreaking approach to autoimmune disease management (48).

Recent Data and Results from Clinical Trials

Over 70% of patients showed a reduction in disease activity, marked by a decrease in both the SLE Disease Activity Index (SLEDAI) and the need for corticosteroids. However, the study also highlighted that while CAR-T therapy showed promise, some adverse effects like Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) remained concerns (49).

Additionally, BCMA CAR-T therapy appeared to offer an advantage over traditional therapies in controlling disease activity, with patients experiencing fewer relapses and a reduced dependency on immunosuppressive drugs. However, researchers emphasized that these promising results require validation in larger clinical trials, particularly due to the potential for adverse events associated with CAR-T cell therapy (50, 51).

Other Toxicities Associated with CAR-T Therapy

Beyond CRS and ICANS, several other toxicities are associated with CAR-T therapy, and these include hematologic, cardiac, and pulmonary complications, as well as long-term risks such as secondary malignancies and autoimmunity (56).

Hematologic Toxicity

Hematologic toxicities, including cytopenias (e.g., anemia, neutropenia, thrombocytopenia), are commonly observed after CAR-T cell therapy. These toxicities occur due to the exhaustion of the hematopoietic stem cell pool, as well as direct cytotoxicity induced by CAR-T cells on normal hematopoietic cells. The risk of severe cytopenias is higher in patients with autoimmune diseases due to the presence of altered immune dynamics. Management of hematologic toxicities generally involves supportive care, such as blood transfusions and growth factor support (e.g., granulocyte colony-stimulating factor [G-CSF]). In some cases, immune suppression may also be required to manage prolonged cytopenias (57).

Cardiac and Pulmonary Toxicity

Although less common, cardiac and pulmonary toxicities have been reported in patients undergoing CAR-T therapy. These include arrhythmias, myocardial infarction, acute pulmonary edema, and respiratory distress. In autoimmune disease patients, these risks may be further complicated by pre-existing cardiovascular and pulmonary involvement, making careful monitoring essential (58).

Secondary Malignancies and Autoimmunity

Long-term use of CAR-T therapy may increase the risk of secondary malignancies, as prolonged immune suppression and T cell activation can alter normal cellular processes (59). Furthermore, there is concern that CAR-T therapy could inadvertently trigger autoimmune responses, leading to the development of new autoimmune diseases or exacerbation of pre-existing conditions like SLE. Long-term follow-up is crucial to monitor for the emergence of secondary cancers or the onset of autoimmune phenomena, which could have profound effects on patient health (60).

CONCLUSION

CAR-T cell therapy holds immense potential for the treatment of autoimmune diseases like SLE. However, the risk of toxicities associated with this innovative therapy remains a major concern. Understanding the underlying mechanisms of toxicities like CRS, ICANS, and hematologic complications, as well as the strategies for managing these toxicities, will be critical in making CAR-T therapy a viable treatment option for autoimmune diseases. With ongoing advancements in CAR-T design, the ability to minimize these risks and maximize therapeutic efficacy will likely improve, paving the way for more targeted and personalized treatments for patients with autoimmune diseases. The future of CAR-T therapy in autoimmune diseases

depends on refining treatment protocols, developing better patient selection criteria, and advancing our understanding of the intricate relationship between the immune system and CAR-T therapy.

Authors' Contribution

Farnaz Eghbalpour and Mohammad Ali Saremi were involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

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REFERENCES

1. Hoi A, Igel T, Mok CC, Arnaud L. Systemic lupus erythematosus. The Lancet. 2024;403(10441):2326-38.
2. Shah NN, Fry TJ. Mechanisms of resistance to CAR T cell therapy. Nature reviews Clinical oncology. 2019;16(6):372-85.
3. Li X, Shao M, Zeng X, Qian P, Huang H. Signaling pathways in the regulation of cytokine release syndrome in human diseases and intervention therapy. Signal transduction and targeted therapy. 2021;6(1):367.
4. Kundnani NR, Levai MC, Popa MD, Borza C, Iacob M, Mederle AL, et al. Biologics in Systemic Lupus Erythematosus: Recent Evolutions and Benefits. Pharmaceutics. 2024;16(9).
5. Riley RS, June CH, Langer R, Mitchell MJ. Delivery technologies for cancer immunotherapy. Nature reviews Drug discovery. 2019;18(3):175-96.
6. Alsalem AN, Scarffe LA, Briemberg HR, Aaroe AE, Harrison RA. Neurologic Complications of Cancer Immunotherapy. Current oncology (Toronto, Ont). 2023;30(6):5876-97.
7. Vukovic J, Abazovic D, Vucetic D, Medenica S. CAR-engineered T cell therapy as an emerging strategy for treating autoimmune diseases. Frontiers in medicine. 2024;11:1447147.
8. Blache U, Tretbar S, Koehl U, Mougiakakos D, Fricke S. CAR T cells for treating autoimmune diseases. RMD open. 2023;9(4).
9. Liu J, Zhao Y, Zhao H. Chimeric antigen receptor T-cell therapy in autoimmune diseases. Frontiers in immunology. 2024;15:1492552.
10. Wang JY, Wang L. CAR-T cell therapy: Where are we now, and where are we heading? Blood science (Baltimore, Md). 2023;5(4):237-48.
11. Lin H, Yang X, Ye S, Huang L, Mu W. Antigen escape in CAR-T cell therapy: Mechanisms and overcoming strategies. Biomedicine & Pharmacotherapy. 2024;178:117252.
12. Sheykhhasan M, Ahmadieh-Yazdi A, Vicidomini R, Poondla N, Tanzadehpanah H, Dirbaziyan A, et al. CAR T therapies in multiple myeloma: unleashing the future. Cancer Gene Therapy. 2024;31(5):667-86.
13. Bui TA, Mei H, Sang R, Ortega DG, Deng W. Advancements and challenges in developing in vivo CAR T cell therapies for cancer treatment. eBioMedicine. 2024;106:105266.
14. Abdalhadi HM, Chatham WW, Alduraibi FK. CAR-T-Cell Therapy for Systemic Lupus Erythematosus: A Comprehensive Overview. International journal of molecular sciences. 2024;25(19).
15. Dingfelder J, Aigner M, Taubmann J, Minopoulou I, Park S, Kaplan CD, et al. Fully Human Anti-CD19 CAR T Cells Derived from Systemic Lupus Erythematosus Patients Exhibit Cytotoxicity with Reduced Inflammatory Cytokine Production. Transplantation and Cellular Therapy. 2024;30(6):582.e1-.e10.
16. Rampotas A, Richter J, Isenberg D, Roddie C. CAR-T cell therapy embarks on autoimmune disease. Bone Marrow Transplantation. 2024.
17. Maldini CR, Ellis GI, Riley JL. CAR T cells for infection, autoimmunity and allotransplantation. Nature reviews Immunology. 2018;18(10):605-16.
18. Xiao X, Huang S, Chen S, Wang Y, Sun Q, Xu X, et al. Mechanisms of cytokine release syndrome and neurotoxicity of CAR T-cell therapy and associated prevention and management strategies. Journal of experimental & clinical cancer research : CR. 2021;40(1):367.
19. Shah D, Soper B, Shopland L. Cytokine release syndrome and cancer immunotherapies - historical challenges and promising futures. Frontiers in immunology. 2023;14:1190379.
20. Megha KB, Joseph X, Akhil V, Mohanan PV. Cascade of immune mechanism and consequences of inflammatory disorders. Phytomedicine :international journal of phytotherapy and phytopharmacology. 2021;91:153712.
21. Fransen JH, van der Vlag J, Ruben J, Adema GJ, Berden JH, Hilbrands LB. The role of dendritic cells in the pathogenesis of systemic lupus erythematosus. Arthritis research & therapy. 2010;12(2):207.

22.Yasmeen F, Pirzada RH, Ahmad B, Choi B, Choi S. Understanding Autoimmunity: Mechanisms, Predisposing Factors, and Cytokine Therapies. International journal of molecular sciences [Internet]. 2024; 25(14).
23.Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood. 2016;127(26):3321-30.
24.Porter D, Frey N, Wood PA, Weng Y, Grupp SA. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel. Journal of hematology & oncology. 2018;11(1):35.
25.Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. International journal of antimicrobial agents. 2020;55(5):105954.
26.Ohno R, Nakamura A. Advancing autoimmune Rheumatic disease treatment: CAR-T Cell Therapies - Evidence, Safety, and future directions. Seminars in Arthritis and Rheumatism. 2024;67:152479.
27.Gu T, Hu K, Si X, Hu Y, Huang H. Mechanisms of immune effector cell-associated neurotoxicity syndrome after CAR-T treatment. WIREs mechanisms of disease. 2022;14(6):e1576.
28.Qin J, Ma Z, Chen X, Shu S. Microglia activation in central nervous system disorders: A review of recent mechanistic investigations and development efforts. Frontiers in neurology. 2023;14:1103416.
29.Burton LB, Eskian M, Guidon AC, Reynolds KL. A review of neurotoxicities associated with immunotherapy and a framework for evaluation. Neuro-oncology advances. 2021;3(Suppl 5):v108-v20.
30.Sterner RC, Sterner RM. Immune effector cell associated neurotoxicity syndrome in chimeric antigen receptor-T cell therapy. Frontiers in immunology. 2022;13:879608.
31.Liu J, Zhao Y, Zhao H. Chimeric antigen receptor T-cell therapy in autoimmune diseases. 2024;15.
32.Khalid F, Gupta R, Gor R, Gor D, Singh V, Eltoukhy H. Neurological Adverse Effects of Immune Checkpoint Inhibitors and Chimeric Antigen Receptor T-Cell Therapy. World journal of oncology. 2023;14(2):109-18.
33.Sievers S, Watson G, Johncy S, Adkins S. Recognizing and Grading CAR T-Cell Toxicities: An Advanced Practitioner Perspective. Frontiers in oncology. 2020;10:885.
34.Grant SJ, Grimshaw AA, Silberstein J, Murdaugh D, Wildes TM, Rosko AE, et al. Clinical Presentation, Risk Factors, and Outcomes of Immune Effector Cell-Associated Neurotoxicity Syndrome Following Chimeric Antigen Receptor T Cell Therapy: A Systematic Review. Transplant Cell Ther. 2022;28(6):294-302.
35.Satyanarayan S, Spiegel J, Hovsepian D, Markert M, Thomas R, Muffly L, et al. Continuous EEG monitoring detects nonconvulsive seizure and Ictal-Interictal Continuum abnormalities in moderate to severe ICANS following systemic CAR-T therapy. The Neurohospitalist. 2023;13(1):53-60.
36.Shahan B, Choi EY, Nieves G. Cerebrospinal Fluid Analysis. American family physician. 2021;103(7):422-8.
37.Gust J, Ponce R, Liles WC, Garden GA, Turtle CJ. Cytokines in CAR T Cell–Associated Neurotoxicity. 2020;11.
38.Schwartz N, Stock AD, Putterman C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. Nature reviews Rheumatology. 2019;15(3):137-52.
39.Li X, Shao M, Zeng X, Qian P, Huang H. Signaling pathways in the regulation of cytokine release syndrome in human diseases and intervention therapy. Signal transduction and targeted therapy. 2021;6(1):367.
40.Lakomy T, Akhoundova D, Nilius H, Kronig MN, Novak U, Daskalakis M, et al. Early Use of Corticosteroids following CAR T-Cell Therapy Correlates with Reduced Risk of High-Grade CRS without Negative Impact on Neurotoxicity or Treatment Outcome. Biomolecules. 2023;13(2).
41.Almizraq RJ, Branch DRJAoB. Efficacy and mechanism of intravenous immunoglobulin treatment for immune thrombocytopenia in adults. 2020. 2020;6.
42.Hussein G, Liu B, Yadav SK, Warsame M, Jamil R, Surani SR, et al. Plasmapheresis in the ICU. Medicina (Kaunas, Lithuania). 2023;59(12).
43.Herzig-Nichtweiß J, Salih F, Berning S, Malter MP, Pelz JO, Lochner P, et al. Prognosis and management of acute symptomatic seizures: a prospective, multicenter, observational study. Annals of Intensive Care. 2023;13(1):85.
44.Müller-Wirtz LM, O'Gara B, Gama de Abreu M, Schultz MJ, Beitler JR, Jerath A, et al. Volatile anesthetics for lung- and diaphragm-protective sedation. Critical care (London, England). 2024;28(1):269.
45.Sarwar S, Mohamed AS, Rogers S, Sarmast ST, Kataria S, Mohamed KH, et al. Neuropsychiatric Systemic Lupus Erythematosus: A 2021 Update on Diagnosis, Management, and Current Challenges. Cureus. 2021;13(9):e17969.
46.Schroeder T, Martens T, Fransecky L, Valerius T, Schub N, Pott C, et al. Management of chimeric antigen receptor T (CAR-T) cell-associated toxicities. Intensive Care Medicine. 2024;50(9):1459-69.
47.Epperly R, Giordani VM, Mikkilineni L, Shah NN. Early and Late Toxicities of Chimeric Antigen Receptor T-Cells. Hematology/oncology clinics of

North America. 2023;37(6):1169-88.
48.Műzes G, Sipos F. CAR-Based Therapy for Autoimmune Diseases: A Novel Powerful Option. Cells. 2023;12(11).
49.Ding Z, Tarlinton D. Chimeric antigen receptor T cells in the fast lane among autoimmune disease therapies. Clinical & translational immunology. 2024;13(4):e1502.
50.Qin C, Tian D-S, Zhou L-Q, Shang K, Huang L, Dong M-H, et al. Anti-BCMA CAR T-cell therapy CT103A in relapsed or refractory AQP4-IgG seropositive neuromyelitis optica spectrum disorders: phase 1 trial interim results. Signal transduction and targeted therapy. 2023;8(1):5.
51.Tian DS, Qin C, Dong MH, Heming M, Zhou LQ, Wang W, et al. B cell lineage reconstitution underlies CAR-T cell therapeutic efficacy in patients with refractory myasthenia gravis. EMBO molecular medicine. 2024;16(4):966-87.
52.Cingireddy A, Flores B, Wuthrich J, Cingireddy A. CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Systemic Autoimmune Diseases. Cureus. 2024;16.
53.Boardman D, Wong M, Rees W, Wu D, Himmel M, Orban P, et al. Flagellin-specific human CAR Tregs for immune regulation in IBD. Journal of Autoimmunity. 2023;134:102961.
54.Mueller F, Taubmann J, Bucci L, Wilhelm A, Bergmann C, Völkl S, et al. CD19 CAR T-Cell Therapy in Autoimmune Disease - A Case Series with Follow-up. The New England journal of medicine. 2024;390:687-700.
55.Pecher AC, Hensen L, Lengerke C, Henes J. The Future of CAR T Therapeutics to Treat Autoimmune Disorders. Molecular diagnosis & therapy. 2024;28(5):593-600.
56.Sheth VS, Gauthier J. Taming the beast: CRS and ICANS after CAR T-cell therapy for ALL. Bone Marrow Transplant. 2021;56(3):552-66.
57.Si X, Gu T, Liu L, Huang Y, Han Y, Qian P, et al. Hematologic cytopenia post CAR T cell therapy: Etiology, potential mechanisms and perspective. Cancer letters. 2022;550:215920.
58.Gill J. Cardiovascular Toxicities with Chimeric Antigen Receptor T-cell Therapy. Current cardiology reviews. 2023;19(1):e230622206353.
59.Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. Nature reviews Clinical oncology. 2023;20(6):359-71.
60.Hamilton MP, Sugio T, Noordenbos T, Shi S, Bulterys PL, Liu CL, et al. Risk of Second Tumors and T-Cell Lymphoma after CAR T-Cell Therapy. N Engl J Med. 2024;390(22):2047-60.

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Therapeutic Potential of Probiotics in Burn Management: Mechanisms, Clinical Applications, and Future Directions

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Abstract:

Extensive burns impair systemic homeostasis by precipitating a hyperinflammatory reaction. The dysregulation predetermines the development of complications in patients, including infections, sepsis, and metabolic disorders. Probiotics are live microorganisms that have been associated with health-promoting effects at sufficient doses, generating an increasing clinical interest in the role of probiotics during the treatment of burn-injured patients in reducing the incidence of complications and accelerating the recovery process. The current review examines the molecular and physiological mechanisms involved in the effects of probiotics on gut microbiota, host defense, inflammation, and wound healing in burn management. The findings indicate that probiotics may enhance the healing process by modulating the immune response and promoting a balanced gut microbiome. Further investigations are needed to establish standardized protocols for probiotic administration in clinical settings, ensuring optimal outcomes for patients with burn injuries. It also reviews the scientific and clinical data that supports probiotic use in infection prevention, wound repair, and systemic inflammation control. Lastly, the article explains the issues related to the clinical use of probiotic therapy and suggests future areas of research to maximize its use in burn treatments.

Keywords: Probiotics, burn management, gut microbiota, immune modulation, infection prevention.

Introduction

The growing occurrence of burns, which rank among the most devastating injuries, demands prompt action. On top of being a common cause of sickness and impairment, they endanger millions of lives every year, to varying degrees. Surface skin and tissue damage isn't the only thing burns do; they can also trigger a cascade of other, more catastrophic complications. Burn victims have an increased risk of significant inflammation, reduced immune function, sepsis, multi-organ failure, slower wound healing, and subsequent infections. The length and severity of the burn, coupled with the body's reaction to it, considerably determine the

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prognosis and recovery process (1, 2, 3).

There are a lot of aspects that determine how the body handles burns. A skin injury damages the epidermis, the skin's protective barrier, setting off a chain reaction of inflammatory reactions and changes in the immune system. Although some degree of inflammation is normal and even expected after a small burn, it can become life-threatening in the event of a severe burn. Opportunistic infections are more common due to this disorder's inflammatory effects and immune system weakness. Additionally, systemic inflammation can cause harm to distant organs and an increased risk of mortality (4, 5).

Changes to the gut flora as a result of burns have received less focus from researchers. In terms of homeostasis and immunity, the stomach is a factor. Intestinal pathogens and their toxins can enter the bloodstream through weakened intestinal barriers caused by thermal damage. Endotoxemia and systemic inflammation could both be worsened by this. When the gut microbiota is out of whack, a condition known as dysbiosis, burn patients have a harder time recovering and have worse clinical outcomes (7). Recently. The therapeutic application of probiotics in medicine and surgery has gained increasing scientific and clinical interest. Probiotics are live microorganisms that, when consumed moderately, can benefit host health. They inhibit the growth of pathogens, maintain the gut microbial balance, and promote mucosal barrier function (9). Probiotics have immunomodulatory effects that help the body keep its inflammatory and anti-inflammatory responses in check, increase production of pro-inflammatory cytokines, and boost regulatory T cell activity. Uncontrolled inflammation and impaired immunity significantly contribute to the clinical worsening of burn patients, making these features all the more important for these patients (10).

Probiotics lessen the likelihood of burn complications, such as the fatal sepsis and pneumonia, according to animal and human research. As a result of their beneficial effects on the intestinal microbiota, probiotics reduce systemic inflammation and prevent harmful bacteria from penetrating the bloodstream. Furthermore, probiotics speed wound healing, which may be because of their effects on growth factors, angiogenesis, and epithelial remodeling, according to multiple studies (11).

According to this article, probiotics can change the microbiota, boost immunity, reduce inflammation, and help with tissue regeneration. Beyond that, it evaluates the existing clinical evidence, identifies research gaps, and proposes probiotic-enhanced future operations. The use of the microbiota in novel burn treatments is an emerging field of study, which includes this review.

The Role of Probiotics in Rehabilitation from Burns

The gut microbiota plays a crucial role in human health by regulating inflammation, maintaining an intact intestinal barrier, and aiding in immune system homeostasis. The trillions of bacteria and other microbes that call the intestines home make up what is known as the gut microbiome, and its effects reach well beyond the digestive tract (12). In addition to strengthening the immune system, preserving the integrity of the gut's epithelial barrier, and creating important metabolites like short-chain fatty acids (SCFAs) are also vital functions performed by these microorganisms. To be healthy, one needs a diverse and balanced gut flora. The reason behind this is that it regulates the immune system's response to foreign antigens, prevents the spread of dangerous microorganisms, and keeps cytokines in balance (13).

Gut dysbiosis is a condition that can arise when the delicate microbial balance is upset. This imbalance can be triggered by burn damage. Opportunistic pathogens, particularly Enterobacteriaceae, can overwhelm beneficial commensal bacteria, such as Lactobacillus and Bifidobacterium species, leading to the development of dysbiosis (14). Reduced blood supply to the gastrointestinal tract, systemic inflammation, antibiotic use, decreased gut motility, and other factors may hasten the shift in microbial composition. A lot of people who have burns go through all of these things. Endotoxins and bacteria in the intestines are able to breach the mucosal barrier and enter the circulation because of these modifications (15).

Those who suffer from burns may be at risk for major effects if they encounter dysbiosis in their gut. Some of the potentially deadly outcomes include significant systemic inflammation, impaired immunology, delayed tissue repair, an increased risk of sepsis, and failure of multiple organs (16). The majority of secondary infections in burn patients are caused by bacterial translocation as a consequence of decreased barrier function (17). Probiotics may lessen the severity of these side effects by reestablishing a healthy balance of gut bacteria. Taking these live microbial supplements at the correct dosages can cause a number of positive changes in the gut ecology (18). In addition to creating bacteriocins and organic acids, which limit the spread of dangerous bacteria, they also encourage the growth of good bacteria while inhibiting the growth of bad bacteria. Increased levels of tight junction proteins and host defense peptides, as well as a stronger intestinal barrier, are all benefits of probiotics (19).

All aspects of the immune system are affected by probiotics because they have the ability to change the

microbiota and improve the performance of regulatory T cells simultaneously. Furthermore, they have the ability to reduce the levels of inflammatory mediators like TNF-α and IL-6, while simultaneously elevating the levels of cytokines that promote inflammation inhibition, such as IL-10. These immunological benefits are of the utmost importance since burns present a delicate and frequently dangerous balance between the suppression of the immune system and the excessive inflammation that occurs alongside it. By lowering the inflammatory cascade and boosting mucosal immunity, probiotics create an environment that is more conducive to the healing of wounds and improving the likelihood of systemic recovery (20).

To summarize, the multi-pronged approach to treating burn injuries with probiotics aims to improve clinical outcomes by restoring microbial balance, preserving the intestinal barrier, modifying the immune response, and other similar mechanisms. The rationale for this is that probiotic therapy is an excellent supplement to traditional burn care, and there is emerging evidence that it ought to be a component of future techniques that will assist burn patients in recovering more quickly and with less difficulty.

Probiotic-Induced Immune Modulation in Burn Injuries

The immune system undergoes a complex series of events over many weeks or months following burns or other traumas. Inflammation (also known as SIRS) and immunosuppression (also known as CARS) are the two phases of the illness progression (21). Opportunistic infections, sepsis (the leading cause of mortality in burn victims), significant tissue damage, and a delayed healing process are just a few of the many problems that can arise when the immune system is overactive. The dual danger of immune suppression and systemic inflammation necessitates immediate efforts to discover treatments that might normalize the immune system and strengthen the host's defenses (22).

Immunological responses in burn patients may be impacted by interactions between probiotics and gut-associated lymphoid tissue (GALT), an important node in the systemic immune regulation network (23). Intestinal epithelial cells, dendritic cells, and pattern recognition receptors such toll-like receptors (TLRs) are just a few of the cell types that probiotics can interact with once they enter the intestines. These interactions impact the innate and adaptive immune systems via the signaling pathways that they trigger or regulate (24).

By increasing the number and activity of macrophages and natural killer (NK) cells, probiotics strengthen the host's first line of defense against invaders within the framework of innate immunity. They influence the function of antigen-presenting cells and are critical for the activation and maturation of T lymphocytes. Dendritic cells are referred to by various names. It is possible that probiotics and dendritic cells will work together to modify T cell responses in a way that is less inflammatory and more regulated (25). Researchers have found that numerous probiotics, particularly those belonging to the Lactobacillus and Bifidobacterium genera, have the ability to reduce quantities of significant pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. This aids in the regulation of these cytokines. Increased blood levels of these cytokines after heat damage (26). An integral aspect of the body's inflammatory response system are these cytokines. They cause harm to different organs, malfunction of the endothelium, and leakage of capillaries. Intestinal inflammation is reduced by probiotics because they decrease their expression (27).

The body produces more anti-inflammatory cytokines, including transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10), and regulatory T cells (Tregs), with the help of probiotics. Reducing the likelihood of collateral tissue damage while keeping the ability to resist infections is achieved by improving immunological tolerance and avoiding the over-activation of immune responses (28).

The effects of these immunomodulators go well beyond the gastrointestinal tract and have the potential to affect immune responses systemically. Since microbial substances and pro-inflammatory signals can travel through the epidermal and mucosal barriers, burn sufferers are at a higher risk of developing sepsis. The ways in which probiotics influence systemic inflammation and mucosal immunity allow them to alleviate or eliminate septic sequelae (29).

A healthy gut microbiota supports human health by reducing inflammation, preserving strong barriers, and improving immunological stability. The gut microbiota has an impact beyond digestion (12). There are billions of bacteria and other living things in this huge network. These microorganisms make short-chain fatty acids (SCFAs), which help keep the gut epithelial barrier strong and boost the immune system. A varied and balanced gut microbiota is associated with improved health. This is because it affects how the immune system reacts to foreign antigens, stops harmful pathogens from getting in, and controls the production of cytokines (13, 14).

A burn victim who develops stomach dysbiosis may experience life-threatening complications. Death can happen because of a weak immune system, a higher risk of getting infections, slow healing of tissues, or organ failure (15, 16). A lot of people who get burned end up in the hospital or die from their

injuries because of secondary infections. The main reason for these problems is that bacteria get through the body's defenses (17).

Probiotics help by bringing back a healthy balance of gut flora. When used as directed, these live microbial supplements can help the gut in many ways (18). They make organic acids and antibiotic bacteriocins, which help good bacteria and stop bad bacteria from growing. Probiotics increase levels of gut tight junction protein and host defense peptide, which strengthens the gut barrier (19).

Probiotics affect the immune system in many ways, including changing the microbiota and making regulatory T cells work harder. They also raise IL-10 levels and lower inflammatory mediators like TNF-α and IL-6. The immunological benefits are essential because the immune system is already working hard to keep a fragile balance between inflammation and suppression because of the burns. Probiotics help the body heal from systemic disorders and wounds by reducing inflammation and boosting the immune system (20).

Protecting microbiota, changing how the immune system works, and using probiotics to treat burn injuries are all parts of a complete plan to improve clinical outcomes. More and more evidence suggests that probiotic therapy may help burn victims heal faster and feel less pain. This is why it works well with other treatments for burns. Changes to the permeability of the intestines and the movement of bacteria A diverse and balanced gut microbiota is associated with health due to its regulation of immune responses to external antigens, its role in preventing pathogenic microbial invasion, and its influence on cytokine production (13).

People who have burns are more likely to have dysbiosis, which is an imbalance in the gut microbiota. Dysbiosis occurs when pathogenic bacteria, such as Enterobacteriaceae, outnumber commensal bacteria, like Lactobacillus and Bifidobacterium species (14). The microbiota of burn patients is further complicated by systemic inflammation, antibiotic administration, diminished gastrointestinal motility, and decreased blood flow to the gastrointestinal tract. These changes let endotoxins and pathogens get into the bloodstream from the gut (15).

Reduction of Nosocomial Infections

Health complications caused by infections contracted while in the hospital are a leading cause of death and disability among burn sufferers. The unique vulnerability of this patient group is the result of multiple interrelated variables. Among these are disruptions to the immune system, several invasive procedures, extended hospital stays, and significant loss of the skin's protective outer layer. When combined, these factors create an ideal environment in which an illness might spread (21). The already high risk is exacerbated by the widespread and often necessary use of broad-spectrum antibiotics, which disrupt the gut microbiota and decrease colonization resistance, making patients more susceptible to opportunistic infections and MDROs (22).

A significant consequence of this disruption is gut dysbiosis, which increases intestinal permeability and decreases mucosal immunity. Translocation of infections and microbial toxins into the systemic circulation is made easier with a compromised gut barrier, which raises the risk of sepsis, multiorgan failure, and localized infections (23).

Using probiotics is an intriguing new way to reduce burn care infections. Probiotics help restore the microbial balance and maintain gut integrity while also supporting the immune system and reducing the vulnerability to bacterial colonization (24).

Their protective effects are mediated by multiple mechanisms:

As a result of competitive exclusion, pathogens are unable to attach to mucosal surfaces and cause an illness (25). Make antimicrobial compounds including bacteriocins, organic acids, and hydrogen peroxide, which directly inhibit harmful organisms (26).

Increased secretory IgA synthesis, improved antigen presentation, and balanced cytokine signaling are all ways in which the host immunological response can be regulated, leading to a more controlled and efficient immune defense (27). Limiting the loss of epithelial cells, improving intercellular connections, preventing bacterial translocation, and reducing systemic inflammation (28).

Probiotics may aid burn patients in reducing healthcare-associated infections (HAIs), according to mounting clinical evidence. One mechanism by which probiotics alleviate these infections and their potential systemic effects is by repopulating the gut with beneficial bacteria and thereby blocking the harmful effects of toxins. Probiotics also help in other ways, such as by influencing the urogenital flora and enhancing mucosal immune defenses. Finally, probiotics have the ability to decrease the occurrence of ventilator-associated pneumonia and other respiratory tract infections by regulating the gut-lung axis and improving systemic immunity. Supplementing with probiotics may slow the development and spread of MDROs by filling in beneficial bacterial roles in the digestive tract and reducing the need for broad-spectrum antibiotics (29). Along with reducing infection rates, this also helps.

Modulation of Sepsis Risk and Systemic Inflammation

On the other hand, severe sepsis continues to be the major cause of death, hospitalization, and

morbidity among people who have had burns. There are a number of mechanisms that contribute to the complicated pathophysiology of sepsis in this group of individuals. These mechanisms include severe tissue damage, prolonged systemic inflammation, immunological dysregulation, and microbial translocation from injured mucosal surfaces, particularly in the gastrointestinal tract (30).

When the immune system reacts to a severe burn, it becomes overactive and releases inflammatory cytokines such TNF-α, IL-1β, and IL-6. This causes the immune system to become overactive. The over activity of this cytokine storm, which was initially designed to reduce the risk of infection and injury to tissues, frequently results in endothelial dysfunction, capillary leakage, and involvement of organs (31).

In addition, probiotics contribute to the reduction of epithelial apoptosis, the maintenance of tight junction integrity, and the enhancement of mucus formation, all of which contribute to the strengthening of the gut barrier. These various elements are continually impacting one another in a reciprocal manner. The most common causes of sepsis in burn patients are endotoxemia and bacterial translocation; the use of these procedures reduces the risk of both of these conditions occurring (32).

It has been demonstrated in a number of studies that probiotics have positive benefits, which raises the idea that they may be able to alleviate some of the adverse consequences that are associated with sepsis. Patients who took probiotics had an improvement in their immunological profiles, a reduction in the number of bacteremia episodes that occurred, and a decrease in the levels of inflammatory markers in their bodies. These results suggest that probiotic supplements may be effective in burn care sepsis prevention programs (33) despite the fact that additional large-scale randomized controlled studies are required to be conducted. When all of these factors are brought together, the result is an environment that is optimized for the rapid spread of sickness (34). It is possible that the use of drugs that have a broad spectrum could lead to an increase in the prevalence of opportunistic infections and multidrug-resistant organisms (MDROs), both of which are previously common (35). This is due to the fact that they have the ability to change the gut flora and decrease colonization resistance.

This disruption has a number of serious effects, one of which is a dysbiosis in the gastrointestinal system. This dysbiosis lowers the mucosal immunity and makes the intestines more permeable. There are a number of consequences that can occur when microorganisms are able to get through the gastrointestinal barrier and into the bloodstream. These complications include sepsis, organ failure, and localized infections (36). A promising new approach in the treatment of burns is the utilization of probiotics for the purpose of lowering the incidence of infections. There are many benefits associated with probiotics, two of which are the maintenance of the natural bacteria balance in the gut and the facilitation of the immune system (37). As one of the many preventive mechanisms that it possesses, competitive exclusion (38), they reduce the likelihood that germs would cling to mucosal surfaces and cause sickness.

The elimination of harmful bacteria can be accomplished through the production of antimicrobial compounds, such as bacteriocins, organic acids, and hydrogen peroxide (39).

It is possible to modulate the immunological response of the host in order to increase the generation of secretory IgA, the presentation of antigens, and the balance of cytokine signalping (40). By doing so, we will be able to cultivate an immune defense that is more under control and efficient.

Reducing systemic inflammation, decreasing the loss of epithelial cells and intercellular connections, and limiting the transmission of germs are the mechanisms by which these objectives can be accomplished (41).

Additionally, probiotics have a wide variety of other positive effects on the body. In conclusion, probiotics have the potential to reduce the requirement for hospitalization due to respiratory infections such as pneumonia by enhancing the immune system as a whole and altering the relationship between the gut and the lungs. In order to reduce the development and spread of MDROs, one method that can be utilized is to take probiotic supplements (42). Due to the fact that they are able to perform a useful function as bacteria in the digestive system, they reduce the need for antibiotics, which are capable of warding off a wide range of illnesses. It is possible to lessen the likelihood of infection, which is an exciting additional benefit. Severe sepsis is a leading cause of death, hospitalization, and overall morbidity and mortality in burn victims. This is due to the fact that it causes a high rate of fatalities. In this particular population, the complicated pathophysiology that leads to the development of sepsis is comprised of severe tissue destruction, prolonged systemic inflammation, immunological dysregulation, and microbial translocation from wounded mucosal surfaces (especially the gastrointestinal tract) (43). There is a correlation between each of these factors and the onset of sepsis.

In the aftermath of a severe burn, the immune system experiences a spike of inflammatory cytokines, which include TNF-α, IL-1β, and IL-6. This surge causes the immune system to become hyperactive. It is possible for this cytokine storm to cause endothelial dysfunction, capillary leakage, and organ involvement when it becomes excessive.

This is despite the fact that its primary objective is to reduce tissue damage and infection (44).

Intestinal barrier enhancement is further supported by probiotics through the reduction of epithelial apoptosis, the rise in mucus production, and the maintenance of the integrity of the tight junction area. In burn patients, bacterial translocation and endotoxemia are two of the most common causes of sepsis (45). These approaches have the potential to ameliorate both of these conditions.

Patients whose therapy included probiotics demonstrated improved immunological profiles, lower inflammatory markers, and fewer incidences of bacteremia, according to the findings of several investigations. A conclusion that can be drawn from these data is that probiotics have the potential to lessen the severity of the difficulties that are linked with sepsis. In spite of the fact that additional large-scale randomized controlled studies are required, these findings suggest that the incorporation of probiotic supplementation into burn care sepsis prevention strategies may prove to be advantageous (46).

For those who have suffered from burns, healthcare-associated infections remain the leading cause of death and physical disability. Specifically, this is due to the fact that infections are the most prevalent of all medical conditions. This particular patient population is extremely vulnerable due to a complex web of interconnected factors that contribute to the state of affairs. Alterations to the immune system, several invasive surgical operations, prolonged hospital stays, and significant epidermal degradation are some examples of the complications that can arise. In the event that all of these elements come together, there is an increased probability of disease transmission (47), which is one of the fundamental reasons. The widespread use of broad-spectrum antibiotics, despite the fact that they are necessary, has a deleterious impact on the microbiota in the gut, which in turn diminishes colonization resistance and makes opportunistic infections and MDROs worse (40).

The dysbiosis that occurs in the gut is the most obvious result of this imbalance. This dysbiosis leads to a reduction in mucosal immunity and an increase in intestinal permeability. In patients who have damage to their gut barrier, the risk of developing sepsis, failure of several organs, and localized infections is significantly increased. It is possible for certain bacteria and pathogens to pass through the intestinal barrier and enter the bloodstream, which is the reason for this phenomenon (41).

One novel and intriguing strategy to the treatment of burns could be to make use of probiotics in order to lower the incidence of infections. For example, taking probiotics can help improve the immune system, maintain a healthy balance of bacteria in the gut, and keep the gut healthy (42). This is just one of the many benefits of taking probiotics. It has been suggested that competitive exclusion is one of the mechanisms that mediates the protective effects of pathogens (43). By virtue of this process, viruses are unable to attach themselves to mucosal surfaces and so prevent human infection. Bacteriocins are another example of an antibacterial agent, and hydrogen peroxide is yet another example (44). An organic acid is an example of an antibacterial agent. There is a possibility that you could manufacture these chemicals.

An immune defense that is more regulated and effective can be achieved by managing the immunological response of the host, which involves increasing the production of secretory IgA, enhancing the presentation of antigens, and maintaining a balanced cytokine signaling system (45). Maintaining control over the immunological response of the host is one approach that can be taken to achieve this goal. The reduction of systemic inflammation, the reduction of epithelial cell loss, the strengthening of connections between cells, and the reduction of bacterial translocation are some of the things that are involved in this process (46).

According to the findings of recent clinical trials, probiotics may have the potential to lower the number of healthcare-associated infections (HAIs) that occur in burn patients. Additionally, the possible systemic impacts of these disorders can be minimized with the assistance of probiotics, which allow for more effective management of these conditions. In order to achieve this goal, good bacteria are reintroduced into the digestive system, which in turn reduces the severity of infections. In addition to modifying the bacteria that are present in the urogenital tract and boosting the immunological defenses of the mucosal barrier, probiotics have a number of other beneficial effects. The use of probiotics has been shown to reduce the incidence of respiratory tract infections, particularly pneumonia associated with the use of ventilators. It is necessary to make adjustments to the gut-lung axis and to strengthen the immune system in order to achieve this goal. According to the findings of some research (48), taking probiotic supplements may result in a reduction in the quantity of MDROs that are created and transported throughout the body (49, 50). To achieve this goal, beneficial bacteria that live in the gut have the ability to take over and cover the bases in the event that antibiotics are ineffective. In addition to being helpful, it also helps to reduce the number of infections that occur (51, 52).

Enhancement of Wound Healing and Tissue Regeneration

The process of wound healing is a multi-step

procedure that includes hemostasis, inflammation, proliferation, and tissue remodeling. Typically, burn injuries are accompanied by significant tissue damage, a higher risk of infection, and immunological dysregulation, all of which might make this process more challenging (53). The inflammatory phase, which is a very carefully balanced portion of the process, might result in hypertrophic scarring that is not under control, wounds that do not heal, and a delay in the healing process. It has been proven that probiotics can boost wound healing responses through a variety of mechanisms, including metabolic remodeling, inflammatory management, collagen synthesis increase, matrix remodeling regulation, and epithelium regeneration promotion (54). Probiotics have been shown to have these effects.

Modulation of Inflammatory Response in Wound Healing

The removal of dead tissue, activation of immune cells, and beginning of the healing process after a burn all require inflammation throughout the healing phase. The opposite is true for keratinocyte function, surrounding sick tissue, and progression to the proliferative phase in an extremely severe or chronic inflammatory state. Probiotic bacteria may help keep the immune system from stepping in at the wound site by reducing the inflammatory response (55).

Evidence from multiple studies suggests that specific probiotic bacterial strains, such as Lactobacillus rhamnosus GG and Bifidobacterium breve, can reduce levels of inflammatory mediators like TNF-α and IL-1β while increasing levels of cytokines that can control inflammation, like IL-10 and TGF<. Tissue repair and regeneration are aided by these immunomodulatory actions because they decrease inflammation (56). In addition, key growth factors such as transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEFG) can be enhanced by using probiotics. In order to facilitate angiogenesis, fibroblast activation, collagen deposition, and epithelial cell proliferation, VEFG ensures that the nutritional and oxygen supply reaches the repaired tissue. When compared, TGF-β improves these procedures. These actions, when combined, shorten the duration of the inflammatory phase and speed up the healing process (57).

Collagen Synthesis and Extracellular Matrix Remodeling

Collagen formation and organization are in charge of rebuilding the structure and tensile strength of injured skin. To repair the extracellular matrix (ECM), stimulated fibroblasts predominantly create type I and type III collagens. Taking probiotics improves wound healing and tensile strength by increasing fibroblast activity and collagen formation. Because of this, probiotics may exacerbate preexisting inflammatory diseases. Matrix metalloproteinases (MMPs) serve an equally significant role in promoting healing. Zinc-dependent proteases govern extracellular matrix remodeling. Fibrosis and ECM degradation have been linked to conflicts over matrix metalloproteinase (MMP) activity. It appears that probiotics affect matrix metalloproteinases (MMPs) and the proteins that inhibit them (TIMPs). Perhaps this will help manage the synthesis and breakdown of the extracellular matrix. This coordinated remodeling is critical for promoting normal tissue regeneration and preventing chronic wounds (59).

Epithelial Regeneration and Maintenance of Skin Integrity

An essential step in wound healing, re-epithelialization involves the migration and proliferation of keratinocytes, which restore the skin's protective barrier. A major hurdle to epithelial cell regeneration may be burn injuries, which damage the basal layer and cause long-term inflammation. The wound microenvironment and keratinocytes are two places where probiotics can affect the function of epithelial cells (60). Probiotics, when applied topically or taken orally, has been shown to hasten epithelial regeneration, decrease wound size, and shorten healing time in animal burn models. By increasing levels of epidermal growth factor (EGF) and causing cytoskeletal reorganization, some probiotic strains promote cell migration and proliferation throughout the wound bed. This is accomplished by elevating EGF levels. By enhancing local immunological monitoring and microbial defense, probiotics may aid in the avoidance of recurrent infections (61).

The long-term effects of probiotics on health and beauty are unclear. Reduced pathogenic inflammation, increased normal tissue regeneration, and decreased hypertrophic scarring are the means by which this is achieved. Burn victims can benefit greatly from this technique because reducing scarring is a crucial aspect of both their physical and mental recovery (62).

DISCUSSION

Multiple sclerosis remains a complex disease in which the interplay of inflammation, demyelination, and neurodegeneration progressively undermines neurological function. While current immunomodulatory therapies effectively reduce relapse rates and new lesion formation, they fail to halt the insidious accumulation of disability in progressive disease (63). This therapeutic gap underscores the urgent need to shift the focus from inflammation control alone toward strategies that actively promote remyelination and neuroprotection (64).

Challenges of Endogenous Repair

Despite the presence of oligodendrocyte precursor cells (OPCs) within demyelinated lesions, their capacity to develop into mature myelin products-called oligodendrocytes-is significantly impaired in chronic MS. Inflamatory mediators, oxidative stress, and oxidation of the extracellular matrixform a microenvironment actively inhibitory to OPC differentiation65. Astrocytic scar formation and ongoing activation of microglia further enhances these inhibitory signals. Collectively, these trusts are taken to explain why remyelination is often robust in early disease but become inefficient or absent in progressive stages. Importantly, this progressive failure of repair is not a by-product of chronic inflammation, but a key pathomechanism in long standing neurodegeneration (66).

Limitations of Conventional Therapies

Approved disease-modifying therapies (DMTs) such as interferon-beta, glatiramer acetate and high-efficacy monoclonal antibodies generally target the immune system (67). Although they are highly effective in relapsing/tremolating MS, the failure to restore myelin acquisition leaves negative patients lacking with irreversible latent cheating of axonal damage. Moreover, the substantial patient-to-patient variability in response underscores the biological heterogeneity of MS, and an emphasis on precision strategies that go beyond immune modulation68.

Emerging Remyelination Approaches

A number of novel strategies are being studied to directly stimulate repair. Stem cell-based therapies such as mesenchymal, neural and induced pluripotent stem-cell based approaches initially hold promise to help with replenishment of oligodendrocyte pool, and trophic support. Early-phase clinical studies provide a sense of feasibility and potential improvements in function, but there are concerns related to the engraftment of the cells, the immunogenicity, the long-term integration and the potential for it to turn cancerous (69).

Pharmacological and biological agents provide the alternative way. Growth factors like IGF-1 and FGF-2 or small molecules like clemastine fumarate have shown promise in improving the differentiation of OPCs, and remyelination (70). However, it had been difficult to translate such findings into consistent clinical benefit, such as seen with the use of anti-LINGO-1 therapy (opicinumab), which despite a strong preclinical rational had poor efficacy. These experiences point toward the complexity of remyelination biology, and the difficulty with single target interventionsm (71).

Gene therapy, nanotechnology are turning out to be the particularly attractive ways. Gene-editing tools and viral vectors allow for the targeted grading of signaling pathways that dictate the fate of OPCs, and nanocarriers provide novel solutions to surmount the restrictive blood-brain barrier and treat therapeutics to demyelinated locations. Although these modalities are still in an experimental phase, they reflect a paradigm shift into more precision, localized CNS repair (72).

Challenges and Future Directions

In spite of the fact that probiotics have shown some promising outcomes when used as an adjuvant therapy within burn care, there are still a number of substantial obstacles to overcome before the widespread implementation process using probiotics in clinical practice can be concerned or carried out. One of the biggest problems is identifying the probiotic strains that are the most effective (73). Not all probiotics have the same impact in terms of immunological modulation, gut barrier integrity or wound healing. This is because there is a wide variety of probiotic species and strains that each have their own unique set of biological activities. Due to the fact that the available information is inadequate and often inconsistent, it is of the utmost importance to decide what strains or mixtures of strains are most beneficial to burn patients (74).

The issue of how to find the optimum dosages and means of delivery is another major obstacle to clear up. There is no agreement amongst experts on the best concentration, dosing frequency, and treatment time duration for probiotics in order to induce obvious therapeutic effects. This is because there is not a general agreement concerning these factors. The clinical decision-making process is made even more difficult because these criteria range from trial to trial, giving trials inconsistent results. In addition, the effect of probiotic administration on colonization and efficacy of these treatments is unknown in burn patients (75). This is regardless of whether probiotics are best supplied topically or orally-or even the ideal combination of the two.

A major complication is that many drugs, most notably antibiotics, have a negative interaction with probiotics. Burn patients must take antibiotics to ward off infections, but these drugs may deplete the efficacy and shelf life of probiotics without meaning to. It's important to consider whether probiotics will have antagonistic or synergistic effects, and when to deliver the probiotics, if we want the highest possible therapeutic results from antibiotic treatment (76).

CONCLUSION

The use of probiotic in burns treatment is an interesting new field of research with a great impact in enhancing results for burn victims. Probiotics can potentially accelerate the healing of burns through

restoration of a balanced microbiome, reduction in inflammatory and immunological processes and facilitate wound healing. While there may be promising advances we must act quickly to fund well-known designed studies if we are to find successful medications and their working. Integrating probiotics into current burn treatment protocols on a daily basis have the potential to be the norm in the future.

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REFERENCES

1. Jeschke MG, van Baar ME, Choudhry MA, Chung KK, Gibran NS, Logsetty S. Burn injury. Nature reviews Disease primers. 2020;6(1):11.
2. Wang X, Du C, Subramanian S, Turner L, Geng H, Bu HF, et al. Severe gut mucosal injury induces profound systemic inflammation and spleen-associated lymphoid organ response. Frontiers in immunology. 2023;14:1340442.
3. Dobson GP, Morris JL, Letson HL. Pathophysiology of Severe Burn Injuries: New Therapeutic Opportunities From a Systems Perspective. Journal of Burn Care & Research. 2024;45(4):1041-50.
4. Burgess M, Valdera F, Varon D, Kankuri E, Nuutila K. The Immune and Regenerative Response to Burn Injury. Cells. 2022;11(19).
5. Pelizzo G, Calcaterra V, Marinaro M, Baldassarre P, Canonica CPM, Zuccotti G. Metabolic and Hormonal Changes in Pediatric Burn Patients: Mechanisms, Evidence, and Care Strategies. 2025;6(2):17.
6. Soranno DE, Coopersmith CM, Brinkworth JF, Factora FNF, Muntean JH, Mythen MG, et al. A review of gut failure as a cause and consequence of critical illness. Critical care (London, England). 2025;29(1):91.
7. Di Tommaso N, Gasbarrini A, Ponziani FR. Intestinal Barrier in Human Health and Disease. International Journal of Environmental Research and Public Health [Internet]. 2021; 18(23).
8. Latif A, Shehzad A, Niazi S, Zahid A, Ashraf W, Iqbal MW, et al. Probiotics: mechanism of action, health benefits and their application in food industries. Frontiers in microbiology. 2023;14:1216674.
9. Gul S, Durante-Mangoni E. Unraveling the Puzzle: Health Benefits of Probiotics-A Comprehensive Review. Journal of clinical medicine. 2024;13(5).
10. Mazziotta C, Tognon M, Martini F, Torreggiani E, Rotondo JC. Probiotics Mechanism of Action on Immune Cells and Beneficial Effects on Human Health. Cells. 2023;12(1).
11. Wang Z, Huang J, Zhao P. Unveiling the Therapeutic Potential of Probiotics in Sepsis: A Review. Food science & nutrition. 2025;13(6):e70364.
12. Beltrán-Velasco AI, Clemente-Suárez VJ. Harnessing Gut Microbiota for Biomimetic Innovations in Health and Biotechnology. Biomimetics (Basel, Switzerland). 2025;10(2).
13. Zhao Ma, Chu J, Feng S, Guo C, Xue B, He K, et al. Immunological mechanisms of inflammatory diseases caused by gut microbiota dysbiosis: A review. Biomedicine & Pharmacotherapy. 2023;164:114985.
14. Herrnreiter CJ, Murray MG, Luck M, Ganesa C, Kuprys PV, Li X, et al. Bacterial dysbiosis and decrease in SCFA correlate with intestinal inflammation following alcohol intoxication and burn injury. eGastroenterology. 2025;3(1):e100145.
15. Huang Z, Huang Y, Chen J, Tang Z, Chen Y, Liu H, et al. The role and therapeutic potential of gut microbiome in severe burn. Frontiers in cellular and infection microbiology. 2022;12:974259.
16. El Baassiri MG, Raouf Z, Badin S, Escobosa A, Sodhi CP, Nasr IW. Dysregulated brain-gut axis in the setting of traumatic brain injury: review of mechanisms and anti-inflammatory pharmacotherapies. Journal of Neuroinflammation. 2024;21(1):124.
17. Oami T, Shimazui T, Yumoto T, Otani S, Hayashi Y, Coopersmith CM. Gut integrity in intensive care: alterations in host permeability and the microbiome as potential therapeutic targets. Journal of intensive care. 2025;13(1):16.
18. Abdul Manan M. The role of probiotics in personalized therapeutics: Advances in gut microbe-driven interventions. The Microbe. 2025;8:100497.
19. Yang S, Qiao J, Zhang M, Kwok L-Y, Matijašić BB, Zhang H, et al. Prevention and treatment of antibiotics-associated adverse effects through the use of probiotics: A review. Journal of Advanced Research. 2025;71:209-26.
20. Ullah A, Shen B. Immunomodulatory effects of anti-diabetic therapies: Cytokine and chemokine modulation by metformin, sodium-glucose cotransporter 2 inhibitors, and glucagon-like peptide-1 receptor agonists (2013–2025). European

Journal of Medicinal Chemistry. 2025;299:118065.
21.Osuka A, Shigeno A, Matsuura H, Onishi S, Yoneda K. Systemic immune response of burns from the acute to chronic phase. Acute medicine & surgery. 2024;11(1):e976.
22.Norbury W, Herndon DN, Tanksley J, Jeschke MG, Finnerty CC. Infection in Burns. Surgical infections. 2016;17(2):250-5.
23.Aziz N, Bonavida B. Activation of Natural Killer Cells by Probiotics. Forum on immunopathological diseases and therapeutics. 2016;7(1-2):41-55.
24.Szydłowska A, Sionek B. Probiotics and Postbiotics as the Functional Food Components Affecting the Immune Response. Microorganisms. 2022;11(1).
25.Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Research. 2020;30(6):492-506.
26.Chen P, Huang N-T, Chung M-T, Cornell TT, Kurabayashi K. Label-free cytokine micro- and nano-biosensing towards personalized medicine of systemic inflammatory disorders. Advanced Drug Delivery Reviews. 2015;95:90-103.
27.Pagnini M, Visciglia A, Deusebio G, Pane M, Celi A, Amoruso A, et al. Dose-Dependent Anti-Inflammatory Effects of Live and Heat-Treated Ligilactobacillus salivarius and Bifidobacterium breve via NF-κB and COX-2 Modulation in an In Vitro Model of Airway Inflammation. Nutrients. 2025;17(15).
28.Shi P, Yu Y, Xie H, Yin X, Chen X, Zhao Y, et al. Recent advances in regulatory immune cells: exploring the world beyond Tregs. 2025;Volume 16 - 2025.
29.Korkmaz HI, Flokstra G, Waasdorp M, Pijpe A, Papendorp SG, de Jong E, et al. The Complexity of the Post-Burn Immune Response: An Overview of the Associated Local and Systemic Complications. Cells. 2023;12(3).
30.Ren Z, Zheng Z, Feng X. Role of gut microbes in acute lung injury/acute respiratory distress syndrome. Gut microbes. 2024;16(1):2440125.
31.Soliman N, Kruithoff C, San Valentin EM, Gamal A, McCormick TS, Ghannoum M. Small Intestinal Bacterial and Fungal Overgrowth: Health Implications and Management Perspectives. Nutrients [Internet]. 2025; 17(8).
32.Mohammadi S, Saghaeian Jazi M, Zare Ebrahimabad M, Eghbalpour F, Abdolahi N, Tabarraei A, et al. Interleukin 10 gene promoter polymorphisms (rs1800896, rs1800871 and rs1800872) and haplotypes are associated with the activity of systemic lupus erythematosus and IL10 levels in an Iranian population. International journal of immunogenetics. 2019;46(1):20-30.
33.Vázquez-Galán YI, Guzmán-Silahua S, Trujillo-Rangel W, Rodríguez-Lara SQ. Role of Ischemia/Reperfusion and Oxidative Stress in Shock State. Cells. 2025;14(11).
34.Potruch A, Schwartz A, Ilan Y. The role of bacterial translocation in sepsis: a new target for therapy. Therapeutic advances in gastroenterology. 2022;15:17562848221094214.
35.Kocot AM, Jarocka-Cyrta E, Drabińska N. Overview of the Importance of Biotics in Gut Barrier Integrity. International journal of molecular sciences. 2022;23(5).
36.Abouelela ME, Helmy YA. Next-Generation Probiotics as Novel Therapeutics for Improving Human Health: Current Trends and Future Perspectives. Microorganisms. 2024;12(3).
37.Monteagudo-Mera A, Rastall RA, Gibson GR, Charalampopoulos D, Chatzifragkou A. Adhesion mechanisms mediated by probiotics and prebiotics and their potential impact on human health. Applied microbiology and biotechnology. 2019;103(16):6463-72.
38.Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of Action of Probiotics. Advances in nutrition (Bethesda, Md). 2019;10(suppl_1):S49-s66.
39.Strassle PD, Williams FN, Weber DJ, Sickbert-Bennett EE, Lachiewicz AM, Napravnik S, et al. Risk Factors for Healthcare-Associated Infections in Adult Burn Patients. Infection control and hospital epidemiology. 2017;38(12):1441-8.
40.Dongre DS, Saha UB, Saroj SD. Exploring the role of gut microbiota in antibiotic resistance and prevention. Annals of medicine. 2025;57(1):2478317.
41.Takiishi T, Fenero CIM, Câmara NOS. Intestinal barrier and gut microbiota: Shaping our immune responses throughout life. Tissue barriers. 2017;5(4):e1373208.
42.Maftei N-M, Raileanu CR, Balta AA, Ambrose L, Boev M, Marin DB, et al. The Potential Impact of Probiotics on Human Health: An Update on Their Health-Promoting Properties. Microorganisms [Internet]. 2024; 12(2).
43.Wang H, Huang J, Jiang X. Perspectives on Using a Competitive Exclusion Approach to Control Listeria monocytogenes in Biological Soil Amendments of Animal Origin (BSAAO): A Review. Applied Microbiology [Internet]. 2023; 3(3):[786-804 pp.].
44.Darbandi A, Asadi A, Mahdizade Ari M, Ohadi E, Talebi M, Halaj Zadeh M, et al. Bacteriocins: Properties and potential use as antimicrobials. Journal of clinical laboratory analysis. 2022;36(1):e24093.
45.Hansen IS, Baeten DLP, den Dunnen J. The inflammatory function of human IgA. Cellular and molecular life sciences : CMLS. 2019;76(6):1041-55.

46.Zhang Y, Zhu X, Yu X, Novák P, Gui Q, Yin K. Enhancing intestinal barrier efficiency: A novel metabolic diseases therapy. Frontiers in nutrition. 2023;10:1120168.
47.Mills JP, Rao K, Young VB. Probiotics for prevention of Clostridium difficile infection. Current opinion in gastroenterology. 2018;34(1):3-10.
48.Newman AM, Arshad M. The Role of Probiotics, Prebiotics and Synbiotics in Combating Multidrug-Resistant Organisms. Clinical therapeutics. 2020;42(9):1637-48.
49.Zhang P, Zou B, Liou YC, Huang C. The pathogenesis and diagnosis of sepsis post burn injury. Burns & trauma. 2021;9:tkaa047.
50.Van Den Eeckhout B, Tavernier J, Gerlo S. Interleukin-1 as Innate Mediator of T Cell Immunity. 2021;Volume 11 - 2020.
51.Ghosh S, Whitley CS, Haribabu B, Jala VR. Regulation of Intestinal Barrier Function by Microbial Metabolites. Cellular and molecular gastroenterology and hepatology. 2021;11(5):1463-82.
52.Merenstein D, Pot B, Leyer G, Ouwehand AC, Preidis GA, Elkins CA, et al. Emerging issues in probiotic safety: 2023 perspectives. Gut microbes. 2023;15(1):2185034.
53. Eghbalpour F, Aghaei M, Ebrahimi M, Tahsili MR, Golalipour M, Mohammadi S, et al. Effect of indole-3-carbinol on transcriptional profiling of wound-healing genes in macrophages of systemic lupus erythematosus patients: an RNA sequencing assay. Lupus. 2020;29(8):954-63.
54.Wilkinson HN, Hardman MJ. Wound healing: cellular mechanisms and pathological outcomes. Open biology. 2020;10(9):200223.
55.Yang Y, Huang J, Zeng A, Long X, Yu N, Wang X. The role of the skin microbiome in wound healing. Burns & trauma. 2024;12.
56.Cristofori F, Dargenio VN, Dargenio C, Miniello VL, Barone M, Francavilla R. Anti-Inflammatory and Immunomodulatory Effects of Probiotics in Gut Inflammation: A Door to the Body. Frontiers in immunology. 2021;12:578386.
57.Wang Y, Bai M, Peng Q, Li L, Tian F, Guo Y, et al. Angiogenesis, a key point in the association of gut microbiota and its metabolites with disease. European Journal of Medical Research. 2024;29(1):614.
58.Singh D, Rai V, Agrawal DK. Regulation of Collagen I and Collagen III in Tissue Injury and Regeneration. Cardiology and cardiovascular medicine. 2023;7(1):5-16.
59.Kandhwal M, Behl T, Singh S, Sharma N, Arora S, Bhatia S, et al. Role of matrix metalloproteinase in wound healing. American journal of translational research. 2022;14(7):4391-405.
60.Ter Horst B, Chouhan G, Moiemen NS, Grover LM. Advances in keratinocyte delivery in burn wound care. Adv Drug Deliv Rev. 2018;123:18-32.
61.Knackstedt R, Knackstedt T, Gatherwright J. The role of topical probiotics on wound healing: A review of animal and human studies. International wound journal. 2020;17(6):1687-94.
62.Satish L, Gallo PH, Johnson S, Yates CC, Kathju S. Local Probiotic Therapy with Lactobacillus plantarum Mitigates Scar Formation in Rabbits after Burn Injury and Infection. Surgical infections. 2017;18(2):119-27.
63.Hao D, Nourbakhsh M. Recent Advances in Experimental Burn Models. Biology. 2021;10(6).
64.Virk MS, Virk MA, He Y, Tufail T, Gul M, Qayum A, et al. The Anti-Inflammatory and Curative Exponent of Probiotics: A Comprehensive and Authentic Ingredient for the Sustained Functioning of Major Human Organs. Nutrients [Internet]. 2024; 16(4).
65.DiMattia Z, Damani JJ, Van Syoc E, Rogers CJ. Effect of Probiotic Supplementation on Intestinal Permeability in Overweight and Obesity: A Systematic Review of Randomized Controlled Trials and Animal Studies. Advances in nutrition (Bethesda, Md). 2024;15(1):100162.
66.Bădăluță VA, Curuțiu C, Dițu LM, Holban AM, Lazăr V. Probiotics in Wound Healing. International journal of molecular sciences. 2024;25(11).
67.Fijan S, Frauwallner A, Langerholc T, Krebs B, Ter Haar Née Younes JA, Heschl A, et al. Efficacy of Using Probiotics with Antagonistic Activity against Pathogens of Wound Infections: An Integrative Review of Literature. BioMed research international. 2019;2019:7585486.
68.Kotzampassi K. Why Give My Surgical Patients Probiotics. Nutrients. 2022;14(20).
69.Theis BF, Park JS, Kim JS, Zeydabadinejad S, Vijay-Kumar M, Yeoh BS, et al. Gut Feelings: How Microbes, Diet, and Host Immunity Shape Disease. Biomedicines [Internet]. 2025; 13(6).
70.Saputro ID, Putra ON, Pebrianton H, Suharjono. Effects of probiotic administration on IGA and IL-6 level in severe burn patients: a randomized trial. Annals of burns and fire disasters. 2019;32(1):70-6.
71.Mishra A, Jena SK, Srinivasan A, Tripathy A, Maiti R, Hota D. Effect of an Add-On Multi-Strain Probiotic Formulation in the Prevention of Recurrent Urinary Tract Infections: A Double-Blind Randomized Placebo-Controlled Trial. Microbiology Research [Internet]. 2024; 15(4):[2330-40 pp.].
72. Mey G, Mahajan K, DeSilva T. Neurodegeneration in multiple sclerosis. WIREs Mechanisms of Disease. 2022;15.
73.Villoslada P. Neuroprotective therapies for

multiple sclerosis and other demyelinating diseases. Multiple Sclerosis and Demyelinating Disorders. 2016;1.
74.Sahel A, Ortiz FC, Kerninon C, Maldonado PP, Angulo MC, Nait-Oumesmar B. Alteration of synaptic connectivity of oligodendrocyte precursor cells following demyelination. 2015;Volume 9 - 2015.
75.Traiffort E, Kassoussi A, Zahaf A, Laouarem Y. Astrocytes and Microglia as Major Players of Myelin Production in Normal and Pathological Conditions. Frontiers in cellular neuroscience. 2020;14:79.
76.Longbrake EE, Parks BJ, Cross AH. Monoclonal antibodies as disease modifying therapy in multiple sclerosis. Current neurology and neuroscience reports. 2013;13(11):390.

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Oncolytic Viruses: Mechanisms, Engineering Strategies, and Clinical Advances

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Abstract:

Today, personalized medicine advanced therapies play a pivotal role in the future of healthcare, an innovative breakthrough in personalized medicine that is shifting the paradigm in care delivery towards an exponentially more customized philosophy of healthcare delivery. These therapies harness the power of multidimensional patient data, such as clinical history, genomic sequences, proteomic and metabolomic profiles, epigenetic landscapes, and lifestyle to tailor interventions in a way that is optimal on an individual basis (maximizing efficacy and minimizing adverse effects). Technological advances that include second-generation sequencing techniques, high-throughput and omics, bioinformatics, and artificial intelligence have catalyzed the development of disease predispositions, molecular subtypes, and predictive biomarkers enabling custom patient stratification and treatment selections. In oncology, advanced therapies include targeted drugs selected by biomarkers, immune checkpoint inhibitors, CAR-T cell therapies, gene editing, and oncolytic viral platforms and are better therapies in specific subsets of patients. Even with all these implementations, hurdles abound, such as the need to standardize large amounts of data, ethical and privacy issues, exorbitant healthcare costs and fair access. Advanced therapies bridge the gap between multi-omics and more sophisticated methods of therapy, offering a promising platform behind which effective and patient-oriented approaches to treatment may become a reality against a wide variety of diseases, becoming a paradigm of new healthcare transformation worldwide.

Keywords: Genomics; Biomarkers; metabolomic signatures, Targeted therapy, Omics technologies.

Introduction

Viruses were considered to be typically morbid and mortal causative agents that could cause significant pathologies historically. The connotation of their image was associated with epidemics like influenza, polio and smallpox and the very idea that they can be used to create therapeutic benefit was counterintuitive (1). However, the entirely opposite notion involving the oncolytic viruses (OVs) redefines such an attitude as those noble agents that are only able to target malignant cells and destroy them leaving no trace on the healthy tissues. This dual ability lysis of tumor cells and stimulation of antitumor immunity lies in the basis of oncolytic virotherapy, the new therapeutic

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modality on the border of virology, immunology and oncology (2).

Early clinical observations tracing the roots of this field may be traced to occasional clinical observations in the first half of the twentieth century, when cancer regressions were reported in individuals with viral infections (measles, influenza, hepatitis) by chance. These tidbits led to experimental studies of naturally occurring lytic viruses, such as West Nile, rabies, yellow fever and hepatitis. Though crude in concept and not more than mechanistically revealed, these experiments planted the concept in the soil that, under certain conditions, viral replication could exert a de-growth of tumor effect (3).

The deficiencies of naturally occurring viruses, however, by the end of the twentieth century- poor selectivity towards tumor cells, safety issues, and inconsistent effectiveness limited the practical use of naturally occurring viruses. The introduction of molecular cloning, recombinant DNA technology and the development of advanced cell culture technology in the 1990s is a major shift (4). As the new millennium dawned, scientists started making genetic modifications to the wild-type viruses, to maximize therapeutic index. Other strategies were the removal of viral genes required to replicate in normal cells but non-essential in tumor cells thus creating increased tumor specificity; the addition of therapeutic transgenes such as cytokines, immune regulators, or prodrug converting enzymes; and the modification of regulatory cues to further control viral replication and immunogenicity (5).

This shift in approach, on the one hand resulting in the rational synthesis of OVs, made a big difference in the perception of OVs as viable anticancer compounds. Soon clinical translation appeared, and adenoviruses, herpes simplex viruses, vaccinia viruses, and reoviruses became major candidates. Notably these engineered viruses do not only exert direct oncolytic effects, but also discharge tumor antigens and danger signals, which essentially vaccinates the host against remaining malignancies (6). The position of oncolytic virotherapy, therefore, is a distinct niche between targeted tumor cytotoxicity and systemic immunization against tumor, and the prospect of synergy with other cancer treatments in the form of chemotherapy, radiotherapy, or immune checkpoint inhibitors (7).

Mechanisms of Action

This therapeutic activity is based on a carefully balanced interaction between viral replication, immunostimulatory effects and tumor cell sensitivity of oncolytic viruses (OVs). Oncolytic viruses wield specificity to exploit cancer cell-specific vulnerabilities, such as impaired tumor-suppressor pathways, impaired interferon-based antiviral antitumor response, and overexpressed cell surface receptors, which bias the virus to attack the cancer cells over sparing the normal cells. Response to treatment thus depends not only on the inherent characteristics of the virus, but also the molecular signature of the tumor to be treated (8).

The fact that OVs multiply selectively in the case of intratumoral replication systems represents a key advantage because it results in the development of the respective cytopathic effects which will lead into a series of forms of programmed cell death, some of which include apoptosis, necrosis, pyroptosis, autophagy, and ICD (9). In particular, release of tumor-associated antigens (TAAs), danger-associated molecular patterns (DAMPs) and cytokines by CLD, resulting in dendritic cell maturation and cross-priming of cytotoxic T lymphocytes is of importance. This way, direct oncolysis is coupled with induction of systemic antitumor immunity in the form of an in situ vaccine (10).

Along with a direct cytotoxic effect, OVs transform the TME to a significant extent. Local inflammation caused by viral infection, augmented antigen presentation, and attracting innate and adaptive immune effectors (like natural killer (NK) cells, macrophages, and T lymphocytes) are the results of this stimulation (11). These immunostimulatory activities also reverse immunosuppressive factors in the TME like Tregs, MDSCs and inhibitory cytokines. This wide-spectrum immune activation distinguishes OVs to any one-pathway targeting agent, such as immune checkpoint inhibitors, or small-molecule agents (12).

The single-cell level is modulated by proliferation rates, the metabolic activity, and the genetic alterations to influence the susceptibility of the tumor to OV-mediated cytotoxicity (13). Tumors with mutations in RAS, p53 or RB pathways tend to be less restrictive of viral replication. The anti-cancer efficacy is dynamic to maintain a balance between viral spread, immune responses, and tumor growth and needs to be extensive enough to generate oncolysis but insufficient to trigger an immune-mediated response (14).

The success of OVs is based on the combination of a direct antitumor effect through tumor cell killing together with a indirect immune effect. Such a dual mechanism can not only minimize local tumor load, but also induce systemic antitumor immunity sufficient to attack metastases and prevent re-growth (15). Through synergistic effects in the TME and activation of diverse immune repertoires, OVs are a multipronged approach that can be used complementarily with current cancer therapies, such as chemotherapy, radiotherapy, or immunotherapy (16).

Preclinical and Clinical Advances

Over the last 20 years, considerable preclinical

research has comprehensively assessed the potential of oncolytic viruses (OVs) in cancer therapy, including both viruses naturally occurring viruses, such as reovirus and vesicular stomatitis virus (VSV), as well as engineered viruses, including adenoviruses, vaccinia viruses and herpes simplex viruses (HSVs)(17). Preclinical models have demonstrated how OVs become tumor selective through a variety of mechanisms involving tumor inhibited pathways of tumor suppressors, altered interferon signaling and tumor enhanced surface receptors. Such studies have shown the ability of OVs to trigger many types of programmed cell death, including apoptosis, necrosis, pyroptosis, autophagy, and especially immunogenic cell death (ICD) at the same time they promote the migration and activation of innate and adaptive immune effector cells (18). In addition, therapeutic transgenes/modulators that can be transduced into engineered OVs can include cytokines, chemokines, or tumor antigens, to boost antitumor immune response and reshape suppressed tumor microenvironment (TME). In sum, these results established mechanistic support of developing OVs into a clinical trial (19).

A number of clinical milestones have established the feasibility, safety and therapeutic efficacy of OVs in humans. A genetically engineered adenovirus, H101, became the first OV to be approved by regulators in China in 2005 to treat nasopharyngeal carcinoma, and showed great efficacy in patients who could otherwise not respond to conventional treatment (20). The United States Food and Drug Administration (FDA) thereafter cleared an HSV-1-based oncolytic virus, talimogene laherparepvec (T-VEC), in advanced melanoma in 2015. T-VEC was described with direct oncolytic activity plus a capacity to produce a granulocyte-macrophage colony-stimulating factor (GM-CSF) that activates dendritic cell recruitment and a system-breadth antitumor immunity (21). Delytact is another genetically modified OV to be approved in 2021 in Japan, as malignant glioma, representing the increase in clinical use of OVs in hard-to-treat tumors. More broadly, what all four approved oncolytic virus therapies share is a variety of viral platforms that harness both cytolytic and immunomodulatory effects (22).

The clinical experience has observed that OVs can be optimally entailing the highest efficiencies when used in combination regimens as opposed to being issued as monotherapies. A mixture of viral replication, susceptibility of cancer cells and the immune system of the host has resulted in monotherapy as potentially inadequate in extending the response to tumors that are heterogeneous (23). The complementary mechanisms of action of different treatment modalities make combination with OVs of interest: OVs + immune checkpoint inhibitors (ICIs): combination with ICIs such as anti-PD-1, anti-PD-L1, or other T-cell-activating immunotherapies may augment T-cell-mediated antitumor immunity OVs + chemotherapy or radiotherapy: combination with chemotherapy or radiotherapy can boost viral penetration, tumor antigen release, immunogenic cell death OVs + targeted therapies: combination with targeted therapies Preclinical studies have repeatedly shown that such combinations are synergistic or additive to tumor growth, leading to a clinically significant increased regression, survival and systemic immunity when compared to monotherapies (24).

In addition, biomarkers and immune surveillance are also becoming an important component of the clinical trials to better design combination regimens. Studies of tumor-infiltrating immune cells, cytokines, and viral dynamics can inform on the mechanisms and predictive markers of response. Examples include those in which high levels of infiltration of cytotoxic T lymphocytes, NK cells, and dendritic cells in treated tumours are associated with better clinical outcomes, as a guide to the rational design of OV-containing regimens (25). Adaptive trial designs and phase I/II trials are evaluating combinations and regimens of doses to maximize direct oncolysis and systemic immune activation and minimize toxicity (26).

Overall, the translational history of oncolytic viruses constitutes a paradigm of mechanistic clarity, engineering know-how, and clinical synergising. These preclinical data have laid solid grounds to the tumor-selective immunostimulatory nature of these agents, and clinical milestones have revealed the safety and therapeutic potential across a variety of malignancies (27). The leading directions include combinations of therapies that are targeting tumor biology and host immune context supported by biomarker-based patient selection. By combining direct cytolytic killing and broad immune activation, OVs are a multi-faceted and increasingly validated type of anticancer agents, able to treat localized disease and metastatic disease (29).

Representative Oncolytic Viruses

Reovirus

Reovirus is a non-enveloped, two-stranded RNA virus that has tropism on the cancer cell level via junctional adhesion molecule-A (JAM-A) receptor, which is over expressed in several different malignancies, such as breast, ovarian, and colorectal cancers. In tumors with activated RAS signaling, its oncolytic specificity is further improved since activating RAS mutations inactivate the antiviral pathway protein kinase R (PKR), permitting productive viral replication (28). The type 3 Dearing strain, which is commercially available as Reolysin, has been studied substantially both preclinically

and clinically, showing a relatively favorable safety profile, the practicality of systemic administration (intravenous administration), and clinically achievable anti-tumor activity as a monotherapeutic agent and in combination with chemotherapeutic agents. Its application in solid tumors such as pancreatic, head and neck, and lung Cancers has been investigated in a clinical trial, indicating that it can complement the conventional treatment (29).

Single-Stranded RNA (ssRNA) Viruses

Coxsackievirus: The viruses of this enterovirus family also use the receptors, decay-accelerating factor (DAF) and intercellular adhesion molecule-1 (ICAM-1), to enter the tumor cells. Engineered Coxsackievirus A21 (CVA21) has been shown to have potential oncolytic effects in melanoma, multiple myeloma, and other solid malignancies, with clinical trials proving induction of tumor necrosis, immune Activity, and increased immune effector penetration of tumors (30).

Seneca Valley Virus (SVV-001): It is a naturally occurring picornavirus with a specificity to target neuroendocrine tumors such as small cell lung carcinoma and pediatric solid tumors. Although preclinical activity was oncolytic, there has been a mixed outcome in the clinic, which points to the need to select patients and the potential use of combined immune-modulatory agents (31).

0762 Poliovirus: The recombinant and attenuated poliovirus variants like HRV2-IRES chimera take advantage of the overexpressed CD155 receptor in glioblastoma cells. The engineering of viruses is being explored to probe whether they can enter the central nervous system, induce tumor lysis and thereby drive local antitumor immunity, without causing poliomyelitis. There have been early-stage trials with good safety and survival outcomes in recurring glioblastoma (32).

Paramyxoviridae Family

Measles Virus: These attenuated Edmonston measles viruses have been genetically altered so as to reduce pathogenicity, but not tumor tropism. It makes use of CD46, which is often overexpressed on cancerous cells or signalling lymphocytic activation receptors (SLAM) as entry receptors (33). Clinical applications have so far been in multiple myeloma, ovarian cancer, and glioblastoma with engineered strains expressing immunomodulatory transgenes (e.g., sodium iodide symporter, cytokines) that improve both direct-oncolysis and overall systemic immunity (34).

Newcastle Disease Virus (NDV): NDV is innately non-pathogenic in humans, and has intrinsic tumor selectivity as it preferentially infects cells with impaired interferon responses. STRs like MEDI5395 are already in clinical testing of solid malignancies and hematologic malignancies, and they are safe and efficiently induce strong immune activity, such as recruitment of NK cells and T cells to the tumor microenvironment (35).

Vesicular Stomatitis Virus (VSV): An enveloped, negative-stranded RNA virus, VSV enters cells by means of LDL receptors. VSV is a promising oncolytic virus since tumor cells with impaired innate immunity type I due to defects in type I interferon signaling are especially vulnerable to viral replication by VSV (36). To improve safety and anti-tumor effects, VSV-sodium-iodide-symporter- NIS, and interferon-B, that is, VSV-IFN beta-NIS, has been produced. Phase I/II studies are underway testing these strains against hematologic malignancies and solid tumors, and occasionally in combination with immune checkpoint inhibitors to synergistically enhance systemic antitumor responses in antitumor immunity (37).

Engineering Strategies

Enhancing Tumor Specificity

Tumor specificity is a central concept to the design of oncolytic viruses (OVs) as highly specific targeting minimizes bystander effects on noncancerous tissue, so viral replication and oncolysis can be focused without broad collateral toxicity (38). One of the most commonly used approaches includes receptor retargeting, whereby viral surface proteins are genetically engineered or adapted to target and bind since they are over-expressed on cancer cells. As an example, Ad5/F35 chimeras have been designed to target selectively CD46, which is often overexpressed in multiple tumors, including ovarian, prostate, and hematologic cancer (39). Similarly, the measles virus has been engineered to express an antigenic configuration that recognizes CD20, thus selectively targeting lymphoma cells but disruption of normal B lymphocytes. In addition to targeting via a single receptor, clever strategies have been developed to target multiple tumor-associated surface proteins using chimeric fibers, bispecific adaptors, and ligand-fused capsid proteins: these OVs can recognize novel targets simultaneously, e.g., epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and mesothelin (40). These adaptations increase the viral tropism, and thus provide efficient attachment, internalization and consequent replication of tumor cells. Other approaches in conjunction with receptor-retargeting are recombination with tumor-specific promoters or microRNA-regulated expression systems, additional modes to minimize viral migrating to normal cells (41). Together, these engineering endeavors enhance the predictability and security of OVs, making them as therapeutically potent as possible and as off-target toxic as minimal, as well as pave the way to

personalized oncolytic treatment that targets the specific molecular characteristics of individual tumors (42).

Improving Replication Selectivity

The selectivity of transduction and the specificity of killing of oncolytic viruses (OVs) is a key drug design feature of OVs, in that OVs need to be designed in a way that will allow the viral replication and killing process to be constrained within the tumor mass as opposed to all surrounding tissues, maximizing antitumor activity and minimizing adverse effects in normal tissue (43). A common strategy is to delete viral genes needed to replicate in the normal cell but not required in the cancer cell because it has acquired specific molecular defects. The best known example is the E1B 55kD deletion of adenoviruses, as used in H101 and ONYX-015, which only replicates in cells lacking p53 pathways, but not in normal cells (44). Besides gene deletions, tumor-specific promoters are used to regulate viral gene expression. Expression of such promoters as survivin, GP73, or E2F-1 is cancer cell-specific, which further contributes to safety and therapeutic specificity by ensuring that essential viral genes are transcribed only in a malignant setting (45). A third model is herpes simplex virus (HSV) based OVs, such as T-VEC, where replication of the virus in normal neurons is prevented by deletion of the neurovirulence gene, 34.5, and the local immune response and remote anti-tumor effects are potentiated by GM-CSF codominance (46). The increased selectivity of OVs can be achieved with dually controlled translation/transcriptional OVs (TTDR-OVs), which have tumor-specific transcriptional elements and either microRNA or another translational controlling element (47). These methods can limit viral action to the tumor site but also limit off-target effects, systemic toxicity, and permit systemic administration in a safer manner. More generally, enhancing replication selectivity is a synthesis of molecular virology, cancer biology, and genetic engineering, the basis of precision-targeted therapies that can exploit aberrations unique to malignant cells (48).

Safety Enhancements

Although tumor selectivity has been improved, the safety of oncolytic viruses (OVs) has been a key issue in the development and translational study of OVs. Several measures have been undertaken to mitigate any possible risk that may be brought about by viral therapy. The activity abatement strategy is a major intervention, whereby neurovirulence or other pathogenicity-related genes are removed or altered, compromising systemic safety and inhibiting infection of other healthy tissues (49). An example is herpes simplex virus (HSV)- based OVs, which can commonly be modified using a deletion of the 734.5 gene so as to reduce neurovirulence without affecting its specificity in tumor targeting (50).

The other important safety measure is the introduction of pharmacologic off-switches. Some of the engineered OVs can be sensitive to clinically accepted anti-viral drugs, and this option would give physicians a means to stop viral replication in case the side effects develop. To illustrate, VG161 harbors a thymidine kinase (TK) gene, and this allows the treatment to be controlled by the use of acyclovir, thus increasing the manageability of the treatment clinician-wise (51).

It is also important to control tropism to off-target organs. The adenovirus, like other OVs, tends to accumulate in organs such as the liver as a result of interaction with the blood factors. Viral capsid modifications, including elimination of factors X (FX) binding sites, have also been used to diminish hepatic sequestration and increase safety (52).

The other factor to consider is the genetic and environmental stability of OVs. Some viruses, including Newcastle disease virus (NDV) and vesicular stomatitis virus (VSV), can, in theory, revert to virulent forms in the presence of selective pressures (53). Clearly, to address this risk, strong genetic controls are incorporated into OV design and deployed, such as multi-gene deletions, synthetic regulators that contain or inactivate OVs or self-limiting systems of propagation (54).

Taken together, the safety improvements, such as attenuation, contact sensitivity, control of organ tropism, and genetic stability, are needed to allow the reliable clinical use of OVs, namely systemic administration with minimum off-target effects and maximum therapeutic benefit.

Integrated Considerations

Contemporary OV therapeutics is taking an increasingly combinatorial approach, involving combinations of objectives in a given therapeutic vehicle. A current development integrates receptor retargeting, transcriptional, and translational control, immunomodulatory transgene expression, and in-built safety switches to make a multi-layered platform (55). Combining viral-specific uptake within the tumor, specific infection of neoplastic cells, and activation of antitumor immune responses, this synergism repeatedly benefits the oncolytic potential of the virus and concurrent triggering of innate immune responses (56).

Receptor-specific structural changes result in specific binding and uptake of tumor cells, and transcriptional/translational control limits viral gene expression in non-tumor cells (57). Immunomodulatory payloads, e.g., cytokines, chemokines or checkpoint-blocking agents, in turn, add to the modification of the tumor

microenvironment (TME), facilitating infiltration and activation of cytotoxic T lymphocytes, natural killer cells, and dendritic cells. Safety features, such as gene deletions, drug sensitivity modules and environmental containment, are employed to protect against systemic toxicity and/or unintended viral release (58).

With the maturation of the field, rational OV design has been increasingly driven by information on tumor genomics, epigenetics and microenvironmental profiling to develop highly personalized precision virotherapies. By doing this, vectors are able to target both molecular weaknesses, immune profiling and the stromal nature of single tumors, further raising the chances of clinical response with minimal adverse effects (59).

This combined engineering approach therefore places oncolytic viruses in a highly flexible and versatile therapeutic platform, able to provide multimodal anticancer activity unique to the tumor biology of individual patients. With the combination of selectivity, immunogenicity, and safety in a single delivery vehicle, next-generation OVs are on the cusp of reshaping the use of virotherapy at the individualized level (59).

The Cold Weapons of Oncolytic Viruses

Engineering of modern oncolytic viruses (OV) is becoming more holistic in design, implementing several mechanisms on board an individual therapeutic vector to achieve the highest levels of effectiveness and mitigate safety. Modern designs are multiple receptor retargeting, transcriptional and translational control, immunomodulatory transgene expression and added safety switches to create a complex, multi-layered platform (60). This complex approach simultaneously augments tumor-specific lysis, blocks viral effects on nonmalignant host tissues, and activates anticancer immunity, profoundly increasing local oncolytic activities and mediating system-wide effects in addition (61).

The cell type-specific insertion of receptor-targeting mods ensures that the virus is only preferentially attached and internalized in tumor cells, whereas translation and transcription ensure only important viral genes are expressed under tumor conditions, reducing the risk of off-target replications in healthy tissues (62). The available knowledge is shown in the immunomodulatory payloads, e.g., cytokines, chemokines, or checkpoint-blocking antibodies, further redesigning the tumor microenvironment (TME), helping infiltration and activation of cytotoxic T lymphocytes, natural killer cells, and dendritic cells. Safety systems to prevent systemic toxicity and unintended viral proliferation are in place, such as system deletion of genes, drug-sensitivity modules, and environmental confinements (63).

As the field matures, rational OV design is facing an ever-greater influence of tumor genomics, epigenetics, and microenvironmental profiling, and as such, highly personalized precision virotherapies are being developed. With this kind of customization, vectors can target molecularly defined vulnerabilities, immune profiles, and stroma of individual cancers and have a higher chance of clinical response and a lower incidence of side effects (64).

Overall, the approach represents oncolytic viruses as a highly multipurpose and designable anticancer therapeutic that could address much more, and more effectively, than perhaps oncolytic viruses were initially intended to achieve. Seamless integration of selectivity, immunogenicity, and safety into one vector has allowed next-generation OVs the potential to revolutionize personalized oncology and to dramatically extend the clinical applicability of virotherapy (65).

Arming Oncolytic Viruses: Transgene Strategies to Enhance Antitumor Efficacy

The use of oncolytic viruses (OVs) to selectively infect and kill tumor cells has the potential to be augmented by genetic engineering of these viruses to incorporate transgenes to enhance their antitumor efficacy. Such cold weapons can help adjust the cancer microenvironment (TME), activate the body's immune system, or kill the cancer cells themselves (66). Among the strategies that have been the subject of most studies is the addition of immune-stimulatory genes, including granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-12 (IL-12), or interferon-beta (IFN-β). The expression of such cytokines draws in dendritic cells, increases antigen presentation, and activates cytotoxic T cells, in effect making the tumor an in situ vaccine (67).

Other transgenes produce pro-apoptotic proteins, e.g. TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), which activate the programmed cell death pathways in malignant cells directly. Moreover, the presence of the genes, which alter the TME through degradation of extracellular matrix elements, decrease of the immunosuppressing cells, or preventing angiogenesis, contributes to promoting the spread of the virus and immune cell infiltration (68).

Newer approaches include bispecific T-cell engagers (BiTEs), or chimeric antigen receptor (CAR) ligands inserted into the viral genome, which can mediate T-cell bridging with tumor cells, bystander killing, and the enhancement of local cytotoxicity. Combination strategies might also include genes that predispose to additional treatment agents, e.g. increasing tumor cell sensitivity to chemotherapy, radiotherapy, or immunotherapy (69).

Modern OVs comprising a combination of selective tumor tropism, regulated viral replication,

and transgene-mediated immunomodulation are highly modifiable cancer therapeutic tools. This versatile engineering allows the design of a custom oncolytic targeted towards the cells of a particular tumor, depending on genetic background or immune microenvironment to maximize the desired therapeutic effect and minimize adverse effects (70).

DISCUSSION

The development of oncolytic viruses (OVs) is renewable to one of the most impressive examples of the convergence of virology, immunology and molecular engineering in revolutionizing cancer therapy. From their first identification as in vivo incidental findings of viral infections that resulted in tumor regression, OVs have become a rationally designed and clinically viable therapeutic platform (5).

Balancing Oncolysis and Immunity

The dual mechanism of OVs, where these vectors induce both lysis of tumor cells and elicit a systemic antitumor immunity is what makes them more different from the use of traditional anticancer agents. Direct oncolysis relieves tumor burden locally, and the release of tumor antigens and danger signals make the tumor an in situ vaccine (5). This duality has profound implications: OVs do not only act as cytotoxic agents, but they are also immune modulators that can reprogram the tumor microenvironment (TME)(72). Unlike immune checkpoint inhibitors, which target one pathway et seq., OVs can produce broad spectrum immune activation, which include dendritic cells, natural killer cells, cytotoxic TL and reversal of immunosuppressive networks (73).

Engineering Breakthroughs and Clinical Realities

Genetic engineering has played a major role in overcoming the shortcomings of the natural viral strains, especially their lack of tumor selectivity and safety issues. Strategies including receptor retargeting, tumor-specific promoters, gene deletions, and transgene insertions have helped dramatically improve not only the therapeutic index but also the safety of OVs.71 However, while those strategies have improved selectivity, they highlight the intricacy of balancing replication potency with the safety of the host cell population. Clinical translation has revealed that recrudescence of disease may occur following monotherapy with OVs, that OVs are often safe although preliminary responses are often limited in heterogeneous tumours indicating the need for rational combination regimens (71, 72).

Combinatorial Therapies: Toward Synergy

The most transformative direction that has emerged from clinical studies is that oncolytic viruses are more effective in combination therapies rather than acting as a monotherapy (32). Combining oncolytic viruses with either immune checkpoint inhibitors may promote longer-lived systemic immunity, but their combination with either chemotherapy or radiotherapy promotes leaky viral entry and triggers immunogenic cell death (72). Novel combinations with targeted medicines show promise, especially in tumours with defined molecular weaknesses. In the future, classification based on biomarkers will be essential in order to optimize these combinations, and get rid of trial and error approaches (73).

Challenges and Future Directions

Despite remarkable advances, several hurdles remain. One of the most pressing issues is the immune system itself: while OVs rely on immune activation for efficacy, premature antiviral clearance can limit viral spread and persistence. Engineering “stealth” viral particles, transient immune modulation, or repeated dosing strategies may help overcome this paradox (74). Another challenge lies in delivery: systemic administration is desirable for metastatic disease, but neutralizing antibodies and the restrictive blood–tumor barrier remain barriers to efficacy. Nanoparticle encapsulation, carrier-cell approaches, and localized delivery are being actively explored to address these limitations (75).

Equally important are regulatory and ethical considerations. The long-term safety of genetically engineered viruses, potential horizontal transmission, and risks of uncontrolled viral replication require stringent monitoring frameworks. Moreover, the high cost of development and manufacturing may limit accessibility, raising equity concerns in global oncology (76).

CONCLUSION

Oncolytic viruses (OVs) are a family of new antitumor agents with combined tumor cell destruction by direct lysis and the induction of a body-wide immune response. Their therapeutic success is linked to their tumor-specific viral replication, programmed cell death induction, such as immunogenic cell death, and/or effects on the tumor microenvironment. Reaction OVs hold promise as multifunctional platforms that can overcome resistance and engage systemic antitumor immunity by making tumors more specific, immune-stimulatory and safer through genetic engineering and transgene arming. The translational potential of their clinical advances, such as H101, T-VEC, and Delytact regulatory approval, is shown. With the fast-developing precision engineering and biomarker-guided interventions, OVs will take a central role in multimodal cancer treatment of the future.

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REFERENCES

1. Chertow DS, Kindrachuk J. Influenza, Measles, SARS, MERS, and Smallpox.
2. Zheng M, Huang J, Tong A, Yang H. Oncolytic Viruses for Cancer Therapy: Barriers and Recent Advances. Molecular therapy oncolytics. 2019;15:234-47.
3. Sakai T, Morimoto Y. The History of Infectious Diseases and Medicine. Pathogens (Basel, Switzerland). 2022;11(10).
4. Zuo K, Gao W, Wu Z, Zhang L, Wang J, Yuan X, et al. Evolution of Virology: Science History through Milestones and Technological Advancements. Viruses [Internet]. 2024; 16(3).
5. Ma XY, Hill BD, Hoang T, Wen F. Virus-inspired strategies for cancer therapy. Seminars in cancer biology. 2022;86(Pt 3):1143-57.
6. Lin D, Shen Y, Liang T. Oncolytic virotherapy: basic principles, recent advances and future directions. Signal transduction and targeted therapy. 2023;8(1):156.
7. Wang X, Shen Y, Wan X, Hu X, Cai WQ, Wu Z, et al. Oncolytic virotherapy evolved into the fourth generation as tumor immunotherapy. Journal of translational medicine. 2023;21(1):500.
8. Tian Y, Xie D, Yang L. Engineering strategies to enhance oncolytic viruses in cancer immunotherapy. Signal transduction and targeted therapy. 2022;7(1):117.
9. Guo ZS, Liu Z, Bartlett DL. Oncolytic Immunotherapy: Dying the Right Way is a Key to Eliciting Potent Antitumor Immunity. Frontiers in oncology. 2014;4:74.
10. Wu YY, Sun TK, Chen MS, Munir M, Liu HJ. Oncolytic viruses-modulated immunogenic cell death, apoptosis and autophagy linking to virotherapy and cancer immune response. Frontiers in cellular and infection microbiology. 2023;13:1142172.
11. Wang R, Lan C, Benlagha K, Camara NOS, Miller H, Kubo M, et al. The interaction of innate immune and adaptive immune system. MedComm. 2024;5(10):e714.
12. Ibrahim A, Mohamady Farouk Abdalsalam N, Liang Z, Kashaf Tariq H, Li R, O. Afolabi L, et al. MDSC checkpoint blockade therapy: a new breakthrough point overcoming immunosuppression in cancer immunotherapy. Cancer Gene Therapy. 2025;32(4):371-92.
13. Shi R, Tang YQ, Miao H. Metabolism in tumor microenvironment: Implications for cancer immunotherapy. MedComm. 2020;1(1):47-68.
14. Pérez-Domínguez F, Quezada-Monrás C, Cárcamo L, Muñoz JP, Carrillo-Beltrán D. Oncolytic Viruses as a Novel Therapeutic Approach for Colorectal Cancer: Mechanisms, Current Advances, and Future Directions. Cancers [Internet]. 2025; 17(11).
15. Ma N, Gao J, Pang X, Wu K, Yang S, Wei H, et al. Formulation-optimized oncolytic viruses: Advancing systemic delivery and immune amplification. Journal of Controlled Release. 2025;383:113822.
16. Ma R, Li Z, Chiocca EA, Caligiuri MA, Yu J. The emerging field of oncolytic virus-based cancer immunotherapy. Trends in cancer. 2023;9(2):122-39.
17. Lin D, Shen Y, Liang T. Oncolytic virotherapy: basic principles, recent advances and future directions. Signal transduction and targeted therapy. 2023;8(1):156.
18. Safarzadeh M, Saadat N, Abbasi-Molaei S, Rastegari-Pouyani M. Extracellular vesicles as missiles for enhanced anti-tumor efficacy of oncolytic viruses: from disseminating oncolysis and anti-tumor immunity to targeted delivery. Cell communication and signaling : CCS. 2025;23(1):276.
19. Zhou X, Hu S, Wang X. Recent advances in oncolytic virus combined immunotherapy in tumor treatment. Genes & Diseases. 2025;12(6):101599.
20. Tian Y, Xie D, Yang L. Engineering strategies to enhance oncolytic viruses in cancer immunotherapy. Signal transduction and targeted therapy. 2022;7(1):117.
21. Ferrucci PF, Pala L, Conforti F, Cocorocchio E. Talimogene Laherparepvec (T-VEC): An Intralesional Cancer Immunotherapy for Advanced Melanoma. Cancers [Internet]. 2021; 13(6).
22. Stergiopoulos GM, Concilio SC, Galanis E. An Update on the Clinical Status, Challenges, and Future Directions of Oncolytic Virotherapy for Malignant Gliomas. Current treatment options in oncology. 2024;25(7):952-91.
23. Sun L, Zhao Q, Miao L. Combination therapy with oncolytic viruses for lung cancer treatment. Frontiers in oncology. 2025;15:1524079.
24. Dong H, Li M, Yang C, Wei W, He X, Cheng G, et al. Combination therapy with oncolytic viruses and immune checkpoint inhibitors in head and neck squamous cell carcinomas: an approach of complementary advantages. Cancer cell international. 2023;23(1):1.
25. Sankar K, Ye JC, Li Z, Zheng L, Song W, Hu-Lieskovan S. The role of biomarkers in personalized

immunotherapy. Biomarker research. 2022;10(1):32.
26.Zang Y, Guo B, Qiu Y, Liu H, Opyrchal M, Lu X. Adaptive phase I-II clinical trial designs identifying optimal biological doses for targeted agents and immunotherapies. Clinical trials (London, England). 2024;21(3):298-307.
27.Du W, Na J, Zhong L, Zhang P. Advances in preclinical and clinical studies of oncolytic virus combination therapy. Frontiers in oncology. 2025;15:1545542.
28.Müller L, Berkeley R, Barr T, Ilett E, Errington-Mais F. Past, Present and Future of Oncolytic Reovirus. Cancers (Basel). 2020;12(11).
29.Ghosh R, Kumar M, Komal K, Kumar S, Sharma R, Das Gupta G. Exploring the potential of oncolytic viral vectors in targeted cancer therapy: advances, challenges and future directions. Discover Medicine. 2025;2(1):182.
30.Sakunchotpanit G, Patil MK, Venkatesh K, Rohan TZ, Cheng D, Nambudiri VE. Treatment of malignant melanoma with coxsackievirus A21 (V937): An emerging oncolytic virotherapy. 2024;33(9):e15169.
31.Lauer UM, Beil J. Oncolytic viruses: challenges and considerations in an evolving clinical landscape. Future Oncology. 2022;18(24):2713-32.
32.Su Y, Su C, Qin L. Current landscape and perspective of oncolytic viruses and their combination therapies. Translational Oncology. 2022;25:101530.
33.Guillerme JB, Gregoire M, Tangy F, Fonteneau JF. Antitumor Virotherapy by Attenuated Measles Virus (MV). Biology. 2013;2(2):587-602.
34.Msaouel P, Iankov ID, Dispenzieri A, Galanis E. Attenuated oncolytic measles virus strains as cancer therapeutics. Current pharmaceutical biotechnology. 2012;13(9):1732-41.
35.Jafari M, Abdoli S, Asgari M, Moghaddam Pour M, Shokrgozar MA, Sharifzadeh Z. Combination Therapy of Oncolytic Newcastle Virus and Lenalidomide Enhanced Cytotoxicity in Prostate Cancer Cells %J Iranian Biomedical Journal. 2025;29(1):9-19.
36.Porosnicu M, Quinson A-M, Crossley K, Luecke S, Lauer UM. Phase I study of VSV-GP (BI 1831169) as monotherapy or combined with ezabenlimab in advanced and refractory solid tumors. Future Oncology. 2022;18(24):2627-38.
37.Guillerme J-B, Gregoire M, Tangy F, Fonteneau J-F. Antitumor Virotherapy by Attenuated Measles Virus (MV). Biology [Internet]. 2013; 2(2):[587-602 pp.].
38.Scanlan H, Coffman Z, Bettencourt J, Shipley T, Bramblett DE. Herpes simplex virus 1 as an oncolytic viral therapy for refractory cancers. Frontiers in oncology. 2022;12:940019.
39.Wu J, Liang J, Zhang Y, Dong C, Tan D, Wang H, et al. Strategic Advances in Targeted Delivery Carriers for Therapeutic Cancer Vaccines. International Journal of Molecular Sciences [Internet]. 2025; 26(14).
40.Dabkowska A, Domka K, Firczuk M. Advancements in cancer immunotherapies targeting CD20: from pioneering monoclonal antibodies to chimeric antigen receptor-modified T cells. 2024;Volume 15 - 2024.
41.Jafari M, Kadkhodazadeh M, Shapourabadi MB, Goradel NH, Shokrgozar MA, Arashkia A, et al. Immunovirotherapy: The role of antibody based therapeutics combination with oncolytic viruses. 2022;Volume 13 - 2022.
42.Wang J-H, Gessler DJ, Zhan W, Gallagher TL, Gao G. Adeno-associated virus as a delivery vector for gene therapy of human diseases. Signal transduction and targeted therapy. 2024;9(1):78.
43.Zhang Y, Shi X, Shen Y, Dong X, He R, Chen G, et al. Nanoengineering-armed oncolytic viruses drive antitumor response: progress and challenges. MedComm. 2024;5(10):e755.
44.Mantwill K, Klein FG, Wang D, Hindupur SV, Ehrenfeld M, Holm PS, et al. Concepts in Oncolytic Adenovirus Therapy. International Journal of Molecular Sciences [Internet]. 2021; 22(19).
45.Montaño-Samaniego M, Bravo-Estupiñan DM, Méndez-Guerrero O, Alarcón-Hernández E, Ibáñez-Hernández M. Strategies for Targeting Gene Therapy in Cancer Cells With Tumor-Specific Promoters. Frontiers in oncology. 2020;10:605380.
46.Khushalani NI, Harrington KJ, Melcher A, Bommareddy PK, Zamarin D. Breaking the barriers in cancer care: The next generation of herpes simplex virus-based oncolytic immunotherapies for cancer treatment. Molecular therapy oncolytics. 2023;31:100729.
47.Bommareddy PK, Patel A, Hossain S, Kaufman HL. Talimogene Laherparepvec (T-VEC) and Other Oncolytic Viruses for the Treatment of Melanoma. American journal of clinical dermatology. 2017;18(1):1-15.
48.Howells A, Marelli G, Lemoine NR, Wang Y. Oncolytic Viruses-Interaction of Virus and Tumor Cells in the Battle to Eliminate Cancer. Frontiers in oncology. 2017;7:195.
49.Li K, Zhao Y, Hu X, Jiao J, Wang W, Yao H. Advances in the clinical development of oncolytic viruses. American journal of translational research. 2022;14(6):4192-206.
50.Campbell SA, Mulvey M, Mohr I, Gromeier M. Attenuation of herpes simplex virus neurovirulence with picornavirus cis-acting genetic elements. Journal of virology. 2007;81(2):791-9.
51.Guo C, Long Z, Lin P, Shen Y, Zhong Y, Qian J, et al. BRD9 inhibition overcomes oncolytic virus therapy resistance in glioblastoma. Cell Reports Medicine. 2025;6(8):102258.
52.Naumenko VA, Stepanenko AA, Lipatova AV, Vishnevskiy DA, Chekhonin VP. Infection of non-cancer cells: A barrier or support for oncolytic virotherapy? Molecular Therapy - Oncolytics.

2022;24:663-82.
53.Ahmed MM, Okesanya OJ, Ukoaka BM, Ibrahim AM, Lucero-Prisno DE. Vesicular Stomatitis Virus: Insights into Pathogenesis, Immune Evasion, and Technological Innovations in Oncolytic and Vaccine Development. Viruses [Internet]. 2024; 16(12).
54.Hallum JV, Thacore HR, Youngner JS. Factors affecting the sensitivity of different viruses to interferon. Journal of virology. 1970;6(2):156-62.
55.Tripodi L, Sasso E, Feola S, Coluccino L, Vitale M, Leoni G, et al. Systems Biology Approaches for the Improvement of Oncolytic Virus-Based Immunotherapies. Cancers [Internet]. 2023; 15(4).
56.Zheng M, Huang J, Tong A, Yang H. Oncolytic Viruses for Cancer Therapy: Barriers and Recent Advances. Molecular Therapy - Oncolytics. 2019;15:234-47.
57.Tomuleasa C, Tigu A-B, Munteanu R, Moldovan C-S, Kegyes D, Onaciu A, et al. Therapeutic advances of targeting receptor tyrosine kinases in cancer. Signal transduction and targeted therapy. 2024;9(1):201.
58.Anantha Rajah D, Tan HS, Farghadani R. Aptamers as immune checkpoint inhibitors in cancer immunotherapy: targeting CTLA-4/B7 and PD-1/PD-L1 pathways. International Immunopharmacology. 2025;164:115339.
59.Al-Obaidi I, Sandhu C, Qureshi B, Seymour LW. The implications of oncolytic viruses targeting fibroblasts in enhancing the antitumoural immune response. Heliyon. 2024;10(20):e39204.
60.Zhang J, Xiao Y, Zhang J, Yang Y, Zhang L, Liang F. Recent advances of engineered oncolytic viruses-based combination therapy for liver cancer. Journal of translational medicine. 2024;22(1):3.
61.Boagni DA, Ravirala D, Zhang SX. Current strategies in engaging oncolytic viruses with antitumor immunity. Molecular therapy oncolytics. 2021;22:98-113.
62.Maginnis MS. Virus-Receptor Interactions: The Key to Cellular Invasion. Journal of molecular biology. 2018;430(17):2590-611.
63.Yu J, Kong X, Feng Y. Tumor microenvironment-driven resistance to immunotherapy in non-small cell lung cancer: strategies for Cold-to-Hot tumor transformation. Cancer drug resistance (Alhambra, Calif). 2025;8:21.
64.Jinglu Y, Xiaoni K, Yu F. Tumor microenvironment-driven resistance to immunotherapy in non-small cell lung cancer: strategies for Cold-to-Hot tumor transformation. Cancer Drug Resistance. 2025;8:21.
65.Dorta-Estremera S, Colbert LE, Nookala SS, Yanamandra AV, Yang G, Delgado A, et al. Kinetics of Intratumoral Immune Cell Activation During Chemoradiation for Cervical Cancer. International Journal of Radiation Oncology, Biology, Physics. 2018;102(3):593-600.
66.Zhang Y, Shi X, Shen Y, Dong X, He R, Chen G, et al. Nanoengineering-armed oncolytic viruses drive antitumor response: progress and challenges. 2024;5(10):e755.
67.Lasek W, Zagożdżon R, Jakobisiak M. Interleukin 12: still a promising candidate for tumor immunotherapy? Cancer immunology, immunotherapy : CII. 2014;63(5):419-35.
68.Mohammad RM, Muqbil I, Lowe L, Yedjou C, Hsu H-Y, Lin L-T, et al. Broad targeting of resistance to apoptosis in cancer. Seminars in cancer biology. 2015;35:S78-S103.
69.Alsajjan R, Mason WP. Bispecific T-Cell Engagers and Chimeric Antigen Receptor T-Cell Therapies in Glioblastoma: An Update. Current oncology (Toronto, Ont). 2023;30(9):8501-49.
70.Enow JA, Sheikh HI, Rahman MM. Tumor Tropism of DNA Viruses for Oncolytic Virotherapy. Viruses. 2023;15(11).
71.Jiang W, Tian Y, Gu H, Guan W. Optimizing Oncolytic Virotherapy for Malignant Glioma: From Bench to Bedside. Cancer management and research. 2025;17:1537-54.
72.Simpson GR, Relph K, Harrington K, Melcher A, Pandha H. Cancer immunotherapy via combining oncolytic virotherapy with chemotherapy: recent advances. Oncolytic virotherapy. 2016;5:1-13.
73.Zhu Z, McGray AJR, Jiang W, Lu B, Kalinski P, Guo ZS. Improving cancer immunotherapy by rationally combining oncolytic virus with modulators targeting key signaling pathways. Molecular cancer. 2022;21(1):196.
74.Khare R, Chen CY, Weaver EA, Barry MA. Advances and future challenges in adenoviral vector pharmacology and targeting. Current gene therapy. 2011;11(4):241-58.
75.Wang R, Kubiatowicz LJ, Zhang R, Bao L, Fang RH, Zhang L. Nanoparticle approaches for manipulating cytokine delivery and neutralization. 2025;Volume 16 - 2025.
76.Brokowski C, Adli M. CRISPR Ethics: Moral Considerations for Applications of a Powerful Tool. Journal of molecular biology. 2019;431(1):88-101.

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Next-Generation Photodynamic Therapy: Combining Light and Nanotechnology for Targeted Cancer Treatment

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Abstract:

Photodynamic therapy (PDT) has received significant interest as one of the least invasive and spatially selective cancer treatments. It uses photosensitizers excited by light of a certain wavelength to produce cytotoxic reactive oxygen species (ROS) to discriminately destroy cancerous cells, leaving normal tissue intact. PDT is effective in the treatment of superficial malignancies; however, the applicability is limited by poor light penetration, poor selectivity of photosensitizers about tumor specificity, and systemic side effects, among others. Nanotechnology has offered radical solutions to overcome these challenges by enabling the possibility of designing nanoparticle (NP)-based systems to increase the aqueous solubility of the photosensitizer, as well as targeting the tumors and effective production of reactive oxygen species. This review sums up the recent advances of nanoparticle-mediated PDT over the last decade, including approaches and designs of nanoplatforms, targeted PDT, photo-physical activation approaches, generation of ROS, therapeutic safety, and translation. We highlight the challenges we cannot overcome so far, such as nanoparticle synthesis reproducibility, light dosimetry, hypoxia in tumors, and regulatory barriers, and the new technologies that are only going to gain more significance, such as nanomedicine controlled by artificial intelligence (AI) and combination therapy. Collectively, they represent a paradigm shift towards a next-generation PDT as a safe, precise and personalized cancer treatment.

Keywords: Photodynamic therapy, Targeted cancer therapy, Reactive oxygen species, Nanomedicine, Light-activated therapy.

Introduction

Cancer has been one of the most recalcitrant health issues, and globally it triggers up to 10 million deaths annually. Despite the immense advances in the field of conventional oncological treatments, like surgery, chemotherapy, and radiotherapy, remain highly constrained (1, 2). Even though these therapies may be effective in reducing tumor load, they are also typically associated with systemic toxicities, destruction of normal cells not targeted, and countermeasures by the tumor cells. Not only do these limitations decrease the overall effectiveness

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of treatments, but they also influence the quality of life of patients, and, therefore, innovative and more selective and less invasive treatment methods are required urgently (3).

Photodynamic therapy (PDT) has garnered quite a significant amount of attention as a possible competitive or complementary therapeutic modality among cancer patients. PDT relies on a combination of three key components: a photosensitizing agent (photosensitizer, PS), light of a certain wavelength that fits within the absorption spectrum of the PS and molecular oxygen that is present in tissues (4). Upon exposure to the activating light, the PS is substoichiometrically excited to long-lived triplet multiplicity by a photochemically induced ground-state to excited-singlet transfer followed by intersystem crossing to the long-lived triplet. That excited PS can then convert its energy to surrounding molecular oxygen, producing highly reactive oxygen species (ROS), mainly singlet oxygen (1 O 2), and other radicals. These ROS cause local oxidative damage to valuable cellular molecules such as lipids, proteins, and nucleic acids, causing cancerous cells to die. Additionally, PDT can cause tumor vessels and tumor microenvironment damage and enhance antitumor immunity and contribute to the prolonged therapeutic response (5).

Absence of Targeting Specificity: The traditional PSs lack tumor selectivity and are prone to the occurrence in non-targeted tissues, which has been noted as one of the factors leading to the need for developers of enhanced targeting controls (6).

Over the past couple of years, nanotechnology has been redefining the operations of the drug delivery field and biomedical imaging, offering new answers to problems that are bound to emerge in PDT. The photosensitizers can also be encapsulated by NPs (10-200 nm) to enhance solubility, provide protection against early degradation, and minimize the circulation time (7). Besides these, nanoparticles can improve the selective delivery of PSs to the tumor through passive accumulation based on the enhanced permeability and retention (EPR) effect and active targeting based on the recognition of tumor-specific receptors by surface-functionalized ligands. Further nanoplatforms possess inherent stimuli-responsive features that enable the release of the PS at tumor microenvironment to desirable locations and under controlled conditions in response to particular stimuli such as acidic pH, redox gradients or enzyme activity (8).

New nanomaterials may also carry agents to overcome tumor hypoxia, such as loading the material with oxygen-impermeable materials, or catalysts to create supplemental oxygen (urgently required by the cells) internally. The other pivotal development is the upconversion nanoparticles (UCNPs) that turn deep red/near-infrared (NIR) light into visible light to actuate a conventional PS in vivo, which can be seen as simply penetrating tissue (9).

Taken together, these developments could considerably increase the efficacy of PDT, its safety rate, and its use in the clinic, where its efficacy may be extended to a wider range of tumors, including deep-seated tumors (10).

This review will explain in detail the use of nanotechnology in the treatment of cancer through photodynamic therapy. We review methodically the recent advances in nanoparticle platforms design, molecular and cellular tumor targeting, photophysics of ROS-generating, preclinical, clinical and safety issues. We also discuss critically the problem of translation to nanoparticles-facilitated PDT and promising prospects and opportunities. We hope to leave a methodological roadmap that can guide the research and professional contribution of the future towards the creation of the next generation of PDT protocols that will transform the arena of targeted cancer therapy.

Nanoparticle Platforms in PDT: Design and Functionalization

Nanoparticles (NPs) have emerged to be multi-functional and versatile delivery vehicles that can enhance the sensitivity and specificity of photodynamic therapy (PDT). Encapsulation or conjugation of NPs to photosensitizers (PSs) offers the potential to improve solubility, stability, pharmacokinetics and tumor targeting of PSs with reduced systemic toxicity (11). Moreover, the nanoparticle may be modified to respond to some stimuli in the tumor or in the external environment, causing the therapeutic drug payload to be released and activated. During this session, a list of the most researched nanoplatforms employed in PDT is provided with a detailed description of structural characteristics and how they can be functionalized, in addition to the advantages of using such structures (12).

Liposomes and Micelles

An example of a vesicle that is bilayered and rounded and which is mainly made of phospholipids is called a liposome and has the same structure as the cell membranes. This similarity to the structure offers extremely high biocompatibility and enables the encapsulation of a broad therapeutic repertoire of drugs. Liposomes mimic the cancer core-shell system that allows to entrap of water-soluble photosensitizers in the hydrophilic core and lipophobic compounds in the hydrophobic bilayer (13). They have high PS solubility when stored in liposomes and are not easily digested by enzymes or degraded. It is also notable that certain liposomal PDT systems (including

verteporfin liposomes) had already gained regulatory and clinical approval, and that they represented their potential translation (14).

The significance of surface modification of liposomes is, it must proceed in a manner that it prolongs the circulation period and increases the specificity of targeting. PEGylation of nanoscopic carriers to achieve hydrophilicity inhibits opsonin socialization and uptake in the RES and prolongs systemic circulation. Active targeting, in which the PS binds to overexpressed receptors on tumor cells or tumor-associated vasculature, may be incorporated once again into functionalized PS delivery (15). Also, immunomodulatory molecules may be added to regulate the tumor microenvironment.

Nanosized objects formed by self-assembling amphiphilic block copolymers, in their turn, are called micelles and contain hydrophilic and hydrophobic parts. Photosensitizers with lipophilic properties (that most PS molecules are limited to only by a few constraints of water solubility) are readily dissolved in their hydrophobic interstitium (16). The micelles are smaller (10-100 nm) than liposomes, and this can be translated into greater penetration depth and cellular uptake efficiency in the tumor cell. Improved micellar systems utilize stimuli-sensitive polymers that may be liberated by PSs in response to low-basic environments, elevated enzyme concentrations or redox environments commonly found in the tumor microenvironment. This would minimize the off-target effects and maximize the therapeutic index (17).

Gold Nanoparticles

Special physicochemical properties of gold nanoparticles have been achieved due to the scattering of light by collective oscillation of conductive electrons (surface plasmon resonance, or SPOR) (18). This makes AuNPs highly absorbent and optically scattering at the visible wavelengths and the NIR wavelengths that are used twice in the PDT. In addition to the ability to deliver PSs, the AuNPs can also adopt light energy and subsequently transform it into heat, referred to as the photothermal effect, and can induce synergistic effects but not combinatoric effects when combined with PDT-mediated generation of ROS (19).

AuNPs with objectively determinable optical properties (size dependence) as well as biodistribution and surface chemistry can be prepared in varying sizes and shapes (spheres, rods, shells, cages). These surfaces can easily accept thiolated ligands and consequently can be conjugated to PS molecules, target group antibodies or peptide or stealth coating such as PEG (20). It enables the surveillance and targeting of tumors with the assistance of multi-functionalization. Additionally, to reach integrated theranostic applications, photoacoustic imaging, computed tomography (CT), and surface-enhanced Raman scattering (SERS) imaging technologies may use AuNPs as contrast agents (21).

Mesoporous Silica Nanoparticles (MSNs)

Mesoporous silica nanoparticles possess highly ordered pore structures and adjustable pore sizes ranging between 2-10 nm with very large surface areas and pore volumes, resulting in high loading capacities compared to conventional silica nanoparticles. The range of photosensitizers into which one can introduce the SNs is typically broad, encompassing synergistic therapeutics that can include chemotherapeutics, gene therapies or oxygen-generating catalysts (1, 2).

Any biomedical application of the material is attributed to inherent biocompatibility and chemical stability, and is associated with MSNs. It is worth noting that MSNs are readily modified on their surface with multiple functional groups, and surface-bound functional groups can be conjugated to both targeting ligands (e.g., folate, transferrin) and stimuli-sensitive formulations, called gatekeepers, that prevent lock-up of potential PS-leakage before its occurrence (3). These gatekeepers can be designed to react to tumor targeting cues such as acidic pH, glutathione or proteolytic enzymes such that cargo release is specific to the tumor (4).

Alongside this, the co-delivery of agents to achieve tumor hypoxia, e.g. catalase or perfluorocarbon compounds, could be used in MSNs to increase oxygen in the local area to enhance the production of ROS and PDT efficacy. It is this multi-functional nature that makes MSNs a highly useful platform in combination therapy and precision oncology (5).

Carbon Nanomaterials

A significant subset of nanoparticles is represented by carbon-based nanomaterials, including graphene oxide (GO), carbon dots (CDs), and carbon nanotubes (CNTs) with unique optical, electronic, and chemical properties in PDT. Oxidized PS on two-dimensional graphene (GO) has a high surface area, allowing conjugation and photothermal and photodynamic properties. Targeting ligands have been incorporated into the functionalization, resulting in high uptake in tumor cells and high biocompatibility via high dispersibility in water (6).

Carbon dots are nanometric fluorescent carbon nanoparticles that are photostable and can be tuned. Their intrinsic fluorescence may enable concomitant imaging and therapy (theranostics). CdS nanoporous objects may be functionalised with PS molecules to form functioning ROS makers in the presence of light (7).

CNTs are hollow cylinders composed of graphene

that have good thermal conductivity and absorption of [NIR]. The multifunctional systems with carbon nanomaterials can be combined with diagnostic imaging, drug delivery and phototherapy to kill tumor cells synergistically (8).

Polymeric Nanoparticles

Polymeric nanoparticles made out of biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), chitosan and poly(ethylene glycol) (PEG) have been used extensively as controlled drug delivery vehicles in PDT. These polymers can be customized selectively concerning their particle size, surface charge, degradation profile, and drug release profile by altering its molecular weight, ratio of copolymer, and surface functionalization (9).

Polymeric nps provide defense against encapsulated PSs that eliminate premature degradation by improving pharmacokinetics and biodistribution (10). The use of stimuli-sensitive bonds or coatings would enable release of PS under tumor-specific conditions (low pH, high glutathione, active enzymes, etc.). These smart polymeric systems enhance the target drug delivery and minimize the side effects of the drug on the system (11). Also, polymeric nanoparticles can support concurrent delivery of therapeutic, chemotherapeutic and immunomodulatory payloads (e.g., PSs), and provide synergistic effects in anticancer therapy. The modularity of polymer chemistry also allows incorporation of imaging agents and offers the opportunity to image-guide PDT, and in real time, track drug distribution (12).

Upconversion Nanoparticles (UCNPs)

The new type of nano-material is called upconversion nanoparticles, which can transform low-energy near-infrared (NIR) photons into higher-energy visible or ultraviolet light through an anti-Stokes luminescence reaction. Lanthanide ions (e.g. Yb3+, Er3+, Tm3+) are usually doped in UCNPs and possess the advantage of absorbing tissue-penetrating NIR light (c. 980 nm) and emitting shorter wavelengths that can, in turn, trigger conventional photosensitizers that would otherwise need visible light excitation (13).

This characteristic feature effectively overcomes one of the main weaknesses of PDT, namely, low tissue penetration of activating light, to permit non-invasive therapy of deep-set tumors. UCNP-PDT systems have been demonstrated to possess ideal photostability and low autofluorescence backdrop in addition to creating minimal tissue damage, owing to the intrinsic utilization of NIR (14).

Moreover, UCNP surfaces might be designed to be effectual delivery- and conjugation-oriented to PS molecules, resulting in tumor specificity and enhanced treatment efficacy. UCNPs are the nanotechnology of the future of PDT as they target and penetrate tissues ultra-deeply (15).

Targeting Strategies in Nanoparticle-Enhanced PDT

Photosensitizers (PSs) selective distribution and activation in the tumor tissues, but not in healthy cells, is a highly reliable indicator of the therapeutic efficacy of photodynamic therapy (16). Nanoparticle-based delivery platforms significantly enhance a tumor-specific delivery through multiple mechanisms of tumor targeting that capitalize on tumor-specific physiological and molecular features. These include passive targeting based on physiological abnormalities to localise to the tumor, active targeting based on ligand receptor interactions, and stimuli-responsive modalities that aim to exploit the unique tumor microenvironment. Nanopurified-enhanced PDT has a superior efficacy, fewer side effects, and a greater therapeutic index (17).

Passive Targeting via the Enhanced Permeability and Retention (EPR) Effect

One of the earliest mechanisms to have been exploited, and by far the most common in the present day, is passive tumor targeting under the Enhanced Permeability and Retention Effect (EPR) effect. The aberrant, disorganized vasculature of solid tumors is usually non-uniform with distances of 100 nm to 2 micrometers between endothelial cells (18). The resulting injury to vessel integrity enables the extravasation of circulating nanoparticles (usually 10 100 nm in diameter) into the vascular system out of the tumor interstitial space. The fact that tumors also have defective lymphatic drainage and, therefore, retention of the nanoparticles in the tumor microenvironment over time is also normal (19).

The EPR effect consequently allows the accumulation of PSs in tumor tissue over normal organs to a favorable degree, increasing PS local concentration and consequently local efficacy in selectivity of PDT. The other opportunistic effects of the improved retention include increased duration of therapeutic exposure and subsequent expanded exposure to become light-activated (20).

Being the most fundamental of the foundations, the EPR effect demonstrates a significant heterogeneity among the types of tumor, their stage, and even among patients with the same stage. Tumor blood flow, rate of perfusion, interstitial pressure, and matrix have all been found to be highly significant in EPR efficacy (21). In the case of highly vascularized tumors such as glioblastomas, the EPR can be high compared to poorly vascularized tumors, such as pancreatic adenocarcinomas, with a dense stroma that can experience low nanoparticle penetration.

Moreover, the age of the patient, sites of his/her tumor and past treatment procedures are among such systemic components that affect the delivery of nanoparticles via EPR (22).

Single administration of EPR is hence likely to yield inadequate and heterogeneous therapeutic results emphasizing the role of further targeting methodologies to improve therapeutic performance and precision within clinical PDT (23).

Active Targeting Through Ligand-Receptor Interactions

Nanoparticles can also be engineered to address the inherent negative attributes of passive accumulation, including active targeting with ligands that can bind receptors or other biomarkers that appear in excess on cancer cells or other stromal elements. This endocytosis has two advantages: massive uptake and intracellular delivery of PSs and an added specificity due to a reduced off-target effect (24).

More generally engaged ligands, and their targets are:

Folate and Folate Receptors: Folate receptors have been over-expressed in numerous malignant cells, including ovarian, breast and lung cancer. Folate-conjugated nanoparticles exploit this interaction between the receptor and ligand to enable higher tumor cell targeting and uptake. To allow the successful tumor targeting without the production of immunological responses, folate is a small molecule ligand (25).

Transferrin and Transferrin Receptors: The Transferrin receptors in the cancer cells are augmented during rapid cell growth to cope with the augmented demand for iron. Nanoparticles conjugated with transferrin are the only nanoparticles that endocytose through receptor-mediated endocytosis and therefore exhibit high uptake and intracellular delivery of PSs (26).

Peptides (e.g. RGD Motif): RGD peptides (RGD) bind integrin receptors, of which 8 is highly expressed on tumour endothelium and cancer cells, resulting in a higher tumour targeting and penetration. GD-functionalized nanoparticles are also capable of producing anti-angiogenic effects (27).

Targeting Agents: Monoclonal antibodies may serve to target the nanoparticles to particular attractive sites on the tumor, including epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and other tumor-associated antigens. This extreme specificity of targeting improves selective binding to malignant cells and endocytosis, leading to a high PS delivery (28).

Aptamers and Other Ligands: DNA- or RNA-based aptamers represent another, and possibly low-immunogenicity, alternative to antibodies to address a wide spectrum of tumor-associated targets (29).

Parallel to tumor cell specificity, active targeting could be employed to maximize other PDT effects, such as control of the tumor microenvironment, such as vascular disruption, immune cell recruitment and stroma remodelling (30).

Stimuli-Responsive and Environment-Sensitive Targeting

Compared to normal tissue, tumor microenvironments are radically distinct and are characterized by acidic levels of extracellular pH, hypoxia, increased concentrations of reactive oxygen species (ROS), and excess enzymes. A new approach to add more precision and site-specificity to therapeutic potential and minimize systemic effects is the nanoparticles that can recognize such stimuli and release or activate PS (31).

Key types of stimuli-responsive targeting systems include:

pH-Responsive Systems: Extracellular pH of solid tumors tends to be low (pH 6.5-6.8) relative to the normal pH (~7.4) due to disrupted metabolism and low perfusion (32). Acid-functionalized nanoparticles (e.g., hydrazone, cis-aconityl) or acid-sensitive polymer switch and degrade in acidic conditions, leading to the release of PSs in the acidic environment, more commonly in the tumor microenvironment or even within the cells (endosomes/ lyosomes). The pH-sensitivity offers low early drug release in the bloodstream and prefers drug bioavailability in tumor bone location (33).

Redox-Responsive Linkers: The reducing agent, glutathione (GSH), defines the intracellular environment of cancer cells, as the concentrations of reducing agents are usually more than 100 and 1000 times higher than in extracellular body fluids. A disulfide bond or other redox-labile bond is a nanoparticle that uses this gradient to specifically release PSs in tumor cells. This method provides intracellular PDT activation of certain agents (34).

Enzyme-Responsive Nanoparticles: Certain enzymes, like matrix metalloproteinases (MMPs), cathepsins, and phospholipases, are in excess or exuded in tumor cells. In NP-based systems, protective coating layers or gatekeepers that are conjugated to the NP via enzyme-cleavable peptides or bonds are also inert in circulation but interact with target enzymes in the tumor to allow the NP to unzip and release the PS load (35). This is a more specific enzyme-activated release, and physiological constraints to drug delivery are avoided (36). Hypoxia-Activated Prodrugs and Systems: Since hypoxic areas of tumors inhibit the formation of ROS, and thus effective treatment, there exists the issue of hypoxia and tumor areas that must be treated by a prodrug process. Other novel methods involve hypoxia-responsive element, which either activates prodrugs or liberates oxygen-producing

molecules in the low oxygen regions. In another example, nanoparticles can be used to introduce catalase to break down overexpressed hydrogen peroxide in tumors into oxygen, decreasing hypoxia. Alternatively, the PSs may be hypoxia-activated to induce little or no activity when there is oxygen and only in the hypoxic areas of tumor cells (37).

Externally Triggered Systems: In addition, nanoparticles can be programmed to respond to externally induced stimuli (e.g. temperature (thermo-responsive) or magnetic field (magneto-responsive) or ultrasound (sonodynamic activation) or light of a specific wavelength), and spatiotemporal regulation of PS activation may be employed (38).

Molecular Mechanisms of ROS Generation and Photophysical Principles

Nanoparticle platforms can enhance these photophysical and photochemical processes in many ways, often by several different mechanisms (40):

In protruding the lifetime PS Triplet State: PS lifetime may be enhanced by encapsulating or conjugating PS molecule in nanoparticles, which entraps the PS in a kind of nano protection coating. This trapping increases the lifetime of the excited state triplet, which increases the probability of energy transfer to the molecular oxygen to stimulate the formation of ROS (41).

Metallic NanoPlasmonic Enhancement: Metallic nanoparticles, particularly gold and silver, have localized surface plasmon resonance (LSPR) whereby conduction electrons vibrate as a mass upon the illumination of light. This effect enhances the electromagnetic field around the nanoparticle, so PS molecules are more easily excited and the energy transfer processes are improved to generate more ROS (42).

Co-delivery of Catalytic or Enzyme-Mimetic Agents: Nanocarriers can be designed such that they deliver PSs in combination with catalytic or enzyme-mimetic agents that can be used to generate a catalytic amount of the synthesis of oxygen, peroxides or other oxidized products (43). These catalysts regulate the tumor microenvironmental condition by degrading disease-endogenous hydrogen peroxide to produce molecular oxygen, which relieves hypoxia, and supplies enough molecular oxygen to facilitate vigorous ROS production. Such a co-delivery approach will overcome the major limitation of PDT in the hypoxic tumors (44). Enhanced Light Absorption due to Nanoparticle Photonic Upconversion: The nanoparticles would enhance the light absorption cross-section of the PSs. Upconversion nanoparticles (UCNPs) are one such example; they convert deep penetrating near-infrared (NIR) light to visible light that can then power PSs to generate ROS efficiently in deep-seated tumors where direct light excitation is challenging to attain (45).

Though optimum action of ROS is vital as far as elimination of tumors is concerned, the balance in this sensitive action must be monitored so as to prevent collateral damage. Excessive levels of ROS can overwhelm antioxidant systems in the surrounding normal tissues and lead to unintended cytotoxicity and inflammation (46). In contrast, production of ROS may be suboptimal, resulting in failure to kill a tumor and therapeutic failure. In this way, PDT nanoparticle characteristics, including ROS generation dynamics and targeting, have to be optimized to simplify its use to the maximum benefit and mitigate its side effects (47).

Preclinical and Clinical Advances in Nanoparticle-Enabled PDT

Preclinical Efficacy in Diverse Cancer Models

These are validated in an expanding literature of in vitro and in vivo experiments that have shown the increased effectiveness of nanoparticle-enhanced PDT in a broad range of cancer models (48).

Breast cancer: EGFR-targeted, gold nanorods conjugated to chlorin e6 (Ce6) are demonstrated to reduce tumor volume by 80 percent in a mouse with a combination of photothermal and photodynamic effects (49).

Lung cancer: PDT of mesoporous silica nanoparticles in lung carcinoma cells in the presence of mitochondrial-targeting IR-780 led to the development of a necrotic cell death resulting from the production of ROS and mitochondrial dysfunction (50).

Glioblastoma: Conjugation of porphyrin derivatives with graphene oxide and activation by NIR light increased the survival of mice with intracranial glioma by increasing BBB crossing and prolonged generation of ROS (51).

Colon cancer: PH-sensitive upconversion nanoparticles that are loaded with a near-infrared dye called indocyanine green (ICG) have shown 70 percent suppression of tumor growth in xenograft models (52).

Clinical Trials and Translation

This was shown to be safe and moderately efficacious in a phase II trial of liposomal benzoporphyrin derivative (BPD) activated by laser in head and neck cancer. In pancreatic cancer, a Phase I trial of porphyrin-nanoparticle showed synergistic targeting at low toxicity. The barriers to clinical use include scalability of the nanoparticles, reproducibility of the nanoparticles, regulatory concerns, and complexity of customized lighting configurations on the patient (53).

Safety and Biocompatibility Considerations

Safety, biocompatibility is one of the most critical

issues related to the development of a nanoparticle-based PDT system. The adsorptive interaction of nanoparticles with the biological milieu is also determined by various significant factors, including the size, surface charge, chemical composition and degradation characteristics of the nanoparticles. All these parameters interact to affect the biodistribution, immune recognition, their clearance, and potential toxicity which all need to be optimized to provide the most desirable therapeutic effect whilst reducing the adverse effects (54).

The size range of nanoparticles can be extensive (10 to 200 nanometers), and through the so-called enhanced permeability and retention (EPR) effect, they can be concentrated in a tumor tissue by passive targeting. Within this size range, nanoparticles are also prone to sequestration through the mononuclear phagocyte system (MPS), including in the liver, the spleen, and the kidney cells. This extrasystemic deposition or accumulation causes the risk of multiple organ toxicities or organ-selective toxicities when given repeatedly as a result of the long-term retention, which may cause inflammation or dysfunction of the organs (55).

The question of the surface charge of a nanoparticle is also a major consideration in how it communicates with the plasma or with the immune cells. Nanoparticles that are positively charged will be more likely to have an affinity with the cells; they will also cause higher degrees of cellular toxicity and complement activation, resulting in an immune response (56). Conversely, neutral or negatively charged particles have a lower probability of binding nonspecifically to proteins, and immune clearance and immune recognition do not depend on the surface chemistry or reactive functional groups on them (57).

Further effects on the biocompatibility and degradation depend on the composition of the materials. Inorganic nanoparticles (e.g., gold or silica), which are non-biodegradable or slowly bio-persistent in vivo, are desirable due to attractive optical or structural characteristics, but there is concern over their long-term persistence and possible chronic toxicity. The benefits of biodegradable polymers are that they can be degraded in a controlled manner with non-toxic by-products, thereby being less prone to accumulation and aiding in safer clearance in the body (58).

The other notable observation is that nanoparticle preparations can also be immunogenic. Unintentional activation of innate immune responses, particularly through the complement cascade, can lead to unwanted effects up to mild inflammation and acute cardiovascular or respiratory adverse events in the manifestation of reaction to complement activation related pseudoallergy (CARPA). Not only do these immune responses harm patient safety, they may accelerate the clearance of nanoparticles to diminish the effects of therapy (59).

A series of design solutions is added to reduce such risks. The steric repulsive force formed by covalent conjugation of nanoparticles with hydrophilic polymers such as polyethylene glycol (PEG) prevents protein adsorption (opsonization), and immune recognition and causes a marked prolongation of the circulatory life of the nanoparticle in the body (60). PEGylation is widely practised and is effective in reducing immunogenicity; however, in certain patient groups, anti-PEG antibodies are appearing, due to which other stealth coatings using zwitterionic polymers, polysaccharides, or biomimetic cell membrane-derived polymers are being explored with assertion of superior biocompatibility and immune evasion (61).

Targeted surface functionalization with tumor-specific binders (e.g. antibodies, peptides and small molecules) has the benefits of improving tumor specificity, reducing off-target binding and inducing immunotoxicity. To this effect, systemic exposures and consequent toxicities by nanoparticles can be minimized through close dosage tuning and targeting of nanoparticles at sites of local delivery (preferable to systemic delivery by nanoparticles wherever possible) (62).

In the evaluation of the safety of nanoparticle-PDT systems, preclinical toxicological testing is required. In vitro cytotoxicity tests, hematology, biochemical, organ histopathology, immunotoxicology and pharmacokinetic studies are primarily subject to extensive testing to identify biodistribution and excretion. Physicochemical characterization, including particle size distribution, surface charge, concentration of endotoxin, and state of aggregation, should be standardized to ensure reproducibility as well as be regulation-compliant (63).

Their safety and quality must be adequately guaranteed by regulatory bodies, e.g., the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), before clinical approval. Early safety in nanoparticles development facilitates more convenient transfer to the clinic and avoids unexpected toxicities, and accelerates regulatory approval (64).

Challenges and Opportunities for Next-Generation PDT

Technical and Biological Barriers

Effective delivery of an adequate light dose of the photosensitizers (PSs) in the deep tumor tissues is one of the most significant constraints of photodynamic therapy (PDT). The fact that visible light will not penetrate the biological tissue more than a few millimeters, often restricts the usefulness of PS to the topical lesions, or the invasive techniques will be

necessary. Improvements in fiber-optic technology, light-emitting implantable systems, and upconversion nanoparticles that enable the conversion of near-infrared (NIR) light to visible wavelengths are significant to overcome these challenges and enable uniformity and control of light delivery in tumors to clinically relevant depths (65).

The biologic barriers to PDT activity are significant tumor hypoxia. The availability of molecular oxygen is closely linked to the formation of reactive oxygen species (ROS), yet hypoxia has been reported to occur in a number of solid tumors due to the presence of a hydrophobic circulatory system and elevated cellular proliferation rate (66). This removes much of the ROS production that is threatening cytotoxicity. Multiple approaches to overcome this hypoxic microclimate include concomitant administration of oxygen carriers, e.g. hemoglobin-based nanoparticles, perfluorocarbon emulsions or catalase-mimicking enzymes that produce O2 locally. Furthermore, the development of hypoxia-activated photosensitizers capable of producing cytotoxic species at a hypoxic setting offers a possible alternative to the traditional PDT (67).

Heterogeneity refers to the problem of nanoparticle manufacturing. Reproducibility, efficacy of therapeutics and safety factors may be adversely affected by potential variability of size distribution, surface chemistry, payload loading, and batch-to-batch reproducibility conditions (68). This inconsistency is dangerous when it comes to quality regulation and regulatory approval processes that demand rigid standardization of synthesis procedures and solid dependence of characterization methods. Effective clinical translation and the probability of nanoparticle-enhanced PDT becoming a widely utilized technology depend critically on the ability to prepare nanoparticles in a stable form, especially concerning their homogeneity (69).

Emerging Innovations

Theranostics: Nanoparticle platform allows the co-delivery of imaging agents to allow simultaneous diagnosis, real-time monitoring of treatments and directed delivery of photodynamic therapy (70). To determine the biodistribution of nanoparticles, evaluate therapeutic response and remodel parameters of treatment continuously, to optimize treatment response and minimize side effects, this two-prong system is possible (71).

Multifunctional Nanoplatforms: Multi-functional nanocarriers may be employed to deliver photosensitizers concomitantly with chemotherapeutic agents or immunomodulatory therapeutic molecules and/or gene editing technologies such as CRISPR-Cas9. The advantage of the combinatorial approach is the promotion of synergistic therapeutic effects, to overcome cancer through multiple, which will overcome drug resistance and escalate total therapy expenses (72).

Machine Learning and Artificial Intelligence: ML-based algorithms are applied to extremely large datasets to refine nanoparticle design parameters to optimize features, including size and surface chemistry and cargo loading; ML can also be used to optimize an individualized approach to treatment based on patient-specific tumor features. These data-oriented plans facilitate quick building, improve target exactness, and streamline PDT plans that are of utmost treatment worthiness (73).

External Stimuli -Triggered Release: This enables the application of external stimuli remotely to release photosensitizer like ultrasound waves, magnetic and electric pulses. With stimuli-responsive systems, a spatiotemporal control of therapy is possible, and thereby, off-target effects are minimized, or the therapy is made more specific (74).

DISCUSSION

Oncolytic viruses (75) represent a rapidly maturing class of cancer therapeutics that combine direct tumor lysis with stimulation of systemic antitumor immunity. Unlike conventional treatments that primarily target malignant cells or pathways, OVs exploit tumor-specific vulnerabilities such as impaired antiviral signaling and abnormal surface receptor expression to selectively replicate in cancer cells (76). This unique mechanism enables OVs to serve as both cytotoxic agents and immune modulators, positioning them at the interface of virotherapy and immunotherapy (77).

A central advantage of OVs is their dual mechanism of action. Direct oncolysis leads to rapid tumor cell destruction, while the release of tumor-associated antigens, damage-associated molecular patterns, and viral pathogen-associated signals activates innate and adaptive immunity (78). In this sense, OVs act as an in situ cancer vaccine, promoting recruitment of dendritic cells, priming of cytotoxic T cells, and reversal of immunosuppressive networks within the tumor microenvironment. This broad immunomodulatory effect distinguishes OVs from immune checkpoint inhibitors, which act on specific pathways, and underpins their potential as combination partners across diverse therapeutic modalities (79).

Advances in genetic engineering have been key to translating OVs from experimental systems to clinical applications. Tumor-selective promoters, receptor retargeting, insertion of immunomodulatory transgenes, and deletion of pathogenic viral genes have markedly improved safety and specificity (80). Indeed, combinatorial regimens represent one of the most promising avenues for OV development.

Preclinical and clinical data demonstrate strong synergy between OVs and immune checkpoint inhibitors, where viral infection enhances tumor immunogenicity and overcomes resistance to checkpoint blockade (81). Similarly, chemotherapy and radiotherapy can improve viral penetration, disrupt tumor stroma, and induce immunogenic cell death, further amplifying OV activity. More recently, targeted therapies have been paired with OVs to exploit tumor-specific vulnerabilities. Moving forward, biomarker-driven patient selection and rational trial design will be essential to avoid empirical combinations and fully realize the synergistic potential of these regimens (82).

Despite substantial progress, important challenges remain. A major paradox is the role of the immune system: while immune activation is necessary for durable responses, premature antiviral clearance can limit viral replication and spread. Strategies such as transient immunosuppression, repeated dosing, or development of "stealth" viral particles are under investigation to balance these competing dynamics (83). Delivery is another critical barrier, particularly for metastatic disease. Systemic administration is often hindered by neutralizing antibodies and physical barriers such as the extracellular matrix. Novel delivery methods—including nanoparticle encapsulation, cell-carrier approaches (e.g., mesenchymal stem cells), and locoregional injections—are actively being explored to improve biodistribution and efficacy (84).

Regulatory, safety, and economic considerations also warrant careful attention. Concerns about insertional mutagenesis, uncontrolled replication, or horizontal viral transmission necessitate rigorous long-term monitoring in clinical trials (85). Furthermore, the complexity and cost of OV manufacturing may limit accessibility, especially in low- and middle-income countries. Addressing these issues will be critical to ensuring that OV-based therapies are not restricted to highly resourced healthcare systems (86).

Future Perspectives

The combination of intelligent nanomedicine is driving photodynamic therapy (PDT) toward precise control of dose, activation and monitoring (87). Advances in artificial intelligence behaviour may optimize nanoparticle formulation, dosing and light exposure further for individualized treatment of maximum effect with as few side effects as possible. Emerging preclinical models such as tumor organoids and microfluidics systems provide more accurate assessment of PDT with nanoparticles (84). Combining PDT with immunotherapy and specifically immune checkpoint inhibitors has the potential to increase systemic antitumor immunity for durable responses. Real-time imaging modes such as MRI, PET, and photoacoustic imaging parrots the possibility of dynamic in vivo monitoring and adaptive therapy. Collectively these innovations are likely to make PDT become a versatile and highly effective precision oncology modality (88).

CONCLUSION

The nanotechnology-based PDT is a significant innovation in cancer treatment and can address most of the problems of a nonnanotechnological photodynamic therapy. They do so by commercializing on the designed nanoplatforms, which can deliver a targeted platform, controlled and stimuli-responsive delivery and integrating synergistic therapies. Next-generation PDT approaches are transforming next-generation PDT systems into the oncologic arena with highly precise and personalized treatments. Most of the problems associated with clinical translation, regulatory acceptance, and production standardization have been abandoned; the discipline is being sped up by the constant interchange between disciplines and the use of industrial technology. Nanomedicine convergence with photonics and cancer care promises a paradigm shift of safer, more effective, and personalized cancer management with the potential of greatly improving patient outcomes and quality of life.

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Authors's Contribution

Yasaman Vojgani: Conceptualization, Writing and Editing the draft. The author read and confirmed the final manuscript.

Conflicts of interest

None of the authors has any conflicts of interest to declare.

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REFERENCES

1.Malekmohammadi S, Mohammed RUR, Samadian H, Zarebkohan A, García-Fernández A, Kokil GR, et al. Nonordered dendritic mesoporous silica nanoparticles as promising platforms for advanced methods of diagnosis and therapies. Materials Today Chemistry. 2022;26:101144.

2.Meng X, Shen Y, Zhao H, Lu X, Wang Z, Zhao

Y. Redox-manipulating nanocarriers for anticancer drug delivery: a systematic review. Journal of nanobiotechnology. 2024;22(1):587.
3.Florensa M, Llenas M, Medina-Gutiérrez E, Sandoval S, Tobías-Rossell G. Key Parameters for the Rational Design, Synthesis, and Functionalization of Biocompatible Mesoporous Silica Nanoparticles. Pharmaceutics. 2022;14(12).
4.Singh R, Srinivas SP, Kumawat M, Daima HK. Ligand-based surface engineering of nanomaterials: Trends, challenges, and biomedical perspectives. OpenNano. 2024;15:100194.
5.Li X, Chen L, Huang M, Zeng S, Zheng J, Peng S, et al. Innovative strategies for photodynamic therapy against hypoxic tumor. Asian journal of pharmaceutical sciences. 2023;18(1):100775.
6.Jayaprakash N, Elumalai K, Manickam S, Bakthavatchalam G, Tamilselvan P. Carbon nanomaterials: Revolutionizing biomedical applications with promising potential. Nano Materials Science. 2024.
7.Rani R, Kumar V, Rizzolio F. Fluorescent Carbon Nanoparticles in Medicine for Cancer Therapy: An Update. ACS medicinal chemistry letters. 2018;9(1):4-5.
8.Alfei S, Reggio C, Zuccari G. Carbon Nanotubes as Excellent Adjuvants for Anticancer Therapeutics and Cancer Diagnosis: A Plethora of Laboratory Studies Versus Few Clinical Trials. Cells [Internet]. 2025; 14(14).
9.Geszke-Moritz M, Moritz M. Biodegradable Polymeric Nanoparticle-Based Drug Delivery Systems: Comprehensive Overview, Perspectives and Challenges. Polymers. 2024;16(17).
10.Prieložná J, Mikušová V, Mikuš P. Advances in the delivery of anticancer drugs by nanoparticles and chitosan-based nanoparticles. International Journal of Pharmaceutics: X. 2024;8:100281.
11.Huang Y, Guo X, Wu Y, Chen X, Feng L, Xie N, et al. Nanotechnology's frontier in combatting infectious and inflammatory diseases: prevention and treatment. Signal Transduction and Targeted Therapy. 2024;9(1):34.
12.Romero-Ben E, Goswami U, Soto-Cruz J, Mansoori-Kermani A, Mishra D, Martin-Saldaña S, et al. Polymer-based nanocarriers to transport therapeutic biomacromolecules across the blood-brain barrier. Acta Biomaterialia. 2025;196:17-49.
13.Mohan M, Poddar R. Polymerically engineered upconversion nanoparticles (UCNPs) as contrast agent for functionally modified optical coherence tomography (OCT). Materials Science and Engineering: C. 2021;121:111841.
14.Zhao W, Wang L, Zhang M, Liu Z, Wu C, Pan X, et al. Photodynamic therapy for cancer: mechanisms, photosensitizers, nanocarriers, and clinical studies. MedComm. 2024;5(7):e603.
15.Li J, Wang S, Fontana F, Tapeinos C, Shahbazi M-A, Han H, et al. Nanoparticles-based phototherapy systems for cancer treatment: Current status and clinical potential. Bioactive Materials. 2023;23:471-507.
16.Cai Y, Chai T, Nguyen W, Liu J, Xiao E, Ran X, et al. Phototherapy in cancer treatment: strategies and challenges. Signal Transduction and Targeted Therapy. 2025;10(1):115.
17.Elumalai K, Srinivasan S, Shanmugam A. Review of the efficacy of nanoparticle-based drug delivery systems for cancer treatment. Biomedical Technology. 2024;5:109-22.
18.Nakamura Y, Mochida A, Choyke PL, Kobayashi H. Nanodrug Delivery: Is the Enhanced Permeability and Retention Effect Sufficient for Curing Cancer? Bioconjugate chemistry. 2016;27(10):2225-38.
19.Vagena I-A, Malapani C, Gatou M-A, Lagopati N, Pavlatou EA. Enhancement of EPR Effect for Passive Tumor Targeting: Current Status and Future Perspectives. Applied Sciences [Internet]. 2025; 15(6).
20.Al-Jamal AN, Al-Hussainy AF, Mohammed BA, Abbas HH, Kadhim IM, Ward ZH, et al. Photodynamic Therapy (PDT) in drug delivery: Nano-innovations enhancing treatment outcomes. Health Sciences Review. 2025;14:100218.
21.Golombek SK, May JN, Theek B, Appold L, Drude N, Kiessling F, et al. Tumor targeting via EPR: Strategies to enhance patient responses. Adv Drug Deliv Rev. 2018;130:17-38.
22.Subhan MA, Yalamarty SSK, Filipczak N, Parveen F, Torchilin VP. Recent Advances in Tumor Targeting via EPR Effect for Cancer Treatment. Journal of personalized medicine. 2021;11(6).
23.van Straten D, Mashayekhi V, de Bruijn HS, Oliveira S, Robinson DJ. Oncologic Photodynamic Therapy: Basic Principles, Current Clinical Status and Future Directions. Cancers. 2017;9(2).
24.Sharifi M, Cho WC, Ansariesfahani A, Tarharoudi R, Malekisarvar H, Sari S, et al. An Updated Review on EPR-Based Solid Tumor Targeting Nanocarriers for Cancer Treatment. Cancers [Internet]. 2022; 14(12).
25.Ebrahimnejad P, Sodagar Taleghani A, Asare-Addo K, Nokhodchi A. An updated review of folate-functionalized nanocarriers: A promising ligand in cancer. Drug Discovery Today. 2022;27(2):471-89.
26.Sousa de Almeida M, Susnik E, Drasler B, Taladriz-Blanco P, Petri-Fink A, Rothen-Rutishauser B. Understanding nanoparticle endocytosis to improve targeting strategies in nanomedicine. Chemical Society reviews. 2021;50(9):5397-434.
27.Javid H, Oryani MA, Rezagholinejad N, Esparham

A, Tajaldini M, Karimi-Shahri M. RGD peptide in cancer targeting: Benefits, challenges, solutions, and possible integrin-RGD interactions. Cancer medicine. 2024;13(2):e6800.
28.Akbarzadeh Khiavi M, Safary A, Barar J, Ajoolabady A, Somi MH, Omidi Y. Multifunctional nanomedicines for targeting epidermal growth factor receptor in colorectal cancer. Cellular and molecular life sciences : CMLS. 2020;77(6):997-1019.
29.Mahmoudian F, Ahmari A, Shabani S, Sadeghi B, Fahimirad S, Fattahi F. Aptamers as an approach to targeted cancer therapy. Cancer cell international. 2024;24(1):108.
30.Karimi S, Bakhshali R, Bolandi S, Zahed Z, Mojtaba Zadeh SS, Kaveh Zenjanab M, et al. For and against tumor microenvironment: Nanoparticle-based strategies for active cancer therapy. Materials Today Bio. 2025;31:101626.
31.Zhou W, Jia Y, Liu Y, Chen Y, Zhao P. Tumor Microenvironment-Based Stimuli-Responsive Nanoparticles for Controlled Release of Drugs in Cancer Therapy. Pharmaceutics. 2022;14(11).
32.Du J, Lane LA, Nie S. Stimuli-responsive nanoparticles for targeting the tumor microenvironment. Journal of controlled release : official journal of the Controlled Release Society. 2015;219:205-14.
33.AlSawaftah NM, Awad NS, Pitt WG, Husseini GA. pH-Responsive Nanocarriers in Cancer Therapy. Polymers [Internet]. 2022; 14(5).
34.Iyer R, Nguyen T, Padanilam D, Xu C, Saha D, Nguyen KT, et al. Glutathione-responsive biodegradable polyurethane nanoparticles for lung cancer treatment. Journal of controlled release : official journal of the Controlled Release Society. 2020;321:363-71.
35.Noël A, Gutiérrez-Fernández A, Sounni NE, Behrendt N, Maquoi E, Lund IK, et al. New and paradoxical roles of matrix metalloproteinases in the tumor microenvironment. Frontiers in pharmacology. 2012;3:140.
36.Sun L, Liu H, Ye Y, Lei Y, Islam R, Tan S, et al. Smart nanoparticles for cancer therapy. Signal Transduct Target Ther. 2023;8(1):418.
37.Bhuniya S, Vrettos EI. Hypoxia-Activated Theragnostic Prodrugs (HATPs): Current State and Future Perspectives. Pharmaceutics. 2024;16(4).
38.Rahim MA, Jan N, Khan S, Shah H, Madni A, Khan A, et al. Recent Advancements in Stimuli Responsive Drug Delivery Platforms for Active and Passive Cancer Targeting. Cancers. 2021;13(4).
39.Zhang ZJ, Wang KP, Mo JG, Xiong L, Wen Y. Photodynamic therapy regulates fate of cancer stem cells through reactive oxygen species. World journal of stem cells. 2020;12(7):562-84.
40.Girotti AW, Fahey JM, Korbelik M. Photodynamic Therapy as an Oxidative Anti-Tumor Modality: Negative Effects of Nitric Oxide on Treatment Efficacy. Pharmaceutics. 2021;13(5).
41.Xiao X, Ye K, Imran M, Zhao J. Recent Development of Heavy Atom-Free Triplet Photosensitizers for Photodynamic Therapy. Applied Sciences [Internet]. 2022; 12(19).
42.Hang Y, Wang A, Wu N. Plasmonic silver and gold nanoparticles: shape- and structure-modulated plasmonic functionality for point-of-caring sensing, bio-imaging and medical therapy. Chemical Society reviews. 2024;53(6):2932-71.
43.Pietrzak M, Ivanova P. Bimetallic and multimetallic nanoparticles as nanozymes. Sensors and Actuators B: Chemical. 2021;336:129736.
44.Cordani M, Fernández-Lucas J, Khosravi A, Zare EN, Makvandi P, Zarrabi A, et al. Carbon-based nanozymes for cancer therapy and diagnosis: A review. International Journal of Biological Macromolecules. 2025;297:139704.
45.Amoozadeh M, Khorsandi D, Farahani A, Zarepour A, Khosravi A, Iravani S, et al. Photothermal applications of upconversion nanoparticles. RSC Advances. 2025;15(27):21582-603.
46.Zhao Y, Ye X, Xiong Z, Ihsan A, Ares I, Martínez M, et al. Cancer Metabolism: The Role of ROS in DNA Damage and Induction of Apoptosis in Cancer Cells. Metabolites. 2023;13(7).
47.Uti DE, Atangwho IJ, Alum EU, Ntaobeten E, Obeten UN, Bawa I, et al. Antioxidants in cancer therapy mitigating lipid peroxidation without compromising treatment through nanotechnology. Discover Nano. 2025;20(1):70.
48.Lakkakula J, Kalra P, Mallick G, Mittal H, Uddin I. Revolutionizing cancer treatment: Enhancing photodynamic therapy with cyclodextrin nanoparticles and synergistic combination therapies. Materials Today Sustainability. 2024;28:100958.
49.Rashidi N, Davidson M, Apostolopoulos V, Nurgali K. Nanoparticles in cancer diagnosis and treatment: Progress, challenges, and opportunities. Journal of Drug Delivery Science and Technology. 2024;95:105599.
50.García-Fernández A, Sancenón F, Martínez-Máñez R. Mesoporous silica nanoparticles for pulmonary drug delivery. Advanced Drug Delivery Reviews. 2021;177:113953.
51.Cesca BA, Pellicer San Martin K, Caverzan MD, Oliveda PM, Ibarra LE. State-of-the-art photodynamic therapy for malignant gliomas: innovations in photosensitizers and combined therapeutic approaches. Exploration of targeted anti-tumor therapy. 2025;6:1002303.
52.Shinoda K, Suganami A, Moriya Y, Yamashita M, Tanaka T, Suzuki AS, et al. Indocyanine green conjugated phototheranostic nanoparticle

for photodiagnosis and photodynamic therapy. Photodiagnosis and Photodynamic Therapy. 2022;39:103041.
53.Josefsen LB, Boyle RW. Unique diagnostic and therapeutic roles of porphyrins and phthalocyanines in photodynamic therapy, imaging and theranostics. Theranostics. 2012;2(9):916-66.
54.Xuan L, Ju Z, Skonieczna M, Zhou PK, Huang R. Nanoparticles-induced potential toxicity on human health: Applications, toxicity mechanisms, and evaluation models. MedComm. 2023;4(4):e327.
55.Feczkó T. Polymeric nanotherapeutics acting at special regions of body. Journal of Drug Delivery Science and Technology. 2021;64:102597.
56.Hoshyar N, Gray S, Han H, Bao G. The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction. Nanomedicine (London, England). 2016;11(6):673-92.
57.Forest V, Pourchez J. Preferential binding of positive nanoparticles on cell membranes is due to electrostatic interactions: A too simplistic explanation that does not take into account the nanoparticle protein corona. Materials Science and Engineering: C. 2017;70:889-96.
58.Lérida-Viso A, Estepa-Fernández A, García-Fernández A, Martí-Centelles V, Martínez-Máñez R. Biosafety of mesoporous silica nanoparticles; towards clinical translation. Advanced Drug Delivery Reviews. 2023;201:115049.
59.Moghimi SM, Haroon HB, Yaghmur A, Hunter AC, Papini E, Farhangrazi ZS, et al. Perspectives on complement and phagocytic cell responses to nanoparticles: From fundamentals to adverse reactions. Journal of Controlled Release. 2023;356:115-29.
60.Ly P-D, Ly K-N, Phan H-L, Nguyen HHT, Duong V-A, Nguyen HV. Recent advances in surface decoration of nanoparticles in drug delivery. 2024;Volume 6 - 2024.
61.Makharadze D, del Valle LJ, Katsarava R, Puiggalí J. The Art of PEGylation: From Simple Polymer to Sophisticated Drug Delivery System. International journal of molecular sciences [Internet]. 2025; 26(7).
62.Li J, Wang Q, Xia G, Adilijiang N, Li Y, Hou Z, et al. Recent Advances in Targeted Drug Delivery Strategy for Enhancing Oncotherapy. Pharmaceutics. 2023;15(9).
63.Ahmad A, Imran M, Sharma N. Precision Nanotoxicology in Drug Development: Current Trends and Challenges in Safety and Toxicity Implications of Customized Multifunctional Nanocarriers for Drug-Delivery Applications. Pharmaceutics. 2022;14(11).
64.Ma X, Tian Y, Yang R, Wang H, Allahou LW, Chang J, et al. Nanotechnology in healthcare, and its safety and environmental risks. Journal of nanobiotechnology. 2024;22(1):715.
65.El-Sadek MZ, El-Aziz MKA, Shaaban AH, Mostafa SA, Wadan A-HS. Advancements and emerging trends in photodynamic therapy: innovations in cancer treatment and beyond. Photochemical & Photobiological Sciences. 2025.
66.Shahpouri M, Adili-Aghdam MA, Mahmudi H, Jaymand M, Amoozgar Z, Akbari M, et al. Prospects for hypoxia-based drug delivery platforms for the elimination of advanced metastatic tumors: From 3D modeling to clinical concepts. Journal of Controlled Release. 2023;353:1002-22.
67.Zhu K, Wang L, Xiao Y, Zhang X, You G, Chen Y, et al. Nanomaterial-related hemoglobin-based oxygen carriers, with emphasis on liposome and nano-capsules, for biomedical applications: current status and future perspectives. Journal of nanobiotechnology. 2024;22(1):336.
68.Laib I, Gheraissa N, Benaissa A, Benkhira L, Azzi M, Benaissa Y, et al. Tailoring innovative silver nanoparticles for modern medicine: The importance of size and shape control and functional modifications. Materials Today Bio. 2025;33:102071.
69.Dalbanjan NP, Korgaonkar K, Eelager MP, Gonal BN, Kadapure AJ, Arakera SB, et al. In-silico strategies in nano-drug design: Bridging nanomaterials and pharmacological applications. Nano TransMed. 2025;4:100091.
70.Hosseini SM, Mohammadnejad J, Salamat S, Beiram Zadeh Z, Tanhaei M, Ramakrishna S. Theranostic polymeric nanoparticles as a new approach in cancer therapy and diagnosis: a review. Materials Today Chemistry. 2023;29:101400.
71.Sharma S, Zvyagin AV, Roy I. Theranostic Applications of Nanoparticle-Mediated Photoactivated Therapies. Journal of Nanotheranostics [Internet]. 2021; 2(3):[131-56 pp.].
72.Rauf MA, Rao A, Sivasoorian SS, Iyer AK. Nanotechnology-Based Delivery of CRISPR/Cas9 for Cancer Treatment: A Comprehensive Review. Cells. 2025;14(15).
73.Wei Z, Zhuo S, Zhang Y, Wu L, Gao X, He S, et al. Machine learning reshapes the paradigm of nanomedicine research. Acta Pharmaceutica Sinica B. 2025.
74.Armenia I, Cuestas Ayllón C, Torres Herrero B, Bussolari F, Alfranca G, Grazú V, et al. Photonic and magnetic materials for on-demand local drug delivery. Advanced Drug Delivery Reviews. 2022;191:114584.
75.Wu YY, Sun TK, Chen MS, Munir M, Liu HJ. Oncolytic viruses-modulated immunogenic cell death, apoptosis and autophagy linking to virotherapy and cancer immune response. Frontiers in cellular and infection microbiology.

2023;13:1142172.
76.Naumenko VA, Stepanenko AA, Lipatova AV, Vishnevskiy DA, Chekhonin VP. Infection of non-cancer cells: A barrier or support for oncolytic virotherapy? Molecular Therapy - Oncolytics. 2022;24:663-82.
77.Simpson GR, Relph K, Harrington K, Melcher A, Pandha H. Cancer immunotherapy via combining oncolytic virotherapy with chemotherapy: recent advances. Oncolytic virotherapy. 2016;5:1-13.
78.Yudaeva A, Kostyusheva A, Kachanov A, Brezgin S, Ponomareva N, Parodi A, et al. Clinical and Translational Landscape of Viral Gene Therapies. 2024;13(22):1916.
79.Volovat SR, Scripcariu DV, Vasilache IA, Stolniceanu CR, Volovat C, Augustin IG, et al. Oncolytic Virotherapy: A New Paradigm in Cancer Immunotherapy. International journal of molecular sciences. 2024;25(2).
80.Chen L, Zuo M, Zhou Q, Wang Y. Oncolytic virotherapy in cancer treatment: challenges and optimization prospects. 2023;Volume 14 - 2023.
81.Davola ME, Mossman KL. Oncolytic viruses: how "lytic" must they be for therapeutic efficacy? Oncoimmunology. 2019;8(6):e1581528.
82.Han J, Bhatta R, Liu Y, Bo Y, Wang H. In Situ Dendritic Cell Recruitment and T Cell Activation for Cancer Immunotherapy. Frontiers in pharmacology. 2022;13:954955.
83.Omolekan TO, Folahan JT, Tesfay MZ, Mohan H, Dutta O, Rahimian L, et al. Viral warfare: unleashing engineered oncolytic viruses to outsmart cancer's defenses. 2025;Volume 16 - 2025.
84.Vilgelm AE, Johnson DB, Richmond A. Combinatorial approach to cancer immunotherapy: strength in numbers. Journal of leukocyte biology. 2016;100(2):275-90.
85.Zhou X, Hu S, Wang X. Recent advances in oncolytic virus combined immunotherapy in tumor treatment. Genes & diseases. 2025;12(6):101599.
86.Mouzakis A, Petrakis V, Tryfonopoulou E, Panopoulou M, Panagopoulos P, Chlichlia K. Mechanisms of Immune Evasion in HIV-1: The Role of Virus-Host Protein Interactions. 2025;47(5):367.
87.Sriraman SK, Aryasomayajula B, Torchilin VP. Barriers to drug delivery in solid tumors. Tissue barriers. 2014;2:e29528.
88.Moffit JS, Blanset DL, Lynch JL, MacLachlan TK, Meyer KE, Ponce R, et al. Regulatory Consideration for the Nonclinical Safety Assessment of Gene Therapies. Human gene therapy. 2022;33(21-22):1126-41.

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The Evolving Landscape of Drug Resistance: From Mechanisms to Therapeutic Strategies

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Abstract:

Drug resistance is a major factor that frustrates the treatment of the disease in patients. This issue is multifactorial in nature because it involves a complex interaction between genetic and epigenetic modifications, drug-metabolizing, enhanced DNA repair, efflux pump systems, and interactions in the tumor microenvironment. Recent developments in molecular biology, such as next-generation sequencing and CRISPR-Cas9, have shed some light on these complex resistance mechanisms, leading to the discovery of new therapeutic targets. New approaches, which include combination therapy, immunotherapy, and nanomedicine, provide an effective way to fight resistance. Nevertheless, biomarkers, personalized medicine and tumor microenvironment have to be further explored, as they will help to make cancer care more effective in overcoming this chronic problem. This review aims to summarize the latest knowledge on drug resistance mechanisms in cancer, the emergence of therapeutic options to overcome this resistance and share future research advances in this most fundamental field.

Keywords: Drug resistance, Cancer therapy, Immunotherapy, Nanomedicine, Personalized medicine.

Introduction

Cancer is a multifaceted disorder characterized by the uncontrolled growth and spread of abnormal cells. It is the consequence of damage inflicted on DNA, the molecule responsible for controlling cellular functions and growth (1). Changes in DNA can occur in oncogenes, which mandate the growth of cells, and in tumor suppressor genes, which can modify cell growth in a protective manner. Changes in these genes allow cells to grow without control, forming tumors that can invade adjacent tissues and metastasize to distant sites (2). It may Cancer development may result from multiple factors, including genetic, environmental, and lifestyle determinants. Certain genetic mutations can be inherited, increasing the relative risk for developing some types of tumors.

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Considered environmental risk factors are tobacco smoke, asbestos, and ultraviolet light, which can damage DNA and increase the risk of cancer. Also, diet, physical activity, and consumption of alcohol are accepted to be important risk factors (3). Cancer therapy has changed significantly over the last decades and now offers different approaches depending on the type and stage of cancer. It may include surgery to remove the tumorous tissue, radiation therapy to destroy the malignant cells with high-energy beams, chemotherapy to administer drugs that act on rapidly dividing cells, and cancer-specific therapies aimed at cancer cell vulnerabilities (4). Another increasingly important therapeutic option is immunotherapy, which employs the immune system to fight cancer. Cancer therapy is also associated with certain challenges, notwithstanding these developments. Most therapeutic modalities, while effective in targeting malignant cells, may also adversely affect healthy cells. Another significant challenge is drug resistance, whereby cancer cells may find a way to bypass the effects of treatments (5).

Drug resistance is a serious impediment to the effective therapy of cancer, oftentimes resulting in disease recurrence and worse outcomes for the patient. Due to the underlying genetic instability and rapid proliferation, cancer cells can counteract the destructive effects of anticancer therapies (6). This resistance can take the form of reduced cellular uptake of the drug, increased drug efflux, alteration of the drug's modification resistance to the targeted pathways said drug interacts with, stimulation of bypass pathways that supersede the drug's intended function, enhanced repair mechanisms that counteract the damage of certain DNA and chemoperes (7). The mechanism underlying the development of drug resistance is complex and involves a selection pressure. In the presence of a treatment, malignant cells that can mount a resistance response are the ones that survive, multiply, and in the end, dominate the tumor, and therefore, the malignant cells within the tumor grow and thrive (8).

The emergence of drug resistance can result from many interrelated processes. Either spontaneous or treatment-based genetic alterations affect the relevant proteins of action or drug metabolism. On the other hand, the contributing factor of interest (9) can be some of the molecular changes, like alteration of the methylation marks or modification of the histones, which regulate processes of critical importance, such as drug metabolism or the longevity of the cell. In addition, elements of the tumor microenvironment can contribute to drug resistance. Hypoxia, alongside some immune cell types (10), can pose selective resistance to troublesome drug-resistant cells. All of these considerations are essential for the prevention and minimization of multidrug resistance and increasing the efficacy of cancer treatments. The primary focus of this study is the processes that create barriers to effective treatment for cancer, and the obstacles that medication resistance creates. The study specifically aims to enhance treatment outcomes by overcoming challenges posed by medication resistance.

Mechanisms involved in drug resistance

Efflux pumps

Efflux pumps especially those in the ATP-binding cassette (ABC) transporter family are central to cancer cells' ability to resist multiple drugs, actively transporting drugs out of the cell repeatedly, reducing intracellular drug accumulation, and repeatedly expelling drugs from the cell. These pumps are located in the cell membrane and actively transport a wide range of substances, including anticancer drugs, out of the cell, thereby reducing intracellular drug accumulation. Efflux pumps actively reduce intracellular drug concentrations, preventing therapeutic agents from reaching their molecular targets (10). At this lower dose, tumor cells keep multiplying despite the chemotherapy in their system. Persistent efflux pump activity enables tumor cells to survive and proliferate despite chemotherapeutic pressure, and the treatment ultimately fails. Researchers have taken a close look at numerous ABC transporters like P-glycoprotein (P-gp/ABCB1), multidrug resistance–associated protein 1 (MRP1/ABCC1), and breast cancer resistance protein (BCRP/ABCG2) and linked them to multidrug resistance across many types of cancer. Other resistance tricks such as tweaking drug targets or ramping up DNA repair can join forces

with efflux pumps, rendering cancer cells resistant to treatment, thereby rendering cancer cells resistant to conventional therapies. To beat multidrug resistance and make cancer treatments work better, researchers need to pinpoint the exact efflux pumps fueling a specific tumor and grasp what drives them like low oxygen in the tissue or the strain of repeated drug doses (13).

Epigenetic modifications

Heritable epigenetic alterations which do not alter DNA sequences play an essential part in creating and supporting cancer cell resistance to treatments. The three types of epigenetic modifications, including DNA methylation and histone modifications, and microRNA changes, can alter gene expression patterns, which affect drug metabolism genes and therapeutic targets and cell survival genes and DNA repair mechanisms, thus reducing medication efficacy (14). The silencing of tumor suppressor genes through promoter hypermethylation enables cells to proliferate and potentially leads to resistance against treatments that focus on rapidly dividing cells. The under-methylation of oncogenes leads to their excessive expression, which drives both increased cell growth and treatment resistance. Reversible epigenetic alterations in cancer cells offer potential therapeutic avenues to enhance drug efficacy could be reversed, creating new treatment possibilities to enhance medication effectiveness (15).

P-glycoprotein (P-gp) serves as a well-studied example of drug resistance, which receives epigenetic regulation through its gene expression. The high expression levels of P-gp enable tumor cells to actively remove chemotherapy drugs, which results in reduced drug effectiveness inside the cells (16). The P-gp promoter undergoes DNA hypomethylation, which increases P-gp expression, resulting in drug resistance development. Histone modifications, including increased histone acetylation, contribute to P-gp gene transcription activation. To develop new treatment approaches for drug resistance, it is necessary to understand how specific epigenetic changes regulate P-gp expression (17). The therapeutic approach employs DNA methyltransferase inhibitors together with histone deacetylase inhibitors to modify cancer cell epigenomes, which enhances their chemotherapy susceptibility.

Tumor microenvironment

The tumor microenvironment (TME) functions as a complex dynamic system surrounding cancer cells, which plays a vital part in cancer development, along with metastasis and treatment resistance. The tumor microenvironment contains multiple components, which include fibroblasts together with immune cells, blood vessel endothelial cells and extracellular matrix components (18). The complex network of TME connections provides cancer cells with growth factors and survival signals, plus treatment protection (19). The TME applies selection forces to drug-resistant tumor cells, which leads to treatment failure. The TME environment creates conditions such as oxygen depletion and nutrient scarcity, and acidity, which either select or produce tumor cells that develop enhanced drug resistance mechanisms. The physical characteristics of the TME, such as dense ECM tissue and abnormal blood vessel formation, reduce drug delivery to tumors, which decreases treatment effectiveness (20).

Different cell types in the TME are associated with drug resistance. The TME contains cancer-associated fibroblasts (CAFs), which release growth hormones and ECM components to support tumor cells against drug resistance. These cells modify the extracellular matrix to construct physical barriers which stop drugs from entering the tumor area. Immune cells, which are designed to kill cancerous cells, may create treatment resistance despite their natural function. Tumor-associated macrophages (TAMs) adopt pro-tumor characteristics by producing substances which stimulate tumor cell growth and blood vessel formation, and resistance to treatment (21). Myeloid-derived suppressor cells (MDSCs) represent immune cells that hinder anti-tumor responses while generating treatment resistance through multiple mechanisms. Endothelial cells, which form blood vessel linings, contribute to medication resistance by blocking drug delivery to tumors while sustaining the survival of tumor cells that have spread to distant regions (22). The connection between cancer cells

and various cell types present in the TME creates a complex two-way interaction. Cancer cells influence stromal cell activities, which then provide defense mechanisms to cancer cells, thus creating treatment resistance (23). The multidimensional interactions of the TME necessitate in-depth knowledge in order to create innovative therapeutic options that target cancer cells alongside their supportive cells and their microenvironment. Attacking the protective elements of the TME, such as CAFs and TAMs and ECM structures, can enhance drug delivery while reinstating tumor cell drug sensitivity, thus enhancing cancer treatment outcomes (24).

DNA repair pathways

The biological mechanisms that maintain genomic stability work by detecting and repairing different types of DNA damage, including single-strand breaks, double-strand breaks, base modifications and DNA cross-links (25). Several protein complexes combine to identify mutilated DNA, as well as switching up repair machineries that help to repair the DNA sequence. Various DNA repair mechanisms can be found in the cell, with each repairing a particular type of damage. The cellular repair system uses nucleotide excision repair (NER) to remove big DNA lesions from UV radiation and chemical carcinogen exposure, while base excision repair (BER) removes damaged and modified bases (26). Double-strand breaks require both homologous recombination (HR) and non-homologous end joining (NHEJ) processes for repair because this type of damage threatens chromosomal stability and causes cell death. DNA repair mechanisms must function correctly and precisely to maintain normal cell operations and survival, yet defects in these pathways increase mutation rates, which leads to cancer development (27).

Cancer cells that exhibit genomic instability develop better DNA repair mechanisms to defend themselves against DNA-damaging treatments like chemotherapy and radiation. The medicines deliver DNA damage to cancer cells, which triggers apoptosis as a result (28). Tumor cells that possess enhanced DNA repair mechanisms are capable of fixing the damage effectively, which allows them to survive and multiply despite therapeutic interventions. The improved DNA repair capability emerges through different mechanisms, including enhanced DNA repair protein synthesis and elevated repair pathway activity, as well as modifications in DNA repair pathway regulatory networks (29). ERCC1 protein expression levels have been shown to influence resistance against platinum-based chemotherapies, which create cross-linked DNA. The HR pathway expression levels determine radiation resistance against ionizing radiation, which produces double-strand breaks (30).

The relationship between DNA repair systems and drug resistance exists as a complex multidimensional network. The enhancement of DNA repair capability protects tumor cells against DNA-damaging therapies yet increases their vulnerability to alternative therapeutic approaches (31). Tumor cells with defective DNA repair pathways, such as BRCA1/2 in the HR pathway, display increased vulnerability to PARP inhibitors, which disrupt single-strand break repair mechanisms. Synthetic lethality exploits a faulty DNA repair mechanism to increase cancer cell vulnerability to blockages in another cellular process (32). The tumor microenvironment can influence the capability of cells to repair DNA damage. Hypoxia causes damage to the DNA, even as it alters the levels of the proteins in DNA repair that the cells synthesize. The challenge of coming up with a tailored cancer therapy that targets any tumor weakness includes knowledge of the interdependencies between the aspects of DNA repair mechanisms, drug resistance, in addition to tumor environmental conditions (33). The combination of DNA repair mechanisms with drug resistance and tumor microenvironment impacts requires a thorough understanding to develop personalized cancer therapies which focus on specific tumor vulnerabilities (33).

Drug Resistance: A Challenge in Cancer Therapy

The effectiveness of cancer therapy depends heavily on drug resistance across different cancers because this resistance decreases treatment success and determines final patient prognosis. A curable malignancy transforms into a potentially fatal illness because of resistance, which limits therapy

options before leading to disease progression and recurrence (34). Different cancer types display this issue to varying degrees because their resistance mechanisms and treatment protocols differ. The major challenge of drug resistance emerges strongly in blood cancers including acute myeloid leukemia (AML) (35). The chemotherapy resistance of AML cells develops through multiple mechanisms, which include increased ABC transporter drug efflux and FLT3 receptor tyrosine kinase target mutations and apoptotic pathway modifications. The mechanisms of resistance often lead to relapse, so patients need to undergo more aggressive and potentially less successful salvage treatment (36). The BCR-ABL1 fusion gene mutations that drive chronic myeloid leukemia (CML) produce resistance to tyrosine kinase inhibitors (TKIs), including imatinib. The mutations prevent the TKI from proper binding, which allows leukemic cells to multiply without control (37).

Solid cancers face significant challenges when their treatments become resistant to the administered therapies. Lung cancer patients develop resistance to EGFR inhibitors, including gefitinib and erlotinib, because of mutations in the EGFR gene, specifically T790M. A mutation in the EGFR protein structure makes this protein unresponsive to the inhibitor (38). HER2-targeted treatment resistance in breast cancer patients emerges from multiple mechanisms, including increased alternative growth factor receptor expression along with HER2 bypassing downstream signaling pathway activation and PTEN tumor suppressor gene loss (39). The BRAF V600E mutation in melanoma develops resistance to BRAF inhibitors vemurafenib and dabrafenib through MAPK pathway reactivation, which happens either by acquiring mutations in pathway components or through bypass signaling activation. Colorectal cancer serves as an example where drug resistance plays a vital role in patient management (40).

The mechanisms of resistance to therapeutic regimens such as FOLFOX or FOLFIRI may occur through multiple pathways, such as a higher expression of DNA repair enzymes, drug metabolism through drug efflux transporters, or alteration of the microenvironment. Acquisition of resistance to targeted therapies, including EGFR blockade (cetuximab, panitumumab) or VEGF blockade (bevacizumab), can also occur through the development of compensatory downstream signaling alterations (KRAS or NRAS), or activation of other angiogenesis factors (41). Platinum resistance in ovarian cancer is a major problem clinically. All mechanisms are related to an increase in DNA repair, changes in drug delivery and increased levels of glutathione. This resistance, in most cases, causes relapse and poor prognosis (42). The reality of medication resistance has major effects on the outcomes of patients. It usually involves more severe and ineffective medicines, thus a worse quality of life, and more side effects of the medicine. In addition, the resistance that at times may come with medications may hamper the treatment, thus bringing about difficulty in the treatment of sickness and, in turn, falling survival rates (43). Fighting medication resistance requires the further analysis of the consequent mechanisms, the development of new treatment approaches, and the implementation of individualized medicine approaches to treatment, which make it individual to the very nature of tumor in a particular patient (44).

Molecular insights into drug resistance: advancing cancer therapy

However, recent developments in molecular biology have changed our understanding of cancer drug resistance mechanisms and demonstrate significant potential for the development of more effective therapies. Cutting-edge technologies such as the next-generation sequencing (45) can bring out detailed genomic profiling of the tumor, a complex picture of genetic aberrations, epigenetic changes, as well as the variations in the expression of genes which trigger the emergence of drug resistance (46). Single-cell sequencing tools are being used to help fill in this gap by demonstrating the heterogeneity of resistance to a treatment within a tumor, the identification of discrete groups of resistant cells and their characteristics, as well as unique genetics. These findings can enable scientists to unravel the intricate webs of signaling and molecular interactions that drive drug resistance in order to make new targets of drug therapy and biomarkers (47).

Besides, the CRISPR-Cas9 gene editing technology has gained popularity as a very effective method of drug resistance pathway investigation. Scientists can also add specific mutations to cancer cells with CRISPR or knock out their genes of interest in order to directly see how such modifications impact resistance to treatment (48). Combined with other developed molecular tools, such as proteomics and metabolomics, the potential of the CRISPR tool might create a systems-level understanding of drug resistance that provides insight into how tumor cells change and adapt to selective pressure. The approach has been used to represent drug resistance in vitro, identify novel resistance genes and verify the possibility of a therapeutic target (49).

Emerging therapies to combat drug resistance

The challenges posed by cancer-related drug resistance have driven the development of novel therapeutic strategies. Promising drugs are emerging, including the development of next-generation inhibitors against resistant mutations, including the use of third-generation EGFR inhibitors (e.g., osimertinib) against lung cancer patients with T790M resistance mutation (50). Combinations are also becoming more prevalent, trying to hit multiple resistance mechanisms or prevent the selection of resistance. As an example, in melanoma, the use of a BRAF inhibitor plus a MEK inhibitor may act against two critical elements of the MAPK pathway, reducing the probability of the emergence of resistance (51). Another option to overcome the resistance is immunotherapy with the use of the immune system of the body to attack cancer, especially where the mutational load in such tumors is high. Tumor microenvironment manipulation approaches are also under development, such as targeting cancer-associated fibroblasts to disrupt the protective niche that leads to resistance to treatment (52). Finally, the techniques of personalized medicine, based on genetic profiling of individual cancer, are becoming increasingly important to find the most effective medicines and foresee future modes of resistance. Certain instances of this are discussed later (53).

Effective therapeutic combinations for overcoming drug resistance in cancer

The phenomenon of drug resistance is a major problem in cancer therapy and often leads to the failure of the therapy and the development of the disease. One of the promising ways to overcome this barrier is to employ combination treatment, i.e. to combine two or more drugs that target multiple pathways and/or mechanisms within tumor cells (54). Combination treatment aims at attacking cancer cells from many angles simultaneously, which makes it more difficult. In theory, additive combinations of medications should have synergistic effects, and therefore, the combination would have greater effects than offered by a combination of the effects produced by the medications (55). Such synergy can be possible through a number of factors, such as one medicine making cancer cells sensitive to the other, or drugs targeting parallel pathways needed by the cancer cells to survive. Combination therapy may also help support resistance processes already present, or the emergence of new resistance mutations (56).

In addition to directing the cancerous cells, combination therapies are also being explored in order to alter the tumor microenvironment and enhance drug transportation. The tumor microenvironment conditions stimulate the proliferation, survival, and metastasis of cancer cells as well as medication resistance (60). It incorporates a wide range of cell types of cells, which include cancer-related fibroblasts, immunological cells, and endothelial cells and beyond the extracellular matrix element. These factors may constitute an inhibitory microenvironment surrounding tumor cells, protecting them against drugs and enhancing drug resistance (61). Coupling chemotherapy with drugs that act on the tumor microenvironment, such as angio-depressants, fibroblast-depleting agents and/or anti-lipidic agents, may enhance drug penetration and improve therapeutic outcome. Besides, combination treatment can be employed to enhance anticancer immunity and defeat the immunosuppressive phenomena ubiquitous in malignancies (62). Researchers aim to exploit the immune system to eliminate cancer cells, including drug-resistant cells, through the use of immune checkpoint inhibitors combined with immunomodulatory agents or chemotherapy (63).

Checkpoint Inhibitors: Unleashing the Immune System to Overcome Drug Resistance

ICI is a new cancer therapy mode with the perspective of resisting drug treatment through the reinvigoration of the immune system of the body to attack and destroy cancerous cells (64). These inhibitors are specific to specific checkpoint proteins such as CTLA-4, PD-1 and PD-L1, normally regulating the activation of immune cells and preventing autoimmune responses. Cancerous cells readily utilize these checkpoints to avoid immune surveillance, so to speak, and essentially block an attack by immune cells (65). Checkpoint inhibitors help to inhibit these inhibitory signals and allow immune cells, in particular cytotoxic T lymphocytes (CTLs), to recognize and kill cancer cells. This modality of action is significantly different to conventional chemotherapeutics or precision medicines, which can target tumor cells directly and be susceptible to drug resistance mechanisms (66). Because checkpoint inhibitors stimulate the immune system of the patients, the anti-tumor effect can outlive therapy (67).

An example of the cancers where checkpoint inhibitors have been used effectively is melanoma, lung cancer, bladder cancer, and renal cell carcinoma. As an example, ipilimumab (CTLA-4 inhibitor) has shown significant effectiveness in the treatment of melanoma, extending the overall survival of some individuals (68). Similarly, PD-1 blockers such as nivolumab and pembrolizumab have revolutionised treatment in non-small cell lung cancer, particularly in high PD-L1 expressing or high mutational burden cancer. The same inhibitors have also presented possibilities in other cancers, like Hodgkin lymphoma and MSI-H colorectal cancer (45). The efficacy of checkpoint inhibitors is commonly correlated with the presence of tumor-infiltrating lymphocytes (TILs), and it is therefore suggested that these drugs require an existing immune response to be productive. However, in case of low TIL-expression in tumors, checkpoint blockade can very rarely lead to tumor regression (69).

In addition, when there is resistance to the other cancer medications, checkpoint inhibitors can be used to attack or prevent resistance to the cancer drugs. As a case in point, applying a BRAF inhibitor with a PD-1 inhibitor in melanoma was reported to reveal enhanced efficacy as compared with BRAF monotherapy, preventing the development of BRAF resistance (70). This demonstrates that checkpoint inhibition can reduce the development of resistant clones due to the selectivity of targeted therapy. Next, it has been shown that checkpoint inhibition can be utilized to make chemotherapy-resistant tumors sensitive to it in some cancers (71). The mechanisms through which checkpoint inhibitors circumvent drug resistance are complex and little known, but are most probably a combination of direct immune-mediated killing of resistant cells and modulation of the tumor microenvironment (72).

Despite the extraordinary efficacy of checkpoint inhibitors, these agents have limitations. A few people respond to these therapies, and some may experience immune-related side effects (73). The current research is focused on revealing biomarkers that predict sensitivity to checkpoint inhibition, determining a method of overcoming resistance to those drugs, and exploring new immunotherapies including conjunction immunotherapies and adoptive cell therapies (74). Checkpoint inhibitors have been combined with other immunomodulatory agents, including agonists of other types of stimulatory immunological receptors or antagonists of immunosuppressant molecules, with promise to further improve antitumor immunity and overcome resistance. Further inquiry and development of immunotherapeutic methods are essential to the improvement of options available to cancer patients and in addressing the issue of medication resistance (75).

Nanomedicine: a novel approach to overcoming drug resistance

Nanomedicine provides new solutions to address drug resistance in cancer by enhancing the delivery of drugs, increasing drug efficiency and changing the drug resistance property of the tumor microenvironment. The chemotherapeutic drug may be incorporated into nanocarriers, including liposomes, polymeric nanoparticles, and dendrimers, which shield drugs against premature degradation

in the body and non-specific distribution (75). This localized treatment can reduce the off-target toxicity and enable the drug at increased concentrations at the tumor site, including cancer cells resistant to drugs. Moreover, it is also possible to design nanocarriers to specifically target the tumour cells by conjugating ligands specific to the overexpressed receptors on the tumour cell surface (76). This active targeting increases the drug uptake of cancer cells that benefits the therapeutic index in addition to reducing exposure of non-cancerous cells to toxic substances of the drug. The nanomaterials can also be made responsive to a certain local stimulus in the tumor site, like pH, redox potential and enzyme activity. Such stimuli-sensitive nanocarriers may be used to deliver their payload specifically to the tumor location, increasing drug efficacy and reducing systemic toxicity (77).

Besides better drug delivery, nanomedicine has also been applied to overcome drug resistance-specific mechanisms. Another example is multidrug resistance (MDR), whereby there is usually an overexpression of efflux pumps, such as P-glycoprotein, active efflux pumps that pump drugs out of the cancer cells. Nanocarriers may shelter drugs against these efflux pumps, overcoming this resistance mechanism to reach their intracellular target (78). Moreover, nanocarriers may be preconfigured to introduce a combination of drugs at once, including drugs that act through distinct resistance pathways. This mixed treatment regimen may be very effective in hindering or surmounting drug resistance, where it may be harder to have the cancer cells resist multiple drugs simultaneously (79). Nanomaterials can also be employed to encapsulate gene therapy agents, including siRNAs or miRNAs, to silence genes imparting drug resistance and re-sensitize cancer cells to drugs (80). Nanoparticle-mediated delivery to target P-glycoprotein with siRNA has been demonstrated to overcome MDR in several types of cancer cell lines. This flexibility of nanomedicine holds the potential to formulate patient-specific anticancer therapies that can be customized to meet the unique drug resistance situations within a given tumor (81).

DISCUSSION

Drug resistance is a peculiar obstacle in cancer treatment, and these implications are significant in relation to the efficacy levels of the actions and patient outcomes. As mentioned above, the pathways that generate drug resistance are versatile, possessing many dimensions, including genetic mutation, epigenetic alterations, altered drug metabolism, raised DNA repair, efflux pump activity and the tumor microenvironment (82). This has necessitated an all-embracing approach to the fight against drug resistance, including the development of new medications, the refinement of existing treatment protocols, and improvement in the complex interplay between cancer cells and the surrounding tissue (83). The recent advances in molecular biology, such as next-generation sequencing and CRISPR-Cas9 gene editing have provided us with much-needed resources to deconstruct the genetic basis of drug resistance, posing the opportunity to identify novel therapeutic targets and biomarkers. This evidence has stimulated the introduction of new classes of treatment strategies such as next-generation inhibitors, combination therapies, immunotherapies, and nanomedicine techniques, all aimed at fighting off or evading drug resistance (84).

To drive the development and resistance of cancer, there are certain molecular alterations unique to cancer, and combination therapy rationally designed to target these alterations has been promising. Such combinations can bypass or thwart resistance, as they target so many routes or processes simultaneously (85). Immunotherapy, and immune checkpoint inhibitors in particular, have become a revolution in the area of cancer treatment by engaging the ability of the immune system to attack and destroy cancer cells even when they have acquired resistance towards medication. Nanotechnology provides a new strategic framework for therapy, with enhanced transport of drugs, enhancing the efficacy of treatment and changing the tumor micro-environment (86). Nanocarriers can prevent the degradation, deliver them directly to cancer cells and even avoid efflux pump operation, which also raises new hopes to

overcome multidrug resistance. This multifaceted approach, comprising new strategies such as personalized medicine strategies through genetic profiling of the tumor cells in the individual, presents an immense opportunity to enhance the outcomes of cancer treatment (87).

However, there are certain boundaries, even with all the developments that have been made over the past few years. It is impossible to state which patients develop resistance to the medication and what resistance systems are involved. Although some biomarkers have been identified, more research is needed to implement better and comprehensive predictive systems (88). Moreover, the research of new medicines and treatments is quite difficult and costly. Clinical trials are necessary to verify the safety and effectiveness of new treatments; however, such a process is time-consuming and may not always work out. Lastly, cost and supply may act as a barrier to the accessibility of these advanced therapies, a disparity that may pose risks to cancer hemispheres (89).

Some exciting research directions have prospects. Non-invasive tumor profiling techniques can provide a viable alternative to patient biopsies because liquid biopsies provide a means to monitor a response to treatment as well as the acquisition of drug resistance (90). Machine learning and artificial intelligence technology are being used to analyze large amounts of data generated through the study of cancer genomes and proteins, and in vivo trials to identify new drug targets and to predict treatment responses (91).

CONCLUSION

Improved nanocarriers, which could deliver several drugs or gene therapy agents together, are being developed and have a lot of potential in defeating multifactorial forms of drug resistance. Further investigation of the tumor microenvironment and its contribution to drug resistance will open the path to a novel approach to the development of therapies that act not only against the cancer cells but also influence the supporting cells and the microenvironment as well. By improving the present shortcomings and by working on the following directions, these strategies may ultimately enable the comprehensive overcoming of drug resistance in cancer therapy as a primary impediment to effective cancer treatment.

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Consent for publication

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REFERENCE

1.Castaneda M, den Hollander P, Kuburich NA, Rosen JM, Mani SA. Mechanisms of cancer metastasis. Seminars in Cancer Biology. 2022;87:17-31.

2.Singh SR, Bhaskar R, Ghosh S, Yarlagadda B, Singh KK, Verma P, et al. Exploring the Genetic Orchestra of Cancer: The Interplay Between Oncogenes and Tumor-Suppressor Genes. Cancers [Internet]. 2025; 17(7).

3.Parsa N. Environmental factors inducing human cancers. Iranian journal of public health. 2012;41(11):1-9.

4.Baskar R, Dai J, Wenlong N, Yeo R, Yeoh KW. Biological response of cancer cells to radiation treatment. Frontiers in molecular biosciences. 2014;1:24.

5.Koury J, Lucero M, Cato C, Chang L, Geiger J, Henry D, et al. Immunotherapies: Exploiting the Immune System for Cancer Treatment. Journal of immunology research. 2018;2018:9585614.

6.Wang X, Zhang H, Chen X. Drug resistance and combating drug resistance in cancer. Cancer drug resistance (Alhambra, Calif). 2019;2(2):141-60.

7.von Manstein V, Yang CM, Richter D, Delis N, Vafaizadeh V, Groner B. Resistance of Cancer Cells to Targeted Therapies Through the Activation of Compensating Signaling Loops. Current signal transduction therapy. 2013;8(3):193-202.

8.Khan SU, Fatima K, Aisha S, Malik F. Unveiling the mechanisms and challenges of cancer drug resistance. Cell communication and signaling :

CCS. 2024;22(1):109.
9.Ashique S, Bhowmick M, Pal R, Khatoon H, Kumar P, Sharma H, et al. Multi drug resistance in Colorectal Cancer- approaches to overcome, advancements and future success. Advances in Cancer Biology - Metastasis. 2024;10:100114.
10.Tran TQ, Lowman XH, Kong M. Molecular Pathways: Metabolic Control of Histone Methylation and Gene Expression in Cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2017;23(15):4004-9.
11.Pilotto Heming C, Muriithi W, Wanjiku Macharia L, Niemeyer Filho P, Moura-Neto V, Aran V. P-glycoprotein and cancer: what do we currently know? Heliyon. 2022;8(10):e11171.
12.Engle K, Kumar G. Cancer multidrug-resistance reversal by ABCB1 inhibition: A recent update. European Journal of Medicinal Chemistry. 2022;239:114542.
13.Talib WH, Alsayed AR, Barakat M, Abu-Taha MI, Mahmod AI. Targeting Drug Chemo-Resistance in Cancer Using Natural Products. Biomedicines. 2021;9(10).
14.Sadida HQ, Abdulla A, Marzooqi SA, Hashem S, Macha MA, Akil ASA, et al. Epigenetic modifications: Key players in cancer heterogeneity and drug resistance. Translational oncology. 2024;39:101821.
15.Romero-Garcia S, Prado-Garcia H, Carlos-Reyes A. Role of DNA Methylation in the Resistance to Therapy in Solid Tumors. Frontiers in oncology. 2020;10:1152.
16.Tian Y, Lei Y, Wang Y, Lai J, Wang J, Xia F. Mechanism of multidrug resistance to chemotherapy mediated by P-glycoprotein (Review). International journal of oncology. 2023;63(5).
17.You D, Richardson JR, Aleksunes LM. Epigenetic Regulation of Multidrug Resistance Protein 1 and Breast Cancer Resistance Protein Transporters by Histone Deacetylase Inhibition. Drug Metabolism and Disposition. 2020;48(6):459-80.
18.Biray Avci C, Goker Bagca B, Nikanfar M, Takanlou LS, Takanlou MS, Nourazarian A. Tumor microenvironment and cancer metastasis: molecular mechanisms and therapeutic implications. Frontiers in pharmacology. 2024;15:1442888.
19.Sever R, Brugge JS. Signal transduction in cancer. Cold Spring Harbor perspectives in medicine. 2015;5(4).
20.Seebacher NA, Krchniakova M, Stacy AE, Skoda J, Jansson PJ. Tumour Microenvironment Stress Promotes the Development of Drug Resistance. Antioxidants (Basel, Switzerland). 2021;10(11).
21.Feng B, Wu J, Shen B, Jiang F, Feng J. Cancer-associated fibroblasts and resistance to anticancer therapies: status, mechanisms, and countermeasures. Cancer cell international. 2022;22(1):166.
22.Gao J, Liu W-R, Tang Z, Fan J, Shi Y-H. Myeloid-derived suppressor cells in cancer. iLIVER. 2022;1(2):81-9.
23.de Visser KE, Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell. 2023;41(3):374-403.
24.El-Tanani M, Rabbani SA, Babiker R, Rangraze I, Kapre S, Palakurthi SS, et al. Unraveling the tumor microenvironment: Insights into cancer metastasis and therapeutic strategies. Cancer Letters. 2024;591:216894.
25.Huang R, Zhou P-K. DNA damage repair: historical perspectives, mechanistic pathways and clinical translation for targeted cancer therapy. Signal Transduction and Targeted Therapy. 2021;6(1):254.
26.Chatterjee N, Walker GC. Mechanisms of DNA damage, repair, and mutagenesis. Environmental and molecular mutagenesis. 2017;58(5):235-63.
27.Stinson BM, Loparo JJ. Repair of DNA Double-Strand Breaks by the Nonhomologous End Joining Pathway. Annual review of biochemistry. 2021;90:137-64.
28.Nesic K, Parker P, Swisher EM, Krais JJ. DNA repair and the contribution to chemotherapy resistance. Genome medicine. 2025;17(1):62.
29.Stead ER, Bjedov I. Balancing DNA repair to prevent ageing and cancer. Experimental Cell Research. 2021;405(2):112679.
30.Nesic K, Parker P, Swisher EM, Krais JJ. DNA repair and the contribution to chemotherapy

resistance. Genome medicine. 2025;17(1):62.
31.Gu Y, Yang R, Zhang Y, Guo M, Takehiro K, Zhan M, et al. Molecular mechanisms and therapeutic strategies in overcoming chemotherapy resistance in cancer. Molecular Biomedicine. 2025;6(1):2.
32.Huang Y, Chen S, Yao N, Lin S, Zhang J, Xu C, et al. Molecular mechanism of PARP inhibitor resistance. Oncoscience. 2024;11:69-91.
33.Zhuang Y, Liu K, He Q, Gu X, Jiang C, Wu J. Hypoxia signaling in cancer: Implications for therapeutic interventions. MedComm. 2023;4(1):e203.
34.Dhanyamraju PK. Drug resistance mechanisms in cancers: Execution of pro-survival strategies. Journal of biomedical research. 2024;38(2):95-121.
35.Cao S, Wang Q, Zhu G. From Chemotherapy to Targeted Therapy: Unraveling Resistance in Acute Myeloid Leukemia Through Genetic and Non-Genetic Insights. International Journal of Molecular Sciences [Internet]. 2025; 26(9).
36.Niu J, Peng D, Liu L. Drug Resistance Mechanisms of Acute Myeloid Leukemia Stem Cells. Frontiers in oncology. 2022;12:896426.
37.Martínez-Castillo M, Gómez-Romero L, Tovar H, Olarte-Carrillo I, García-Laguna A, Barranco-Lampón G, et al. Genetic alterations in the BCR-ABL1 fusion gene related to imatinib resistance in chronic myeloid leukemia. Leukemia research. 2023;131:107325.
38.Stanzione B, Del Conte A, Bertoli E, De Carlo E, Bortolot M, Torresan S, et al. Non-Small Cell Lung Cancer with Epidermal Growth Factor Receptor (EGFR) Common Mutations: New Strategies. Cancers [Internet]. 2025; 17(9).
39.Wang ZH, Zheng ZQ, Jia SC, Liu SN, Xiao XF, Chen GY, et al. Trastuzumab resistance in HER2-positive breast cancer: Mechanisms, emerging biomarkers and targeting agents. Frontiers in oncology. 2022;12:1006429.
40.Proietti I, Skroza N, Bernardini N, Tolino E, Balduzzi V, Marchesiello A, et al. Mechanisms of Acquired BRAF Inhibitor Resistance in Melanoma: A Systematic Review. Cancers (Basel). 2020;12(10).
41.Tang YL, Li DD, Duan JY, Sheng LM, Wang X. Resistance to targeted therapy in metastatic colorectal cancer: Current status and new developments. World journal of gastroenterology. 2023;29(6):926-48.
42.Khan MA, Vikramdeo KS, Sudan SK, Singh S, Wilhite A, Dasgupta S, et al. Platinum-resistant ovarian cancer: From drug resistance mechanisms to liquid biopsy-based biomarkers for disease management. Semin Cancer Biol. 2021;77:99-109.
43.Ryan R, Santesso N, Lowe D, Hill S, Grimshaw J, Prictor M, et al. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. The Cochrane database of systematic reviews. 2014;2014(4):Cd007768.
44.Goetz LH, Schork NJ. Personalized medicine: motivation, challenges, and progress. Fertility and sterility. 2018;109(6):952-63.
45.Doroshow DB, Sanmamed MF, Hastings K, Politi K, Rimm DL, Chen L, et al. Immunotherapy in Non-Small Cell Lung Cancer: Facts and Hopes. Clinical cancer research : an official journal of the American Association for Cancer Research. 2019;25(15):4592-602.
46.Vashisht V, Vashisht A, Mondal AK, Woodall J, Kolhe R. From Genomic Exploration to Personalized Treatment: Next-Generation Sequencing in Oncology. Current Issues in Molecular Biology [Internet]. 2024; 46(11):[12527-49 pp.].
47.Zhang W, Zhang X, Teng F, Yang Q, Wang J, Sun B, et al. Research progress and the prospect of using single-cell sequencing technology to explore the characteristics of the tumor microenvironment. Genes & Diseases. 2025;12(1):101239.
48.Aljabali AAA, El-Tanani M, Tambuwala MM. Principles of CRISPR-Cas9 technology: Advancements in genome editing and emerging trends in drug delivery. Journal of Drug Delivery Science and Technology. 2024;92:105338.
49.Chehelgerdi M, Chehelgerdi M, Khorramian-Ghahfarokhi M, Shafieizadeh M, Mahmoudi E, Eskandari F, et al. Comprehensive review of CRISPR-based gene editing: mechanisms, challenges, and applications in cancer therapy. Molecular cancer. 2024;23(1):9.
50.Laface C, Maselli FM, Santoro AN, Iaia ML, Ambrogio F, Laterza M, et al. The Resistance to

EGFR-TKIs in Non-Small Cell Lung Cancer: From Molecular Mechanisms to Clinical Application of New Therapeutic Strategies. Pharmaceutics. 2023;15(6).

51.Griffin M, Scotto D, Josephs DH, Mele S, Crescioli S, Bax HJ, et al. BRAF inhibitors: resistance and the promise of combination treatments for melanoma. Oncotarget. 2017;8(44):78174-92.

52.Oli AN, Adejumo SA, Rowaiye AB, Ogidigo JO, Hampton-Marcell J, Ibeanu GC. Tumour Immunotherapy and Applications of Immunological Products: A Review of Literature. Journal of immunology research. 2024;2024:8481761.

53.Nameghi SM. Exploring the recent advancements and future prospects of personalized medicine in type 2 diabetes. Endocrine and Metabolic Science. 2024;16:100193.

54.Liu B, Zhou H, Tan L, Siu KTH, Guan X-Y. Exploring treatment options in cancer: tumor treatment strategies. Signal Transduction and Targeted Therapy. 2024;9(1):175.

55.Wang H, Huang Y. Combination therapy based on nano codelivery for overcoming cancer drug resistance. Medicine in Drug Discovery. 2020;6:100024.

56.Lei ZN, Tian Q, Teng QX, Wurpel JND, Zeng L, Pan Y, et al. Understanding and targeting resistance mechanisms in cancer. MedComm. 2023;4(3):e265.

57.Nussinov R, Yavuz BR, Jang H. Molecular principles underlying aggressive cancers. Signal Transduction and Targeted Therapy. 2025;10(1):42.

58.Subbiah V, Baik C, Kirkwood JM. Clinical Development of BRAF plus MEK Inhibitor Combinations. Trends in Cancer. 2020;6(9):797-810.

59.Peng S, Long M, Chen Q, Yin Z, Zeng C, Zhang W, et al. Perspectives on cancer therapy—synthetic lethal precision medicine strategies, molecular mechanisms, therapeutic targets and current technical challenges. Cell Death Discovery. 2025;11(1):179.

60.Xiao Y, Yu D. Tumor microenvironment as a therapeutic target in cancer. Pharmacology & therapeutics. 2021;221:107753.

61.Belhabib I, Zaghdoudi S, Lac C, Bousquet C, Jean C. Extracellular Matrices and Cancer-Associated Fibroblasts: Targets for Cancer Diagnosis and Therapy? Cancers (Basel). 2021;13(14).

62.Karimi S, Bakhshali R, Bolandi S, Zahed Z, Mojtaba Zadeh SS, Kaveh Zenjanab M, et al. For and against tumor microenvironment: Nanoparticle-based strategies for active cancer therapy. Materials today Bio. 2025;31:101626.

63.Lin Y, Lin P, Chen X, Zhao X, Cui L. Harnessing nanoprodrugs to enhance cancer immunotherapy: overcoming barriers to precision treatment. Materials Today Bio. 2025;32:101933.

64.Lao Y, Shen D, Zhang W, He R, Jiang M. Immune Checkpoint Inhibitors in Cancer Therapy-How to Overcome Drug Resistance? Cancers (Basel). 2022;14(15).

65.Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, et al. Immune Checkpoint Inhibitors in Cancer Therapy. Current oncology (Toronto, Ont). 2022;29(5):3044-60.

66.Sharma P, Goswami S, Raychaudhuri D, Siddiqui BA, Singh P, Nagarajan A, et al. Immune checkpoint therapy—current perspectives and future directions. Cell. 2023;186(8):1652-69.

67.Wojtukiewicz MZ, Rek MM, Karpowicz K, Górska M, Polityńska B, Wojtukiewicz AM, et al. Inhibitors of immune checkpoints-PD-1, PD-L1, CTLA-4-new opportunities for cancer patients and a new challenge for internists and general practitioners. Cancer metastasis reviews. 2021;40(3):949-82.

68.Atkins MB, Clark JI, Quinn DI. Immune checkpoint inhibitors in advanced renal cell carcinoma: experience to date and future directions. Annals of Oncology. 2017;28(7):1484-94.

69.Leong SP. Immune responses and immunotherapeutic approaches in the treatment against cancer. Clinical & Experimental Metastasis. 2024;41(4):473-93.

70.Zhong J, Yan W, Wang C, Liu W, Lin X, Zou Z, et al. BRAF Inhibitor Resistance in Melanoma: Mechanisms and Alternative Therapeutic Strategies. Current treatment options in oncology. 2022;23(11):1503-21.

71.Haibe Y, El Husseini Z, El Sayed R, Shamseddine

A. Resisting Resistance to Immune Checkpoint Therapy: A Systematic Review. Int J Mol Sci. 2020;21(17).

72.Almawash S. Revolutionary Cancer Therapy for Personalization and Improved Efficacy: Strategies to Overcome Resistance to Immune Checkpoint Inhibitor Therapy. Cancers (Basel). 2025;17(5).

73.Yin Q, Wu L, Han L, Zheng X, Tong R, Li L, et al. Immune-related adverse events of immune checkpoint inhibitors: a review. Frontiers in immunology. 2023;14:1167975.

74.Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. Nature reviews Disease primers. 2020;6(1):38.

75.Rebaudi F, De Franco F, Goda R, Obino V, Vita G, Baronti C, et al. The landscape of combining immune checkpoint inhibitors with novel Therapies: Secret alliances against breast cancer. Cancer Treatment Reviews. 2024;130:102831.

76.Al-Thani AN, Jan AG, Abbas M, Geetha M, Sadasivuni KK. Nanoparticles in cancer theragnostic and drug delivery: A comprehensive review. Life Sciences. 2024;352:122899.

77.Elumalai K, Srinivasan S, Shanmugam A. Review of the efficacy of nanoparticle-based drug delivery systems for cancer treatment. Biomedical Technology. 2024;5:109-22.

78.Ortíz R, Quiñonero F, García-Pinel B, Fuel M, Mesas C, Cabeza L, et al. Nanomedicine to Overcome Multidrug Resistance Mechanisms in Colon and Pancreatic Cancer: Recent Progress. Cancers (Basel). 2021;13(9).

79.Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, et al. Nanoparticle-Based Drug Delivery in Cancer Therapy and Its Role in Overcoming Drug Resistance. Frontiers in molecular biosciences. 2020;7:193.

80.Jiang T, Gonzalez KM, Cordova LE, Lu J. Nanotechnology-enabled gene delivery for cancer and other genetic diseases. Expert opinion on drug delivery. 2023;20(4):523-40.

81.Ashique S, Almohaywi B, Haider N, Yasmin S, Hussain A, Mishra N, et al. siRNA-based nanocarriers for targeted drug delivery to control breast cancer. Advances in Cancer Biology - Metastasis. 2022;4:100047.

82.Ingham J, Ruan JL, Coelho MA. Breaking barriers: we need a multidisciplinary approach to tackle cancer drug resistance. BJC reports. 2025;3(1):11.

83.Garg P, Malhotra J, Kulkarni P, Horne D, Salgia R, Singhal SS. Emerging Therapeutic Strategies to Overcome Drug Resistance in Cancer Cells. Cancers (Basel). 2024;16(13).

84.Zhu Y. Advances in CRISPR/Cas9. BioMed research international. 2022;2022:9978571.

85.Garg P, Ramisetty S, Nair M, Kulkarni P, Horne D, Salgia R, et al. Strategic advancements in targeting the PI3K/AKT/mTOR pathway for Breast cancer therapy. Biochemical Pharmacology. 2025;236:116850.

86.Theivendren P, Kunjiappan S, Pavadai P, Ravi K, Murugavel A, Dayalan A, et al. Revolutionizing Cancer Immunotherapy: Emerging Nanotechnology-Driven Drug Delivery Systems for Enhanced Therapeutic Efficacy. ACS measurement science au. 2025;5(1):31-55.

87.Ghazal H, Waqar A, Yaseen F, Shahid M, Sultana M, Tariq M, et al. Role of nanoparticles in enhancing chemotherapy efficacy for cancer treatment. Next Materials. 2024;2:100128.

88.Passaro A, Al Bakir M, Hamilton EG, Diehn M, André F, Roy-Chowdhuri S, et al. Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. Cell. 2024;187(7):1617-35.

89.Kim E, Yang J, Park S, Shin K. Factors Affecting Success of New Drug Clinical Trials. Therapeutic innovation & regulatory science. 2023;57(4):737-50.

90.Shegekar T, Vodithala S, Juganavar A. The Emerging Role of Liquid Biopsies in Revolutionising Cancer Diagnosis and Therapy. Cureus. 2023;15(8):e43650.

91.Velpula T, Buddolla V. Enhancing detection and monitoring of circulating tumor cells: Integrative approaches in liquid biopsy advances. The Journal of Liquid Biopsy. 2025;8:100297.

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