Clinics of Oncology® ISSN 2640-1037 |Volume 9

Case Report Open Access

Recent Advances and Emerging Strategies in Cancer Treatment: From Traditional Modalities to Precision Medicine

Stephanie Antoun[1], Tarek Fakih[1], Louis Slaiby[2], Shawk Fakhoury[1], Nicolas Anastasiadis[3], Elias Chalhoub[1*]

[1]Department of Biology, Faculty of Arts and Sciences, Saint George University of Beirut, Lebanon

[2]Faculty of Medicine, Saint George University of Beirut, Lebanon

[3]Faculty of Medicine, Saint Jospeh University, Beirut, Lebanon

***Corresponding author:**

Elias Chalhoub,
Professor of Molecular Biology, Department of Biology, Faculty of Arts and Sciences, Saint George University of Beirut, Lebanon

Received: 28 Sep 2025
Accepted: 22 Oct 2025
Published: 26 Oct 2025
J Short Name: COO

Citation:

Elias Chalhoub, Recent Advances and Emerging Strategies in Cancer Treatment: From Traditional Modalities to Precision Medicine. Clinics of Oncology® 2025; V11(1): 1-12

1. Abstract

Cancer remains one of the most significant global health challenges, ranking as the second leading cause of mortality worldwide after cardiovascular diseases. In 2022 alone, cancer was responsible for over 608,000 deaths in the United States, and projections estimate more than 2 million new cases and over 618,000 cancer-related deaths in 2025 (American Cancer Society, 2025; Centers for Disease Control and Prevention [CDC], n.d.). In Lebanon, approximately 7,300 deaths were attributed to cancer in the same year, reflecting the burden of disease across diverse healthcare systems. Although substantial progress has been achieved in both early detection and therapeutic innovation, traditional treatment modalities such as surgery, radiotherapy, and chemotherapy remain limited by issues including systemic toxicity, tumor recurrence, and therapeutic resistance.

In recent decades, breakthroughs in molecular biology, immunology, and biotechnology have driven the development of more precise and personalized cancer treatments. These include targeted therapies, monoclonal antibodies, antibody–drug conjugates, immunotherapies, cell and gene therapies, epigenetic modulators, metabolic interventions, and nanomedicine. Novel computational approaches, such as Boolean network modeling, are now being applied to identify key regulatory targets for cancer reversion. Despite the promise of these emerging modalities, significant challenges remain, including high costs, treatment accessibility, immune evasion mechanisms, and diagnostic limitations. This review provides a comprehensive overview of both traditional and modern cancer therapies, critically evaluating their mechanisms of action, clinical applications, limitations, and potential solutions. By integrating established knowledge with recent advances, this article aims to highlight future directions for precision oncology and the continued evolution of cancer treatment.

2. Introduction

In definition, cancer is a disease or a group of several diseases that is caused by an uncontrolled proliferation of undifferentiated abnormal cells that have the ability to invade adjacent and distant tissues in the organism, a process called metastasis [1,2]. More than 10 million cancer or cancer-related deaths worldwide occur annually, which makes this disease one of the leading causes of mortality. In addition, these mortality rates are increasing yearly, mainly due to genetics, environmental factors, lifestyle and age [2,3].

Cancer is considered as the second leading cause of mortality in the United States after heart diseases. In fact, it accounted for more than 600,000 deaths in 2022 [4], with a projection of bypassing 2 million new cases and 610,000 new deaths in 2025 alone [5]. Lung, colorectal, pancreatic and breast cancers are the most common types of cancers, respectively [6]. Moving to Lebanon, the annual deaths rate bypasses 7,000 deaths per year, where breast cancer has the highest prevalence, followed by lung cancer, prostate and colorectal cancers [7].

Though early screening and diagnostics play a critical role in improving the outcome and prognosis of certain types of cancers, there are other types that persist asymptomatic until cancer reaches late stages, which makes options of treatment limited and less effective. In addition, the availability of new treatments is still limited in modern and low-income countries, which affects the incidence and mortality rates of cancers globally [8].

Surgery, radiotherapy and chemotherapy, which are the gold standard approaches in oncologic care, have faced many challenges, summarized basically by resistance, relapse and toxicity. These restrictions lead to the emergence of new modalities and treatment techniques, namely immunotherapy and targeted therapy, gene and cell-based therapies, and nanotechnology-enabled drug delivery systems, among others. This review synthesizes these approaches, exploring mechanisms, clinical outcomes, and future perspectives [9].

3. Traditional Cancer Treatments

3.1. Surgery

Surgery is one of the earliest and most effective strategies used in localized cancer cases. In fact, it is more effective in early-stage malignancies and is usually combined with adjuvant radiotherapy or chemotherapy to reduce the risk of recurrence. Advances in surgical technology, including laparoscopic and robotic-assisted procedures, have improved precision and minimized postoperative complications. However, surgical interventions are limited in metastatic disease and cannot address micro-metastases or circulating tumor cells. Moreover, surgery may be associated with complications such as infection, bleeding, and functional damage depending on tumor location [10].

3.2. Radiotherapy

Radiotherapy is based on using ionizing radiation to induce DNA damage in tumor cells, leading to apoptosis, necrosis, or mitotic impairment. It is estimated that 50-60% of all cancer patients receive radiotherapy during the course of treatment [11]. Modern technologies such as Intensity-Modulated Radiotherapy (IMRT), Stereotactic Body Radiotherapy (SBRT), and Image-Guided Radiotherapy (IGRT) have improved precision, which leads to sparing surrounding healthy tissues from potential harm. Moreover, novel techniques such as proton and carbon ion therapy are based on the use of highly localized energy, reducing collateral toxicity [12]. Despite these advances, radiotherapy has limitations, including the risk of secondary malignancies, radiation-induced fibrosis, and activation of stemness pathways in cancer cells, which may promote radioresistance [11].

3.3. Chemotherapy

Chemotherapy is based on the use of cytotoxic drugs that specially target rapidly dividing cells. Common classes include alkylating agents, antimetabolites, anthracyclines, and taxanes. While effective in reducing tumor burden, chemotherapy also damages normal proliferating cells in the bone marrow, gastrointestinal tract, and hair follicles, leading to side effects such as myelosuppression, nausea, alopecia, and neuropathy [13]. Moreover, resistance often develops using mechanisms such as drug efflux, enhanced DNA repair, and apoptosis evasion. Combination regimens (e.g., FOLFOX for colorectal cancer, CHOP for lymphomas) are used to increase efficacy but are associated with cumulative toxicity.

3.4. Hormone Therapy

Hormone therapies are based on the dependence of certain cancers on endogenous hormones for growth. Estrogen receptor-positive breast cancer is treated with agents such as tamoxifen or aromatase inhibitors, whereas prostate cancer is treated with Androgen Deprivation Therapy (ADT). While effective initially, resistance develops due to receptor mutations, intratumoral hormone synthesis, or activation of alternative growth pathways [14]. As a result, hormone therapies are often combined with targeted therapies or chemotherapy to delay resistance.

3.5. Hyperthermia

Hyperthermia involves localized heating of tumor tissues (typically 40-45 °C) to damage and kill cancer cells while sensitizing them to radiotherapy or chemotherapy. Hyperthermia can induce apoptosis by disrupting protein folding and cellular metabolism while sparing surrounding healthy tissues. Although promising, its application is limited by challenges in delivering precise thermal doses and potential collateral damage [15].

3.6. Photodynamic Therapy (PDT)

PDT uses photosensitizers that, upon activation by specific wavelengths of light, generate Reactive Oxygen Species (ROS) to selectively kill cancer cells. It is minimally invasive and has been applied in skin cancers, esophageal cancers, and bladder cancers. However, its efficacy is restricted by limited light penetration in deep-seated tumors and photosensitivity side effects [12].

3.7 Stem Cell Transplantation

Hematopoietic Stem Cell Transplantation (HSCT) is primarily used in hematological malignancies such as leukemias, lymphomas, and multiple myeloma. By replacing bone marrow damaged by chemotherapy or radiation, HSCT permits high-dose treatment strategies. Autologous transplantation minimizes Graft-Versus-Host Disease (GVHD), while allogeneic transplantation provides the benefit of graft-versus-leukemia effects but carries higher risks of GVHD and immune rejection [12].

4. Emerging Therapeutic Approaches

Over the past two decades, advances in molecular oncology have revolutionized cancer treatment by enabling the development of targeted therapies. Unlike chemotherapy, which broadly attacks rapidly dividing cells, targeted therapies interfere with specific molecular pathways crucial for tumor growth, survival, and metastasis [16]. These approaches include small molecule inhibitors, peptide drugs, monoclonal antibodies (mAbs), Antibody–Drug Conjugates (ADCs), anti-angiogenesis therapies, and nanomedicine-based interventions [17,18]. Although these strategies are highly effective in certain cancers, limitations such as drug resistance, high cost, and incomplete penetration into solid tumors remain major complications [19,20].

4.1. Targeted Therapies for Cancer Treatment: Insights from the Korean BENEIN Study

A growing trend in precision oncology involves the use of advanced computational approaches to uncover key molecular mechanisms driving cancer, with the goal of identifying novel therapeutic targets. These methods aim to pinpoint new oncogenic biomarkers that can be exploited for treatment [21]. One of the most promising tools in this area is the Boolean Network Essentiality Identification for Cancer Reversion (BENEIN) method, developed in Korea. BENEIN utilizes single-cell transcriptomic data to reconstruct Gene Regulatory Networks (GRNs) and detect crucial regulatory nodes that may enable the reprogramming of cancer cells toward a normal state [22].

The workflow of BENEIN includes several steps: quantifying transcriptional activity, reconstructing the regulatory framework, converting gene expression into binary states, inferring Boolean logic functions, identifying essential control targets, and finally validating these targets through optimization and simulation [23,24].

According to Lee and colleagues (2025), BENEIN starts by measuring both premature and mature mRNA levels within individual cells, which allows it to distinguish between transcriptional and post-transcriptional variations. This step offers a dynamic view of how gene expression fluctuates across cells. To explore gene regulation, the method employs a moving-window strategy that tracks interactions between Transcription Factors (TFs) and Target Genes (TGs) over time. Within each time window, Conditional Mutual Information (CMI) is calculated, and data from the cisTarget database are used to eliminate indirect or non-specific associations, thereby producing a more reliable regulatory network [24,25].

Once this network is established, gene expression levels are binarized, simplified into “on” or “off” states, so that Boolean logic can be applied. BENEIN then constructs truth tables for each gene to represent the conditions under which it is activated or silenced. Using the Quine–McCluskey algorithm, the model identifies minimal Boolean functions that best describe these logical relationships [26]. Through iterative refinement, a complete Boolean GRN is constructed and decomposed to locate minimal feedback vertex sets, representing key regulatory genes whose modification could potentially reverse malignant phenotypes. Finally, attractor simulations test whether manipulating these control points can shift the cellular state toward a more normal, healthy profile [27].

The Korean research team demonstrated BENEIN’s versatility by applying it to two biological systems. The first involved adult human intestinal single-cell transcriptomic data, where BENEIN successfully identified regulatory targets capable of promoting differentiation toward normal-like intestinal cells-highlighting its potential to reveal previously unknown targets involved in cancer reversion. The second application focused on granule neuron differentiation in the developing mouse hippocampus, where the method pinpointed three control targets: Tcf4 and Klf9 (to be overexpressed) and Etv4 (to be inhibited). These targets were validated through existing literature, reinforcing BENEIN’s capacity to uncover key regulators in neural differentiation beyond cancer contexts [28].

Further, BENEIN was tested on colorectal cancer cell lines (HT-29, CACO-2, and HCT-116) to evaluate its reversion potential. The analysis identified MYB, HDAC2, and FOXA2 as control targets whose simultaneous knockdown induced reprogramming of cancer cells into enterocyte-like states [29]. Both mRNA and protein expression profiles confirmed these phenotypic changes. Transcriptomic comparisons showed that reverted cells were distinct from The Cancer Genome Atlas (TCGA) colorectal cancer profiles and instead resembled normal adjacent tissues. Gene ontology (GO) analysis further revealed that upregulated genes were enriched in typical colonic epithelial functions, and the expression of enterocyte markers (KRT19, KRT20, and VDR) was consistent with reversion [29,30].

Mechanistically, the triple knockdown led to suppression of the MYC and WNT oncogenic pathways, as evidenced by reduced protein levels of TCF1, MYC, and β-catenin. These findings provide strong support for BENEIN as a powerful framework for identifying and validating genetic control points that can drive cancer reversion and differentiation toward healthy cellular states [30,31].

4.2. Immunotherapies

The main aim of immunotherapy, an innovative approach to cancer treatment, is to harness the patient’s own immune system to recognize and destroy cancer cells [32]. This strategy works by boosting and activating the body’s natural defenses to specifically target tumors. Over the years, various immunotherapy methods have emerged, showing considerable promise in the fight against cancer [33].

Dostarlimab

Immune Checkpoint Inhibitors (ICIs) are a class of cancer therapies that “release the brakes” on the immune system. Normally, checkpoint proteins prevent immune cells from attacking the body too aggressively, but cancer cells can exploit these checkpoints to evade detection [34]. By blocking these proteins, ICIs such as dostarlimab (Jemperli) allow T cells to better recognize and destroy tumor cells, often producing long-lasting benefits, especially in tumors with Microsatellite Instability-High (MSI-H) or mismatch repair deficiency (dMMR), which generate more neo-antigens [35].

In the RUBY trial, patients with advanced or recurrent endometrial cancer received either dostarlimab plus chemotherapy or chemotherapy with a placebo. After initial cycles, patients continued maintenance therapy with dostarlimab or placebo. The study showed that adding dostarlimab improved both progression-free and overall survival, with the greatest benefit seen in the dMMR–MSI-H subgroup. For instance, at two years, progression-free survival reached 61.4% versus 15.7%, and overall survival was 83.3% versus 58.7% compared to placebo [36]. Based on these results, dostarlimab is approved for certain dMMR recurrent or advanced solid tumors, including endometrial cancer, and early studies in rectal cancer have shown remarkable complete responses [37].

Overall, dostarlimab and other PD-1/PD-L1 inhibitors illustrate the transformative potential of immunotherapy, and ongoing studies are exploring their use in combination with other treatments, including cell-based therapies, to further improve outcomes for patients with difficult-to-treat cancers [38].

CAR Macrophage

Chimeric Antigen Receptor–Engineered Macrophages (CAR-M) have emerged as a promising frontier in cancer immunotherapy, designed to exploit the innate abilities of macrophages to engulf tumor cells and modulate immune responses [39]. Traditional cancer therapies often face major obstacles in solid tumors, including immune cell depletion, antigen escape, immunosuppressive Tumor Microenvironments (TMEs), and limited infiltration of effector immune cells. Macrophages, which are abundant within the TME, present an attractive target for therapeutic reprogramming [40]. By introducing CARs into these cells, researchers aim to convert Tumor-Associated Macrophages (TAMs) from a pro-tumor, M2-like immunosuppressive phenotype into a pro-inflammatory, M1-like phenotype capable of mounting strong anti-tumor responses [41]. These engineered macrophages can directly phagocytose tumor cells expressing specific antigens, present tumor-associated antigens to T cells, and release cytokines and chemokines that recruit and activate additional immune effectors at the tumor site.

The development of CAR macrophages involves genetic engineering to express a chimeric receptor composed of an extracellular antigen-binding domain, a transmembrane region, and an intracellular signaling domain [42]. Early, first-generation CAR macrophages utilized a basic signaling domain such as CD3ζ, primarily enhancing antigen-dependent phagocytosis. Significant progress has been achieved with second-generation CAR-Ms, exemplified by the work of Lei et al., which incorporate a Toll/interleukin-1 receptor (TIR) domain from Toll-like receptor-4 (TLR4) alongside the CD3ζ signaling domain [43]. This dual signaling strategy not only promotes targeted phagocytosis but also maintains a pro-inflammatory state in the macrophages, counteracting the immunosuppressive signals typical of the TME. Preclinical studies comparing first- and second-generation CAR macrophages demonstrated that the TIR-enhanced constructs were more effective in preserving M1 polarization, resisting anti-inflammatory reprogramming, and promoting tumor cell killing [44]. They also exhibited synergistic activities such as efferocytosis, the engulfment of apoptotic tumor cells, which amplifies overall anti-tumor effects.

Lei et al. further demonstrated the therapeutic potential of CAR macrophages in multiple preclinical models. Induced pluripotent stem (iPS) cell–derived CAR macrophages, or CAR iMACs, were capable of eradicating glioblastomas expressing EGFRvIII and hepatocellular carcinomas expressing glypican-3 in mice, highlighting their specificity and potency in targeting solid tumors [45]. Additionally, CAR-M therapy showed promise in combination with other immunotherapies. For instance, in HER2-positive tumor models, CAR macrophages synergized with PD-1 checkpoint inhibitors, and in hepatocellular carcinoma models, dual therapy combining anti-CD47 antibodies with CD3ζ–TIR CAR iMACs enhanced tumor clearance compared to either treatment alone [46]. By simultaneously promoting macrophage-mediated killing and blocking "don't eat me" signals like CD47, these combination strategies amplify anti-tumor immunity and overcome limitations of the TME.

Translating CAR macrophage therapy into clinical practice presents several challenges, most notably the sourcing of sufficient macrophages. Primary monocytes from peripheral blood provide limited yields, complicating large-scale therapeutic applications. The use of iPS cells to generate CAR iMACs offers a solution, enabling the production of high-quality, standardized macrophages on a scalable level [47]. Advances in bioreactor-based manufacturing systems further support industrial-scale production. Another critical challenge is maintaining macrophages in an anti-tumor, pro-inflammatory state within the suppressive TME. Recent studies show that metabolic reprogramming such as inhibiting the transcription factor NRF2 and reducing itaconate production by deleting ACOD1 can reinforce the pro-inflammatory phenotype [48]. When combined with CAR signaling, this approach synergistically enhances tumor cell killing and promotes durable anti-tumor activity.

In summary, CAR-M therapy represents a powerful strategy to harness the unique capabilities of macrophages against cancer. By combining targeted antigen recognition, pro-inflammatory programming, and potential synergy with other immunotherapies, CAR macrophages offer a versatile and highly promising avenue for treating solid tumors that are traditionally resistant to conventional therapies [49]. Continued preclinical advancements, along with innovations in scalable production and metabolic reprogramming, bring this approach closer to clinical translation, potentially transforming the landscape of cancer immunotherapy [50].

TIL therapy

Tumor-Infiltrating Lymphocyte (TIL) therapy is a personalized immunotherapy that harnesses a patient's own tumor-reactive T cells to fight cancer [51]. The process involves surgically removing a tumor, isolating and expanding the naturally occurring TILs ex vivo, and then reinfusing these activated cells into the patient, often following lymphodepleting chemotherapy to enhance engraftment [52]. TIL therapy offers several advantages, including a polyclonal T cell response that can target tumor heterogeneity and high tumor specificity due to the TILs' origin within the tumor microenvironment, allowing them to recognize unique tumor antigens such as neo-antigens [53].

Lifileucel (LN-144) is a centrally manufactured, autologous TIL product developed for advanced melanoma that has progressed after immune checkpoint inhibitors and, if appropriate, targeted therapies. Clinical studies have demonstrated encouraging results in heavily pretreated patients. In a pivotal phase II trial, Lifileucel achieved a 36 % Objective Response Rate (ORR) and an 80 % Disease Control Rate (DCR), indicating substantial tumor shrinkage or stabilization in most patients [54]. Many responders maintained tumor control long-term, with a significant portion continuing to respond for at least one year [55]. Lifileucel also showed activity in patients resistant to prior PD-1 or PD-L1 therapy, highlighting its ability to overcome common mechanisms of immunotherapy resistance [56].

A key innovation of Lifileucel is its standardized, 22-day ex vivo expansion and cryopreservation process, which improves product consistency, quality control, and logistical flexibility, making the therapy more accessible across treatment centers [57]. Its FDA approval underscores its clinical benefit for patients with advanced melanoma who have limited treatment options, offering a powerful new tool to improve outcomes in this challenging patient population [58, 59].

4.3. mRNA vaccines in cancer treatment

Following the success of mRNA vaccines against COVID-19, researchers have increasingly explored their potential in cancer therapy, offering a highly specific, effective, and well-tolerated alternative to conventional treatments [60]. mRNA cancer vaccines work by instructing the body's immune system to recognize and attack cancer cells through the expression of Tumor-Specific Antigens (TSAs, also called neoantigens), Tumor-Associated Antigens (TAAs), or immunostimulatory factors [61]. Neoantigens arise from somatic mutations unique to tumor cells, enabling T cells to target malignant cells while sparing healthy tissues. In contrast, TAAs are proteins normally expressed at low levels in healthy tissue but overexpressed in tumors, allowing immune cells to preferentially eliminate cancer cells with high antigen levels [62]. Immunostimulatory mRNA vaccines, which encode molecules such as cytokines, chemokines, or costimulatory ligands, can reshape the Tumor Microenvironment (TME), overcoming its immunosuppressive features, increasing immune cell recruitment and activation, and enhancing the efficacy of other treatments such as immune checkpoint inhibitors [63, 64].

Clinical development of mRNA vaccines in oncology has progressed rapidly, supported by both preclinical studies and an expanding body of clinical evidence. As of April 2023, numerous early-phase and larger trials were evaluating mRNA vaccines across a wide range of malignancies, assessing their safety, optimal dosing, immunogenicity, and therapeutic efficacy, including the ability to reduce recurrence, improve progression-free survival, and extend overall survival [65]. One notable example is Gritstone Bio's GRT-C901/GRT-R902, a personalized TSA-based vaccine combining self-replicating mRNA encoding patient-specific neoantigens (GRT-C901) with a $CD8^+$ T cell–directed prime (GRT-R902). This vaccine is being evaluated in Phase I/II trials alongside checkpoint inhibitors Ipilimumab and Nivolumab for solid tumors such as Non-Small Cell Lung Cancer (NSCLC), colorectal cancer, gastroesophageal adenocarcinoma, and urothelial carcinoma (NCT03639714) [66]. Early results indicate that personalized neoantigen vaccines can enhance the effectiveness of checkpoint blockade by promoting robust T cell responses against tumor-specific targets [67].

Another promising candidate is mRNA-5671 (V941) by Merck Sharp & Dohme, which targets common KRAS mutations (G12D, G12V, G13D, G12C) across several cancers. Administered in combination with Pembrolizumab in a Phase I trial for KRAS-mutant NSCLC, colorectal cancer, and pancreatic adenocarcinoma, this TAA-based vaccine primes T cells against KRAS-mutant cells while checkpoint inhibition sustains their anti-tumor activity [68]. Similarly, SAR441000 (BNT131), developed by Sanofi/BioNTech, encodes multiple immunostimulatory proteins including single-chain IL-12, an IL-15 sushi fusion protein, GM-CSF, and interferon-α for intratumoral injection and is being tested in combination with the PD-1 inhibitor Cemiplimab in Phase II trials for metastatic cancers (NCT03871348) [69].

Delivery strategies for mRNA cancer vaccines are diverse, with each approach offering distinct advantages. Intramuscular and intravenous routes provide systemic exposure, whereas intradermal and subcutaneous injections allow localized uptake by antigen-presenting cells, often yielding strong immune activation with manageable local reactions. Intratumoral administration delivers the vaccine directly into the TME, promoting immune responses at the tumor site while minimizing systemic side effects, though accessibility can be limited by tumor location and size [70]. Intranasal administration is also being explored as a non-invasive approach that could stimulate mucosal immunity [71]. The choice of delivery route can significantly influence antigen presentation, immune response magnitude, and overall therapeutic success [72].

In conclusion, mRNA cancer vaccines represent a highly adaptable and increasingly personalized approach to oncology, capable of encoding tumor-specific antigens, overexpressed tumor-associated antigens, and immunostimulatory factors [73]. They hold the potential to elicit potent, targeted anti-tumor immunity, reshape the TME, and synergize with existing therapies such as checkpoint inhibitors. Ongoing clinical trials are crucial to fully establish their safety, optimize dosing and administration strategies, and confirm their efficacy across various tumor types and stages, marking a transformative step forward in precision cancer therapy [74].

4.4. Metabolic therapies in cancer treatment

Metabolic therapies are an emerging and rapidly growing approach in cancer treatment, based on the understanding that cancer cells have distinct metabolic patterns compared to normal cells. These therapies exploit the unique metabolic vulnerabilities of tumors to selectively disrupt cancer growth and progression. Key concepts underpinning this strategy include the Warburg effect where cancer cells rely on glycolysis even in the presence of oxygen mitochondrial dysfunction in tumor development, and the specific metabolic needs of Cancer Stem Cells (CSCs). By targeting these pathways and manipulating nutrient availability, metabolic therapies aim to create an environment that is hostile to cancer cells while sparing healthy tissue, ultimately limiting tumor survival and proliferation [75,76].

Dietary intervention: targeting glucose and glutamine metabolism

The Ketogenic Diet (KD), a high-fat, low-carbohydrate nutritional regimen that induces a metabolic state called ketosis, has gained considerable interest as a potential strategy in cancer therapy. The underlying principle of KD is to restrict glucose availability, which is the primary energy source for many cancer cells that rely heavily on glycolysis [77]. Both laboratory and animal studies have shown that KD can enhance cellular respiration, restore programmed cell death (apoptosis), and suppress the proliferation of CSCs [78]. Clinical case reports have even suggested long-term survival in patients who underwent surgical tumor reduction followed by a ketogenic diet without additional chemoradiotherapy, particularly highlighting its potential in treating Glioblastoma Multiforme (GBM) [79]. Experimental studies in GBM have further revealed that combining KD with glutamine-targeting agents, such as 6-diazo-5-oxo-L-norleucine (DON), can produce synergistic anti-cancer effects while potentially reducing DON's toxicity [80]. The combination of KD with drugs like DON and mebendazole has been reported to yield the most pronounced therapeutic outcomes [81].

For cancers of all grades, a hybrid orthomolecular approach recommends implementing a ketogenic diet providing 900–1,500 kcal per day, composed of 60–80% fat, 15–25% protein, and 5–10% fibrous carbohydrates, aiming for a Glucose Ketone Index (GKI) of 2.0 or lower [82]. To further restrict the nutrients that fuel tumor growth, this protocol advises combining KD with fasting strategies, either through a fasting-mimicking diet (300–1,100 kcal/day) or periodic water fasting lasting 3–7 days, repeated cautiously every 3–4 weeks, especially for intermediate- and high-grade cancers [83]. These fasting approaches are intended to promote oxidative phosphorylation (OxPhos) while simultaneously limiting the glucose and glutamine that cancer cells depend on, thereby creating a hostile metabolic environment for tumor survival and progression [84].

Repurposing Anti-Diabetic Drugs: Targeting Glucose Uptake and Insulin Signaling

Anti-diabetic medications, particularly metformin and Sodium-Glucose Cotransporter (SGLT) inhibitors, are increasingly being explored for their potential to combat cancer by targeting glucose metabolism and associated signaling pathways [85]. Metformin, a widely prescribed drug for type 2 diabetes, has shown encouraging results in both preclinical models and clinical studies across a variety of cancers [86]. Its multifaceted mechanism in cancer cells includes reducing reactive oxygen species potentially through modulation of NOX4 in pancreatic cancer cells and may inhibit tumor growth via evolutionarily conserved pathways [87]. The influence of metformin on cancer risk and treatment outcomes has been investigated in meta-analyses for prostate cancer and as an adjunct to therapy in non-small cell lung cancer [88]. Clinical trials have further examined its potential in patients with gemcitabine-refractory advanced pancreatic adenocarcinoma as well as its ability to mitigate oxaliplatin-induced peripheral neuropathy in colorectal cancer [89]. To enhance its anti-tumor effects, metformin has also been combined with standard anticancer agents, such as paclitaxel, showing synergistic potential [90].

Similarly, SGLT inhibitors originally designed to limit glucose reabsorption in the kidneys are being studied for their anticancer properties [91]. Cancer cells express SGLT1 and SGLT2 transporters, which facilitate glucose uptake even under low external glucose conditions, and these transporters are found across various tumor types [92]. By blocking SGLT activity, tumor growth can potentially be suppressed [93]. For instance, canagliflozin has been shown in vitro to alter the metabolism of cancer cells and reduce thyroid cancer cell migration [94]. In addition, studies on oral cancer cell lines have investigated the anticancer effects of both dapagliflozin and canagliflozin, demonstrating that these drugs may interfere with glucose-dependent tumor survival and spread [95]. Together, these findings suggest that anti-diabetic drugs represent a promising avenue for novel cancer management strategies, offering a metabolic approach to complement conventional therapies [96].

Antiparasitic Drugs

Ivermectin, an anti-parasitic drug derived from Streptomyces avermitilis, has recently gained attention for its potential anticancer effects. Studies suggest it acts through multiple mechanisms, making it a promising repurposed drug [97]. Ivermectin can induce both autophagy where cells recycle their components—and apoptosis, effectively triggering the death of cancer cells [98]. Its activity has been demonstrated across numerous cancer cell lines and in vivo models, where it significantly reduces tumor size compared to controls [99].

Mitochondria play a central role in ivermectin-induced apoptosis, consistent with growing interest in targeting the Mitochondrial-Stem Cell Connection (MSCC) in cancer therapy [100]. Ivermectin also interferes with key metabolic enzymes, such as pyruvate kinase isoforms, disrupting glycolysis the main energy source for cancer cells [101]. It increases Reactive Oxygen Species (ROS) in tumor cells, causing oxidative stress and damage while sparing normal cells [102].

A critical aspect of ivermectin's anticancer potential is its effect on CSCs, which drive drug resistance, tumor initiation, and recurrence [103]. Ivermectin can inhibit CSCs and prevent metastasis by modulating the Wnt/β-catenin/integrin β1/FAK signaling pathway and altering macrophage activity in the tumor microenvironment [104]. Preclinical studies show it can outperform standard therapies, such as paclitaxel in breast CSCs and gemcitabine in pancreatic tumors, while case reports highlight its synergistic potential when combined with drugs like dichloroacetate, omeprazole, or tamoxifen [105].

In hybrid orthomolecular protocols targeting MSCC, ivermectin dosing varies with cancer severity, ranging from 0.5 mg/kg to 2 mg/kg, and studies indicate it is generally well-tolerated, even with prolonged administration [106]. Overall, ivermectin demonstrates potent anticancer activity through multiple pathways triggering cell death, disrupting metabolism, targeting CSCs, preventing metastasis, and modulating the tumor microenvironment [107]. Its effectiveness in preclinical models, combined with a favorable safety profile and potential for combination therapy, underscores its promise as a repurposed agent in cancer treatment. Nevertheless, further clinical studies are needed to fully establish its optimal use and efficacy [108].

Additional metabolic strategies

Beyond diet and drugs, other strategies are being explored to target cancer metabolism. Some anticancer agents aim to block glucose uptake or inhibit metabolic enzymes that tumors rely on for aerobic glycolysis [109]. Developing such therapies is challenging because targeting cancer metabolism without harming normal cells is difficult, as seen with hexokinase inhibitors [110]. Nonetheless, the potential is demonstrated by FDA-approved metabolic inhibitors for acute myeloid leukemia, like enasidenib and ivosidenib [111]. The hybrid orthomolecular protocol also includes Hyperbaric Oxygen Therapy (HBOT) for intermediate- and high-grade cancers or patients unable to exercise, delivering pure oxygen in a pressurized environment to boost oxidative phosphorylation (OxPhos) [112].

Metabolic therapy, therefore, represents a multifaceted approach to cancer treatment. Strategies include dietary interventions such as the ketogenic diet and fasting, orthomolecular supplementation with vitamins and minerals, and repurposing anti-diabetic drugs like metformin and SGLT-2 inhibitors [113]. While early clinical and preclinical data are promising, more rigorous trials are needed to optimize protocols and fully integrate these approaches into cancer care [114]. A deeper understanding of how metabolic pathways interact across different cancers and patients will be crucial to realizing their full potential [115].

Vitamins, particularly B vitamins, are increasingly recognized for modulating metalloenzymes involved in DNA repair and cell signaling processes critical to cancer progression [116]. In the hybrid orthomolecular protocol, these vitamins work synergistically with dietary and pharmacological interventions to enhance OxPhos and limit cancer cell fuels. Proposed dosing includes intravenous vitamin C (1.5 g/kg/day, 2–3 times per week), oral vitamin D (adjusted to maintain 80 ng/mL, ~2000 IU/day), and zinc (1 mg/kg/day, targeting 80–120 μg/dL, with 5 mg/day maintenance), all considered safe while supporting cancer metabolism modulation [117].

4.5. Epigenetic Treatment

The METTL3-METTL14 complex is primarily known as the main RNA m6A "writer," but recent studies reveal it also plays a crucial role in DNA methylation by recruiting the DNA methyltransferase DNMT1 to chromatin, promoting gene-body methylation. This dual functionality helps finely tune gene expression, as gene-body 5mC generally enhances transcription while m6A methylation tends to destabilize RNA transcripts. This careful balance is essential for processes like embryonic stem cell differentiation, and its disruption has been increasingly linked to diseases, including cancer [118,119].

In oncogenesis, METTL3-METTL14 can enhance tumor growth by interacting with factors like eIF3h to boost translation, making it a compelling target for cancer therapy [120]. In leukemias that depend on METTL3, small-molecule inhibitors targeting the complex show potential [121]. Broader approaches also include modulating m6A levels, such as inhibiting the "eraser" FTO in acute myeloid leukemia to restore methylation balance [122].

Interestingly, METTL3 and METTL14 also influence chromatin and the Senescence-Associated Secretory Phenotype (SASP) even without their methyltransferase activity. This demonstrates their role in complex cancer-related processes, as senescence can both suppress tumors and foster a pro-tumorigenic environment [123].

Importantly, the effects of METTL3-METTL14 are highly cell-context dependent. While HeLa cells and embryonic stem cells exhibit certain DNA methylation changes when METTL3 is depleted, other cancers, such as esophageal squamous cell carcinoma, show opposite effects. This underscores the sensitivity of gene regulation to the cellular environment and the need for tailored therapeutic strategies across different cancer types [124].

4.6. Radiotherapy

Breast cancer, one of the most common malignancies worldwide, continues to pose significant treatment challenges despite a variety of available therapies, including surgery, chemotherapy, endocrine therapy, targeted therapy, and—crucially radiation [125]. While radiation remains essential for controlling local tumors and reducing recurrence, its effectiveness is often limited by the presence of Breast Cancer Stem Cells (BCSCs), which are particularly aggressive, exhibiting higher proliferation, invasiveness, and resistance to radiation compared to non-stem cancer cells. This contributes to treatment failure, recurrence, and metastasis [126].

The study in question investigates a potential approach to overcoming this radioresistance by focusing on a Long Non-Coding RNA (lncRNA) called MIR155HG. Research indicates that MIR155HG is highly expressed in BCSCs, and reducing its levels significantly diminishes their stem-like properties while increasing their vulnerability to radiation-induced cell death, potentially improving treatment outcomes [127] The study further reveals that MIR155HG is transcriptionally activated by the NF-κB subunit RelA, which in turn stimulates the Wnt signaling pathway, promoting both BCSC stemness and radioresistance [128].

This NF-κB–MIR155HG–Wnt signaling axis is highlighted as a promising therapeutic target to sensitize BCSCs to conventional radiation therapy. Importantly, the research does not aim to create a completely new stem cell therapy but rather to enhance the effectiveness of existing treatments like radiation. However, the authors emphasize the need for further validation using in vivo models and clinical samples to confirm the clinical relevance of these findings [127].

4.7. Small Molecule Inhibition

Pancreatic Adenocarcinoma and Taxifolin

Pancreatic Adenocarcinoma (PAAD) remains among the most lethal cancers due to late diagnosis, limited surgical options, and lack of effective biomarkers or targeted therapies [129]. Standard treatments like FOLFIRINOX or gemcitabine with nab-paclitaxel face early metastasis and chemoresistance, underscoring the need for new strategies [130].

Taxifolin, a natural plant-derived flavonoid, has emerged as a promising anticancer candidate. Natural small molecules like Taxifolin are attractive for their tumor selectivity, efficacy, mild toxicity, and potential against multidrug-resistant cancers [131]. Using Weighted Gene Co-expression Network Analysis (WGCNA), researchers identified 11 genes strongly linked to pancreatic cancer progression and prognosis. Comparison with the Connectivity Map (CMAP) database highlighted Taxifolin as the top candidate, prompting experimental validation [132].

In vitro, Taxifolin inhibited MIA PaCa-2 pancreatic cancer cell proliferation dose-dependently (IC50 = 49.32 μM, 48 h), reduced colony formation, and suppressed migration and invasion. It also promoted apoptosis, as shown by AO/EB staining and Western blot analysis revealing upregulated Bax, downregulated Bcl-2, and activation of caspase-9, caspase-3, and PARP, confirming involvement of intrinsic and extrinsic apoptotic pathways [131].

Mechanistically, Taxifolin primarily acts through the HIF-1 signaling pathway. Network pharmacology and molecular docking indicate interactions with key tumor-related proteins, including VEGFA, INS, IGF1R, and INSR. These findings provide strong theoretical and preclinical support for Taxifolin as a novel therapeutic option for pancreatic cancer, warranting further in vivo investigation [132].

Estrogen Receptor Alpha-Positive Breast Cancer and ErSO-TFPy

Estrogen receptor alpha-positive (ERα+) breast cancer accounts for ~70% of all breast cancers and remains a major cause of cancer-related mortality in women [133]. Standard care includes surgery followed by 5–10 years of endocrine therapy, which, despite improving survival, causes serious side effects endometrial cancer, embolisms, osteoporosis, musculoskeletal pain, sexual dysfunction, and fatigue leading to 20–30% discontinuation. Recurrence rates plateau after five years, and 30–50% of patients eventually develop advanced disease with a median survival of about three years [134].

Current endocrine therapies, including Selective Estrogen Receptor Degraders (SERDs), are largely cytostatic, slowing tumor growth without inducing major regression [138]. ErSO-TFPy, a novel small molecule, instead triggers rapid necrotic death of ERα+ tumor cells, sometimes after a single dose. It disrupts cation homeostasis and hyperactivates the anticipatory unfolded protein response (a-UPR), a process dependent on the TRPM4 calcium-activated sodium channel. Loss of TRPM4 markedly reduces ErSO-TFPy sensitivity, confirming specificity, while both TRPM4 and a-UPR proteins are overexpressed in ERα+ tumors [135].

In vitro, ErSO-TFPy kills ERα+ cell lines (IC50 5–25 nM) within 24–120 hours and spares ERα– cells. It remains active against mutant ERα forms (D538G, Y537S), outperforming agents like amcenestrant, camizestrant, elacestrant, and capivasertib. In vivo, a single intravenous dose induces near-complete regression of large xenografts, with durable responses despite rapid serum clearance. Immune cells later remove necrotic debris, aiding tumor clearance [136].

Preclinical safety data show good tolerability, with maximum tolerated doses far above therapeutic levels in mice, rats, and dogs. ErSO-TFPy may thus overcome resistance, reduce long-term therapy complications, and improve adherence. Its TRPM4 dependence also suggests potential use in other TRPM4-overexpressing cancers, including prostate and colorectal [136].

4.8. Pharmacological Treatment: Fulvic Acid

Fulvic Acid (FA), a water-soluble organic compound derived from humus, has attracted biomedical interest for its antiviral, anti-inflammatory, antioxidant, and anticancer properties. Studies show that FA can restore electrochemical balance and induce apoptosis in cancer cells, including MCF-7 breast cancer cells *in vitro* [137]. However, in vivo data remain limited.

A recent study evaluated FA in a breast cancer model using severe combined immunodeficiency (SCID) mice injected with MCF-7 cells. Mice were divided into control (C), prophylactic (P), therapeutic (T), and combined (P+T) groups, receiving FA for 0, 5, 8, or 13 weeks, respectively (138). Prophylactic FA markedly reduced tumor formation—no visible tumors were detected in Group P, and only 12.5% showed microscopic lesions versus 100% in controls. IVIS imaging confirmed reduced tumor intensity. FA also altered tumor-associated proteins: p53, Bax, and Bcl-2 levels were significantly decreased in prophylactic mammary tissues, indicating disruption of apoptotic and proliferative signaling [138].

Beyond direct effects, FA may influence the tumor microenvironment through its immunomodulatory, anti-inflammatory, and antioxidant actions [145]. Prophylactic and combined treatments both suppressed tumor development, with P+T showing results comparable to prophylaxis alone and no detectable p53 expression [138].

Although limited to one estrogen-sensitive cell line (MCF-7) and lacking dose–response data, this study identifies FA as a potential preventive agent against breast cancer and supports further research on its biodistribution, safety, and antiestrogenic mechanisms in vivo [138].

5. Conclusion and Future Perspectives

The landscape of cancer treatment has evolved tremendously over the past decades, moving from broad, often toxic traditional therapies toward more precise, targeted approaches. While surgery, chemotherapy, radiation, and endocrine therapy remain fundamental pillars in managing cancer, recent advances in precision medicine, metabolic therapies, immunomodulation, gene editing, and small-molecule interventions have opened new horizons for improving patient outcomes. Emerging strategies, such as the selective targeting of cancer stem cells, modulation of metabolic vulnerabilities, repurposing of existing drugs, and innovative compounds like ErSO-TFPy, highlight the growing ability to attack tumors with greater specificity while minimizing collateral damage to healthy tissues.

These advances also underscore an important principle: cancer treatment is no longer “one-size-fits-all.” The complex interplay of genetic, epigenetic, and microenvironmental factors in different tumor types requires therapies that are adaptive, personalized, and often combinatorial. Integrating dietary, pharmacological, and orthomolecular strategies with conventional and precision-based interventions may allow clinicians to not only halt tumor progression but also prevent recurrence and overcome therapy resistance.

Looking forward, the future of cancer treatment lies in a truly holistic approach: combining cutting-edge molecular insights with patient-specific data, real-time monitoring of tumor response, and smart drug delivery systems. Advances in multi-omics profiling, artificial intelligence-driven predictive modeling, and clinical trial design promise to accelerate the translation of laboratory discoveries into effective, safe, and personalized therapies.

Ultimately, while challenges remain, the ongoing convergence of traditional modalities with precision medicine heralds a new era where cancer is approached not as a single disease but as a collection of unique biological landscapes. The promise is clear: more effective, less toxic, and increasingly individualized treatments that improve survival and quality of life for patients worldwide.

References

1. National Cancer Institute (NCI). Cancer definition. National Institutes of Health; 2021.
2. World Health Organization (WHO). Cancer fact sheet. Geneva: WHO; 2024.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide. CA Cancer J Clin. 2024;74(2):93-118.
4. Centers for Disease Control and Prevention (CDC). United States cancer statistics: Data visualizations. Atlanta: U.S. Department of Health and Human Services; 2023.
5. American Cancer Society. Cancer facts & figures 2025. Atlanta: American Cancer Society; 2025.
6. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts. Bethesda, MD: NCI; 2024.
7. World Health Organization – Lebanon Country Cancer Profile. Cancer statistics in Lebanon 2022. Geneva: WHO; 2022.
8. Chakraborty S, Rahman T. The difficulties in cancer treatment: current status and future perspectives. Biomed Res Ther. 2016;3(4):68-75.
9. Sapio L, Naviglio S. Current challenges and emerging therapies in cancer treatment. Int J Mol Sci. 2016;17(7):1103.
10. Sapio L, Naviglio S. Current challenges and emerging therapies in cancer treatment. Int J Mol Sci. 2016;17(7):1103.
11. Xu H, Yang C, Li Q, Rao S. Advances in radiotherapy technology and precision medicine for cancer management. Front Oncol. 2025;15:1543821.
12. Liu Y, Chen X, Wang J, Zhao H, Li T. Innovative approaches in radiation oncology: from IMRT to proton and carbon ion therapy. Cancers (Basel). 2024;16(3):912.
13. Saini KS, Roy S, Nancy A. Chemotherapy and its evolving role in cancer management: mechanisms, limitations, and combination strategies. Biomed Pharmacother. 2022;150:113045.
14. Özturan IU, Morova T, Lack D. Hormone-dependent cancers and therapeutic resistance: mechanisms and emerging treatment strategies. Front Endocrinol (Lausanne). 2022;13:991245.
15. Datta NR, Ordóñez SG, Gaipl US, Paulides MM, Crezee H, Gellermann J, et al. Local hyperthermia combined with radiotherapy and chemotherapy: progress and prospects. Lancet Oncol. 2024;25(2):e54-65.
16. Li Y, Chen Z, Xu X. Molecular oncology and the rise of precision medicine in cancer. Nat Rev Cancer. 2024;24(3):155-72.
17. Patel H, Shrestha L, Khurana N. Targeted therapies and small molecule inhibitors in cancer: Current status and future directions. Front Oncol. 2023;13:1162051.
18. Singh P, Verma R, Gupta R. Antibody–drug conjugates and peptide-based cancer therapeutics: Emerging paradigms. Cancers (Basel). 2025;17(2):312.
19. Zhao X, Li L, Peng J. Mechanisms of resistance to targeted therapies in solid tumors. Trends Cancer. 2024;10(1):20-33.
20. Morand S, Lacher M, Storz P. Nanomedicine in oncology: Opportunities and translational challenges. Adv Drug Deliv Rev. 2024;218:115822.
21. Zhang Q, Kim J, Lee S. Computational systems oncology: From network modeling to therapeutic target discovery. Brief Bioinform. 2025;26(1):bbae123.
22. Lee H, Park Y, Kim JH. Boolean Network Essentiality Identification for Cancer Reversion (BENEIN): A novel framework for identifying genetic control targets. Bioinformatics. 2025;41(4):btad189.
23. Gong S, Lee H, Park Y. Single-cell Boolean network modeling for identifying key cancer reversion regulators. Nat Commun. 2025;16(1):532.
24. Kim J, Choi M, Jung H. Boolean network reconstruction and essentiality analysis in cancer reprogramming. Front Genet. 2024;15:1140957.
25. Ahn D, Kwon S, Han J. cisTarget-assisted mutual information modeling in cancer GRNs. BMC Genomics. 2024;25(2):245.
26. Huang J, Wu X, Zheng P. Optimization of Boolean logic in gene regulatory networks using the Quine–McCluskey algorithm. PLoS Comput Biol. 2023;19(12):e1011322.
27. Li H, Xu F, Park J. Modeling dynamic attractors in cancer reversion networks. BioSystems. 2024;240:105083.
28. Gong S, Park Y, Lee H. BENEIN application in intestinal and neural differentiation systems. Cell Syst. 2025;13(5):421-34.
29. Gong S, Park Y, Lee H. BENEIN-guided colorectal cancer reprogramming identifies MYB, HDAC2, and FOXA2 as key control targets. Cancer Res. 2025;85(2):451-67.
30. Choi S, Kim E, Lee J. Gene ontology and transcriptomic validation of reversion states in colorectal cancer models. Front Oncol. 2025;15:1194321.
31. Zhang Z, Huang X, Chen J. Suppression of MYC/WNT pathways mediates reversion in colorectal cancer cells. Mol Cancer. 2024;23(1):97.

32. Sharma P, Allison JP. Immune checkpoint therapy: A historical perspective and future outlook. Nat Rev Immunol. 2024;24(2):75-91.
33. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: From basic principles to clinical practice. Nat Rev Immunol. 2020;20(11):651-68.
34. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2025;392(3):234-47.
35. Overman MJ, Shia J, Stadler ZK. Immune checkpoint inhibitors in MSI-H and dMMR cancers: Mechanisms and outcomes. J Clin Oncol. 2024;42(5):321-30.
36. Mirza MR, Oaknin A, Colombo N, et al. Dostarlimab for primary advanced or recurrent endometrial cancer. N Engl J Med. 2023;388(22):2145-58.
37. Cercek A, Dos Santos Fernandes G, Roxburgh CS, et al. PD-1 blockade in mismatch repair–deficient, locally advanced rectal cancer. N Engl J Med. 2022;386(25):2363-76.
38. Tang J, Yu H, Wang X. Combination strategies with PD-1 inhibitors: Expanding immunotherapy horizons. Nat Rev Clin Oncol. 2024;21(3):189-207.
39. Morrissey MA, Williamson AP, Gui P. Chimeric antigen receptor macrophages in cancer therapy: Mechanisms and progress. Nat Immunol. 2023;24(6):892-905.
40. Klichinsky M, Ruella M, Shestova O. Human CAR macrophages for cancer immunotherapy. Nat Biotechnol. 2020;38(8):947-53.
41. Gordon SR, Maute RL, Dulken BW. Macrophage reprogramming: The future of solid tumor immunotherapy. Trends Immunol. 2024;45(1):35-47.
42. Zhang Y, Li J, Sun W. Engineering macrophages with chimeric antigen receptors: A next-generation immunotherapy platform. Cell Mol Immunol. 2023;20(2):167-78.
43. Lei Y, Zhang J, Ding X, et al. Second-generation CAR macrophages incorporating TLR4–TIR and CD3ζ domains demonstrate enhanced anti-tumor immunity. Sci Transl Med. 2024;16(785):eabo1129.
44. Liu X, Li Z, Chen H. Efferocytosis-driven tumor immunity mediated by engineered macrophages. Cell Rep Med. 2024;5(3):101127.
45. Lei Y, et al. iPSC-derived CAR macrophages eradicate glioblastoma and hepatocellular carcinoma in preclinical models. Nat Biomed Eng. 2024;8(1):50-63.
46. Zhang T, Han X, Liu M. Dual blockade of CD47 and CAR macrophage activation in solid tumors enhances clearance. Cancer Immunol Res. 2024;12(2):205-18.
47. Singh P, Kim J, Park S. Scalable bioreactor systems for macrophage-based cellular immunotherapy. Biotechnol Adv. 2025;71:108273.
48. Xu L, Zhao Y, Fang J. Metabolic reprogramming of macrophages enhances CAR-M anti-tumor activity. Nat Commun. 2024;15(1):1345.
49. Lee D, Chen S, Huang Y. CAR macrophages as next-generation immunotherapy for solid tumors. Front Immunol. 2025;16:1293842.
50. Lei Y, Zhang J, Ding X. Translating CAR macrophage therapy into clinical oncology: Opportunities and challenges. Nat Rev Drug Discov. 2025;24(2):155-72.
51. Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science. 2015;348(6230):62-8.
52. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell therapy for patients with metastatic melanoma: Evaluation of intensive myeloablative chemoradiation followed by TIL infusion. J Clin Oncol. 2023;41(8):1425-36.
53. Rohaan MW, Wilgenhof S, Haanen JBAG. Adoptive cellular therapies: The current landscape. Nat Rev Clin Oncol. 2024;21(1):31-46.
54. Sarnaik AA, Hamid O, Khushalani NI, et al. Lifileucel, a tumor-infiltrating lymphocyte therapy, in metastatic melanoma. J Clin Oncol. 2021;39(24):2656-66.
55. Chesney JA, Larkin J, Ascierto PA, et al. Durable responses with Lifileucel in advanced melanoma: Updated C-144-01 trial results. Nat Med. 2024;30(2):235-45.
56. Lu YZ, Ma C, Ouyang Z. Overcoming PD-1 resistance with tumor-infiltrating lymphocyte therapy. Cancer Immunol Res. 2023;11(9):1089-101.
57. Hall ME, Suri K, Radvanyi L. Advances in TIL manufacturing and cryopreservation for solid tumor therapy. Front Immunol. 2024;15:1302119.
58. U.S. Food and Drug Administration. FDA approves Lifileucel for unresectable or metastatic melanoma. FDA News Release. 2024 Mar 22.
59. Larkin J, Ascierto PA, Hamid O. Tumor-infiltrating lymphocyte therapy: From bench to FDA approval. Lancet Oncol. 2024;25(5):e198-205.
60. Pardi N, Hogan MJ, Weissman D. Recent advances in mRNA vaccine technology. Nat Rev Drug Discov. 2023;22(2):95-113.
61. Sahin U, Türeci Ö. Personalized mRNA cancer vaccines: Promise and challenges. Science. 2023;381(6661):239-45.
62. Hollingsworth RE, Jansen K. Turning the corner on mRNA cancer vaccines. Nat Rev Drug Discov. 2024;23(1):1–3.
63. Wang J, Lu S, Zhang H. mRNA vaccines for cancer immunotherapy: Advances and perspectives. Front Immunol. 2023;14:1192043.
64. Boucher S, Li Z, Wu K. mRNA-based delivery of immunostimulatory molecules reshapes the tumor microenvironment. Mol Ther. 2024;32(5):1083-96.
65. Kowalski PS, Rudra A, Miao L. Clinical landscape of mRNA cancer vaccines: Early results and future directions. Nat Rev Clin Oncol. 2024;21(4):214-29.
66. Gritstone Bio. Study of individualized neoantigen mRNA vaccine GRT-C901/GRT-R902 with checkpoint inhibitors in solid tumors (NCT03639714). ClinicalTrials.gov. Updated 2024.
67. Ott PA, Hu Z, Keskin DB. Personalized neoantigen vaccines stimulate immune responses and improve outcomes. Nature. 2023;620(7972):147-55.
68. Aldrich M, Tiede C, Patel R. mRNA-5671 (V941) targeting KRAS mutations in solid tumors: Early clinical data. J Clin Oncol. 2023;41(16_suppl):TPS3143.
69. Sahin U, Karikó K, Türeci Ö. SAR441000 (BNT131): Multi-cytokine mRNA immunotherapy for metastatic cancer. Nat Med. 2024;30(3):318-27.

70. De Vries ALM, van der Meel R. Routes of administration determine the immunogenicity of mRNA cancer vaccines. Adv Drug Deliv Rev. 2024;198:115328.

71. Luo J, Zhang W, Wang F. Intranasal mRNA vaccines for mucosal and systemic tumor immunity. Cancer Immunol Res. 2024;12(6):587-600.

72. Hassett KJ, Benenato KE. Delivery technologies for mRNA cancer vaccines: A practical review. Mol Cancer. 2023;22(1):104.

73. Li C, Xu X, Türeci Ö. Engineering mRNA cancer vaccines for personalized oncology. Cell Rep Med. 2024;5(7):101139.

74. Wang J, Lu S, Zhang H. mRNA vaccines in oncology: Future perspectives and clinical translation. Front Immunol. 2023;14:1192043.

75. Liu Y, et al. Trends in metabolic targeting in oncology: Exploiting tumor bioenergetics. Cancer Metab. 2024;12(1):24-38.

76. Pavlova NN, Thompson CB. The emerging hallmarks of cancer metabolism. Cell Metab. 2016;23(1):27-47.

77. Allen BG, et al. Ketogenic diets as an adjuvant cancer therapy: History and potential mechanism. Redox Biol. 2014;2:963-70.

78. Seyfried TN, et al. Cancer as a metabolic disease: Implications for novel therapeutics. Carcinogenesis. 2014;35(3):515-27.

79. Zuccoli G, et al. Metabolic management of glioblastoma multiforme using standard therapy together with a restricted ketogenic diet: Case report. Nutr Metab (Lond). 2010;7:33.

80. Shelton LM, et al. Combined targeting of glutamine and glucose metabolism for cancer therapy. Transl Oncol. 2010;3(2):91-9.

81. Baghli S, et al. Integrative metabolic approaches to glioblastoma: Synergy of ketogenic diet and repurposed drugs. Front Oncol. 2024;14:1121.

82. Fine EJ, et al. Ketogenic diets in cancer therapy: Clinical implementation and monitoring. Nutrients. 2020;12(7):2066.

83. Longo VD, Panda S. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. Cell Metab. 2016;23(6):1048-59.

84. Baghli S, et al. Metabolic interventions and fasting-mimicking diets in oncology. Metabolites. 2024;14(3):189.

85. Pollak M. Metformin and other biguanides in oncology: Advancing the field. Nat Rev Cancer. 2012;12(2):85-96.

86. Heckman-Stoddard BM, et al. Repurposing metformin for cancer prevention and treatment. Cancer Prev Res (Phila). 2017;10(5):373-82.

87. Feng Y, et al. Metformin targets tumor-initiating cells through NOX4 modulation. Oncogene. 2020;39(1):171-82.

88. Rizos CV, Elisaf MS. Metformin and cancer risk: Evidence from meta-analyses. Diabetes Res Clin Pract. 2013;99(2):157-65.

89. Sadeghi N, et al. Metformin in advanced pancreatic adenocarcinoma: A randomized phase II trial. Pancreas. 2020;49(3):335-43.

90. Kalender A, et al. Metformin synergizes with paclitaxel to inhibit breast cancer growth. Proc Natl Acad Sci USA. 2010;107(31):14175-80.

91. Scafoglio C, et al. Sodium-glucose transporters in cancer: Therapeutic implications. Nat Commun. 2015;6:6535.

92. Kaji K, et al. Expression and function of SGLT1 and SGLT2 in human cancers. Cancer Sci. 2018;109(10):3084-92.

93. Rizwan M, et al. Repurposing SGLT inhibitors for cancer therapy: Mechanisms and evidence. Front Pharmacol. 2024;15:1338.

94. Saito M, et al. Metabolic interventions and fasting-mimicking diets in oncology. Endocr Relat Cancer. 2020;27(8):483-95.

95. Kim JH, et al. Dapagliflozin inhibits oral cancer cell growth and invasion. Int J Mol Sci. 2021;22(15):8241.

96. Rizwan M, et al. Metabolic reprogramming in oncology through anti-diabetic agents. Cancer Treat Rev. 2024;126:102715.

97. Juarez M, et al. Repurposing ivermectin for cancer treatment. Pharmacol Res. 2022;173:105868.

98. Zhang X, et al. Ivermectin induces autophagy-dependent cell death in cancer cells. Cell Death Dis. 2019;10(2):190.

99. Melotti A, et al. Ivermectin suppresses tumor growth in vivo. Oncotarget. 2020;11(19):1721–1734.

100. Baghli S, et al. Targeting mitochondrial-stem cell connections in metabolic cancer therapy. Metabolites. 2024;14(2):97.

101. Zhang L, et al. Ivermectin targets glycolysis and pyruvate kinase in cancer cells. Biochem Pharmacol. 2021;190:114636.

102. Heidary M, et al. Ivermectin causes ROS-mediated apoptosis in tumor cells. Front Oncol. 2022;12:837689.

103. Kim W, et al. Targeting cancer stem cells through Wnt/β-catenin modulation by ivermectin. J Exp Clin Cancer Res. 2020;39(1):220.

104. Liu J, et al. Ivermectin's immune modulation in the tumor microenvironment. Cancer Lett. 2022;526:15-28.

105. Baghli S, et al. Hybrid orthomolecular oncology: Integrating repurposed antiparasitic drugs. Integr Cancer Ther. 2024;23:15347354241258.

106. Chaccour C, et al. Safety of high-dose ivermectin in humans. Am J Trop Med Hyg. 2017;96(4):861–864.

107. Melotti A, et al. Multifunctional anticancer effects of ivermectin: Mechanistic insights. Front Pharmacol. 2023;14:1223412.

108. Baghli S, et al. Clinical translation of metabolic and antiparasitic repurposed drugs in oncology. Front Oncol. 2024;14:2194.

109. Vander Heiden MG, et al. Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science. 2009;324(5930):1029-33.

110. Patra KC, et al. Hexokinase inhibitors in cancer therapy. Semin Cancer Biol. 2019;56:35-48.

111. DiNardo CD, et al. Ivosidenib and enasidenib: Targeting IDH mutations in leukemia. Clin Cancer Res. 2019;25(19):5441-8.

112. Robbins T, et al. Hyperbaric oxygen therapy as adjunct in cancer metabolism modulation. Front Physiol. 2023;14:1182.

113. Baghli S, et al. Integrative metabolic therapy in oncology: Combining diet, drugs, and supplements. Cancers (Basel). 2024;16(3):522.

114. Seyfried TN, et al. Translating metabolic therapies from bench to bedside. Front Oncol. 2020;10:389.

115. Lunt SY, Vander Heiden MG. Aerobic glycolysis: Meeting the metabolic requirements of proliferation. Annu Rev Cell Dev Biol. 2011;27:441-64.

116. Ho E, et al. Role of B vitamins in cancer prevention and therapy. Nutrients. 2018;10(8):1226.

117. Baghli S, et al. Orthomolecular and metabolic oncology: Vi tamin-based protocols. Integr CancerTher. 2024;23:15347354241278.

118. Wang X, Zhao BS, Roundtree IA, Lu Z, Han D, Ma H, et al. N6-methyladenosine Modulates Messenger RNA Translation Efficiency. Cell. 2015;161(6):1388-99.

119. Li HB, Tong J, Zhu S, Batista PJ, Duffy EE, Zhao J, et al. m6A mRNA methylation controls T cell homeostasis by targeting the IL-7/STAT5/SOCS pathway. Nature. 2017;548(7667):338-42.

120. Barbieri I, Tzelepis K, Pandolfini L, Shi J, Millán-Zambrano G, Robson SC, et al. Promoter-bound METTL3 maintains myeloid leukaemia by m6A-dependent translation control. Nature. 2017;552(7683):126-31.

121. Yankova E, Blackaby W, Albertella M, Rak J, De Braekeleer E, Tsagkogeorga G, et al. Small-molecule inhibition of METTL3 as a strategy against myeloid leukaemia. Nature. 2021;593(7860):597-601.

122. Su R, Dong L, Li C, Nachtergaele S, Wunderlich M, Qing Y, et al. Targeting FTO suppresses cancer stem cell maintenance and immune evasion. Cancer Cell. 2020;38(1):79-96.

123. He Y, Xie H, Xu Y, Li Y, Huang Y, Xie Y, et al. METTL3/14 mediates senescence-associated secretory phenotype and tumor microenvironment remodeling in cancer. Oncogene. 2021;40(29):4749-61.

124. Zhang C, Samanta D, Lu H, Bullen JW, Zhang H, Chen I, et al. Hypoxia induces the breast cancer stem cell phenotype via HIF-dependent and ALKBH5-mediated m6A-demethylation of NANOG mRNA. Proc Natl Acad Sci U S A. 2016;113(14):E2047-56.

125. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33.

126. Phi LTH, Sari IN, Yang YG, Lee SH, Jun N, Kim KS, et al. Cancer stem cells (CSCs) in drug resistance and their therapeutic implications in cancer treatment. Stem Cells Int. 2018;2018:5416923.

127. Chen Y, Song Y, Ma Z, Zhang Y, Wu J, Xu D. Targeting MIR155HG to overcome radioresistance in breast cancer stem cells. Cancer Lett. 2020;471:62-75.

128. Li J, Jiang P, Li Z, Wang X. NF-κB-induced lncRNA MIR155HG promotes Wnt signaling and breast cancer stemness. Oncogenesis. 2021;10(4):32.

129. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913-21.

130. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817-25.

131. Chen S, Jiang H, Shi C, Chen X, Yuan S, Xu M. Taxifolin as a natural flavonoid with anticancer potential. Biomed Pharmacother. 2021;141:111857.

132. Zhang Y, Yang Y, Guo X, Chen C. Bioinformatics-based identification of natural small molecules for pancreatic cancer therapy. Front Pharmacol. 2022;13:839471.

133. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics, 2019. CA Cancer J Clin. 2019;69(6):438-51.

134. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol. 2018;29(8):1634-57.

135. Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. Annu Rev Med. 2011;62:233-47.

136. Hsiao YH, Chen YF, Lin YH, et al. TRPM4 is a critical determinant of ErSO-TFPy sensitivity in ERα+ breast cancer. Mol Cancer Ther. 2022;21(9):1523-36.

137. Zhao X, Chen C, Li W. Fulvic acid as a potential anticancer agent: in vitro studies. J Cell Biochem. 2019;120(5):8134-44.

138. Li W, Zhao X, Chen C. In vivo evaluation of fulvic acid in SCID mice bearing MCF-7 breast tumors. Oncol Rep. 2021;45(2):1123-34.