Precision Oncology: Current Status of Targeted Therapies and Prospective Advances

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ABSTRACT

With an emphasis on precision intervention that blocks particular biochemical pathways necessary for tumor growth and survival, targeted therapies in cancer provide a revolutionary approach to treatment. This review examines the range of targeted medicines, including biologics, small molecule inhibitors, and cell and gene therapies, emphasizing their benefits, drawbacks, and new developments. Cancer-driving kinases and other signaling proteins can be directly inhibited by small molecule inhibitors, which frequently work intracellularly. Monoclonal antibodies and other biologics use extracellular targets to interfere with signaling and identify cancer cells for immune destruction. By altering biological pathways or specifically targeting cancer genomes, cell and gene therapies—such as CAR-T cells and CRISPR-based interventions—offer individualized approaches. Notwithstanding their accuracy, each modality has drawbacks such as biologics may be constrained by immune-related side effects, cell and gene therapies are difficult to produce and deliver, and small molecule inhibitors may cause drug resistance through mutations. Combination treatments, innovative delivery systems, and adaptive dosing techniques are some of the current solutions that try to reduce these problems. From drug development and patient stratification to real-time treatment efficacy monitoring, artificial intelligence presents a viable path toward optimizing targeted medicines. AI can detect resistance patterns, find predictive biomarkers, and recommend combinatory strategies by evaluating large datasets, opening the door to customized, adaptable cancer treatments.

Keywords: Precision oncology, Targeted therapies, Small molecule inhibitors, Monoclonal antibodies, Gene editing

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Introduction—The Advent of Personalized Therapies in Oncology

In the last 50 years, there has been a significant evolution in cancer treatment, transitioning from general chemotherapies to more targeted and individualized therapies. Initially, treatment options were mainly surgery, radiation, and chemotherapy, all focused on eliminating cancer cells but frequently harming healthy tissues. Although these methods were successful in certain instances, they lacked precision and often led to high toxicity, thus limiting their effectiveness in the long run.

In the 1970s and 1980s, a shift from conventional treatments began with the emergence of targeted therapies. These medications, such as tamoxifen used for breast cancer, were designed to target specific molecular markers linked to the growth and survival of cancer cells, providing more accuracy and fewer side effects compared to traditional chemotherapy. This period was succeeded by the introduction of monoclonal antibodies in the 1990s, with drugs like rituximab transforming treatment by specifically addressing cancerous cells while preserving healthy ones.[1]

The Human Genome Project in the early 2000s brought about a significant change in cancer treatment by providing a deeper understanding of the molecular and genetic aspects of cancer. This led to the emergence of small molecule inhibitors, including tyrosine kinase inhibitors (TKIs), which aim at disrupting oncogenic signaling pathways crucial for tumor survival. Drugs like imatinib, designed to target the BCR-ABL fusion protein in chronic myeloid leukemia (CML), exemplified the concept of precision medicine by showing how a medication can specifically address a molecular abnormality responsible for driving cancer while minimizing harm to healthy cells.

Over the past 10 years, there have been advancements in cancer treatment due to the emergence of next-generation targeted therapies, immune checkpoint inhibitors, and the incorporation of cell and gene therapies. To combat drug resistance, a prevalent issue in cancer treatment, small molecule inhibitors like Osimertinib have been created. These inhibitors function by specifically targeting mutations that arise during treatment, such as EGFR mutations in non-small cell lung cancer (NSCLC), thereby overcoming the limitations of initial therapies.

The emergence of immunotherapies, especially immune checkpoint inhibitors such as pembrolizumab and nivolumab, has fundamentally changed the approach to leveraging the immune system against cancer. These treatments work by blocking signals that inhibit T cells from attacking tumors, leading to long-lasting responses in cancers like melanoma and lung cancer.

Additionally, cell and gene therapies, such as CAR T-cell therapy, are pushing the boundaries of cancer treatment. By modifying a patient's own immune cells to target cancer, therapies like Axicabtagene ciloleucel for B-cell lymphomas have achieved impressive results, introducing a new approach for cancers that don't respond to traditional treatments. Furthermore, gene editing technologies like CRISPR are being investigated for their potential to fix cancer-driving mutations, expanding the possibilities in oncology.

The significance of this new class of targeted, immunological, and gene therapies lies in its ability to provide individualized treatment plans, lower systemic toxicity, and induce long-term remission—even in malignancies that were previously thought

to be incurable. A promising move toward more efficient and less hazardous cancer treatment methods is the emphasis on comprehending tumor biology at the molecular level, which keeps opening up new therapeutic opportunities. Figure 1 depicts various personalized cancer treatment modalities and their mechanism of action.

Small Molecule Targeted Therapies

Small molecule targeted therapies are a class of cancer drugs (<500 Da) designed to specifically target and inhibit key proteins involved in cancer cell proliferation, survival, or metastasis.[2,3–9] Unlike traditional chemotherapy, which non-selectively attacks rapidly dividing cells, small-molecule inhibitors aim at molecular abnormalities specific to cancer cells. These therapies are typically administered orally and can penetrate the cell membrane to interfere with intracellular targets, making them particularly effective for modulating various signaling pathways involved in oncogenesis.

Classes of Small Molecule Inhibitors and Their Mechanisms of Action

There are various kinds of small molecule inhibitors that target distinct biochemical pathways necessary for the survival of cancer cells. Table 1 summarizes the US Food and Drug Administration (US FDA)-approved drugs currently on the market. The main classes are as follows:

Inhibitors of Tyrosine Kinase (TKIs)

Non-receptor and receptor tyrosine kinases (RTKs). Action Mechanism: Tyrosine residues on growth factor receptors, including epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and vascular epidermal growth factor receptor (VEGFR), are phosphorylated by TKIs, which inhibits downstream signaling pathways like the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR cascades. Apoptosis and decreased cancer growth result from the suppression of these mechanisms, which are essential for cell survival and proliferation.[10] Some examples of FDA-approved TKIs are Imatinib, which targets BCR-ABL (Philadelphia chromosome) in CML, Erlotinib which inhibits EGFR and is approved in NSCLC, and Lapatinib which is a dual EGFR and HER2 and is used in breast cancer. Sotorasib (Lumakras®) is the first targeted therapy for NSCLC with KRASG12C mutation, while Adagrasib (Krazati®), another class of drug targeting the same mutation in combination with Cetuximab (Erbitux®), was recently approved by the US FDA in colorectal cancer.

Proteasome Inhibitors

These inhibitors block the proteasome's ability to degrade proteins, leading to the accumulation of misfolded or damaged proteins in the cell. This causes cellular stress and apoptosis, particularly in cancer cells that have higher proteasome activity to manage abnormal protein production. Some examples are Bortezomib® and Carfilzomib® used in multiple myeloma treatment.

Cyclin-Dependent Kinase (CDK) Inhibitors

CDKs regulate the cell cycle, and their inhibition leads to cell cycle arrest, especially in rapidly proliferating cancer cells. This disruption prevents cancer cells from

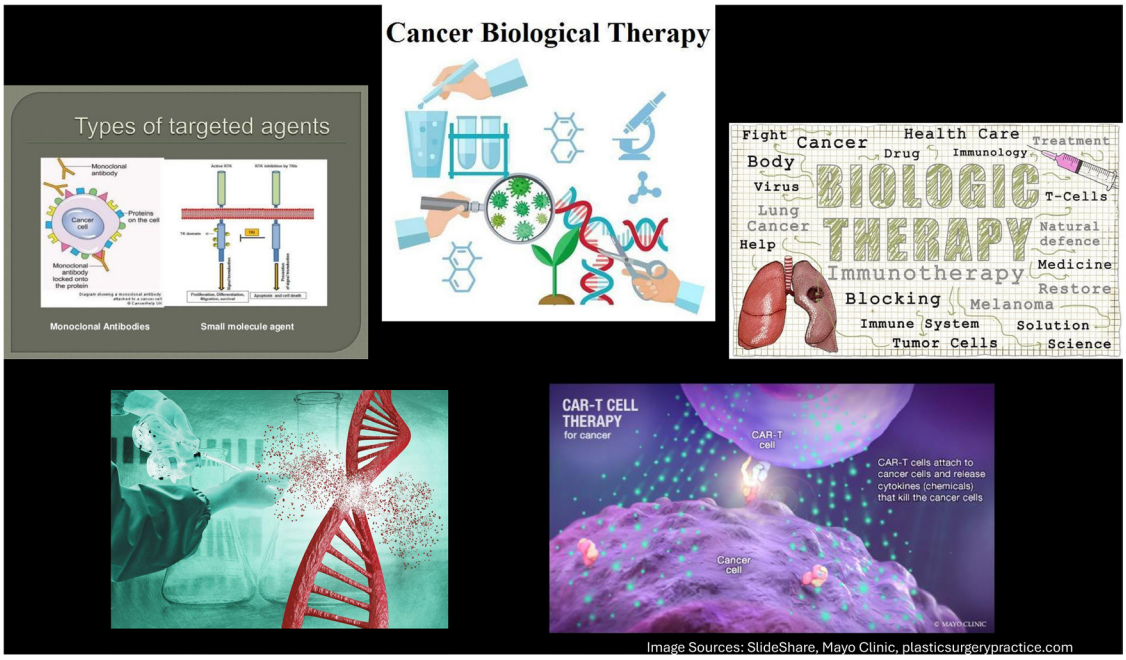

Fig 1| An overview of the advent of various personalized therapies and their mechanism of action developed for cancer treatment

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Table 1 | The US Food and Drug Administration (US FDA)-approved small molecule inhibitors and their mechanism of action

Drug Name	Mechanism of Action	Approved Indications
Alectinib	ALK inhibitor	ALK-positive non-small cell lung cancer (NSCLC)
Erlotinib	EGFR tyrosine kinase inhibitor	EGFR-mutated NSCLC, pancreatic cancer
Dabrafenib	BRAF inhibitor	BRAF V600E-mutant melanoma, NSCLC
Imatinib	BCR-ABL tyrosine kinase inhibitor	Chronic myeloid leukemia (CML), gastrointestinal stromal tumors (GIST)
Vemurafenib	BRAF V600 inhibitor	BRAF V600-mutant melanoma
Olaparib	PARP inhibitor	BRCA-mutated ovarian, breast, pancreatic, and prostate cancers
Lenvatinib	VEGFR, FGFR, and PDGFR kinase inhibitor	Thyroid cancer, hepatocellular carcinoma (HCC), renal cell carcinoma (RCC)
Sunitinib	VEGFR, PDGFR, c-Kit inhibitor	RCC, GIST
Crizotinib	ALK and ROS1 inhibitor	ALK or ROS1-positive NSCLC
Trametinib	MEK inhibitor	BRAF V600-mutant melanoma (in combination with dabrafenib)
Sotorasib	KRAS G12C inhibitor	NSCLC

transitioning through critical checkpoints like G1 to S phase. Palbociclib and Abemaciclib are inhibitors of CDK4/6 used in hormone-receptor-positive breast cancer.

PARP Inhibitors

PARP inhibitors block the repair of single-stranded DNA breaks by inhibiting the PARP enzyme, leading to the accumulation of DNA damage and subsequent cancer cell death, particularly in cells with existing BRCA1/2 mutations which are deficient in homologous recombination repair. Olaparib and Rucaparib are approved in BRCA-mutated breast and ovarian cancers.

Histone Deacetylase (HDAC) Inhibitors

HDAC inhibitors cause the accumulation of acetylated histones, leading to the activation of tumor suppressor genes and induction of cancer cell apoptosis. They also affect non-histone proteins, which play roles in cell cycle regulation and apoptosis. Vorinostat and Romidepsin are two such inhibitors that have been approved for cutaneous cell lymphoma.

BRAF and MEK Inhibitors

BRAF and MEK inhibitors specifically target mutations in the BRAF gene (commonly BRAF V600E mutation) and inhibit the MAPK/ERK pathway, which is essential for cell growth and division. Vemurafenib targets BRAF V600E used in melanoma while Trametinib inhibits MEK, often used in combination with BRAF inhibitors.

FLT3 Inhibitors

FMS-like tyrosine kinase 3 (FLT3) blocks the activity of FLT3, a receptor tyrosine kinase that is mutated in a subset of acute myeloid leukemia (AML) cases, leading to impaired proliferation and survival of leukemic cells. Midostaurin is approved for FLT3-mutated AML.

Advantages of Small Molecule Inhibitors in Cancer Therapy

Accuracy and Specificity

Small molecule medications are made to target particular proteins or pathways—like kinases or growth factor receptors—that are implicated in the development of cancer. Compared to conventional chemotherapy, this selectivity reduces systemic toxicity by minimizing damage to healthy cells.

Oral Dispensing

Compared to intravenous treatments, several small molecule medicines are more convenient and improve patient adherence when taken orally.

Focusing on Intracellular Substances

The range of actionable cancer-driving proteins is increased by small compounds, which, in contrast to monoclonal antibodies, can pass through cell membranes and inhibit intracellular targets.

Possibility of Combination Treatments

To increase effectiveness and get around resistance mechanisms, small molecules are frequently utilized in conjunction with other treatments, such as immunotherapies or chemotherapies.

Biomarker-Based Methods

Complementary diagnostics that detect individuals with particular genetic mutations or protein expressions (such as EGFR, ALK, or BRAF mutations) are frequently associated with the development of small molecule medicines. This makes it possible to implement individualized treatment plans, which enhances results.

Quick Pharmacokinetics

Because small compounds usually have shorter half-lives, dose modifications can be made quickly in response to side effects or ineffectiveness.

Large Molecule (Biologics) Targeted Therapies in Cancer

Biologics, also known as large molecule targeted medicines, are a revolutionary approach to the treatment of cancer, typically monoclonal antibodies, or other biologically derived substances. Large molecules target cell-surface receptors or ligands and act on certain pathways or molecules implicated in cancer growth, proliferation, or survival, in contrast to small molecule medicines, which are chemically manufactured and frequently enter cells. By minimizing off-target effects, this specificity enhances efficacy and lowers toxicity.[11,12] Table 2 lists some of the biological therapies currently approved in different indications of cancer.

Proteins that are essential for tumor development, angiogenesis, immune evasion, or metastatic dissemination can be inhibited or their functions altered by large molecule targeted therapy.

Table 2 | Some of the biological therapies and their mechanism of action currently approved for cancer treatment

Drug Name	Mechanism of Action	Approved Indications
Trastuzumab emtansine	HER2-targeted ADC	HER2-positive breast cancer
Brentuximab vedotin	CD30-targeted ADC	Hodgkin lymphoma, anaplastic large cell lymphoma
Tislelizumab	PD-1 inhibitor	Esophageal squamous cell carcinoma
Talquetamab	Bispecific targeting GPRC5D and CD3	Multiple myeloma
Mosunetuzumab	CD20 and CD3 bispecific	Follicular lymphoma
Glofitamab	CD20 and CD3 bispecific	Diffuse large B-cell lymphoma
Mirvetuximab soravtansine	Folate receptor-alpha- targeted ADC	Ovarian cancer
Tebentafusp	gp100 and CD3 bispecific (TCR-based)	Uveal melanoma
Elranatamab	BCMA and CD3 bispecific	Multiple myeloma
Epcoritamab	CD20 and CD3 bispecific	Diffuse large B-cell lymphoma
Ipilimumab	CTLA-4 inhibitor	Unresectable or metastatic melanoma
Pembrolizumab (Keytruda)	PD-1	Melanoma, NSCLC, head and neck SCC, Hodgkin lymphoma, urothelial carcinoma, colorectal cancer, gastric cancer, esophageal cancer, cervical cancer, endometrial cancer
Nivolumab (Opdivo)	PD-1	Melanoma, NSCLC, Renal cell carcinoma, hepatocellular carcinoma, esophageal SCC, gastric cancer, colorectal cancer
Cemiplimab (Libtayo)	PD-1	Cutaneous SCC, NSCLC, basal cell carcinoma
Atezolizumab (Tecentriq)	PD-L1	NSCLC, urothelial carcinoma, triple-negative breast cancer
Avelumab (Bavencio)	PD-L1	Merkel cell carcinoma, urothelial carcinoma, renal cell carcinoma
Durvalumab (Imfinzi)	PD-L1	NSCLC, biliary tract cancer, endometrial cancer
Ipilimumab (Yervoy)	CTLA-4	Melanoma, NSCLC, renal cell carcinoma, colorectal cancer
Relatlimab + Nivolumab (Opdualag)	LAG-3 + PD-1	Unresectable/metastatic melanoma
Durvalumab (Imfinzi)	PD-L1	Non-small cell lung cancer, small cell lung cancer, biliary tract cancer
Dostarlimab (Jemperli)	PD-1	Endometrial cancer
Cemiplimab (Libtayo)	PD-1	Squamous cell carcinoma, basal cell carcinoma, non-small cell lung cancer

These treatments have demonstrated impressive efficacy in treating a variety of cancer types, providing a more individualized and efficient oncology strategy. The main classes of big molecule targeted therapies, their modes of action, and FDA-approved treatments for various cancer indications are reviewed here.

1. mAbs, or monoclonal antibodies

Lab-produced monoclonal antibodies attach to particular antigens on cancer cells or other pertinent targets in the tumor microenvironment, acting similarly to natural antibodies.[13–16] Through a variety of methods, such as immune-mediated cytotoxicity, growth factor signaling inhibition, or direct delivery of cytotoxic chemicals to cancer cells, these antibodies can prevent the growth and survival of cancer cells.

Mechanisms of Action

- **Targeting Tumor Antigens:** mAbs can bind to antigens on cancer cells, marking them for destruction by immune cells (e.g., antibody-dependent cellular cytotoxicity or complement-mediated cytotoxicity).
- **Inhibiting Growth Factor Signaling:** mAbs can block growth factor receptors, such as EGFR or HER2, that are overexpressed in certain cancers, thereby preventing signal transduction necessary for tumor proliferation.
- **Conjugated mAbs (Antibody-Drug Conjugates, ADCs):** These mAbs are attached to cytotoxic agents, allowing targeted delivery of chemotherapy directly to cancer cells while minimizing systemic toxicity.

FDA-Approved Monoclonal Antibodies in Cancer

- **Trastuzumab (Herceptin):** It is approved for HER2-positive breast cancer and HER2-positive gastric cancer. Trastuzumab binds to the HER2 receptor and inhibits downstream signaling, ultimately leading to cell death.
- **Rituximab (Rituxan):** This targets CD20, a surface marker on B cells, and is used for the treatment of B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL). It promotes cell death through antibody-dependent cytotoxicity and complement activation.
- **Pembrolizumab (Keytruda) and Nivolumab (Opdivo):** These immune checkpoint inhibitors target PD-1 on T cells, blocking the inhibitory signals that prevent immune cells from attacking cancer cells. It is approved for a wide range of

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cancers including melanoma, NSCLC, renal cell carcinoma (RCC), and more.
- **Cetuximab (Erbitux):** This targets EGFR and is approved for metastatic colorectal cancer and head and neck squamous cell carcinoma. It inhibits EGFR-mediated signaling pathways involved in cancer proliferation and survival.

2. Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are a subclass of monoclonal antibodies that modulate the immune system's response to cancer. Tumor cells often evade immune destruction by exploiting checkpoint pathways, which are negative regulators of immune activation. Checkpoint inhibitors "release the brakes" on the immune system, allowing T cells to attack cancer cells.[17–20]

Mechanisms of Action:
- **PD-1/PD-L1 Blockade:** PD-1 is an immune checkpoint on T cells, and PD-L1 is its ligand, often expressed on tumor cells. Binding of PD-L1 to PD-1 inhibits T-cell activation. Anti-PD-1 and anti-PD-L1 antibodies block this interaction, enhancing T-cell-mediated immune response against tumors.
- **CTLA-4 Blockade:** CTLA-4 is another checkpoint receptor on T cells that inhibits their activation. Anti-CTLA-4 antibodies block this inhibitory signal, leading to enhanced immune activity against cancer cells.

FDA-Approved Checkpoint Inhibitors:
- **Pembrolizumab (Keytruda)**: It is approved for a variety of cancers, including melanoma, NSCLC, bladder cancer, and microsatellite instability-high (MSI-H) tumors. It blocks PD-1, allowing T cells to attack tumors.
- **Nivolumab (Opdivo)**: Similar to pembrolizumab, it targets PD-1 and is approved for cancers such as melanoma, NSCLC, and RCC.
- **Atezolizumab (Tecentriq)**: It targets PD-L1 and is approved for urothelial carcinoma and NSCLC.
- **Ipilimumab (Yervoy)**: A CTLA-4 inhibitor, primarily used in combination with nivolumab for melanoma and other cancers.

3. Antibody-Drug Conjugates (ADCs)

ADCs are an innovative class of large-molecule therapies that combine the targeting specificity of monoclonal antibodies with the potent cell-killing activity of cytotoxic drugs.[20,21] The antibody portion of the ADC binds to specific antigens on the cancer cell surface, and once internalized, the cytotoxic drug is released inside the cancer cell, leading to targeted cell death.

Mechanisms of Action:
- **Targeted Cytotoxicity**: The antibody binds to the cancer cell, and once the ADC is internalized, the cytotoxic agent (e.g., a microtubule inhibitor or DNA-damaging drug) is released to kill the cell.
- **Reduced Off-Target Effects:** The targeted delivery of chemotherapy reduces damage to healthy cells, thereby lowering the side effects typically associated with systemic chemotherapy.

FDA-Approved ADCs:
- **Brentuximab Vedotin (Adcetris):** It targets CD30 and is approved for Hodgkin lymphoma and anaplastic large cell lymphoma. It delivers a microtubule-disrupting agent to CD30-positive cells, inducing cell death.
- **Trastuzumab Emtansine (Kadcyla):** A HER2-targeting ADC approved for HER2-positive breast cancer. It combines trastuzumab with a cytotoxic agent (DM1), providing HER2-specific chemotherapy delivery.

4. Cytokine-based Therapies

Cytokines are signaling proteins that modulate immune responses, and certain cytokine-based therapies have been developed to boost the body's immune response against cancer.[22,23] These therapies are less specific than monoclonal antibodies but have shown efficacy in certain cancer types.

Mechanisms of Action:
- **Immune Activation:** Cytokines, such as interleukins and interferons, enhance the activation and proliferation of immune cells like T cells and natural killer (NK) cells, which then target and destroy cancer cells.

FDA-Approved Cytokine Therapies:
- **Interleukin-2 (IL-2, Proleukin):** It is approved for metastatic RCC and metastatic melanoma. IL-2 stimulates the proliferation of T cells and NK cells, which can attack cancer cells.
- **Interferon-alpha (Intron A):** It is approved for certain types of leukemia, melanoma, and Kaposi's sarcoma. It boosts immune responses and inhibits tumor cell proliferation.

Gene Therapies in Oncology

Principles of Gene Therapy

In oncology, gene therapy is a novel method of treating cancer by directly changing the genetic makeup of immune or cancer cells to strengthen their resistance to the illness. Targeted delivery of therapeutic genes into a patient's cells to either fix damaged genes add new genes, or quiet dangerous ones is the fundamental idea of gene therapy. To do this, a number of vectors are used, most frequently modified viruses, which serve as carriers to transfer the desired genetic material into cells. Finding a particular genetic mutation or pathway that promotes tumor growth or treatment resistance is the first step in the procedure. By focusing on this mutation, gene therapy seeks to alter the cell's behavior, either causing malignant cells to die or restoring normal function. On the other hand, gene therapy can improve the immune system's ability to identify and combat cancer cells by altering immune cells (such as

T-cells) to more efficiently target particular cancer antigens, as demonstrated by chimeric antigen receptor (CAR) T-cell treatment.[24]

History of Gene Therapies in Oncology

Since its beginning in the 1970s, gene therapy has experienced substantial growth. Technical obstacles, such as the difficulty of safely and successfully delivering genes to target cells and the difficulty of regulating the expression of the inserted genes, dampened the initial optimism. In 1990, a patient with severe combined immunodeficiency (SCID) was treated in the first human gene therapy trial. The potential of gene therapy to address the genetic foundations of malignancies immediately made cancer research a key emphasis, even though oncology was not the first field to benefit. Serious side effects like immunological reactions to viral vectors and the possibility of insertional mutagenesis, in which the introduced gene could disrupt normal gene function and produce additional difficulties like leukemia, were among the setbacks that plagued early experiments in the 1990s and early 2000s. Progress was further slowed by safety concerns following the sad death of Jesse Gelsinger in 1999 during a gene therapy trial.

The use of gene therapy in oncology has increased because of developments in vector design, gene editing technologies, and immunotherapy. A significant milestone was reached in the mid-2010s when CAR T-cell treatments were approved, proving that gene therapies could effectively treat hematologic malignancies.[25,26]

Important mechanisms consist of:

Gene addition is the process of replacing damaged or absent genes with functional ones.
Gene silencing is the process of preventing oncogenes from being expressed by RNA interference (RNAi) or other techniques.
Gene editing: Methods such as CRISPR-Cas9 enable accurate gene modification to eliminate hazardous sequences or fix mutations.
Oncolytic viral therapy: Using genetically modified viruses that specifically attack and destroy cancer cells while simultaneously triggering an anti-tumor immune response is known as oncolytic viral therapy.

Types of Gene Therapies Available in the Market

Treatments Using RNAi: RNAi is a method that inhibits the production of certain genes, especially oncogenes. These treatments can lower the expression of genes linked to tumor growth by introducing tiny interfering RNAs (siRNAs) into the body. For instance, RNAi treatments are being investigated for tumors that overexpress vascular endothelial growth factor (VEGF), which contributes to angiogenesis.[27]

Treatments Using Gene Editing: With the development of CRISPR-Cas9 technology, it is now possible to directly edit cell mutations that cause cancer. The technology holds great promise for tumors caused by particular genetic defects, enabling precise DNA-level changes, even if the majority of CRISPR-based cancer treatments are still in clinical trials.[28]

Treatments Using Oncolytic Viral Therapy: Genetically modified viruses are used in oncolytic viral therapy to specifically infect and lyse cancer cells. Talimogene laherparepvec (T-VEC), an oncolytic herpesvirus authorized for the treatment of melanoma, is one of the prominent instances. T-VEC triggers a more comprehensive immune response against cancer in addition to directly killing tumor cells.[29]

One of the most effective gene therapy approaches in oncology is **CAR-T cell treatment**. By altering a patient's T-cells to express a receptor that identifies particular antigens on cancer cells, this treatment improves the immune system's capacity to identify and eliminate malignant cells. The first CAR T-cell therapies approved were for hematologic cancers like B-cell acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL). Products such as Kymriah® (tisagenlecleucel) and Yescarta® (axicabtagene ciloleucel) have set the stage for broader applications.[30]

CAR-T Cell Therapies

Cancer immunotherapy has been transformed by the novel adoptive cell transfer technique known as chimeric antigen receptor T-cell (CAR-T) treatment. The receptors expressed by CAR-T cells are genetically modified to specifically target cancer cells. The procedure starts with the collection of a patient's T cells, which are subsequently altered to express a CAR in a lab. An extracellular antigen-recognition domain, usually derived from a monoclonal antibody that recognizes a tumor-associated antigen, a transmembrane domain, and one or more intracellular signaling domains that activate the T cell upon antigen binding comprise this receptor, which is a fusion protein.[31]

Reintroducing the patient to the CAR-T cells causes T-cell activation, proliferation, and cytotoxicity by binding to certain antigens on the surface of cancer cells. Through processes including the release of cytolytic molecules (such as granzyme and perforin) and pro-inflammatory cytokines like tumor necrosis factor (TNF) and interferon-gamma (IFN-γ), the tumor cells are destroyed. Direct tumor destruction, immunological recruitment, and long-lasting T-cell memory to fight off lingering illness are the outcomes.

CAR-T Cell Therapy Types

Based on how the CAR constructs are generated and which particular cancer antigens they target, CAR-T therapy can be categorized.

First-generation CARs: Usually produced from the CD3ζ chain, these CARs have only one signaling domain and one antigen-recognition domain. They established the groundwork for future CAR-T developments despite their limited clinical effectiveness because of inadequate T-cell activation and durability.

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Second-generation CARs: T-cell activation, proliferation, and persistence have been enhanced by the inclusion of a co-stimulatory signaling domain (such as CD28 or 4-1BB) in addition to CD3ζ. This category includes the majority of FDA-approved CAR-T treatments, which provide a balance between safety and efficacy.

Third-generation CARs: These CARs combine several co-stimulatory domains (such as CD28 and 4-1BB) to further improve T-cell activity. The clinical utility of third-generation CARs is still being investigated, despite encouraging preclinical evidence.

Incorporating cytokine signaling molecules (such as IL-12), **fourth-generation CARs** (TRUCKs, or T cells Redirected for Universal Cytokine Killing) improve anti-tumor activity by boosting the immune response of CAR-T cells as well as by attracting and activating additional immune cells in the tumor microenvironment.

Fifth-Generation CARs: These more recent constructions have domains that connect cytokine receptors and T-cell receptor (TCR) activation. Their goals are to oppose tumor inhibitory signals and enhance CAR-T cell proliferation and persistence in hostile tumor environments.

Compared to their application in hematologic malignancies, CAR-T cell treatments for solid tumors are still in the experimental stage and have had less success. This is because solid tumors present special obstacles, including heterogeneity of antigens, an immunosuppressive tumor microenvironment, and trouble directing CAR-T cells to the tumor site. Nonetheless, a number of CAR-T treatments are being studied in clinical trials for different solid tumors, and some of them are showing encouraging outcomes.[32–34]

Glioblastoma

- **Target:** EGFRvIII (a mutant form of the EGFR protein specific to glioblastoma)- While initial trials showed some tumor shrinkage, EGFRvIII is not expressed uniformly in all glioblastoma cells, leading to incomplete responses. Efforts are ongoing to target multiple antigens or to modify the tumor microenvironment to improve efficacy.[35]

Ovarian Cancer

- **Target:** MUC16 (a glycoprotein overexpressed in ovarian cancer cells)- Early-phase clinical trials have demonstrated some anti-tumor activity but significant challenges remain, particularly in overcoming the immunosuppressive tumor microenvironment of ovarian cancer.[36]

Prostate Cancer

- **Target:** PSMA (prostate-specific membrane antigen)—Initial trials have shown some efficacy in metastatic prostate cancer, but responses are generally short-lived. There is ongoing work to enhance CAR-T cell persistence and activity.[37]

Pancreatic Cancer

- **Target:** Mesothelin (a tumor-associated antigen overexpressed in pancreatic cancer)—Although preclinical data have shown potential, early clinical trials have faced issues with poor CAR-T cell persistence and an immunosuppressive environment within pancreatic tumors. New strategies, such as combining CAR-T therapy with checkpoint inhibitors or modifying the CAR design, are being explored.[38]

Lung Cancer

- **Target:** HER2, MUC1, or mesothelin—Some early-phase clinical trials have reported minor tumor regressions, but the dense stroma and poor infiltration of CAR-T cells into lung tumors present significant obstacles. Approaches to modify the tumor microenvironment are currently under investigation.

Colorectal Cancer

- **Target:** CEA (carcinoembryonic antigen)—Preclinical studies have shown promising anti-tumor effects, but clinical trials are still ongoing to determine efficacy and safety. The immunosuppressive nature of colorectal tumors has been a challenge, necessitating combination approaches.[39]

Table 3 summarizes available cell and gene therapy modalities in cancer.

Advantages of Large Molecule Targeted Therapies in Cancer Immunotherapies

Durable Responses

Immunotherapies, such as immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1 and anti-CTLA-4 antibodies), can lead to long-lasting tumor control by reactivating the immune system.

Broad Spectrum of Targets

These therapies can target multiple tumor types and often work across a variety of cancer settings.

Immune Memory

Activated immune cells can provide long-term protection against cancer recurrence, functioning as a "living drug."

Synergy with Other Therapies

Immunotherapies are often combined with traditional treatments (e.g., chemotherapy, radiation) or other targeted agents for enhanced efficacy.

Antibody-Drug Conjugates

Targeted Cytotoxicity

ADCs combine the specificity of monoclonal antibodies with the potency of cytotoxic drugs, delivering the payload directly to cancer cells while sparing normal tissues.

Reduced Systemic Toxicity

By selectively delivering drugs, ADCs minimize off-target effects associated with traditional chemotherapies.

Table 3 | Summary of available cell and gene therapy modalities and their mechanism of action for different indications of cancer

Therapy	Type	Mechanism	Indication
Abecma (idecabtagene vicleucel)	CAR-T	Targets BCMA (B-cell maturation antigen) on myeloma cells	Multiple myeloma
Breyanzi (lisocabtagene maraleucel)	CAR-T	Targets CD19 on B cells	Large B-cell lymphoma
Carvykti (ciltacabtagene autoleucel)	CAR-T	Targets BCMA on myeloma cells	Relapsed/refractory multiple myeloma
Kymriah (tisagenlecleuc el)	CAR-T	Targets CD19 on B cells	Acute lymphoblastic leukemia (ALL) and lymphoma
Tecartus (brexucabtagen e autoleucel)	CAR-T	Targets CD19	Mantle cell lymphoma, ALL
Afami-cel	TCR-T	Targets MAGE-A4 antigen on synovial sarcoma cells	Synovial sarcoma (experimental)
Lifileucel	TIL	Tumor-infiltrating lymphocytes that recognize and attack cancer cells	Advanced melanoma
Tebentafusp	TCR bispecific	Targets gp100 and CD3 to redirect T cells to melanoma cells	Uveal melanoma
Imlygic (talimogene laherparepvec)	Oncolytic virus	Genetically modified herpesvirus to infect and lyse melanoma cells	Advanced melanoma
Obe-cel	CAR-T	Next-gen CAR-T therapy for relapsed/refractory cases	B cell acute lymphoblastic leukemia (B-ALL, experimental)
Let-cel	TCR-T	Targets NY-ESO-1 antigen on specific sarcoma cells	Synovial sarcoma and myxoid/round cell liposarcoma

Flexible Design
ADCs can be engineered to address different cancers by modifying the antibody, linker, or payload.

Cell Therapies

Personalized Treatment
Therapies like CAR-T cells (engineered T cells) are tailored to the patient's immune system and cancer profile, offering highly specific tumor eradication.

High Efficacy in Certain Cancers
CAR-T therapies have shown remarkable success in hematological malignancies, such as B cell leukemias and lymphomas.

Immune Memory
Similar to immunotherapies, engineered T cells can provide long-lasting protection.

Expanding Targets
Ongoing advancements aim to extend the success of CAR-T from blood cancers to solid tumors.

Gene Therapies

Durable and Curative Potential
Gene therapies aim to correct or modify the genetic drivers of cancer, offering potentially curative treatments.

Versatility
Can be used to deliver therapeutic genes, silence oncogenes, or repair genetic mutations driving tumorigenesis.

Broader Reach
Can be combined with other therapies (e.g., gene-edited CAR-T cells) to enhance efficacy.

Challenges in Targeted Therapies for Cancer

By offering more precise modes of action than conventional chemotherapy, targeted therapies—which include small chemicals, monoclonal antibodies, and more recent modalities like cell and gene therapies—have completely changed the way that cancer is treated. Notwithstanding these developments, a number of issues still prevent their broad use, safety, and effectiveness.

1. Resistance and Toxicity Small Molecule Mechanisms

Although small molecule inhibitors, especially TKIs, have demonstrated notable effectiveness in treating a variety of cancers, their application is constrained by serious issues with toxicity and resistance. Although the purpose of these medications is to specifically target oncogenic drivers, off-target effects sometimes result in harmful toxicities like hepatotoxicity, cardiotoxicity, and dermatological consequences. For example, TKIs targeting EGFR are associated with cutaneous toxicities, whereas ALK (anaplastic lymphoma kinase) inhibitors have been linked to neurotoxic effects.

Another significant barrier is resistance. Multiple strategies, including histologic transformation, alternate signaling pathway activation, and secondary mutations in the target protein, are used by tumor cells to adapt. One well-established resistance mechanism in EGFR-mutated lung cancer

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is the appearance of secondary mutations like T790M. Research on using combination therapy or second- and third-generation inhibitors to overcome resistance is still ongoing.[40–43]

2. Efficacy and Scalability Issues in Cell and Gene Therapies

A major advancement in the treatment of cancer has been made possible by cell and gene therapies, especially CAR-T therapies and gene-editing methods like CRISPR-Cas9. Their therapeutic effectiveness, particularly in solid tumors, is not usually long-lasting, though. For instance, the immunosuppressive tumor microenvironment and the difficulties of CAR-T cells penetrating solid tumor masses have hindered the effectiveness of CAR-T therapy in solid tumors, despite its impressive success in hematologic malignancies.

Furthermore, there are major obstacles in the production and expansion of these treatments.

Large-scale manufacture is difficult and expensive because CAR-T cell therapy necessitates intricate and customized ex vivo alteration of patients' T cells. Similar problems arise with gene therapies as well, especially when it comes to creating the viral vectors required for gene delivery. The high cost and time associated with manufacturing cell and gene therapies limit their accessibility, and efforts to streamline production processes while ensuring quality and safety remain a focus of ongoing research.[44,45]

3. Regulatory Hurdles and Evolving Guidelines

Targeted therapy regulatory approval procedures are difficult and frequently lag behind scientific advancements, particularly for innovative modalities like gene and cell therapies. It is challenging for organizations like the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) to create suitable regulatory frameworks for these intricate medicines. For example, when new safety issues, such as the long-term impacts of gene editing and insertional mutagenesis, arise, standards for the safety assessment of gene treatments are always changing.

The FDA's Breakthrough Therapy designation and Accelerated Approval programs are examples of expedited approval procedures that regulatory bodies must balance with the need to ensure adequate clinical evidence for long-term safety and efficacy. With the increasing number of gene therapies and customized treatments available on the market, post-marketing monitoring and adaptive surveillance and adaptive regulatory frameworks will become increasingly important.[46,47]

4. Cost and Accessibility

Because of the intricate manufacturing procedures, targeted medicines are sometimes prohibitively expensive, particularly for cell-based and biological therapies. Access to these potentially life-saving therapies becomes unequal as a result. The requirement for continuous therapy when resistance arises, which necessitates the use of combination regimens or second-line medicines, adds to the financial burden of targeted therapies. Therefore, it is imperative that insurance companies and healthcare systems modify their reimbursement schemes to cover these expensive procedures.[48,49]

Overcoming resistance and efficacy issues with synergistic approaches

Targeted therapies have revolutionized cancer treatment by focusing on specific molecules or pathways involved in cancer progression. These therapies, when combined, often exhibit **synergistic effects**, meaning their combined impact exceeds the sum of their individual effects. This synergy can enhance efficacy, reduce drug resistance, and improve patient outcomes.

BRAF and MEK Inhibitors: In melanoma with BRAF V600E mutations, combining BRAF inhibitors (e.g., vemurafenib) with MEK inhibitors (e.g., cobimetinib) prolongs progression-free survival and reduces resistance compared to monotherapy.

PARP Inhibitors with Anti-angiogenics: Combining PARP inhibitors (e.g., olaparib) with VEGF inhibitors (e.g., bevacizumab) shows improved outcomes in ovarian cancers, leveraging hypoxia-induced DNA repair vulnerabilities.

EGFR and MET Inhibitors: In NSCLC, resistance to EGFR inhibitors due to MET amplification can be countered by combining EGFR inhibitors (e.g., osimertinib) with MET inhibitors (e.g., tepotinib).

VEGF Inhibitors with Immune Checkpoint Inhibitors:

- Bevacizumab (anti-VEGF) combined with atezolizumab (anti-PD-L1) in advanced RCC shows superior progression-free survival compared to monotherapy, due to improved immune infiltration and reduced immunosuppression.

EGFR Inhibitors with Immunotherapy:

- In NSCLC, EGFR inhibitors (e.g., osimertinib) combined with PD-1 inhibitors have shown potential in preclinical models by enhancing tumor antigenicity and immune infiltration.

PARP Inhibitors with Immune Checkpoint Blockade:

- PARP inhibitors like olaparib increase neoantigen release and upregulate interferon signaling, sensitizing tumors to anti-PD-1/PD-L1 therapies.

BRAF/MEK Inhibitors with Immunotherapy:

- In BRAF-mutant melanoma, combining BRAF/MEK inhibitors with immune checkpoint inhibitors (e.g., nivolumab) enhances both direct tumor cytotoxicity and immune-mediated killing.

There are advantages observed with combining small molecule targeted therapies of overcoming drug resistance, lower dosing, and broad patient applicability. However, predicting synergy, management of toxicity profiles, and tumor evolution contributing to decision on cycle of modalities are some key issues.

On the other hand, combination therapies with existing immunotherapies provide the advantage of enhancing tumor immune response with sustained long-term memory overcoming tumor heterogeneity in a tumor-agnostic manner. Nevertheless, key issues regarding the identification of appropriate biomarkers, toxicity profiles, and treatment timing remain.

Enhancing Targeted Cancer Therapies—Possibilities with Artificial Intelligence

Drug resistance, tumor heterogeneity, and the identification of suitable biomarkers for patient selection are some of the obstacles that targeted therapies still confront, despite their potential. By improving clinical decision-making, improving patient stratification, predicting treatment outcomes, and optimizing drug discovery, artificial intelligence (AI) has become a potent tool to overcome these constraints. Certain tumors, particularly hematologic malignancies, have responded remarkably well to treatment with CAR-T therapy and gene editing methods like CRISPR. Treatment-related toxicities, manufacturing complexity, patient variability, and the high cost of development are some of the difficulties these medicines must overcome. In order to overcome many of these obstacles, AI is becoming a game-changing tool that can optimize the entire cell and gene therapy development process, from discovery to patient delivery.[50,51]

1. Improving the Discovery of Biomarkers

Large datasets from proteomic, transcriptomic, and genomic research can be analyzed by AI and machine learning (ML) algorithms to find new biomarkers that predict treatment response. When it comes to identifying which patients would benefit from particular targeted medicines, biomarkers are essential. Conventional methods for finding biomarkers take a lot of time and could overlook minute trends in intricate datasets. AI, however, excels at pattern recognition and can uncover previously unrecognized molecular signatures that predict drug efficacy or resistance.

For instance, by examining gene expression profiles and locating indicators such as PD-L1 expression levels, deep learning algorithms have been utilized to forecast patient reactions to cancer immunotherapy. Similar to this, AI-driven models have demonstrated potential in detecting genetic changes in malignancies including breast cancer and non-small-cell lung cancer (NSCLC), which could result in more precise patient selection for targeted treatments.

2. Predicting Drug Resistance and Tumor Evolution

Drug resistance, which can arise via tumor evolution and the selection of resistant cancer cell clones, is one of the biggest obstacles to targeted cancer therapy. AI provides a potent way to forecast the formation of resistance and model the progression of tumors. Large collections of tumor genomic data can be used to train ML algorithms that can identify the mutations or molecular alterations that are most likely to cause resistance to specific drugs.

According to recent research, AI models are capable of precisely forecasting when resistance mutations would arise in response to targeted treatments, such EGFR inhibitors in lung cancer. Clinicians can modify treatment plans, such as combining therapy or switching to different medications, before resistance manifests clinically by anticipating resistance early.

3. Optimizing Cell Manufacturing and Quality Control

To guarantee safety and effectiveness, the production of cell treatments, including CAR-T cells, is intricate and demands strict quality control. Automation powered by AI can expedite the generation of cells, guaranteeing constant cell quality and lowering human error. In order to optimize the production of therapeutic cells, AI-based models can also forecast the best culture conditions, processing durations, and cell expansion procedures.

By examining enormous datasets of cellular phenotypes and production parameters, ML techniques are being utilized to enhance quality control. For instance, throughout the production process, AI can spot minute cellular characteristics or patterns that are linked to effective treatment results. This lowers the possibility of batch variability and aids in production standardization, both of which are critical when expanding cell treatments for broad clinical applications.

4. Predicting and Managing Treatment Toxicities

The possibility of serious immune-related toxicities including cytokine release syndrome (CRS) and neurotoxicity is one of the biggest obstacles to cell and gene therapies, especially CAR-T therapy. When it comes to anticipating these toxicities before they happen, AI can be really helpful. ML models can predict patients at high risk of experiencing serious adverse events by combining patient clinical data, genomic profiles, and early therapy responses.

5. Enhancing Target Discovery and Gene Editing

AI has demonstrated significant potential in speeding up the identification of new therapeutic targets for gene and cell therapies. Finding the appropriate target genes for CRISPR editing or antigens for CAR-T cell treatments is essential to their effectiveness. Large-scale genomic and transcriptomic data can be analyzed by AI-powered algorithms to find gene mutations or antigens unique to a tumor that may be targeted for treatment.

AI is being utilized, for example, to forecast off-target consequences in CRISPR-based gene editing,

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which aids in the development of safer and more accurate treatments. Based on genomic data, ML algorithms can evaluate the probability of off-target mutations and enhance the design of guide RNAs for CRISPR editing.

6. Personalizing Cell and Gene Therapies

AI is a vital tool for customizing cell and gene therapies because of its capacity to evaluate enormous volumes of patient data, including genomic, proteomic, and clinical data. By determining which patients are most likely to respond to particular cell or gene therapies, AI can help precision oncology, which tries to customize treatments to the distinct genetic composition of each patient's tumor.

AI can optimize dosage schedules and forecast patient response by integrating various data kinds. Deep learning algorithms, for instance, can predict the possibility of a good response to CAR-T therapy by analyzing tumor microenvironment features and patient-specific genetic signatures. Additionally, AI-powered algorithms are assisting in risk-based patient stratification, guaranteeing that high-risk patients receive more intensive care while reducing needless interventions for low-risk patients.

Reducing Costs and Expanding Access

One of the main obstacles to the widespread use of cell and gene therapies is their high cost. By increasing the effectiveness of therapeutic production, streamlining manufacturing procedures, and cutting down on the duration and cost of clinical trials, AI can assist in lowering these expenses. AI can also find ways to automate parts of the production process, which minimizes production errors and lessens the need for highly specialized staff.

Furthermore, AI-powered models can streamline the logistics of patient delivery of cell therapies, cutting down on treatment time and guaranteeing that patients receive treatments in the best possible condition. For autologous treatments like CAR-T, where cells must be extracted, altered, and then given back to the same patient, this is very crucial.

Conclusions

Targeted therapies have revolutionized cancer treatment in the past 10 years by providing more individualized and accurate interventions that enhance patient outcomes for patients with a variety of cancer types. These treatments have made it possible to move away from conventional chemotherapy and radiation, which frequently damage both healthy and malignant cells, by focusing on particular molecular markers and pathways involved in the growth of cancer. For many patients, this method has improved their quality of life by lowering negative side effects and increasing therapeutic efficacy. Additionally, patients with resistant or recurring malignancies now have new options thanks to the emergence of treatments that target previously incurable mutations, such as those in EGFR, HER2, BRAF, and KRAS opening the door for more individualized regimens based on genetic and molecular profiles.

Despite these advances, limitations remain, particularly in terms of drug resistance and the limited applicability of targeted therapies to cancers lacking well-defined molecular targets. Tumor heterogeneity, both within a patient and across populations, also complicates treatment, leading to variability in therapeutic responses and occasional failure of even the most precisely designed treatments. These issues underscore the need for more adaptive and scalable strategies to expand the benefits of targeted therapies to a broader patient base.

Looking forward, AI holds immense promise in addressing these challenges. By leveraging vast datasets from patient records, genetic profiles, and treatment outcomes, AI can identify new biomarkers, predict patient responses, and optimize treatment plans with unprecedented accuracy. ML algorithms, for instance, can help distinguish subtle patterns that may indicate resistance mechanisms, aiding in the development of novel combination therapies to prevent or mitigate resistance. Moreover, AI-driven platforms can facilitate drug discovery by analyzing potential drug-target interactions more efficiently than traditional methods. As AI continues to integrate with oncology, it has the potential to enhance the precision of targeted therapies, overcoming current limitations and steering cancer treatment into an era of even more personalized and effective care.

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