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A Review Of Anticancer Treatment Therapy

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Abstract

Along with heart disease, cancer is one of the main causes of death in the US. Conventional chemotherapy has always been the cornerstone of cancer care. Chemotherapeutic medications are made to target cells that divide quickly, such as cancer cells, as well as some normal cells, such the intestinal epithelium. A new generation of cancer medicines, known as targeted cancer therapies, has emerged in recent years. Targeted cancer therapies, like traditional chemotherapy, employ pharmacological drugs that prevent growth, boost cell death, and limit the spread of cancer. Targeted therapies, as their name implies, prevent particular proteins implicated in cancer from doing their jobs. For many cancer types, including lung, colorectal, breast, lymphoma, and leukaemia, targeted cancer therapies may be more therapeutically helpful than broad-based cancer treatments because they concentrate on specific molecular changes that are specific to a particular malignancy. In addition, new developments have made it possible to assess patient tumors and customise therapies accordingly. Targeted cancer therapies primarily fall into one of three categories: monoclonal antibodies, small chemical inhibitors, or immunotoxins. The biology of these three groups of targeted cancer medicines will also be covered in detail in this review.

Keywords :-

Apoptosis, chemotherapy, and medicines Antisense oligonucleotides and ionising radiation Ribozymes with dominant-negative mutations.

Introduction

The second greatest cause of death worldwide is cancer. Cancer is responsible for 7.6 million deaths worldwide, or 13% of all fatalities [1]. The three most common therapeutic modalities for cancer are surgery, chemotherapy, and radiation therapy, with chemotherapy playing a crucial role in cancer patients' care. The lack of selectivity for tumor cells over normal cells, which results in insufficient drug concentrations in tumors, systemic toxicity, and the emergence of drug-resistant tumor cells, limits the effectiveness of this approach [2]. Alternative formulations, such as liposomes [3], resistance modulation, such as PSC833 [4], antidotes/toxicity modifiers, such as ICRF-187 [5], and gene therapy are a few of the treatments that have been suggested. Due to its sensitivity towards cancer cells while minimizing harm to off-target cells, targeted therapy has recently gained prominence. The goal of targeted therapy is to deliver medications to specific genes or proteins that are unique to cancer cells or the tissue milieu that supports the formation of cancer. The key to the therapy's success is the precise placement of medicines at the site of the disease while limiting unintended side effects on healthy tissues. It frequently works in tandem with chemotherapy and other cancer therapies. In targeted therapy, poisonous compounds are delivered selectively to cancer cells in order to kill them. These toxic substances may be medications that prevent cancer cell proliferation, encourage cell cycle regulation, or trigger apoptosis or autophagy. Utilizing monoclonal antibodies or small-molecule oral medications is a part of targeted therapy. [6].

Since the mid-1970s, when the manufacturing of tailored monoclonal antibodies was first reported, monoclonal antibodies have been the subject of considerable research in the realm of cancer therapies. The creation of monoclonal antibodies, antibody engineering with display, and screening advancements like phage display allowed for the exceptionally precise binding of antibodies to a broad spectrum of targeted antigens. Gemtuzumab (Mylotarg®; Wyeth, CT, USA), a CD-33-specific monoclonal antibody conjugated to a calicheamicin used for the treatment of acute myeloid leukemia, is employed in cancer immunotherapy [7]. Similar to this, imaging (immunoscintigraphic) and radioimmunotherapy techniques have been developed using radioisotope-conjugated targeting antibodies. For use in clinical therapy, 90Y metal isotope-based anti-CD20 ibritumomabtiuxetan (Zevalin®; Spectrum Pharmaceuticals, CA, USA) has been created. [8,9].

Additionally, antibodies are used as targeting agents in addition to being therapeutic agents. For the delivery of active therapies [10], prodrug activation enzymes [11,12], and chemotherapeutic toxins [13–15], they are employed in targeted therapy. Monoclonal antibodies prevent a particular target from interacting with cancer cells or the tissue around them. Chemotherapeutic agents and radioactive materials are delivered to cancer cells directly via monoclonal antibodies. These drugs are often injected intravenously due to their bulk.

The two-step procedure of prodrug cancer therapy begins with the targeting of the drug-activating enzyme and its expression in tumor’s. Next, the nontoxic prodrug, which serves as the substrate for the foreign enzyme that is targeted and expressed in tumor’s, is administered systemically [16–18]. As a result, high amounts of activated anticancer medicines (toxic medications) are more easily localized in tumors. The enzyme should be of nonhuman origin or a human protein that is either absent from or expressed at low levels in normal tissues [19–20], but that is sufficiently expressed in tumors with significant catalytic activity [21] for the prodrug therapy to be successful.

The prodrug must be a good substrate for the expressed enzyme in tumors rather than being activated by endogenous enzymes in non-tumor tissues. The prodrug should have a high potential for cytotoxicity and be highly diffusible and activated in the tumors cell. Additionally, it must actively be taken up by the nearby cancer cells that aren't expressing it in order to have a "bystander" killing impact. While exhibiting a bystander effect, the prodrug's half-life ought to be long enough to prevent drug leakage into the systemic circulation [22]. The transport of genes encoding prodrug-activating enzymes to tumors tissues (GDEPT, VDEPT, GPAT, etc.) and the transfer of active enzymes into tumors tissues are the two main categories of targeting techniques for enzymes and prodrugs (ADEPT).

Delivering a gene that codes for a foreign enzyme to tumors cells, where it finds expression and activates a systemically supplied nontoxic prodrug, is referred to as gene-directed enzyme prodrug treatment [16,23,24]. HSV-TK/GCV, Escherichia coli CD/5-FC, and E. coli NTR/CB1954 are three enzyme/prodrug systems used in GDEPT that function intracellularly by transforming prodrugs into active medications inside cancer cells. Effective killing requires cell-cell interaction for this mode of action. An extra-cellular cytotoxic effector system contains the secreted form of lysosomal human glucuronidase, which transforms an inactive glucuronidated derivative of doxorubicin (HMR 1826) into the cytotoxic doxorubicin in the tumors cells.

The hydrophilic prodrug, which targets both transduced and nontransduced cells, is transformed into a lipophilic, cell-permeable cytotoxic drug in the extracellular system. Due to the fact that cell-cell interaction is not necessary for a bystander effect, it demonstrates increased cytotoxic potential [16].

In order to transfer a gene encoding an enzyme that can transform a systemically administered harmless prodrug into a lethal agent within tumors cells, virus-directed enzyme prodrug therapy (VDEPT) uses viral vectors. After retroviral transduction and expression of the E. coli NTR gene, the NTR/CB1954 combination is employed against colorectal and pancreatic cancer cells to sensitize them to CB1954 [25,26].

Retroviruses, adenoviruses, HSV [27], adeno-associated virus [28, 29], lentivirus, and EBV [31] are among the viruses employed in VDEPT. The bulk of these drug-activating enzyme gene/prodrug combinations were delivered into tumors in vitro or in vivo by VDEPT over the years, using the retroviral and adenoviral vectors CD/5-FC or HSV-TK/GCV [32].

Using the known transcriptional differences between normal and malignant cells, genetic prodrug activation therapy (GPAT) causes the selective expression of a drug-metabolizing enzyme for activation of the prodrug into a hazardous moiety [33,34]. Several genes that are either tumor-specific or tumor-associated antigens, such as CEA for colorectal cancer or N-myc for neuroblastoma, have been employed as tumor-specific Transcription Responsive Elements (TREs) [2].

When injected systemically, a combination of tumor-specific antibodies and a drug-activating enzyme targets tumors tissues. This treatment method is known as antibody-directed enzyme prodrug therapy (ADEPT). The systemically delivered nontoxic prodrug is transformed into a toxic drug by this targeted enzyme, which is localized on the tumors surface, causing cytotoxic effects in the tumors cells [12,35]. Diffusible small molecules that can enter both antigen-positive and antigen-negative tumors cells and result in a bystander effect are the best medications for ADEPT [35–37]. To increase the conjugate accumulation in tumors and prevent their leakage to blood and normal tissues, the time gap between the delivery of the enzyme and the prodrug should be maximized in order to prevent systemic toxicity.

2. Small molecule inhibitors for the treatment of cancer

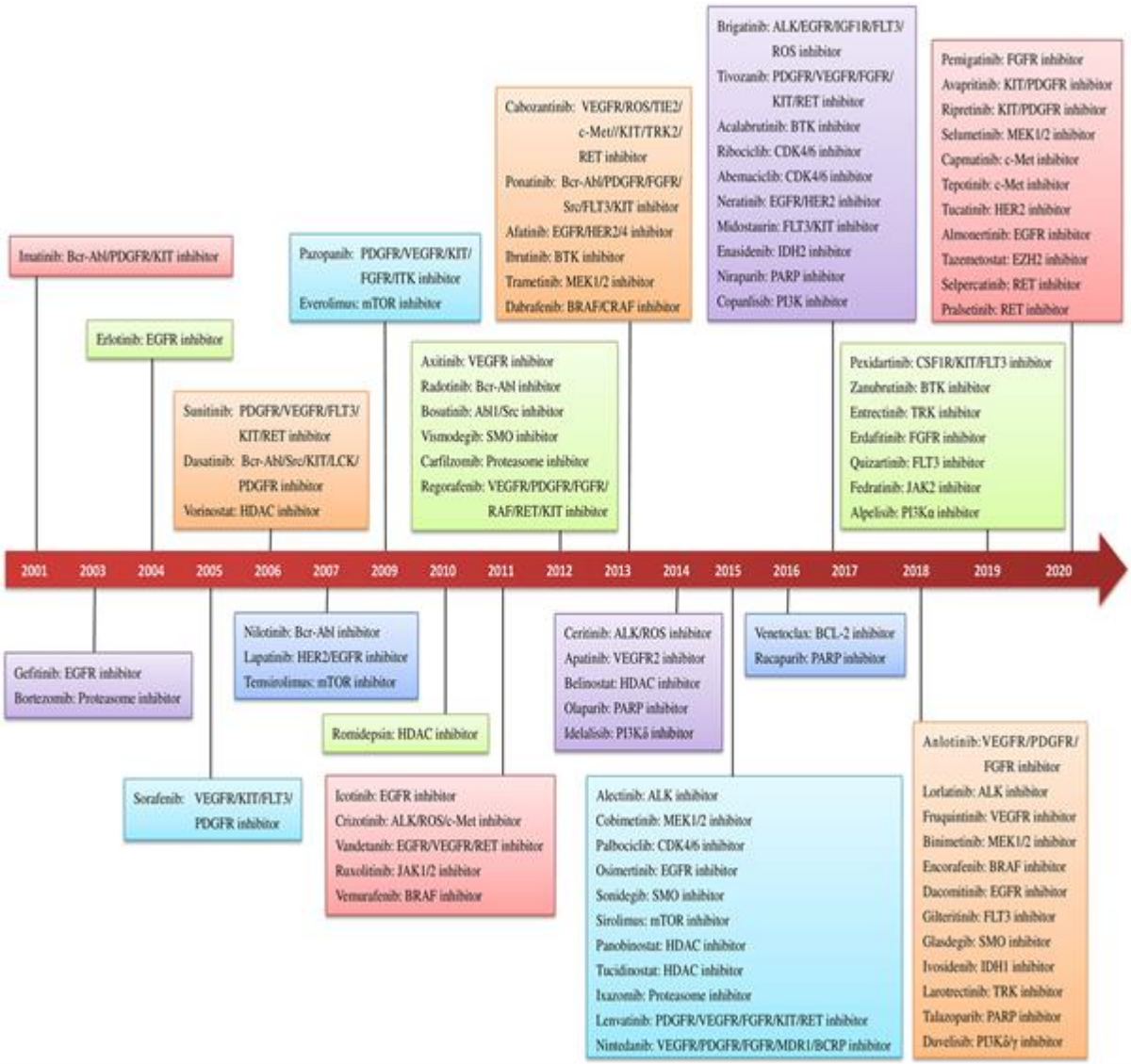
A tablet is a little medicinal dose taken orally by the patient. The body absorbs them better because they have fewer chemical components than monoclonal antibodies. Small medicines typically target particular molecular targets that are crucial for cancer cell growth, metastasis, or angiogenesis. Small molecule inhibitors that operate against novel molecular targets that control the therapeutic result are the main focus of the present stage of cancer therapy research and development. Numerous cancer patients' lives have been made better by molecularly focused cancer therapy. All-trans retinoic acid [38] has been used to treat acute promyelocytic leukemia patients with translocations in the RAR retinoic acid receptor gene and chronic myeloid leukemia patients with the cancer. [39,40] serve as evidence for the idea that a tiny chemical can be used to address pathogenetic driver anomalies in a clinical environment. Other small molecule inhibitors of cancer targets include, for example, gefitinib, an inhibitor of EGFR kinase, and erlotinib, an inhibitor of EGFR in patients with non-small cell lung cancer (NSCLC); lapatinib, an inhibitor of EGFR/ERBB2 for patients with breast cancer that is positive for ERBB2 and the vascular epidermal growth factor receptor inhibitor sorafenib (VEG)

The most recent additions to the list are abiraterone, a CYP171A1 inhibitor that blocks androgen synthesis and is approved for the treatment of late-stage, castration-resistant prostate cancer [42], crizotinib, a protein kinase ALK inhibitor that is approved for the treatment of NSCLC patients with a pathogenic ALK gene rearrangement [43],

and vemurafenib, a BRAF kina The effectiveness of protein-based treatments, particularly antibodies, is a reflection of the development of small molecule medications, as demonstrated by the use of the anti-ERBB2 monoclonal antibody trastuzumab in ERBB2-positive breast cancer [45,46]. These instances offer strong proof of the effectiveness of focusing on the pathogenic factors that cancer "addicted" to [47,48].

The development of novel molecularly focused medicines has significantly advanced cancer therapy, yet many patients still have few therapeutic alternatives, and the process of developing new drugs is frustratingly lengthy and has a high failure rate. The cause of the slow progress is that patients with certain anatomically and histologically defined solid tumors frequently respond to treatment with a specific class of kinase inhibitors that matches the predominant pathogenic driver mutation, for example, NSCLC patients with EGFR mutations respond to EGFR inhibitors while those with ALK translocations respond to ALK inhibitors. It makes it necessary to comprehend the importance of precise gene targeting and the choice of companion biomarkers that are patient-specific in the development of cancer drugs. The sequencing of multiple cancer genomes revealed exceptional complexity with numerous genetic mutations and significant genetic heterogeneity, not only between different tumors but also within individual cancers. Another crucial challenge is the identification of specific molecular targets. Furthermore, the heterogeneous population of tumors also tends to include host cells that promote tumors growth, such as resistant stem cells. Due to this heterogeneity, there is a need for combinatorial therapy and drug resistance. The next problem is choosing and confirming the best targets after identifying a potential novel therapeutic target. To deliver a therapeutically significant biological effect in pertinent experimental models, it is necessary to show a causal relationship between the intended target and the target modification. For medicinal chemists who use tiny compounds for drug development, the "drug ability gap" is the key area of concern. The 'drug ability gap' is a term used to describe the inability to use small compounds to target certain promising targets, such as RAS proteins, c-MYC, or hypoxia-inducible factor (HIF). As recently demonstrated by the successful conclusion of clinical trials by crizotinib and vemurafenib, it is unfortunate that cancer cells can develop resistance to medications with therapeutic efficacy. This might be caused by a target gene mutation, the triggering of feedback mechanisms, or the emergence of new oncogenic pathways. A combinatorial regimen aids in resolving such issues in such circumstances.

Fig. 1 Timeline for the approval of small-molecule targeted anti-cancer drugs



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Kinase inhibitors

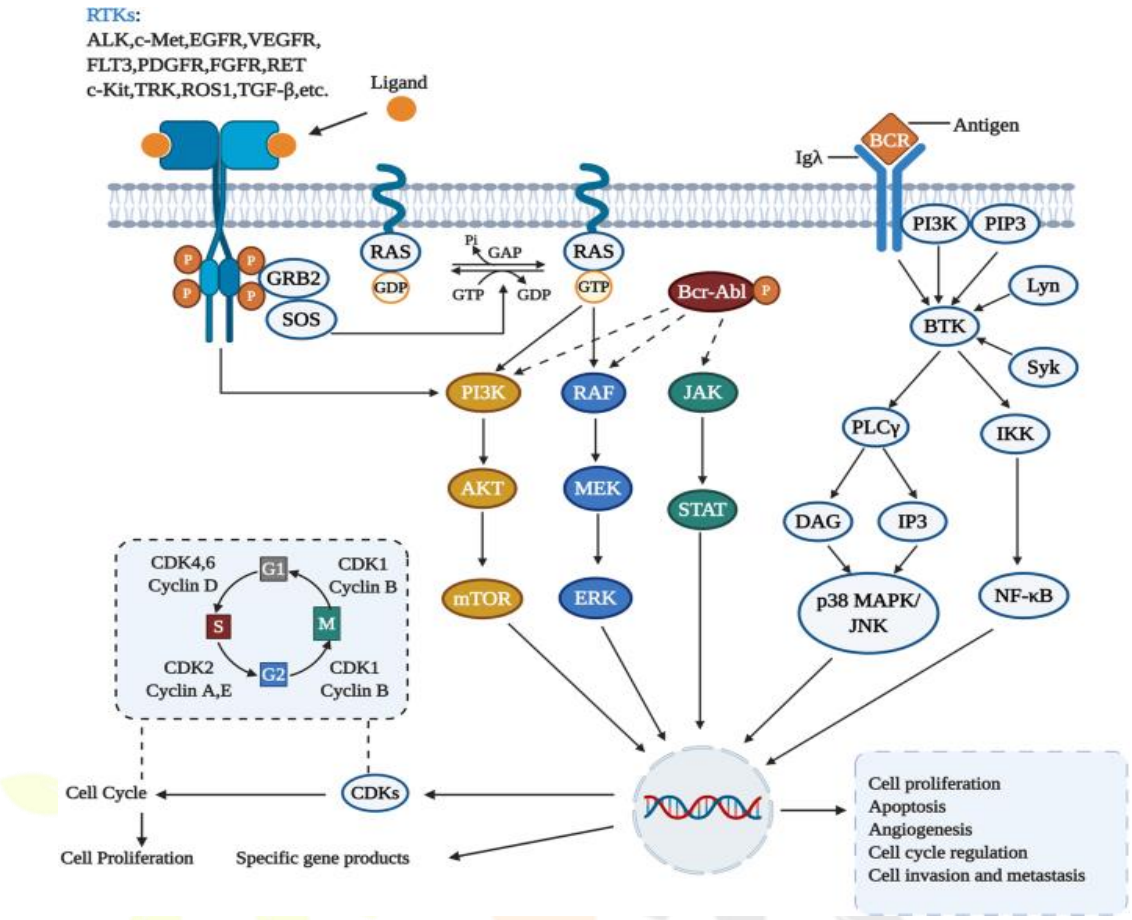
KINASE INDUCERS An enzyme called protein kinase facilitates the transfer of the phosphate group from ATP to protein residues that contain hydroxyl groups. It plays a crucial part in cell division, growth, and proliferation (Fig. 2). About 535 protein kinases make up the human kinome. 6 Protein kinases can be categorized as tyrosine kinases (including both receptor and non-receptor tyrosine kinases), serine/threonine kinases, and tyrosine kinase-like enzymes based on the substrate residues. Protein kinase dysregulation has been linked to a number of illnesses, most notably cancer. The most extensively researched tumors therapy targets are protein kinases.

There are numerous protein kinase inhibitors on the market right now. These kinase inhibitors can be categorized into many groups using a variety of methods. One of the most popular techniques is the integrated classification system Roskoski suggested, which we adopted in this case. This classification scheme divides protein kinase inhibitors into six categories (Type-I–VI).

The active conformation of the kinase (DFG-Asp in, C-helix in) is where type-I inhibitors interact. Type-II inhibitors bind to an inactive DFG-Asp conformation with the C-helix out, whereas type-II inhibitors bind to an inactive DFG-Asp conformation with the outward C-helix. These inhibitors attach to the hinge region that connects the enzyme's small and large lobes by hydrogen bonds and occupy a portion of the adenine binding pocket. Type-I1 and type-II antagonists among them can be further broken down into A and B subtypes.

While type B inhibitors are unable to stretch into the rear cleft, type A inhibitors do so past the Sh2 gatekeeper residue. The fact that type A inhibitors bind to their targets more slowly than type B inhibitors suggests that this distinction may be significant. Kinase inhibitors of type III and type IV have an allosteric structure. Type III inhibitors bind to an allosteric location in the cleft between the small and large kinase lobes close to the ATP-binding pocket to limit kinase activity.

Type IV inhibitors, on the other hand, bind outside of the cleft. In addition, type V inhibitors are the bivalent compounds that cover two different areas of the kinase domain. All type-I-V inhibitors have reversible effects. Type VI inhibitors, on the other hand, are substances that bind covalently to the kinase active site (irreversible kinase inhibitors)



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various protein kinase-dependent pathways being activated. A small number of intermediaries, including phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinases (MAPK), are influenced by the group of RTKs, which in turn activates the intricate signaling networks involved in cell proliferation, differentiation, adhesion, apoptosis, and migration. Critical processes regulating cell cycle turnover include the periodic CDK-cyclin complex's aggregation, activation, and depolymerization. Graph produced using BioRender.com

RECEPTOR TYROSINE KINASE INHIBITORS

ALK inhibitors

One transmembrane tyrosine kinase of the insulin receptor family, anaplastic lymphoma kinase (ALK), is encoded by the ALK gene[50]. ALK plays a significant function in the development of the nervous system and has the ability to activate numerous downstream signalling pathways[51]. Numerous human malignancies, including anaplastic large cell lymphoma, diffuse large B-cell lymphoma (DLBCL), inflammatory myofibroblastic tumor,[52] and non-small cell lung cancer (NSCLC)[53], have been found to have constitutive activation of ALK due to point mutations or chromosomal rearrangements. In 2007 [54], it was discovered that echinoderm microtubule-associated protein-like 4 and ALK can fuse in NSCLC.

An ALK gene rearrangement has been identified in 3-7% of NSCLC patients. The EML4-ALK gene fusion is brought about by an inversion in the short arm of chromosome 2 that places the N-terminal of the EML4 promoter and the kinase domain of the ALK gene next to one another. This results in ligand-independent constitutive activation of ALK and promotes the growth and survival of cancer cells. Other ALK gene fusions have also been identified, including NPM-ALK, ATIC ALK, and RANBP2-ALK; these rearrangements identify a particular subset of cancer patients that can be treated with selective ALK inhibitors. A first-generation ALK inhibitor, crizotinib, was approved in 2011 and targets several tyrosine kinases, including ALK, cellular mesenchymal-epithelial transition factor (c-Met), and proto-oncogene tyrosine-protein kinase reactive oxygen species (ROS) [56]. In patients with advanced ALK-rearranged NSCLC, crizotinib outperformed chemotherapy in two randomised phase III trials (NCT00932893, NCT01154140), and it is now the go-to medication for metastatic ALK-positive NSCLC. 18,19 Unfortunately, most patients gain crizotinib resistance within a year, particularly L1196M and G1269A mutations that might cause relapse. The most frequent location of relapse in NSCLC patients receiving crizotinib is the central nervous system (CNS), perhaps as a result of the low blood-brain barrier (BBB) permeability of the CNS.

EGFR inhibitors

A transmembrane protein known as the epidermal growth factor receptor (EGFR) is involved in a number of biological processes. Members of this family also include the extramembrane ligand-binding regions ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4, as well as the single-stranded transmembrane regions and the highly conserved intra-EGFR membrane tyrosine kinase regions. The downstream intracellular signalling cascades that are intimately related to cell proliferation, survival, and death are activated when the EGFR extracellular domain interacts to its ligand, such as EGF and TGF-. This is done by EGFR dimerizing and autophosphorylating. An major factor in the carcinogenesis of several cancer types, particularly lung cancer, breast cancer, and pancreatic cancer, is abnormal activation of EGFR mutations. There are various clinically available EGFR TKIs. Gefitinib, erlotinib, and icotinib are examples of the first generation of EGFR TKIs, which are reversible inhibitors with a quinazoline structure. Patients with NSCLC who have EGFR-activating mutations respond quite well to these medications. In the clinic, they showed that platinum doublet chemotherapy had a considerable PFS advantage. Erlotinib has additionally been utilised in pancreatic cancer clinical trials in conjunction with gemcitabine. The primary reason for treatment failure (>50%) following administration of first-generation EGFR inhibitors is the EGFR L858R/T790M dual mutation. [56] Afatinib and dacomitinib, second-generation irreversible EGFR-TKIs, are made to combat the T790M mutation. [57,58]. They exhibit more pharmacological efficacy than gefitinib and can covalently bind to the EGFR's ATP-binding pocket. Their clinical doses are nevertheless constrained by the fact that they also severely inhibit wild-type EGFR and result in severe rash and diarrhoea. As a result, these medications are exclusively prescribed to NSCLC patients who have EGFR-sensitive mutations and cannot help those who have the T790M mutant. Third-generation novel pyrimidine-based EGFR TKIs exhibit modest inhibitory efficacy against wild-type EGFR but have inhibitory effects on EGFR-activating mutations and the T790M mutation specifically. Osimertinib, the first third-generation EGFR inhibitor to be approved, can extend PFS in patients with the EGFR T790M mutation to more than 10 months. Osimertinib counterpart almonertinib was created by Hansoh Pharma. This medication, which the NMPA recently approved for NSCLC therapy, also shown significant anti-cancer effects in individuals with NSCLC who were resistant to treatment throughout clinical trials. Osimertinib and almonertinib's strong potency and selectivity against the EGFR T790M mutation are primarily responsible for their effectiveness in overcoming acquired resistance.

NON-RECEPTOR TYROSINE KINASE INHIBITORS

Bcr-Abl1 inhibitors C-Abl is a member of the Abl family of non-receptotyrosine kinases and is encoded by the abelson murine leukaemia 1 (ABL1) gene on chromosome 9. It has been linked to a number of biological functions, including the control of cell differentiation, the cell cycle, and survival. ABL1 and the breakpoint cluster region (BCR) of chromosome 22 are molecularly positioned next to one another as a result of the Philadelphia (Ph) chromosome translocation, creating an abnormal BCR-ABL fusion gene on chromosome 22. This gene generates a 210 kDa oncoprotein (p210 Bcr-Abl1) that can autophosphorylate and constitutively activate the downstream pathway, which in almost all cases of CML and in around 20% of patients with ALL leads to the unchecked proliferation of leukaemia cells. While Bcr-Abl1 fusion tyrosine kinase is thought to be a sensitive target for some leukaemias, the BCR-ABL fusion gene has been found as a particular biomarker for diagnosis and prediction of therapy response.

JAK inhibitors

The family of non-receptor tyrosine kinases includes the Janus kinases (JAKs), which are made up of four isoforms with up to 70% homology: JAK1, JAK2, JAK3, and TYK2. While JAK3 is only expressed in bone marrow and lymphatic-derived cells, JAK1, JAK2, and TYK2 are extensively expressed in a variety of tissues and cells. JAKs can mediate DNA transcription and protein expression as well as deliver extracellular signals to the nucleus. When inflammatory cytokines like interleukin and interferon connect to cytokine receptors, receptor-coupled JAKs can be activated. Then JAKs recruits and phosphorylates downstream signal transducer and activator of transcription (STAT) proteins in addition to catalysing the phosphorylation of receptor tyrosine residues. The regulation of target-gene transcription and expression is facilitated by activated STAT proteins' translocation to the nucleus. Cytokine receptors with diverse cytoplasmic domains activate various JAKs and STATs. More than 50 cytokines and growth factors are downstream of the JAK/STAT pathway, which is thought to be the main immune system communication mechanism. JA-7 Targeting JAK/STAT is thought to be a viable approach for the treatment of numerous autoimmune illnesses, such as rheumatoid arthritis and systemic lupus erythematosus, given the significant role of the JAK/STAT pathway in cytokine signal transduction. Additionally, it has been discovered that STAT signals (such as STAT3, STAT5, or STAT6), which are involved in cell proliferation, survival, invasion, or inflammation, are frequently activated in malignant tumors, particularly hematopoietic malignancies. JAKs are prospective cancer therapeutic targets since they are a crucial upstream protein of STAT signalling. Hematologic malignancies are the primary target of JAK inhibitor usage in cancer. Four JAK inhibitors have so far received clinical use approval. The first JAK inhibitor to be commercially available, ruxolitinib targets JAK1 and JAK2 while having only limited efficacy against TYK2. In 2011, the FDA approved it for the treatment of bone marrow cancer, polycythemia vera, and myelofibrosis (a myeloproliferative neoplasm). Clinicians utilise fedratinib, a recently approved selective JAK2 inhibitor, to treat myelofibrosis. In the meantime, fedratinib has reportedly demonstrated effectiveness in treating NSCLC in preclinical investigations. It has the ability to eliminate PD-L1 expression, which is a key component of immune checkpoint blockade therapy for NSCLC, and to reverse the resistance of NSCLC cells to erlotinib. Tofacitinib and baricitinib are two more JAK inhibitors that have been approved. They are all employed in the clinical management of autoimmune disorders. Recent clinical trials are evaluating the effectiveness of many novel JAK inhibitors in the treatment of cancer. A new JAK2 and STAT3 inhibitor, WP1066 has little effect on JAK1 and JAK3 activity. To assess WP1066's effectiveness in the treatment of melanoma and glioblastoma, a phase I trial was conducted (NCT01904123). Gandotinib (LY2784544) is an oral, highly effective JAK1 and JAK2 inhibitor. In patients with myeloproliferative neoplasms, clinical studies have shown that gandotinib has adequate effectiveness, safety, and tolerability profiles (NCT01594723). Lestaurtinib (CEP701), a multikinase inhibitor, targets the neurotrophin receptor TrkA, FLT3, and JAK2 kinases. Lestaurtinib has been used in experimental or clinical investigations to treat a variety of cancers, including AML, Hodgkin lymphoma, neuroblastoma, prostate cancer, and myeloproliferative diseases. Lestaurtinib showed modest effectiveness and moderate but frequent gastrointestinal damage in individuals with myelofibrosis, according to a phase II research (NCT00668421). To determine its clinical benefits, more research is still required. An efficient JAK1 inhibitor, INCB039110 has >20-fold selectivity over JAK2 and >100-fold selectivity over JAK3 and TYK2.

Myelofibrosis-related symptoms in an open-label phase II trial (NCT01633372) clearly improved following INCB039110 administration. Pacritinib (SB1518), a dual JAK2 and FLT3 inhibitor, can also prevent FLT3 and FLT3-D835Y mutations in addition to JAK2 and JAK2 V617F mutations. It has demonstrated success for myelofibrosis therapy in clinical trials with patients who had the disease plus AML (NCT03645824, NCT02532010). Myelofibrosis, polycythaemia vera, ulcerative colitis, and other immune-mediated disorders (such as rheumatoid arthritis, ulcerative colitis, and psoriatic arthritis) can all be effectively treated with JAK

inhibitors. After INCB039110 medication, myelofibrosis-related symptoms in an open-label phase II trial (NCT01633372) significantly improved. In addition to preventing JAK2 and JAK2 V617F mutations, the dual JAK2 and FLT3 inhibitor pacritinib (SB1518) also inhibits FLT3 and FLT3-D835Y mutations. Clinical trials with patients who had myelofibrosis and AML have shown that the treatment is effective (NCT03645824, NCT02532010). JAK inhibitors can be used to successfully treat a variety of immune-mediated conditions, including myelofibrosis, polycythaemia vera, ulcerative colitis, and psoriatic arthritis. Anemia, hypercholesterolemia, malignancy, neutropenia, venous thromboembolism, and even malignancy. The primary negative side effect of using these inhibitors is increased susceptibility to different infections. As a result, during the medication process, effective preventative and monitoring techniques are required. [33]

EPIGENETIC INHIBITORS

A subfield of genetics called epigenetics investigates heritable variations in gene expression that don't affect the nucleotide sequence of genes. Numerous chemical altering enzymes and recognition proteins, sometimes known as "writers," "erasers," and "readers," are absolutely responsible for controlling it. 411,412 The authors make reference to enzymes such as DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), and histone lysine methyltransferases that transfer chemical groups to DNA or histones (KMTs). The erasers, which consist of histone deacetylases (HDACs) and histone lysine demethylases, remove post-translational changes (KDMs). The readers are proteins, including as members of the methyl-binding domain and bromodomain and extra-terminal (BET) families of proteins, that can identify changed histones or DNA. (Fig. 3). A number of diseases, including cancer, immunological disorders, and several uncommon diseases, are also tightly correlated with abnormal epigenetic control. Only a small number of epigenetic medications are now authorised for clinical usage, despite the fact that many epigenetic regulatory proteins have been discovered as potential disease targets.

PROTEASOME INHIBITORS

All eukaryotic cells express huge multicatalytic enzyme complexes called proteasomes, which are in charge of more than 80% of the protein degradation in human cells. The ubiquitin-proteasome system (UPS) is crucial for cellular protein homeostasis maintenance and for controlling a wide range of biological processes, including DNA repair, antigen presentation, signal transduction, cell survival, and signal transduction. Most broken, misfolded, or unassembled proteins that could otherwise combine into potentially hazardous substances are destroyed via UPS, which involves ubiquitin-tagging proteins, which the proteasome complex subsequently recognises and breaks down into tiny peptides. (Fig. 2). The 20S proteasome is the structural core that unites all proteasomes. The 20S core is made up of a cylinder with four stacked rings: two identical outer and inner rings, each with seven different yet connected subunits. The peptide bond on the N2 terminal threonine residue of the 1, 2, and 5 subunits determines the 20S proteasome's selectivity for substrate activity. Since the UPS's dysfunction is linked to a variety of human diseases, including cancer, autoimmune disorders, and genetic disorders, extensive research has been done on the UPS as a potential therapy option. Paraprotein production by multiple myeloma (MM) cells is excessive, and signalling pathways controlled by the proteasome are necessary for their expansion. Therefore, proteasome inhibition is particularly effective against MM cells, and proteasome inhibitors (PIs) have evolved into the cornerstone of MM clinical therapy. The first approved PI for the treatment of relapsed or resistant MM is bortezomib. It is a peptide boronic acid and reversibly affects the proteasome's catalytic subunit 5. Long-term results for MM patients are greatly improved by the clinical use of bortezomib. Additionally, Bortezomib has been authorised for the management of MCL. Currently, bortezomib is the subject of more than 200 clinical trials that examine its interactions with other drugs, effectiveness in various malignancies, and even non-cancer uses including graft-versus-host disease. However, bortezomib treatment has a number of drawbacks, including the development of dose-limiting peripheral neuropathy in MM and MCL patients and primary resistance in these patients (PN) Second-generation PIs have been created to overcome these restrictions, and many of them are generated from synthetic and natural materials. A second-generation PI that was given FDA approval in 2012, carfilzomib is derived from the natural substance epoxomicin. Carfilzomib, in contrast to bortezomib, is an irreversible inhibitor with an epoxyketone warhead that has the potential to covalently attach to the 20S proteasome's N-terminal threonine-containing active sites. Carfilzomib's effectiveness, even in MM patients who relapsed from are refractory to bortezomib, is a result of its irreversible nature. Additionally, the carfilzomib-containing regimens show much less peripheral neurotoxicity, while carfilzomib-treated MM patients experienced cardiovascular events. For MM patients who have had at least one prior therapy, the second-generation PI ixazomib was approved in 2015 when used in conjunction with lenalidomide and dexamethasone. The N-capped dipeptidyl leucine boronic acid ixazomib reversibly inhibits the 20S proteasome's CT-L proteolytic (5) site. While ixazomib and bortezomib contain the same pharmacophore boronic acid residue, the former's elimination half-life is significantly shorter than the latter's (18 vs. 110 min), It could explain why xazomib has a

safer safety profile than bortezomib. Ixazomib therapy can still be helpful for patients who are resistant to bortezomib. Additionally, it is important to note that ixazomib is the first oral PI and a prodrug, whereas bortezomib and carfilzomib both require parenteral (intravenous or subcutaneous) dosing. Under physiological circumstances, ixazomib is quickly degraded to the active form.

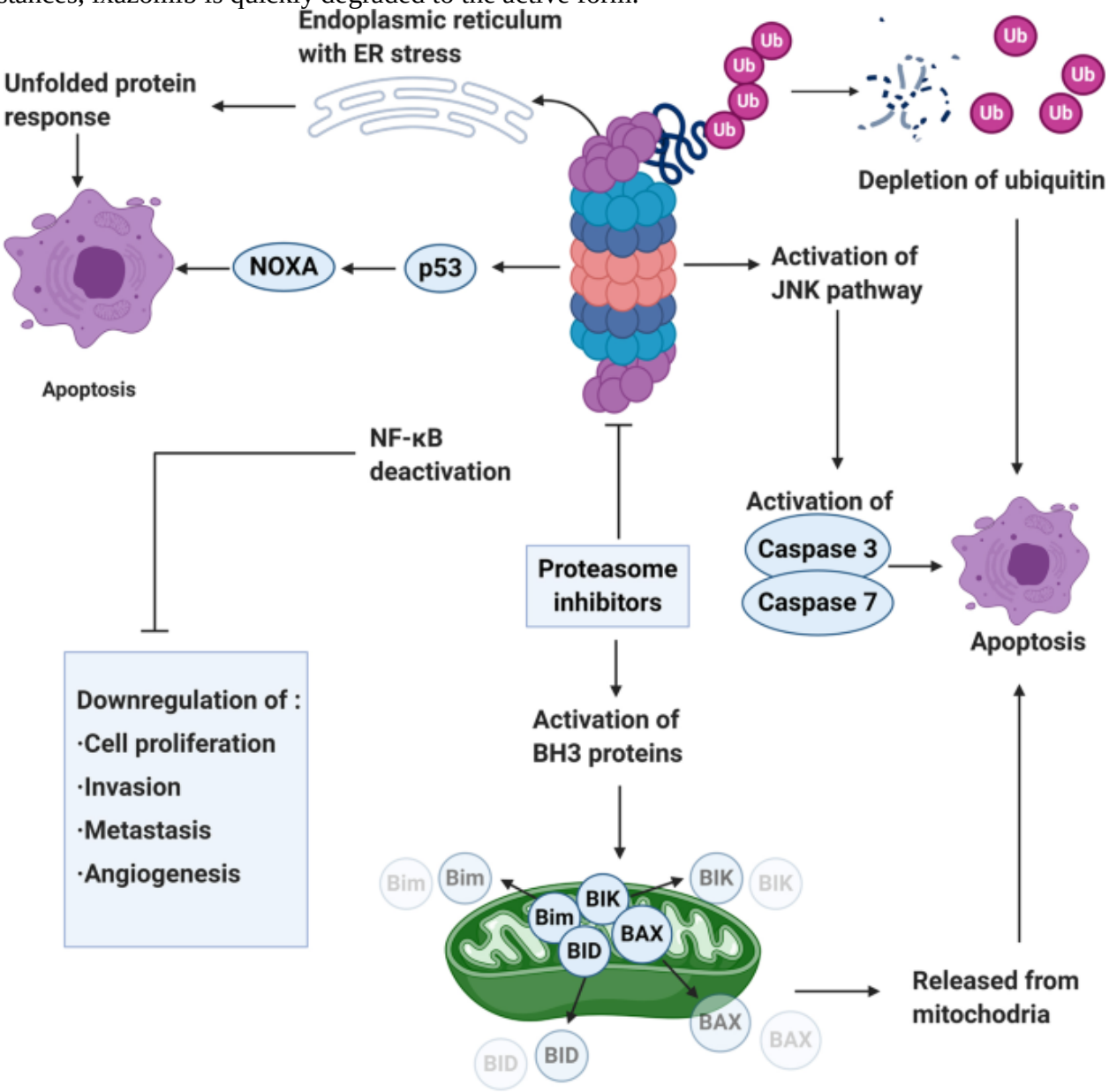

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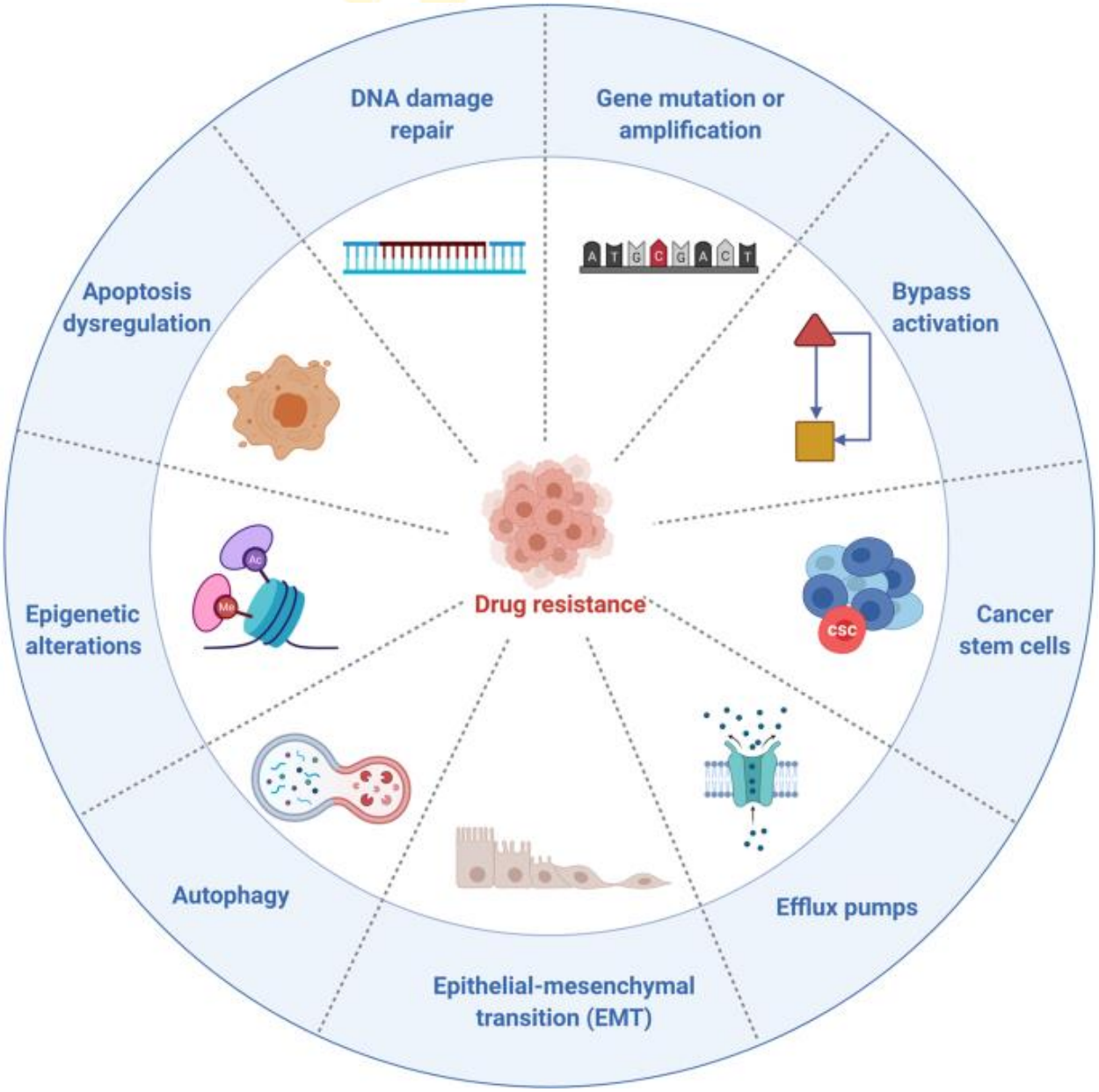
Figure

Multiple methods, including proteasome inhibition, cause cell apoptosis. Proteasome inhibition causes NF-B to become inactive, which in turn inhibits a number of pro-cancerous pathways involved in cell growth, invasion, metastasis, and angiogenesis. Through the JNK signalling pathway and caspase 3 and 7, programmed cell death is brought on by proteasome inhibition. Additionally, proteasome inhibition can indirectly trigger apoptosis by blocking the breakdown of NOXA, BAX, BID, BIK, and other members of the pro-apoptotic family of proteins. Proteasome inhibition inhibits ubiquitinated proteins from being degraded, which can raise ER stress and activate the UPR, cause cell cycle arrest, and lead to death. Graph produced using BioRender.com

CONCLUDING REMARKS: CHALLENGES AND FUTURE PERSPECTIVES:-

- Small-molecule targeted anti-cancer therapies have advanced quickly in their creation thanks to the growth of contemporary molecular biology and the application of several cutting-edge technologies including computer-aided drug design, structural biology, and combinatorial chemistry. The FDA and/or NMPA have approved 89 small-molecule targeted medicines to date to treat different malignancies (Fig. 1). Clinical studies for the treatment of cancer are being conducted on thousands of targeted medicines. Many of their potential agents have progressed to phase III trials. Targeted pharmaceuticals will be the "primary force" in the worldwide anti-cancer drug industry, which the Business Research Company predicts will reach 200 billion dollars in 2021. Small-molecule focused anti-cancer medications still confront several difficulties despite the substantial advancements made.
- Drug resistance is the first important obstacle. After a certain amount of time in clinical usage, almost all targeted anti-cancer medications encounter resistance. Numerous mechanisms, including as gene mutation, amplification, CSCs, efflux transporters, apoptotic dysregulation, autophagy, etc., have been connected to drug resistance (Fig. 8). The primary factor causing anti-cancer treatment resistance is gene mutation. Regarding drug-resistant gene mutations, there are two opposing perspectives. One is that certain medications can cause gene alterations. The second is that there have already been drug-resistant mutations. Cancer cells with drug-sensitive mutations predominate in the early stages of treatment and control the growth of cancer cells with drug-resistant mutations. After cells with sensitive mutations are eliminated, those with resistant mutations proliferate and exhibit resistance. Another often occurring cause of anti-cancer medication resistance is the amplification of other genes. For instance, 20% of instances that are resistant to EGFR inhibitors are caused by MET amplification. [46] Additionally, CSCs are believed to have a significant role in medication resistance and recurrence. According to the CSC theory, a single subpopulation of cells with stem cell-like properties of self-renewal and differentiation give rise to both the various cells in a tumors and the metastases that result from it. Targeted anti-cancer medication resistance is also influenced by the overexpression of efflux transporters, such as multidrug resistance transporter proteins, particularly P-glycoprotein, which renders the resistance to chemotherapy treatments. Apoptosis dysregulation and autophagy may potentially be to blame for anti-cancer medication resistance in addition to these factors. Low efficiency is another another significant obstacle for tailored cancer treatments. Targeted cancer medications, as previously said, effective in a small percentage of patients. For instance, fewer than 20% of NSCLC patients respond to EGFR inhibitors (e.g., gefitinib and erlotinib). Patients with EGFR activating mutations are reported to be responsive to certain EGFR inhibitors (for example, exon 19 deletion or exon 21 L858R point mutations). No matter the type of cancer or the patient's age, TRK inhibitors larotrectinib and entrectinib have been licenced for the treatment of patients with NTRK gene rearrangements. Although the occurrence of these rearrangements is about 1% of all malignancies, they can be discovered at high frequency (up to 90%) in some cancer types, such as infantile fibrosarcoma (a rare disease). efficient in only a tiny proportion of cases. For instance, EGFR inhibitors only work in less than 20% of NSCLC patients (e.g., gefitinib and erlotinib). According to reports, several EGFR inhibitors are effective for treating patients with EGFR activating mutations (for example, exon 19 deletion or exon 21 L858R point mutations). The TRK inhibitors larotrectinib and entrectinib have been approved for the treatment of patients with NTRK gene rearrangements regardless of the kind of cancer or the patient's age. Although these rearrangements only occur in roughly 1% of all malignancies, they can be found up to 90% of the time in some cancer forms, such as infantile fibrosarcoma (a rare disease).
- The first one is the development of new cancer medication targets. Some new epigenetic regulatory proteins, for instance, RNA m6A methylation-related proteins (METTL3/14, FTO, ALKBH5, WTAP, and YTHDFs), have attracted more attention recently. Another novel class of cancer targets is microRNAs (miRNAs), which are frequently dysregulated in malignancies and may offer interesting targets for cancer treatment. Currently, various efforts have been made to find small-molecule inhibitors of miRNAs, such as the Lin28-let-7 inhibitors 6-hydroxy-DLDOPA, SB/ZW/0065, and KCB3602.604, and the miR-21 inhibitor AC1MMYR2 (also known as NSC211332). Additionally, several proteins that were once believed to be insurmountable may also provide interesting anti-cancer targets. KRAS, the RAS proto-oncogene isoform that is most frequently altered, serves as an exampleIt largely contributes to the development and spread of cancer. 605,606 Due to the intrinsic ligand GTP's high binding affinity, the comparatively tiny size and smooth surface of KRAS, and the considerable flexibility of KRAS switch regions, decades of attempts to target KRAS with small compounds have been unsuccessful. But recently, things have started to shift in this predicament. Covalent allosteric inhibitors for the KRAS G12C mutant, inhibitors of protein-protein interactions that bind to the switch I/II pocket or the A59 site, and GTP-competitive inhibitors that target the nucleotide-binding site are just a few of the novel small molecules being developed that directly target KRAS. 609,610 Four KRAS G12C covalent inhibitors (AMG510, JNJ-74699157, MRTX849, and GDC-6036) have made it to clinical trials so far and share similar allosteric mechanisms. The second involves combining immunotherapy with small-molecule targeted medicines like the PD-1 antibody. In 2018, the FDA classified lentitinib plus pembrolizumab, a PD-1 antibody, as a breakthrough therapy for patients with advanced or metastatic RCC. For all RCC patients getting this combination therapy, the ORR was 63.3%, and in the context of first-line therapy, it was 83.3%. 617 Inspiringly, pembrolizumab and another small-molecule inhibitor of angiogenesis, axitinib, have been licenced for use in combination for the treatment of patients with advanced RCC. 618,619 Additionally, this is the first PD-1 antibody + targeted medication combination therapy to be authorised

by the FDA for the first-line treatment of advanced RCC. Antibody-drug conjugate (ADC) medications are the third option. People did not lose faith in ADC medications, even though the first ADC therapy (Mylotarg, Pfizer) experienced a setback in 2010 as a result of the constraints of coupling technology, targeting, and effectiveness. Ten antibody-conjugate medications (ADCs) have been approved by the FDA over the past ten years as a result of advancements in antibody-conjugate technology, including polatuzumab vedotin-piiq (Polivy), enfortumab vedotin-ejfv (Padcev), fam-trastuzumab deruxtecan-nxki (Enhertu), sacit Future development efforts will focus heavily on ADC medicines. The fourth one is called PROTAC, and it uses tiny molecules to draw target proteins to be ubiquitinated and eliminated by the proteasome When compared to conventional "target occupying" inhibitor therapy, PROTAC technology is unique. By accelerating their breakdown, it lowers the activity of target proteins. This approach can significantly impede the recovery of target protein function because target proteins have a slow rate of production. With the ability to overcome many of the difficulties currently encountered in contemporary drug development programmes, PROTAC is a fast developing alternative treatment technique. Two medications (ARV110 and ARV-471) created using PROTAC technology are presently in clinical development. Both of them were created by Arvinas and received FDA phase I clinical study approval in 2019 . Among these, ARV-110 is used to treat individuals with metastatic CRPC because it specifically binds to the androgen receptor (AR) and facilitates AR degradation. An ER protein-degrading agent is ARV-471. In preclinical tests, ARV-471 displayed substantial growth inhibition in a number of ER-driven xenograft models and caused tumors cells to virtually totally degrade their ER. For the treatment of patients with locally advanced or metastatic ER+/HER2-breast cancer, it is currently being clinically investigated. The fifth is called synthetic lethality.



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Reference

1. jemal a, bray f. center mm, ferlay j, ward e, forman d. global cancer statistics. *ca cancer j clin.* 2011;61:69–90. doi: 10.3322/caac.20107. [pubmed] [crossref] [google scholar]
2. xu g, mcleod hl. strategies for enzyme/prodrug cancer therapy. *clin cancer res.* 2001;7:3314–24. [pubmed] [google scholar]
3. krishna r, mayer ld. liposomal doxorubicin circumvents psc 833-free drug interactions, resulting in effective therapy of multidrug-resistant solid tumors. *cancer res.* 1997;57:5246–53. [pubmed] [google scholar]
4. fracasso pm, westervelt p, fears cl, rosen dm, zuhowski eg, cazenave la. phase i study of paclitaxel in combination with a multidrug resistance modulator, psc 833 (valspodar), in refractory malignancies. *j clin oncol.* 2000;18:1124–34. [pubmed] [google scholar]
5. hasinoff bb, chee gl, thampatty p, allan wp, yalowich jc. the cardioprotective and dna topoisomerase ii inhibitory agent dexrazoxane (icrf-187) antagonizes camptothecin-mediated growth inhibition of chinese hamster ovary cells by inhibition of dna synthesis. *anticancer drugs.* 1999;10:47–54. doi: 10.1097/00001813-199901000-00007. [pubmed] [crossref] [google scholar]
6. gerber de. targeted therapies: a new generation of cancer treatments. *am fam physician.* 2008;77:311–9. [pubmed] [google scholar]
7. sorokin p. mylotarg approved for patients with cd33+ acute myeloid leukemia. *clin j oncol nurs.* 2000;4:279–80. [pubmed] [google scholar]
8. jacobs sa. yttrium ibritumomab tiuxetan in the treatment of non- hodgkin's lymphoma: current status and future prospects. *biologics.* 2007;1:215–27. [pmc free article] [pubmed] [google scholar]
9. vitolo u, ladetto m, boccomini c, evangelista a, gamba e, russo e. brief chemoimmunotherapy r-fnd with rituximab consolidation followed by randomization between rituximab maintenance vs. observation as first line treatment in elderly patients with advanced follicular lymphoma (fl): final results of a prospective randomized trial by italian lymphoma foundation (fil) *blood.* 2011;118:352–53. [google scholar]
10. lode hn, xiang r, becker jc, gillies sd, reisfeld ra. immunocy- tokines: a promising approach to cancer immunotherapy. *pharmacol ther.* 1998;80:277–92. doi: 10.1016/s0163-7258(98)00033-3. [pubmed] [crossref] [google scholar]
11. kerr de, vrudhula vm, svensson hp, siemers no, senter pd. comparison of recombinant and synthetically formed monoclonal antibody-beta-lactamase conjugates for anticancer prodrug activation. *bioconjug chem.* 1999;10:1084–89. doi: 10.1021/bc990075w. [pubmed] [crossref] [google scholar]
12. wolfe la, mullin rj, laethem r, blumenkopf ta, cory m, miller jf. antibody-directed enzyme prodrug therapy with the t268g mutant of human carboxypeptidase a1: *in vitro* and *in vivo* studies with prodrugs of methotrexate and the thymidylate synthase inhibitors gw1031 and gw1843. *bioconjug chem.* 1999;10:38–48. doi: 10.1021/bc980057z. [pubmed] [crossref] [google scholar]
13. kawakami k, nakajima o, morishita r, nagai r. targeted anticancer immunotoxins and cytotoxic agents with direct killing moieties. *thescientific world journal.* 2006;6:781–90. doi: 10.1100/tsw.2006.162. [pmc free article] [pubmed] [crossref] [google scholar]
14. hamann pr, hinman lm, hollander i, beyer cf, lindh d, holcomb r. gemtuzumab ozogamicin, a potent and selective anti-cd33 antibody-calicheamicin conjugate for treatment of acute myeloid leukemia. *bioconjug chem.* 2002;13:47–58. doi: 10.1021/bc010021y. [pubmed] [crossref] [google scholar]
15. henry md, wen s, silva md, chandra s, milton m, worland pj. a prostate-specific membrane antigen-targeted monoclonal antibody- chemotherapeutic conjugate designed for the treatment of prostate cancer. *cancer res.* 2004;64:7995–8001. doi: 10.1158/0008-5472.can-04-1722. [pubmed] [crossref] [google scholar]
16. weyel d, sedlacek hh, muller r, brusselbach s. secreted human beta-glucuronidase: a novel tool for gene-directed enzyme prodrug therapy. *gene ther.* 2000;7:224–31. doi: 10.1038/sj.gt.3301072. [pubmed] [crossref] [google scholar]
17. hamstra da, rehemtulla a. toward an enzyme/prodrug strategy for cancer gene therapy: endogenous activation of carboxypeptidase a mutants by the pace/furin family of propeptidases. *hum gene ther.* 1999;10:235–48. doi: 10.1089/10430349950019020. [pubmed] [crossref] [google scholar]
18. springer cj, niculescu-duvaz i. prodrug-activating systems in suicide gene therapy. *j clin investig.* 2000;105:1161–67. doi: 10.1172/jci10001. [pmc free article] [pubmed] [crossref] [google scholar]
19. riggs cd. meiotin-1: the meiosis readiness factor? *bioessays.* 1997;19:925–31. doi: 10.1002/bies.950191013. [pubmed] [crossref] [google scholar]
20. rainov ng, dobberstein ku, sena-esteves m, herrlinger u, kramm cm, philpot rm. new prodrug activation gene therapy for cancer using cytochrome p450 4b1 and 2-aminoanthracene/4-ipom- eanol. *human gene ther.* 1998;9:1261–73. doi: 10.1089/hum.1998.9.9-1261. [pubmed] [crossref] [google scholar]

21. niculescu-duvaz i, spooner r, marais r, springer cj. gene-directed enzyme prodrug therapy. *bioconjug chem.* 1998;9:4–22. doi: 10.1021/bc970116t. [pubmed] [crossref] [google scholar]
22. friedlos f, court s, ford m, denny wa, springer c. gene-directed enzyme prodrug therapy: quantitative bystander cytotoxicity and dna damage induced by cb1954 in cells expressing bacterial nitroreductase. gene ther1998; 5: 105–12. [pubmed]
23. clark aj, iwobi m, cui w, crompton m, harold g, hobbs s. selective cell ablation in transgenic mice expressing e-coli nitroreductase. *gene ther.* 1997;4:101–10. doi: 10.1038/sj.gt.3300367. [pubmed] [crossref] [google scholar]
24. bridgewater ja, knox rj, pitts jd, collins mk, springer cj. the bystander effect of the nitroreductase cb 1954 enzyme prodrug system is due to a cell-permeable metabolite. *human gene ther.* 1997;8:709–17. doi: 10.1089/hum.1997.8.6-709. [pubmed] [crossref] [google scholar]
25. mcneish ia, green nk, gilligan mg, ford mj, mautner v, young ls. virus directed enzyme prodrug therapy for ovarian and pancreatic cancer using retrovirally delivered *e-coli* nitroreductase and cb1954. *gene ther.* 1998;5:1061–69. doi: 10.1038/sj.gt.3300744. [pubmed] [crossref] [google scholar]
26. grove ji, searle pf, weedon sj, green nk, mcneish ia, kerr dj. virus-directed enzyme prodrug therapy using cb1954. anti-cancer drug des 1999; 14: 461–72. [pubmed]
27. nakamura h, mullen jt, chandrasekhar s, pawlik tm, yoon ss, tanabe kk. multimodality therapy with a replication-conditional herpes simplex virus 1 mutant that expresses yeast cytosine deaminase for intratumoral conversion of 5-fluorocytosine to 5-fluoroura- cil. *cancer res.* 2001;61:5447–52. [pubmed] [google scholar]
28. warrington kh, teschendorf c, cao lg, muzyczka n, siemann dw. developing vdept for dt-diaphorase (nqo1) using an aav vector plasmid. *int j radia oncol biol phys.* 1998;42:909–12. doi: 10.1016/s0360-3016(98)00357-5. [pubmed] [crossref] [google scholar]
29. kanazawa t, urabe m, mizukami h, okada t, kume a, nishino h. gamma-rays enhance raav-mediated transgene expression and cytocidal effect of aav-hsvtk/ganciclovir on cancer cells. *cancer gene ther.* 2001;8:99–106. doi: 10.1038/sj.cgt.7700282. [pubmed] [crossref] [google scholar]
30. fukui t, hayashi y, kagami h, yamamoto n, fukuhara h, tohnai i. suicide gene therapy for human oral squamous cell carcinoma cell lines with adeno-associated virus vector. *oral oncol.* 2001;37:211–5. doi: 10.1016/s1368-8375(00)00093-2. [pubmed] [crossref] [google scholar]