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# Targeted Therapy for Cancer

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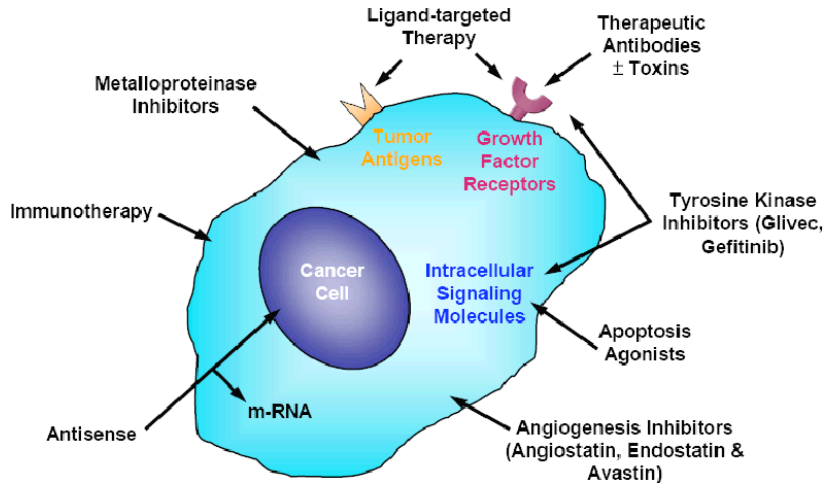
ABSTRACT

Cell proliferation that is out of control or aberrant is a hallmark of the disease cancer. The cells multiply, infiltrate nearby tissues, and frequently start angiogenesis. Depending on the severity of the malignancy, treatment options for it include surgery, chemotherapy, and radiation therapy, or a combination of these. Unfortunately, hair follicle cells, red bone marrow cells, and cells lining the gastrointestinal system are also fast-dividing, and chemotherapy targets rapidly dividing cells. As a result, chemotherapy side effects include hair loss owing to the death of hair follicle cells, vomiting and nausea due to the death of cells lining the stomach and intestines, and infection susceptibility due to the sluggish generation of white blood cells in the red bone marrow. Drugs for targeted therapy don't all function the same. similar manner to conventional chemotherapeutic medicines. By targeting the cancer cells' internal workings, or the programming that distinguishes them from healthy, normal cells, they are frequently able to attack cancer cells while causing less harm to regular cells. We have addressed targeted therapy for the treatment of cancer in this review paper.

Keywords: Chemotherapy, Multidrug resistance, Prodrug, Targeted therapy.

## INTRODUCTION

Initially thought of as "targeting missiles," antibodies have proven to be much more complicated in their targeting and biology characteristics than the field's pioneers anticipated. MoAbs have become crucial therapeutic agents for a variety of malignancies. they have been shown to be safe and efficient for the treatment of many cancers, and as a result, were licenced by the US FDA. In addition to serving as anticancer agents on their own, the capacity to target tumours also makes it possible for them to increase the selectivity of other anticancer drugs, some of which are ineffective when used alone.
Murine antibodies are easily converted into human or humanised forms such that the human immune system is less likely to mistake them for alien substances. Novel antibody-based structures are alsowith multiple antigen recognition sites, altered size, or effector domains have been shown to influence the targeting ability of antibodies. Antibody-based therapeutics are increasingly being used in the treatment of cancer in conjunction with the identification of effective cancer targets. They can be effective when used alone, in combination with chemotherapy or radiation therapy, or when coupled to toxic moieties like toxins, chemotherapy agents, or radionuclides.




A new class of anti-cancer medications known as targeted therapy aim to block a particular target protein that is thought to be essential for the development or progression of tumours. This method differs from the traditional cytotoxic chemotherapeutics utilised in the majority of cancer treatments in previous decades. The discovery of cancer antigens at the molecular level has created new opportunities for the creation of efficient immunotherapies, antibody treatments, and ligand-targeted medicines for cancer patients. A successful method for reducing the selective toxicity of anticancer treatments is ligand-targeted therapy.

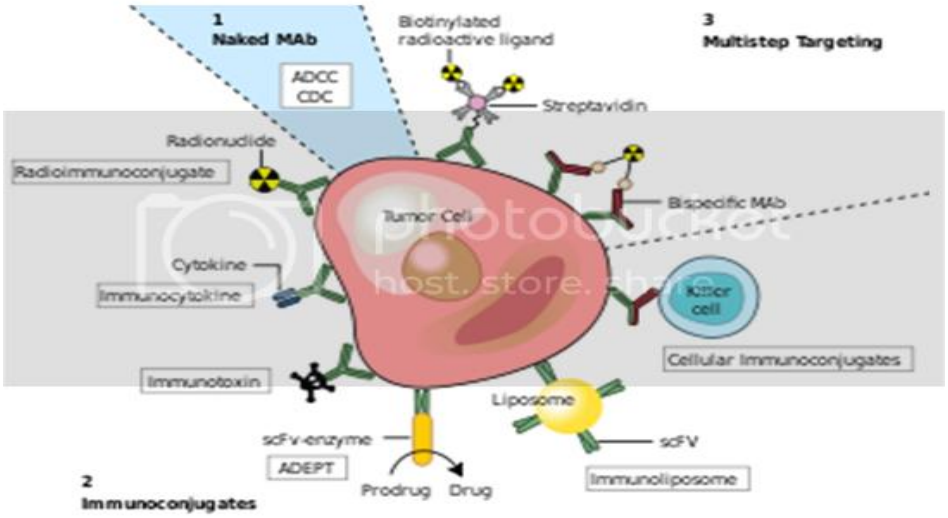
**generation of therapeuticantibodies:**

The earliest antibodies investigated were pure proteins from rats, rabbits, or mice that had been immunised with a target antigen. Patients frequently produced host antibodies to these alien antigens, also known as HAMA (human anti-mouse antibody) or HARA (human anti-rat antibody or human anti-rabbit antibody). By prematurely removing the treatment antibody and restricting the options for subsequent immunotherapy, the host antibody lessens the efficiency of the therapy.HAMA or HARA reactions may be linked to unfavourable immune complex-related outcomes such as serum sickness and anaphylaxis. With the advancement of MoAb engineering and the production of entirely human antibodies, the issue of immunogenicity of murine and chimeric MoAbs might be promptly resolved. The therapeutic agent in solid tumours must get through a number of barriers, such as the vascular endothelium, stromal and epithelial barriers, and high interstitial pressure. Furthermore, solid tumours are highly diverse, making it challenging to completely target them..Smaller recombinant MoAb structures, such as single-chain antibodies, should have better efficiency than the parental antibody when used to target them. The drawback of this benefit is that tiny complexes like these have shorter half-lives because they are removed from the plasma more quickly. Targeting the tumour microenvironment in general and the endothelium of tumour blood vessels, in particular, is a promising strategy for treating solid tumours because multiple tumour endothelial indicators are well described. Human immune effector activities including antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), which are required to promote the destruction of a malignant cell, are not always able to be enlisted by murine, rabbit, or rat antibodies.

Fc receptors are expressed on monocytes, macrophages, natural killer (NK) cells, killer cells, and granulocytes, which are able to cause cytotoxicity. When the attached antibody attaches to NK cells, ADCC occurs. While the opposing Fc section of the antibody connects to Fc receptors on NK cells, the Fab component of the antibody adheres to the cancerous cell. The target is eliminated via the release of cell-lysing chemicals by the NK cells. Longer half-lives of genetically modified antibodies have improved their efficacies. As opposed to 28 hours for the murine equivalent, ibritumomab, the half-life of the chimeric anti-CD20 antibody, rituximab, is 76 hours after a single infusion and 206 hours after four infusions.

## Origins of monoclonal antibody therapy

**Monoclonal antibodies for cancer**




monoclonal antibodies that fight cancerMAb, or monoclonal antibody; scFv, or single-chain Fv fragment; ADEPT, or antibody-directed enzyme prodrug therapy; ADCC, or antibody-dependent cell-mediated cytotoxicity; CDC, or complement-dependent cytotoxicity.

**specific conditions**

**Cancer**

Malignant cells can be targeted by anti-cancer monoclonal antibodies in a number of ways:

- Murine antibodies that have been radioactively conjugated and directed against cellular antigens are used in radioimmunotherapy (RIT). Due to lymphomas' high radiosensitivity, their use in these cancers is now the focus of most studies. Murine antibodies were specifically chosen to reduce radiation exposure due to their high immunogenicity, which facilitates quick removal from the body. Non-Hodgkins lymphoma is represented by tositumomab.
- Antibody-directed enzyme prodrug treatment (ADEPT) includes the administration of monoclonal antibodies coupled to a drug-activating enzyme that is associated with cancer. A non-toxic substance that is later administered systemically changes into a toxic medication and has a cytotoxic impact that can be directed at cancerous cells. Treatments using ADEPT have had very patchy clinical success thus far.Nevertheless, it shows significant promise and recent results indicate that it will play a part in oncological treatment in the future.
- Antibody-conjugated liposomes are known as immunooliposomes. Drugs or therapeutic nucleotides can be carried by liposomes, and when combined with monoclonal antibodies, they may be directed against cancerous cells. Despite the fact that this approach is still in its early stages, significant progress has been made. Using an antibody fragment against the human transferrin receptor, immunooliposomes have been effectively employed in vivo to deliver tumour-suppressing genes to specific tumours. Immunoliposomes have also proved successful in delivering tissue-specific genes to breast cancer and brain tissue.

## Example FDA-approved therapeutic monoclonal antibodies

In 1986, OKT3 (also known as Murom nab), a murine IgG2a CD3-specific transplant rejection medication, became the first therapeutic monoclonal antibody to get FDA approval. When recipients of solid organ transplants developed steroid resistance, this medication was used. Clinical trials for hundreds of treatments are being conducted. The majority are focused on oncological and immunological targets.

**Targeted therapy by small molecules**

The potential for developing novel agents has increased with our expanding understanding of the molecular processes that underlie the aetiology of many cancers as well as the signalling processes essential for the survival and proliferation of cancer cells. The objective of this new kind of chemotherapy, known as targeted therapy, is to give molecularly-based medicines that are more selective for cancer cells. Rational and empiric approaches are typically utilised in parallel or in combination in the majority of modern drug discovery efforts. Through molecular screening, inhibitors for molecular targets are discovered in lead compounds.

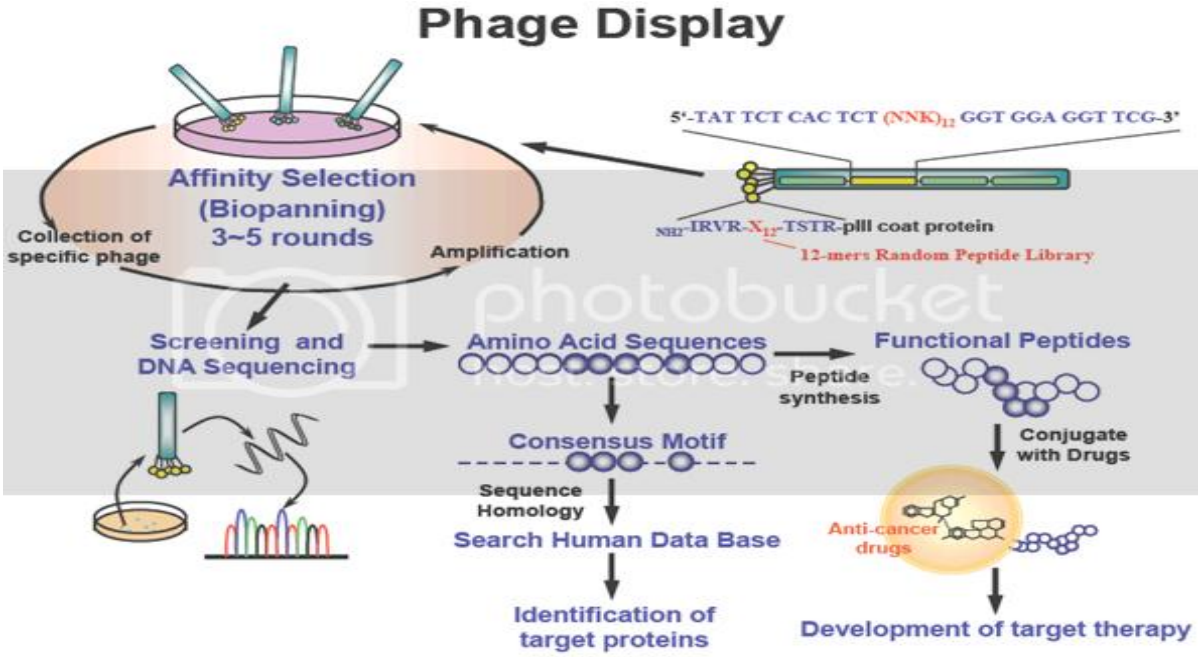
Most elements of cell life are regulated by protein phosphorylation, but aberrant phosphorylation can cause or contribute to disease, particularly in cancer biology, where it can lead to improper proliferation, anti-apoptosis, and angiogenesis. Numerous studies have also shown that, as compared to normal cells, malignancies can activate protein phosphorylation-related pathways by mutation or overexpression. Due to these factors, targeted therapy favours drugs that are as close to mono-specific as feasible in order to prevent the negative side effects that can occasionally accompany conventional treatments. As a result, protein kinase small molecule inhibitors have become crucial for researching target treatments.

The protein kinases that are connected with the plasma membrane have received the most attention from medication developers. Hiroyoshi Hidaka created the first kinase inhibitors at the beginning of the 1980s, about 20 years ago. The calcium-binding protein calmodulin has already been targeted through the development of naphthalene sulphonamides. The two most well-known small molecule inhibitors are Glivec and Gefitinib, and there are currently more than 30 such medicines in clinical development. The first selective tyrosine kinase inhibitor to be approved for the treatment of cancer was Glivec (imatinib mesylate, Gleevec, STI571; Novartis).

Glivec, a 2-phenylaminopyrimidine, suppresses the constitutively activated Bcr-Abl tyrosine kinase, a particular genetic alteration encoding aberrant protein linked to human cancer, by competitively inhibiting ATP binding to the Abl kinase. Since Bcr-tyrosine Abl's kinase activity is essential for its transforming activity, it is conceivable that this unregulated gene's enzymatic activity may be categorised as an alluring pharmacological target for treating Bcr-Abl-related chronic myelogenous leukaemia (CML).

**Ligand-targeted therapy**

The majority of cancer cells have a lot in common with the healthy host cells from which they originated. Because anticancer chemotherapeutics lack specific molecular targets that would distinguish them from normal cells, large degrees of selective toxicity cannot be reached. Increased toxicity toward healthy tissues, such as bone marrow, the digestive system, and hair follicle tissues, may result from this. Furthermore, we frequently administer sub-optimal doses of anticancer chemotherapeutics in an effort to prevent the side effects that result from toxicities to normal tissues, which ultimately leads to the failure of therapy, which is frequently accompanied by the emergence of drug resistance and metastatic disease.By either increasing the concentration of the medication that reaches the cancer tissue or decreasing the concentration of the drug that reaches the normal tissues, an anticancer agent's selective toxicity can be raised. As a result, ligand-targeted therapy enables tumour selectivity and minimal toxicity and holds potential for the creation of cutting-edge cancer treatments. Ligand-targeted therapy may overcome challenges posed by cytotoxic chemotherapy and deliver larger dosages of medication to the tumour tissue. Drug resistance, increased tumour interstitial fluid pressure (IFP), and cancer stem cells are a few of the challenges in cancer therapy (CSCs).




We discovered a 12-mer peptide (L-peptide) preferentially binding to nasopharyngeal cancer (NPC) cells using these methods. Most NPC cell lines and biopsy samples have Lphage and synthesised L-peptide attached to the tumour cell surfaces. The L-phagesare specifically bound to the tumour mass in

SCID mice carrying NPC xenografts. In the competitive inhibition assay, it was discovered that synthetic L-peptide prevented L-phage particles from adhering to the tumour mass. Once the cancer cells' targeting ligands have been identified, we can combine the peptides with a chemotherapeutic Phage display is used to find ligands that target cancer cells. Peptide or antibody libraries can be expressed as fusion proteins with a bacteriophage's coat protein (pIII), which causes the fused proteins to be displayed on the surface of the virion. A potent method of finding peptide ligands for targets of interest is affinity selection (biopanning) using phage displayed peptide libraries. Phage-displayed peptide library was pre-cleared by normal cells and affinity was selected with cancer cells in order to test for targeted ligands. Targeting phage clones were chosen by ELISA, flow cytometry, immunofluorescence, and in vivo homing assays after biopanning three to five times. By using a synthetic peptide binding and competition experiment, targeting ligands were also discovered and described. Cell surface indicators can be found via targeting ligands and ligand-targeted therapy.

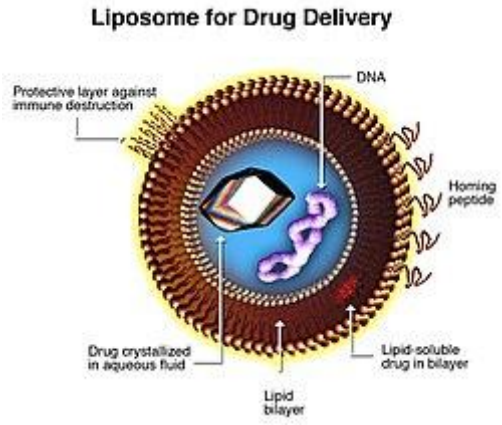
Phage-based search targeting ligands Phage display is a selection method that displays the fusion peptide or protein on the surface of the virion when a peptide or protein is expressed as a fusion with a bacteriophage coat protein. The ability to map B-cell epitopes and protein-protein interactions, choose bioactive peptides coupled to receptors or proteins, look for disease-specific antigen mimics, and identify cell- and organ-specific peptides are all advantages of phage-displayed random peptide libraries. We recently created phage display techniques to recognise the receptors particularly expressed on cancer cells and tumour vasculature.

The method for finding tumormedicines to create ligand-targeted treatments, which precisely kill cancer cells. Due to the following benefits, we have decided to conjugate targeted ligands with liposomes:

(1) extended blood circulation,

(2) adequate tumour accumulation, and

(3) regulated drug release and uptake by tumour cells with a release profile that matches the medication's pharmacodynamics.




Liposomes are phospholipid-based composite structures that may also contain trace amounts of other substances. Unilamellar liposomes, as shown here, are typically in the lower size range with different targeting ligands attached to their surface, allowing for their surface attachment and accumulation in pathological areas for the treatment of disease. Liposomes can range in size from low micrometre range to tens of micrometres.

**Targeting cancer (liposomes)**

The EMEA has designated new liposomal cancer medications including liposomal cisplatin (Lipoplatin of Regulon Inc.) as an orphan medicine for pancreatic cancer.

## Conclusion

The pharmaceutical industry has been successful in finding numerous novel cytotoxic medications that may be used to treat cancer, a life-threatening disease that continues to cause up to 7 million deaths annually worldwide and is on the rise.

Therefore, it is vital to continue designing and discovering new cancer therapies. In general, serious side effects and acquired drug resistance are frequently associated with chemotherapy for cancer. So, we eagerly anticipate the introduction of target therapy that will enable more precise targeting.

Recently, several attempts have been undertaken to achieve this goal, including using monoclonal antibodies or tiny chemicals to stop the growth of tumours. The idea of "pathway-specific" targeted medicines still has substantial limitations, despite the encouraging clinical outcomes from the drugs we have highlighted. Only tumour forms that depend on the pathways being blocked or the expression of tumour antigens are responsive to these drugs. It is obvious that the majority of solid tumours are the consequence of many genetic changes, hence blocking a particular biological route might not have a big therapeutic impact.

Agents that are designed to target many pathways may have a greater therapeutic effect but also raise the potential of harmful side effects from the treatment. The half-life has been extended using liposomes containing different lipid derivatives of polyethene glycol (PEG). To reach the tumour site, they require a tumour-targeting ligand, though. Because immunoconjugates are unable to readily penetrate tumour tissue, they have only limited utility for drug delivery in solid malignancies, which account for more than 90% of all cancers in humans. Consequently, the discovery of peptide ligands and the creation of peptide-targeting

Having a liposome is really desirable. By using targeting liposomes for ligand-targeted therapy, we may be able to deliver greater medication dosages to the tumour tissue and get around some of the barriers to successful cancer treatment.

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