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Review Article

Review on Liposome as Novel Approach for Cancer Therapy

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A B S T R A C T

The main objective is to study the importance of liposome in drug targeting in cancer cells andgo through various research work going through on liposome. The importance of liposomes to study the flexibility to couple with the specific ligands toachieve active targeting. Cancer can be treated by surgery, radiation, chemotherapy, gene therapy, immunotherapy, hormone therapy. Cancer is the uncontrolled growth of abnormal cell anywhere in a body. The abnormal cells aretermed cancer cells, malignant cells, or tumor cells. There were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in 2018 worldwide. 57% (8 million) of new cancer cases, 65% (5.3 million) of the cancer deaths and 48% (15.6 million) of the 5-year prevalent cancer cases occurred in the less developed regions.

Key Words:-Liposome, Targeted drug delivery system, controlled drug delivery, Immunotherapy.

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INTRODUCTION:

Cancer is a class of diseases characterized by out-of-control cell growth. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected. Cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called tumors (except in the case of leukemia where cancer prohibits normal blood function by abnormal cell division in the blood stream). Tumors can grow and interfere with the digestive, nervous, and circulatory systems and they can release hormones that alter body function. Tumors that stay in one spot and demonstrate limited growth is generally consideredto be benign. More dangerous, or malignant, tumors form when two things occur: -

- A cancerous cell manages to move throughout the body using the blood or lymph.
- That cell manages to divide and grow, making new blood vessels to feed itself in a process called angiogenesis.

When a tumor successfully spreads to other parts of the body and grows, invading and destroying other healthy tissues, it is said to have metastasized. This process itself is called metastasis, and the result is a serious condition that is very difficult to treat. In 2007, cancer claimed the lives of about 7.6 million people in the world. Physicians and researchers who specialize in the study, diagnosis, treatment, and prevention of cancer are called oncologists. [1,2,3,4]

Causes, incidence, and risk factors

Cells are the building blocks of living things. Cancer grows out of normal cells in the body.

Normal cells multiply when the body needs them, and die when the body doesn't need them.

Cancer appears to occur when the growth of cells in the body is out of control and cells divide

too quickly. It can also occur when cells forget how to die.

There are many different kinds of cancers. Cancer can develop in almost any organ or tissue,

such as the lung, colon, breast, skin, bones, or nerve tissue.

There are many causes of cancers, including:

- Benzene and other chemicals
- Drinking excess alcohol
- Environmental toxins, such as certain poisonous mushrooms and a type of poison that can grow on peanut plants (aflatoxins)
- Excessive sunlight exposure
- Genetic problems

- Obesity
- Radiation
- Viruses

Symptoms

Symptoms of cancer depend on the type and location of the cancer. For example, lung cancer can
cause coughing, shortness of breath, or chest pain. Colon cancer often causes diarrhea,
constipation, and blood in the stool.
Some cancers may not have any symptoms at all. In certain cancers, such as pancreatic cancer,
symptoms often do not start until the disease has reached an advanced stage.
The following symptoms can occur with most cancers:

- Chills
- Fatigue
- Fever
- Loss of appetite
- Malaise
- Night sweats
- Weight loss

Signs and tests

Like symptoms, the signs of cancer vary based on the type and location of the tumor. Common tests include the following:

- Biopsy of the tumor
- Blood tests (which look for chemicals such as tumor markers)
- Bone marrow biopsy (for lymphoma or leukemia)
- Chest x-ray
- Complete blood count (CBC)
- CT scan
- MRI scan

Most cancers are diagnosed by biopsy. Most cancers are diagnosed by biopsy. Depending on the location of the tumor, the biopsy maybe a simple procedure or a serious operation. Most patients with cancer have CT scans todetermine the exact location and size of the tumor or tumors. A cancer diagnosis is difficult to cope with. It is important, however, that you discuss the type,size, and location of the cancer with your doctor when you are diagnosed. You also will want to ask about treatment options, along with their benefits and risks.It's a good idea to have someone with you at the doctor's office to help you get through the diagnosis. If you have trouble asking questions after hearing about your diagnosis, the personyou bring with you can ask them for you.

Types of Cancer

There are over 200 types of cancer; far too numerous to include in this introductory article. However, the NCI lists several general categories (see list in first section of this article). This list is expanded below to list more specific types of cancers found in each general category; it is not all inclusive and the cancers listed in quotes are the general names of some cancers:

Carcinoma: Cancer that begins in the skin or in tissues that line or cover internal organs -"skin, lung, colon, pancreatic, ovarian cancers," epithelial, squamous and basal cell carcinomas, melanomas, papillomas, and adenomas.

Sarcoma: Cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue -- "bone, soft tissue cancers," osteosarcoma, synovial sarcoma, liposarcoma, angiosarcoma, rhabdosarcoma, and fibro sarcoma.

Leukemia: Cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood -- "leukemia," lymphoblastic leukemias (ALL and CLL), myelogenous leukemias (AML and CML), T-cell leukemia, and hairy-cell leukemia.

Lymphoma and myeloma: Cancers that begin in the cells of the immune system -- "lymphoma," T-cell lymphomas, B-cell lymphomas, Hodgkin lymphomas, non-Hodgkinlymphoma, and lymphoproliferative lymphomas.

Central nervous system cancers: Cancers that begin in the tissues of the brain and spinal cord -- "brain and spinal cord tumors," gliomas, meningiomas, pituitary adenomas, vestibularNot included in the above types listed are metastatic cancers; this is because metastatic cancer cells usually arise from a cell type listed above and the major difference from the above types is that these cells are now present in a tissue from which the cancer cells did not originally develop. Consequently, if the terms "metastatic cancer" is used, for accuracy, the tissue from which the cancer cells arose should be included. For example, a patient may say they have or are diagnosed with "metastatic cancer" but the more accurate statement is "metastatic (breast, lung, colon, or other type) cancer."

Cancers are often referred to by terms that contain a prefix related to the cell type in which the cancer originated and a suffix such as -sarcoma, -carcinoma, or just -coma. Common prefixes include [1]

- Adeno- = gland
- Chondro- = cartilage
- Erythro- = red blood cell
- Hemangio- = blood vessels
- Hepato- = liver
- Lipo- = fat
- Lympho- = white blood cell
- Melano- = pigment cell
- Myelo- = bone marrow
- Myo- = muscle
- Osteo- = bone
- Uro- = bladder
- Retino- = eye
- Neuro- = brain

Treatment of Cancer

Cancer treatment depends on the type of cancer, the stage of the cancer (how much it has spread), age, health status, and additional personal characteristics. There is no single treatment for cancer, and patients often receive a combination of therapies and palliative care. Treatments usually fall into one of the following categories: surgery, radiation, chemotherapy, immunotherapy, hormone therapy, or gene therapy.

Surgery

Surgery is the oldest known treatment for cancer. If a cancer has not metastasized, it is possible to completely cure a patient by surgically removing the cancer from the body. This is often seen in the removal of the prostate or a breast or testicle. After the disease has spread, however, it

is nearly impossible to remove all of the cancer cells. Surgery may also be instrumental in helping to control symptoms such as bowel obstruction or spinal cord compression.

Immunotherapy

Immunotherapy aims to get the body's immune system to fight the tumor. Local immunotherapy injects a treatment into an affected area, for example, to cause inflammation that causes a tumor to shrink. Systemic immunotherapy treats the whole body by administering an agent such as the protein interferon alpha that can shrink tumors. Immunotherapy can also be considered nonspecific if it improves cancer-fighting abilities by stimulating the entire immune system, and it can be considered targeted if the treatment specifically tells the immune system to destroy cancer cells. These therapies are relatively young, but researchers have had success with treatments that introduce antibodies to the body that inhibit the growth of breast cancer cells. Bone marrow transplantation (hematopoietic stem cell transplantation) can also be considered immunotherapy because the donor's immune cells will often attack the tumor or cancer cells that are present in the host.

Chemotherapy

Chemotherapy utilizes chemicals that interfere with the cell division process - damaging proteins or DNA - so that cancer cells will commit suicide. These treatments target any rapidly dividing cells (not necessarily just cancer cells), but normal cells usually can recover from any chemicalinduced damage while cancer cells cannot. Chemotherapy is generally used to treat cancer that has spread or metastasized because the medicines travel throughout the entire body. It is a necessary treatment for some forms of leukemia and lymphoma. Chemotherapy treatment occurs in cycles so the body has time to heal between doses. However, there are still common side effects such as hair loss, nausea, fatigue, and vomiting. Combination therapies often include multiple types of chemotherapy or chemotherapy combined with other treatment options.

Hormone therapy

Several cancers have been linked to some types of hormones, most notably breast and prostate cancer. Hormone therapy is designed to alter hormone production in the body so that cancer cells stop growing or are killed completely. Breast cancer hormone therapies often focus on reducing estrogen levels (a common drug for this is tamoxifen) and prostate cancer hormone therapies often focus on reducing testosterone levels. In addition, some leukemia and lymphoma cases can be treated with the hormone cortisone.

CONCEPT OF DRUG TARGETTING [4,5,6,7]

Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at predefined target in therapeutic concentration while restricting its access to non-target normal cellular linings thus minimizing toxic effects and maximizing therapeutic index. maximizing therapeutic index. The concept of designing specified delivery system to achieve selective targeting has been originated from the perception of Paul Ehrich who proposed drug delivery to be as a magic bullet. It was the very first report published on targeting drug delivery as an event where a drugcarrier complex, deliver drug to the preselected target cells in specific manner.

Approaches are being adopted either to control the distribution of drug by incorporating it in a carrier system or by altering the structure of the drug at the molecular level or by controlling the input of the drug into the bio distribution. The efforts to improve drug effectiveness in therapeutics have been assisted by parallel developments in molecular and cell biology.

RATIONALE OF DRUG TARGETING [8, 9, 10, 11]

Intravenous route of administration is considered as the most promising route for liposomal formulation. The role of the liposome (containing the drug) is to circulate in the blood in order toreach the desired organ or tissue. The liposomal membrane acts as a barrier protecting the drug from premature elimination or metabolism. At the same time, the liposome membrane iscontrolling the release of the cytotoxic agent. The liposome carrier may also direct drugs to the tumour site. Thereby, the therapeutic window and toxicity profile of drug compounds can be improved. The liposomal accumulation at tumour site is referred to as the enhanced permeability and retention effect and is based on dissimilarities of healthy and cancerous tissues. The endothelial walls of blood vessels in tumors are leakier than those in healthy tissues because of an increased number of bigger gaps. Thus, small liposomes are able to extravasate and penetrate into solid tumors. At the same time, the liposomes stay longer within the tumour site since the removal by the lymphatic system is greatly reduced in cancerous tissue.

LEVEL OF DRUG TARGETING [12, 13, 14]

Targeted drug delivery may be achieved by using carrier system where reliance is placed on exploiting both intrinsic pathway that these carriers follow, and the bioprotection that they can offer to drugs during transit through the body. The various approaches of vectoring the drug to the target site can be broadly classified as:

- Passive targeting
- Inverse targeting
- Active targeting (Ligand mediated targeting and physical targeting)
- Dual targeting
- Double targeting
- Combination targeting

CARRIER SYSTEM USED FOR DRUG TARGETED DRUG DELIVERY [15, 16, 17, 18]

1. **Colloidal Carriers**
   a) **Vascular systems-** liposome noisome Phamacosome, virosomes, imunoliposome.
   b) **Micro particulate systems-** Microparticles, nanoparticle, magnetic microsperes, albumin microspheres,nanocapsules.
2. **Cellular carrier**

   Resealed erythrocytes, serum, albumin, antibodies, platelets, leukocytes.

3. **Supramolecular delivery systems**

   Micelles, reversed micelles, mixed micelles, polymeric micelles, liquid crystal lipoprotein.

4. Polymer based system

Signal sensitive muco- adhesive, biodegradable soluble synthetic polymeric carrier

5. Macromolecular carriers

(a) Protein glycoprotein neo glycoproteins artificial viral envelopes

(b) Glycosylated water soluble polymers

(c) Mabs, immunological Fab fragments

(d) Toxins, immunotoxin & rCD4 toxin conjugates

LIPOSOMES AS DRUG DELIVERY SYSTEM [19, 20]

The applicability of drugs is always a compromise between their therapeutic effect and side effects. Liposomal drug delivery systems not only enable the delivery of higher drugconcentrations, but also a possible targeting of specific cells or organs. Harmful side effects can therefore be reduced owing to minimized distribution of the drug to non-targeted tissues. Like allother carrier systems, the use of liposomes in drug delivery has advantages and disadvantages. The amphiphilic character of the liposomes, with the hydrophobic bilayer and the hydrophilic inner core, enables solubilization or encapsulation of both hydrophobic and hydrophilic drugs.

Along with their good solubilization power, a relatively easy preparation and a rich selection of physicochemical properties have made liposomes attractive drug carrier systems. Efficient drug delivery systems based on liposomes need to possess a large number of special qualities. First, good colloidal, chemical and biological stability is required. The fact that liposomes are nonequilibrium structures does not necessarily mean that they are unsuitable for drug delivery. On the contrary, a colloidally stable nonequilibrium structure is less sensitive to external changes than equilibrium structures, such as micelles. Hence, colloi dally stable liposomes often work well in pharmaceutical applications. Biological stability includes control over the rate of clearance of liposomes from the circulatory system or compartments of the body, if the drug has been administered locally. The rate of clearance is dose dependent and varies according to the size and surface charge of the liposomes. Early studies using conventional liposomes revealed that the clearance was too rapid for an effective *in vivo* drug delivery. However, circulation times that were sufficiently long were achieved by the development of the so-called sterically stabilized liposomes. In addition, biological stability also comprises retention of the drug by the carrier en route to its destination (a phenomenon known as sustained release). For example, blood proteins were found to remove phospholipid molecules rapidly from the bilayer, leading to a disruption of the liposomes and hence drug loss before the carriers reached their target destination. In contrast to a sustained release, liposomes also have to be able to release the encapsulated drug, which might not be as easy as it sounds, and, they should preferably also be targeted.

LIPOSOMES [21,22,23]

Definition and background

Liposomes are spherical vesicles composed of lipid bilayer arranged around a central aqueous core. They can be composed of natural constituents such as phospholipids and may mimic naturally occurring cell membranes. Liposomes have the ability to incorporate lipophilic and amphiphilic drugs within their phospholipid membrane or they can encapsulate hydrophilic compounds within the aqueous core as shown in Figure 1.2. Liposome formulations can therefore increase safety and efficiency in reaching the site of action. Liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Drug delivery and targeting has enable to used as therapeutic tool in fields like tumour targeting gene and antisense therapy, genetic vaccination, immunomodulation, lung therapeutic, fungal infections and skin care and topical cosmetic products.

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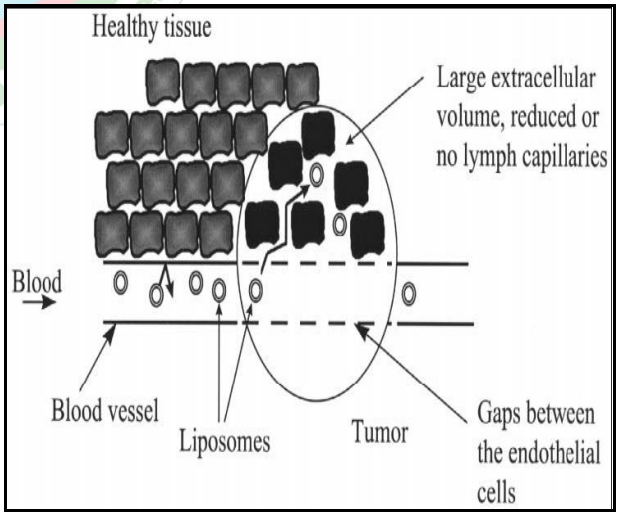

Figure:1 The enhanced permeability and retention effect

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   e) Lectins & polysaccharides

LIPOSOMES AS DRUG DELIVERY SYSTEM [28, 29, 30]

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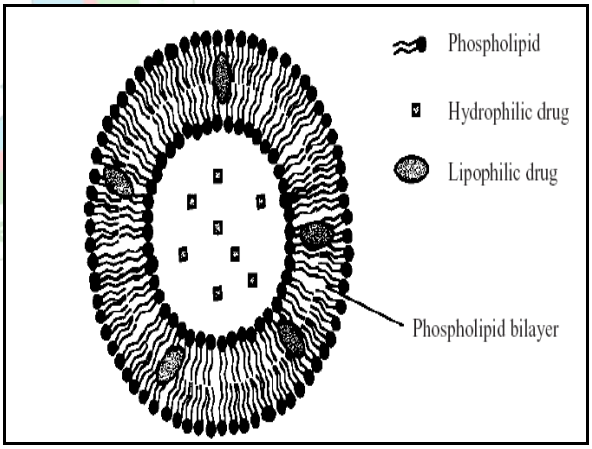

Figure: 2 A schematic representation of incorporation and encapsulation of drugs into a liposome

Advantages of liposomes[5]

- Provide passive targeting to tumour tissue
- Increased efficacy and therapeutic index
- Increased stability via encapsulation
- Reduction in toxicity of the encapsulated agents
- Site avoidance effect
- Improved pharmacokinetic effect
- Flexibility to couple with site specific ligands to achieve active targeting

Mechanism of the liposome formation

Phospholipids are amphipathic molecules as they have a hydrophilic tail and hydrophilic or polar head. The hydrophobic tail is composed of two fatty acid chains containing 10-24 carbon atoms. The polar end of the

molecules is mainly phosphoric acid bound to a water soluble molecule. Among the amphiphilic used in the drug delivery viz soaps, detergents, polar lipids, the latter are often employed to form concentric bilayer structures. The most common natural polar phospholipids are phosphatidylcholine. These are amphipathic molecules in which a glycerol bridge links to a pair of hydrophobic acyl hydrocarbon.

Molecules of PC are not soluble in aqueous in the physical chemistry sense. Liposomes are formed when thin lipid films or lipid cakes are hydrated and stacks of liquid crystalline bilayer become fluid and swell. Once these vesicles are formed a change in the vesicle shape and morphology requires energy input in the form of sonic energy.

Characterization of liposomes

Classifications of liposomes are based on their size and lamellarity. Different size and lamillarity depends on their composition and their method of preparation. Liposomes are usually categorized in to three main types, based on the size and lamellarity, as follows.

Multilamellar vesicles (MLVs) is one of the three categorizes. These are vesicles with a size ranging from 100 nm to several micrometers, depending on the method of preparation. They consist of a large number concentric lamellar, and due to their large lamellarity they are more suited to incorporation of lipophilic molecules compared to hydrophilic substances

Small unilamellar vesicles (SUVs) are vesicles consisting of single bilayer and can theoretically be as small as about 20 nm. They are more suitable for parenteral administration than MLVs, because of their homogeneity in size. Their small size results in lower amount of encapsulation of hydrophilic drugs.

Large unilamellar vesicles (LUVs) are vesicles generally with size in the order of 100 nm, consisting of one single lamellar. They can entrap a higher amount of hydrophilic drugs due to their larger aqueous core compared with SUVs.

The role of liposome size

The rate of the opsonisation and clearance by the reticuloendothelial system (RES) of the injected liposomes from the blood circulation is dependent on the composition and size.RES is part of the immune system and their main function is to eliminate foreign materials from the body. RES consists of cells such as blood monocytes and macrophages found mainly in the Kupffer cells in liver, the lung and the spleen. Shortly after i.v injection, the liposomes become coated by serum proteins called opsonins. Once they are opsonised, they will rapidly be phagocyted by the RES cells and the major part of the injected liposomes will be accumulated in the liver and spleen. Large liposomes (>200 nm in diameter) are rapidly opsonised and taken up by the (RES) disappear from the blood circulation within short time and primarily end up in the spleen. Opsonisation decreases with a decreasing in liposome size. Small liposomes have a relatively larger surface area, and will have a lower density of opsonins on the membrane surface which results in lower uptake by the macrophages. Liposomes with a size of 70 to 200 nm will have a greater chance to escape from RES and remain in the circulation longer and then reach the target. Due to extravasations through the fenestrated capillary walls in the liver, the small liposomes (< 70 nm in diameter) show shorter circulation time. The structure and architecture of the blood capillary walls varies in different organs and tissues. There are structure differences between healthy and tumour capillaries and blood supply to the organs and tissues is somewhat different.

The role of the surface charge and membrane characteristics

Lipid organization in the liposome membranes has a major role on the physical membrane properties such as permeability, membrane elasticity, surface charge and binding properties of proteins, and is of equal importance for clearance as compared to liposome size. Neutral-charged liposomes with tightly packed membranes tend to remain longer in the circulation and exhibit increased drug retention, compared to charged systems. Protein opsonisations onto the liposome surface are reduced due to the tightly packed and rigid membrane. The presence of Cholesterol in liposome formulations may change the packing of the phospholipids to a more ordered and rigid membrane and may stabilize to avoid drug leakage.

Liposomes in cancer therapy

- Liposomes are used for drug delivery in cancer therapy due to their unique properties. They have the distinct advantages of being non-toxic and degradable in the body because of their naturally occurring lipids as main content.
- Liposomes have also a unique ability to entrap both hydrophilic and lipophilic drugs to its compartment and lead to a controlled release effect.
- Drug entrapment in the liposomes has also shown reduced drug toxicity due to minimized uptake in other tissues such as heart, kidneys and gut.
- Beside their ability to protect the entrapped drugs from degradation in the blood stream.
- Their most important properties is the ability to accumulate in the tumors by passive targeting due to the enhanced permeability and retention effect (EPR) (Figure 1.3).
- The EPR effect is due to the differences between the vasculature in tumors and healthy tissues. Because of the angiogenesis, the blood vessels in tumor are more leaky and have less perfect cellular packing leading to bigger gaps between the cells. Furthermore, the lymphatic system which is responsible for removing substances such as liposomes or other nanoparticles from the tissues is marginally expressed compared to normal tissue. By utilizing the EPR effect, small liposomes (< 70 nm) are able to escape vasculature within tumors and accumulate there via passive targeting effect.

SUMMARY AND CONCLUSION-

In study of various literature and study work we found and concluded that liposomes asanticancer for use in targeted cancer therapy have solely been investigated in the pre-clinical setting. Obtained results certainly provide a promise that in the future this drug carrier system could achieve more specific and less toxic clinical delivery of a wide variation of anticancer drugs in cancers such as

glioblastoma multiform, where currently available therapy lacks efficiency. However, for liposome-based anticancer therapy to display maximal effect and minimal side effects, it requires identification of specific target molecules and appropriate drugs to be delivered.

Targeting of several distinct tumour compartments by combining Immuno-liposomes of different targeting specificities could aid in directing drugs to a larger proportion of the tumour. It can be difficult to achieve a sufficient drug delivery using only one targeting agent due to the heterogeneous molecular profile of both cancer cells and tumour endothelial cells. In addition, applying liposomes directed to a single target probably could result in development of cellular resistance mechanisms, as observed in the clinical setting when ad-ministering molecular targeted drugs as mono therapy. Simultaneous liposomal drug delivery to several distinct cell populations within the tumour, such as cancer cells and tumour endothelial cells, as well as putative cancer stem cells, might generate synergistic therapeutic effects and minimize drug resistance.

An advantage of using the post insertion technique for preparation of cancer targeted Immuno-liposomes is that this technique has the potential for development of a "mix and match" strategy. Based on the molecular profile of a specific tumor, patient-specific antibodies can be conjugated to commercially available untargeted liposomes, tailoring drugloadedImmuno-liposomes to the tumor cells. If an arsenal of liposomes containing different therapeutic molecules is made available, this approach allow not only for tailoring the targeting antibody but also the active drug to the molecular profile of the target cell. Thus, based on the molecular characteristics of the different cell populations within a specific tumor, Immuno-liposomes that target a highly expressed molecule and contain a drug of anticipated effect can be prepared specifically for the chosen target cell population. In the clinical setting, this allows application of highly "personalized", multi targeted Immuno liposomes for the single patient.

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