Novel Innovation Of Drug Changing Mechanism Improvement Towards Delivery System Using Prodrugs : A Paradigm Shift In Cancer Treatment.

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Abstract: **"Cancer treatment has traditionally relied on systemic chemotherapy, often resulting in significant toxicity and limited efficacy. The emergence of prodrugs and targeted delivery systems has revolutionized this approach, enabling the selective delivery of therapeutic agents to tumor sites. This review provides an in-depth analysis of prodrug design, synthesis, and delivery systems, highlighting their potential to improve cancer treatment outcomes. We also discuss the challenges associated with these approaches and future directions for research. Cancer remains a leading cause of mortality worldwide, necessitating the development of innovative therapeutic strategies. Prodrugs and targeted delivery systems have emerged as promising approaches to enhance the efficacy and reduce the toxicity of cancer treatments. This review provides a comprehensive overview of recent advances in prodrug design, synthesis, and delivery systems, including nanoparticles, liposomes, and conjugates. We discuss the challenges and opportunities associated with these approaches and highlight their potential to revolutionize cancer treatment.**

Keywords: **Prodrugs, API, Pharmacodynamics-Kinetics, ADME.**

INTRODUCTION

By definition, a prodrug is a material that undergoes biotransformation before exhibiting its therapeutic effects.[1] These are actually bioreversible drug derivatives, which means that even after going through an enzymatic and/or chemical change in vivo, the active parent drug may still have the necessary pharmacological effect. These include a bond that must be broken by the body's enzymes between the active and inactive moieties.[1] Using a range of techniques, including increased solubility, enhanced permeability, and They can increase therapeutic efficacy and/or reduce side effects due to their tissue-targeted dispersion, extended half-life, and bioavailability. The most important developments in prodrug design over the last five years have been in techniques to achieve tumor-specific targeting and boost oral bioavailability. Chemical changes that add alkyl moieties to the medication can increase its lipophilicity to the drug molecule or create salts for a quicker rate of dissolution; yet, these modifications can result in a reduction or elimination of the drug's pharmacological activity as compared to the original treatment.[2]Numerous formulation techniques can be employed to overcome physicochemical barriers , albeit they may not always result in adequate drug delivery. The prodrug approach provides a potentially practical solution to these problems.In the past ten years, the US Food and Drug Administration (FDA) has approved about thirty prodrugs, which make up 12% of all newly approved small-molecule compounds. Approximately 10% of all medications sold commercially globally are prodrugs.[2]

1 Targeting tumors: Mechanism

The goal of cancer treatment is to selectively target tumor cells with an inactive prodrug so that the active drug can be released without endangering healthy, normal tissue.[3,4] Due to the high rates of tumor cell proliferation and bio-reductive activity, these cells frequently have higher levels of certain enzymes, which have been used in targeted prodrug-tumor delivery[5]. A prodrug that is activated by tumor-selective enzymes has been developed in response to the requirement for decreased normal tissue exposure of the cytotoxic drug 5-fluorouracil (5-FU)[6,7]. An enzyme called carboxylesterase causes the first dilapidation in the liver, which is followed by deamination by cytidine deaminase, which is found in both the liver and tumor cells. Thymidine phosphorylase then selectively releases 5-FU in the tumor cells, demonstrating significantly greater activity in tumor cells than in normal cells. Following oral capecitabine treatment, 5-FU has a bioavailability of almost 100% and reaches its Tmax in 1.5–2 hours.Figure 2: Capecitabine prodrug's several enzymatic activation stages.[7] The two most popular methods for expanding the range of malignancies amenable to enzyme-prodrug cancer therapy are gene-directed enzyme prodrug therapy (GDEPT) and

antibody-directed enzyme prodrug therapy (ADEPT). One method to address the issues with tumor selectivity is ADEPT. An An enzyme called carboxylesterase causes the initial hepatic dilapidation, which is followed by the injection of an antibody against a tumor antigen into the bloodstream, which causes the enzyme in the tumor to bind selectively. The administration of a prodrug into the blood circulation, which is converted to an active cytotoxic drug by the enzyme, only within the tumor. Selectivity is achieved by the tumor specificity of the antibody and by delaying prodrug administration until there is a large differential between tumor and normal tissue enzyme levels [8,9]. GDEPT is a two-step process. In the first step, the gene for a foreign enzyme is delivered to the tumor cells and in the second step; a non-toxic agent is administered systematically and converted by the enzyme to its cytotoxic metabolite [10,11].

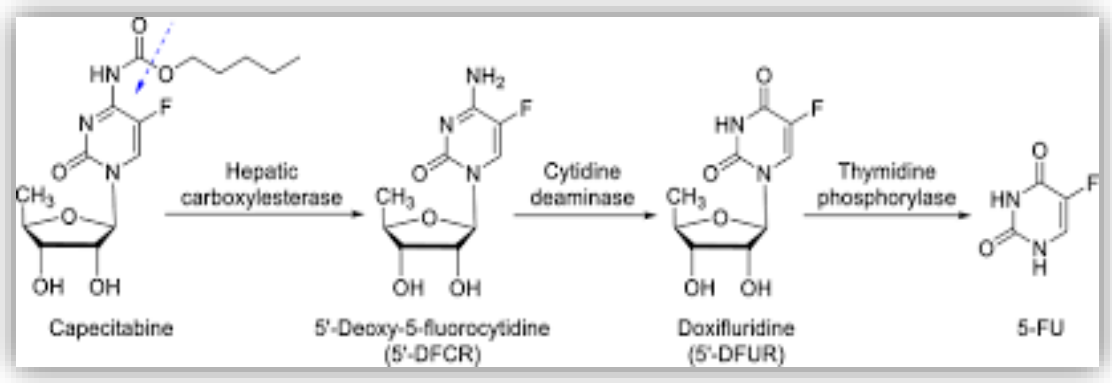

Figure diagram no. 2. Mutiple enzymatic activation steps of capecitabine prodrugs.

2. DRUGS, SYSTEMS & APPROACHES FOR CANCER TREATMENT

2.1.Various Drugs of prodrugs for Cancer Treatment : Chemotherapeutic agent.

Using a succinic spacer arm, paclitaxel was joined to poly (hydroxyl ethyl aspartamide) in two steps: (1) 2′-O-succinyl-paclitaxel synthesis; (2) PHEA-2′-O-succinyl-paclitaxel synthesis. Research using a murine myeloid cell line shown that the polymeric prodrug preserves some of paclitaxel's pharmacological effects. Compared to both the free medication and the naked polymer, the conjugation left the bloodstream considerably faster. It was discovered that a significant buildup of bioconjugate (80% of the dose) remained in the liver for a week.[12] Numerous other paclitaxel prodrugs have been produced, including a number of unsymmetrical polar disulfide prodrugs that were created and produced as prodrugs that have been reductively activated. In vitro, these substances acted as prodrugs on L2987 lung cancer cells.[13] In 1999, endocytes investigated a radioactive indium probe in the form of indium-DTPA folate compound (111In-DTPA-folate) (Fig.3), which demonstrated tremendous potential in localizing tumor locations in phase I/II clinical tests.[14] It seemed appropriate as a radiopharmaceutical to target folate receptors linked to tumors.[15]

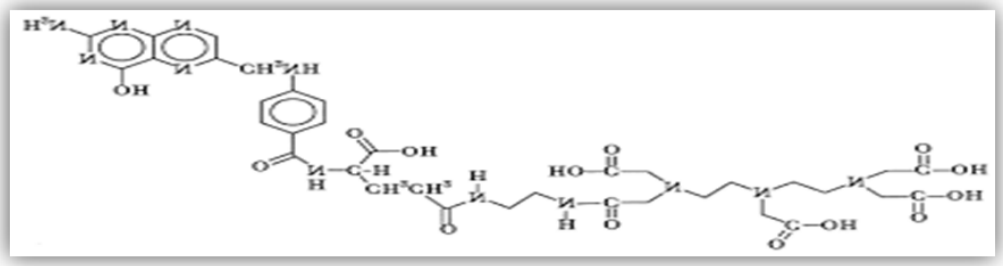

Figure no 3: Indium-DTPA folate conjugate (111In-DTPA-folate)

2.2 Oncology :

Ixazomib :

Ixazomib citrate, an ester prodrug of Ixazomib, is used to treat multiple myeloma (Figure 5). Through

hydrolysis, the prodrug transforms into its parent drug. The reversible suppression of the 20S proteasome's beta 5 subunit is the mechanism of action of ixazomib. In 2015, the FDA approved ixazomib for the first time in combination with dexamethasone and lenalidomide. Takeda Pharmaceuticals presently markets it as ixazomib citrate under the Ninlaro® brand. Ixazomib was the subject of 34 NCTs that examined it either alone or in combination from the beginning of 2013 to the end of 2018. Early NCTs focused on ixazomibin's pharmacokinetics, safety, effectiveness, and tolerance, mostly in patients with multiple myeloma in 2011–2012. More recent NCTs are currently concentrating on ixazomib's impact in Leukemia, sarcoma, lymphoma, and multiple sclerosis.Takeda Pharmaceuticals conducted a phase 1 research (NCT01830816) to assess the safety and pharmacokinetics of ixazomib in patients with advanced solid malignancies and relapsed/refractory multiple myeloma based on renal function. Ixazomib was less well tolerated and had more side effects among patients with reduced renal function, according to a June 2019 study.A combined therapy of ixazomib with cyclophosphamide and low-dose dexamethasone was assessed in patients who were not eligible for transplants in a randomized phase 2 study [16], NCT02046070.

According to the study, this treatment plan has minimal toxicity and is tolerated. Additionally, patients receiving 400 mg/m2 of cyclophosphamide reported higher toxicity rates than those receiving 300 mg/m2 of the combination, indicating the to make the latter dose more bearable.Ixazomib is currently being studied in patients with peripheral T-cell lymphoma (NCT03547700), multiple myeloma (NCT03608501 and NCT03770260), triple-negative breast cancer (NCT02993094), mantle cell lymphoma (NCT04047797 and NCT03616782), B-cell lymphoma (NCT02898259), and HIV (NCT02946047).

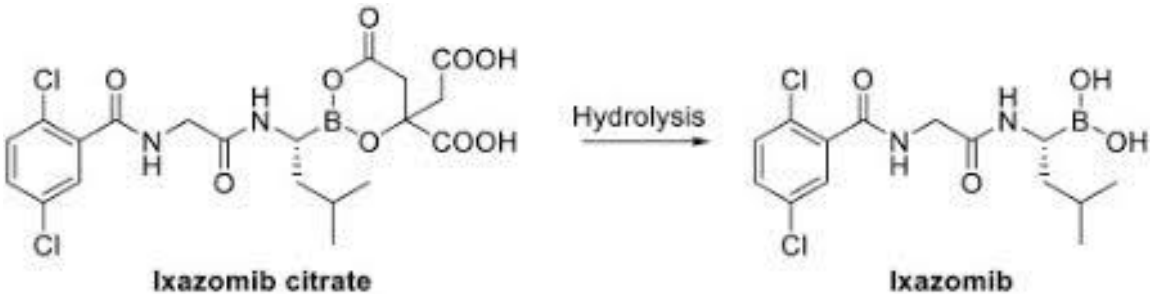

Diagram no.4. Prodrugs Ixazomib.

Evofosfamide :

Evofosfamide is a hypoxia-activated prodrug of brominated isophosphoramide mustard, sometimes referred to as TH-302 (Figure 6). It is a strong DNA alkylator in its active form. The effectiveness of TH-302 is being investigated in a number of cancers, including solid tumors, soft tissue sarcoma, oesophageal, and pancreatic cancers. However, because of low enrollment, ineffectiveness, and failure to fulfill endpoints, several of the trials were discontinued. New research, however, continues to reveal benefits and optimism in using the prodrug [17,18]. This discrepancy in reporting may pave the way for additional research on the medication or hypoxia-activated prodrug method.

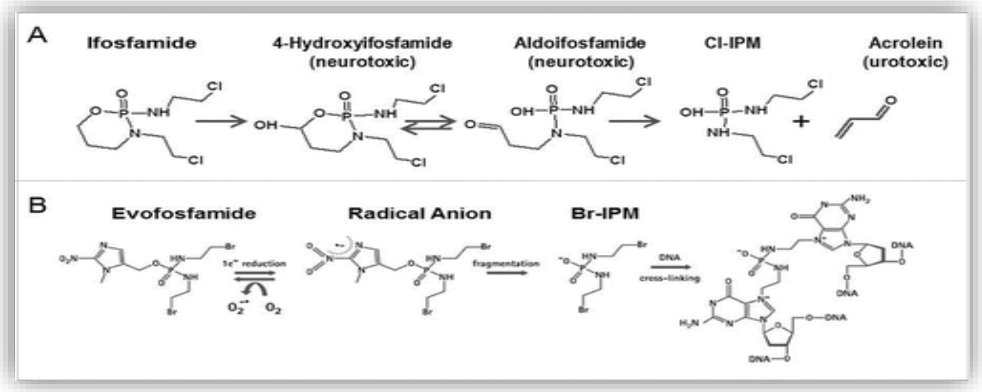

Figure .no.5. Evofosfamide Prodrug

Aldoxorubicin :

Anthracyclines in general and doxorubicin in particular continue to be essential components of sarcoma treatment. However, their prospective utility is severely limited by their considerable toxicities, particularly heart toxicity, and dose-dependent adverse effects [19]. Aldoxorubicin's formation (Figure 8) by conjugation Lower plasma concentrations of doxorubicin were made possible by the ratio of doxorubicin to albumin, which reduced adverse effects. After building up in tumor cells, the compound is broken down by liposomes into albumin and doxorubicin. Stronger tumor inhibition can be achieved by administering greater doses because of fewer adverse effects, according to studies [20]. Although aldoxorubicin's first human trial was documented in 2006 [21], it is being utilized in conjunction with other medications rather than as the only treatment for sarcomas. Nevertheless, a review of aldoxorubicin clinical trial testing revealed that many of the trials lacked adequate design because of the extremely broad definition of "sarcoma." It is important to note that prior preclinical research showed aldoxorubicin to be superior to doxorubicin in the toxicity profile, at least. Thus, it can be assumed that aldoxorubicin deserves more well-designed clinical trials to demonstrate its potential as a superior substitute for doxocorubicin as long as it is still one of the recommended treatment alternatives.

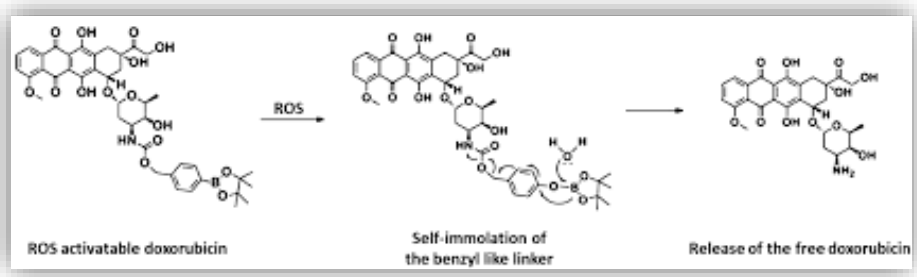

Diagram no.6. Aldoxorubicin prodrug realease.

Triacetate of Uridine :

The acylated prodrug of uridine is called uridine triacetate (Figure7). Esterases break it down to produce active uridine. It is used to counteract overdoses of capecitabine and fluorouracil. Capecitabine is a fluorouracil prodrug that prevents deoxyuridic acid from being methylated to thymidylic acid [22]. Due to genetic differences in the enzymes that metabolize fluorouracil or a shortage in dihydropyrimidine dehydrogenase, this results in toxicity that develops quickly. The prodrug, uridine triacetate, has been reported to deliver 4 to 6 fold more uridine to systemic circulation than equal equimolar doses of uridine alone [23]. This indicates that the prodrug is more bioavailable and effective than its parent drug. This might be due to the slow hydrolysis of the prodrug to its active metabolite

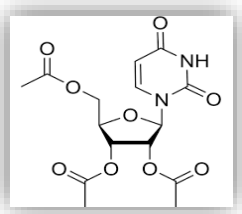

Diagram no.7. Uridine Triacetate.

3.CURRENT SELECTIVE PROTECTION SYSTEMS :METHODS & FORMULATION.

The development of gene-controlled expression in mammalian cells and cloning techniques has made it possible to clarify the three-dimensional structure of enzymes and membrane transporters,structure, enabling the logical development of highly targeted medications with excellent selectivity . The following systems are understood by these sophisticated latent forms: Colon-Specific Drug Delivery System, or CSDDS ADEPT – Antibody-Directed Enzyme Prodrug Therapy; GDEPT/VDEPT Gene-Directed Enzyme Prodrug Therapy/Virus Directed Enzyme Prodrug Therapy.

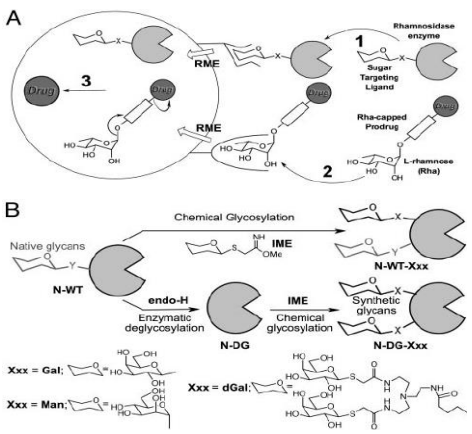

Diagram no.8. The strategy of LEAPT [24]. (A) (Step 1) Sugar-mediated receptor-mediated endocytosis (RME) delivers a glycosylated rhamnosidase (Rha-cleaving) enzyme selectively to certain sites. (Step 2) A Rha-capped prodrug is given, which only the glycosylated rhamnosidase can cleave. (Step 3) The prodrug is activated, causing the parent drug to be released site-selectively. (B) Construction of glycosylated enzymes. Gal stands for •-D-galactose, Man for D-mannose, DG for deglycosylated, RHa for rhamnopyranose, and IME for 2-imino-2-methoxyethyl 1-thioglycoside.

3.1 ADEPT – Antibody-Directed Enzyme Prodrug Therapy:

Cancer chemotherapy is known to be severely hampered by severe pharmacological side effects because of the drugs' inability to selectively target neoplastic cells.[25,24] Consequently, the majority of the research in this field focuses on selective antitumor chemotherapeutic drugs. But bacteria, parasites, and other infectious organisms can also be treated with this strategy.

By definition, the ADEPT method uses a monoclonal antibody in conjunction with an enzyme that the body does not have to activate the prodrug, which is cleaved by this enzyme selectively . The antigen-antibody interaction starts with the administration of the monoclonal antibody-enzyme combination. After the prodrug is given, the enzyme from the complex of enzyme, antibody, and antigen selectively breaks the link between the drug and the carrier, releasing the drug accountable for the activity against the tumor cell or the harmful organism (protozoa, helminths, or bacteria) .[26,27,28,29]Interestingly, there is no requirement for a 100% contact between the enzyme-antibody and the cell surface antigen-conjugate.

To make the method successful, just around 20% of the conjugate enzyme-monoclonal antibody is required to bind the antigen to the surface of the pathogenic cell. It has been demonstrated that numerous human tumors are responsive to various prodrugs, enzymes, and antibodies in ADEPT systems. Clinical trials conducted recently have demonstrated that this Since the precise cell surface antibodies are known, this method may be a useful tool for treating solid tumors . Given that a significant issue with cancer chemotherapy is the inadequate vascularity and physiological barrier of tumor tissue, Fab and scFv antibody fragments can be utilized in place of whole antibodies.[30] For ADEPT prodrugs to also pass across the tumor membrane barrier, they need to have an appropriate partition coefficient.

Furthermore, ADEPT prodrugs need to be less cytotoxic than the drugs, and using them calls for a thorough understanding of structure-activity connections.[30]

Non-mammal and non-human enzymes should be utilized in both the ADEPT and the GDEPT systems to prevent prodrugs from biotransforming before they reach the enzyme-antibody-antigen complex on the surface of bacteria, helminths, and protozoa. In the second stage of the procedure, bacterial enzymes that are easily controlled for immunogenicity are beneficial because they provide a high selectivity for drug release from the prodrug.[30]

1. Based on their place of origin, ADEPT system enzymes can be divided into the following categories[71] : Mammalian enzymes
> α-galactosidase (α-g);
> alkaline phosphatase.
2. Enzymes that are non-mammalian but have similarities to mammals:
> carboxypeptidase A,
> E. coli's β-glucuronidase (β-g),
> nitroreductase (NR).
3. Mammal-free non-mammalian homology:
> carboxypeptidase G2 (CPG2);
> β-lactamase (β-L)
> cytosine deaminase (CD);
> benzylpenicilin amidase (PGA);
> phenoxymethylpenicilin amidase (PVA).

For both ADEPT systems and GDEPT, as will be discussed later, numerous enzyme and prodrug combinations have been suggested. Notably, the combinations that work well for ADEPT can occasionally differ from those that are advised for GDEPT because the former involves activation in the extracellular media, whilst the latter involves activation in the intracellular environment.[27]

1- Examples of ADEPT in Cancer Therapy			
Enzymes	**Antibodies**	**Prodrugs**	**Model systems**
Carboxy-peptidase G2	Anti-CEA antibody	CMDA	Xenograft of human colon carcinoma
Human β-glucuronidase	Humanized CEA-specific binding region	Anthracyclin prodrugs	Murine L 1210 tumor cell Line
Human β -glucuronidase	Single-chain anti-CD20 antibody	Doxorubicin	Fused protein
2- Examples of VDEPT in Cancer Therapy			
Viral vectors Model	**Enzymes delivered**	**Prodrugs**	**Model systems**
EBV	Nitroreductase (NTR)	CB1954	EBV-positive B-cell lines
Retrovirus	Yeast cytosine deaminase	5-FC	Murine squamous carcinoma cells and YCD-expressing tumors
Retrovirus	Human CYP & P450 reductase	CPA & IFA	Gliosarcoma cells and in vivo tumor model
Adenovirus	Human carboxylesterase	Irinotecan	Human lung adenocarcinoma cell lines & nude mice tumor model
3- Examples of GDEPT in Cancer Therapy			
Enzymes	**Prodrugs**	**Model systems**	
Cytosine deaminase	5-FC	Murine fibroblast cells	
Thymidine kinase	GCV	Cisplatin-resistant human ovarian carcinoma cells Cos-1 cells	

Table no. 3 .Enzymes, Prodrugs and Respective Drugs Proposed for Cancer Therapy in ADEPT/GDEPT.

3.2 Gene-Directed Enzyme Prodrug Therapy (GDEPT) & VDEPT (Vírus-Directed Enzyme Prodrug Therapy):

A gene that produces enzymes capable of activating prodrugs is the basis for this procedure. Liposomes, cationic lipids, or viruses (adenovirus or retrovirus) can all carry the genes. Both tumor and healthy cells are reached by these transporters. It is called VDEPT for genes of virus origin. Linking genes in the downstream sequence extremities of tumor transcriptional units allows for the production of those genes.This strategy has been specifically studied for cancer treatments in order to produce highly selective antitumor medicines, and it has demonstrated promise in experimental trials.[27-[31]

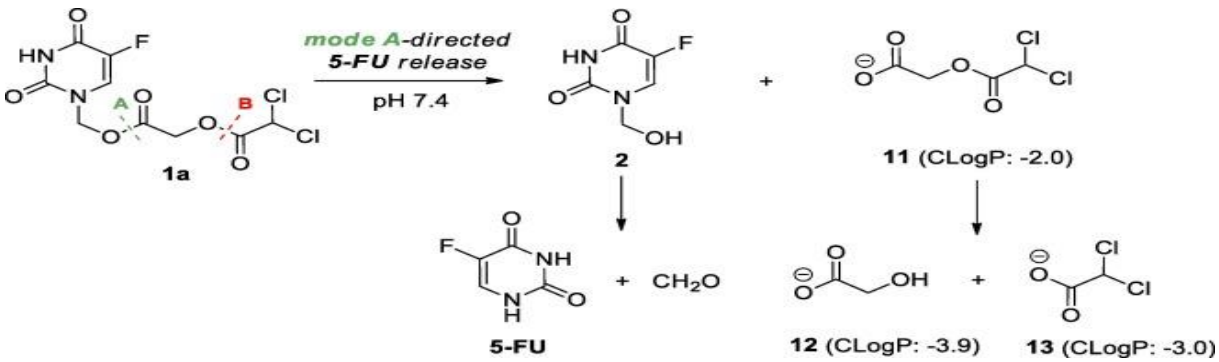

Diagram no. 9. 5-fluorouracil-dichloroacetate mutual prodrugs as anticancer agents.

Examples of GDEPT Prodrugs :

The following examples are applicable to ADEPT systems as well Nitroreductase (NR), which is produced by certain genes, activated a 2 nitroimidazol-5-ylmethyl carbamate prodrug that Hay and colleagues created in 1999.[32] Compared to the standard prodrug administration strategy, this prodrug was 10–24 times more cytotoxic against human ovarian cancer (SKOV3) in GDEPT. Under hypoxy, this activity rose 15–40 times. In 2000 ,[33] Sagnou and colleagues also synthesized three N10-(4 nitrobenzyl)carbamate prodrugs to be tested for application in ADEPT and GDEPT systems employing nitroreductase (NR) activation .

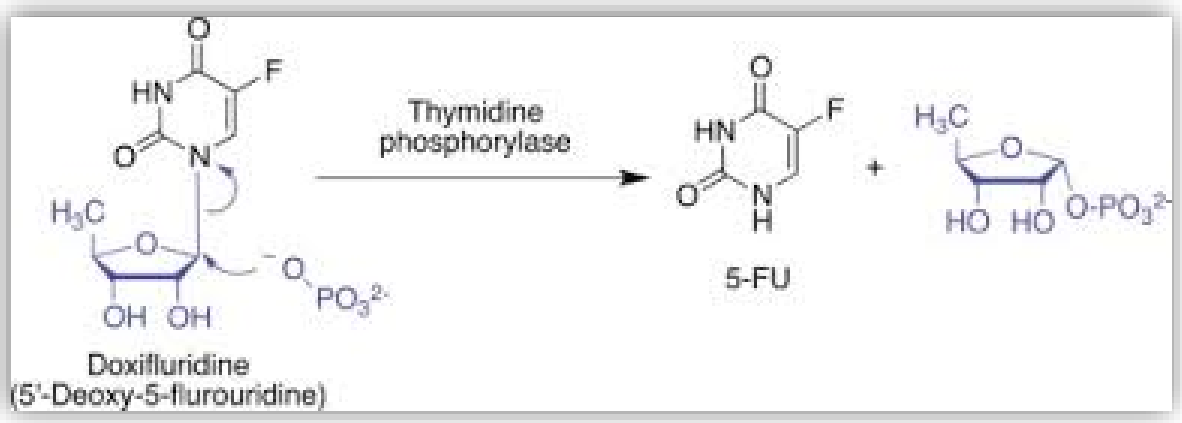

Diagram no.10. Fluordeoxyuridine 5'-dipeptidyl derivatives(FdU).

was 100 times more effective against adenocarcinoma in humans. Furthermore, using aziridinylnitrobenzamides that are activated by nitroreductase in GDEPT systems, Helsby and colleagues have created a SAR (Structure Activity Relationship) study.[34] As antineoplastics against prostatic tumors, prodrugs developed with the GDEPT method are currently in the pre-clinical stage . Despite its great promise in terms of selectivity, GDEPT/VDEPT systems have a crucial characteristic that relates to the type of gene carrier that is better suited. Furthermore, it has been extremely difficult to selectively transfer the genes to the tumor rather than to healthy cells.

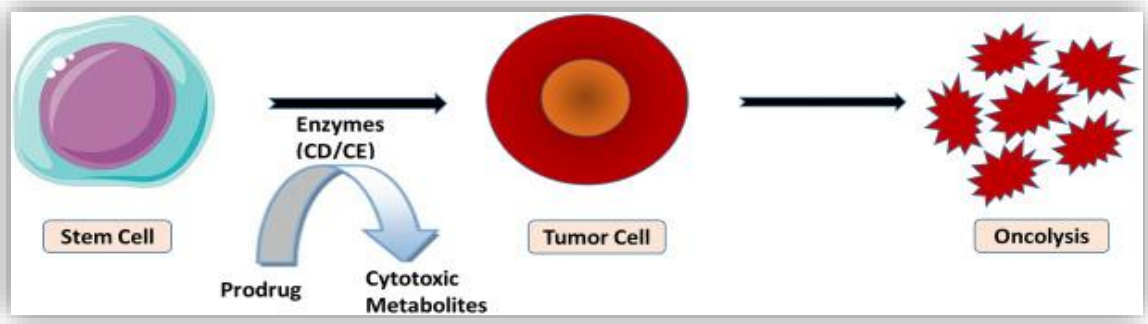

Diagram no.11. ENYZME PRODRUG THERAPY.

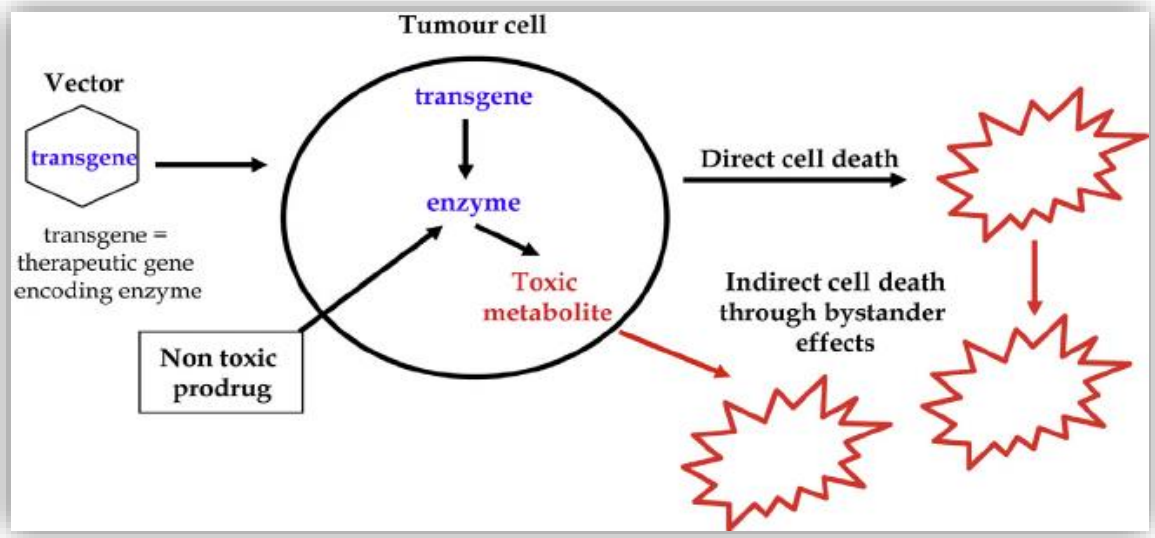

Diagram no.12. GDEPT SYSTEM PRINCIPLE.

3.3 Prodrugs in anticancer photodynamic therapy (PDT):

A clinically authorized treatment for a number of cancer types is photodynamic therapy (PDT).PDT's benefits over other traditional chemotherapy motherapies are its capacity to specifically eliminate cancers that are exposed to light and its minimal systemic toxicity. PDT kills the photosensitized cells by combining a medication having photosensitizing qualities, a photosensitizer or photosensitizing agent, and a certain kind of light. After the photosensitizer is administered and accumulates in a cancerous tissue, the tissue is exposed to light with the right wavelength. When light subsequently activates the photosensitizer, its energy is transferred to molecular oxygen. Consequently, reactive oxygen species are produced, which cause the cells to become cytotoxic.[35] Although porphyrin derivatives are well-known photosensitizers, their low bioavailability and challenging delivery limit their medicinal application.[36] In the 1990s, a prodrug approach centered on the administration of 5-aminolevulinic acid (ALA) was devised in order to address these limitations [37,38,39]. A natural substrate called ALA is employed in the multistep synthesis of hemoglobin. Protoporphirin IX accumulates in cancer cells when exogenous ALA is consumed because catalytic production of ALA is the slowest stage in the heme biosynthesis pathway in vivo. Moreover, ALA can be given orally, intravenously, or transdermally, among other ways [36]. Researchers created cascade prodrugs—double prodrugs, prodrugs of a prodrug—to further boost ALA bioavailability. The production of dendritic derivatives [36] or esterification with long chain alcohols as hexanol or octanol [81] can increase the lipophilicity and, thus, the bioavailability of ALA.In order to address these issues, a prodrug approach centered on 5-aminolevulinic acid (ALA) administration was presented in the 1990s [37,38,39]. In the multistep synthesis process, which breaks down in vivo to the parent chemical, ALA is an endogenous substrate. ALA can also be glycosidated to produce a more cell-friendly derivative devoid of potentially harmful carriers [40]. Short peptide conj ugates are a further modification of the ALA molecule. One significant benefit of these is that they may cause cancer cells to overexpress peptide transporters and enzymes, improving treatment effectiveness and lowering the drug's necessary concentration.

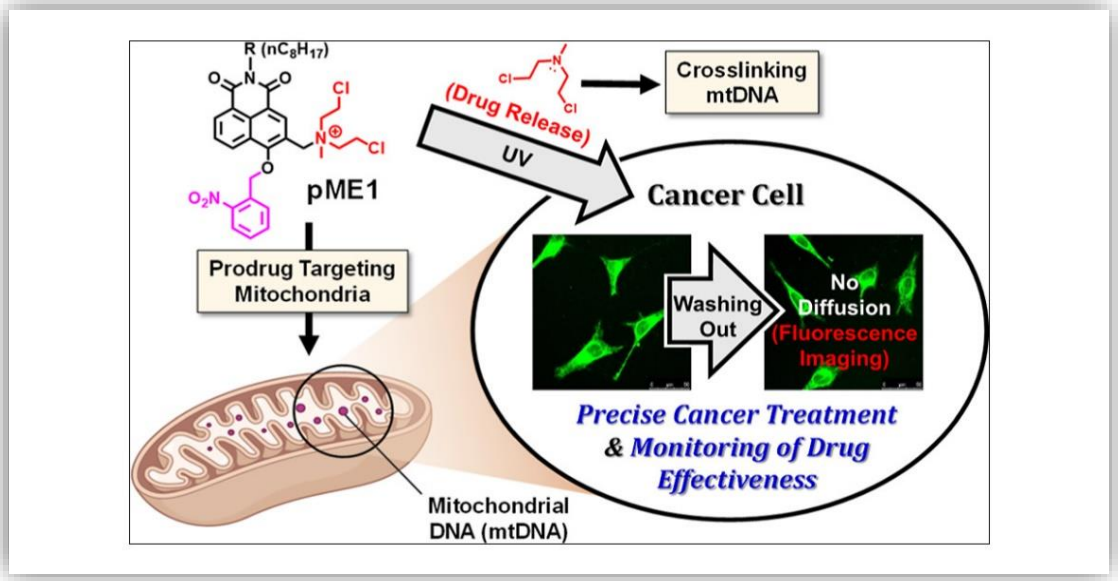

Diagram no.13. Prodrug : Photodynamic Therapy.

FUTURE PROSPECTS

Aldoxorubicin (Figure 8), also known as DOXO-EMCH and INNO-206, is the 6- maleimidocaproyl hydrazone deriva-tive of doxorubicin [41]. Doxorubicin is an effective therapy in sarcoma, though it suffers from dose-dependent cardio-toxicity, bone marrow toxicity, and GI disorders.Aldoxorubicin strongly binds to albumin which, in turn, accumulates in tumour cells due to high cell turnover and poor lymphatic drainage. Due to acid-sensitive linkage of doxor-ubicin in the prodrug, it is cleaved intracellularly releasing

doxorubicin. Several phase I [42], phase II [43], and phase III[44] trials have reported improved safety of aldoxorubicin when compared to doxorubicin . Furthermore, it was reported that doxorubicin remains albumin-bound until its release within cells. Urine contained trace levels of doxorubicinol, the main doxorubicin metabolite linked to cardiotoxicity [45]. Aldoxorubicin's effectiveness as a component of combination therapy is being tested in a number of clinical trials. Formerly known as TH-302, evofosfamide (Figure 6) is a new and promising medication for the treatment of pancreatic cancer. It is an inactive prodrug that has to be activated in a hypoxic atmosphere. Solid tumors like pancreatic cancer are characterized by these hypoxic circumstances. not of normal tissue, but of tumors. Evofosfamide is a prodrug of brominated isophosphoramide mustard (IPM) that resembles nitroimidazole. Then, dibromo isophosphar-amide mustard is released by the radical anion. Clinical trials demonstrate encouraging outcomes in terms of tolerance and efficacy [46,47].

CONCLUSION

Prodrugs and targeted delivery systems, which offer an alternative to conventional systemic chemotherapy, have completely changed the way that cancer is treated. These cutting-edge methods have shown increased patient outcomes, decreased toxicity, and improved efficacy. It is clear that prodrugs and delivery methods will be essential to the creation of tailored cancer treatments as research progresses. To fully appreciate the promise of these approaches and implement them in clinical practice, more research is required.

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