A COMPREHENSIVE REVIEW ON TUMOUR MICROENVIRONMENT-ACTIVATED STIMULI-RESPONSIVE MXENE NANOPLATFORMS FOR PRECISION ONCOLOGY

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ABSTRACT:

Cancer remains one of the leading causes of mortality worldwide, highlighting the need for more effective and targeted therapeutic strategies. Conventional cancer treatments are often associated with poor selectivity, systemic toxicity, and the development of drug resistance. Tumour microenvironment (TME)-activated stimuli-responsive drug delivery systems have emerged as a promising approach to overcome these limitations by enabling site-specific and controlled drug release. Among the various nanomaterials investigated, MXenes have gained considerable attention due to their exceptional physicochemical properties, including large surface area, excellent electrical conductivity, hydrophilicity, high drug-loading capacity, and superior photothermal conversion efficiency. This review summarizes the recent advances in TME-responsive MXene nanoplatforms for precision oncology, with emphasis on endogenous stimuli-responsive systems (pH, enzyme, ion, and biomolecule-responsive) and exogenous stimuli-responsive systems (thermal, magnetic, and photo-responsive). Furthermore, the therapeutic applications of MXene-based

nanoplatforms in photothermal therapy, photodynamic therapy, chemodynamic therapy, and cancer immunotherapy are discussed. The review also highlights current challenges, including oxidative instability, biosafety concerns, large-scale synthesis, and clinical translation. Overall, TME-activated stimuli-responsive MXene nanoplatforms offer a versatile and multifunctional strategy for targeted cancer therapy and hold significant promise for advancing personalized precision oncology through continued research and technological development .summarizes the recent advances in TME-responsive MXene nanoplatforms for precision oncology, with emphasis on endogenous stimuli-responsive systems (pH, enzyme, ion, and biomolecule-responsive) and exogenous stimuli-responsive systems (thermal, magnetic, and photo-responsive). Furthermore, the therapeutic applications of MXene-based nanoplatforms in photothermal therapy, photodynamic therapy, chemodynamic therapy, and cancer immunotherapy are discussed. The review also highlights current challenges, including oxidative instability, biosafety concerns, large-scale synthesis, and clinical translation. Overall, TME-activated stimuli-responsive MXene nanoplatforms offer a versatile and multifunctional strategy for targeted cancer therapy and hold significant promise for advancing personalized precision oncology through continued research and technological development.

KEYWORDS:

Tumour microenvironment (TME), Stimuli-responsive drug delivery systems, Precision oncology, Targeted cancer therapy, Nanomedicine, Photothermal therapy (PTT), Photodynamic therapy (PDT), Chemodynamic therapy (CDT), Cancer immunotherapy

INTRODUCTION:

As the second greatest cause of death globally, cancer continues to be one of the most difficult public health issues to address [1, 2]. Uncontrolled cell proliferation and metastasis are the hallmarks of the disease. In 2020 alone, there were an expected 20.9 million new cases of cancer and 10 million cancer-related deaths. Due to changes in lifestyle and population aging, these numbers are expected to rise significantly in the upcoming decades [3]. Three primary gene types are impacted by genetic alterations. These include DNA repair genes, tumor suppressor genes, and proto-oncogenes. Cancer drivers are the alterations brought about by these genes. Proto-oncogenes aid in cell division and development. Changes to these genes result in aberrant cell development and consequently lead to cancer. Additionally, tumor suppressor genes aid in regulating cell division and proliferation. Sometimes, they divide uncontrollably, which results in cancer (4).

Over 2,300 years ago, "Hippocrates" made an observation that gave rise to the name cancer. The Greek word "Korkinoma" was followed by the Latin word "Cancer." It was discovered by Hooke in the 1600s and Virchow in the 1800s that all living tissues are made up of cells, and that all cells are descended directly from one another [5]. Tumours made of these malignant cells grow more aggressively over time and become deadly when they damage organs and tissues essential to the organism's overall survival [6]. In 2008, there were 100,000 cases of carcinogens, a class of chemicals that directly cause damage to DNA, supporting cancer. Examples of carcinogens include tobacco, asbestos, arsenic, radiation, gamma and x-rays, the sun, and substances found in cars; in 2008, rates ranged from 88 per 100,000 in the Middle East. Carcinogens are present in the body, and free radicals are formed by steel electrons from the body. It affects the cells by free radicals and prevent the function [7]. Cancer is a genetic condition, because it arises from alterations in the genes that regulate our cellular function, particularly how they grow and multiply. Every cell has a version of this gene that escorts as a how-to guide. Secondarily human cancer genes are the hereditary gene, a genetic autosomal dominant congenital propensity that imposes a high risk into cancer development ([8]). When it comes to specific mutations, all tumor types have their own set of unique Trouble. which some allow high number of mutations and some with lower. In a series the four genes identified in previous high-throughput sequencing (HTS) studies where been shown to be altered in more than 20% of the tumours, Of course, not all mutations are cancer causing. It is only when mutated cells can evade the normal protective systems that cancer ensues [9]. Current cancer treatment methods harm healthy cells, tissues, and organs and have negative side effects. The type of cancer, development stages, age, frequency of management, medication dosage, and patient health all play a role in choosing the optimum cancer therapy strategy. Gene therapy, targeted silencing by siRNAs, and the production of genes that cause apoptosis are some of the molecular-based strategies that have recently been the subject of increased investigation [10] .

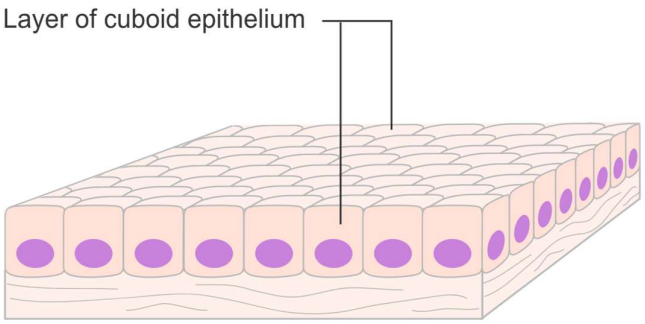
TYPES OF CANCER:

- Carcinoma
- Sarcoma
- Leukaemia
- Lymphoma and myeloma
- Brain and spinal cord cancer

CARCINOMA:

The skin or tissues lining or covering internal organs are where this cancer first appears. Adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma are among the several subtypes. Epithelial tissues are

where cancers begin. These tissues cover the skin and other external body parts of the digestive system covers and encloses every organ within the body, including the
lining the cavities in the body, including the abdominal and chest cavities [11].

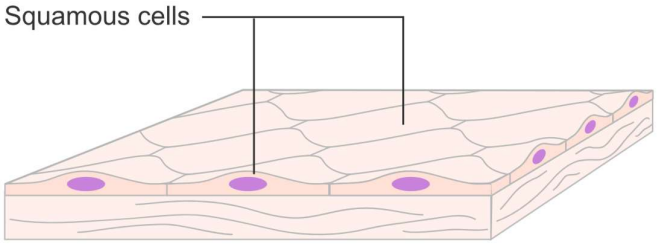


There are different types of epithelial cells, and these can develop into different types of carcinoma. These include:

- Ssquamous cell carcinoma
- Adenocarcinoma
- Transitional cell carcinoma
- Basal cell carcinoma

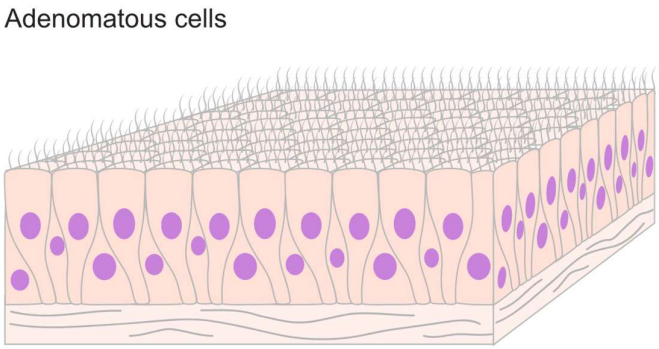
SQUAMOUS CELL CARCINOMA:

Squamous cells are where squamous cell cancer begins. These are the flat, surface-covering cells that are present in the skin, the lining of the neck, and the oesophagus[12].



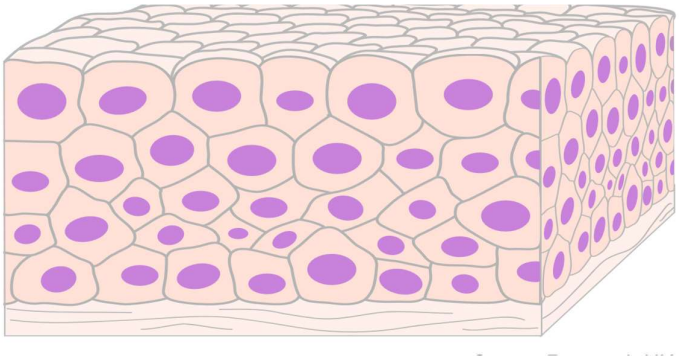
ADENOCARCINOMA:

Adenomatous cells are glandular cells where adenocarcinomas begin. Fluids are produced by glandular cells to maintain tissue moisture[13].



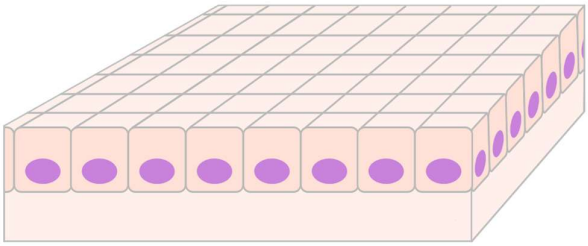
TRANSITIONAL CELL CARCINOMA:

Cells that can expand with an organ are known as transitional cells. They comprise tissues known as transitional epithelium. The bladder lining serves as one illustration. Transitional cell carcinoma is the term for cancers that begin in these cells[14].



BASAL CELL CARCINOMA:

The deepest layer of skin cells is lined by basal cells. Basal cell carcinomas are cancers that originate in these cells[15] .



SARCOMAS:

Connective tissues are where sarcomas begin. These are the body's supporting tissues. Bones, cartilage, tendons, and fibrous tissue supporting organs are examples of connective tissues[16] .

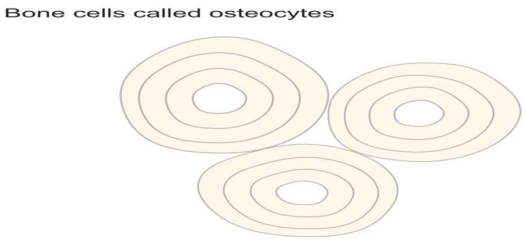
Carcinomas are far more prevalent than sarcomas. There are two primary kinds:

Sarcomas of the bones

Sarcomas of delicate tissues

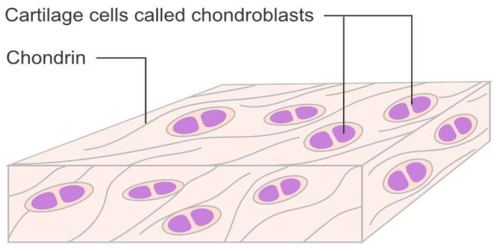
Sarcomas of the bones .

Bone cells are the source of bone sarcomas.



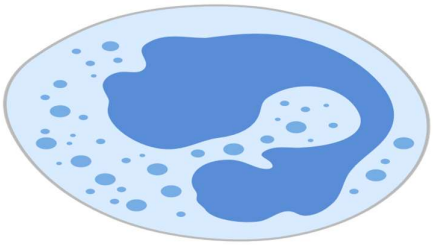
SOFT TISSUE CARCINOMA:

Although they are uncommon, the most prevalent kinds of soft tissue sarcomas begin in muscle or cartilage[17].



LEUKEMIA CANCER OF BLOOD CELLS:

White blood cell cancer is known as leukemia. The bone marrow product produces an excessive number of white blood cells. Because the blood cells are not fully developed, they function incorrectly. The blood becomes accumulated with the aberrant cells[18].

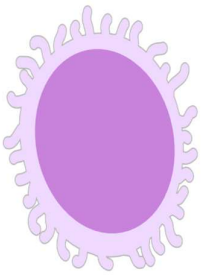


White blood cell
(leucocyte)

LYMPHOMAS AND MYELOMA:

Cancer that begins in the lymph glands or lymphatic system cells is known as lymphoma. Since the lymphatic system is distributed throughout the body, lymphoma can begin almost anywhere.

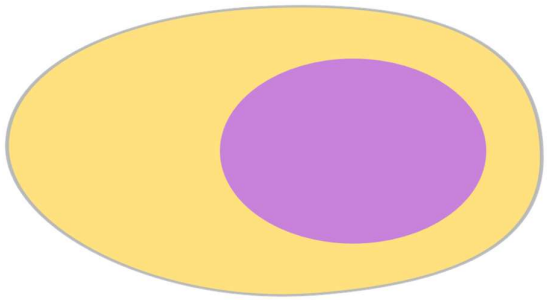
The aberrant cells begin to gather in the lymph nodes and other organs, such as the spleen or bone marrow. After that, they might develop into tumours [19].



Lymphocyte

MYELOMA:

The malignancy known as myeloma begins in the plasma cells. The bone marrow produces a type of white blood cell called a plasma cell. To aid in the battle against infection, they create antibodies, also known as immunoglobulins.

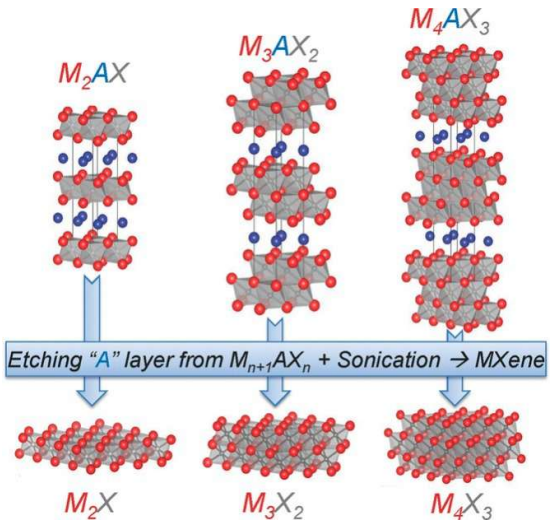


Plasma cell

Plasma cells can become abnormal and multiply out of control. They make a type of antibody that doesn't work properly to fight infection[20].

MXENE NANOMATERIAL:

Mxene with the general formula $M_{n+1}X_nT_x$, where M stands for an early transition metal, X is carbon and/or nitrogen, and T_x designates surface functional groups like –OH, –O, and –F, MXenes are a class of two-dimensional (2D) transition metal carbides, nitrides, or carbonitrides[21]. They are created by selectively etching the "A" layer from MAX phases, resulting in extremely thin layered nanosheets with surfaces that are hydrophilic. MXenes are appealing for biomedical applications because of their strong electrical conductivity, huge surface area, variable surface chemistry, and superior water dispersibility[22].MXene is a viable option for photothermal cancer treatment due to its capacity to convert light, typically NIR (I and II), to heat with enhanced conversion efficiencies. Additionally, medications or nanoparticles can alter the surface of MXenes to provide synergistic photo/chemo and sonodynamic therapy. The literature on MXenes' cytotoxicity and biocompatibility is also examined in this review[23].



TYPES OF MXENE:

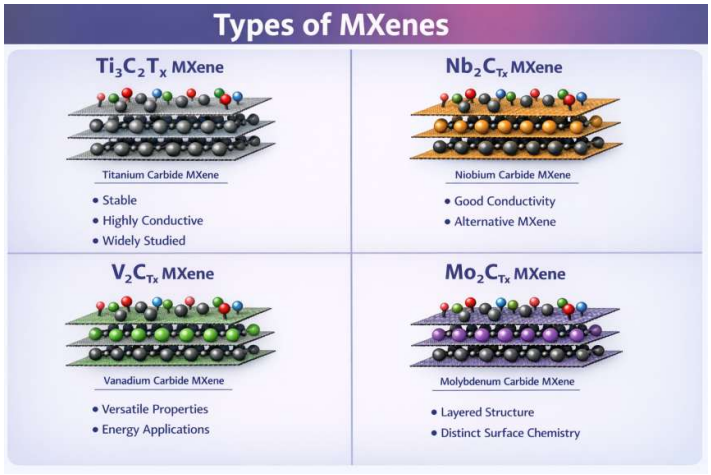
Different MAX phases, including as $Ti_3C_2T_x$, Nb_2CT_x, V_2CT_x, and Mo_2CT_x, have been used to create a variety of MXenes. Because of its high stability, easy synthesis through selective etching, superior electrical conductivity, hydrophilicity, and advantageous physicochemical features for drug transport and biological applications[24].

$Ti_3C_2T_x$

Nb_2CT_x

V_2CT_x

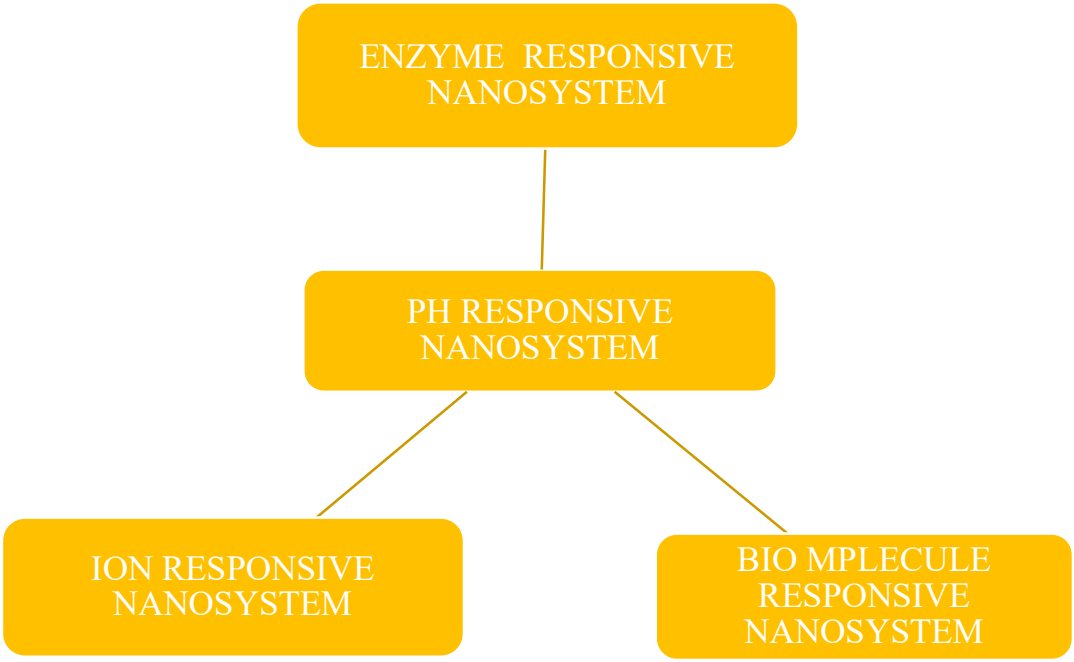
Mo_2CT_x



STIMULI RESPONSIVE DRUG DELIVERY SYSTEM:

Advanced nanocarriers called stimuli-responsive drug delivery systems, or smart drug delivery systems, are made to release therapeutic chemicals in reaction to particular biological or physical stimuli[25]. When subjected to specific stimuli, these systems change structurally or chemically, allowing for controlled and site-specific drug release. Under normal physiological settings, these systems remain stable. This approach reduces systemic toxicity while increasing therapeutic efficacy[26].

INTERNAL ENDOGENEOUS STIMULI:



ENZYME RESPONSIVE SYSTEM:

Enzymes are present in all biochemical and metabolic processes inside the living organisms. Reactions mediated by enzymes mediate structural. Despite having a "lock and key" mechanism, transformations and transitions are distinguished by their great selectivity and substrate specificity. The tetrapeptide Gly-Phe-Leu-Gly is a commonly used polymer conjugate linker. It is stable in circulation and is broken down by lysosomal thiol-dependent proteases, especially cathepsin B [27].Certain pathological conditions, like as cancer and inflammation, are linked to increased production of specific enzymes, which can be used to distribute drugs in an enzyme-responsive manner. For instance, urokinase plasminogen activator (uPA) and membrane-type matrix metalloproteinase (MMP) are two of the hydrolases known as cancer-associated proteases (CAPs) that are overexpressed in tumours and have been thoroughly investigated for the creation of protease-sensitive biomaterials. In particular, MMP expression and activity have been closely linked to tumour invasion and metastasis, such as in the case of CNS glioma, for which several enzyme-responsive Nano systems have been created [28].Numerous enzymes, including hydrolases (such as proteases, phospholipases, and glucosidases), oxidoreductases, and azo reductases, are the foundation of enzyme-responsive Nano systems. These enzymes can be utilised for the enzyme-

responsive delivery of medications and imaging agents, and they are regarded as biomarkers for the prognosis and diagnosis of cancer . Other drug release methods include MSNs blocked by aptamer-based gatekeepers known as "apt valves" and antibody-containing hydrogels that are antigen-responsive. Single-stranded nucleic acids make up aptamers, which are impermeable, metastable structures that are broken by highly particular chemical stimuli [29].Because there is significant changed enzyme expression in addition to the usual leaky vasculature and EPR impact, enzyme-responsiveness is especially helpful in the case of cancer. A nanoparticle can become responsive to the matching enzyme by incorporating an enzyme-labile linkage, and the wide range of enzymes found in tumour settings provides opportunities for numerous such combinations [30].

PH RESPONSIVE NANOSYSTEMS:

One of the most studied concepts in the realm of stimuli-responsive biomaterials and DDSs is pH-responsivity. Systems that react to pH are based on well-defined pH variations within the human body, which are being used to create novel treatments for complicated illnesses like cancer (Fig. 3). These variations can be found along the gastrointestinal (GI) tract, across specific intracellular compartments (such as cytosol, endosomes, and lysosomes), and between normal blood and pathological tissues (such as infection, inflammation, and cancer[31].Instead of oxidative phosphorylation in the mitochondria, which increases proton synthesis, acid fermentation occurs in the cytosol. This, along with inadequate lymphatic drainage and increased interstitial pressure in cancer tissues, results in acidosis of these cells, with extracellular pH falling to as low as in some tumour types .There is a chance for pH-responsive distribution because of the pH difference between circulation and this acidic environment[32].Dendrimers , nanohydrogels , polymersomes , and coated MSNs are further kinds of PH -responsive carriers. For better anticancer drug delivery, polymer-coated pH-sensitive high-density lipoprotein (HDL) carriers have also been produced. Additionally, PAA and chitosan have been used to create multilayers and distribute propranolol. The assembly and mechanical characteristics of the system, and consequently the amount of drug adsorbed, are influenced by the presence of the polyelectrolyte in a pH-dependent way. It was also discovered that the degree of chitosan acetylation affected the loading of propranolol . Lastly, in terms of polyelectrolyte multilayers, MSNs have been coated with poly(styrene sulfonate) (PSS) and poly(allylamine hydrochloride) (PAH) for the pH-responsive delivery of DOX [33].

ION RESPONSIVE NANOSYSTEM:

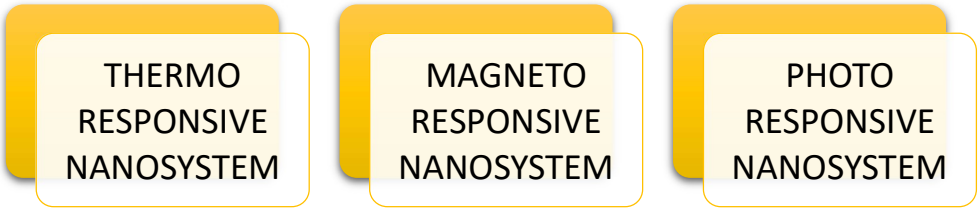
Polymers are the most researched type of Nano biomaterials for the creation of ion-responsive nanocarriers. PNIPAM-based hydrogels are among the most representative examples, however those are rarely documented. For oral ion exchange resins, ion-sensitive polymers have been employed for taste masking, counterion-responsive drug release, and sustained drug release. Additionally, regulated drug release from oral formulations is made possible by polymers that are sensitive to saliva and GI fluid ions, such as those with quaternary ammonium groups. The salting-out effect, in which the LCST of different polymers in aqueous solution is reduced because highly water-soluble materials, like electrolytes, surround the polymers and extract water molecules from them, is a subject of great interest. These polymers are thought to be both ion-sensitive and thermosensitive[34].A pH and sulphide ion-sensitive Nano system loaded with benzotriazole (BTA) and benzalkonium chloride (biocide) was studied for its responsive release, anticorrosion, and antifouling properties. An insoluble Cu-BTA compound, which acts as a pH and sulphide ion-sensitive Nano valve for regulated pore opening, prevented the mesopore openings of the MSN-based system . In order to create vesicles, phytantriol lipid liquid crystalline (LLC) bilayers were modified from cubic to lamellar by the incorporation of a new peptide-lipid conjugate (pep lipid). Ion-responsive applications are made possible when cadmium attaches to the peptide region of the pep lipid, causing the bilayer to undergo a lamellar-cubic phase transition[35].

BIOMOLECULE RESPONSIVE NANOSYSTEM:

In terms of both variety and number, biomolecules are abundant in the natural biological environment. Bio-inspired Nano systems have been developed to target both components generated or overexpressed in specific disease states, as well as components that are present in particular targets . Because of the prevalence of diabetes and its difficult and painful treatment, the most researched nanocarriers in this category for the delivery of insulin are glucose responsive . Adenosine triphosphate (ATP) concentrations, ROS, DNA, and other stimuli are potential candidates[36].Adding the enzyme GOx, which catalyses the oxidation of glucose to gluconic acid and produces hydrogen peroxide (H2O2), which lowers the surrounding pH, is one method of making a Nano system (such as a polymeric network) responsive to glucose concentration. The trapped insulin then diffuses into the surroundings as the pH-responsive network expands and swells in response. Concanavalin A (ConA) and other glucose-binding lectins are used in another method

and synthetic block copolymers containing boronic acid that self-assemble into polymersomes are used in a third method [37].

EXOGENOUS STIMULI:



THERMO RESPONSIVE NANOSYSTEM:

Thermo responsive Nano systems are extensively researched and used in various scientific domains, including therapeutics, where many drug nanocarriers have been created. Their biomaterials' capacity to undergo temperature-dependent phase transitions and cause conformational changes in the morphology of the system is what gives them their "smartness." Because of this, the liposome (Thermosensitive Liposome-TSL), which uses the phospholipid's inherent thermodynamic characteristics, such as the phase transition temperature (Tm), for modulatory controlled drug administration, is the most conventional thermo-responsive formulation. The current Clinical Phase III lysolipid-containing thermosensitive liposome (LTSL), marketed under the name ThermoDox®, was developed using this technique [38].Bubble-generating liposomes and thermosensitive zipper peptides are other methods for creating TLSs. Bubble-generating liposomes have also enhanced ultrasound imaging, even though the majority of thermo bio responsive systems work well with local hyperthermia and MRI [39].

MAGNETO RESPONSIVE NANOSYSTEM:

The use of magnetism in drug delivery appears to have less physical interactions with the body than other stimuli-responsive methods, and it can provide "on-demand," real-time drug release with only a brief stimulus . Magneto sensitive iron oxide nanoparticles, like mag, are usually found in magneto responsive Nano systems made of either magnetite (Fe3O4) or maghemite (Fe2O3). Nanocarriers such as magneto liposomes [96], porous metallic Nano capsules , and core shell nanoparticles are produced by this mixture[40].Pluronic®/PEI nanoparticles and

PNIPAM-based nanogels and nanoparticles are two of the best illustrations of magneto responsive polymeric Nano systems[41].

PHOTO RESPONSIVE NANOSYSTEM:

A chromophore group must be present in any photosensitive biomaterial; in the case of polymers, this group may be located on the side-chain or in the chain backbone . Additionally, lipid vesicles containing caged DNA with a photolabile group have been used to produce green fluorescent protein (GFP) from the nanoparticles when exposed to light . Additionally, photosensitive polypeptides have been produced [42].The poor penetration depth of UV radiation is a significant disadvantage of this technology, which is addressed by using NIR, which is more penetrating and does not harm tissues . Another is "dark toxicity," which requires the patient to spend some time in the dark to prevent exposure to light sources and the ensuing drug release [43].

APPLICATION OF MXENE NANOPLATROM IN CANCER THERAPY:

PHOTOTHERMAL THERAPY:

Because of their high photothermal conversion efficiency and robust near-infrared (NIR) absorption, MXene nanomaterials, especially Ti3C4Tx, have become interesting photothermal agents. MXenes effectively transform light energy into heat upon NIR laser irradiation (typically 808 nm), resulting in localized hyperthermia and subsequent tumor cell necrosis or apoptosis. PTT is a precise and minimally invasive cancer therapy method because of its localized heat creation, which reduces harm to nearby healthy tissues[44].

Additionally, MXenes' hydrophilic functional groups and vast surface area make surface modification and drug loading simple. This enables the creation of multipurpose platforms that combine photothermal therapy with chemotherapy to produce synergistic tumor suppression. Acidic pH and elevated glutathione levels can further improve regulated drug release during PTT in tumors microenvironment (TME)-responsive systems[45].

MXene-mediated PTT dramatically inhibits tumor growth with good biocompatibility and low systemic toxicity, according to studies conducted both in vitro and in vivo. MXene-based PTT is seen as a potential strategy in image-guided cancer therapy and precision oncology because of these benefits[46].

PDT:

PDT is another non-invasive, light-catalyzed cancer treatment option in addition to PTT. PDT uses particular light wavelengths to excite photosensitizers (PSs) that have accumulated in tumor tissue, producing toxic ROS in the TME that kill

tumor cells . PDT is essential to clinical tumor therapy and has a number of benefits, such as robust tumor cytotoxicity, non-invasiveness, good selectivity, and few harmful side effects [47].

However, the effectiveness and use of PDT are severely limited by the absence of O2 in the TME and inadequate PS targeting[48].

CDT:

Bu et al. introduced Ctt CDT, a novel cancer treatment method, in 2016. Through Fenton or Fenton-like reactions, CDT uses CDT agents (metal ions) to accelerate the conversion of endogenous H2O2 in tumor tissues into extremely cytotoxic OH, which causes cell death[49]

However, the low catalytic efficiency and inadequate targeting capacity of traditional CDT agents ($Fe2_3$, Cu_3, and $Mn2_3$) significantly restrict their use . As a result, scientists have used a variety of techniques to boost CDT's tumor-targeting effects, such as creating high-efficiency and high-targeting CDT agents and altering the TME (e.g., raising H2O2 concentrations and reducing pH). MXenes are thought to be the best candidates for effective anti-tumor PDT because of their unique physicochemical characteristics and availability of metallic elements. Using a self-designed micro-explosion technique, Li and associates synthesized non-oxidized Ti3C2Tx quantum dots (NMQDs-Ti3C2Tx) and discovered their potential as CDT agents [50].

The catalytic activity of the oxidized Ti3C2Tx quantum dots is lost when Ti3C2 is oxidized in air and water to generate TiO2. For CDT to be promoted, quantum dots must be kept in their completely unoxidized condition. Zhang et al. recently found that $Nb2_3$ can accelerate anti-tumor CDT therapy in addition to Ti3þ . Nb2C QDs and lactate oxidase (LOD) were encapsulated in red blood cell membranes (Nb2C QDs/LOD@RBC). The composite's circulation period in the bloodstream was extended and its concentration within the TME was enhanced by the encapsulation with RBC membranes. Intratumoral lactate was broken down into H2O2 by LOD, providing a steady supply of substrate for the production of OH[51].

IMMUNOTHERAPY:

Immunotherapy is a novel cancer treatment that has gained a lot of popularity recently and is currently regarded as one of the most promising approaches to cancer treatment. In order to eradicate tumor cells, immunotherapy activates the body's immune system, which depends on its innate immunological processes. Immunotherapy provides patients with advanced cancer with better therapeutic outcomes, less side effects, and longer-lasting effects as compared to other cancer

treatments. Among the many tactics used in immunotherapy, immune checkpoint inhibitors and cancer vaccines have demonstrated successful therapeutic benefits in a number of cancer types[52].

MXenes can accomplish effective drug loading and accurate release because of their distinct spatial structure and stimulus responsiveness. Furthermore, MXenes can achieve PTT-enhanced immunotherapy by causing immunogenic cell death (ICD) in tumor cells through PTT[53].

AuNPs have peroxidase-like activity and produce ROS in the TME to hasten the demise of tumor cells. The development of DCs and the infiltration of T cells in the TME are facilitated by the ICD caused by MXenes and the cell death caused by AuNPs. Furthermore, the OX40 antibody (αOX40) on the platform stimulated CD4þ and CD8þ T cells, which improved immunotherapy by reversing the immunosuppressive state in the TME. Notably, this tactic increased the anticancer activity of M2 macrophages by encouraging their polarization into M1 macrophages.

LIMITATIONS OF MXENE NANOPLATFORM IN CANCER THERAPY

MXene nanoplatforms have great potential for cancer treatment, but their practical application is hampered by a number of important issues. Their lack of stability in physiological and aquatic conditions is a significant obstacle. MXene nanosheets are extremely vulnerable to oxidative degradation, which modifies their physicochemical characteristics, degrades structural integrity, and impairs therapeutic efficacy, including photothermal efficiency and controlled drug release. Unpredictable in vivo behaviour and decreased treatment reliability could be the outcome of this instability.

Biocompatibility and toxicity are a significant additional constraint. Comprehensive long-term research on chronic toxicity, biodistribution, organ accumulation, metabolism, and clearance are still lacking, despite the fact that short-term in vitro and in vivo studies frequently reveal relatively low toxicity. When unmodified MXenes degrade, potentially harmful by-products may be produced, which could cause oxidative stress, inflammatory reactions, and negative biological impacts.

Scalability and repeatability of synthesis are also significant obstacles. In addition to producing materials with uneven size, thickness, surface terminations, and purity, conventional MXene production techniques often entail dangerous chemicals like hydrofluoric acid. Batch-to-batch variability like this makes large-scale manufacturing, quality control, and reproducibility difficult, which delays clinical deployment and regulatory approval. Moreover, controlling exact surface

functionalisation is still challenging. Drug loading capacity, targeting ligand attachment, and release kinetics can all be greatly impacted by changes in surface chemistry and coating uniformity. Therefore, uneven functionalisation may lower therapy predictability and targeting effectiveness.

The pharmacokinetics and biodistribution of MXenes in biological systems are similarly not fully understood. Important factors that are not entirely understood include circulation time, tumour accumulation, tissue distribution, biodegradation processes, and excretion systems. Rational design and dose optimisation for clinical usage are hampered by the absence of systematic in vivo data. Additional limitations include tumour penetration and limited targeted selectivity. MXene nanoplatforms may exhibit inadequate tumour accumulation and poor penetration into dense tumour microenvironments in the absence of optimised physicochemical characteristics or particular targeted ligands. This raises the possibility of off-target harm and decreases treatment efficacy.

Clinical translation is further limited by gaps in regulations and standards. As of right now, there is no widely recognised framework for assessing the quality control, safety, and effectiveness of MXene-based nanomedicines. Cross-study comparisons are challenging and the development of clinical guidelines is slowed by variations in experimental models, characterisation methods, and toxicity assessment procedures. Lastly, applications like photothermal therapy (PTT) and photodynamic therapy (PDT) have modality-specific restrictions. Reactive oxygen species (ROS) production may be poor in MXene-based systems, and cancer cells may evolve defence mechanisms including overexpressing heat shock protein (HSP), which would decrease the effectiveness of treatment. To get the best anticancer results, extra functionalisation or combination techniques are frequently needed9[(54)].

CONCLUSION:

Tumour microenvironment (TME)-activated stimuli-responsive MXene nanoplatforms represent a promising advancement in precision oncology by enabling targeted, controlled, and multifunctional cancer therapy. Their unique physicochemical properties, including high surface area, excellent photothermal conversion efficiency, superior drug-loading capacity, and ease of surface functionalization, make them highly effective carriers for the delivery of anticancer agents. The integration of endogenous and exogenous stimuli-responsive mechanisms further enhances site-specific drug release while

minimizing systemic toxicity and improving therapeutic efficacy. In addition to supporting photothermal,photodynamic,chemo dynamic, and immunotherapeutic approaches, MXene-based nanoplatforms provide opportunities for synergistic treatment strategies and image-guided cancer therapy. However, several challenges remain, including limited long-term biocompatibility data, oxidative instability, scalable synthesis, reproducibility, and regulatory concerns, which must be addressed before clinical translation. Overall, continued research focused on improving MXene stability, biosafety, targeted delivery, and standardized manufacturing processes will accelerate their transition from laboratory research to clinical application. With ongoing technological advancements, stimuli-responsive MXene nanoplatforms have the potential to become an important component of next-generation personalized cancer treatment.

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