Materials Chemistry Horizons

PERSPECTIVE

# MXenes and Their Composites: A Versatile Platform for Biomedical Applications

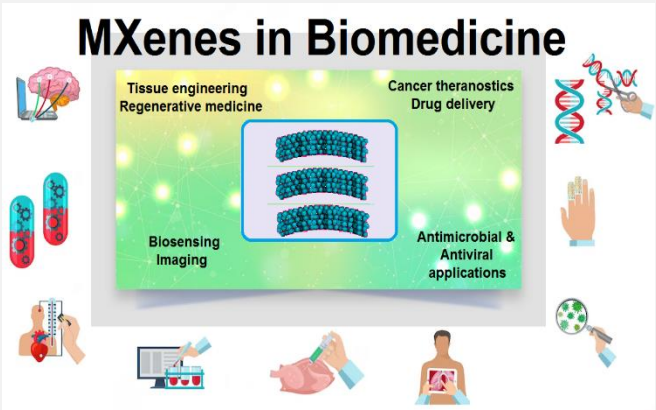
Navid Rabiee[1,2*] & Siavash Iravani[3*]

[1] Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Perth, WA 6150, Australia
[2] School of Engineering, Macquarie University, Sydney, New South Wales, 2109, Australia
[3] Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

**Corresponding author:** nrabiee94@gmail.com (N.Rabiee); siavashira@gmail.com (S.Iravani)

*Mater. Chem. Horizons*, 2023,2(3), 171-184 10.22128/mch.2023.697.1043 OPEN ACCESS

**ABSTRACT**




MXenes have potential applications in biomedicine, ranging from sensors and cancer theranostics to targeted drug delivery and tissue engineering/regenerative medicine. They are characterized by fascinating structural, optical, thermal, mechanical, electronic, and biological features, making them promising for various biomedical purposes. MXenes with high surface area, excellent conductivity, hydrophilicity, biocompatibility, high atomic numbers, and unique paramagnetic behavior have been hybridized with organic/inorganic materials to develop various biomedical devices, biosensors, tissue engineering scaffolds, antimicrobial agents, etc. Ongoing research in this field is expected to lead to the development of even more MXene-based biomedical devices in the future. Despite the biomedical potential of MXene-based composites, their biosafety and potential environmental risks need to be in-depth evaluated. In addition, physiological stability, decomposition rate, and controlled/sustained drug release as well as limited in-vivo studies and systematic guidelines are crucial aspects that should be considered for developing next-generation multifunctional MXene-based composites in biomedicine. Notably, clinical translation studies ought to be systematically addressed before these materials can be used in clinical applications. Despite their promising potential, challenges remain in the large-scale production and functionalization of MXenes. In this perspective, important challenges for in vivo applications, pitfalls, and future outlooks for the employment of MXenes in biomedicine are deliberated. The progress and biomedical applications of MXenes have been briefly reviewed, and the development background of MXenes has been introduced.

**Keywords:** MXenes, biomedical applications, tissue engineering, biosensing, cancer theranostics, drug delivery

## 1. Introduction

The advantageous properties such as hydrophilicity, high conductivity, surface functionality, and flexibility, combined with their exceptional biocompatibility, have positioned MXenes at the forefront of a multitude of biomedical applications [1]. This includes drug delivery, bioimaging, photothermal/photodynamic therapy, biosensing, and tissue engineering (TE), among others [2]. The unique electronic and physicochemical properties of MXenes can be attributed to their 2D layered structures, where the transition metal layers are sandwiched between carbon or nitrogen layers. They display impressive hydrophilicity due to their hydroxyl, oxygen, or fluoride functional groups on their surface, making them compatible with various biological entities. Moreover, MXenes, with their metallic conductivity, facilitate the transfer of electrons and ions, enabling their utility in electrical signal detection, crucial in the development of biosensors [3]. The surface functionality of MXenes can be customized further through different methods such as intercalation, ion exchange, and phase transformations. This allows researchers to engineer these materials to interact with specific biological entities, opening up a wide array of possibilities in targeted drug delivery and personalized medicine. The high near-infrared (NIR) absorbance of MXenes makes them excellent

Received: July 09, 2023
Received in revised: August 10, 2023
Accepted: August 12, 2023

candidates for photothermal and photodynamic therapies, as they can convert light energy into heat to kill cancer cells or activate therapeutic drugs [4].

MXenes, an ever-evolving class of two-dimensional (2D) transition metal carbides, carbonitrides, and nitrides, have caught the attention of the scientific community, particularly for biomedical research [5-8]. MXenes possess a chemical structure represented by the formula $M_{n+1}X_nT_x$, where 'M' denotes an early transition metal, and 'X' embodies carbon, nitrogen, and quite recently, oxygen [9]; 'T' also signifies surface terminations [10]. The representation 'n' in the $M_{n+1}X_nT_x$ formula corresponds to the varying number of M and X layers within a 2D MXene flake and can fluctuate between 1 and 4 [11]. The 'x' in Tx reflects the count of surface terminations per formula unit, typically approximating to ~2. Since the successful creation of the $Ti_3C_2T_x$ MXene, a host of additional MXenes have been produced by selectively etching their precursor materials, predominantly MAX phases. Within a MAX phase, the $M_{n+1}X_n$ layers are linked with an atomically thin layer of an A-group element mainly *via* metallic M–A bonds. The diversity of MAX phase materials is extensive, with over 150 different compositions synthesized so far [12]. Strikingly, only 70 MAX phases were known before 2011, less than half of the current count, which illustrates the escalating discovery of MAX phases stimulated by the exploration of new MXene variants. In the latest developments, MAX phases incorporating lanthanide elements have been identified. However, the MXenes derived from these lanthanide-containing MAX phases, as well as those containing manganese, have not yet been synthesized through selective etching. The fundamental $M_{n+1}X_n$ composition and structure of MXenes stem from the original MAX phase precursor. Therefore, the precise synthesis of the MAX phase is a prerequisite for the successful creation of MXenes. The prevalent method for synthesizing the MAX phase involves reactive sintering of elemental powder at elevated temperatures, typically between 1350-1600°C, which results in a layered crystalline structure. Given that the metallic M–A bonds in the MAX phases are relatively weaker than the M–X bonds, which are either covalent or ionic, and the A layer is more reactive than the $M_{n+1}X_n$ framework, immersing the MAX particles in an acidic liquid etchant or molten salt facilitates the selective removal of the A-group elemental layers. This selective etching technique has also been applied to generate MXenes from layered carbides that are not MAX phases, such as the removal of Ga-Ga layers in $Mo_2Ga_2C$ to produce $Mo_2CT_x$ and $Al_3C_3$ layers in $Zr_3Al_3C_5$ to yield $Zr_3C_2T_x$ MXene [13, 14]. Post the selective etching process, MXene multilayered powders are manufactured, which can be delaminated into individual $M_{n+1}X_nT_x$ sheets.

Despite their promise, the application of MXenes in biomedical research is still in its infancy, with most studies being carried out *in vitro* or small animal models. There is a need for further studies to elucidate the *in-vivo* behavior and long-term biocompatibility of these materials, as well as to develop scalable and reproducible synthesis and modification methods. Moreover, translating MXenes' unique properties into clinical applications presents significant challenges [15]. The lack of standardized protocols for MXene synthesis and modification may lead to inconsistencies in their physicochemical properties, thereby affecting their biocompatibility and performance in biomedical applications. Furthermore, the potential health hazards associated with MXenes, such as cytotoxicity and genotoxicity, need to be thoroughly evaluated to ensure patient safety. Nonetheless, the field of MXenes is experiencing explosive growth, fueled by the multitude of potential applications and the promise of addressing some of the most pressing challenges in biomedical research [16]. This includes the development of non-invasive therapies for cancer, the design of smart drug delivery systems, the engineering of advanced biosensors, and the creation of new materials for TE.

While there is still much to learn and understand about these 2D materials, the potential of MXenes in biomedical research is undeniable. Many reviews have been published in the field of biomedical applications of MXenes [17-22]. In terms of methodologies, researchers have employed various techniques to study MXenes in the context of biomedicine. These include synthesis methods to produce MXene nanosheets with specific properties, characterization techniques to analyze their structure and composition, and *in vitro* and *in vivo* experiments to evaluate their performance in different biomedical applications. In terms of key findings and trends, MXenes have shown great potential in improving drug delivery efficiency and targeting specific sites, enhancing bioimaging capabilities, promoting tissue regeneration, and exerting antibacterial effects. Researchers are continually exploring ways to optimize MXene properties, enhance their biocompatibility, and improve their production scalability for practical biomedical applications. This perspective serves as an introduction to the advances in the biomedical potential of MXenes and their composites, highlighting the important challenges and future perspectives in this exciting and

rapidly evolving field. Undoubtedly, with a thorough understanding of MXenes and their properties, they hold significant promise to revolutionize the future of bio- and nanomedicine.

## 2. MXenes and their composites in biomedicine

MXene-based composites have the potential to open significant new opportunities in the future of bio- and nanomedicine [18, 23-25]. As we dive deeper into this topic, it becomes increasingly apparent that the multidisciplinary nature of MXenes, blending elements of materials science, chemistry, physics, and biomedical research, contributes significantly to their versatility. However, this also necessitates a collaborative approach to understand the potential and limitations of these materials fully. The tunability of MXenes provides opportunities for engineering materials with tailored characteristics to fit specific applications. By manipulating the type of transition metal, the type and number of surface functional groups, and the layer thickness, researchers can control properties such as electrical conductivity, optical absorption, mechanical strength, and chemical stability [26, 27]. This makes MXenes a veritable toolbox for biomedical engineers and scientists, who can pick and choose the properties they need for their specific applications. For instance, the high electrical conductivity of MXenes can be leveraged in biosensors. MXenes' ability to facilitate electron transfer processes could dramatically improve the sensitivity and selectivity of these devices. This could lead to the development of rapid, point-of-care diagnostic tools capable of detecting biomarkers at extremely low concentrations, a critical need in early disease detection [28, 29]. In the realm of drug delivery, the tunable surface chemistry of MXenes allows for the loading of various therapeutic agents, from small drug molecules to large bio-macromolecules. The stimuli-responsive behavior of MXenes, specifically their ability to release loaded drugs in response to changes in the local environment such as pH or temperature, could be used to design smart drug delivery systems that deliver their payload only at the desired site, thereby minimizing side effects [30]. Moreover, the photothermal and photodynamic therapy potential of MXenes offers a promising avenue for minimally invasive cancer treatments. By leveraging their high NIR absorbance, MXenes could be used to destroy tumor cells selectively, without causing damage to healthy surrounding tissues. This could lead to a new generation of therapies that are more effective and less harmful than traditional treatments [31].

Despite these exciting prospects, there is a pressing need to address the potential environmental and health risks associated with MXenes. While some studies suggest that MXenes are biocompatible and non-toxic, others have raised concerns about their potential cytotoxicity and genotoxicity [32]. These contrasting results underscore the importance of conducting comprehensive and rigorous safety assessments before integrating MXenes into biomedical applications. As we delve further into the world of MXenes, we will continue to encounter challenges, some of which we can anticipate, and others that will surprise us. However, the potential of these materials to transform biomedical research and improve human health makes every challenge worthwhile. It is hoped that as we increase our understanding of MXenes, we can harness their full potential and move towards a future where they are an integral part of medical diagnostics, therapies, and biomedical devices. In the meantime, the journey toward this future promises to be a fascinating voyage of discovery, filled with intriguing scientific questions and exciting technological possibilities [33, 34].

The properties of MXenes make them promising materials for TE and regenerative medicine applications, as exemplified in the case of polycaprolactone-MXene nanofibrous scaffolds for TE with a combination of suitable structural, chemical, electrical, and biological properties (**Figure 1**) [35]. In this study, the composite membranes of polycaprolactone-MXene exhibited both inductive and capacitive characteristics. The conductivity parameters of inductance and capacitance reach their maximum and minimum values, respectively, at approximately $8\times10^4$ Hz frequency. The conductivity in the composite could be attributed to electron tunneling between adjacent potential wells, specifically the MXene layers. This could lead to the development of both real and imaginary components of the current, thereby contributing to the inductive properties of the scaffold. The relaxation time value, determined by the resonance frequency, was ~$6.5\times10^{-6}$ s. Analysis using positron annihilation indicated the presence of structural defects in the deposited MXene, which aligned with the biological properties of the composite. The number of deposited MXene layers was a crucial factor in designing polymer-MXene composite scaffolds. Optimal results,

including cellular attachment, proliferation, and a mild antibacterial effect, were achieved with two or three layers of MXene deposited on polycaprolactone electrospun nanofibers [35].

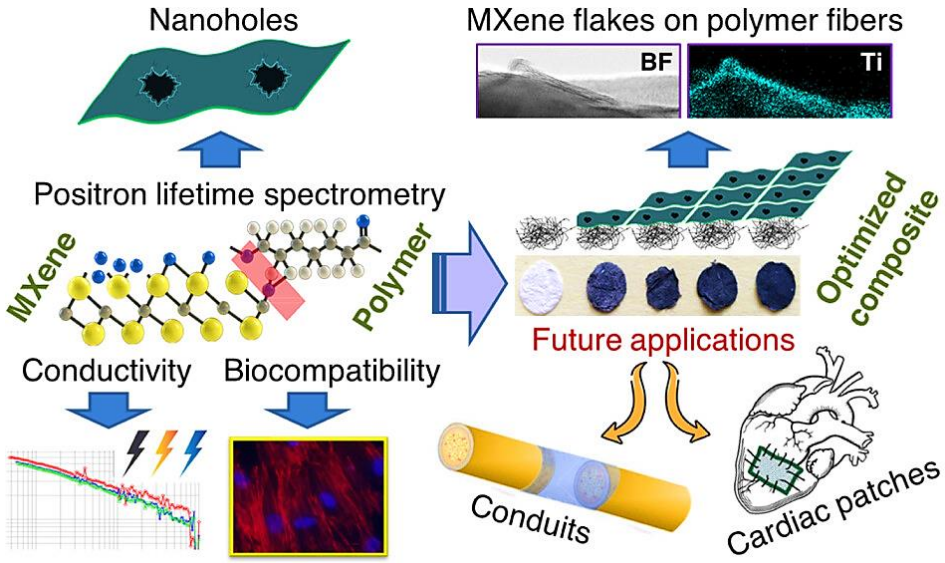



**Figure 1.** Polycaprolactone-MXene nanofibrous scaffolds with tissue engineering applications. Reproduced with permission from ref [35]. Copyright 2023 American Chemical Society.

Ongoing research is exploring new tactics to use MXenes for promoting tissue regeneration and treating various medical conditions [36-38]. In one study, electrically conductive three-dimensional (3D) printed MXene ($Ti_3C_2T_x$)-polyethylene glycol composites were developed through aerosol jet printing for cardiac TE purposes [39]. The composites were seeded with human-induced pluripotent stem cell-derived cardiomyocytes and cultured for one week with no noticeable cytotoxicity, showing excellent potential in the creation of physiologically relevant cardiac patches for treating myocardial infarction [39]. MXenes with their large surface area can be applied for enhancing cell adhesion and proliferation [40]. Huang et al. [41] prepared MXene ($Ti_3C_2$) nanofibers through electrospinning and doping technique for cell culture and TE. The nanofibers exhibited high hydrophilicity owing to a large number of presented functional hydrophilic groups, with a suitable microenvironment for the growth of bone marrow-derived mesenchymal stem cells (BMSCs). Accordingly, these biocompatible nanofibers could highly improve cellular performance, enhancing the differentiation BMSCs to osteoblasts [41]. In addition, MXene ($Ti_3C_2T_x$)/hydroxyapatite composite coatings were fabricated on the surface of 3D printed bone TE Ti-6Al-4V scaffolds through a pulse electrodeposition technique [42]. The MXene-based composite could promote the homogeneous nucleation of hydroxyapatite during the electrodeposition procedure, exhibiting suitable biocompatibility with manifold biological activities. The cell growth was successfully performed on the surface of composite coatings with no noticeable cytotoxicity, and also the morphology of cells exhibited an acceptable spreading state and trend of inward growth [42].

Several MXene-based composites have been designed to promote wound healing *via* enhancement in cell migration and proliferation [40]. Li et al. [43] introduced chitin/MXene composite sponges through the incorporation of MXene-based nanomaterials with different shapes of accordion, intercalated, single-layer, and gold (Au) nanoparticle-loaded single-layer into the network of chitin sponges, thereby providing platforms for preventing massive blood losses and promoting the healing procedure of bacterial-infected wounds. Notably, MXenes could improve the hemostatic efficacy of chitin sponges due to the enhancement in hemophilic and blood coagulation kinetics. The composites exhibited efficient antibacterial performances owing to the synergy between the capture and the photothermal effects, obtaining wound closure rates of 84% on day 9 [43]. In another study, hydrogel composites with injectability and NIR light-responsive behavior were constructed from MXene ($Ti_3C_2$), agarose, and protein, showing flexibility and controllability for the release of protein drugs to regulate cellular behaviors [44]. Accordingly, the delivery of hepatic

growth factor (HGF) was studied for activations of the c-Met-mediated signaling through NIR light, providing improved cell diffusion, migration, and proliferation at targeted sites as well as promotion of angiogenesis and wound healing (*in vivo*) [44].

MXene-based composites have been studied for targeted delivery of anticancer drugs and therapeutic agents. Their unique physicochemical features and 2D planar structure make them promising candidates for drug loading and precision treatment [45]. However, there are still challenges to address on their stability in physiological environments, sustained/controlled release of drugs, and further exploration of their potential in various biomedical applications. NIR light-responsive MXene ($Ti_3C_2$)-cellulose composites were designed for targeted delivery of an anticancer drug (doxorubicin), showing controlled release behavior [46]. These hydrogel composites exhibited suitable photothermal effects and could be employed for targeted chemo-photothermal tumor/cancer therapy [46]. In addition, MXene ($Nb_2C$)-based composites were developed for chemo-PTT of cancers (the inhibition efficiency was ~92.37% ) in the NIR-II biowindow, showing good photothermal conversion efficiency (~28.6%) [47]. Liu *et al*. [48] introduced heterostructured MXene ($Ti_3C_2$)-cobalt (Co) nanowires as multifunctional nanocarriers for targeted chemo-photothermal synergistic therapy, showing magnetic controllability as well as stimuli-responsive release behavior. The as-prepared nanosystems exhibited significant drug loading capability (~225.05%) along with suitable photothermal conversion efficiency under laser irradiation (808 nm). Notably, the release of an anticancer drug (doxorubicin) could be stimulated by acidic conditions (pH = 4-6) and NIR irradiation [48].

MXenes have excellent potential for biosensing and imaging applications owing to their unique properties such as excellent metallic conductivity, rich surface chemistry, hydrophilicity, good biocompatibility, and high anchoring capacity [49, 50]. They have been exploited for the detection of various analytes with extraordinary sensitivity and selectivity. Cui *et al*. [51] developed a highly sensitive and specific fluorescence resonance energy transfer (FRET) aptasensor using monolayer $Ti_3C_2$ MXene. The aptasensor was designed to simultaneously detect insulin and visceral adipose tissue-derived serotonin (vaspin). To achieve this, fluorescein-labeled insulin-binding aptamers (IBAs) and Cy7-labeled vaspin-binding aptamers (VBAs) were attached to MXene, resulting in effective fluorescence quenching through FRET between fluorescein and MXene. The IBAs and VBAs exhibited a higher affinity for insulin and vaspin, respectively, leading to the release of fluorescein from the MXene and subsequent fluorescence recovery. The unique properties of $Ti_3C_2$ MXene, including high fluorescence quenching efficiency and broad wavelength absorption, allow for the simultaneous quenching of two different fluorescence signals at different wavelengths. The aptasensor exhibited high sensitivity, with a low limit of detection (LOD) (~36 pM for insulin and ~45 pM for vaspin). Notably, this MXene-based aptasensor displayed potential for precise detection of insulin and vaspin in human serum, enabling the diagnosis of specific types of diabetes and identification of their causes for subsequent treatment. These findings suggest promising applications of the MXene-based aptasensor in clinical diagnosis and typing of diabetes mellitus [51]. Several MXene-based electrochemical biosensors have been designed for the selective detection of tumor/cancer biomarkers, as exemplified in the case of MXene-Au electrochemical biosensors for the recognition of biomarkers in the tumor-derived exosomes [52]. For instance, circulating tumor cells (CTCs) are crucial indicators for cancer diagnosis and metastasis, and their detection plays a vital role in identifying cancer metastasis [53]. Su *et al*. [53] developed an electrochemical biosensor using Prussian blue (PB)-MXene composite films. A straightforward electrostatic self-assembly method was employed to create a film consisting of PB nanocubes on MXene substrates. The PB-MXene films enabled real-time monitoring of $H_2O_2$ secretion from living CTCs, as PB acted as an artificial peroxidase for $H_2O_2$ sensing. Besides, the biosensors with attached anti-CEA molecules could accurately quantify the corresponding CTCs. The combination of MXene's large specific area and PB's enzyme-free catalysis for $H_2O_2$ could lead to obtaining PB-MXene films with high electrocatalytic activity and low cytotoxicity, facilitating both $H_2O_2$ sensing and capturing of living CTCs. The biosensor exhibited an LOD of 0.57 μM for $H_2O_2$, covering a wide linear range of 1 μM to 500 μM. It also demonstrated excellent sensitivity for CTCs, with an extremely low detection limit of 9 cells/mL within a wide linear range of $1.3 \times 10^1$ to $1.3 \times 10^6$ cells/mL. The biosensor exhibited improved stability along with the anti-interference capability, making it suitable for potential applications in clinical cancer diagnosis and tumor metastasis [53]. In another study, an electrochemical DNA biosensor was developed using a nanocomposite of MXene ($Ti_3C_2$), multi-walled carbon nanotubes, and polypyrrole. The nanobiosensor with high sensitivity and specificity could be applied for the detection of CEACAM5 as an ovarian cancer-related tumor marker in real clinical

samples [54]. An electrochemical biosensor was augmented with nanocomposite of MXene, hierarchical flower-like Au, and poly (n-butyl acrylate), and also actuated by highly special antisense single-stranded DNA (ssDNA) [55]. This biosensor with high sensitivity and specificity as well as desirable stability (stayed stable until 32 days) could be employed to detect miRNA-122 as a biomarker of breast cancer, with a linear range from 0.01 aM to 10 nM and an LOD of 0.0035 aM [55]. However, several challenges are still remained pertaining to the oxidative stability and optimization of synthesis techniques as well as limitations of electrochemical transducers and bio-electrochemical sensors [17, 56].

MXenes have also been used for non-invasive imaging, including magnetic resonance imaging (MRI), positron emission tomography (PET), computerized tomography (CT) scan, fluorescence (FL), and photoacoustic (PA) imaging [49]. The applications of MXenes in biosensors are divided into three main categories: electrochemical biosensors, fluorescent/optical biosensors, and biocompatible field-effect transistor biosensors; MXene-based sensors can be applied for early cancer detection [17, 57]. However, the theoretical perspectives of MXenes in biosensing applications are not yet well explored. While some studies have elucidated the fundamentals of biosensing applications of 2D materials, there is still much to learn about the specific mechanisms and optimization of MXenes for biosensing and imaging. In one study, core-shell nanocomposites were introduced based on MXene ($Ti_3C_2$) and Au nanoparticles (NPs), offering biocompatible MXene-based multifunctional nanostructures for photoacoustic and CT dual-modal imaging applications (**Figure 2**) [58]. Au NPs were grown on the surface of MXene nanosheets to improve their stability and biocompatibility through the thiol modification process; the optical absorption in the NIR region was also accelerated [58].

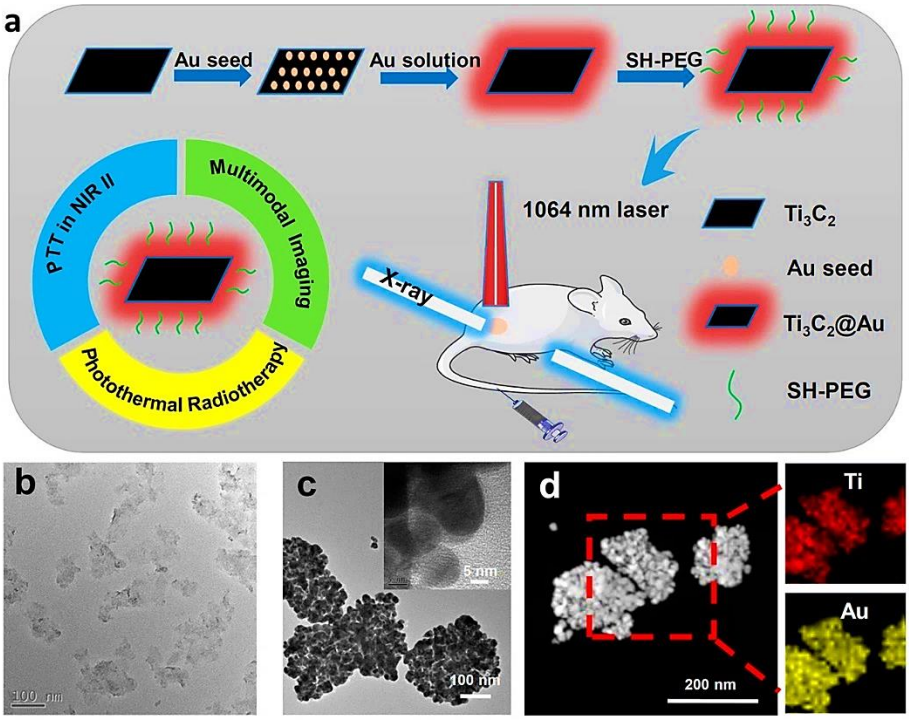



**Figure 2.** The $Ti_3C_2$@Au nanostructure was characterized as follows: (**a**) The theranostic function of $Ti_3C_2$@Au, including the synthesis of $Ti_3C_2$@Au, PEGylation, and *in vivo* PA/CT dual-modal imaging-guided photothermal therapy combined with radiotherapy. (**b, c**) Transmission electron microscopy (TEM) images were taken of the $Ti_3C_2$ nanosheets (**b**) and $Ti_3C_2$@Au nanocomposites (**c**). The corresponding magnified TEM image was also included. (**d**) High-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) images were captured to show individual MXene@Au nanocomposites, with element mappings indicating the distribution of Ti (red) and Au (yellow). PEG: polyethylene glycol. Reproduced with permission from ref [58]. Copyright 2018 American Chemical Society

MXenes have been found to exhibit antibacterial activities against pathogenic bacteria such as *Bacillus subtilis*, *Escherichia coli*, and *Staphylococcus aureus*. For instance, Cu-MXene materials exhibited efficient antibacterial

activity against *E. coli* and *S. aureus* [59]. The mechanism of antibacterial action for MXenes has been attributed to cell membrane disruption and reactive oxygen species (ROS) generation [60, 61]. In addition, MXenes have been shown to have antiviral and immunomodulatory properties against SARS-CoV-2; MXenes have been found to trap viruses and either inactivate or kill them by interacting with the outer spike proteins [62]. It was indicated that the structure at the atomic scale may play an important role in the bioactivity of MXenes of the same chemical composition but with various stoichiometry methods [61]. The specific mechanisms by which MXenes disrupt bacterial and viral cells are still being studied, but research suggests that MXenes exert their antibacterial and antiviral properties through cell membrane disruption, ROS formation, and intracellular mechanisms [63, 64]. In one study, He et al. [65] introduced monolayer high-entropy MXenes with robust oxidase mimic activity and photothermal conversion efficiency (~65.8%) in the second NIR-II biowindow. The nanocomposites could be employed to kill methicillin-resistant *S. aureus* and promptly eliminate the biofilm. Such MXene-based materials with efficient antibacterial effects against antibiotic-resistant bacteria can be applied for promoting the healing of infected tissues [65].

## 3. Challenges and future perspectives

MXenes, a class of 2D transition metal carbides, have been touted as promising materials for a myriad of biomedical applications due to their intriguing physicochemical properties. However, realizing their full potential is not without challenges, which need to be tackled judiciously. One major concern is the cytotoxicity of MXenes. However, in one study, it was indicated that $Ti_3C_2T_x$ had much better cytocompatibility than graphene oxide, making it a promising candidate for future biomedical applications [66]. While some studies indicate that MXenes exhibit good biocompatibility, others have raised concerns about their cytotoxicity. For instance, to assess the potential harm of MXenes to the nervous system, primary Neural Stem Cells (NSCs) and differentiated cells derived from NSCs were chosen as the experimental model. These cells were exposed to different levels of $Ti_3C_2$ nanosheets for 24 hours. Initially, researchers utilized flow cytometry to measure the degree of apoptosis in NSCs following treatment with $Ti_3C_2$. The NSCs were classified into three categories based on Annexin V and propidium iodide dual staining: normal ($Q_1$), cells undergoing apoptosis ($Q_2$+$Q_3$), and necrotic cells ($Q_4$) (**Figure 3A**). Analysis of the proportion of apoptotic cells revealed that exposure to 12.5 μg/mL of MXene ($Ti_3C_2$) nanosheets did not notably elevate the apoptosis levels in NSCs (**Figure 3B**). However, a significant rise in apoptotic NSCs was observed following exposure to $Ti_3C_2$ concentrations of 25 μg/mL and higher (**Figure 3B**). Subsequently, the CCK-8 assay was deployed to ascertain the viability of NSCs upon exposure to $Ti_3C_2$ nanosheets. In accordance with the previous observations, a dosage of 12.5 μg/mL of $Ti_3C_2$ nanosheets exhibited no noticeable influence on NSC viability, while significant effects were observed at concentrations of 25 μg/mL and beyond (**Figure 3C**) [67].

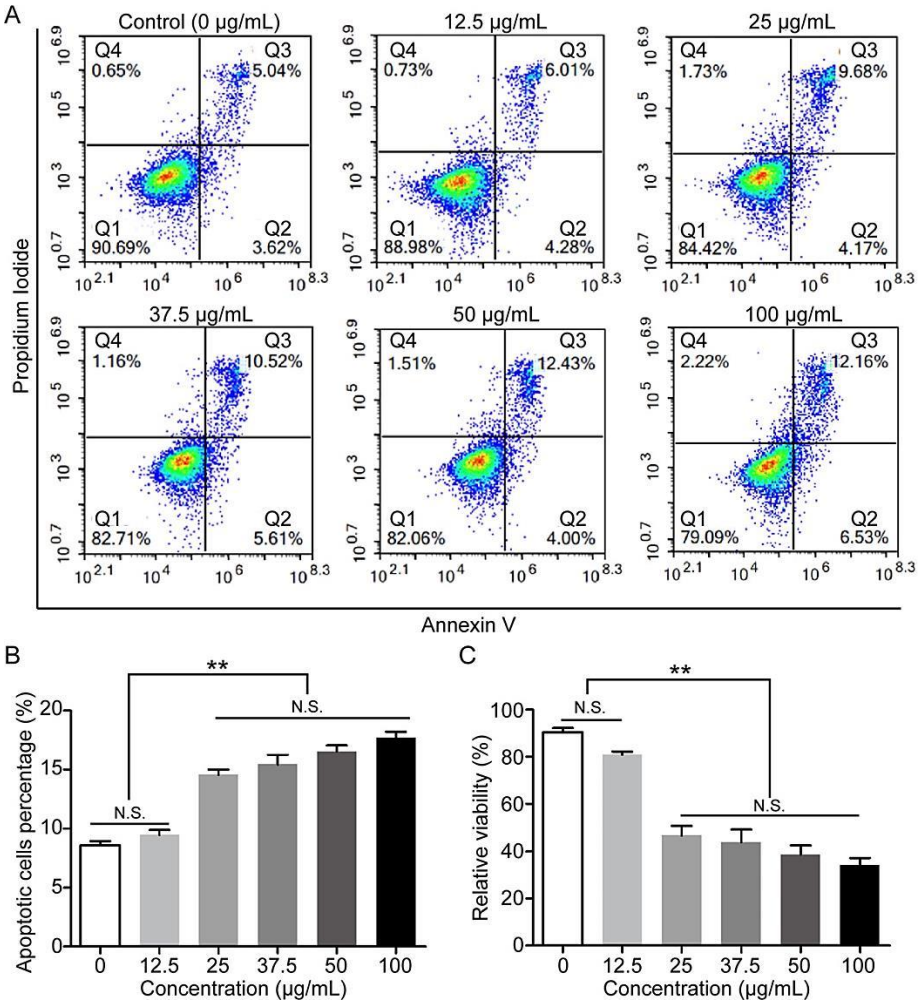



**Figure 3.** The impact of $Ti_3C_2$ nanosheets on the cytotoxicity of neural stem cells (NSCs). (**A**) A depiction of flow cytometry outcomes for NSCs treated with $Ti_3C_2$ and stained with annexin V and propidium iodide. (**B**) Collective data representing flow cytometry analysis of apoptosis in NSCs subjected to $Ti_3C_2$. (**C**) CCK-8 assay assessment of the relative viability of NSCs following exposure to varying concentrations of $Ti_3C_2$. The bars indicate mean ± standard deviation; the sample size is 3; **p<0.01 implies a statistically significant difference; N.S. signifies no significant variance. Reproduced with permission from ref [67]. Copyright 2020, American Chemical Society.

Another research showed that the effectiveness of nanomedicine treatments is largely determined by the degree of intracellular absorption [68]. TEM showed noticeable morphological alterations and increased electron density in the cytoplasm as a result of $Ti_3C_2$-MXene-Au, suggesting efficient cellular uptake of this compound by 4T1 cells and subsequent accumulation in the tumor (**Figure 4a**). Given that the externalization of Damage-Associated Molecular Patterns (DAMPs) is a critical step towards stimulating Dendritic Cell (DC) maturation and initiating ICD-induced antitumor immunity, the levels of DAMPs- encompassing Calreticulin (CRT), High Mobility Group Box 1 (HMGB1), and ATP - in 4T1 cells subjected to different treatments were examined. The group treated with both $Ti_3C_2$-MXene-Au and NIR displayed higher CRT fluorescence intensity and elevated HMGB1 release from 4T1 cells in comparison to other treatment groups (**Figure 4b**). Similarly, ATP levels in the $Ti_3C_2$-MXene-Au + NIR group exceeded those found in other treatment groups (**Figure 4c**). These outcomes suggest that photothermal therapy (PTT) based on $Ti_3C_2$-MXene-Au is capable of initiating ICD effects and enhancing the activation of immune responses. The discrepancies could be due to differences in experimental conditions, such as MXene concentration, exposure time, and cell types used. Therefore, a more systematic evaluation of their toxicity is required. In addition, the potential genotoxicity of MXenes, which is their ability to damage DNA, remains largely unexplored and needs further investigation [68].

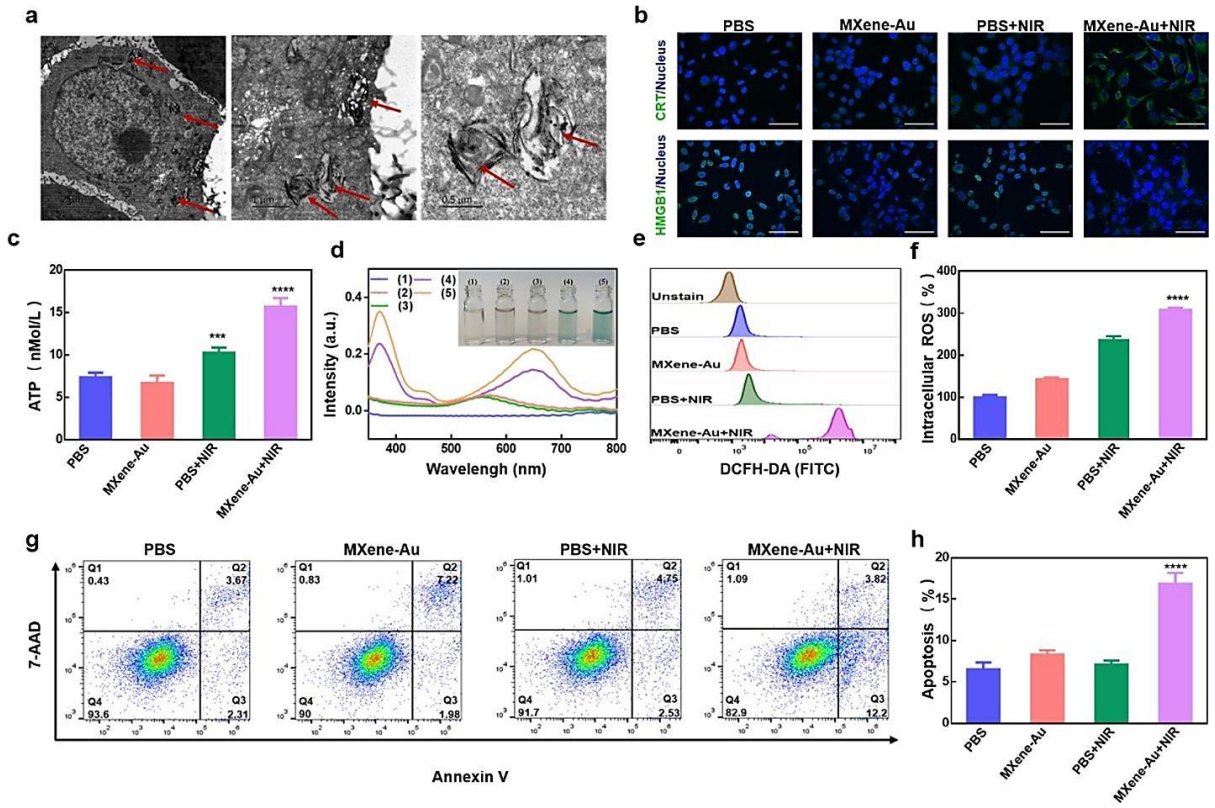



**Figure 4.** Experiments at the cellular level were conducted to examine the effects of the $Ti_3C_2$-MXene-Au nanoplatforms on phagocytosis and immunogenic cell death (ICD) induction, as well as its enzymatic activity. (**a**) TEM images illustrate the presence of $Ti_3C_2$-MXene-Au in tumor cells. (**b**) Immunofluorescence staining was used to monitor the expression of Calreticulin (CRT) and release of High Mobility Group Box 1 (HMGB1) from 4T1 cells under varying treatments. Here, the blue and green fluorescence represents the tumor cell nucleus and signals from CRT or HMGB1 staining, respectively (scale bar, 50 μm). (**c**) ATP concentrations in 4T1 tumor cells were measured using a standard test kit. (**d**) Ultraviolet-visible (UV–Vis) absorption spectra of the oxidized Tetramethylbenzidine (TMB) catalyzed by different combinations, including (1) TMB + $H_2O_2$, (2) TMB + $Ti_3C_2$-MXene-Au, (3) $Ti_3C_2$-MXene-Au + $H_2O_2$, (4) $Ti_3C_2$-MXene-Au + TMB + $H_2O_2$, or (5) $Ti_3C_2$-MXene-Au + TMB + $H_2O_2$ + NIR. Visual depictions of color changes across various treatment groups are displayed in the inset. (**e**) Reactive Oxygen Species (ROS) levels in 4T1 cells treated with varying strategies were measured using flow cytometry. (**f**) Quantitative analysis of ROS concentrations across different groups. (**g**) Cell apoptosis following treatment with either PBS or $Ti_3C_2$-MXene–Au along with 808 nm laser irradiation was assessed using annexin V/7-AAD by flow cytometry. (**h**) Quantification of cell apoptosis based on the data from panel g. All data are represented as mean ± standard deviation (n = 4). Statistical significance was determined using a two-tailed Student's t-test. ***p<0.001, ****p < 0.0001. Reproduced with permission from ref [68]. Copyright 2022, American Chemical Society.

The synthesis of MXenes is another important challenge. Indeed, the selection of appropriate tactics for synthesizing MXenes and their composites depends on parameters such as the desired properties, the target application, and the specific materials involved. Researchers continue to explore and develop new strategies to expand the capabilities of MXenes and their composites in various biomedical applications. The etching method is the most widely used technique for MXene synthesis, involving the selective etching of MAX phase materials, such as MAXenes, using strong etchants like hydrofluoric acid (HF) or mixtures of HF and other acids. This process removes the A-layer elements from the MAX phase, resulting in the formation of MXene nanosheets [69]. MAX phase materials are intercalated with different ions or molecules, followed by subsequent delamination to obtain MXene nanosheets. Intercalation agents like lithium ions, organic solvents, or organic molecules help to expand the interlayer spacing, making it easier to exfoliate the layers and obtain MXene nanosheets [70, 71]. Current synthesis methods usually involve harsh chemical treatments and often produce MXenes with heterogeneous characteristics, which may influence their biological interactions and impede their clinical translation. In addition, the scale-up of MXene production while maintaining its quality and consistency is one of the important hurdles that need to be addressed for

their widespread uses. MXene stability is also an issue that requires attention. MXenes can degrade over time, especially in an aqueous environment. This degradation may release potentially harmful ions into the biological system, affecting the biocompatibility of MXenes. Therefore, strategies to improve the stability of MXenes in biological environments are required.

Despite these challenges, the future of MXenes in biomedicine looks bright. MXenes could revolutionize several aspects of healthcare. For instance, their high conductivity and surface functional ability could be exploited in the development of next-generation biosensors for the rapid and sensitive detection of diseases. MXenes could also play a significant role in targeted drug delivery. By loading therapeutic agents onto MXene flakes, they can be delivered to specific cells or tissues, thereby minimizing side effects. Furthermore, MXenes' ability to absorb NIR light and convert it into heat holds great promise for PTT, a minimally invasive cancer treatment. TE is another exciting area where MXenes could make a substantial impact. MXenes could be used as scaffolds to support the growth and differentiation of cells, potentially aiding in the repair and replacement of damaged tissues. In one study, Chen and colleagues utilized graphene and polytetrafluoroethylene (PTFE) particles to modulate the rheological properties of polydimethylsiloxane (PDMS) prepolymers [72]. Through a 3D printing approach, they created a flexible elastic fiber featuring a conductive core encased within an insulating sheath. These elastic fibers capitalized on the triboelectric effect to achieve the capacity for array tactile sensing, enabled by the strategic design of interwoven warp and weft. The resultant smart textiles showcased excellent tensile strength, durability, and breathability, underlining the significant potential of 3D printing in the fabrication of wearable devices. This approach can be used by the MXenes for wearable sensors, TE, and implantable devices as well in the future.

Overall, while MXenes show promising potential in biomedicine, there are still important challenges and limitations to address for future research. Overcoming these challenges and advancing our understanding of MXenes' interactions with biological systems will contribute to their successful integration into clinical practice and the development of innovative biomedical solutions. Some of the important advantages and challenges are listed below:

**Challenges:**

**Lack of long-term *in vivo* studies:** Many studies conducted on MXenes in biomedicine have been limited to *in vitro* experiments or short-term animal studies. Long-term *in vivo* studies are essential to evaluate the long-term biocompatibility, degradation, and potential toxicity of MXenes and their derivatives.

**Limited clinical translation:** While MXenes show promising results in preclinical studies, their clinical translation and practical implementation in medical settings are still in the early stages. Challenges such as large-scale production, cost-effectiveness, and regulatory approval need to be addressed for their successful integration into clinical practice.

**Limited understanding of biological interactions:** Despite the potential of MXenes in various biomedical applications, the precise mechanisms of their interactions with biological systems remain poorly understood. More elaborative studies are warranted to elucidate the cellular and molecular interactions of MXenes, including their impact on immune responses, cellular signaling, and long-term effects on the body.

**Opportunities and future directions:**

**Versatile material properties:** MXenes exhibit unique properties such as high surface area, tunable surface chemistry, electrical conductivity, and mechanical strength, which make them versatile for various biomedical applications. These unique properties enable tailoring MXenes for specific applications and optimizing their performance.

**Multifunctionality:** MXenes can serve multiple functions, such as drug delivery, bioimaging, and antibacterial activity, within a single material platform. This multi-functionality allows the development of integrated systems that can address different aspects of a specific biomedical challenge.

**Safety and biocompatibility assessment:** Comprehensive studies are needed to assess the long-term safety and biocompatibility of MXenes, particularly their degradation products and potential accumulation in the body. This includes long-term biosafety and toxicity analyses, immunological responses, and biodistribution studies.

**Advanced synthesis strategies:** Further advancements in MXene synthesis, surface modification, and functionalization techniques are required to improve the scalability, reproducibility, and control over the properties of MXenes. This will facilitate the translation of MXenes from laboratory research to real-world applications.

**Combination therapies:** Exploring the potential of MXenes in combination therapies, including synergistic drug delivery, cancer theranostics, and photothermal therapies, can enhance therapeutic efficacy and overcome drug resistance. Investigating the interactions of MXenes with other treatment modalities can pave the way for innovative combination therapies in various biomedical fields.

**Clinical studies and translation:** Conducting well-designed clinical studies to evaluate the safety and efficacy of MXene-based biomedical interventions is pivotal for their clinical translation. Long-term trials involving diverse patient populations would provide valuable insights into the practical utility and potential limitations of MXenes in real-world healthcare settings. In this context, organ-on-a-chip platforms hold significant potential for biosafety and toxicity evaluations, offering improved physiological relevance, predictive capacity, and reduced reliance on animal testing. However, addressing the limitations and exploring new possibilities of research will be necessary to fully unlock the capabilities of these innovative systems and facilitate their integration into regulatory frameworks and industrial applications.

## 4. Conclusion

MXenes have kindled significant interest within the scientific sphere, particularly concerning their potential for biomedical applications. They exhibit a suite of advantageous characteristics like high conductivity, surface functionality, flexibility, and impressive biocompatibility, making them suitable for diverse biomedical purposes such as drug/gene delivery, bioimaging, photothermal/photodynamic therapies, biosensing, and TE. Despite the considerable promise, MXene-based research in the biomedical field is still nascent. Most studies to date have been conducted *in vitro* or on small animal models (or limited *in vivo* models), highlighting the need for additional investigation into their *in vivo* behavior, biodegradability assay, aggregations investigations long-term biocompatibility, stability, greenness factor, and development of scalable and reproducible synthesis and modification methods. Crucially, the potential health risks associated with MXenes, including cytotoxicity and genotoxicity, ought to be exhaustively studied to ensure clinical and even after-clinical (environmental) safety. Further challenges stem from the lack of standardized protocols for MXene synthesis and modification (especially green and environmentally-friendly protocols), potentially leading to inconsistencies in their physicochemical attributes, which in turn may affect their biocompatibility/biodegradability and performance in biomedical applications. Nevertheless, MXene research is witnessing an exponential growth trajectory, propelled by the numerous potential applications and the prospect of resolving critical issues within biomedical research. As our understanding of these intriguing materials expands, they continue to promise a revolutionary impact on the future of medicine, offering avenues for the development of non-invasive therapies for cancer, smart drug/gene delivery systems, advanced (bio)sensors, wearable devices, and innovative materials for TE. Although the journey towards these advancements may present unforeseen challenges, the promise of MXenes in biomedical research remains undeniable. The continued exploration and research into MXenes could indeed herald a new era of medical diagnostics, therapies, and biomedical devices. Thus, the quest to understand and harness the full potential of these fascinating materials is not only necessary but vital for the progression of medical science.

## Authors' contributions

All authors contributed to drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

## Declaration of competing interest

The authors declare no competing interest.

## Funding

This paper received no external funding.

## Data availability

Not applicable.

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