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Biomedical Applications, Emerging Trends and Future Prospects: Two-Dimension Nanomaterials

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Abstract:

2-dimensional (2D) nanomaterials are ultrathin and chemically functional nanomaterials with high anisotropy and anisotropy. Many studies on 2D nanomaterials are only beginning to investigate the unique properties of these materials, and there are just a few publications on how 2D nanomaterials may be used in the medical field. 2D nanomaterials, however, have presented interesting new challenges concerning their interactions with biological moieties as a result of their fast advancement. Two-dimensional nanoparticles, such as carbon-based two-dimensional materials, silicate clays, transition metal dichalcogenides, and transition metal oxides, offer improved physical, chemical, and biological functioning because of their uniform forms and high surface-to-volume ratios, and with a surface charge 2D nanomaterials in biomedicine: current state-of-the-art uses and recent advances in a developing area. The unique properties of 2D nanoparticles and the biocompatibility framework that has been studied so far are described in detail in this paper. Also, to capture the emerging trend in 2D nanomaterials for biomedical applications and uncover interesting new research areas, we give a comprehensive review of prospective uses for newly discovered 2D nanomaterials.

Keywords:

2D nanomaterials, applications, biomedical, nanoparticles, structures

1. Introduction:

Two-dimensional (2D) nanomaterials are ultrathin nanomaterials with a high degree of anisotropy and chemical functionality. Research on 2D nanomaterials is still in its infancy, with the majority of research focusing on elucidating unique material characteristics and few reports focusing on biomedical applications of 2D nanomaterials (Spear, Ewers and Batteas, 2015). Nevertheless, recent rapid advances in 2D nanomaterials have raised important and exciting questions about their interactions with biological moieties. 2D nanoparticles such as carbon-based 2D materials, silicate clays, transition metal dichalcogenides (TMDs), and transition metal oxides (TMOs) provide enhanced physical, chemical, and biological functionality owing to their uniform shapes, high surface-to-volume ratios, and surface charge (Khan *et al.*, 2017). Here, we focus on state-of-the-art biomedical applications of 2D nanomaterials as well as recent developments that are shaping this emerging field. Specifically, we describe the unique characteristics that make 2D nanoparticles so valuable, as well as the biocompatibility framework that has been investigated so far. Finally, to both capture the growing trend of 2D nanomaterials for biomedical applications and to identify promising new research directions, we provide a critical evaluation of potential applications of recently developed 2D nanomaterials.

2D nanomaterials are highly diverse in terms of their mechanical, chemical, and optical properties, as well as in size, shape, biocompatibility, and degradability. These diverse properties make 2D nanomaterials suitable for a wide range of applications, including drug delivery, imaging, tissue engineering, and bio- others. However, However, their low-dimensional nanostructure gives them some common characteristics. For example, 2D nanomaterials are the thinnest materials known, which means that they also possess the highest specific surface areas of all known materials. This characteristic makes these materials invaluable for applications requiring high levels of surface interactions on a small scale (Liu and Zhou, 2019). As a result, 2D nano- materials are being explored for use in drug delivery systems, where they can adsorb large numbers of drug molecules and enable superior control over release kinetics. Additionally, their exceptional surface area to volume ratios and typically high modulus values makes them useful for improving the mechanical properties of biomedical nanocomposites, even at low concentrations. Their extreme thinness has been instrumental for breakthroughs in biosensing and gene sequencing (Gravagnuolo, Morales-Narváez and Martucci, 2021).

Moreover, the thinness of these molecules allows them to respond rapidly to external signals such as light, which has led to utility in optical therapies of all kinds, including imaging applications, photothermal therapy (PTT), and photodynamic therapy (PDT).

Despite the rapid pace of development in the field of 2D nanomaterials, these materials must be carefully evaluated for biocompatibility in order to be relevant for biomedical applications (Gao *et al.,* 2021). The newness of this class of materials means that even the relatively well-established 2D materials like graphene are poorly understood in terms of their physiological. interactions with living tissues. Additionally, the complexities of variable particle size and shape, impurities from manufacturing, and protein and immune interactions have resulted in a patchwork knowledge of the biocompatibility of these materials.

Unfortunately, the biocompatibility of 2D nano- particles cannot be inferred from the corresponding bulk material, as size and shape significantly affect the body's interactions with the material. Additionally, it should be noted that among the various articles reporting the benefits of nanomaterials for biomedical use, there is a notable scarcity of toxic reactions reported. The primary mechanism of harm that nano- materials have been suggested to cause is through oxidative damage from free radicals. Oxidative damage may be the result of immune responses elicited by the material, the presence of oxidizing contaminants, or from intrinsic properties of the molecules themselves or their degradation products. Addition- ally, the slow clearance of some nanoparticles by the body may result in particle accumulation in the liver, kidneys, spleen, or lungs. Damage has also been suggested to occur via apoptosis, hemolysis, or thrombosis.

Some 2D nanomaterials also contain metals not usually found above trace levels in humans. Again, however, none of these mechanisms can be generalized, as toxicity has been shown to depend on nanomaterial size, surface area, and composition. Size and shape might affect toxicity by making phagocytosis by macrophages impossible, or by allowing nanoparticle aggregates to form. Surface area increases the material's ability to interact with the body, which could increase immunogenicity. The composition of nanomaterials can obviously affect biocompatibility. However, it can also affect protein adsorption on the surface of the nanomaterial. It is well established in the biomaterials community that protein adsorption is rapid in vivo and that this process drives the biological response to implanted materials.[4] However, protein adsorption onto nanomaterial surfaces, which will depend on both the chemical composition and the location of the nano- material, remains uncharacterized.

In comparison to other types of nanomaterials, 2D nano- material safety information for materials besides graphene is practically nonexistent. No systematic evaluation of the biocompatibility of any 2D nanomaterial has been completed. With that in mind, preliminary reports have indicated that some of the 2D nanomaterials are highly biocompatible in vitro and in vivo. These materials have been shown to not cause significant harm in individual, small-scale studies. As a result, each of these materials is being regarded with cautious optimism in terms of its potential in biomedicine. A recent literature search indicated immense interest in evaluating the biological properties of different types of 2D nanomaterials for biomedical applications including tissue engineering, cancer therapy and drug delivery, biosensors, and bioimaging (Fig.1). This high level of interest clearly indicates that 2D nanomaterials are an emerging material technology that has transformative potential for biomedical and biotechnological innovation. 2D nanomaterials research is still in its infancy, with the bulk of research focusing on elucidating the unique material properties of 2D nanomaterials. Recently, a range of review articles on 2D nanomaterials have been published that focus on the synthesis and molecular assembly of 2D nanomaterials and highlight their fundamental characteristics and properties, which stem from their unique structures, for electronics applications (Xu, Akbari and Zhuiykov, 2021).

Nevertheless, translational research involving these materials has expanded dramatically. Some of the focused review articles provide a close look at particular subsets of 2D nanomaterials and applications. To date, however, there has not been a review that encompasses all biomedical 2D nanomaterials research and provides a systematic overview of the field and its recent developments and direction, and that compares the emerging biomedical applications of each family of 2D nanomaterials.

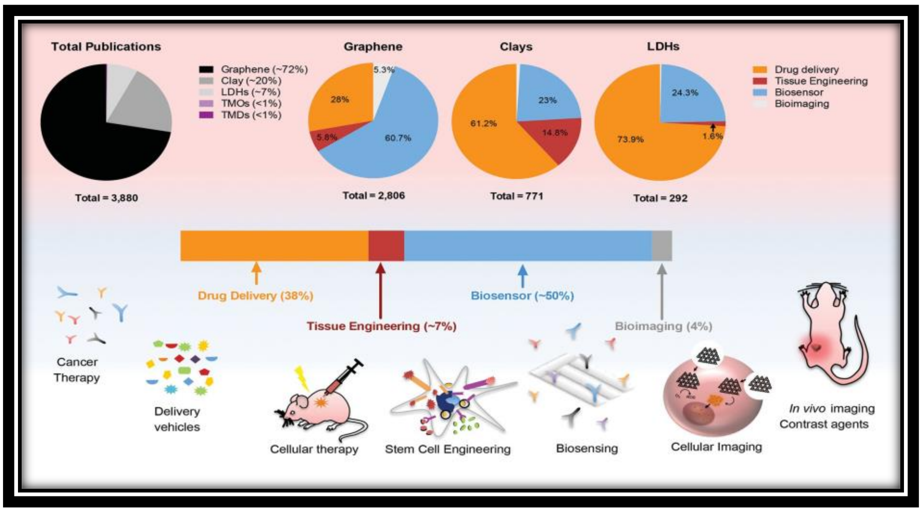

Figure.1: Current research trends in 2D nanomaterials and some of their promising biomedical applications

A recent surge in 2D nanomaterials research is evident from the number of publications in the last few years. The publication data was obtained from ISI Web of Science in April 2015. Carbon-based 2D nanomaterials are being extensively investigated for biomedical applications, followed by clay-based nanomaterials and LDHs. Only a few reports have focused on the biomedical applications of TMOs and TMDs. Most of the biomedical applications of 2D nanomaterials have been in the areas of biosensors and drug delivery, followed by tissue engineering and bioimaging (Cheng *et al.*, 2020).

In this review, we focus on state-of-the-art biomedical applications of 2D nanomaterials, highlight recent developments that are shaping this emerging field, and evaluate the potential applications of recently developed 2D nanomaterials. The discussion is limited to the most promising nanoparticles from each family of 2D nanoparticles (carbon-based, clays, LDHs, TMDs, TMOs, and other types of 2D nanomaterials) that are relevant for biomedical and biotechnological applications. The scope of this paper is to capture the current state of 2D nanomaterial research for biomedical applications and to identify promising new research directions in the field. Addition- ally, we will review the unique characteristics that make 2D nanoparticles such exciting and useful materials (Yu *et al.*, 2018).

2. Structures of 2DNanomaterials:

The physical, chemical and biological properties of nanomaterials strongly depend on their atomic arrangements. 2D nanomaterials are unique compared to other types of nanomaterials because one of their dimensions is only a few atomic layers thick (Fig.2). Graphene is the archetypal 2D nanomaterial and exhibits many of the structural motifs that define this category of nanomaterials. The structure of graphene is a single monolayer of carbon atoms that are bonded together via covalent sp^2 bonds in a flat and regular hexagonal pattern. In contrast, graphene oxide (GO) is based on the same regular hexagonal pattern of carbon atoms, but instead of being entirely composed of sp^2 bonded carbon atoms, it has frequent sp^3 carbons bound to functional groups above or below the plane of the nanomaterial (Tan *et al.*, 2017). This makes GO less flat than graphene and results in significant local polarity of the structure. Reduced graphene oxide (rGO) is a structural intermediate between graphene and GO. It can be synthesized by the reduction of GO via various methods, which remove most of the functional groups and partially restore the sp^2 hybridization. The result is a sparsely functionalized graphene monolayer with a higher concentration of structural defects than graphene (Spear, Ewers and Batteas, 2015).

Other 2D nanomaterials with structures similar to graphene include silicene, germanene, hexagonal boron nitride (hBN), and graphitic carbon nitride (C_3N_4). Silicene and germanene are 2D allotropes of silicon and germanium, respectively, with buckled, rather than flat, monolayers. C_3N_4 on the other hand, is an alternating monolayer of carbon and nitrogen atoms. Similarly, hexagonal boron nitride (hBN) is composed of covalently bound alternating nitrogen and boron atoms.

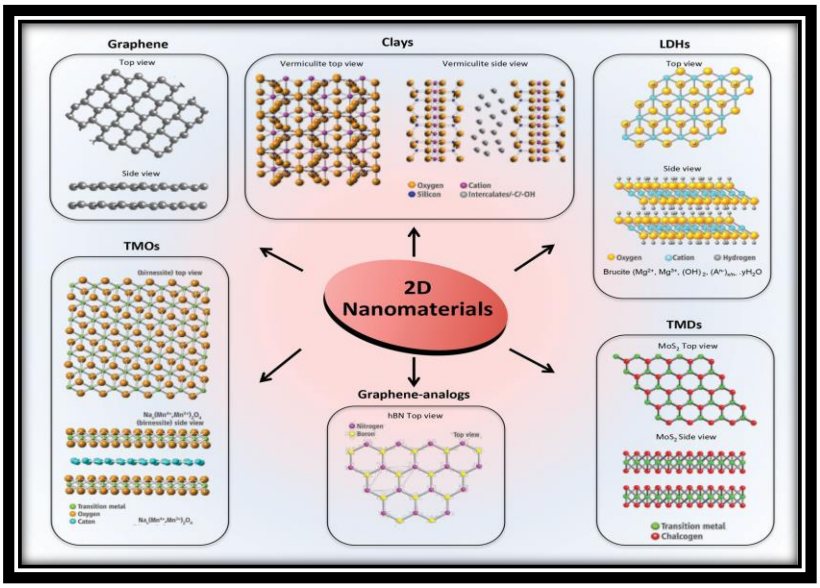

Figure 2: Structures of 2D nanomaterials highlighting a nanosheet network in which one of the dimensions is only a few atomic layers thick. Structures for graphene, clays, LDHs, TMOs, TMDs, and graphene-analogs (hBN) are illustrated here. Adapted with permission.

In contrast to 2D nanomaterials of a monoatomic thickness, some materials like 2D clays, LDHs, TMOs, and TMDs are composed of stable, single crystal units. Laponite, for example, is a 2D nano clay with 3 layers comprising 2 tetrahedral silica sheets sandwiching an interior octahedral layer of magnesium and lithium cations (Hanlon *et al.*, 2014). Substitutions and edge valences give these nanoparticles permanent negative face charges and positive edge charges, both of which can be stabilized by ionic inter- actions. Individual laponite nanoparticles are typically disc shaped, with a diameter of roughly 30 nm and a thickness of less than 1 nm.

LDHs are also called anionic clays; they have positively charged faces, which is a rare quality relative to negatively charged faces. LDHs are structurally similar to brucite, the mineral form of magnesium hydroxide, and consist of magnesium cations surrounded octahedrally by hydroxide ions, but with partial Al^3 substitution for Mg^2, resulting in a positive surface charge. 2D TMOs can have different structures depending on their individual components (Iijima, 1991). MgO_2 and TiO_2, which are the most commonly used, generally have octahedral conformations. Similar to clays and LDHs, they often exist as stacks with interlayer ions holding these stacks together. 2D TMO nanoparticles are less than 1 nm thick but have been synthesized up to widths of 100 microns. 2D TMDs have a three-layer atomic structure where the outside layers are chalcogens covalently bonded to a metal atom inner layer. Each of these layers is in a triangular lattice structure. This crystal structure forms a 2D hexagonal lattice alternating between chalcogenide and metal atoms. TMD monolayers are roughly 0.6 nm thick.

Graphene is the best-researched as well as the oldest 2D nanomaterial, first being isolated in 2004.The application of graphene in tissue engineering expanded swiftly due to its unprecedented mechanical strength, electrical conductivity, biocompatibility, and thermal conductivity. Additionally, graphene has a higher specific surface area, lower production and purification costs, and greater ease of functionalization com- pared to its 1D counterpart, the carbon nanotube (Spear, Ewers and Batteas, 2015). Graphene is often partially oxidized into graphene oxide (GO) in order to increase its hydrophilicity and enable facile functionalization, but this modification comes at the expense of electrical conductivity. Reduced graphene oxide (rGO), which can be easily produced in large quantities from GO, is often used as a substitute for pure graphene due to its lower cost, but it has inferior properties due to structural defects. The graphene family is therefore composed of 3 materials: graphene, GO, and rGO. As numerous reviews are available on graphene-based materials for biomedical applications, we will highlight only some representative recent examples in the areas of tissue engineering, drug delivery and biosensing Graphene. One promising future avenue for graphene-based biomaterials is in the area of tissue engineering.

Recently, Qui et al. synthesized a nanocomposite aerogel with a highly interconnected architecture from poly(*N*-isopropylacrylamide) (PNIPAM) and graphene. The graphene aerogel exhibited one order of magnitude higher modulus compared to graphene-free PNIPAM hydrogels. The addition of graphene also significantly improved the electrical conductivity and thermo-responsive properties of nanocomposite hydrogels compared to PNIPAM hydrogels (Tan *et al.*, 2017). This effect was mostly attributed to the prefabrication of a graphene aerogel, which ensured high connectivity between graphene sheets.

Moreover, building the nanocomposite from an aerogel also obviated the need to functionalize the graphene into GO for dispersal into solution. Using this approach, graphene could be used in place of less conductive GO for a wide range of applications, potentially leading to a new generation of graphene nanocomposites with superior electrical and mechanical properties. Graphene is able to increase the mechanical strength and stiffness of hydrogel scaffolds without compromising cyto- compatibility, and it has been shown to accelerate the adhesion, proliferation, and differentiation of human mesenchymal stem cells (hMSCs) toward an osteogenic cell fate. Nayak et al. showed that in the presence of osteogenic medium, graphene coating enhances the differentiation of hMSCs (Fig. 3). The ability of graphene to promote the differentiation of hMSCs has been attributed to its ability to adsorb proteins and bioactive molecules such as dexamethasone and glycerophosphate. In another study, graphene was used to engineer 3D porous scaffolds for osteogenic differentiation of hMSCs for bone regeneration. A 3D graphene foam structure was fabricated using a temporary scaffold that was fully removed via $FeCl_3$ etching. These graphene foams were capable of inducing osteogenic differentiation of hMSCs without any osteoinductive growth factors (Gravagnuolo, Morales-Narváez and Martucci, 2021). The ability of graphene foams to induce osteogenic differentiation was attributed to the high mechanical stiffness of the foam, as hMSCs are known to respond to high stiffness environments by differentiating into osteoblasts

3. Carbon-Based 2D Nanomaterials for Biomedical Applications:

Due to the high electrical conductivity of graphene-based nanocomposites, these materials are being explored for tissue engineering and biosensing applications that require electrical stimulation for functioning. For example, in a recent study Tang et al. engineered an electrically conductive graphene substrate to direct cell fate by increasing electrical interactions between neural stem cells (NSCs) (Cheng *et al.*, 2020). They observed a nearly two-fold increase in the neuron density and excitability (as measured by spontaneous spikes in calcium ions) on a graphene substrate.

Graphene/GO/rGO have been used to control and direct cellular fate towards osteoblasts, neurons and cardiomyocytes. Osteoblasts images adapted with permission. Neurons images adapted with permission. Cardiomyocytes images adapted with permission.

Printing graphene-based wireless biosensors onto silk that can be dissolved in saliva may be used to detect the presence of germs on tooth surfaces.

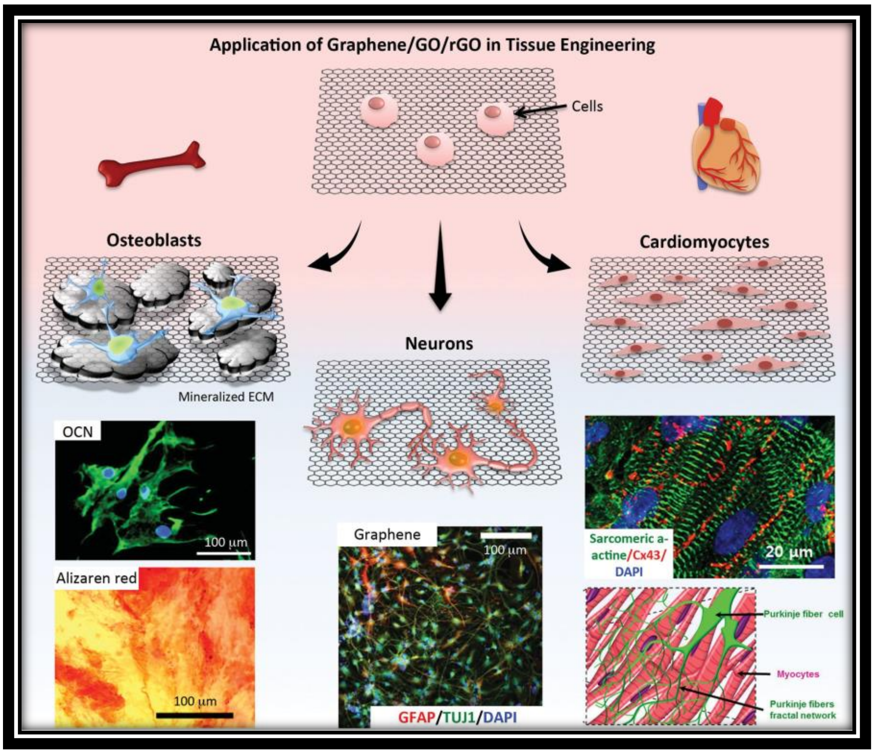

Figure.3: Application of carbon-based 2D nanomaterials for tissue engineering

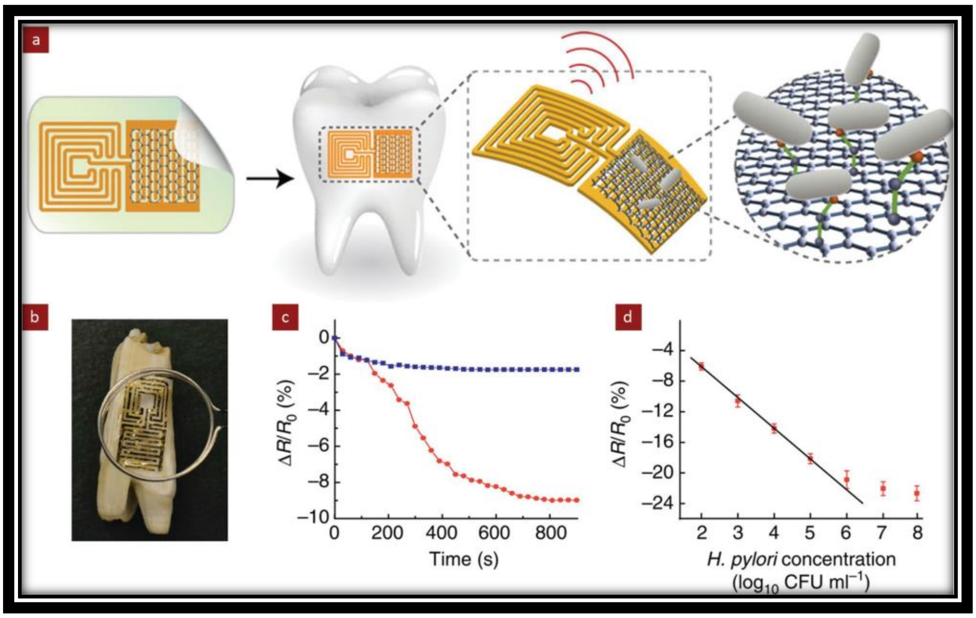

Fig.4: Graphene-based biosensors can detect infections

H. pylori-infected human saliva (red line) was compared to "blank" saliva (blue line) for changes in graphene resistance over time (blue line). graphene-based biosensors are effective because of variations in graphene resistance with pathogen concentration.

Comparing polystyrene to tissue culture (control). There has been an increase in NSC differentiation thanks to the high conductivity of graphene, making it an ideal substrate for both the cultivation of neurons and the development of biocompatible neural interfaces

(Figure 4). An additional graphene-based biosensor has been created for the detection of bacterial adhesion on tooth enamel. Mannoor et al. applied a graphene biosensor to a tooth surface after printing it on a bioresorbable silk substrate (Liu and Zhou, 2019). Graphene was utilised to detect infections using antimicrobial peptides that self-assembled and disassembled. They demonstrated that their peptide-graphene micro sensor could be wirelessly detected by attaching it to a resonant coil (Fig.4). Graphene-based biomaterials have been shown to be useful in tissue engineering and biosensing applications, according to this research (Ganguly *et al.*, 2019).

4. Graphene Oxide (GO)

Its electrical conductivity and mechanical strength are decreased as well as its hydrophilicity is increased, making it more appropriate for biomedical applications when graphene is oxidised to GO by oxidative exfoliation (the Hummer's process). Using this method, biomacromolecules such as proteins, ECM components, and certain medicines may interact with one other in a more efficient way. Additionally, the presence of hydroxyl groups makes GO functionalization, which may improve cytotoxicity and biocompatibility, simple. The ability of GO nanosheets to resist one other with varying forces depending on pH is a beneficial property (Yu *et al.*, 2018). This electrostatic characteristic may be used to make pH-responsive nanocomposites. Synthesized GO-polymer Bai et al (vinyl alcohol). Controlled medication release using a nanocomposite. Because of its ability to retain vitamin B12, this nanocomposite was shown to be stable under acidic circumstances. Nanocomposites, on the other hand, disintegrated quickly in alkaline circumstances, releasing the encapsulated medication. The carboxyl groups on GO were ionized, resulting in the release of GO. Because GO has a large particular surface area, it also considerably inhibited drug transport from the nanocomposite intact. Potentially relevant for pH-triggered drug administration, especially for oral delivery of acid-sensitive medicines, are self-assembling networks.

With its hydroxyl groups on its surface, GO interacts with a wide spectrum of synthetic and natural polymers and offers mechanical reinforcement. The high electrical conductivity of GO allows it to be utilized to build electrically conductive patches for tissue engineering applications (Figure 4). Electron conductivity was increased in nanocomposite hydrogels when methacrylated gelatin was included with GO.

Increased cardiomyocyte proliferation in the presence of the hydrogel surface was attributed to the material's improved electrical conductivity, which suggests that a cardiac patch made of this material would be feasible. It was found that methacrylate groups were used to cross-link the surface of GO with methacrylated gelatin during polymerization in a separate investigation to boost hydrogel rigidity. Small additions of GO to gelatin hydrogels resulted in a two- to three-fold increase in mechanical stiffness (Xiong *et al.*, 2018). Furthermore, these nanocomposite scaffolds facilitated an increase in 3D cell viability, proliferation, and dissemination. For stimuli-responsive nanocomposites for drug delivery, the enormous surface area, aromatic structure, and functional groups make GO an ideal nanocarrier. Polypyrrole (PPy), a conducting polymer, has been employed as an electrically-responsive drug delivery device, however its loading capacity is restricted.

Electrically responsive nanocomposites for regulated medication delivery were produced by Weaver and colleagues in a recent work. Dexamethasone, an anti-inflammatory chemical, could be encapsulated and released two-fold more effectively by the GO–PPy nanocomposites than by pure PPy. Additionally, the introduction of GO resulted in improved sensitivity to electrical stimulation and linear release kinetics across 400 stimulation cycles without any quantifiable drug release in the absence of stimulation. The sonication time of GO was shown to be a controllable factor in drug loading and release rates. The increased surface area of GO was credited with the considerable increase in drug loading and the enhanced release kinetics. Control over release kinetics, drug loading capacity and ability to release entrapped medication might be employed for cancer therapy and immuno-therapies, as well as tissue engineering applications.

Gene therapy for myocardial infarction may also make use of GO-loaded hydrogels. Polyethylenimine (PEI) was applied on the surface of GO to increase the loading and delivery of a VEGF plasmid (Fig.5). GO-functionalized injectable hydrogel was developed for less invasive treatment. Functionalized GO decreased scar formation in vivo compared to VEGF plasmid and hydrogel groups, demonstrating the potential of GO as a gene delivery method (Khan *et al.*, 2017).

A potential new dopant for electrically-responsive nanocomposites for brain interfaces is GO, despite the fact that it is less conductive than graphene. A lack of functional groups on the PEDOT backbone has hindered its usage in brain interfacing, despite its biocompatibility and electrical conductivity. GO–PEDOT nanocomposites with better bio-interfacing were created by Luo et al. to solve this problem.

The electrical conductivity of GO and its capacity to induce neuronal development make it an ideal candidate for doping PEDOT while maintaining its electrical conductivity. The conductivity of the GO–PEDOT nanocomposite was maintained, allowing for the covalent attachment of peptides to its surface. To promote neuron out-growth and attachment, GO was incorporated into PEDOT–PEDOT surfaces, which were then compared to the previous standard, PEDOT–PSS. The high density of carboxyl groups on the surface of GO makes it an ideal surface for enhancing interactions with neurons since it can conjugate numerous biomolecules. There are a variety of fascinating new ways being investigated using graphene-based nano-composites as potential neural application materials.

5. Reduced Graphene Oxide (rGO)

To take advantage of the simplicity with which graphene oxide (GO) may be made and to mimic the characteristics of pure graphene sheets, reduced graphene oxide (RGO) is often created from GO. Reduced GO sheets are left with just the carbon sheet and certain structural flaws after most functional groups are removed. PDT and PTT have been heavily relying on rGO because of its greater availability and higher electrical conductivity than GO.

To store anionic DNAVEGF plasmids, the GO was functionalized with cationic polyethylenimine (PEI). Hydrogels were created by mixing the gelMA prepolymer with fGO/DNAVEGF, which had the plasmid directly attached to the fGO surface, and then weakly crosslinking them. To treat infarcted cardiac tissue, photocrosslinked hydrogels containing fGO/DNAVEGF were injected. Mechanical stiffness was enhanced when fGO/GelMA and GelMA hydrogels were shear-viscosity tested. c) Laz Z staining revealed the gel's location in the infarcted region. d) fGO/VEGF plasmid/GelMa therapy decreased in vivo scar formation (red region). Permission granted to use this material.

Many of the characteristics of graphene sheets may be seen in this material. Reduced nanosheets are left with simply the carbon sheet and certain structural flaws when functional groups are removed. To far, rGO has been employed widely in biosensing applications, including PDT/PTT, because of its greater availability and superior electrical conductivity than the original Go. rGO has a greater specific surface area and better carrier mobility than classic materials like CNTs and silicon nanowires, and has been proven to immobilize high densities of receptor biomolecules on its surface (Tan *et al.*, 2017).

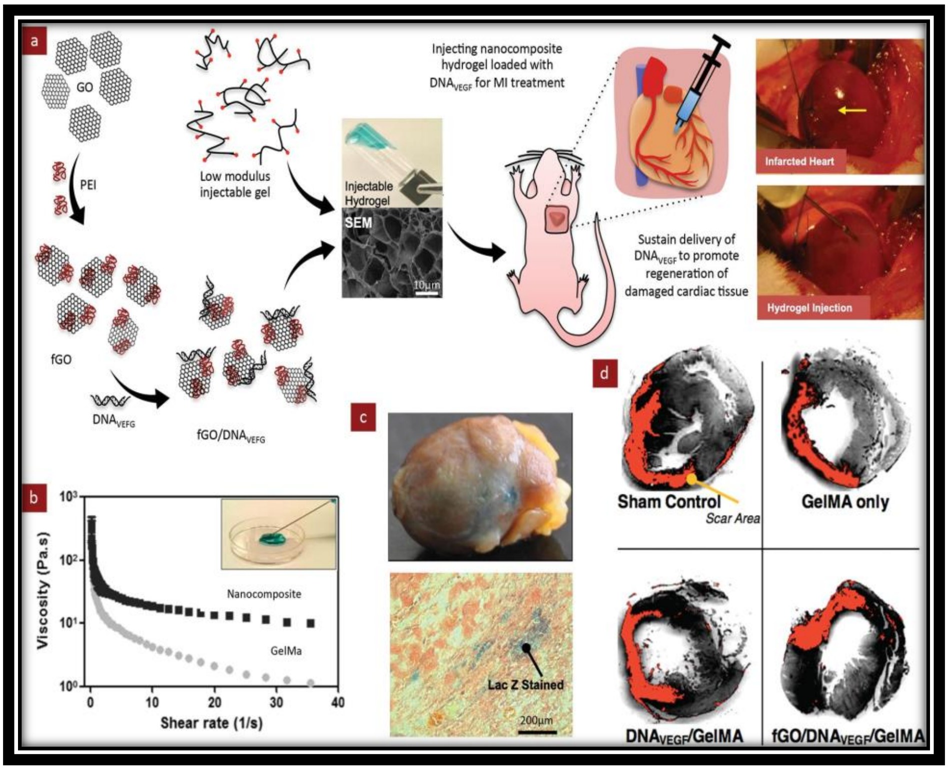

Figure.5: For gene delivery, a nanocomposite hydrogel is filled with functionalized GO (fGO).

This makes rGO an appealing option for biosensors with high sensitivity and high resolution. An ultrasensitive label-free field effect transistor (FET) biosensor built using rGO, for example, is capable of rapidly and accurately detecting prostate-specific antigen at concentrations as low as 100 fg mL1 and as high as 10 ng mL1 without the need of labelling. Other FET biosensors employing rGO have been developed to detect diverse biomolecules, including as DNA and E. coli antigens, among others. To put it another way, the rGO biosensor technologies that are now being developed might lead to enhanced diagnostic approaches and better patient outcomes due of their simplicity of production and cheap cost. Because of their efficacy, cheap cost, and cytocompatibility, rGO-based materials are also being studied as PTT agents in cancer research. Due to GO's weak NIR absorption, huge dosages and power were necessary to generate comparable PTT agents in the past. It absorbs 20% of NIR light, seven times more than GO, since it has more bonds. Compared to GO, CNTs, and gold nanoparticles, rGO has a higher absorptivity, allowing it to be effective at a lower dosage. Redoxorubicin delivery and specific cancer cell targeting have been proven by functionalization of this nanomaterial with ligands for PTT/PDT combination treatment, as well. Because it is cheaper and simpler to mass-produce than gold nanoparticles, rGO is a potential material for PTT. It can also be loaded with chemotherapeutic medicines (Han, Bhatia and Kim, 2015).

6. Biomedical 2D Carbon Nanomaterials Synthesis and Evaluation

Graphene, GO, and rGO are the most common two-dimensional nanomaterials used in biomedical research. Biomedical applications have been explored because of their remarkable physical, chemical, electrical, and biological features, including tissue engineering, drug delivery, bioimaging, and biosensing. A new variety of 2D nanomaterials with unique property combinations are developing, thus it's not certain if these materials will continue to predominate in these sectors (Spear, Ewers and Batteas, 2015).

Carbon-based biomedical research is so extensive that just a few current and important applications have been included in this section. Biocompatibility and in vivo safety are the key issues these materials confront. 2D carbon-based 2D nanomaterials are difficult to manage in terms of dimensions, making it impossible to compare their cyto- and biocompatibility with other nanomaterials. Nanosheet size, dispersion, and functionalization need to be better controlled in order to better understand how these materials interact with biological entities such as proteins, DNA, and cells. However, before we can begin using this novel class of nanomaterials in clinical settings for biosensing and imaging, various issues, such as weak fluorescence and wide emissions, must be resolved in these fields as well.

7. Biologically Active Nanomaterials: Silicate Clays

Silicate clays have been utilised in contemporary medicine for decades as antacids and topical lotions, but their potential as biomaterials has only lately been explored. There are two-dimensional silicate nanoparticles utilised in biomedical engineering that are generally around 10–100 nanometers in diameter and about 1 nanometer thick (Hanlon *et al.*, 2014).

Particles with a layered structure that provides persistent negative surfaces are among the most helpful for biological applications. Nanoparticles of silicate have been found to boost both cell adhesion and survival on hydrogel surfaces over a short period of time. In a PNIPAm–poly (ethylene glycol) (PEG)–silicate nanocomposite, Liu et al. found that silicate nanoparticles improved cell adherence. Another study found silicate nanoparticles boost initial cell adherence, spreading and proliferation when introduced to non-fouling surfaces, as previously reported. Adding silicate nanoparticles to collagen-based hydrogels increased their mechanical stiffness by fourfold.

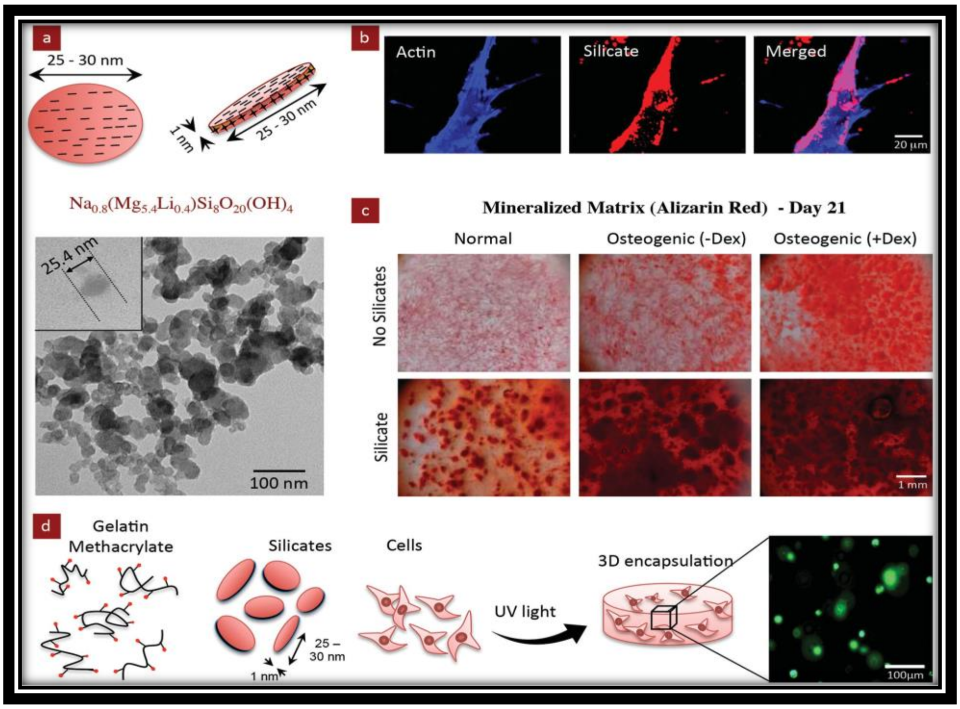

Figure.6: Bioactive silicate nanoclays induce osteogenic differentiation of stem cells and can be used for bone regeneration. a) Schematic and TEM images of silicate nanoparticles showing shape and size. b) Fluorescence imaging demonstrated internalization of silicate nanoparticles within stem cells. c) The effect of silicate nanoparticles on the production of mineralized ECM indicated the osteoinductive properties of silicates. d) Nanocomposite hydrogels for bone regeneration were fabricated by combining photo cross linkable polymer (GelMA), silicate nanoparticles and stem cells. Panels (a-c) reproduced with permission.

They all stem from non-covalent interactions between the polymer chains and the charged nanoparticle surfaces (Tan *et al.*, 2017). They can be broken and re-formed, hence hydrogel nanocomposites may be used for less invasive treatments because of their shear thinning viscoelastic qualities. Cellular structures with highly elastic fibre shapes may be created by manipulating the interactions between silicate nanoparticles and polymers. In vitro matrix mineralization and alkaline phosphatase activity have both been found to be boosted by the addition of silicate nanoparticles. Furthermore, silicate nanoparticles have recently been shown to enhance the bioactivity of other polymers. In one recent work, silicate nanoparticles were shown to improve osteogenic differentiation on electrospun polycaprolactone scaffolds.

8. Emerging Trends and Future Outlook

The biomedical applications of 2D nanomaterials are quickly developing and significant advancements have been proven in fields such as bio-imaging, drug delivery, biosensors, tissue engineering, photo-thermal treatment, photodynamic therapy, and hemostatic wound dressings. Complex interactions between material qualities, structure, form and flaws have arisen as a scientific discipline that is ready for advancement. We are well-positioned to unravel and manage the complexity that affects the functioning of these newly formed 2D materials, thanks to our newly gained understanding of the principles of nature that govern the atomic, nano, micro, and macro scales.

Future research in the subject of 2D nanomaterials is projected to expand to include new materials, as well as a deeper knowledge of the physical, chemical, and biological features that regulate their usefulness in biomedical and biotechnological applications. It will take some time until new 2D nanomaterials, such as silicon and germanium, which have just recently been synthesised, have been thoroughly described and can be put to use in practical applications.

As a result of their discovery, these and other previously unknown materials may hold the secrets to future biological discoveries. Emerging trends in nanomaterials include the creation of novel intelligent structures that are multifunctional, programmable, and biocompatible. Nano-materials engineering may be achieved by integrating computer modelling, physical, chemical, and structural characterizations into the design process. Nanocomposites loaded with nanomaterials with adjustable mechanical, structural, chemical, and biological characteristics may be engineered by controlling the size, shape, and composition of the 2D nanoscale building blocks.

2D nanomaterials, when assembled and oriented correctly, have the potential to form 3D misstructures with characteristics that are unmatched in a wide range of technological applications. Although mesostructured materials are well-known in the materials science community, the implications for biomaterials can be best understood by considering that, while nature uses a variety of nanoscale building blocks, the key properties of cells, tissues, and organisms rely on the proper assembly of these building blocks into larger mesoscale structures. Mesoscale particles containing drug-loaded nanoparticles have showed promising outcomes in the transport of therapeutic medicines across many stages. A better knowledge of how nanomaterials may be built into mesostructured materials and devices might lead to promising advancements in biomedical engineering in the long-term. Since the introduction of 2D nanomaterials to the biomedical industry marks a paradigm change in applying fundamental materials science knowledge to biomedical engineering, we anticipate this will lead to new medical devices being developed in future.

9. Conclusion

These ultra-thin materials have a high surface-to-volume ratio and anisotropic characteristics compared to 3D nanomaterials, which are more dense. 2D nanomaterials interact with biological moieties in a unique manner since one of their dimensions is just a few atomic layers thick. This has sparked fascinating questions concerning their interactions with proteins, cells, and subcellular components. The extraordinary features of these materials have the potential to be transmitted from the bench to the bedside, which might lead to dramatic advancements in biomedical research and clinical outcomes. 2D nanomaterials are a fast-growing and intriguing area, but we've focused on only a few of the most promising technologies here.

Graphene, GO, and rGO are still at the forefront of biomedical research, but emerging 2D nanomaterials including clay, LDH, TMDs, and TMOs have lately piqued researchers' curiosity and are now being investigated. There are several applications for LDH and clays, including drug administration, tissue engineering, hemostatic wound dressing, and biosensing, because to their biocompatibility and bioactivity. Bioimaging, drug delivery, photothermal therapy, photodynamic therapy, and new cancer therapies are all being developed using TMOs and TMDs, which had hitherto been underused. Due to their closeness to graphene, recently studied materials like hBN and C3N4 nanosheets are expected to be widely assessed after the syn- thetic challenges are addressed. The creation of multifunctional, adaptable, programmable, and biocompatible intelligent structures are some of the current themes in 2D nanomaterials. Using multi-component systems and new processing methods, these structures may be created. As a whole, the development of 2D nanomaterials for next-generation technologies in cell biology, medicine, regenerative medicine, stem cell engineering, cancer treatment, bio sensoring, and bioelectronics presents new problems and potential.

10. References

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