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A COMPREHENSIVE REVIEW OF ADVANCED NANO-BIOMATERIALS IN REGENERATIVE MEDICINE AND DRUG DELIVERY

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Abstract. The field of biomedicine is advancing at a considerably faster rate than in the past. Therefore, a class of structures known as nanoscale compounds—such as organic and inorganic nanoparticles—have arisen in the biomedical field with various topologies, surface ornamentation, and sizes. 1 There are numerous well-known instances of how nanoscopic platforms are being used to enhance human health. Due to their customizable physicochemical features, these nanoplatforms are being investigated in regenerative medicine, biosensing, cancer diagnosis, and treatment. This subject focuses on the present situation and future applications of promising nanomaterials in biomedicine. Nanomaterials and related technologies (such as tools to create and characterize nanoscale platforms) have made tremendously interesting progress during the past ten years. Also, there have been some incredibly exciting advancements in the biomedical uses of nanosystems for diabetes, tissue engineering, infectious illnesses, immunotherapy, and cancer Cell-instructive scaffolds can be created using nano-composite bio-ink, or cells can be printed directly on the material. Additionally, the inclusion of nanoparticles in 3D printed constructions enables control of them via a variety of external physical stimuli, adding another tool for medical applications. Last, but not least, there is a growing interest in developing biological constructions with functional traits like sensing, motion, or shape change. With an emphasis on their clinical translation features, we hope to introduce and review the most recent developments in nanomaterials for biomedical applications in this Theme Issue. We'll emphasize the key developments in nanomedicine as well as the principal obstacles still to be overcome.

Keywords: *Biomaterials, regenerative medicine, tissue engineering, nanomedicine.*

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1. Introduction

It has been abundantly obvious during the past ten years that the "nanotechnology age" has begun with the creation of biomaterials. Biomaterials created from nanotechnology are among the fields at the nexus of materials science and biology that are rapidly emerging and developing. These biomaterials have a remarkable impact on medicine. The term "nanotechnology-derived biomaterials" specifically refers to those biomaterials (i.e., 1-100 nm or 109-107 m particle or grain size diameters) whose components or structures demonstrate dramatically new and modified properties when their sizes are at the nanoscale. It should come as no surprise that biomaterials created from nanotechnology have been extensively applied in a wide range of biomedical and biological usage, from medical imaging to drug delivery to artificial implants. These nano-biomaterials range in structure from 0-D (such as particles and dots) to 3-D and

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can be made of hydrogels, polymers, ceramics, metals, and novel self-assembled materials (e.g., tissue engineering scaffolds). A novel multidisciplinary field nanotechnology, materials science, spanning biology has undoubtedly been developed as a result of the rapid growth of nanomaterials. This new field was created because nanotechnology has not only produced unique tools and materials for biological and medical applications, but it has also changed the way we think about using these materials in science and technology. For instance, investigations on the safety and toxicity of nanomaterials at both the occupational and scientific levels have been sparked by the growing usage of nanoscale systems and materials. nanostructured biomaterials studies are becoming more thorough and systematic, leading to a deeper knowledge of the biological mechanisms behind responses to materials.

Since the final effectiveness of nano biomaterials in human applications is not yet known, the complete value of nano-biomaterials cannot be precisely determined at this time, it may be premature to claim that they will be widely used in a variety of therapeutic settings (Deshmukh *et al.,* 2023). The usage of nano-biomaterials in medicine has recently undergone another fast period of development since the turn of the new age, therefore it is undoubtedly valuable to assess the state of the art in this regard. This paper attempts to provide an updated assessment of this rapidly evolving field by reviewing current developments in nano-biomaterials as well as the new opportunities they have generated. This essay is structured by first going over the justification for and uses of nano-biomaterials in medicine, including their usage in surgical implants, regenerative medicine, medication delivery, and medical diagnosis. A section addressing new safety concerns associated with the usage and production of nano-biomaterials is also included, along with a brief description of the characteristics of nanoparticles that make them appealing for medical applications (Khalilov *et al.*, 2018).

2. Drug delivery

Research in the development of drug areas is multidisciplinary and includes computational studies, medicinal chemistry, and biochemistry. It makes use of all the most advanced molecular biology techniques to create a molecule with pharmacological properties. Even though the variety of pharmacologically active molecules is expanding quickly, there are still several difficulties in their transport to the necessary places, including the molecules' physical and chemical characteristics as well as the body's defense mechanisms. Due to the chemical and anatomical barriers that prevent them from targeting, several micro/macromolecular compounds regularly fail to reach their destinations. Nanosystems development and improvements were intended to be employed as a drug carrier for mucosal delivery. The drug is protected from the risk of degradation that may happen during its transit by the drug carriers created using nanotechnology. The purpose of the extra dig carrier molecules is to facilitate the drug's delivery through the various obstacles it faces. The purpose of the next section is to outline the difficulties that delivery encounters and the usage of nano-biotechnology that have been made to solve (Cojocaru *et al.,* 2020).

2.1. Chemical encounters

While choosing a delivery strategy, it is important to keep in mind that the physical and chemical characteristics of the cells inside a biological organism have a significant impact on the pharmacodynamics and pharmacokinetics of the drug.

The primary properties of the drug molecule that affect how well it can enter target cells are its size, charge, and hydrophobicity. The compounds are chosen via combinatorial chemistry frequently exhibit lower solubility in aqueous conditions due to their large molecular size and enhanced hydrophobicity.

The solubility of pharmaceutical agents is a key characteristic since it affects processes including drug dosage, identification, and refinement. The solubility of the medicinal molecule under consideration has a significant impact on the pharmacological dosage. Because it is straightforward and consistent for every patient, oral drug delivery continues to be popular. The oral assimilation of medications is hindered by the limited solubility of pharmaceuticals in gastrointestinal fluids. Also, the medication needs to be sufficiently lipophilic to effectively pass intestinal epithelial cells. An initial pharmacokinetic screening is required for poorly water-soluble compounds to identify a crucial strategy for improving oral bioavailability and the impact of establishing a suitable amount. Lipophilic drug molecules are transported without difficulty over intestinal epithelial barriers during transcellular transport, but hydrophilic and charged molecules are impeded. To enter and exit the target areas, they need specific carrier molecules. They must be overwhelmed by using an appropriate carrier that could improve the oral absorption and bioavailability of the therapeutic particles. Both a blessing and a curse are associated with protein binding in terms of how medications are absorbed by the body. The hydrophobicity of the molecule has a significant impact on protein binding, which can cause the drug's metabolism and elimination to be delayed.

2.2. Specific targeting

The traditional problems of lower site-specificity, stability, and bioavailability come along with non-specific drug delivery. The approach of targeted drug delivery that guarantees target specificity can overcome the drawbacks and boost the bioavailability and stability of the therapeutic molecules in vivo. A very promising alternative to oral drug administration or cancer therapy is the unique approach of guided drug delivery employing pro-drugs. The primary issue for a drug molecule is to travel to the target site by navigating the physiological barriers of the body without losing much of the drug's concentration. Moreover, for cancer therapy, it is crucial that the drug only kills cancer cells and leaves healthy cells alone. The medications' regulated release should guarantee that malignant cells are only killed when necessary. A viable alternative for the greater target specificity is biomaterials that could improve these qualities. Target specificity is a crucial quality for cancer immunotherapy. Research is being done on nanomaterials that might increase the effectiveness and targeted delivery of cancer immunotherapeutics. Targeted medication delivery via nanomaterials may improve the therapeutic efficacy of the pharmaceuticals, particularly in the treatment of cancer. The numerous stimuli-responsive systems, particularly pH and photo-responsive biomaterials, are used for targeted drug delivery.

New biomaterials are made with modifications to particular chemical and physical properties that could function as stimuli and aid in the targeted eradication of malignant cells. This enhances extracellular and intracellular drug delivery. Because they can

effectively deliver the intended medications to the designated sites, these drug delivery systems are frequently referred to as "smart" drug delivery systems.

The balance between using a chemical for medicinal purposes is so flimsy that it might shift anywhere between the therapeutic efficacy and toxicity ranges. Controlling the amount of medicine supplied throughout the procedure is where the main challenges of optimum therapy lie. The parameters of regulated drug distribution and establishing the spatial limitations of the released pharmaceuticals currently determine the general framework of various medication development strategies. A drug delivery system should distribute the active medication molecule as effectively as possible.

Pharmaceutical drug controlled release is becoming increasingly important recently because it allows a patient to receive consistent treatment. The majority of currently available medicines do not have the controlled release property, which reduces their therapeutic efficacy. The creation of a cutting-edge system that might improve regulated release is crucial in the real world for the effectiveness of various therapies. Silk fibroin is recognized as a special biomaterial that can be used for medication delivery via implants and injections among the various biomaterials created for improving controlled release. This biomaterial's stabilizing properties and excellent controllability may be used to create a safe, efficient, practical, and affordable drug delivery system. The incorporation of natural substances into scaffolds has a wide range of advantageous uses in tissue engineering. Recent research on the pharmacological effects of bioactive molecules found in natural pharmaceutical substances, their potential function in bone tissue engineering, and their osteogenic activities were published. The herb turmeric (Curcuma longa), commonly referred to as "Indian saffron," has been utilized for medical purposes for many years.

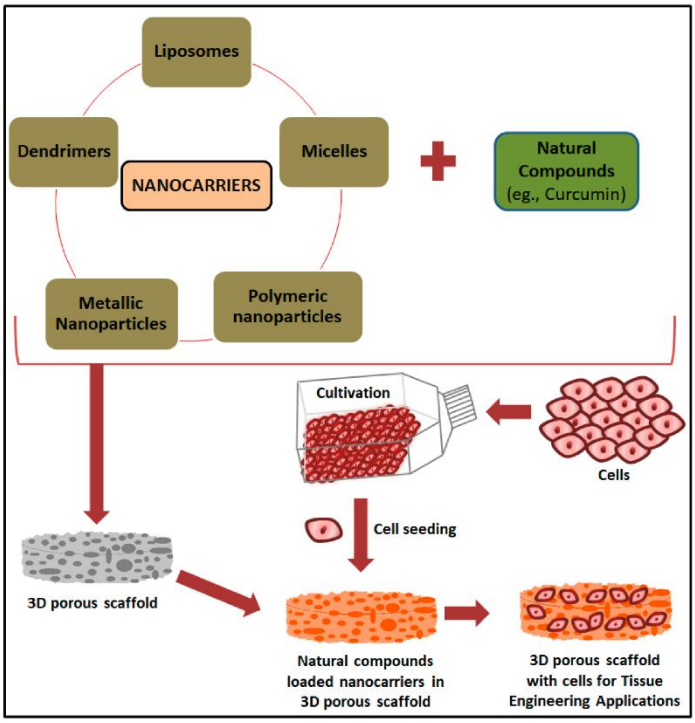

Fig. 1. Shows a biomaterial-based scaffold and nanocarriers for delivering natural pharmaceuticals for tissue engineering applications (Kumar & Abrahamse, 2020)

One of the main bioactive components of turmeric, curcumin, has been shown to have numerous therapeutic advantages in studies. Due to its diverse biological activities, which include anti-inflammatory, antioxidant, and antibacterial properties, it has a wide range of applications in tissue engineering and regenerative medicine. Curcumin has many different uses and is widely used in biological science, but several problems with it prevent it from being used effectively. These problems include low solubility, poor oral bioavailability, a high rate of disintegration in an alkaline pH, and photodegradation. Nanotechnology platforms facilitate the bioavailability of curcumin by incorporation into different types of nanomaterials which include chitosan hydrogel, HA-PLA nanoparticles, gelatin-based biomimetic nanofibrous mats, SF nanoparticles, Pullulan-based nanoparticles, alginate-polysorbate 80 nanoparticles, PLA nanoparticles, PLGA nanoparticles, and polycaprolactone/montmorillonite nanocomposite.

2.3. Nano biomaterials toxicity

When it comes to the topic of medication distribution, it is thought that the toxicity of nanomaterials is the most important problem. The majority of information available on nanotoxicity is related to inorganic NBMs, such as carbon nanotubes, nanoscale titanium dioxide, silver, and zinc oxide NPs. Many factors, including form, size, surface changes, aggregation, and composition, affect how poisonous nanomaterials are. The research in biomaterials in live organisms needs more focus because nano-bio materials are largely applied for scaffolds and delivery. The benefit of nano-biomaterials has sparked an increase in the investigation into areas such as scaffold manufacturing, imaging, and diagnostics, in addition to drug discovery. Even though nanotechnology has many uses and benefits, there are some doubts related to it. Between academia, business, and regulatory organizations, these ambiguities frequently provide serious difficulties. Because of its nanoscale nature, the substance can travel via the lymphatic and circulatory systems and reach different tissues. Compared to conventional approaches, drug targeting with nanomaterials improves biocompatibility, safety, and specificity. The use of nanomaterials also extends the period that medications are in circulation while improving their ability to attach to biomolecules with less immunotoxicity and inflammatory reaction (Akbarzadeh *et al.*, 2018). When compared to conventional medications, the drug's nanoformulations speed up accumulation while simultaneously reducing oxidative stress. Drugs are frequently prepared at the nanoscale to improve efficacy and reduce potential side effects of the larger medication molecules. The frequency of administration, toxicity, and dose can all be decreased by using nanoformulations of drugs since they have longer half-lives and greater bioavailability (Joseph *et al*., 2022). The regulation of nanomedicine faces various obstacles. The particles' tiny size makes it easier for them to circulate the body, which also speeds up their systematic buildup in the organs. The particles' smaller size also aids in their ability to cross the blood-brain barrier, which may compromise normal brain activities. The drug's nanoformulation pharmacokinetics may differ from the expected patterns for small molecules. Additionally, when the nanoformulation is scaled up for industrial manufacturing, its stability is questioned. In addition to these, there are multiple national classifications for nanoparticles and no consistent global regulatory framework. Nanomedicine may fall within the category of drugs or medical equipment. They are subject to different rules. Thus, a global classification that is consistent is required (Khalilov *et al.*, 2018). The international market is also impacted by the classification changes. Due to the possibility that the side effects, it has already passed

in one nation may not be applicable in another. As a result, specific classifications and standards are necessary, and they must be accepted globally. The nanoparticle's physicochemical properties could be different from the materials' bulk properties. Using nanoparticles as a medicine delivery vehicle can lessen toxicity. This discovery was strengthened by publications on the utilization of carbon-based nanomaterials for numerous cancer therapy (Nasibova *et al*., 2021). These nanoparticles are identified to minimize toxic effects connected with traditional drug technologies and be able to be employed to deliver medications to cancer-specific locations. In previous studies, in vitro toxicity of different carbon nanomaterials was examined. According to the study, the anticancer effects of medications delivered utilizing carbon nanomaterials are higher than that of free pharmaceuticals (Joseph *et al*., 2022). The toxicity of the entire formulation is often examined, as opposed to the toxicity of the individual nanoparticles. However, it is important to look at the unaltered particles as well, which may aid in separating the toxicity caused by the drug or nanoparticle, particularly when a slowly decaying or non-degrading substance is utilized. Such substances may build up in the target area over time and potentially trigger persistent inflammatory reactions. Anionic nanoparticles are typically non-toxic, but cationic nanoparticles, such as gold and polystyrene, can cause blood coagulation and hemolysis (Iravani & Varma, 2022). Carbon nanotube exposure has been linked to platelet aggregation and accumulation. The nanoparticle passes through the trans-synaptic transport across the olfactory epithelium or blood-brain barrier to reach the brain. Moreover, studies have shown that the blood-brain barrier is unaffected by neutral and low concentrations of anionic nanoparticles, but is hazardous to high concentrations of both cationic and anionic nanoparticles (Liang *et al.,* 2023). Drug loading to the material's exterior is possible with dendrimers, a particular class of branching polymeric nanomaterial with a size of up to 10 nm. The potential for antibody surface tagging also aids in improving medication delivery. It is difficult for them to categorize something as safe or risk management framework because the investigations produced relatively little data. High surface-to-volume ratio and nanoscale size, two characteristics of the nanomaterial, make them an excellent choice as a drug carrier. The majority of research on these particles is concentrated on maximizing their size, drug loading capacity, drug release kinetics, and cytotoxic effects. The toxicity is frequently examined in several well-established cell lines (Weidner *et al.,* 2023). To fully comprehend the effects of nanoparticles on the biological system, particularly the immune system, a detailed investigation is necessary. To show the toxicity profile of a particle, estimates of exposure and dangers are necessary. The hazard evaluations describe the hazardous effects of the nanoparticle on the biological system, whereas the exposure assessments specify the way and amount of exposure (Pandey *et al*., 2022). Regarding dosage, frequency, and intended effects, nanoparticles are extensively defined in medical applications. However, because of unexpected pathways and cumulative effects, occupational exposure causes a slow buildup of particles in the organs that can deviate from expected results. The route of administration, the individual's age, and their health status are only a few of the variables that affect the exposure assessment. The identification of potential sources is the first stage in the assessment of occupational exposure. It is important to define and access the nano biomaterial's exposure during the phases of synthesis and downstream use (Sun *et al*., 2023). For instance, the milling, grinding, and polishing of material during dental implant operations may expose workers to nanoparticles by inhalation. Dermal or inhalation exposure are two possible

ways to be exposed to work hazards. These occupational hazards can be dangerous for those who work in the healthcare business, pharmaceutical industry, waste management, and facility maintenance (Iravani & Varma, 2022). Different exposure pathways will result in various biodistribution patterns. The nanomaterials can penetrate biological barriers because of their small size. The physical and chemical characteristics of the particle can be related to its toxicity. However, the majority of the information gleaned from in vitro research may not accurately reflect in vivo research. The dyes or marker enzymes utilized in the characterization frequently interact with the nanomaterial. When in touch with a biological system, nanomaterials can undergo surface change, such as the development of protein-corona. Because of the particles' influence on the toxicity effects, this can result in different toxicity data than the in vitro system (Khalilov & Nasibova, 2022). The kind of cell line employed, the period of incubation, the concentration of the nanoparticle, the cell culture medium, and the supplements all play a role in widely used in vitro assays for determining the toxicity profile of the particle (Yang *et al.,* 2022).

2.4. Future perspectives

In the current era of technological developments, the creation of artificial live cells poses a significant problem. A technique for building a synthetic cellular structure involves the development of a lipid bilayer membrane/vesicle covering proteins and cholesterols, which is inspired by the architecture of biological live cells. Joining living cells with non-living elements to create hybrid cells is a common technique for creating artificial cells. Artificial cell-like molecules including enzymes, proteins, DNA, and nanoparticles are examples of non-living components. Nanomaterials including nanoparticles, nanocapsules, liposomes, and polymersomes are created by adding a membrane around the nanostructure, which is a very basic modification that provides a very basic structural outline of a typical cell (Nasibova *et al.,* 2023).

However, unlike simple synthetic subcellular structures, real cells have intricate metabolic processes and linked organelles that cannot be replicated. As one of the early nanobiotechnological methods for creating synthetic Hb, glutaraldehyde was used to crosslink Hb tetramers into PolyHb complexes with a nano dimension thickness. Then, nanocapsules containing Hb and erythrocyte enzymes or biodegradable polymeric membranes (using PEG or PLA) could be inserted into or coupled onto synthetic cellular mimics, such as lipid vesicles. Biomedical and medical applications of nanofluids have not yet been fully developed from their formation in the laboratory to their application in the clinical background, similar to how artificial cells have advanced. The following crucial characteristics of nanofluids—composition, size, crystallinity, and morphology—require additional in vitro and in vivo research on nanofluid stability, agglomeration state, and biocompatibility (Kavetskyy *et al.,* 2022). The kind and quantity of biomolecules in biological fluids, as well as the surface features of nanoparticles, greatly influence the physical characteristics of protein crowns. When a crown of proteins forms on a nanoparticle's surface and blocks the targeting ligands, the nanoparticle loses its ability to target. The immune system of the body also includes strong molecular weapons that can alter the surface that is detected as a foreign body. The body's natural immune system can be better recognized and cleared when corona and antibodies are combined (Aberoumandi *et al.,* 2017).

3. Cartilage regeneration

Natural associations between bone cells and highly nano-rough surfaces exist. The biocompatibility and functionality of the implant can be greatly enhanced by coating it with biomolecules via antigen/antibody, DNA hybridization, or ligand/receptor interactions. The situation in which spiral rosette nanotubes interact with bone cells has been hypothesized to be similar to the Ti surface coated with HRN. It is a new organic material with self-assembling nanoscale nanotubes that was inspired by biology. These physical alterations may serve as direct internal triggers that cause the release of drugs from smart responsive hydrogels. To create responsive, intelligent hydrogels for cartilage and bone tissue engineering in addition to these interior triggers, external triggers can be used (Figure 2). Applying stimuli-responsive hydrogels makes it easier for growth factors or cells to be released on demand, ensuring that they reach the precise tissues that are deficient. They also provide biological and mechanical support for bone and cartilage abnormalities.

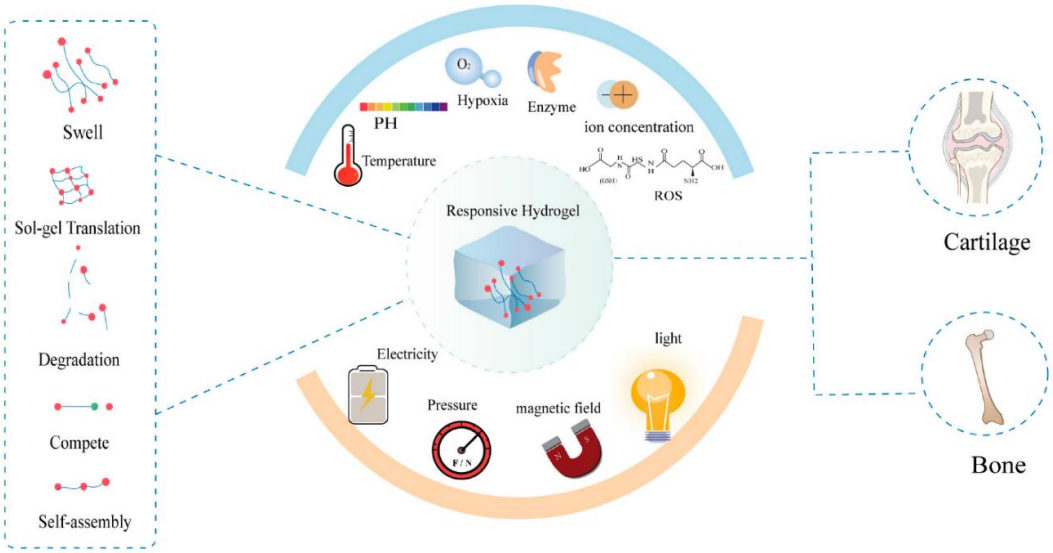

Fig. 2. Shows the use of stimuli-responsive hydrogels in biological systems (Ni *et al.*, 2023)

A typical innovative way to create nanoparticles with exceptional quality (high purity and crystallinity) that can improve the performance of current hydroxyapatite-based medical devices is the production of bone grafts. Inorganic nanoparticles that are biocompatible and hydrophilic, including bio-inert nano-grade alumina, are employed for knee prosthetic connection, maxillofacial reconstruction, and other procedures. Research showed how altering mineral ratios, crystallinity, and size dimensions in inorganic nanoparticulate systems might enhance osteoblast interactions during bone regeneration. Nanoclays are a new family of inorganic nanomaterials with promising applications in the engineering of bone and cartilage. The most researched nano clays for biological applications, according to the literature, are laponite, montmorillonite, and halloysite. The exfoliation of the layered silicate morphology of nano clays releases biologically relevant ions upon contact with biological fluid, which may aid in the healing of bone tissue. Without exogenous growth factors, laponite nanoplatelets were able to cause osteogenic differentiation in stem cells, indicating its potential for use as a

bioactive agent. An intriguing family of multifunctional nanomaterials called nano clays is now available. These materials can modify bulk materials mechanically and rheologically, load drugs, and release them over time.

4. Neuro-sensing applications

Future research on shrinking and enhancing the performance of tiny artificial devices will be greatly aided by the prospective applications of nano neuroscience. For patients suffering from neurological diseases such as paralysis, visual impairment, and epilepsy, improved and more secure brain-embedded drugs are now very likely to become a reality thanks to the collaboration between nanomaterial research and neuroprosthetic innovation. The therapeutic use of nanotechnology in neuroscience is still in its infancy due to the intricacy of neuronal cells and the mammalian nervous system. Notwithstanding these challenges, the development of multidisciplinary teams in the field of nano-neuroscience, as well as the productive collaboration with engineers, physicists, materials scientists, and clinicians, contribute to advancing the field. 5. Bio-Ink applications To induce differentiation in bone or cartilage tissues, certain stimuli are especially required (Figure 3). Chemical cues are critical for stem cell differentiation.

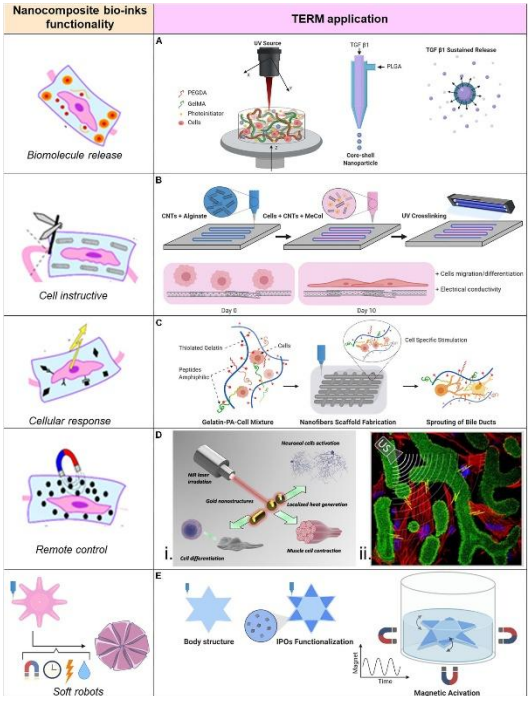

Fig. 3. Shows how tissue engineering and regenerative medicine use nano-composite bio-inks (TERM). (A) Core-shell nanosphere-enhanced mesenchymal stem cell-filled constructs for cartilage tissue engineering. (B) Nano-reinforced hybrid cardiac patch 3D printed with UV assistance for myocardial tissue engineering. (C) Using self-assembly peptides amphiphile (PA) to customize the nano-structure and bioactivity of 3D-printable hydrogels to aid in the development of bile ducts. I Two-photon lithography of 3D nano-composite piezoelectric scaffolds for cell stimulation; (ii) Smart inorganic nano-particles for wireless cell stimulation. For 3D magnetic soft robotics, (E) a stimuli-responsive nanocomposite (Di Marzio *et al.*, 2020).

Since growth factors are in charge of the spatial and temporal functions of cells, they are frequently used in tissue engineering. Sadly, without protection, even when administered in great doses, these molecules degrade and quickly disappear (Chen *et al.*, 2010).

When used in a bio-ink, which has the potential to significantly reduce the stability of delicate proteins, this becomes even more crucial. A unique method developed by Zhu et al. (Figure 3A) enables the placement of nano-carriers for transforming growth factor beta 1 (TGF-1) into the bioprinted cartilage construct. TGF-1 can then be supplied sustainably, significantly improving MSCs' ability to differentiate into chondrogenesis. In this study, the cartilage construct was made using stereolithography-based 3DBP. The square-shaped cartilage construct was crosslinked using a moveable head with a UV source. The bio-ink was made of a hydrogel with a gelatin methacrylate (GelMA) basis that was coupled with TGF-loaded nano-spheres, with an average size of 120 nm. The poly(lactic-co-glycolic acid) (PLGA) shell that surrounds the nano-carrier progressively degrades and sustains the release of its cargo. The qPCR study showed that when the bio-ink was enriched with TGF-1 nano-carriers, the expression levels of collagen II and aggrecan of MSCs loaded into the hydrogel rose. This method of embedding proteins into bio-printed constructions is appropriate. It is possible to simulate the dynamic presence of biomolecules in the ECM using this method. To achieve the correct release profile, however, the biomolecule release may need to be tuned over an extended period. Nevertheless, this top-down production method leaves behind a sizeable amount of unused material, which is not ideal if the material is valuable or has a finite amount of supply. The donor biological material is frequently a limiting issue when considering clinical applications. Also, if the UV-light exposure could be volumetric rather than punctual, as with a UV-light laser source, the fabrication time might be shortened.

5. Cardiovascular Applications

The extracellular matrix (ECM), which is made up of nano dimensions collagen and elastin, is formed of multiple nanoscale characteristics that are arranged hierarchically in natural vascular tissue. To date, great progress has been made in employing nanomaterials to imitate these actual nanostructures in vascular tissues. This lesson from nature encourages material scientists (and nanotechnologists) to build better biomaterials for treating cardiovascular disease. In particular, nanomaterials have been created, produced, and manipulated to enhance and mediate the functions of vascular cells (such as vascular endothelium and smooth muscle cells) and to prevent thrombosis and inflammation on stents. More intriguingly, endothelial cell functions were found to be more competitive than smooth muscle cell functions in several recent investigations. This suggests that endothelial cell functions are superior to those of smooth muscle cells and may help to prevent vascular restenosis (Hasanzadeh *et al.*, 2017).

Many nanostructured grafts or 3-D nano scaffolds for cardiovascular tissue engineering applications have been created by methods including electrospinning and self-assembly, in addition to nano-featured surfaces that are mostly used for vascular stent applications. The ability to easily create highly ordered nano architectures that replicate the directed multilayer structure of blood arteries is a key benefit of these fabrication approaches. By directly bonding polyhedral oligomeric silsesquioxane to segments of urethane, Punshon et al. created a novel nanocomposite vascular graft. In vitro, tests showed that confluent endothelial cell layers formed on the nanocomposites

after 14 days and continued to be viable and confluent for up to 35 days. By electrospinning collagen, elastin, and poly(L-lactic acid), Lee et al. created nanofibrous scaffolds that demonstrated significant smooth muscle cell infiltration. Compared to plane polymer films, electrospun poly(L-lactic-co-caprolactone) (P(LLA-CL)) copolymer scaffolds with aligned nanofibers dramatically enhanced the adherence and proliferation of smooth muscle cells. 23 This study also discovered that smooth muscle cells migrate and adhere in a directed manner along the nanofibers' axes, suggesting that it may be possible to design vascular cells to form the same kind of organized patterns as those found in natural vessels. By using direct solid phase synthesis, self-assembled peptide nano scaffolds were created that improved collagen IV deposition, nitric oxide release (a vital compound in the vasorelaxation process), laminin 1 release, and confluent endothelial cell monolayer formation (Mammadova *et al.,* 2022). The same promising qualities of nano scaffolds that were recently discussed in vitro were also seen in vivo experiments. Enhancement of endothelialization and decreased intimal hyperplasia were seen after tacrolimus eluting biodegradable nanofibers were implanted in a rat model, showing that the nanostructures may inhibit venous anastomosis. In conclusion, the main goal of the current research on nanomaterials for cardiovascular tissue engineering applications is to design nanoscale roughness or architectures that are inspired by biological structures on a variety of metals, ceramics, and polymers.

Nanobiomaterials have therefore been used to create adaptable vascular cell activities both in vitro and in vivo, offering significant promise for enhancing the effectiveness of cardiovascular implants or scaffolds for tissue regeneration without altering basic material chemistry (Nasibova *et al.,* 2022).

6. Risk Management

Flexible and effective design principles went towards creating the risk management framework. It is adaptable enough to handle various assessment objectives based on user requirements. Instead of just meeting predetermined data criteria, it is effective in gathering data for risk assessment based on specified user goals (i.e., focused testing) using optimal Methodology. This is done to strike the best possible balance between the time and money spent gathering the data necessary for a focused and accurate risk assessment and for choosing effective risk control strategies. NBMs utilized in medical applications provide occupational and environmental risks that must be carefully evaluated and addressed in addition to patient safety concerns. For instance, the widespread use of nano-Ag in biomedical applications (such as wound dressing and catheters) is driven by the material's enhanced antimicrobial activity when compared to the bulk form, but concerns have been raised about the material's potential long-term effects on human toxicity and inflammation. The risk management framework intends to assist the industry in meeting regulatory requirements while also fostering the creation of safer NBM applications that preserve their efficacy, performance, and quality to enable their successful entry into the market. The use of proper safety testing and evaluation methodologies based on the most recent scientific research, will offer guidance on how to identify the specific regulatory needs in each stage of the supply chains of these items. It should be understood that the benefit-risk analysis procedure, which is necessary for the market authorization of a new MD or ATMP, and the procedure for evaluating occupational and environmental risks (such as REACH or Environmental Health and Safety regulations), which are fundamentally different and call for different approaches.

This is due in part to the various legislative frameworks in place, but it is also a result of the fact that the two regions have different perspectives on risk and how acceptable it is to take on. Unintentional exposure to the materials determines the risks for employees and the environment. These risks are absolute, and evaluated using conservative assumptions, and any risks beyond the exposure/hazard risk ratio are deemed unacceptable. Contrarily, the patient risks posed by medical applications are always weighed against their therapeutic benefits and can be approved if the clinical advantages surpass the safety worries. These fundamental variations have led to differing requirements in the relevant legislation, which call for various testing methodologies. Yet, some of the (standard) testing techniques, modeling software, and data apply to each of these fields. By identifying areas of cross-fertilization to encourage sharing of ideas, data, and tools, the risk management framework implementation can help with this. In this way, the risk management framework may encourage and foster dialogue and teamwork among researchers in various sectors.

The physicochemical characterization is a significant area of cross-fertilization between the assessment of risks for workers, patients, or the environment. Since the relevant standards are still in the early stages of development and this is essential baseline data on how to proceed with the evaluation of potential dangers, the risk management framework will provide guidelines for testing both intrinsic and extrinsic features in this area. Moreover, guidelines are required to combine (eco)toxicological assessment with the results of physicochemical characterization. To help with the selection of in vitro and in vivo tests based on material identification, the risk management framework offers this assistance in the form of a series of structured Options displayed as decision trees. The plan is to supply IATA using a software-based BIORIMA Decision Support System, which will be freely available online to end users, for risk assessment and management of NBMs utilized in MDs and ATMPs. The use of a life cycle approach is essential in the assessment of environmental and occupational risks since, throughout the stages of formulation and use, workers and healthcare professionals may be significantly exposed, if there are insufficient risk management procedures in place. For instance, creating a customized occupational exposure scenario is necessary for the usage of dental composite made of hydroxyapatite in the dentistry industry. The dentist, if not properly protected, may grind, polish, or shape this paste while applying it, exposing him or her to airborne nanoparticles. This and similar exposure scenarios involving the processing of artificial joints during replacement surgeries are potentially very concerning, and their potential risks should be examined, particularly if the relevant exposure routes diverge from those already considered for the deliberate administration/use of the products by patients.

Therefore, the risk management framework's implementation can help healthcare professionals by raising their awareness of potential occupational dangers and improving their knowledge of suitable preventative and curative interventions. Doctors, dentists, surgeons, and nurses should all receive training on how to handle these substances and how to use the appropriate safety measures to develop an effective risk prevention and control strategy. This is especially important in light of personal protective equipment, which is only effective when used properly. The number of controls that are required must be determined in part by the known level of toxicity of the possibly released NBMs. Such a plan should also be supported by accurate onsite measurements of emissions, releases, and exposure. The complexity and perhaps even uniqueness of a given workplace necessitate exposure assessments based on a combination of personal

and area sampling with the use of suitable equipment and background measurements, even though some processes may be analyzed by lab-scale simulations (Ahmadkhani L. *et al.*, 2017). When evaluating risk management strategies and their efficacy, it is important to take into account the unique characteristics of the healthcare industry, such as the potential for daily exposure to NBMs due to waste management practices or the transfer of NBMs from high-security areas to uncontrolled areas. It is important to thoroughly assess the effectiveness of the protection mechanisms now in place in hospitals (such as those governing the handling of cancer treatment medications) and to develop comparable safeguards for MDs and ATMPs who use NBMs.

In other words, it can be helpful to provide the context for the handling of potentially less toxicologically strong NBMs by reading across from the management of other hazardous substances like anti-cancer medications, biological agents, and/or radioactive materials (Hosainzadegan *et al.*, 2020). While moving to in vivo pre-clinical and clinical studies in the usage phase, the benefit-risk analysis should be carried out to assure patient safety, and it should be compared to the standard of care for the same disease. During the pre-commercial phases of the innovation process, when novel NBM-enabled applications are created and there is a need to evaluate the balance of their predicted clinical advantages and potential safety consequences, such an analysis might also be carried out. In this situation, the risk management framework may also serve as a helpful tool to enhance patient communication regarding the data regarding risks and benefits and how those factors are weighted and assessed. There is a growing understanding of the contribution that engaged patients and the general public can make to better decision-making on health technologies, which will ultimately aid improve adherence to treatments.

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