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Theranostic Applications of Nanomaterials for Ophthalmic Applications

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ABSTRACT

The development of theranostic applications of nanomaterials has presented researchers with a new form of diagnosing and treating diseases, such as cancer, Diabetic Retinopathy, and Age-Related Macular Degeneration. Theranostic have allowed for a bridge between conventional medicine and personalized medicine with the use of nanomaterials. The applications of nanomaterials within medicine (nanomedicine) have changed the diagnosis, monitoring, control, treatment, and prevention of diseases. The effects of the biological interaction of nanomaterials within the human body must be examined further to understand the efficacy, toxicity, and biodistribution. The use of theranostic application of nanomaterials has gained attention in the field of Ophthalmology. The use of theranostic nanomaterials to reduce current treatments, complications, diagnosis, reduce the effects and treat a visually threatening disease is appealing. The benefit of treating ocular diseases with theranostic will allow for better visibility and targeted treatment.

Keywords: nano delivery; drug delivery; theranostic applications; nanocarriers; magnetic material; gold nanoparticles; nanomaterials

INTRODUCTION

In recent years, the use of novel materials such as nanotechnology has emerged and positively impacted nanomedicine. The use of personalized medicine has emerged to be more beneficial and efficient from the design, synthesis, and engineering of nanoparticles, nanospheres, and nano capsules. Treatment for diseases can require gene delivery, drugs, and other techniques. During this treatment period, the body is negatively affected by the treatment or drug therapies' adverse effects. With new advances of the nanoparticles for various areas, the use in theranostic applications has the capabilities of a designed therapeutic and diagnostic application. [1] This combined application has allowed a change in how a person is treated for disease by having a targeted delivery instead of a non-targetability of the drugs. By manipulating different materials at a molecular scale, the nanoparticles' surface can be altered to achieve targeted delivery. [2,3] Current research efforts have been made to explore further the effects of theranostic applications in vitro for targeted delivery, imaging of diseases, and biomarkers.

Nanoparticles have been used as efficient drug delivery systems. The nanoparticles' characteristics are small size, optical properties, high surface area, high stability, high carrier capacity, feasibility in administration routes, and the feasibility of incorporating hydrophilic and hydrophobic substances. [3,4]

The use of nanoparticles has been seen in biomedical applications and stem cell therapy by delivering genes to stem cells, enhancing stem cell retention, and stimulating a proangiogenic effect on the stem cells, stem cell tracking, and mimicking the extracellular environment. [5] Current theranostic applications of stem cell therapies would be labeling mesenchymal stem cells (MSCs) with gold nanospheres in vitro for ophthalmic and medical applications, targeting cancer stem cells to use early detection and possible treatment. [6,7,8]

In addition to stem cell therapies, there is a wide range of nanotechnology delivery. As listed below, there are various types of forms of nanotechnology. Each engineered technology uses nanotechnology for targeted delivery. As can be seen, some contain a controlled release of therapeutic agents. Due to their biochemical makeup, nanomaterials can exhibit biological effects and chemical and physical properties. Compared to conventional drug delivery, the advantages of using nanotechnology are their ability to act as organic and inorganic, high surface-area-to-volume ratio, interaction with biomolecules, and controlled release. [9] Nanotechnology's additional benefits as a mode of delivery include low nanotoxicity, biodistribution, biocompatibility, and reduced clearance within the human body.

The benefits of nanotechnology, each nanocomponent can be designed for different applications.

This review aimed to discuss the theranostic applications of various nanomaterials listed above to use ophthalmic applications and provide a background and overview of the current applications, advantages of theranostic applications, and nanotechnology delivery. The use of Nanomaterials is still novel in the field of ophthalmology and ophthalmic applications.

1. BIOLOGICAL INTERACTION OF NANOMATERIALS

The application of nanomaterials and nanotechnology is still current, and as it is being implemented in medicine, creating the field of nanomedicine can improve disease treatment. [10] The area of nanomedicine is rapidly growing and developing personalized medicine treatments by collecting the genomic and molecular data from each patient in response to a particular disease rather than conventional drug treatments. [11] This potential improvement of drug delivery with nanomaterials has already been demonstrated in a clinic setting, such as the first nanosized therapeutic treatment for metastatic breast cancer and recurrent ovarian cancer (Doxil®, a PEGylated liposomal doxorubicin formulation). [12,13]

To further understand the effects of these nanomaterials, the biological interaction must be examined. As this is an innovative way of delivering medicine, the interactions must be thoroughly examined to understand the benefits and side effects. Understanding will allow for further modifications to deliver the nanomaterials to be done safely and effectively. Nanomaterials and nanotechnology with the body are still being examined and adapted to current research results. Nanomaterials' biological interactions are crucial because as these nanomaterials and nanotechnology are introduced into the body, it comes into contact with many biological fluids like blood, mucosal secretions, or interstitial fluids. [14] The nanomaterials and nanoparticles contain proteins, and when interacted with the body, there could be a loss of properties, surface charge, or loss of performance. [11,14] Seeing how the nanomaterials interact with the body can help change and adapt how nanomaterials are used.

As the use of nanomaterials is still emerging, biological interaction is still being understood for ophthalmic application. With the eye being a susceptible organ within the human body, nanoparticles may provoke an unwanted response when injected or delivered to the eye. Therefore, the use of nanoparticles must be precise in order to prevent any preventable issues.

Function

In the past couple of decades, the use of nanomaterials has piqued the interest of many after the development of colloidal semiconductor nanocrystals, called quantum dots. [15] These quantum dots opened the field to understanding the quantum size effects and the possibility of new applications within quantum mechanics. The nanoscale semiconductor materials have optical and electronic properties that can be used for imaging or injection needs. [16] Within the field of quantum dots, there is a form called Luminescent carbon quantum dots (CQDs) that can be used for chemical sensors, bioimaging, nanomedicine, solar cells, light-emitting diode (LED), and electrocatalysis. [17]

Nanoparticles (NPs) have a dimension under 100 nm and are generated by nanotechnology processes. [18] The innovative advancements of nanoscience and nanotechnology are still new to the field of science.

Their applications are always new and diverse. They have been used in a multitude of fields such as agriculture, medicine, and pharmaceuticals. [19,20] Nanotechnology has many valuable benefits due to its unique physical and chemical properties of high surface area and nanoscale size. [21] In addition to their properties, morphological characterizations are significant because many of the properties and applications of nanomaterials are dependent on morphology. The unique morphological and structural characteristics of nanomaterials can influence their applications within the body. Three applications of nanoparticles that will be examined are diagnostic, therapeutic, and theranostic. The applications have been examined and are currently being developed for more targeted treatments for diseases.

Nanomaterials are nanosized particles that are single-sized units between 1 and 100 nm. These materials have a surface structure in the nanoscale. Most are too small to be seen by the naked eye and sometimes with a conventional microscope. [22] The nanomaterials are engineered in order to adapt to their properties and applications. The benefit of using nanomaterials is that they can be designed in conjunction with drugs to target specific organs, genes, or cells within the body and enhance the therapy's effectiveness and delivery. There have been various techniques to synthesize their nanomaterials, such as composition, size, shape, and surface chemistry. These characteristics enable the nanomaterials to be tailored for specific applications. [23] The synthesis of these nanomaterials all start with simple molecular precursors and are chemically transformed into complex nano-heterostructures.

There are numerous benefits and advantages of using nanomaterials for treatments or imaging. Site-specific-targeted drug delivery using nanomaterials is a therapeutic modulation that can deliver the appropriate drug dose and disease regulation. The use of nanomaterials, targeted drug delivery improves the bioavailability, reduces adverse effects, decrease the toxicity to the site and other organs, and are cost-effective. [24] Nanomaterials used in imaging are unique because they can create imaging probes with better contrast, increased sensitivity, better spatial and temporal information, and multi-function properties.[25] Like treatments, each treatment technique has side effects and limitations of using nanomaterials for therapies and imaging. The overall aim of using nanomaterials is to improve the efficacy and toxicity of therapies *in vivo*. [26] One main limitation is the limitation of biodistribution and efficient targeting. [26]

Many studies have reviewed the function of nanoparticles within the eye to be a less researched topic due to it being novel and the complexity of the eye. Well, the use of theranostic applications seems promising, the concern of safety and toxicity arises. The function of using nanoparticles within the eye is to potentially deliver a targeted drug or providing therapy, such as gene transfer therapy for retinal diseases.

Organ systems

A basic understanding of the use of nanomaterials within organ systems must be established. The organ system is complicated at various levels within the biological system. [27] The use of a particular nanomaterial may have no adverse effect when administered to a specific system but may show adverse effects and potential toxicity in another system. The mechanisms of cellular and organ-specific action of nanomaterials must be emphasized in order to overcome the limitations. The establishment of the biological entries and properties will help overcome poor

solubility, cytotoxicity, and lack of pharmacokinetics and pharmacodynamics. One of the main mechanisms to allow the proper entry of nanomaterials into the system is endocytosis. Usually, there is a translocation of nanoparticles in the plasma membranes that induce challenges for the individual cell membrane, complex reaction, interaction, communication, and entry pathway. [28]

2. THERANOSTIC NANOPARTICAL

As discussed previously, nanoparticles are one of the primary investigations for biomedical nanotechnology and applications. Theranostic nanomedicine is a combined therapy that simultaneously uses diagnosis and treatment into one application. [29] With all treatments and new therapies, the morphology must be examined to understand the treatment options and progress on how the treatment is used. [30] Theranostic nanoparticle applications are unique in the sense that the approach is personalized, and patient centered. This combination of diagnosis and therapeutics is exciting and provides a transition from conventional to personalized medicine. With the patient's genetic information, the treatment is custom made based on the patient providing the option of the "right" drug at the "right" dosage for the patient. [31, 32]

This new formulation provides a more targeted and tailored pharmacotherapy with the capability of being very beneficial and proving to be better than the conventional therapies or delivering medications. With this new form of therapy, the efficacy, toxicity, and bioavailability must be examined to understand the benefits and the limitations of using theranostic. This is important to understand the interaction within the body, but it is beneficial in treating different types of theranostic that advance personalized medicine.

The efficacy of the nanoparticles is dependent on the administering route and the type of nanomaterial being used. These nanomaterials have the potential to increase therapeutic efficacy and reduce side effects compared to conventional treatments. However, the human body has several barriers, immunological, renal, enzymatic, mechanical degradation, vascular endothelium, extracellular matrix, cell membrane, lysosome, and membrane pump. [33,34]

Current investigations progress in understanding the toxicity assessment and application of nanoparticles. [35] The toxicity of the nanoparticles shows possible threats to biological systems and the environment. The assessments of toxicology within the body reveal physicochemical characteristics that negatively impact the biological systems. The main mechanisms of nanotoxicity and cytotoxicity, proliferation, necrosis, apoptosis, DNA damage, and oxidative stress have been examined to understand the long-term complications. [36] The toxicity assessments come from the forms of nanoparticles used, such as those listed in Yang et al. Table 1. [36]. The forms of nanoparticles can exhibit different effects *in vivo* and *in vitro*. The neurotoxicity has been tested to understand the pathological and morphological changes that can be presented. For *in vivo* assessments, nanoparticles exhibited tissue structure changes, inflammation to the organs, and structural specificity. For *in vitro* assessments, it was seen that nanoparticles displayed cell proliferation, necrosis, apoptosis, DNA synthesis and damage, altered gene expression, oxidative stress, and immunogenicity. [37]

Biodistribution, analysis of determining the vector's distribution to the target of nanoparticles are crucial when developing the nanomaterial and therapies. [38] The biodistribution of nanoparticles and nanomaterials can influence and play a crucial role in the therapeutic, diagnostic efficacy, biocompatibility, and toxicity. [39] The biodistribution determination is based on the surface material of the nanoparticles, nanoparticle shape, and the administration route. [39]

Theranostic Applications in Ophthalmology

Theranostic applications in ophthalmology are still in their infancy. In the past, nanoparticles were used for treatment in ophthalmic applications. Numerous factors can have a negative impact on the impact of a diagnostic and therapeutic treatment like theranostic. These treatments, like other treatments for ocular diseases, can have toxic and unnecessary side effects. Various types of therapies can be designed to improve overall delivery, controlled release, and penetration to the eye using theranostic applications.

The use of various nanosystems and nanoparticles is currently being researched and is in its early stages. It has been demonstrated that the use of nanoparticle-based drug delivery systems increases the bioactivity and bioavailability of therapeutic agents within the retina. Anti-VEGF therapies have improved current treatment for neovascular retinal diseases such as age-related macular degeneration and diabetic retinopathy. [96]

It is hoped that this research will be translated into clinical therapies. When combining a fee diagnostic and therapeutic system, the complexity of these nanoscale drug delivery systems can be advantageous. Various nanoscale materials have been designed for specific ophthalmic drug delivery, as discussed later in the paper. These nanosystems are being developed to treat a wide range of common ocular diseases, including glaucoma, infectious endophthalmitis, and fungal keratitis.

3. THERAPIES

The field of treatment and therapies is continually changing and adapting to new diseases and technology, like nanotechnology. [40] Theranostic' use is diverse and has multiple applications like personalized drug therapy, gene therapy, and immunotherapy—each of these therapies has been examined and has had successive results within the eye. Theranostic has already been used successfully for ocular neovascularization imaging and therapy, image-controlled drug delivery, and in-clinic pharmaceutics. [41,42, 43]

The use of theranostic applications with nanomaterials has become popular because of the ability to deliver targeted therapeutics. The benefit of visualizing potential targets allows a precise prediction of the benefit of particular treatments.[44] This allows a better understanding of the direct response and possible toxicity before the treatment is administered.

FIGURE 1: [95]: Theranostic is a term that refers to the combination of diagnostic and therapeutic capabilities. There are numerous types of theranostic deliveries, including drug, gene, and immunotherapy. Each of these delivery systems has a unique method of operation.

Theranostic Drug delivery

One form of theranostic therapy is the use of drug delivery. The use of theranostic drug delivery systems is growing in interest due to their revolutionary method of managing diseases and targeting. [45] It is currently one of the most researched theranostic therapy as it can provide image-guided therapy with targeted drug delivery. Using theranostic nanomaterials and nanoparticles allows for a promising platform for treating diseases, such as cancer therapy and ocular diseases. With various nanocarriers, diseases that could not be adequately viewed, cells or tissues, can now be treated. [46] There can be a higher concentration in which the treatment is being delivered.

Theranostic Gene delivery

Theranostic nanomaterials have been used for image-guided gene therapy for treating various diseases, such as cancer phenotypes, preclinical and clinical oncology, and intracellular gene delivery with spatiotemporal imaging. [47,48,49] Gene therapy is a promising therapeutic approach by modifying gene expression to treat a disease. By implementing theranostic agents, the therapy has the potential to be more effective. One specific nanoparticle that has provided advantages for gene delivery is Magnetic nanoparticles (MNPs). The MNPs have been used to provide an effective contrast agent against Magnetic Resonance Imaging (MRI) because of the precision of particle delivery. [50] Implementing gene therapy with theranostic will allow for image-guided and implement gene imaging therapy that can replace current treatments.

Theranostic Immunotherapy

Immunity is the ability of an organism to resist an infection or toxins by employing and releasing specific antibodies or white blood cells. It is a way of protecting the immune system from harmful microorganisms. There are two components of immunity, specific and nonspecific. Both components are crucial in creating a barrier and eliminating pathogens. [51] Immunotheranostics have emerged as a new, improved way of a new immunotherapy, diagnostics, screening, and evaluation of modalities to prioritize immune disorders. [51] This therapeutic strategy has been used in preclinical and clinical developments for treatment but to identify antibodies like T cell receptors (TCR) to identify intracellular proteins that could be targeted. Currently, the therapy has been used on cancer treatments. Using nanomaterials to analyze immunosuppressive and immunostimulatory cells present in tumor microenvironments. [52] The current immunotherapy treatments are inadequate, but nanomaterials as an immunotherapy treatment could play a critical role in investigating and treating immunologic responses. [53]

4. NANOMEDICINE, THERANOSTIC AND CLINICAL APPLICATIONS

Nanomedicine is the use of nanotechnology (nanoparticles and nanomaterials) in the field of medicine. Nanomedicine has changed the way of diagnosis, monitoring, control, treatment, and prevention of diseases. [54] Nanomaterials within nanomedicine can be applied in three areas: diagnosis (nano diagnosis), controlled drug delivery (nano therapy), and regenerative medicine. [55] These three areas show a promising approach to change the introduction and production of unique medicines implementing diagnosis and treatment. [56]

Nanomedicine

Nanomedicine's intrinsic properties have brought many advantages in pharmaceutical development due to its morphology and physicochemical characterization. The use of nanoparticles, critical components of nanomedicine, is to enhances drug treatment. As stated, nanomedicine has allowed a new treatment for targeted drug delivery, diagnosis, imaging, and the capability to create hybrid treatments such as theranostic. [57] With this new field, the attention goes to why using nanotechnology within medicine when there are treatments. The field of medicine is continuously evolving, and with the use of technology, new treatments can be designed to treat chronic diseases better. With nanomedicine, chronic diseases such as Age-Related Macular Generation, Diabetic Macular Edema, cancer, e.g., can be treated more efficiently using nanomedicine than conventional drug treatments. It is a personalized treatment using theranostic applications using proper diagnosis, imaging, and targeted drug delivery. [57] This is considered to be more beneficial than conventional treatments. The combination therapy has a reduced toxicity level and is more efficient and biocompatible within the body.

The benefit of using nanomedicine is to advance modern medicine into creating more targeted and personalized. Specifically, theranostic therapies use therapeutic and diagnostic functions that, depending on the nanoparticles, are safe and not toxic when interacting with the biological systems. When looking at current cancer chemotherapy treatments, the significant problems are toxicity, resistance, and cancer heterogeneity. When theranostic is proposed for cancer therapies, it presents low therapeutic toxicity, low tumor resistance, binds to intracellular targets, targeting the diverse biomarkers presented in cells in primary and metastatic cancer. [58]

As discussed earlier, theranostic present low toxicity, high efficacy, and bioavailability. In addition, there are many different versions of nanoparticles that can be used with theranostic, such as DNA-encoded, silicon, pH-responsive polypeptide, gold nanoparticles, e.g., these theranostic have shown to be more beneficial and more cost-effective than conventional therapies. [58, 59]

Clinical Applications

The use of nanomedicine, specifically theranostic applications, has already been used in a clinical setting. The capability to create a personalized treatment involving diagnosis and therapeutics has shown to be highly advantageous. Theranostic has already been used in a clinical setting. It has been successful and promising for changing how the disease is diagnosed and treated—being able to advance pharmaceuticals and medicine into the realm of personalized treatments. Theranostic has shown to be more beneficial in examining and target drug delivery, but the use of nanomaterials to deliver the treatment has shown to be more beneficial and efficient. With recent studies that have been released examining the application of theranostic therapies, the benefits of using these therapies deem to be more favorable than the conventional treatments.

Sgouros et al. examined the use of theranostic in radiopharmaceutical therapy (RPT) in cancer. [60] They reviewed the use of RPT to treat various forms of cancer by using radiation and delivering pharmaceuticals to bind to the cancer cells. Xuemei et al. applied multifunctional nanoplatforms and theranostic applications to target Multidrug-Resistant-Bacteria. [61] Using theranostic multifunctional nanoplatforms, an iron nanoparticle, and gold coating, the bacteria were coated with PEG coating, methylene blue dye, and M3038 Antibody specific for MDRM DT104. By creating this nanoplatform, MDRB was sensed using photodynamic (PDT), photothermal (PTT) therapies and targeted in a single procedure. Julian et al. used theranostic applications and nanoparticles to diagnose and provide therapy for atherosclerosis and myocardial infarction. [62]

These are a few examples of using theranostic applications within a clinical setting; there are still challenges of theranostic nanomedicine. The demand for a new personalized treatment requires more understanding and careful coordination. [63]

5. OPHTHALMOLOGICAL NANOMATERIAL APPLICATIONS

Theranostic applications of nanomaterials have gained traction in the field of Ophthalmology. The use of nanomaterials to diagnose and administer treatment to common ocular diseases, such as Age-Related Macular Degeneration, Diabetic Retinopathy, infectious endophthalmitis, and the complexity and delicacy of the eye, and fungal keratitis, can be beneficial. The current treatments for these diseases are invasive, contain numerous side effects, or cannot be treated due to variation. The benefit of using nanomaterials for Ophthalmological applications will allow for a faster treatment to be administered to reduce the effects of the disease and help mitigate the need for repeated intravitreal injections.

Biochemistry of the eye

The retina, or photographic film of the eye, is attached to the back of the eye's inner wall. It is no thicker than a piece of tissue paper. The retina's various layers are responsible for capturing light and processing it, converting photons into electrical signals relayed to the occipital cortex, where visual perception occurs [64]. The retina serves as the primary ocular connection to the brain. It has ten distinct layers that work in tandem to generate a visual output. The order of the layers will be described, from farthest away to closest to the vitreous humor.

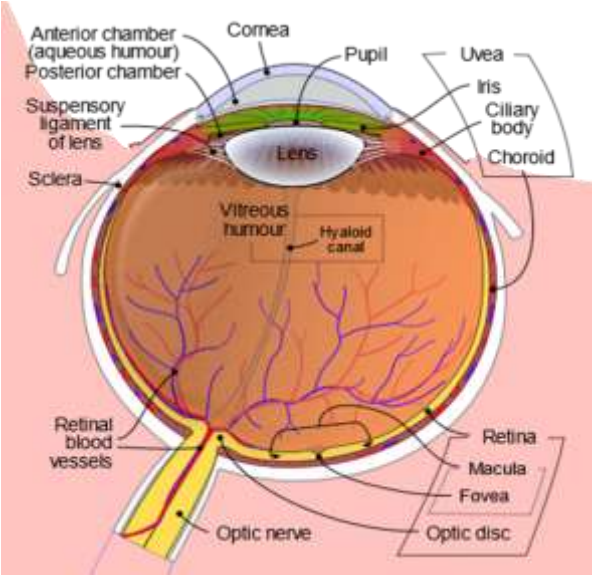

FIGURE 2: [97]: Schematic presentation of the ocular structure

The retinal pigment epithelium is located beneath the retina (RPE). It is composed of a single layer of densely packed hexagonal post-mitotic cells containing pigment granules. These cells are critical in forming a barrier and the maintenance of the photoreceptor layer [65]. Each cell has two layers: an outer non-pigmented layer and an inner pigmented layer. The RPE is located between the choroid's blood supply and the light-sensitive segments of the photoreceptors, forming part of the blood barrier [66]. The RPE's function is to nurture and shield the retina. This is accomplished by transporting ions, water, and nutrients, absorbing light and protecting against photooxidation, isomerization of trans-retinal into cis-retinal, and retinal integrity. [65,67] A specialized neuroepithelial cell that is important in sensory transduction can be found in the photoreceptor layer. This sensory transduction is necessary for the rod, cone, and retinal ganglion cells to convert light into electrical signals. After the photons have been absorbed, the rod and cone photoreceptors release the neurotransmitter glutamate to the bipolar cells. Although it depolarizes, the photoreceptors are released in the dark. The effect of glutamate on bipolar cells will vary depending on the receptor on the cell membrane. This enables the bipolar cells to be excited by light, allowing them to distinguish between color and edges. Light can be sensed in a visual field thanks to this layer. [68]

The limiting membrane on the outside is not an actual membrane. It has a network-like structure of rods and cones that gives it the appearance of a membrane. The function is to protect the inner layers by forming the blood-retina barrier, to prevent any harmful properties from entering the bloodstream, and to aid in the maintenance of the integral structure of the retina. Many rods and cone cell synapses can be found in the outer plexiform layer. The dendrites of the ganglion cells in the inner nuclear layer are interlaced with this layer. The inner nuclear layer is made up of densely packed bipolar, amacrine, and horizontal cells. This layer contains the retinal vasculature. Dendrites of interlaced retinal ganglion cells (RGCs) and the inner nuclear layer are found in the inner plexiform layer. The RGC sends axons to the optic disc. The retinal ganglion cells are found in the ganglion cell layer (RGC). The bipolar and amacrine cells send visual information to these neurons. This layer is the most directly connected to the macula and the optic disc. It processes electrical signals by sending them via axons to the optic nerve and then to the brain. Ganglion cell axons run parallel to the optic disk in the nerve fiber layer (RNFL). It is a fiber extension from the optic nerve. As they move on to the retina and choroid, the nerve fibers from this layer will lose their medullary sheaths as they pass through the lamina cribrosa sclerae, a mesh-like structure of nerve fibers from the optic nerve exit through the sclera. The layer is significant because it consolidates the center for electrical signals sent from the retina's outer layer. These signals are sent to the occipital cortex, which is responsible for visual perception. The topmost layer separating the vitreous body from the retina is the inner limiting membrane, containing astrocytes and Müller cells. Astrocytes are star-shaped glial cells that aid in the maintenance of the blood-brain barrier endothelial cells. This allows for adequate nutrition for the nervous system. [69] Müller cells are a type of glial cell that helps to support the neuron cells in the retina. This cell is essential for the structure's integrity and cell stability. [70]

Ocular Disorders

The two common ocular disorders are Age-Related Macular Degeneration (AMD), dry and neovascular, and Diabetic Macular Edema (DME) caused by Diabetic Retinopathy (DR).

- ***Age-related macular degeneration (AMD)***

In patients over the age of 60, age-related macular degeneration (AMD) is an incurable neurodegenerative ocular medical condition that causes parts of the retina and macula to deteriorate, resulting in blurriness or loss of vision. [71] AMD is the leading cause of blindness in the world. The macula is a 5mm-wide section of the retina that is responsible for central vision. Fine detail and color vision are part of the central vision. The macula contains a high concentration of photoreceptor cells that detect light and send signals to the brain via the optic nerve so that the signals can be interpreted as images. The macula is essential for daily tasks such as reading, driving, recognizing images, and seeing fine details. The retinal pigment epithelium (RPE), a layer of post-mitotic cells that serves as a barrier and a regulator of the photoreceptor layer, is affected by AMD. There is no specific reason for the cause of AMD, but many

lifestyles risk factors, such as diet, genetic history, smoking, high blood pressure, or a high amount of inflammation within the body, have been linked. [72]

AMD is classified into two types: atrophic (dry) and neovascular (wet). The two types are distinguished by the presence or absence of blood vessels that disrupt the retina. [73] The dry form is the most common, affecting 85-90 percent of the population. [74] Drusen, tiny yellow deposits found between the RPE and the Bruch's membrane on an ocular coherence tomography (OCT) scan indicate dry AMD. These deposits are detected beneath the retina and can range in size. These deposits can eventually kill the macula photoreceptors. This type of AMD has mild symptoms, such as progressive vision loss and no therapeutic interventions. Wet AMD is a more advanced form of dry AMD that affects 10-15% of patients. This form is caused by blood vessel leakage or the formation of new blood vessels in the macula. As a result, new blood vessels begin to branch beneath and above the other layers of the retina and macula. [73] Some medications can block the growth of blood vessels and prevent the formation of new blood vessels in the wet version. These medications are administered via intravitreal injections. The injections are anti-vascular endothelial growth factor (anti-VEGF), which inhibits endothelial vascular growth and is beneficial when high concentrations are left in the eye [75]. The medication would be injected into the affected eye by the ophthalmologist. Several medications have been seen to reduce blood vessel presence and allow for partial vision recovery. The shrinking of blood vessels aids in the recovery of retinal cells and their ability to function. Depending on the progression of the AMD, this treatment can be repeated several times.

- **Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME)**

Diabetic Retinopathy (DR) is a progressive microvascular disease that affects the retina and is a common complication of type 1 and type 2 diabetes mellitus. DR affects over 100 million people worldwide. [76] DR is similar to AMD in that it is diagnosed by manifestations of vascular abnormalities in the retina. This microvascular disease is directly related to hyperglycemia pathways. Many pathways have been identified to increase oxidative stress, such as vascular occlusion and inflammation, which leads to DR. [77] DR is associated with damaged neurons and blood vessels in the retina, resulting in reduced blood flow and inner retina dysfunction. When the ocular blood-retinal barrier, which contains retinal epithelial cells held tightly together, preventing substances from entering the retina, contains leaky blood vessels, outer retina dysfunctions begin to occur after the inner. [78] These leaking blood vessels impact the retinal neuropil, which is a nervous system area that connects the brain. When these blood vessels thicken, the vascular smooth muscle cells and pericytes degenerate. When neurons are damaged, the barrier begins to leak, allowing toxins to enter the retinal neuropil. This process can decrease blood flow, microaneurysms, capillary bulges, the attraction of inflammatory cells, and retinal dysfunction. [79] The causes of DR vary, but they are all caused by high fluctuations in blood glucose levels, which cause blood vessels to constrict, resulting in retinal vessel occlusion. [80]

Diabetes-related macular edema is a common cause of DR (DME). This is due to swelling and thickening of the macula caused by the accumulation of fluid and protein deposits in the macula, which is usually detected on an OCT. [81] Severe swelling can cause blurred or double vision, as well as eye floaters, which are deposits of the eye's vitreous humor that have become transparent. [82]

DR is classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). [81] There are several stages of NPDR before reaching PDR. Microscopic changes in blood vessels typically identify the first stage. When NPDR is detected, microaneurysms are present that do not impair vision and usually go unnoticed. [83] After this point, if glucose levels are not appropriately maintained, blood vessels can swell and block nourishment to the retina. More visible changes include blurry vision, vitreous floaters, and DME. In the absence of adequate blood flow, the neurons in the retina will send signals to form new blood vessels. [84] PDR is a more advanced version of NPDR that causes a loss of oxygen flow to the retina. As a result of the oxygen deficiency, new abnormal neovascular blood vessels will form on the optic nerve. [85] Because these blood vessels are fragile, there is a greater risk of bleeding into the vitreous hemorrhage. This can cause retinal ischemia. There is no cure for DR, but it can be treated with intravitreal injections, much like neovascular AMD.

The injections are anti-vascular endothelial growth factor (anti-VEGF), which inhibits endothelial vascular growth and appears to be beneficial in having a high concentration pathway to the eye. [75]

Advantages of Theranostic applications for ocular use

With the benefits of Theranostic applications for ocular use by treating the most common ocular diseases, such as AMD, Glaucoma, and DR, theranostic can allow them to image and target the disease for each patient. The benefit of using theranostic for treating ocular diseases is to directly view and target the optic nerve, the source vision, and starting place of neovascularization of diseases. As discussed previously, theranostic applications can be beneficial when it comes to ocular use because of the possible benefits and decrease in adverse effects compared to conventional treatments, intravenous and topically.

Tang et al. applied theranostic to address ocular neovascularization in the clinical setting. [83] They looked at the clinical implementation of diagnosing and treating neovascular eye diseases, such as Age-Related Macular Degeneration (AMD), dry and neovascular, and Diabetic Macular Edema (DME) caused by Diabetic Retinopathy (DR). The diagnosis and treatment process are a two-step process of first diagnosing using fluorescein angiography to determine the location and the extent of abnormalities and treating it with multiple intravitreal injections. The injections contain anti-vascular endothelial growth factor (anti-VEGF), which blocks the endothelial vascular growth and is beneficial, leaving high concentrations in the eye (37). These intravitreal injections are invasive and can cause complications such as bleeding, retinal tears, pain, infection, and retinal detachments. [84] Using theranostic such as peptide-functionalized silicon nanoparticles (SiNPs) can address the complications associated with the two-step process and allow for simultaneous imaging and therapy. Using theranostic, they were able to produce a treatment specifically for treating neovascular eye diseases with proper biodistribution, biosafety, and low cytotoxicity. They created a theranostic probe using SiNPs-RGD to bind to the human retinal endothelial cells to detect angiogenic endothelial cells *in vitro*. SiNPs-RGD, in conjunction with theranostic probes, shows to have the promising antiangiogenic ability *in vitro* to label blood vessels and neovascularization inhibition simultaneously.

Jin et al. integrated theranostic nanomaterials to target photodynamic therapies against infectious endophthalmitis. [85] Infectious endophthalmitis is a prominent condition that causes irreversible intraocular tissue and optic nerve

damages due to the rapid proliferation of Gram-positive and Gram-negative bacteria, such as biofilms and secretion of exogenous toxins. [86,87] The current clinical treatment and prevention strategy is an intravitreal injection of antibiotics. The diagnosis is first to perform a pathology exam, which takes up to half a day to one day to complete because of the time it takes to develop the bacterial resistance, phenotype changes and biofilm formations, and elimination of infections. [88,89,90] After the diagnosis, the antibiotics, usually vancomycin and ceftazidime, are administered intravitreally. They examined using a theranostic nanoplatform based on UiO-66-NH2 to combine photodynamic therapy and lipopolysaccharide (LPS) targeting through polypeptide (YVLWKRKRKFCFI-NH2) modification. By synthesizing UiO-66-NH2 and using photodynamic therapy, they were able to add a dopamine buffer and formulate PDA-coated UT nanoparticles. Then the polypeptide PEP and PEG were grafted to create UTPP NPs. By injecting the UTPP NPs with photodynamic therapy, therapy detected the infectious endophthalmitis under laser irradiation and optical coherence tomography and then the UTTP NPs. This strategy should have advantages because the theranostic nanoplatforms had bactericidal and biofilm elimination properties and reduced the inflammatory effect.

Huang et al. employed a hydro-based theranostic contact lens to treat fungal keratitis. [91] Fungal keratitis is one of the leading causes of ocular morbidity and blindness. It is an infection of the cornea caused by a fungus, improper care and cleaning of contact lenses, or injury to the cornea. The current diagnosis is to obtain a small sample by scraping the cornea, identify the fungi through electron microscopy and immunofluorescence staining. [92] Once the diagnosis has been made, the antibiotics are administered using topical corticosteroids and intravitreal injections. The current treatments and therapies for keratitis are complicated and inefficient due to drug insensitivity and resistance. [93] Similar to the previous two studies, the use of intravitreal injections has various drawbacks in ophthalmic applications. They used a hydro-based contact lens to administer a controlled drug release using a hydrogel contact lens with integrated antifungal functions for a new form of treatment. They took a quaternized chitosan (HTCC), a natural polysaccharide used in therapeutics and diagnostics that is antimicrobial, biocompatible, biodegradable, low toxicity, and variability in the structure. [94] They combined it with carboxylation, silver nanoparticles, and partial carboxylic groups. This created the hydrogel that provided a usable model for sustained drug delivery. Once the hydrogel was formulated, the hydrogel was combined with silver nanoparticles, which increased the antifungal activity and antimicrobial spectrum, and Vor, an antifungal drug. With the use of theranostic applications, the contact lens matrix was prepared. As can be seen from this study, the use of theranostic was used to reduce the risk of injection treatments and provide a treatment that could be delivered efficiently.

CONCLUSION AND FUTURE PERSPECTIVES

Theranostic application with nanomaterials and nanoparticles is a promising form of therapy that can be applied to nanomedicine. Investigating the nanomaterial and theranostic applications can help advance targeted and personalized drug delivery for organ systems, such as the eye. Understanding the applications of theranostic nanomaterials will assist in developing new targeted drug delivery systems for ocular diseases. The effects and the applications of theranostic can change the way that ocular diseases are treated. Nanomaterials in medicine are emerging as targeted drug therapy, specifically for ocular diseases and ophthalmic applications. Efforts need to be directed to a better understanding of the biological interactions of the nanomaterials when combined with diagnosis, imaging, and treatment efforts. In addition, the use of theranostic in ophthalmology is limited and can change the way physicians view ocular neovascularization, fungal keratitis, or any visual-threatening ocular disease. With the advanced imaging capability, these diseases can be better treated with fewer adverse effects.

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