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Review Article

AN UPDATE ON CLINICAL APPLICATIONS OF NANOPARTICLES IN BRAIN AND RETINAL DISEASE (CNS)

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Abstract. Malignant tumors are one of the highest frequently studied target diseases of nanotherapeutics amongst brain diseases. Chiefly, various pathological mechanisms as well as reactive oxygen species (ROS), biological actions of growth factors, and signaling pathways of proliferative potentials could be addressed with nanoparticle-based therapeutics. Nanoparticles have numerous benefits as therapeutic materials used for many human diseases as well as brain and retinal diseases. These nanomaterials through themselves exert therapeutic activities. Cerium oxide nanoparticles (nanoceria) are recognized to induce anti-inflammatory effects. Nanoneuromedicines are being established to growth drug penetration into locations of active microbial infection while preventive systemic toxicities. Adjunctive therapies are often used in combination with antimicrobials to diminish the inflammatory proceedings that contribute to CNS destruction and long-term damages associated by way of CNS infectious diseases; though, the greatoccurrence of adverse side effects with corticosteroids limits their usage.

Keywords: *Malignant tumors, CNS, ROS, Nanotherapeutics.*

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1. Introduction

Nanoparticles have numerous benefits as therapeutic materials used for many human diseases as well as brain and retinal diseases. Nanoparticles are a subtype of nanostructured materials applied in numerous zones [42, 44]. In adding, they can be used in different biomedical applications for instance medical diagnosis (biomarkers and imaging systems), regenerative medicine (nanostructured

bioreabsorbable implants and scaffolds, nanostructured coatings, biomanufacturing and bioprinting), drug delivery and antitumoral therapy (drug and gene delivery systems, hyperthermia) [81,110]. They can pass over biological barriers, particularly blood-neural barriers such as blood-brain barrier (BBB) and blood-retinal barrier (BRB) [54]. It is serious to advance modalities to improve bioavailability in target organs, the brain and the retina, in the improvement of therapeutic agents for brain and retinal diseases [84]. Simultaneously, as a novel drug delivery system, nanoparticles assistance therapeutic agents to stay lengthier in target tissues. Commonly, physicochemical properties of nanoparticles improve bioavailability of therapeutic agents afterward both systemic and local administration [30, 88]. Moreover, nanoparticles through themselves exert therapeutic activities. Cerium oxidenanoparticles (nanoceria) are recognized to induce anti-inflammatory effects [45]. Remarkably, inorganic nanoparticles for instance gold, silver, and silica nanospheres also demonstration "selftherapeutic" effects without surface modification [1,49]. Nervous system illnesses, due to degenerative disorders, infection or trauma, denote a important societal burden with equivalent broad unmet requirements. In most suitcases, recent treatments are simply inadequate to affect disease progression or even ameliorate symptoms and signs of brain injury or degeneration [32]. Important challenges abound and are related with the transport of therapeutic or imaging contrast agents across the blood–brain barrier (BBB) into the nervous system and retain the capability to achieve targeted delivery to suitable brain or spinal cord subregions [47].

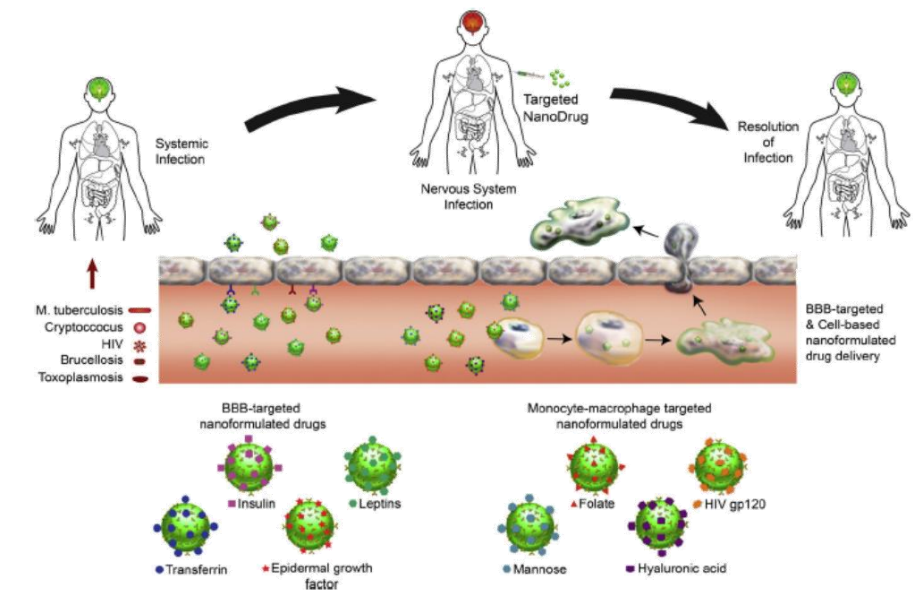

Fig.1. Targeted nanoformulated drug delivery for infectious diseases of the nervous system.

Nanoformulated antimicrobial drugs can be targeted to brain endothelial cell receptors such as insulin, leptin, transferrin and epidermal growth factor receptors

to promote transfer across the blood–brain barrier (BBB). They can also be targeted to monocyte-macrophage receptors such as folate, CD4, mannose and CD44 receptors to promote cell uptake for macrophage-based drug delivery across the BBB. The nanoformulated antimicrobial agent that is decorated with the appropriate ligand for the targeted cellular receptor can be administered systemically with the insurance it will find either a BBB-target cell or an appropriate carrier cell such as MPs that support transport across the BBB. Once inside the brain the drug cargo can be released from free nanoparticles or macrophages to facilitate resolution of microbial infection.

Nanoneuromedicines are being established to growth drug penetration into locations of active microbial infection while preventive systemic toxicities. Longer acting medicines would as well increase regimen adherence. Consequently, to simplify drug therapeutic efficiency using increasing pharmacokinetics and disease region-specific nervous system drug biodistribution as well as immune-directed microbial clearance finest defines the field of infectious disease-linked nanoneuromedicine [101]. The overarching aim is to actively target, and then abolish locations of insistent infection, inflammation or degeneration [68,57] currently, a number of nanomedicines were technologically advanced for the treatment, recognition and prevention of infectious diseases [10].

The CNS infections where nanomedicines are at this time being advanced consist of bacterial meningitis, rabies, malaria and HIV. Investigation is active in pattern of human disease and in translational investigation. For instance, treatment plans for Staphylococcus aureus and Cryptococcus neoformans meningitis in rabbits were effective with self-assembled cationic antimicrobial peptides of cholesterol-conjugate G3R6TAT [64,104].

Studies indicated that delivery of vancomycin into a drug-resistant S. aureus strain using a folic acid-conjugated chitosan nanocarrier enhanced delivery of the medicine, emphasizing the opinion which nanoparticle delivery could confidently affect treatment results for multidrug resistance in bacteria [103]. Advantage were realized with such an tactic in decreasing oxidative stress that tracks S. aureus infections. Actually, reduced lipid peroxidation, protein oxidation, nitrite generation, DNA hurt and glutathione were realized with the emergence of antioxidant enzymes. Adjunctive therapies are often used in combination with antimicrobials to diminish the inflammatory proceedings that contribute to CNS destruction and long-term damages associated by way of CNS infectious diseases [11,95]; though, the great occurrence of adverse side effects with corticosteroids limits their usage [24]. In a current research, nano-sterically stabilized liposomal constructions of the glucocorticoid β-methasone hemisuccinate were used in conjunction with artemisone to increase the efficiency of the antiplasmodial in an investigational mouse model of cerebral malaria with no glucocorticoid-related side effects. The use of nanoparticles for delivery of anti-inflammatory agents has also been described for Escherichia coli-induced meningitis [87] and revealed which a water-soluble malonic acid derivative of carboxy fullerene could diminish CNS stages of TNFα and IL-1β and prevent neutrophil infiltration across the BBB.

Nanoparticles have been technologically advanced for increase the immunogenicity and efficiency of vaccines against numerous CNS infectious diseases. A dendrimer DNA complex (dendriplex) using a plasmid vaccine construct of the rabies virus glycoprotein gene was complexed with a novel poly (ether imine) (PETIM) dendrimer and used to immunize mice that were subsequently challenged with a standard rabies virus strain [96]. Nanoparticle-based detection systems are being advanced to make available early and sensitive means for diagnosis in order to infectious disease. Initial diagnosis is censoriously significant for effective treatment of CNS infections. Reddy and coworkers newly defined the use of Au nanoparticles to improve recognition of meningococcal antigen by an acoustic wave immunosensor technique several nanoparticle-based approaches have also been defined for treatment of HIV infection in the CNS [82]. These notably contain drug polymer conjugates, dendrimers, micelles, liposomes, SLNs, nanosuspensions, polymeric nanoparticles and cell-mediated nanoparticle delivery [25].

2. Nanoparticles and brain diseases

Brain tumor

Such as in other organs, malignant tumors are one of the highest frequently studied target diseases of nanotherapeutics amongst brain diseases. Chiefly, various pathological mechanisms as well as reactive oxygen species (ROS), biological actions of growth factors, and signaling pathways of proliferative potentials could be addressed with nanoparticle-based therapeutics [3, 53]. Furthermore, double functions of nanoparticles in together imaging and therapy, so called theranostics, are still attractive notions [67]. A prominent features of nanoparticles is that it is possible to increase bioavailability of therapeutic agents in brain tumors by way of conjugation of specific ligands on the surface of nanoparticles which are loaded with therapeutic materials. BBB could be an difficulty to therapeutic agents along with toxic materials [56]. Bioavailability can be improved by ligand revision with peptides targeting cell surface receptors which are abundant in endothelial cells lining brain vasculatures, such as transferrin receptor and low-density lipoprotein receptor [58,115]. Therapeutic materials as well as conventional chemotherapeutic agents and minor interfering RNA could be loaded in nanoparticles. Furthermore, ligand adjusted nanoparticles develops cellular uptake of therapeutic materials into malignant tumor cells by conjugation with ligands which fix to surface molecules specific to glioma cells [31]. Packing with two or extra therapeutic materials into nanoparticles is also a plausible approach in the treatment of brain tumor [63].

Glioblastoma multiforme (GBM) accounts for approximately 50% of Reported malignant brain tumors. GBM is a prime tumor of astrocytes that, in spite of years of investigation, remains resistant to treatment even with improvements in surgical methods, neuroimaging, and adjuvant modalities for instance chemotherapy and radiation [6,48]. Clinical observations recommend that these tumors migrate by way of single cells, chiefly along white matter tracts [7, 105]. Conventionally, cancer cell migration has been evaluated using a Numeral

of two dimensional (2D) assays, such as the micro liter migration evaluate [34, 99] or the wound healing assay [99]. Though, these assays employ rigid plastic substrates that are far from the aligned nanofibrous topography features of white matter tracts. Particular to GBM migration, some brain mimetic hydrogels, as well as hyaluronic acid, have been working by ourselves [85] and others [2, 106, 46]. Polymeric electrospun nanofibers are substitute neural tissue engineering substrates [20, 33, 93, 107, 80] that have been used as conductors for neural reparation and regeneration [20,56,58] and substrates for Schwann cell maturation [17] and neural stem cell variation [18]. Ranged electrospun nanofibers are mostly fascinating as neural guides because of their topographical resemblance to white matter [38] Moreover, aligned electrospun nanofibers (i.e., poly(ε-caprolactone) (PCL)) reproduce the morphological and molecular signs of glioma migration ex vivo [35, 39]. These tunable materials have not been employed formerly to survey the character of microenvironment, specifically mechanics and chemistry, on GBM behaviors [83].

Neurodegenerative diseases, for instance Parkinson's, Huntington's and Alzheimer's diseases, are as well the aims of nanoparticle-based therapeutic methods. Equally tomalignant tumors, overcoming BBB is one of the reasons for the expenditure of nanoparticles in order to treatment of neurodegenerative diseases. Biomolecules such as nerve growth factor (NGF), thyrotropin-releasing hormone (TRH) brain-derived neurotrophic factor, and (TRH) brain-derived neurotrophic factor exert neuroprotective special effects, but then are limited in the biological motion for the reason that they are quickly metabolized in systemic circulation and could not overcome BBB. Nanoparticle-based Tactics open the chance for these molecules in the treatment of neurodegenerative diseases [50,91]. Intravenous administration of NGF-containing poly (butyl cyanoacrylate) nanoparticles covered with polysorbate 80 reveals the effective transference of NGF across the BBB [50]. Polysorbate 80 coating is instrument aimed at targeting of therapeutic nanoparticles to brain. In a recent study use of biodegradable nanoparticles, anticonvulsant effects of TRH are detected with intranasal delivery of TRH-loaded polyactide nanoparticles even lacking surface revision with particular ligands [100]. Similarly, poly(lactic-co-glycolic) acid (PLGA) nanoparticles improves brain delivery of nicotine, which make available neuroprotection in contrast to ROS-induced parkinsonism [86]. Furthermore, ligand modification with lactoferrin, of which receptor is extremely articulated in neurons, can be approach to rise the focuses of therapeutic agents in the brain [66].

Ischemic damage in the brain might take profits from the improvement of suitable nanotherapeutics. Overcoming pathological happening srelated with reperfusion is the concentration of the advance of therapeutic agents for ischemic stroke. In this context, investigates have been accomplished to increase the bioavailability of antioxidant molecules and to study the antioxidant effects of nanoparticles by themselves [4,98,109]. Dendrigraft poly-L-lysine nanoparticles conjugated with dermorphin, a μ-opiate receptor-specific heptapeptide, increases the delivery of short hairpin RNA targeting apoptosis signal-regulating kinase 1, that is complicated in oxidative stress, to the brain with intravenous administration

[5]. Similarly, PLGA nanoparticles including superoxide dismutase, one of antioxidants, also exposed localization in the brain, decrease infarction volume, and enhanced behavior in mice with cerebral ischemia-reperfusion injury [109]. Another interesting part regarding therapeutic. Potential of nanoparticles is that they use therapeutic actions by themselves without surface modification. 3 nm-sized platinum nanoparticles and nanoceria determine protecting effects on ischemic cell death in mice [59, 98]. These methods demonstrate the therapeutic potential of nanoparticle-based therapeutics in the treatment of numerous brain diseases.

Nanoparticles and retinal diseases

Based on BRB, containing of retinal endothelial cells and pigment epithelial cells, it is tough for systemically injected therapeutic agents to influence the retina at in effect deliberations. In this context, the possible of nanoparticles has been considered in a sequence of papers. Formerly were studied therapeutic efforts using nanoparticles in the treatment of retinal diseases [40]. Equally in brain diseases, the delivery of therapeutic genetic material is one of approaches in the management of retinal degeneration in numerous degenerative diseases as well as retinitis pigmentosa and Stargardt disease. For instance, subretinal injection of DNA compacted nanoparticles proficiently induces gene expression in retinal neuronal cells and Slows degenerative variations in mice with a haploinsufficiency mutation in the retinal degeneration slow gene [12].

A dissimilar method is the use of nanoceria in the treatment of retinal degeneration [14,16]. By way of scavenging ROS, nanoceria down-regulate the status of oxidative stress in the retina and stop pathological variations induced by degeneration of photoreceptor cells. Additionally, they apply anti-angiogenic influence on pathological retinal angiogenesis with parallel mechanisms [13,51]. The further noticeable anti-angiogenic effects of nanoparticles by themselves arisen from inorganic nanoparticles for instance gold, silver, silica, and titanium dioxide nanoparticles. Fascinatingly, like anti-angiogenic effects of inorganic nanospheres have been frequently reported from numerous investigation groups [36, 37, 52, 46, 49, 74, 76]. Particularly, have been detected anti-angiogenic special effects of inorganic nanospheres on choroidal and retinal neovascularization, that is involved in the improvement of vision-threatening complaints counting age-related macular degeneration, diabetic retinopathy, and retinopathy of prematurity with in travitreous injection, local administration of nanoparticles into the vitreous cavity of the eye [36, 37, 46, 52]. There are also temporary methods using nanoparticles by way of drug carriers containing therapeutic peptides, genetic materials, and presently used anti-VEGF monoclonal antibody [55, 62, 66, 89].

These method simproves the delivery of therapeutic materials to the retina and more the concentrations of pathological events, choroidal and retinal neovascularization. The other target disease of nanotherapeutics in the eye is uveitis, an inflammatory disease in uveal tissues such as iris, biliary body, and choroid [40]. Uveitis is categorized by chronic clinical progresses. Hence, prolonged administration of therapeutic agents is one of aims in the treatment of

uveitis for the conquest of chronic inflammation. Mutually poly (lactic acid) nanoparticles containing betamethasone phosphate and polyethylene glycol (PEG) nanoparticles loaded with tamoxifen effectively suppress the inflammatory variations in mice with experimental autoimmune uveitis and preserve the focuses of therapeutic materials for prolonged times [22, 90].

Nanotechnology-guided treatment of retinal vascular disease

Ocular neovascularization

A chief pathologic target for therapy in retinal vascular diseases for instance neovascular (‘‘wet’’) AMD and proliferative diabetic retinopathy take in the unusual growing of blood vessels (‘‘ocular neovascularization’’), that can interrupt and harm retinal construction and cause vision damage. Anti- vascular endothelial growth factor (VEGF) treatments, while effective in a significant number of patients, still do not stop the progress to legal blindness in various patients [9]. Additionally, treatment using anti-VEGF therapies needsonce-a-month intraocular injections and might have side effects throughout the body. Nonetheless, these vessel growth-arresting therapies keep on a frontline approach in several diseases and nanomedicine has the potential to increase upon the clinical results using this method. Potential benefits of nanoengineering of anti-VEGF therapies may contain condensed dosing regularity and preservation of anti-VEGF drugs at a therapeutically-effective dose for a extended dated of time at the disease site, using plans based upon sustained release nanoparticles.

For instance, Yandrapu et al. advanced a technology fin order to encapsulation of nanoparticles in porous microparticles (NPinPMP) for the sustained release of the anti-VEGF antibody bevacizumab [108]. This strategy involves the encapsulation of poly lactic acid (PLA) nanoparticles coated with bevacizumab within porous sustained release poly lactic co-glycolic acid (PLGA) nanoparticles. This drug delivery approach enabled sustained release of anti-VEGF for a number of months in rat models, which has significant implications for decreasing injection incidence in patients. Equally, polymers containing of polycaprolact one dimethacrylate (PCM) and poly hydroxyethyl methacrylate (poly HEMA) showed sustained release of bevacizumab ranging up to 4 months in rabbit models [97]. These kinds of polymeric systems offer fascinating benefits of being injectable as a liquid through the needle, then gelling (either naturally or via a light-activated stimulus, depending on polymers used) in situ within intraocular compartments, enabling sustained depot release of drug over weeks to months.

Nanotechnologies as well enable sustained release and improved bioavailability of small molecules related to the treatment of ocular neovascularization. New dipeptide based nanotubes comprised of phenylalanine and a,b-dehydrophenylalanine were presented to be effective vehicles for the sustained intravitreal delivery of pazopanib, a small molecule inhibitor of receptor tyrosine kinase intricate in the intracellular signaling of VEGF and a figure of other growth factors involved in ocular neovascularization [75]. Nanoparticles based on polylactic acid (PLA) and polyethylene oxide (PEO) were revealed to enter retina and localize within RPE, and were accomplished of sustained release

of integrin antagonists for therapy of choroidal neovascularization (CNV) [60]. If these nanomedicine-based methods can be effectively translated, sustained release of anti-VEGF and further anti-angiogenic therapies in patients at a therapeutically-relevant concentration possibly will increase results while minimizing dosage intervals. Polymers for instance PLA, PLGA, and PEO or PEG are previously incorporated within a number of FDA approved drug formulations, thus their continued incorporation into drug delivery systems for clinical applications is expected. As an alternate to sustained delivery of anti-angiogenic therapies in the eye, technologies for targeting gene therapies to particular locations of ocular neovascularization can be utilized. As an example, Luo et al. developed PLGA nanoparticles that were surface functionalized with RGD peptide for the targeted delivery of recombinant Flt23k intraceptor plasmid to prevent progress of CNV lesions in primate and murine AMD models upon intravenous administration (Fig. 2) [61].

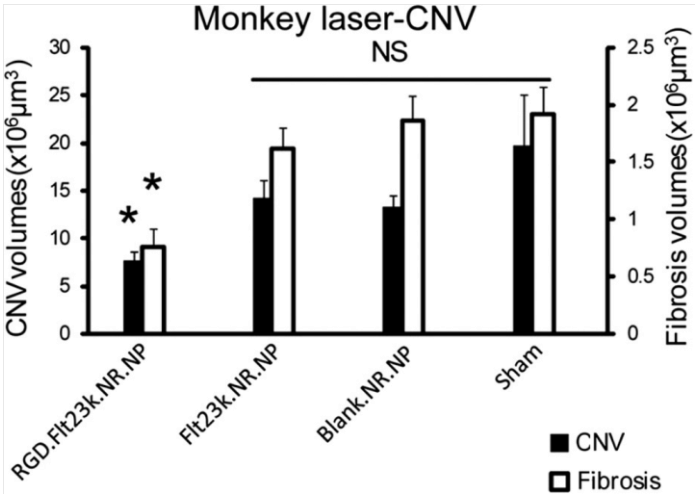

Fig. 2. Targeted therapy of CNV lesions using RGD-targeted nanoparticles. In a monkey model of laser induced CNV, RGD targeted nanoparticles loaded with Flt23k intraceptor plasmid suppressed CNV formation (perlecan staining) and fibrosis (collagen I staining) 4 weeks following a single intravenous injection of nanoparticles. Reproduced with permission from [61].

RGD motifs fix to integrin receptors which are up regulated in ocular neovascularization [28]. Flt23k intraceptor binds to VEGF and sequesters it in the endoplasmic reticulum for effective inhibition. Long-lasting gene therapies delivered systemically have the potential benefit of removing the requirement for intraocular injections, and also decreasing dosing regularity as the therapeutic period of gene therapies may be longer compared to small molecules or antibodies. Additionally these forms of targeting plans enable confinement of therapy to where it is wanted in the retina, that is significant given the opportunity of off-target effects and toxicity related with anti-VEGF administration [92, 94]. Similarly, gene therapies encoding short hairpin RNAs (shRNA) and delivered using nanoparticles are as well promising for clinical translation. As a current sample, PLGA nanoparticles encapsulating a plasmid containing VEGF-A shRNA

were also revealed to be efficacious in regression of murine corneal vascularization [78].

Alternatively, small interfering RNA (siRNA) therapies can be delivered to the retina for relatively transient but potent inhibition of neovascularization. Newly, Zhang et al. used a PEGylated liposome-protamine-hyaluronic acid nanoparticle system formerly advanced to deliver siRNA targeting the VEGFR1 mRNA to RPE cells and a laser induced murine CNV model [69]. SiRNA is professionally encapsulated by these nanoparticulate formulations, and CNV was inhibited significantly compared to control vehicles and naked siRNA. Synthetic gene therapy vehicles have tough potential for translation; gene therapy vectors such as nanoparticles based on poly-lysine compaction of DNA are well-tolerated by way of the retina [23]. Moreover, protamine is a naturally occurring polycation and hyaluronic acid is a polyanionic polysaccharide, and neither polymer exhibits toxicity as proved by preclinical studies. Though, extensive clinical studies are warranted to confirm this observation [29].

Nanoparticle systems for ocular gene therapy

Gene therapy that can be well-defined as the transmission of nucleic acids into a cell, tissue or organ [102] eventually goals to treat the source rather than the symptoms of a disease. This can either happen by the introduction of corrective genes into cells or by blocking malfunctioning genes using RNA interference mechanisms. Though, the absence of effective and harmless viral and non-viral delivery systems has posed substantial difficulties for gene therapy applications in the previous. At this point, non-viral nanoparticles can extremely help not merely to compact the DNA but also to protect it and effectively deliver it to the target tissue.

The eye is an idyllic candidate for gene therapy especially in the context of intravitreal injections because of numerous outstanding structures. First of all, it's extremely compartmentalized anatomy allows precise delivery of nanoparticle vectors into specific tissues in the eye, which concomitantly minimizes systemic dissemination. Second of all ,meanwhile the ocular tissue contains of a stable population of cells, extremely efficient transduction with suitable longevity can be expected [5]. And the last but not the least, due to the eye's immune privilege, an immunogenic reaction can be typically avoided [8]. For ocular applications, a number of different modalities of gene Therapy and gene delivery have been examined for the nanoparticle-based treatment of choroidaland retinal neovascularizations [26, 27, 41, 43, 71, 111, 112, 113, 114].

In one methods, gene therapy has been mostly used tomodify the expression of VEGF, the important regulator of angiogenesis and vascular permeability. The two greatest noticeable strategies used were increasing the expression of VEGF-capturing molecules or anti-angiogenic factors or directly decreasing the VEGF expression or manipulating VEGF-signaling cascades. One of the major cases of nanomaterial-based intraocular gene therapy to reduction the VEGF expression was demonstrated by Marano and coworkers closely 10 years ago. By synthesizing a lipid-lysine dendrimer they were able to deliver a sense oligonucleotide with anti-VEGF activity into the choroidal lesions. Interestingly,

eyes that were subject to photocoagulation two months after intravitreal injection of the dendrimer oligonucleotide complex still displayed smaller CNV areas, demonstrating the longevity of the anti-CNV activity [72]. The complexes not only inhibited CNV advance for numerous months, but were also found through the whole retina up to the RPE and showed no apparent toxicity [79]. Similarly, PEGylated cationic liposomes loaded with small interfering RNA (siRNA) targeted to VEGF receptor 1 mRNA lowered the CNV area after intravitreal injection [70]. In order to delivery of plasmids encoding anti-angiogenic proteins, nanoparticles made of FDA-approved PLGA have been greatest widely examined for ocular applications. Such as polyesters, PLGA nanoparticles are biodegradable. After injection, they experience hydrolysis and release their payload in a sustained fashion [77].

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