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A REVIEW ON CLEARING THE PATH: OVERCOMING BARRIERS IN OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

Ocular drug delivery remains significant challenges due to the unique anatomy and physiology of the eye, which limits drug penetration and bioavailability. It has numerous barriers the major barriers includes the precorneal tear flim, corneal epithelium, conjunctival clearance, blood-aqueous barrier and blood-retinal barrier. These protective mechanisms restrict drug absorption necessary for frequent dosing and leading to suboptimal therapeutic outcomes. The metabolism of cornea and lens and regulation of intra-ocular fluids are directly influenced by blood-aqueous barrier. It includes various routes of adminstration in ocular drug delivery system as topical (eye drops) intraviteral, periocular and systemic drug delivery system enhance the drug penetration. This review mainly explores the advantages, disadvantages and application various field that improved bioavailability, sustained drug release, enhanced permeation and has mainly influenced targeted therapy. The articles provides an overview of ocular drug delivery.

KEYWORDS

Posterior segment, Lacrimal fiuid, Visual function, Gelatinoids structure and Periocular route.

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INTRODUCTION

The eyes is complex organ with unit anatomy and physiology the structure of the eye is divided into the two parts of mainly anterior and posterior segment of the eye. The anterior segment of the eye is located in front of the vitreous humor[1]. The posterior segment of the eye is located behind the lens. This defense system is further assisted by enzymes example, sclera, retinal etc[2]. The eye contains multible number of neurons and has light sensitive along with pigmented epithelial cells with

choroid and capillaries. One of the main approches consist of more efficient routes of ocular drug delivery system. The future investigation of novel drug delivery system capable of better targeted and controll therapy[3]. Furthermore, vision impairment is also related to aging, diabetes, and fungal, infection. Examples of ocular diseases include age - related macular degeneration (AMD), diabetic retinopathy (DR), retinoblastoma and fungal keratitis. Ocular gels and ointments (semi-solid) could significantly enhance resisdence time. Solid dosage forms could be used to deliver water - sensitive drugs (powder), provide zero order release model (insert), or sustain resisdence time (therapeutic contact lens). There are many approaches for characterization such as visual appearance, stability, size, zeta potential, possible interactions. pH measurement and other important *ex vivo* and *in vivo* evaluation[4]. Options available include modifying the formulation (suspensions, emulsions, hydrogels), inserting reservoirs of active products (inserts, micro-polymer systems, liposomes), increasing tissue permeability by iontophoresis or using substances known as penetration enhancers or absorption promoters[5].

BARRIERS OF OCULAR DRUG DELIVERY SYSTEM

LACRIMAL FLUID -EYE BARRIERS

Absorption of the drug from the lacrimal fluid can be limited by corneal epithelium present in the eye. Tight junction formed from corneal epithelium as a limited permeation of the drug. The permeation of the drug as a various classification is hydrophilic and liphophilic drugs[6]. The lipophilic drug has higher permeation of drug compared with hydrophilic. Continuous renewal of lacrimal fluid helps to maintaining eye hydration, preventing pathogens or dust from the eye. It is to maintain effective drug activity, resisdence time of administrated and attained the sustained release of drug with different mechanism[4]. Corneal epithelium as the limited absorbtion of the eye. Drug absorbtion across the bulbar conjunctiva is also fairly permeable to the hydrophilic molecules therefore route of absorption for a larger bio-organic compounds such as protein and peptides. It has two membranes passive and active the passive extensively investigated but active is sparsely studies[7]. It was shown in the (Figure No.1: Lacrimal fluid of the eye barriers).

BLOOD OCULAR BARRIERS

The blood-ocular barriers systemic formed by two main barriers: the blood aqueous barriers and blood retinal barriers. The blood ocular barrier has the limiting membrane of the retina, the vessels of the choroid, retinal pigment epithelium. The blood aqueous barrier as blood vessels of the ciliary body, ciliary epithelium, Iridial epithelium, vessels of Iris[8]. The blood ocular barriers clinical studies have made it possible to clarify and expand the concept of the blood - ocular barrier, including the blood-tissue system, as well as to talk about the existence of its three components in norm and pathology: iridociliary, chorioretinal and papillary. The blood-ocular barrier provides ophthalmic homeostasis in normal operation. Throughout its entire length, the blood- ocular barrier is not a single structure[9]. Aqueous humor is secreted into the posterior chamber by ciliary processes where it flows through the pupil into anterior chamber and leaves the eye by bulk flow at the chamber of trabecular or uveoscleral routes. In blood- retinal barriers only few important metabolites are allowed and it is responsible for homeostasis of the neuroretina[10]. New perspectives on the clinical significance of breakdown of the blood-retinal barrier are responsible for glucose transport in diabetes and drug delivery to the retina can improved by blood-retinal barrier permeability, chemical modification of the drug for better blood-retinal barrier penetration and liposome encapsulation[11]. It was shown on the (Figure No.2: Blood ocular barriers).

VITREOUS OCULAR BARRIERS

The vitreous body appears as a gelatinous structure (98-99% water) filling the space between the lens and the retina called vitreous chamber. The vitreous ocular barrier refers to the role of the vitreous

humor in regulating the movement of substances between the anterior and posterior segment of the eye it also involves in drug diffusion, immune responses and disease progression within the eye[12]. The ideal vitreous substitute should mimic all positive qualities of the vitreous body (transparency, elasticity, buffer capacity and biocompability with neighboring tissues) and avoid some of the negative properties associated with the native substance such as liquefaction and biodegrtation. Then high water content of the vitreous led many clinicians to believe that the vitreous plays a relatively minor role, most vitreous substitutes are currently used to maintain intraocular pressure and the biomechanical and optical properties of the vitreous space[13]. The natural vitreous body is a transparent, gelatinoids structure occupying four - fifths of the volume of the eye. Although the several vitreous substitutes available include inert gas, silicone oil, heavy silicone oil and hydrogels, to date, octafluoropropane and sulfur hexafluoride, are the most commonly used in clinics[14]. It was shown on the (Figure No.3: Vitreous ocular barriers).

CORNEAL BARRIERS

The ocular surface is a mucosal structure directly exposed to a great variety of environmental agents, some of the noxious, such as pathogens, allergens or irritants. An altered corneal epithelium result in a vulnerable cornea and it is a frequently associated with an increased risk of sterile or infectious corneal ulceration or persistent epithelial defects for instance[15]. Altered corneal epithelial barrier function is the cause for ocular irritation and visual morbidity in dry eye disease. This appears to be because of accelerated loss of tight junction bearing superficial corneal epithelial cells, perhaps by proteolytic cleavage of occludin[16]. Corneal epithelium function as a barrier that separates the eye from the outside environment. Zonula occludens or tight junction encircle the cells just below the apical surface and constitute the principle barrier to passive movement of fluids, electrolytes[17]. To maintain a smooth optical surface, corneal epithelium has to continuously renew itself to function as a barrier so that it protects the eye from various environmental insults. The adult corneal epithelium is maintained homeostatically by an integrated process of cell proliferation, migration, differntiation, stratification and desquamation\ apoptosis[18]. It was shown on the (Figure No.4: Corneal barriers).

TEAR FILM BARRIER

The tear flim barrier is a thin, multi-layered structure covering the surface of the eye. It plays a crucial role in maintaining eye health by providing lubrication, protecting against infection and ensuring clear vision. Althogh tear substitutes have been historically used to provide eye lubrication to the ocular surface, in dry eye disease (DED). Tear substitutes are electrolites solution consisting of different buffers and with widely different properties of the types of preservatives, viscosity and p^H of colour surface[19]. Common feature of DES include ocular surface epitheliopathy, tear hyperosmolality, an unstable preocular tear film, varying degrees of inflammation and symptoms of ocular irritation. The preocular tear film has trationally been described as a trilaminar structure, predominantly consisting of a watery aqueous phase, overlying a thin mucous layer, with a superficial coating of liquid. Early estimates of tear film thickness were based on invasive tests, such as placing glass fibres against the cornea, measuring fluorescence after instilling fluorescein[20]. It was shown on the (Figure No.5: Tear flim barriers).

ROUTES OF OCULAR DRUG DELIVERY SYSTEM

TOPICAL ROUTE

The topical application of drugs is the most common method of drug delivery for the treatement, of opthalmic ailments. They are of sufficient flexibility to allow synthesis in various sizes and can be formulated as eye drops, gels and ointments for for topical delivery. However the conventional liposomes had the disadvantage of being unstable, getting aggreated and were

susceptible to phagocytosis[21]. When the focus treatement is the anterior segment of the eye, such as the inner cornea or the aqueous humour, the layers of the cornea, in particular the outermost, called the epithelium, hinder drug penetration, therapy, local bioavailability of the drug decrease. Thus it is necessary to administer high concentration of the drug therapy, many systemic side effects, are generated[22]. It was shown on the (Figure No.6 Topical route). Topical eye drop is the most convenient and also used in smart drug delivery system drug formulation that release medication in environmental condition such as p^H, or temperature changes[23].

INTRAVITREAL OR INTRAOCULAR ROUTE

Intravitreal injection (IVI) is a key method for delivering drug directly into the vitreous humor of the eye, commonly used to treat retinal disease it has been increasingly in opthalmology it has various techniques for intravitreal injection and it is safe and effective techniques for ocular drug delivery[24]. The main advantages of intravitreal injection immediate drug release and increased therapeutic dose and injection of the drug through vitreous cavity. Intraviteral injection plays a critical role in opthalmic practices and has targeted delivery with high concentration at the retina and choroid[25]. It was shown on the (Figure No.7: Intravitreal or intraocular route). It has more complications and has some potential risk like endophthalmitis, vitreous hemorrhage and cataract formation but it improve the safety and efficacy of the drug[26].

PERIOCULAR ROUTE

Drug delivery to the posterior segment of the eye is useful in treating various disorders. Including degenerative, vascular and proliferative disorders. Systemically administered therapeutic agents reach the retina to a limited extent due to the presence of blood - ocular barriers, which include the blood - aqueous and blood - retinal barriers. If a drug administered by the routes, it can be delivered to the sclera, chroid, retinal pigment epithelium, neural retina and vitreous in that order. As the routes are showing promise for retinal delivery of some drugs, the following discussion provides a description of the methods of administration, pharmacokinetics, mechanisms of delivery, sustained - release systems and pharmacodynamics for periocularly administered drugs[27]. It was shown on the (Figure No.8: Periocular route). Periocular injections of some drug have commonly used to treate ocular inflammatory conditions and ocular surgery this injection delivered drug to the vitreous body on the aqueous humor[28].

SYSTEMIC ROUTE

The systemic route in ocular drug delivery refers as an administration of the drug through oral or intravenous (IV) routes to reach ocular tissues through systemic circulation. Common barriers to the systemic delivery of ophthalmic drugs are blood-aqueous barrier and blood-retinal barrier (BRB) for the anterior segment and posterior segments of eye respectively.The drug is administrated in oral, IV, IM, SC. Drug enter into the aqueous humor and penetrate the membrane. It gives the therapeutic action for glaucoma, diabetic retinopathy and optic neuritis[29]. It was shown on the (Figure No.9: Systemic route).

TRANSSCLERAL ROUTE

Transscleral is a non invensive method which have weak electric current used to penetrate charged molecules into percutaneous tissue transscleral barriers have the drug molecules have cross the several layer of tissue and increases the bioavailability of the drug with high dose frequency very effectively. It was shown on the (Figure No.10: Transscleral route). Transscleral injection is a method of delivery in the drug by passing the cornea and directly introduce in the sclera for treating the posterior segment high disease but it as limited permeability with high drug clearnce but it extensively used in gene and nano particle delivery etc[30].

Table No.1: Advantage, disadvantage and application of lacrimal fluid of eye barriers

S.No	Advantage	Disadvantage	Application
1	Nutrient supply	Rapid drug elimination	Lubrication and cleansing
2	Waste removal	Poor retention time	Antimicrobial defense
3	Healing and regeneration	Limited bioavailability	Smooth optical surface

Table No.2: Advantage, Disadvantage and application of Blood ocular barriers

S.No	Advantages	Disadvantages	Application
1	Maintain homeostasis	Delayed response to systemic infection	Stem cell therapy and gene editing
2	Prevents immune overreaction	Difficulties in treat retinal disorders	Prodrug and permeability enhancers
3	Preserves visual function	Compromised barrier in disease	Nanotechnology and drug carriers

Table No.3: Advantage, Disadvantage and application of Vitreous ocular barriers

S.No	Advantage	Disadvantage	Application
1	Barrier function	Very short duration of refractive index	Monitoring disease biomarkers
2	Maintaining eye shape and function	Only approved reactivity	Developing new therapies
3	Role in oxygen metabolism	Low interfaciation	Nonviral gene therapy

Table No.4: Advantage, Disadvantage and application of corneal barriers

S.No	Advantage	Disadvantage	Application
1	High optical clarity	Prone to injury	Vision correction surgery
2	Fast healing	Corneal disease	Contact lences
3	No blood vessels	Risk in surgical procedure	Drug delivery

Table no.5: Advantage, Disadvantage and application of Tear film barriers

S.No	Advantage	Disadvantage	Application
1	Nutrient supply	Evaporation issues	Contact lens design
2	Optical clarity	Tear film imbalance	Dry eye treatements
3	Waste removal	Tear film breakup	Ocular disease diagnosis

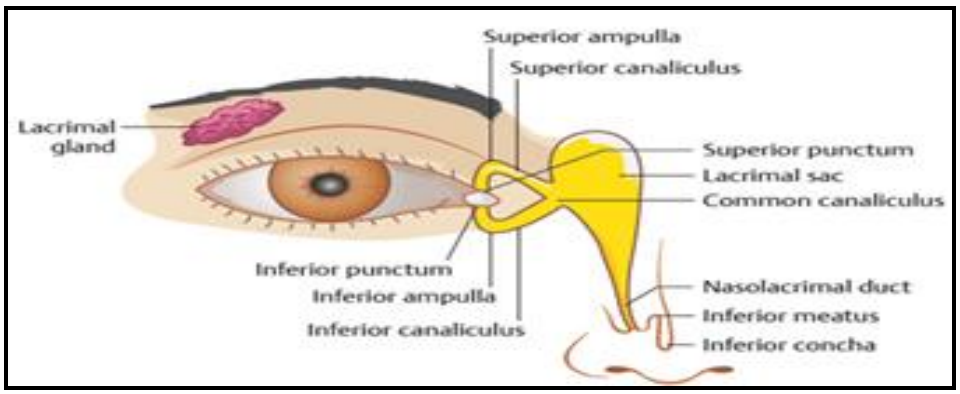

Figure No.1: Lacrimal fluid - Eye barriers

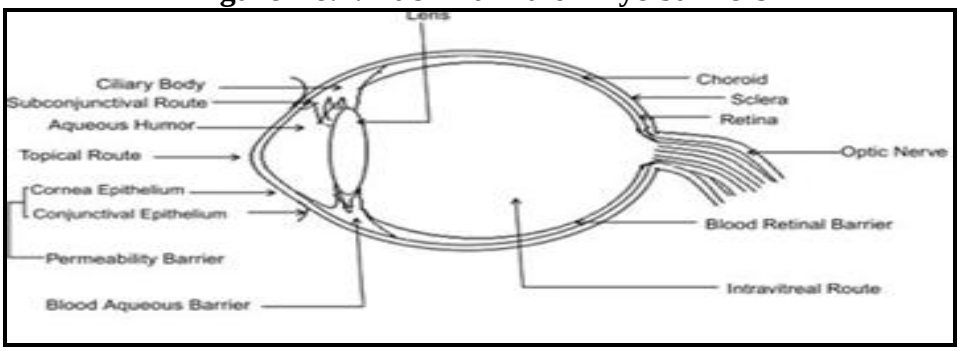

Figure No.2: Blood ocular barriers

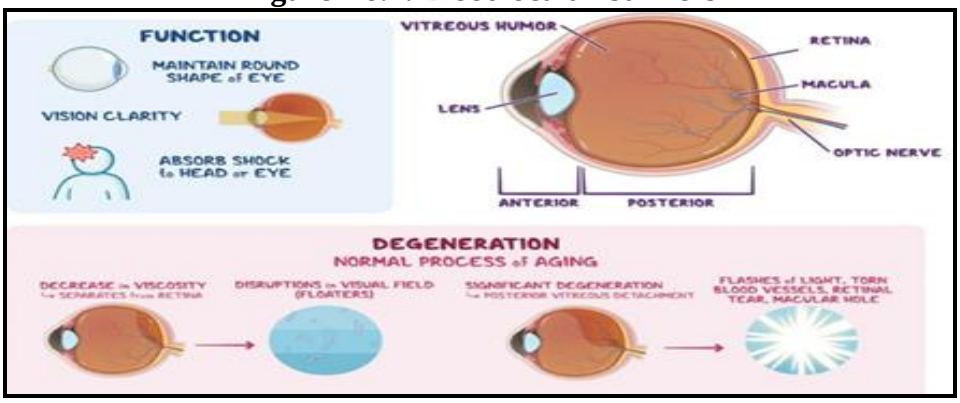

Figure No.3: Vitreous ocular barriers

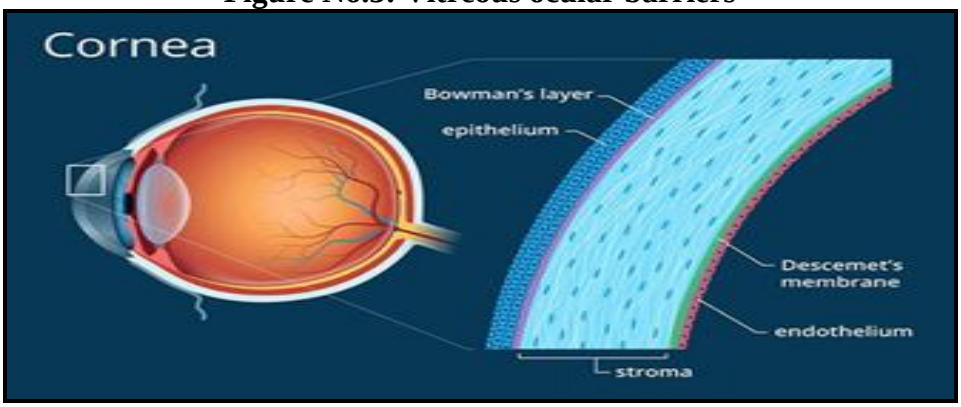

Figure No.4: Corneal barriers

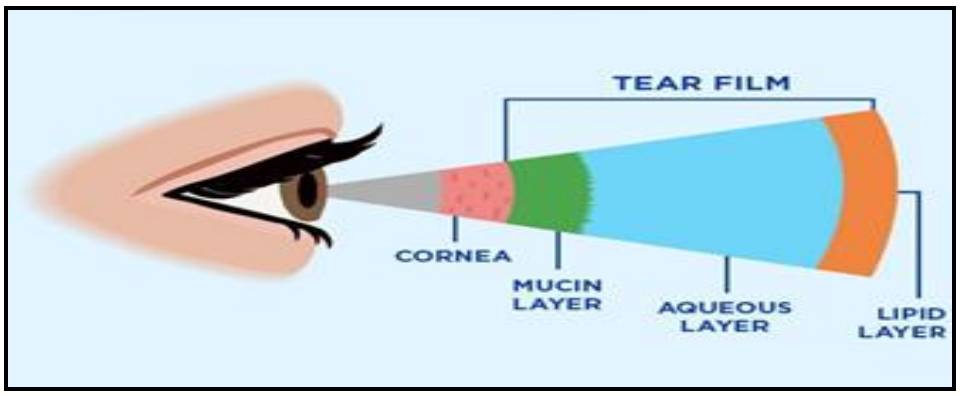

Figure No.5: Tear film barriers

Figure No.6: Topical route

Figure No.7: Intravitreal or Intraocular route

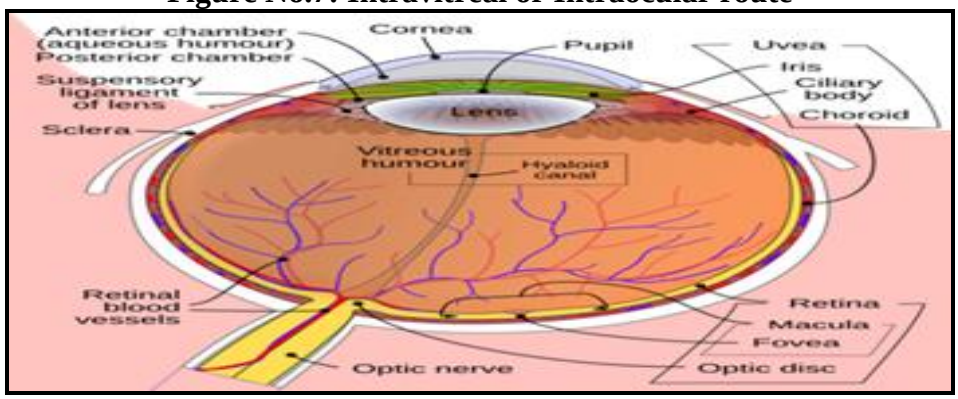

Figure No.8: Periocular route

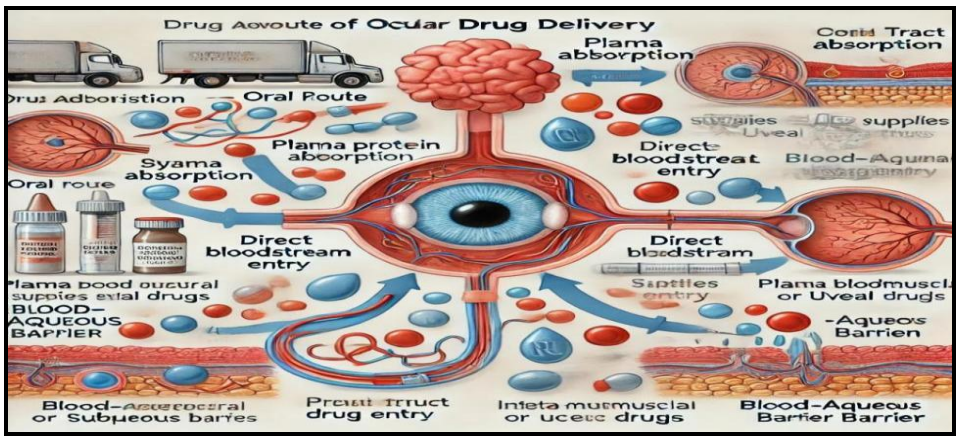

Figure No.9: Systemic route

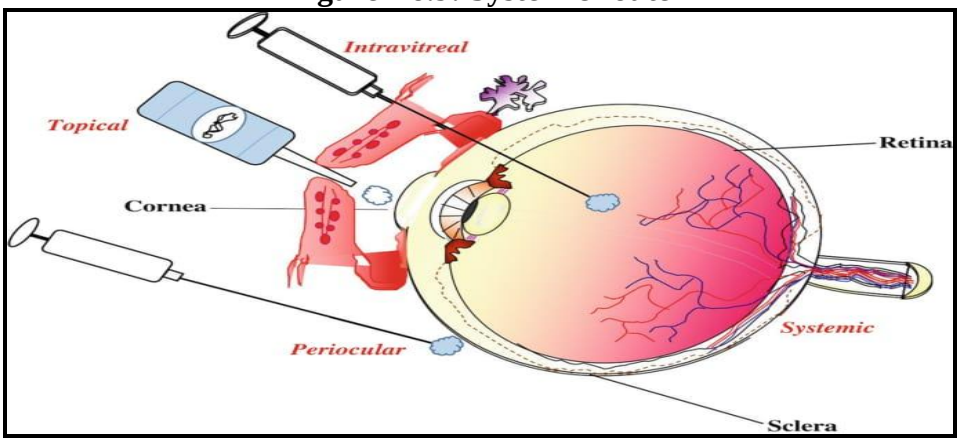

Figure No.10: Transscleral route

CONCLUSION

Here to conclude the efficacy of drug delivery system of ocular with various routes of administration like topical, systemic, periocular, trans scleral route. Some of the barriers have the high permeability of drug through the circulation. Administration of drugs have the conventional formulation with different carriers of ocular drug delivery because it has both anterior and posterior segment for delivery the therapeutic effect of drug levels. This review examined the more widely studied strategies that have used to improve the bioavailability of drug through various routes. The potential for physical methods to improve drug permeation together and easy to use in non-invasive method and increases the delivery in posterior segment of the eye.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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