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(54) Title: METHOD AND MEANS FOR PREVENTING SECONDARY CATARACT

(57) Abstract

Method and means for extracapsular cataract extraction with or without posterior chamber intraocular lens implantation comprising chemical modification of the posterior surface of the lens capsule, at least in the optical portion of said capsule, for preventing cell attachment and growth.

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Method and means for preventing secondary cataract.

The present invention is related to the field of ophthalmology and more specifically to methods and means for preventing secondary cataract, a longterm complication after extracapsular cataract extraction with or without intraocular lens implantation.

A great number of intraocular lens (IOL) models have been developed and tested over the years and these as well as the techniques for implantation have been improved so that extracapsular cataract extraction with intraocular lens implantation are now well established procedures with a high success rate. Opacification of the posterior capsule in the optical axis is however still a significant longterm complication, reported to occur in about 50% of the cases after two to five years. This condition is often referred to as secondary cataract or after-cataract.

The risk for opacification seems to be less pronounced with older patients and young age is considered to be the most significant risk factor. It is also to be noticed that even if a surgeon routinely uses a particular implantation technique and the same IOL type, the results might differ in a quite unpredictable way. Very good results with no opacification are obtained in some patients while others, operated under similar conditions, suffer from severe opacification. Prevention of opacification is accordingly of great importance in order to improve the long term outcome of cataract surgery.

A number of techniques for preventing secondary cataract have been tested over the years, both with regard to the IOL as such and the technique used for surgery. One such example is the barrier ridge IOL described by Hoffer (US 4244060). One aim of this design was to create a mechanical barrier to inhibit migration of residual lens epithelial cells and their derivatives into the optical zone behind the IOL.

Secondary cataract is treated by making an opening in the opcified posterior len capsule. This opening is today usually made with a NdYag laser. A laser beam is shot through the pupil

and the IOL and focused on the posterior lens capsule. Several complications have been observed with this method which is reported to increase the incidence of retinal detachment and cystoid macular oedema.

One object of the present invention is to provide an improved method for preventing opacification in connection with extracapsular cataract extraction and intraocular lens implantation, by chemical modification of the posterior capsule wall in order to decrease adhesion and proliferation of cells. Another object is to provide means for such modification.

Surface modification of devices for implantation in general, in order to provide a surface with desired cell interaction characteristics, has been utilised for a long time. In certain applications the aim is to completely avoid cell attachment, while good cell attachment and growth is essential for good results in other applications. Hydrophilic as well as hydrophobic surfaces have been developed for this reason and there are also examples when the surface has been modified chemically with positive charges and various other functional groups in order to increase cell adhesion. Various heparin coatings, frequently used when preparing catheters of various kinds for insertion, are examples of hydrophilic surface modifications having very specific biological activity. Other examples of compounds also giving very hydrophilic surfaces are polyethylene glycol (PEG), dextran and phosphatidyl choline. The unique properties regarding protein/cell rejection of a PEG coated surface have been explained by an extensive hydration of the surface layer in the aqueous phase, which gives rise to a steric repulsion force between the very mobile PEG-molecules and components outside the surface such as proteins and cells. Hydrophobic surfaces utilized in certain connections have been obtained by applying a layer of for instance silicone or a tetrafluoroethylene polymer (Teflon).

There are only a few publications, as far as we know, which are related to surface modifications of living tissue. In one such example (Pathak C.P., Sawhney A.S., Dunn R.C. and Hubbel J.A. Fourth World Biomaterial Congress Berlin 1992 Transactions and final program p.231) rat cecum and rabbit

uterine horn were modified with a biodegradable hydrogel (polyethylene glycol glycolidyl diacrylate). The surfaces of the tissues were reported not to be biologically adhesive and formed a biocompatible mechanical barrier to prevent adhesions.

Modification of the lens capsule of the eye according to the present invention is characterized by chemical modification of the capsule, resulting in a stable deposit which for instance can be covalently linked to chemical groups in the tissue or forming an interpenetrating network with the lens capsule tissue. Polymers can also have particular structures with adhesive properties like the 2,3-dihydroxyphenylalanine-rich polyphenolic protein secreted by the marine mussel Mytilus Eulis (Waite J.H., Chem.Tech. Nov.1987 p. 692-697) and polymers containing the RGD peptide sequence (Piersbacher, M.D and Ruoslahti, E., Nature 1984, **309**, 30-33) would also show affinity for tissue.

The stable or permanent layer that is created in accordance with this invention is water-insoluble and is clearly distinguished from the temporary layer that is created when for example hyaluronic acid is injected into the capsule in connection with implantation of an intraocular lens.

In one embodiment of the invention polymers, for example polyethylene glycol (PEG), polysaccharides, polyethylenepolypropylene glycol (poloxamer, i.e. Pluronic and Synperonic),and polyvinyl alcohols or derivatives of these are further derivatized to contain functional or active groups which are used for grafting, crosslinking or polymerizing the macromonomer onto the tissue.

Derivatives useful in this connection include those reacting with carboxylic groups, hydroxyl groups, amino groups or thiol groups of proteins in the lens capsule tissue. As examples of such derivatives can be mentioned aldehydes, anhydrides, activated esters such as: (alkyl-oxy-formyl) carboxylates, nitrophenyl carbonate esters, carboxylate succinimidyl esters, carbonate succinimidyl ester, carboxylate p-nitrophenyl ester, oxycarbonylimidazole, trifluoro acetates; alkyl and arylsulfonates such as toluene sulfonates, methyl sulfonates, trifluoroethyl sulfonates; carboxymethyl hydrazides

that upon treatment with nitrite forms the corresponding carboxymethyl azide; thiols, epoxides, isocyanates, 5-phenylisoxazolium-3'-sulfonate derivatives; halogenides like chloride, bromide and iodide; cyanuric chloride derivatives; and aryl azides, that form covalent linkages to the lens capsule upon UV irradiation.

In a preferred aspect of the invention the derivatised polymer is PEG.

Examples of polysaccharides and derivatives thereof are mucopolysaccharides like hyaluronic acid, heparin, chondroitin sulfates and dermatan sulfate; dextran, starch and starch derivatives like carboxymethyl starch, cellulose and cellulose derivatives like carboxymethyl cellulose and hydroxypropylmethyl cellulose.

Interpenetrating networks are formed when monomeric or macromeric substances are first allowed to diffuse into tissue and then polymerized. This can be achieved by monomers or macromers containing polymerizable groups or derivatized to contain such groups. Examples of compounds and substituents suited for radical polymerization are acrylic amides and esters, cinnamic derivatives, vinyl esters and styrene derivatives.

Examples of macromer backbones are PEG and polyethylene glycol polypropylene glycol copolymers (poloxamers like Pluronic and Synperonic).

Radical polymerization can be accomplished thermally with initiators of for instance peroxide or azo compounds like banzoylperoxide, azoisobutyronitrile and ammonium persulfate, or by irradiation.

In order to increase the rate of initiation in the peroxide system at body temperatue (around 37 ^{o}C) a promotor is preferrably added. Examples of such promotors are metals like Co, Fe, Mn, V, Cu etc, and tertiary amines like N,N,N',N'-tetramethyl-ethylenediamine (TEMED). The peroxide and the promotor form a redox system, which creates the radicals necessary for polymerization and/or crosslinking of the monomers or macromonomers used. The at present preferred

systems are prepared by using hydrogen peroxide and ammonium persulfate resp. TEMED and Fe.

Another way of starting the reactions of the double bond functionalized macromonomers is to initiate the reaction by irradiation. In this process the macromonomers are subjected to an excitation energy, which is sufficient to produce radicals directly on the macromonomer or on a photo-initiator, which will start the reactions. The active radicals can then be used as a grafting site for grafting onto the tissue on the capsule or start propagation (polymerization) of the double bonds forming an interpenetrating network.

Yet another way of depositing polymers and probably to some extent obtain covalent substitution with subsequent formation of an interpenetrating network with the lens capsule tissue is the use of condensation polymerization as illustrated in Example 9 below where PEG carboxylic acid chloride and polyoxypropylene amine is reacted with each other.

In a further embodiment of the invention a polyvinyl alcohol titanium complex was deposited on the lens capsule tissue, resulting in substantial reduction of the growth of lens epithelial cells.

Complex formation to obtain water insoluble coatings can naturally be obtained in several ways for example based on charge interactions between two oppositely charged polyelectrolytes.

Binding various molecules to a surface is known from several technical fields and already the techniques used in one such area, chromatography, indicate a large number of ways to obtain a desired deposit as soon as the general concept is known from this specification.

One specific example can be mentioned in this connection: nitrite activation of heparin as disclosed in US 4810784 (Larm), for binding heparin in a controlled way to an amino group rich substrate.

We have also found that besides using compounds of the type mentioned above, also low molecular weight compounds can be utilized in the modification of lens capsule tissue. Treatment of lens capsule with bromoacetic acid introduces

carboxylic groups, creating a negatively charged surface at physiological pH. Also such a layer of low molecular weight substituents forming a charged surface are within the scope of the term deposit as used in this connection.

Treatment of the lens capsule with reagents for creating the deposit can be done in that monomers, macromers, polymers or any other component needed for the reaction are dissolved in a biologically acceptable solvent like dimethylsulfoxide and placed on the tissue whereafter the reaction is initiated and the desired layer is formed. Any remaining and unreacted components are then removed by washing the tissue with a physiologically acceptable aqueous solution, preferably containing also hyaluronic acid which is frequently used in various ophthalmological applications. Water insoluble polymers can also be deposited on lens capsule tissue if applicated as a solution in a biologically acceptable solvent. When water is added the polymer is precipitated on the tissue.

The invention further relates to compositions adopted for ophthalmic use, which contain an effective amount of one or more of the substances defined above in a carrier.

In still another aspect of the invention a dosage device is provided which consists of a syringe for intraocular injection containing an ophthalmologically adopted composition comprising an effective amount of a physiologically acceptable cell attachment and cell growth preventing substance, as defined above, in a carrier.

The invention will now be illustrated by a series of examples, the majority of which for obvious reasons have been carried out in an in vitro test system. This system has been designed to be relevant to the in vivo situation so that lens epithelial cells attachment and morphological development can be evaluated on a modified model substrate. One series of tests have been carried out in a rabbit cataract model.

As in vitro model substrates posterior lens capsules or extra capsular matrix (ECM) coated culture dishes (Biological Industries Kibbutz Beth Haemek Israel) have been used.

The lens epithelical cells used were cultured in the following way: New Zealand White rabbit lenses were removed

from freshly enucleated eyes, the anterior capsules were isolated and cut in pieces. The capsular pieces with adherent LEC were cultured in Dulbeccos Modified Eagle Medium supplemented with 10% fetal calf serum 20% Hams' F-12, 1% Non Essential Amino Acids, 1% L-Glutamine and 1% Antibiotic Antimycotic Solution (all from Gibco). After reaching confluence, the cells were passed with 0.05% trypsin and 0.02% EDTA for 10 minutes and split 1:3. The cells were incubated at 37 ^{o}C and 5% CO_2.

The lens capsules were prepared according to the following procedure using fresh bovine cadaver eyes: An equatorial cut was made through the eye globe with a pair of scissors and the vitreous was removed. The remaining vitreous on the posterior part of the lens capsule was removed with a cotton swab. The lens capsule was cut into an anterior and a posterior part with a pair of scissors. The posterior part was transferred to a glass plate with the interior surface upwards, was then allowed to dry and was finally fixed onto the glass plate with a ring of silicone rubber (RTV Silicone GEC) that also forms a well for fluid treatment of the capsule surface.

Before and after the various treatment procedures the lens capsules were thoroughly rinsed with physiological saline solution. The capsules were stored in such a solution until they were used for cell adhesion experiments.

Cell incubation on the surfaces used for the tests was standardised as follows: In the 4th passage the cells were transferred to the lens capsules and culture dishes for the attachment experiments. 10,000-20,000 cells were used per capsule and approximately 50,000 cells per culture dish. The samples were incubated for 48 hours as described above. The culture medium was removed and the cells were fixed in 1% glutaraldehyde, rinsed with PBS and stained with Mayer's Hematoxylin for 15 minutes. The samples were rinsed in tap water and the cellular adhesion and morphology was evaluated using a light microscope.

The surfaces of the unmodified capsules and culture dishes were completely covered with lens epithelial cells after the incubation procedure. The morphology of the cells was either

the typical epithelial polygonal one or a more irregular morphology with flattened and more spread out cells. The cells appeared viable with a proliferative capacity.

In all the examples given below the modification procedures described have given rise to surfaces exhibiting significant reduction of the lens cell attachment to the modified substrate surface. The morphology of the cells showed that the cells were rounded and unable to spread out and consequently not able to completely attach. After 48 hours in culture the cells showed no proliferative capacity. It should be noticed that for in vivo use some of these methods might require special administration procedures.

Example 1.

Lens capsule modification with (isobutyl-oxy-formyl) PEG succinate.

Monomethoxy PEG3000 (MeOPEG3000-Hoechst) was converted to the succinate ester through reaction with succinic anhydride in pyridine according to Abuchowski et al (Cancer Biochem Biophys 7 (1984) 176).

5 g MeOPEG3000 succinate ester was dissolved in 40 ml methylene chloride. 490 µl triethylamine and 481 µl isobutyl chloroformate were added. The solution was stirred for 30 minutes after which the solvent was evaporated at 30 °C. The residue was washed five times with 50 ml petroleum ether portions.

The substance was used for treatment of lens capsules and ECM coated culture dishes. 175 mg of the substance was quickly moistened in 1 ml 0.25M borate buffer pH 8 or 9.5. Before the substance had dissolved it was applied onto the lens capsule or the culture dish. The surfaces were treated for 5 minutes each. The PEG substitution was also confirmed by ESCA spectroscopy.

Example 2.

Lens capsule modification with a 5-phenylisoxazolium-3'-sulfonate derivative of PEG.

3 g of methoxy PEG3000 succinate ester was dissolved in 25 ml dry acetonitrile. The solution was cooled in an ice bath. 139 µl triethylamine was added and thereafter 0.253 mg N-ethyl-5-phenylisoxazolium-3'sulfonate. The solution was stirred for 2 hours while the solution was allowed to obtain room temperature. The solvent was evaporated and the substance washed twice with petroleum ether.

250 mg of this derivative was rapidly dissolved in 0.25 M borate buffer pH 9.5. The solution was immediately applied onto a lens capsule for 5 minutes. The coating procedure was repeated one more time.

Example 3.

Lens capsule modification with azido derivatives of PEG.

300 mg PEG1000 (Fluka) was dissolved in toluene and the solvent was evaporated. This procedure was repeated one more time. The substance was dissolved in 5 ml 60% potassium hydroxide solution. 80 mg 4-azido-1-fluoro-2-nitrobenzene (Aldrich) dissoved in 10 ml toluene was mixed with the PEG solution. The two phase system was stirred rapidly in the dark for three days. Thin layer chromatography of the toluene phase revealed a mixture of di-and monosubstituted PEG-azido derivatives. The toluene phase was shaken with water. The monoazido substituted derivative was partitioned into the water phase and the diazido derivative was retained in the toluene phase. The phases were evaporated to dryness.

40 mg of the dry monoazido substituted material was dissolved in 0.5 ml water. The solution was applied onto a lens capsule that was UV irradiated for 10 minutes.

The diazido derivative obtained from evaporation of the toluene phase was also used. 20 mg of this material was emulsified in water in an ultrasonic bath. The emulsion was applied onto lens capsules that were irradiated with UV light (UV lamp Philips TL K40W/09N 90mW/cm^2) for 15 minutes.

Example 4.

Lens capsule modification with an azido derivative of polyvinyl alcohol (PVA).

300 mg PVA (100% hydrolysed M_W 14,000 EGA Sweden) was dissolved in 5 ml water during heating. 1 g potassium hydroxide was added. The solution was cooled to room temperature. 75 mg 4-azido-1-fluoro-2-nitrobenzene was dissolved in 10 ml toluene and mixed with the PVA solution. The two phase system was vigorously stirred in the dark over night.

25 ml water was added to the formed emulsion and the mixture was centrifuged. The water phase was separated and neutralised with acetic acid and dialysed against distilled water to a final volume of approximately 35 ml.

The dialysed PVA solution was applied onto a lens capsule for 5 minutes. The solution was withdrawn and the capsule was UV irradiated (as in example 4) for 10 minutes.

Example 5.

Lens capsule modification with epoxy activated dextran.

2 g dextran Mw 20,000 (Dextran T20 Pharmacia Fine Chemicals) was dissolved in 20 ml 0.5% NaOH solution. 2 g 1,4-butanediol diglycidyl ether was added to the solution which was stirred for half an hour and dialysed overnight. The product was precipitated in ethanol and dried.

100 mg of the thus obtained epoxy activated dextran was dissolved in 1 ml borate buffer pH 9.5. The solution was applied onto a lens capsule for half an hour.

Example 6.

Lens capsule modification with polyacrylonitrile.

25 mg polyacrylonitrile M_W 150,000 (Polysciences) was dissolved in 1 ml dimethyl sulfoxide (DMSO). The solution was applied to a lens capsule for 5 minutes. The capsule was then briefly washed with DMSO and subsequently with saline.

Examples 7 a, b and c.

Lens capsule modification with PEG-acrylates.

a) 0.3 g PEG-diacrylate 400 (Polysciences) and 5 mg N,N,N',N'-tetramethylethylenediamine (TEMED) was dissolved in 1 ml of saline. Nitrogen was bubbled through the solution for 4 minutes in order to remove oxygen. The solution was then applied onto a lens capsule for 5 min whereafter the solution was withdrawn and replaced with a solution of ammonium persulfate (0.5% in 0.9% saline) for 5 minutes. This persulfate treatment was repeated once.

b) 0.4 g PEG-diacrylate 400 and 10 mg $FeSO_4$ was dissolved in 1 ml of saline. Nitrogen gas was bubbled through the solution for 4 minutes in order to remove oxygen. The solution was then applied onto a lens capsule for 5 min, whereafter the solution was withdrawn and replaced with a solution of hydrogen peroxide (2% in 0.9% saline) for 5 minutes.

c) 0.3 g PEG-diacrylate 400 and 5 mg of the initiator Quantacure BTC (Ward Blenkinsop.) were dissolved in 1 ml saline solution. The solution was applied onto a lens capsule for 5 min, whereafter the solution was withdrawn and the capsule was subjected to UV irradiation (as in example 3) for 2 minutes.

Example 8.

Lens capsule modification with acrylated poloxamer.

25 g poloxamer (propylene-ethylene oxide copolymer - Synperonic F127 Mw 12,000 ICI) was treated with toluene as in Example 3.. The substance was dissolved in 175 ml methylene chloride. The solution was cooled in an ice bath and 6.67 ml pyridine and 7.23 ml acryloyl chloride were added. The solution was stirred and allowed to reach room temperature overnight.

200 ml methylene chloride was added and the solution was filtered. The filtrate was precipitated in 2,500 ml diethyl ether. The precipitated substance was dissoved in water and dialysed overnight. The dialysed solution was lyophilised.

125 mg of the dried substance was dissolved in 1 ml 0.9% saline. 6.4 µl TEMED was added and the solution degassed

with nitrogen. The solution was applied onto a lens capsule for 5 minutes whereafter the solution was withdrawn and replaced with a solution of ammonium persulfate (0.5% in 0.9% saline) for 5 minutes. The persulfate treatment was repeated once.

Example 9.

Lens capsule modification with a condensation polymer of PEG dicarboxylic acid chloride and polyoxypropyleneamin.

10 g PEG600-diacid (Fluka) was treated with toluene as in Example 3. The substance was dissolved in 75 ml methylene chloride. The solution was cooled to 0 ^{o}C under nitrogen. 5 ml thionyl chloride was added and the solution stirred overnight. The solvent was evaporated, 50 ml toluene added and the solvent was then evaporated once again.

2 g polyoxypropylene triamine (Jeffamine T-403, Texaco) was dissolved in 20 ml water. The pH of the solution was lowered to 9.5 with hydrochloric acid. The solution was applied onto a lens capsule for 5 minutes and thereafter withdrawn. 0.2 g of the PEG acid chloride was quickly dissolved in 2 ml water and instantly applied to the pre-treated lens capsule and left for one minute.

Example 10.

Lens capsule modification with a PVA titanium complex.

500 mg PVA (see Example 4) was dissolved in 10 ml 0.9% saline with heating. The solution, cooled to room temperature, was applied to a lens capsule for 15 minutes. The lens capsule was then rinsed with saline.

300 mg TYZOR^{R}TE (titanium isopropoxy(triethanolaminato)-isopropyl alcohol from du Pont) was dissolved in 2 ml water. The pretreated lens capsule was treated with this solution for 1 minute.

Example 11.

In vivo evaluation of lens capsule modification with polyethylene glycol disuccinimidyl propionate.

150 mg of PEG 3400 disuccinimidyl propionate ($(SPA)_2$-PEG3400, Shearwater Polymers, Huntsville, Alabama) was rapidly

dissolved in 1 ml of isotonic Sörensen phosphate buffer pH 8.0 (Sörensen (1909), Biochem. Zeits., 21, 131). An analogues product based on PEG 400 was prepared similarly. After preparation the resp. solution was immediately applied onto the lens capsule to be treated, as described below.

The in vivo tests were performed in albino rabbits (New Zealand White) in a model for studies on secondary cataract (see Lundgren et al (Lundgren B, Jonsson E & Rolfsen W (1992) Secondary Cataract. An in vivo model on secondary cataracts in rabbits. Acta Ophthalmol Suppl 205:25-28). Rabbits are known to rapidly develop secondary cataracts after IOL implantation and therefore of great interest at an early stage scanning of potential systems for treatment, even if it should be pointed out that the situation in humans might be different.

The animals were kept under standardised conditions one by one and given tap water and food ad libitum.

In all 12 rabbits were used and 6 of these have been analyzed after an 8 week's period. The remaining 6 will be analyzed at a later stage.

The animals were anaesthetised with ketamine hydrochloride (Ketalar® Parke-Davis, UK) and zylazine chloride (Rompun®, Bayer AG, Germany), 35 resp 5 mg/kg body weight i.m. Pupil dilation was performed by repeated instillation of Cyclogyl® 1% (Alcon Fort Worth, Texas, USA) and Neosynephrine 10 % (Sterling-Winthrop, New York, USA) 2-3 times with approximately 5 minutes interval in each eye. Topical application of Tetracain® (Smith & Nephew, UK) was used for local anaesthesia. A 2-3 mm corneal incision was made with a Superblade® (Kabi Pharmacia, Uppsala Sweden), and after injection of Healon® (Kabi Pharmacia), a circular capsulorhexis was made. The lens was extracted with Phaco emulsification using BSS (Alcon Fort Worth, Texas, USA).

The anterior chamber was filled with Healon®. 75 mg of the polyethylene glycol disuccinimidyl propionate was rapidly dissolved in 0.5 ml sterile isotonic Sörensen buffer pH 8.0 (as above). Approximately 200 µl of the solution was injected into the capsule under the Healon®. cover and the solution was left in the capsular bag for 5 minutes. The PEG solution was then

aspirated with the Phaco tip. A fresh PEG succinimide solution was prepared and the capsule was filled once again as above. After 5 minutes the PEG solution was aspirated, the capsule was filled with Healon® and an intraocular lens (Model 720A, Kabi Pharmacia AB) was implanted. The Healon® was removed by irrigation and the corneal incision was closed by a continuous x-suture, using 9-0 nylon.

In the contralateral, eye which was used us a control, an intraocular lens was implanted but the capsule was not treated with PEG succinimide solution.

After the operation, 5 mg of Garamycina® (Schering Corp., N.J., USA) and 1 mg of Celestona®.(Schering Corp., N.J., USA) was injected subconjunctivally. Postoperatively, the animals were treated with Isopto®-Maxidex 1 mg/ml (Alcon Fort Worth, Texas, USA) 3 times daily and Mydriacyl (Alcon) 2 times daily for 7 days. All eyes remained clam after surgey and no differencies could be seen between the treated and the control eyes.

After 8 weeks the animals were euthanized and the eyes were enucleated. Each enuclated globe was sectioned in the coronal place just anterior to the equator. The secondary cataracts were carefully removed and weighed to the nearest mg according to Lundgren et al (Lundgren B, Jonsson E & Rolfsen W (1992) Secondary Cataract. An in vivo model on secondary cataracts in rabbits. Acta Ophthalmol Suppl 205:25-28.

Results:

Animal No.	PEG-succinimide M_W	Weight of samples (g) Control eye	PEG-succinimide treated eye
1	3400	0.0873	0.0780
2	3400	0.1291	0.0834
3	3400	0.1618	0.0964
4	400	0.2020	0.0461
5	400	0.0836	0.1459
6	400	0.0996	0.0575

In the majority of animals tested and evaluated till today in this in vivo model the development of secondary cataract was significantly higher in the control eye compared to the eye treated with a substance preventing adherence and subsequent growth of cells, thus indicating the potential importance of the present concept.

Claims.

1. Method for extracapsular cataract extraction with or without posterior chamber intraocular lens implantation characterized in that the posterior surface of the lens capsule, at least in the optical portion of said capsule, is chemically modified for preventing cell attachment and growth.

2. The method according to claim 1 wherein a stable layer of a cell attachment preventing compound is deposited onto the posterior surface of the lens capsule.

3. The method of claim 2 wherein the deposit is covalently bound to the capsule tissue.

4. The method of claim 2, wherein the deposit forms an interpenetrating network with the capsule tissue.

5. The method according to any ono of claims 1-4, wherein the deposit is a polymer selected from the group consisting of polyethylene glycols, polysaccharides, polyethylenepolypropylene glycols and polyvinyl alcohols and derivatives of these.

6. The method according to claim 5, wherein the polymer is a polyethylene glycol or a derivative thereof.

7. The method of any one of claims 5 or 6, wherein said polymer is a polymerizable derivative or contains reactive groups capable of reacting with functional groups on the tissue surface, such as carboxylic groups, hydroxyl groups, amino groups and thiols, to form the deposit.

8. The method of claim 7 wherein the reactive group is selected among aldehydes, anhydrides, activated esters, sulfonates, azides, thioles, epoxides, isocyanates, halogenides, acrylic and vinylic groups.

9. The method of claim 5 wherein said polymer is selected from the group consisting of (isobutyl-oxy-formyl) polyethylene glycol; 5-phenylisoxaozolium-3' sulfonate derivative of polyethylene glycol; azido derivative of polyethylene glycol; polyethylene glycol disuccinimidyl propionate; polyethylene glycol diacrylate; condensation polymer of polyethylene glycol dicarboxylic acid chloride and polyoxypropyleneamine; azido derivative of polyvinyl alcohol; polyvinyl alcohol titanium complex; epoxy activated dextran; and acrylated copolymer of propylene oxide and ethylene oxide.

10. The method of claim 4 herein said network is formed by diffusing a moonomeric or macromeric substance into capsule tissue and then polymerizing said substrate in situ.

11. The use of an effective amount of a chemical substance, for preparation of a medicament for coating of the posterior surface of the lens capsule in order to prevent cell attachment and growth after extracellular cataract extraction.

12. The use according to claim 11, wherein the substance is selected among polyethylene glycols, polysaccharides, polyethylenepolypropylene glycols and polyvinyl alcohols or derivatives of these.

13. The use according to claim 12, wherein the substance is a polymerizable monomers or a derivative which contains aldehyde, anhydride, activated ester, sulfonate, azide, thiole, epoxide, isocyanate, halogenide, acrylic and vinylic groups

14. The use according to claim 13, wherein the substance is polyethylene glycol or a derivative thereof.

15. Composition adopted for intraocular ophthalmic use for coating of the posterior surface of the lens capsule of the eye comprising an effective amount of a physiologically acceptable cell attachment and cell growth preventing substance and a carrier.

16. Composition according to claim 15, wherein the substance is selected among polyethylene glycols, polysaccharides, polyethylenepolypropylene glycols and polyvinyl alcohols and derivatives or polymerizable monomers of these.

17. Composition according to claim 16, wherein the substance contains aldehyde, anhydride, activated ester, sulfonate, azide, thiole, epoxide, isocyanate, halogenide, acrylic and vinylic groups

18. Dosage device for coating the posterior surface of the lens capsule, consisting of a syringe for intraocular injection which contains an ophthalmologically adopted composition comprising an effective amount of a physiologically acceptable cell attachment and cell growth preventing substance and a carrier.

19. Dosage device according to claim 18, wherein the cell attachment and cell growth preventing substance is selected among polyethylene glycols, polysaccharides, polyethylenepolypropylene glycols and polyvinyl alcohols and derivatives or polymerizable monomers of these.

20. Dosage device according to claims 18 or 19, wherein the cell attachment and cell growth preventing substance contains aldehyde, anhydride, activated ester, sulfonate, azide, thiole, epoxide, isocyanate, halogenide, acrylic and vinylic groups.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00047

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5: A61F 2/16, A61L 27/00, A61K 9/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K, A61L, A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A1, 0299467 (OPHTHALMIC RESEARCH CORPORATION ET AL.), 18 January 1989 (18.01.89), see page 2 - page 3, line 7, claims --	11,15,18
X	Dialog Information Services, file 155, MEDLINE, Dialog acc.no. 08244901, Medline acc.no. 92382901, Rose G E: "Fibrinous uveitis and intraocular lens implantation. Surface modification of polymethyl-methacrylate during extracapsular cataract surgery", & Ophthalmology (UNITED STATES) Aug 1992, 99 (8) p1242-7 --	11-12,15-16, 18-19

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 May 1994	25 -05- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00047

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Dialog Information Services, file 155, MEDLINE, Dialog acc.no. 04210540, Medline acc.no. 81038540, Olson R.J. et al: "Polyvinyl alcohol as a protective coating on intraocular lenses", & Arch Ophthalmol (UNITED STATES) Oct 1980, 98 (10) p1840-2 --	11-20
A	Dialog Information Services, file 155, MEDLINE, Dialog acc.no. 07018160, Medline acc.no. 89320160, Matsumoto T. et al: "Fibrin deposits on the surface modified PMMA IOLsâ", & Nippon Ganka Gakkai Zasshi (JAPAN) Jan 1989, 93 (1) p118-23 --	11-20
A	EP, A2, 0286433 (UNIVERSITY OF FLORIDA), 12 October 1988 (12.10.88) -- --------	11-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00047

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-10
because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods (see PCT Rule 39.1(iv)).

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

16/04/94

International application No.
PCT/SE 94/00047

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0299467	18/01/89	AU-B- 602993	01/11/90
		AU-A- 1904388	19/01/89
		JP-A- 1100133	18/04/89
		US-A- 4918165	17/04/90
EP-A2- 0286433	12/10/88	AU-B- 594233	01/03/90
		AU-A- 1327488	13/10/88
		DE-A- 3875364	26/11/92
		JP-A- 64002644	06/01/89
		US-A- 4806382	21/02/89
		US-A- 4961954	09/10/90
		US-A- 5094876	10/03/92
		US-A- 5290548	01/03/94