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Session 21-206
Room 7 A

“Nano-Ophthalmology: State of art, practical applications and perspectives”

Senior Instructor:
Tatiana Naoumidi MD PhD

Instructor:
Dimitrii D Dementiev MD
Kenneth J Hoffer MD
Ioannis Pallikaris MD PhD
Matteo Piovella MD

Thursday, April 21, 2015
10.00 AM – 11.30 AM
# Index

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nano-ophthalmology: state of the art, practical application perspective</td>
<td>3</td>
</tr>
<tr>
<td>I. State of the art</td>
<td></td>
</tr>
<tr>
<td><em>Jorge L Alio MD, PhD</em></td>
<td></td>
</tr>
<tr>
<td>Remote Controlled Delivery Systems: microcages and nanospheres</td>
<td>7</td>
</tr>
<tr>
<td><em>Tatiana L. Naoumid MD, PhD</em></td>
<td></td>
</tr>
<tr>
<td>Nanotechnologies and Contact Lenses</td>
<td>9</td>
</tr>
<tr>
<td><em>Matteo Piovella MD</em></td>
<td></td>
</tr>
<tr>
<td>Hoffer Split Bifocal History</td>
<td>15</td>
</tr>
<tr>
<td><em>Kenneth J Hoffer, MD</em></td>
<td></td>
</tr>
<tr>
<td>ADDRESESS</td>
<td>17</td>
</tr>
</tbody>
</table>
Nano-ophthalmology: state of the art, practical application and perspectives

I. State of the art

Jorge L Alio MD, PhD

I have seen the future of medical ophthalmology and its name is sustained-release drug delivery

J. Heimer, Senior Editor, Ophthalm. M mg 1/1/2010
Drugs to consider

- **Hydrophobic:** Moxifloxacin, vancomycin, timolol, dexamethasone and timolol, latanoprost and travoprost, acyclovir, memantine, CNTF, brimonidine, nepafenac and olopatadine (partially)
- **Hydrophilic:** ciprofloxacin

*Hydrophobic molecules have a tendency to accumulate more in the vitreous, whereas hydrophilic molecules tend to show greater concentrations in the aqueous humor.*

Ocular Control Release systems

- **Non-erodible**
  - Ocusert, Prosert, Vitrasert, Retisert, CL
- **Erodible**
  - Lacrisert, SODI, Minidisc, plugs, Ozurdex
- **Drug-Eluting IOLs**
- **Surgical Implants** (MEMS, ODTx capsules)
- **Nanoparticles**
- **Liposomes**
- **Cationic emulsions**

IOP Lowering Sustained Release Platforms in Clinical Development

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Delivery Method</th>
<th>Clinical Development</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>Latanoprost</td>
<td>Subconjunctival/preVethal</td>
<td>Phase 1/2</td>
<td>Releasing</td>
</tr>
<tr>
<td>Alcon</td>
<td>Retimodine</td>
<td>Intravitreal</td>
<td>Phase 3</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Allergan</td>
<td>Latanoprost</td>
<td>Subconjunctival suture fixation</td>
<td>Projected to start phase 1/2 in 2025</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Aerie</td>
<td>Latanoprost</td>
<td>Punctum plug</td>
<td>Phase 2</td>
<td>Completed</td>
</tr>
<tr>
<td>OcuLab</td>
<td>Transpore</td>
<td>Punctum plug</td>
<td>Phase 1</td>
<td>Completed</td>
</tr>
<tr>
<td>OCU</td>
<td>Latanoprost</td>
<td>Punctum plug</td>
<td>Phase 1</td>
<td>Completed</td>
</tr>
</tbody>
</table>

Anterior segment IOP lowering implants (1)

- pSivida (collaboration with Pfizer)
  - Since 2011 develops a subconjunctival insert delivering latanoprost
  - The companies are now engaged in phase 1/2 clinical trials at the University of Kentucky

Anterior segment IOP lowering implants (2)

- **Aerie Pharmaceuticals** (in precl dev/ment)
  - latanoprost-loaded ocular insert with subconjunctival suture fixation
  - insert produced by compressing latanoprost pellets and then coating them with a membrane such as ethylene vinyl acetate.
  - insert may better control the burst effect thanks to its porosity and membrane thickness, allowing hydrophilic drugs to permeate the sclera.

Anterior/posterior segment IOP lowering implants (3)

- **Intravitreal insert**
  - Allergan's topical brimonidine is said to work effectively in glaucoma not only by lowering IOP but also by wielding potential neuroprotective properties. Allergan is conducting clinical trials of implants designed similarly to Ozurdex but containing brimonidine to treat geographic atrophy associated with AMD along with glaucoma.

**Anterior segment IOP lowering implants**

- **Anecortave acetate** (4)
  - Subconjunctival or sub-Tenon injection, Alcon
  - Cortical derivative – angiostatic cortisone

  - **Pros:**
    1. no glucocorticoid activity.
    2. no anti-inflammatory properties
    3. no cataractogenic properties
    4. claims to elevate the aqueous flow
    5. 3 months duration

  - **Cons:**
    1. only 2-4 mm Hg IOP reduction
    2. sub-Tenon or subconjunctival inj
    3. reflux of the drug from the Tenon space

- **Punctum plug insertion**

  - There is a 1989 paper by Timothy Huang and David Lee published in AJO that compares IOP reduction in eyes that received a simple IOP-lowering treatment and eyes treated with the same medication but with a simple lower punctum occlusion with a plug (3 total of 19 patients). The IOP drop in puncted eye was 1.82 mmHg greater.

**Anterior segment IOP lowering implants**

- **Punctal plugs**

  - **(A) QLT – hydrogel b/d punctum plug**
    - Initial application of the active ingredient to the surface of the plug (either inner or outer) - antibiotics, prostaglandins, antihistamine
    - Drug delivery via ocular implant – US patent 2010/0046670 A2
    - Currently in phase 2 clinical studies

  - **Pros:**
    - 60% of patients at 1 week experienced an IOP drop of 5 mm or more
    - Improved retention of the plug
    - Duration of latanoprost release – 3 months

  - **Cons:**
    - IOP-lowering effect remains inferior to that of daily topical Xalatan when used with ideal patient adherence to the prescribed regimen
    - Plugs still often fall out

- **QLT plug insertion**

  - QLT Punctum Plug
  - Drug Core
  - QLT Insertion Tool
  - QLT Insertion Tool

**Anterior segment IOP lowering implants**

- **(B) Ocular Therapeutix**

  - Polyethylene glycol hydrogel plug with drug-loaded polylactide-co-glycolide (PLGA) microspheres to release drug in a sustained fashion (moxifloxacin, steroids, travoprost).
  - Each plug contains a visualization agent for retention monitoring.
  - Primary endpoints include intraocular pressure reduction from baseline and retention of the plug through 30 days.

- **Ocusert (Alza, Akorn, Inc)**

  - Pilocarpine - cluting insert, n/d. Duration: 7 days
  - Release rate: 20-40 mg/hr. Consists of two polyethylene membranes and a ring of the same material filled with pilo
  - Cons: easy to fall out, foreign body sensation

Anterior segment IOP lowering implants

Contact lenses
- The lenses used are presoaked hydrophilic lenses. The drug release can be up to 180 hours.

Pros:
- Soft contact lenses, consisting of polymers of N.N-diethylamylamine and methacrylic acid, have been shown to deliver timolol for longer periods and effectively lower IOP.

Cons:
- Water-soluble drugs erode very quickly from the highly hydrated polymer networks.
- Lenses stored in a hydrated state have the potential for the drug to leak out of the lens over time.
- Allergens stick to the surface of the lens.

Miscellaneous anterior segment implants

(1) Lacrisert b/d (intr. 1981)
- Rod-shaped hydroxypropyl cellulose artificial tear insert to treat dry eye syndrome (keratitis sicca).
- Weight 5 mg, 12.7 mm X 3.5 mm
- Placed into inferior fornix

(2) Minidisc Implants-SODI
- Soluble ocular drug insert (SODI)-small oral wafer developed for cosmonauts not able to use eye drops in weightless conditions.
- Acrylamide N-vinylpyrrolidone and ethylacrylate forming sterile thin films of oval shape weighing 15 to 16 mg in cul de sac wetted by tear film it softens in 10-15 seconds and assumes the curved configuration of the globe.
- The film turns into viscous polymer mass in 10-15 min and becomes a polymer solution in 30-60 min.
- Replaces 4-12 drops instillation or 3-6 applications of ointment.

(3) Minidisc Implants (b/d)
- Polyethylene oxide of different molecular weights (Sigma)
- These figures are comparable to BODI (5.0 X 2.0 mm, 20.5 mg weight) and SODI (9 X 4.5 mm X 0.35 mm 15-16 mg weight).
- It is made up of counter disc with Convex front and Concave back surface in contact with the eye ball, hydrophilic or hydrophobic.
- Released up to 7 days.

Miscellaneous anterior segment implants

(4) Both OTx and QLT punctum plugs
- Possibility for drug delivery
  - Prostaglandins (PGAs), steroids, fluoroquinolones (FQs)
  - OTx: Moxifloxacin Punctum Plug: The active ingredient is embodied in polymeric material.
  - OTx plug retention in 10 days, data not assessed by day 30.
  - Pharmacokinetic testing demonstrated that drug levels were maintained between 2,000 ng/mL and 3,000 ng/mL, levels achieved in tear fluid were MIC90 = 0.25, enough to treat target organisms: S. aureus, S. pneumoniae N. gonorrhoeae, H. influenzae, P. acnes for 7 days.
Remote Controlled Delivery Systems: microcages and nanospheres
Tatiana L. Naoumidi MD, PhD

Remote Control
- Magnetic field
- Optical Addressing
- Ultrasound
- Radiofrequency

Layer-by-layer Capsules
Size and shape are determined by templating colloid particle
Layer constituents:
- synthetic polyelectrolytes and biopolymers
- inorganic nanoparticles

The Capsule Wall is tunable in the nanometer range. Its thickness, composition and functionality are controlled by constituents and the number of layers.

Ultrasound stimulated release
- Induced release without damage of tissues
- Higher depth of operation inside the body

Medical range ~1MHz, 1 - 3W

Intracellular Sensors
- Encapsulated pH – sensor, SNARF-based dye
- Green – low pH
- Red – high pH
- Emission 580nm
- Inside cell endosome
- Red - high pH
- Emission 580 nm
- Outside cell
In vivo degradation

Capsules are injected subcutaneously in mice and tissue sections are taken at several time points.

The tissue reaction includes:
- Mild tissue reaction
- Good cellular uptake by phagocytes
- Capsule degradation by phagocytes
- Infiltration border -> center


Considerations

1. Which is the effective dose of the drug?

There are limits to the amount of drug that can be formulated with a polymer and limits on the amount that can be delivered to the eye. Several studies indicate that both the IOP-lowering medications and potential neuroprotective agents have a low enough effective concentration to be suitable for sustained delivery.


2. We should consider the drug’s stability and its interaction with, what is most likely, a hydrophobic polymer environment. Stronger association between a drug and polymer increases the possibility for long-term, sustained delivery.

3. It is extremely important whether the drug, especially a complex large molecule such as a growth factor, is bioactive after being released from the polymer carrier.
Nanotechnologies and Contact Lenses
Matteo Piovella MD

Quotidia Aloe: Therapeutic and Scleral

Quotidia Therapeutic Aloe Specifications
- External and internal aspheric surface
- High totality
- 14.3 diameter
- Double Base Curve (8.60 / 8.40)

Quotidia Scleral Aloe Specifications
- External and internal aspheric surface
- High totality
- 16.0 diameter
- Double Base Curve (8.60 / 6.70)

Inflammatory Phase

Vessel dilation and increased peribehelal capillary permeability

Extravascular diffusion of protein and leukocyte

Pain by stimulation of corneal nerves with photophobia, and mucous secretion

Corneal Injury and their evolution regenerative

- Inflammatory phase
- Coagulative phase
- Regenerative phase
Coagulative Phase

- Involving two plasma proteins
  - Fibrinogen
  - Fibroneitin
- Fibrin binds to the surface abnormal corneal
- Natural chemical mediator regeneration
- Temporary matrix with attraction of leukocytes origin of the lamellar
- Lysis process primed by the system Plasminogen - Plasmin

Regenerative Phase

- Sliding on the temporary matrix of epithelial cells
  - The wound margins toward corneal center
- Fibrinogen stimulated by the chemotactico
  - (2 mm per day)
- MITOSIS - PHAGOCYTOSIS
- Reconstruction of the basement membrane after 72 hours
- Renewal of the fibers anchor

Injury PRK

- Exudation
- Fibrinogen
  - Membrane Coagulative
  - Activation of cells and migration
    - Mitosis (O2)
  - Synthesis of extracellular material
  - Phagocytosis
- Contact Lens: Decrease Pain
- Contact Lens: OK High

Bacterial Infection after PRK

- CONCLUSIONS:
  - The incidence of infectious keratitis after surface ablation was 0.20%.
  - Infectious keratitis is a potentially vision-threatening complication. Prompt and aggressive management with an intensive regimen of fortified antibiotic agents is strongly recommended.
- Contact Lens: Ionic Material

INSTABILITY tear film AFTER PRK (Epithelial Stress)

- Alteration of the aqueous component
- Alteration of the mucosal component: Decreased mucous secretion resulting in less hydrophilia of O.S.
- Alteration of the lipid component

- High hydrophilia Drop Out
- Wetting properties of the Contact Lens
Essential requirements of LAC after PRK include:

- Material: Ionicity, DK; DK/T; H2O
- Geometry: diameter, thickness, asphericity
- Medicines and Wettability: Hyaluronic Acid, Aloe

The ionic bond is a chemical bond of electrostatic nature which is formed when the chemical-physical characteristics of the two atoms are distinctly different, and there is especially a big difference in electronegativity between the components.

The ionicity of the surface of the lens determines material compatibility with drugs.

Group 1
Low Water (<50% H2O)
Nonionic Polymers
Teflon (38%) (Dk = 9.5)
Teflon A (43%) (Dk = 9)
Cordrow (36%) (Dk = 10)
Hemiflow A (45%) (Dk = 12)
Mediflow (33%) (Dk = 4)
Polymer (38%) (Dk = 9)
Silicon Hydrogel

Group 2
High Water (>50% H2O)
Ionic Polymers
Lobron A (70%) (Dk = 38)
Surfcon A (74%) (Dk = 35)
Lobron A (70%) (Dk = 31)
Natron A (65%) (Dk = 34.5)
Heffcon (57%)
Alloflex A (56%) (Dk = 32)
Omiflex A (56%) (Dk = 33)
Valeflex A (74%) (Dk = 36.1)
Hecoflex A (59%) (Dk = 38)
Neffcon A (65%) (Dk = 28)
Maxiflex A (70%) (Dk = 35)
Maxiflex B (59%) (Dk = 22)

Group 3
Low Water (<50% H2O)
Nonionic Polymers
Buflon A (45%) (Dk = 18)
Gelaflex A (43%) (Dk = 10)
Pheniflex A (38%) (Dk = 9)

Group 4
High Water (>50% H2O)
Ionic Polymers
Buflon A (55%) (Dk = 18)
Elastiflex A (56%) (Dk = 28)
Foamiflex A (55%) (Dk = 16)
Octiflex B (53%) (Dk = 18)
Octiflex C (55%) (Dk = 16)
Octiflex D (55%) (Dk = 18.7)
Octiflex E (55%) (Dk = 22)
Octiflex F (59%) (Dk = 24.3)
Pheniflex A (55%) (Dk = 18)
Metaflex A (45%) (Dk = 18)
Metaflex B (55%) (Dk = 18)
Wilflon A (55%) (Dk = 18)

FDA Group
FDA – (Food and Drug Administration) is a U.S. government body that oversees contact lenses, microlens/kneese & eye drops.

Silicon Hydrogel
High oxygen permeability

<table>
<thead>
<tr>
<th>Name</th>
<th>Material</th>
<th>H2O</th>
<th>DK</th>
<th>Diameter</th>
<th>Base Curve</th>
<th>Central Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>PureVision</td>
<td>Bausch &amp; Lomb</td>
<td>36%</td>
<td>99</td>
<td>14.0</td>
<td>8.6</td>
<td>90</td>
</tr>
<tr>
<td>Focus Night</td>
<td>(Ciba)</td>
<td>24%</td>
<td>140</td>
<td>13.8</td>
<td>8.4</td>
<td>70</td>
</tr>
</tbody>
</table>

Geometry: diameter, thickness, asphericity

Quoted Scleral (Oval): Double internal radius of curvature
External Rb 4.0
Diameter 1.3 mm
Aspheric External / Internal

11
**SCLERAL Lens**

<table>
<thead>
<tr>
<th>Name</th>
<th>Material</th>
<th>H2O</th>
<th>DK</th>
<th>Diameter</th>
<th>Base Radius (double)</th>
<th>Central Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovlens</td>
<td>Methafilcon A</td>
<td>55%</td>
<td>18</td>
<td>17.5</td>
<td>8.6/8.8</td>
<td>100</td>
</tr>
<tr>
<td>Quotidia Aloe</td>
<td>Scleral Aloe</td>
<td>Increased Comfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Medicines and Wettability:**

**Hyaluronic Acid, Aloe**

**Quotidia Aloe (Ovlens)**

- **Regenerative:** stimulates the growth of the epithelium in the wounds.
- **Proteolytic and healing:** dissolves and absorbs the enzymatically dead or damaged cells, stimulating the regeneration process.
- **Antinflammatory:** accompanies and helps to overcome the inflammatory process.
- **Antistress:** relieves burning from sunburn, inflammation and fever.
- **Humectant:** is moisturizing, favoring the water retention in the tissues of the skin.
- **Analgesic:** gives pain relief, even in the depths.
- **Fungicide:** impedes the growth of fungi.
- **Virostatic:** inhibits the growth of viruses.
- **Bacteriostatic:** inhibits the growth of bacteria.
- **Antipruritic:** relieves itching.
- **Detoxification:** helps detoxify the body from toxins impurities.

**Conclusion**

Today there is not a perfect contact lens for use in post-PRK.

- **Silicon Hidrogel**
  - DK High
  - No Ionic Material
  - Increases Mitosis

- **Scleral Aloe**
  - Ionic Material
  - Increases comfort
  - Bacteriostatic
  - Reduces pain
  - High wettability

**A.H.S: Aloe Hydra System Advantages**

- Stimulates epithelium regeneration
- Proteolytic function: absorbs damaged or dead cells
- Humectant function: improves water retention within the tissues
- Blocks virus, bacteria and fungi
- Antipyretic and anti-inflammatory action to ease after surgery recovery

**Nanotechnology in contact lens**

Diabetes may soon be able to wear contact lenses that continuously alert them to variations in their glucose levels by changing colours, replacing the need to routinely draw blood throughout the day.

Non-Invasive technology uses extremely small nanoparticles embedded into hydrogel lens. These engineered nanoparticles react with glucose molecules found in tears, causing a chemical reaction that changes their colour.

*Study and research made by Professor Jin Zhang, MD at the University of Western Ontario*
Nanotechnology in contact lens

Fluctuation of intraocular pressure (IOP) is characteristic of glaucoma. One issue in managing glaucoma is the measurement of IOP over time. The ability to continuously monitor intraocular pressure would be a valuable asset.

Mafteo Leonardi MD and a team of Swiss colleagues developed a new contact lens with a sensor embedded in it, capable of measuring changes of the corneal curvature produced by changes of IOP.

Nanotechnology in contact lens: Drug delivery

Many of the conditions that affect the eye are treatable through the ocular surface or ocular surface. Conventional delivery systems are not always optimal because of tear dynamics, dilution due to reflexive tearing, relative corneal impermeability to many medications and the influence of ocular surface health on drug absorption (typically less than 5% of instilled drug penetrates the cornea).

Main Objectives:

- How to link the drugs to the lens?
- What kind of drugs are fundamental to use with contact lenses?
- How much time the drug need to be effective (gradual time release)?

In principle, any pharmaceutical substance may be linked to a polymer base for contact lenses but it must be linked in order to be released and then only for implantation without the creation of chemical bonds with the polymer. The most useful substances in addition to drugs can be those as those for glaucoma may be substances capable of improving the epithelial metabolism and promoting re-epithelialization, anti-inflammatories, dehydrating the cornea (the lens itself can be used as drying agent). It appears very difficult to reintegrate such substances or liquids that can stabilize the tear film and experimenting with volumizing of tears resulted a failure.

Today Applications

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractive Surgery:</td>
<td>Corneal abrasions A&amp;E</td>
</tr>
<tr>
<td>LASIK and PRK</td>
<td>Dry Eye Syndrome</td>
</tr>
<tr>
<td>Pharyngum surgery</td>
<td>Meibomian Gland Dysfunction</td>
</tr>
<tr>
<td>Trabeculectomy</td>
<td></td>
</tr>
<tr>
<td>Cross Linking</td>
<td></td>
</tr>
</tbody>
</table>

The substances may be related to the lens or with strong bonds - hydrogen bonds in red - or only by inhibition i.e. for occupation of the space between the meshes of the polymer. The substances bound to the polymer with strong ties cannot be released passively but only for bond rupture. Instead, the imbibed substances can be passively released.
The release of imbibed substances with no integration alters the dimensional set as well as lens hydration. At present this is an obstacle to the development of pharmaceutical contact lenses. A solution could be the replacement of the material released by the lens with other tear-derived substances, as this would preserve the intrinsic features of the lens. Nevertheless, this is not easy due to the reduction of tear production caused by the lens presence on the eye and the consequent adaptation process.

In addition, if the substance which must be released by the lens is in high quantity, for instance in case of hyaluronic acid, the polymer should have sufficiently wide bonds in order to be able to imbibe a lens with this substance. Moreover it is quite difficult to re-imbibe a similar contact lens with the tear normally produced by an individual having no lens, even less by a contact lens patient as a consequence the lens will get dry and the polymer will definitely collapse.

Comment

The development of ophthalmic drugs for topical use is linked to the research of appropriate solutions allowing as much penetration as possible of active principles into the eye. A particular procedure is based on so-called corneal penetration enhancers, i.e. on substances capable of temporarily weakening the barrier system of the corneal epithelium by means of a "damaging action" both of the epithelial cells themselves - cytotoxic action - and of the intercellular tight junctions - ionic surface-active agents. The most comfortable materials have always been the preserving substances.

Comment

Contact lenses have a quite similar effect to that produced by preservatives with a merely metabolically action: the eye surface compartmentalization and the reduced oxygen availability for the corneal epithelium alters the cell exchange and breaks off the intercellular tight junctions, thus enhancing the penetration of any eventual substances connected with the lens itself.

Because of these intrinsic features, contact lenses are not a suitable system for drugs which are not conceived for penetration inside eyeball.

Comment

The usefulness of the lenses' release of drugs that are useful for the only ocular surface - i.e. tear integrators, re-epithelializing drugs – is strongly limited above all by the lens-induced compartmentalization. For the case of re-epithelialized eye it would theoretically permit to make use of low quantities of active principle and reduce the toxic effects of such substances, meanwhile favouring the re-epithelialization process through the cornea mechanic protection. At the same time cornea should be provided with an adequate metabolie balance, allowing an excellent gaseous exchange sufficient to grant increased oxygen consumptions as well as higher carbon dioxide production.

Thank you for your attention
Hoffer Split Bifocal History

Kenneth J Hoffer, MD
Implanted OCT & NOV 1990

2010 Oculentis MPlus

2012 LensTec

2014 NanoVision

Nano Hoffer Ridge

NOTE: That the axis of light is parallel to the axis of the loops.

Loop cause decentration. This way both segments stay in the pupil.
Address

TATIANA NAOUMIDI MD, PhD
A’ Ophthalmology Dept/ment
Aristotelion Univ. Hospital, Cornea Service
Private Practice: 30 Egnatia str.
Thessaloniki, GR
Ph: +30 2313 022 038
email: Tatiana@naoumidi.com

DIMITRII DEMENTIEV MD
Dementiev Eye Care
Blue Eye Center
P.za Fontana 6
20129 – Milano - Italy
Ph. +39 02-29531307
Fax +39 02-93585308
e-mail: eye3d@mail.ru

KENNETH J HOFFER MD
Clinical Professor of Ophthalmology, Stein Eye Institute,
University of California, Los Angeles
St. Mary’s Eye Center
411 Lincoln Blvd, Santa Monica, CA 90402 USA
e-mail: KHofferMD@aol.com

IOANNIS PALLIKARIS MD PhD
Professor in Ophthalmology,
School of Medicine, University of Crete, Department of Ophthalmology, 71110
Heraklion, Crete, Greece
e-mail: pallikar@med.uoc.gr

MATTEO PIOVELLA MD
C. M. A.
Centro Microchirurgia Ambulatoriale
Via Donizetti, 24 - 20900
Monza- Italy
Ph.: +39 039389498
Fax:+39 0392300964
e-mail: piovella@piovella.com