FUTURE THERAPY OPTIONS IN GLAUCOMA

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Components of Glaucomatous Neuropathy

- Loss of neural tissue
- Activation of microglia
- Tissue remodeling
- Blood flow disturbances
Elevated IOP is the most important risk factor for onset and progression of glaucoma.

Increased ECM material in TM:
- Disturbed balance between ECM deposit and degradation
- Disturbed balance between TGF-β2 and the bone morphogenetic proteins (BMP-7i and BMP-4)

Lowering the IOP (baroprotection) remains the only current therapeutic approach

Future Glaucoma Treatments

- Baro-Protection
- Neuro-Protection
- Vaso-Protection
- Gene Therapy
BAROPROTECTION

A. Increase trabecular meshwork outflow

• Two main new therapeutic targets:
  1. Alterations in TM cell activities or behaviour
     • affect cell volume and shape
     • loosen cell-to-cell junction TM/Schlemm inner wall
     • loosen cell-to-ECM adhesion TM/Schlemm inner wall
  2. Modulation of contractility of TM

B. Increase uveoscleral outflow

C. Decrease aqueous humour production

New therapeutic targets that lower intraocular pressure

**Rho Kinase Inhibitors**

The Rho family is a group of guanosine triphosphatases (GTPases)

- Central role in cellular processes:
  - actin cytoskeleton activity
  - cell contraction and motility (actin-myosin related)

- Rho associated coiled coil-forming protein kinase (ROCK) is a downstream effector of Rho in the Rho-dependant signal pathway

Rho Kinase Inhibitors

• Rho kinases are expressed in ocular tissues, including TM and CM.
• Inhibition of ROCK activity induces alterations in TM cellular responses:
  ▪ migration
  ▪ adhesion
  ▪ changes in cell shape

Rho Kinase Inhibitors

- Rho kinase inhibitors are widely considered as a new treatment for glaucoma.
- Rho kinase inhibition has been shown *in vitro* and *in vivo* to lower intraocular pressure.
- Furthermore, in the first clinical reports involving healthy human subjects, the results were quite promising.
- The inhibition of Rho kinase lowers the intraocular pressure by increasing the outflow through the TM.
- Increased blood flow to the optic nerve and a possible delay of optic nerve cell death has also been reported.

Colligris B et al. *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery* 2012; 6:89-98
ROCK inhibitors offer at least four distinct applications relevant to glaucoma management:
- significant IOP-lowering effects
- improvement in ocular blood flow
- inhibition of postoperative scarring
- promotion of retinal ganglion cell survival and axon regeneration

Over the past decade, a considerable number of ROCK inhibitor candidates have failed during clinical testing.

Nonetheless, four ROCK inhibitor-based drugs (K-115, AR-13324, PG324, AMA0076) have continued to show promise as future glaucoma therapeutics.

Human Clinical Trials

• Among the farthest along in the clinical trial process is K-115, developed by Kowa (Aichi, Japan).

• During phase II trials, dose-response treatment of 210 patients with primary open-angle glaucoma or ocular hypertension resulted in a mean IOP reduction of 4.5 mmHg for 0.4% K-115 after 2 hours. ¹

• Another promising ROCK inhibitor designed for glaucoma therapy is AR-13324, Aerie Pharmaceuticals Inc., (Research Triangle Park, NC, USA). ²

• Phase IIb demonstrated that once-daily administration could significantly lower IOP by 5.7–6.2 mmHg in patients with elevated IOP. ²

• PG324 (triple action) is combination of latanoprost and AR-13324 (Phase IIb)

New Prostaglandin Analogues

• Several new prostaglandin analogs (PGA) are in various stages of development.
• A second generation F2α prostaglandin agonist, -AR-102:
  ▪ 150-fold greater selectivity
  ▪ 30-fold greater potency at the FP receptor (vs. latanoprost)
  ▪ greater IOP efficacy in comparison with latanoprost
  ▪ a better tolerability than travoprost
• This product is planned to be delivered as an ocular implant (Aerie pharmaceuticals, Inc. data).
• Re-evaluation of PGE₂ analogues (butaprost 0.1%)

Potential Antiglaucoma Molecules

• Latanoprost and nitric-oxide donating molecules:
  ▪ greater IOP lowering that latanoprost action through specific mechanisms, including relaxation of ciliary muscle

• Investigational nitric-oxide donating topical carbonic anhydrase inhibitor (CAI), dorzolamide

• Cholesterol-lowering statins:
  ▪ induce changes in cell morphology and actin cytoskeletal organization through decreasing Rho guanosine triphosphatase (GTPase) activity

Potential Antiglaucoma Molecules

- Recent studies have demonstrated the presence of cannabinoid CB1 and CB2 receptors in the TM cells\(^1\)
- Some agents that are selective CB1 and CB2 receptors increase aqueous humor outflow through changes of TM cell morphology\(^2\)
- Noladin, given topically, lowers IOP immediately, with maximum efficacy of 17% of IOP reduction, observed 2 hours after administration\(^3\)

Potential Antiglaucoma Molecules

• Anecortave acetate, an angiostatic cortisone without corticosteroid effects:
  ▪ administered by sub-Tenon’s injection,
  ▪ IOP lowering (about 30%) for 3–12 months after a single injection

• Mifeprostone (RU-486), an antiprogesterone steroid:
  ▪ a non-selective and selective corticosteroid receptor antagonist
  ▪ administered topically
  ▪ binds to the glucocorticoid receptor in TM cells
  ▪ prevents binding of endogenous glucocorticoids to this receptor

• Diuretics

Vasoprotection represents an IOP-independent strategy for glaucoma.

Activated astrocytes up-regulate the production of various molecules, including NOS-2, MMPs, TNF-\(\alpha\) and endothelin.

- Aminoguanidine and G-nitro-L-Arginine-Methyl Ester (L-NAME): NOS-2 inhibition
- Down-regulation production of MMP-2 and MMP-9: Ilomastat
- Endothelin-1 blockage: calcium channel blockers

It appears you both have a gene that causes extreme stubbornness. Would you like me to remove that so your child does not inherit it?

Yes!

NO!
Gene-based therapies delivered to the anterior chamber could lower IOP, delivered to the posterior chamber could protect retinal ganglion cells. Neurotrophic factors delivered to the posterior chamber could protect retinal ganglion cells from glaucoma-related apoptosis.

Stem cells delivered to the anterior chamber could restore trabecular outflow pathway function, delivered to the posterior chamber could repair and/or protect retinal ganglion cells.
GENE THERAPY

- Potential target structures or cells for glaucoma gene therapy:
  - trabecular meshwork (TM)
  - ciliary epithelium (CE)
  - ciliary muscle (CM)
  - RGCs, and Müller cells (MC)
  - conjunctiva

- The viral vectors have proven to be the most effective gene transfer system in experimental glaucoma.
- Adenovirus (Ad) vectors appear to be optimal for anterior segment delivery, especially to the TM and CE.
- Adeno-associated virus (AAV) vectors have highly selective tropism for RGC (intravitreal injection).

Manipulation of the biochemistry of TM by gene transfer:
- modulate outflow resistance
- achieve IOP reduction

Adenovirus vector carrying the MMP or myocilin reach TM cells after intracameral injection.

Modulation of the activity of TGF-β2

Adenovirus-delivered caldesmon in cultured human TM cells induced reorganization of the actin cytoskeleton, disruption of cell-cell and cell-matrix adhesions.

STEM CELL THERAPY

- Reprogramming of adult somatic or germ cells to become induced pluripotent cells or somatic nuclear transfer cells
- Adult stem/progenitor cell might be expanded ex vivo to replace missing or nonfunctional TM cells in glaucomatous patients.
- Experimental studies on graft mesenchymal stem cells and mature retinal cells to replace the dead RGCs are being advanced.

Novel Drug Delivery Methods

• New methods of drug delivery may be available soon.

• Nanocarriers, can also be used to enhance ocular drug delivery and to improve treatment efficacy:
  - nanoparticles (NP)
  - dendrimers
  - liposomes

NP can be engineered from natural (albumin) or synthetic (polylactide and polylactide-co-glycolide) biocompatible polymers.

• Experimentally, carbonic anhydrase inhibitors can be successfully attached to the NP<100 nm.

• Several stimuli-responsive NP have also been described for self-regulated drug delivery.

CONCLUSION

• IOP lowering will remain the most important therapeutic strategy over the next decade.

• However, recent advances in the fields of neurobiology, genetics and nanotechnology point to a number of novel promising glaucoma therapies in the 21st century.