Non-compliance in Glaucoma

- Even if a patient is compliant, only 33-50% are actually instilling them correctly.
- 20% of patients depend on another person to instill their eyedrops.

Non-compliance in glaucoma

- It has been said that the only glaucoma patients in which we can accurately evaluate compliance are the ones who walk in the office and say that they haven't taken their medicine for months.
- The reason that most patients fail medical therapy isn't because the drugs don't work, it's because patients can't use them.

Advantages to drops

- Relatively easy & inexpensive manufacturing
- Portable
- Non-invasive
- Accepted standard of care

Disadvantages to drops

- Difficult to instill
- Variable dosing
- Dilution and washout
- Require high drug concentrations
- Ocular and systemic side effects

Major compliance and execution issues

Current Topical Ophthalmic Drug Delivery

$5+ Billion Market
Eye Drops (95%), gels, ointments
Treating five disease conditions

- Glaucoma
- Allergy
- Dry-eye
- Infection
- Inflammation
Developing new medications

- On average, it takes more than 10 years to develop a new drug
- Fewer than 1 in 20,000 new drug candidates ever make it to approval
- Average cost is well over $1 billion
- Fewer than 25% of approved drugs even cover their own developmental costs

There has to be a better way!

Strategic Drug Delivery

- Companies can make more patient-friendly products and do it at a fraction of the time, risk, and cost of developing a new drug molecule
- Can use existing medications
- We already have excellent drugs, just need to deliver them in a better fashion

Drug Delivery Innovations

- Different methods currently being developed to improve drug delivery to the eye and thus treatment outcomes in glaucoma
- Many approaches aim to control IOP over a period of several months
- Site of delivery varies from topical, sub-conjunctival, or intraocular

Ideal Drug Delivery Device

- Consistent delivery of drug for possibly up to six months
- Comfortable without side effects
- Close to 100% retention rate
- Could be placed by a non-physician

Drug Delivery Innovations

- Punctal Plugs
- Gel-Forming Drops
- Injectables and Implants
- Drug-Eluting Contact Lenses

Punctal Plugs

- Promising way to deliver glaucoma drugs
- Plugs are inserted into tear ducts where they stay for two to three months
- Plugs made of different polymers
  - Silicone
  - Hydrogel
  - Polycaprolactone
- Currently at least two companies actively developing plugs for glaucoma treatment
Ocular Therapeutix

- Developing drug-eluting polyethylene glycol hydrogel plugs to deliver three types of medications
  - anti-infectives
  - corticosteroids
  - Travoprost

Pilot Clinical Study

- Purpose:
  - The clinical study was conducted to evaluate the OTX-TP for IOP reduction over 60 days in ocular hypertensive or glaucoma patients.

- Primary Endpoints:
  - Plug retention at all timepoints through day 60.
  - Mean IOP at each timepoint.
  - Mean IOP change from baseline and mean IOP percent change from baseline.

OTX-TP2

- OTX-TP2 delivers travoprost to ocular surface for two to three months, then resorbs and passes out through nasolacrimal system

Methods

- Prospective, single-arm study at 2 sites in South Africa
- 20 patients (36 eyes)
  - 11 male
  - 9 female
- The OTX-TP2 was inserted into one punctum of each patient’s affected eye(s) on Day 0.
- Subjects with bilateral glaucoma or ocular hypertension were treated in both eyes but only the eye with the higher IOP was included in the efficacy analysis.
- All eyes were included in the safety analysis.
- Follow-up assessments:
  - Day 3, 15, 45 (8am only)
  - Day 30, 60 (8am, noon, 4pm)
  - Post-60 days (every 15 days) until OTX-TP2 not present

Interim Results

<table>
<thead>
<tr>
<th>Day</th>
<th>N</th>
<th>mmHg</th>
<th>%</th>
<th>mmHg</th>
<th>%</th>
<th>mmHg</th>
<th>%</th>
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<tbody>
<tr>
<td>3</td>
<td>20</td>
<td>-5.0</td>
<td>-17.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>15</td>
<td>19</td>
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<td>-21.4</td>
<td>-5.1</td>
<td>-18.6</td>
<td>-5.6</td>
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</tr>
<tr>
<td>45</td>
<td>16</td>
<td>-6.5</td>
<td>-23.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>60</td>
<td>13</td>
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<td>-23.5</td>
<td>-5.1</td>
<td>-18.6</td>
<td>-4.3</td>
<td>-16.0</td>
</tr>
</tbody>
</table>

Mean baseline IOP range: 23.7-32.7 mm Hg
Interim Results

**OTX-TP2 Summary**
- The OTX-TP2 is well-retained overall.
- Patients comfortable; no unanticipated, unexpected or serious adverse events.
- Insertion and retention of the OTX-TP2 proved to be safe and well tolerated.
- OTX-TP2 provides therapeutic benefit for targeted duration of 60 days.
- Further clinical evaluation is warranted to evaluate OTX-TP2 platform as a potential alternative to topical drop administration for glaucoma and ocular hypertension for 90-day therapy.

**Interim Results**

**Diurnal IOP Measurement**

<table>
<thead>
<tr>
<th>Days</th>
<th>8:00 AM</th>
<th>12:00 PM</th>
<th>4:00 PM</th>
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<tbody>
<tr>
<td>0</td>
<td>26</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>28</td>
<td>28</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>60</td>
<td>28</td>
<td>26</td>
<td>24</td>
</tr>
</tbody>
</table>

**Hyperemia score (0 to 4)**

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tr>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>60</td>
<td></td>
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</tr>
</tbody>
</table>

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**Mati Therapeutics (QLT)**

- QLT reported in October 2012 that two Phase 2 clinical studies demonstrated positive trends on efficacy and safety of a latanoprost punctal plug delivery system in subjects with OAG and OHTN.
- Studies assessed two different delivery doses as well as use of plugs in upper vs. lower punctum or in both puncta simultaneously.
- Mati Therapeutics bought QLT’s punctal plug therapy in April 2013 and plans to advance to phase 3 trials in 2014.

**Punctal Plugs - Challenges**

- Plug is a foreign object with potential to move, cause irritation, or fall out.
- Movement may affect drug release.
- Changes in environment, including tear film and enzymes, can cause plug to malfunction.
- Potential for bacterial buildup.
- May need preservative in formulation.
- Plug should be able to release drug at constant rate for months.
Gel-Forming Drops

- Long-lasting gel incorporating a drug
- Sidesteps problem of foreign object in eye
- Being developed by two groups:
  - Pentablock copolymer
  - InSite Vision - Durasite

Pentablock Copolymer

- Recently patented by Ashim Mitra, PhD at University of Missouri – Kansas City
- Biodegradable pentablock copolymer that can serve as a vehicle for topical or intraocular drug delivery
- Five polymer blocks are all FDA approved for use in the eye

Pentablock Copolymer

- Topical version starts by adding drug in polymer drop which is not viscous
- Drop reacts with body temperature upon touching eye
- Transforms from solution to gel that cannot be washed away
- Gel forms a film under lid where drug is released slowly over time, and polymer eventually degrades
- Time course could be two, four, or six months depending on drug dose

Pentablock Copolymer

- One problem is “burst effect” where 30-40% of drug is rapidly released, but so far pentablock copolymer has been strong enough to hold drug for slow release
- Five polymers can be configured to work with specific drugs
  - Plan to add pentablock copolymer to timolol or latanoprost

Pentablock Copolymer

- Dr. Mitra envisions a time where drugs can be tailored for each individual
- Right now we give same dose to everybody, but one day may be able to titrate particular rate of release needed for an individual patient and be able to maintain that for many months
InSite Vision - Durasite

- Durasite incorporates a polymer-based formulation meant to extend drug residence time compared to conventional topical drugs
- Polyacrylic acid is cross-linked with divinyl glycol to result in hydrogen-bonding with mucus and the epithelium (corneal and conjunctival), which are negatively charged, and thus extend the drug residence time to hours on the ocular surface

- Already being developed for ocular antibiotics, NSAIDs and steroids
  - azithromycin and besifloxacin
  - bromfenac and dexamethasone
- Recent 2013 ARVO poster reported a significantly improved bimatoprost 0.03% delivery to rabbit eyes compared with bimatoprost 0.03% solution
- Increased ocular penetration would allow lower concentrations needed for treatment to also lessen ocular side effects

Injectables and Implants

- **Icon Bioscience, Inc.:** IBI-60089
  - Single injection of IBI-60089 through 30-gauge needle into anterior chamber
  - Vehicle degrades and eventually disappears as active agent is released over time
- **pSivida:** Durasert
- **Replenish, Inc.:** Ophthalmic MicroPump™
- **Euclid Systems:** Collagen-based drug-delivery systems

- **Verisome® technology** encompasses over 20 related, but distinct, novel and proprietary drug delivery systems
- Final product can be manufactured in a biodegradable solid, gel or liquid form capable of releasing drug in a controlled manner for extended periods of time
- IBI-60089 is a biodegradable product for the delivery of therapeutic levels of latanoprost to the anterior chamber

- Verisome® formulation designed for 6 month to one year delivery in anterior chamber and the vitreous
- Ultrasound of an intravitreal Verisome® formulation injected in the eye
- Product designed to disappear in weeks to months (as required) when injected into the anterior chamber of the eye

- Company announced plans to initiate phase I/II clinical trials in 1st quarter of 2014
pSividia

- Already developed two approved sustained-release intravitreal devices:
  - Iluvien and Retisert
  - Now developing Durasert, in conjunction with Pfizer
- Biodegradable drug delivery system for latanoprost that is injected into subconjunctival space with 25-gauge needle
- Phase I/II clinical trials currently underway

Durasert latanoprost implant

- Implant is bioerodible and is expected to deliver an appropriate dosage of latanoprost for about three months
- Depending on the results of the Phase I/II dosing study, might last as long as six months.
- Since the implant is bioerodible, it will be absorbed by the eye and will not have to be surgically removed.

pSividia

Replenish, Inc.

- Developing Ophthalmic MicroPump™ System
- Implanted in sclera
- Glaucoma and Retinal versions
- Injects programmed amounts of drug at set times for up to 12 months
- Device is refillable when medication is exhausted

Durasert latanoprost implant

- Tiny translucent cylindrical polymer tube, between 3 to 4 mm in length and about 0.4 mm in diameter
- About the size of a grain of rice, and is designed to provide a low daily dose of latanoprost

- Compromised of four subsystems
  - Anterior MicroPump™ (AMP)
    - The AMP has a similar cannula system and insertion point to glaucoma drainage devices.
  - Posterior MicroPump™ (PMP)
    - The PMP is similar to the AMP, except the drug delivery outlet is fitted with a PARS PLANA CLIP™ and has a larger reservoir volume.
  - EyeLink™
    - The EyeLink™ is a wireless programmer/charger for bi-directional communication with the MicroPump implants.
  - Drug Refill System™
    - Separate console unit used to fill and refill the MicroPump™ implants with drug. A disposable refill tubing kit with 31-gauge needle is used to fill and refill the implant.
Euclid Systems

- Developing two collagen-based systems to provide sustained release of latanoprost.
- Injectable in situ gelling collagen solution
- 2mm x 4mm collagen wafer implanted in sclera
- Demonstrated release of latanoprost for up to 180 days

Drug-Eluting Contact Lenses

- Combined efforts of researchers at the Massachusetts Eye and Ear/Harvard Medical School Department of Ophthalmology, Boston Children's Hospital, and the Massachusetts Institute of Technology
- Published results in January 2014 describing drug-eluting contact lens designed for prolonged delivery of latanoprost for treatment of glaucoma

Drug-Eluting Contact Lenses

- Latanoprost-eluting contact lenses were created by encapsulating latanoprost–poly(lactic-co-glycolic acid) films in methafilcon by ultraviolet light polymerization.
- In vitro and in vivo studies showed an early burst of drug release followed by sustained release for one month.
- Contact lenses containing thicker drug–polymer films demonstrated release of greater amount of drug after the initial burst.

Drug-Eluting Contact Lenses

- Use of soft contact lenses has been proposed as a method to deliver drugs to the eye in an efficient manner.
- Contact lenses restrict the drug from being lost to tear drainage by releasing the drug into two tear layers on either side of the contact lens, where it ultimately diffuses into the eye.
- By using loaded soft contact lenses, continuous drug release for extended period is possible

Drug-Eluting Contact Lenses

- Improved ocular bioavailability of drugs can be obtained when wearing drug-impregnated conventional soft contact lenses.
- Amount of drug which is diffused toward corneal surface is five times higher than that released toward external lacrimal fluid.
- Cornea remains in contact with high concentrations of drug for longer periods of time and drug penetration is more efficient.
Drug-Eluting Contact Lenses

- *In vivo*, single contact lenses were able to achieve, for at least one month, latanoprost concentrations in the aqueous humor that were comparable to those achieved with topical latanoprost solution.
- The lenses appeared safe in cell culture and animal studies.
- This contact lens design can potentially be used as a treatment for glaucoma and as a platform for other ocular drug delivery applications.

TODDD™ - Material

- Composed of polymers selected for comfort and biocompatibility
- Drug is polymerized into a drug specific material matrix
- Drug molecule unaffected by the polymerization
- TODDD releases drug at a therapeutic rate over numerous months

TODDD™ Topical Ophthalmic Drug Delivery Device

- Developed by Amorphex Therapeutics
- Drug containing soft elastomeric material
- Rests on the sclera (under the eyelid)
- Insert once for 3 to 90+ days of 24/7 drug delivery

Drugs Incorporated in TODDD™:

- (partial list)
  - Timolol maleate
  - Prostaglandins
  - Pilocarpine
  - Brimonidine
  - Dexamethasone
  - Prednisolone
  - Ciprofloxacin
  - Ibuprofen
  - Lidocaine

TODDD™ Configuration Options

- Matrix – drug is dispersed throughout the device material
- Drug Depot Carrier – drug material is contained in distinct chambers
- Combination – Matrix and Carrier
- One TODDD can dispense multiple drugs simultaneously

New Approach = Technical Breakthrough

Modify contact lens design features and create other elements to provide sustained comfort, retention, stability, and capacity

- Central curvature
- Peripheral curves
- Lenticulation
- Edge apex contours
- Edge lift
- Corneal relief curve
TODDD™ with Anterior Drug Depots and Tear Flow Features

TODDD™ - Competitive Advantages

- Non-invasive
- Many options for replacement
  - Not just physician’s office or hospital setting
  - At home, by patient, visiting nurse
- Replaced in less than a minute
- Excellent retention and easy confirmation by patient
- Much greater capacity
  - Longer duration
  - Delivery of multiple drugs simultaneously

Volume for Sustained Delivery

Note for comparison a punctal plug in one of TODDD’s two available drug depots

TODDD™ Drug Delivery

- Easier and more accurate delivery compared to drops delivery
- Provides inherent compliance
- Acts as a non-invasive, continuous low-dose ocular treatment
  - Drug readily absorbed, no reflex tearing
- Unlike drops, no detectable drug in plasma
  - Eliminating systemic side effects

Human TODDD Experiment

- Timolol TODDD – 1 eye
- IOP monitored at independent institution
- Examiners blind to fact of treatment
- Subject normotensive, no glaucoma
  - Expected reduction with drops 2 – 3 mm (average over 90 days)

Competitive Comparison of Ocular Drug Delivery in Development

<table>
<thead>
<tr>
<th></th>
<th>TODDD</th>
<th>Punctal Plug</th>
<th>Pellet Injection</th>
<th>Prolonged Drops</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solves eye drop instillation issues</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Inherent Compliance</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>One dose multi-month delivery</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Delegate placement of device</td>
<td>Yes</td>
<td>Yes</td>
<td>Rarely</td>
<td>Yes</td>
</tr>
<tr>
<td>Replaceable by layperson</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fast and easy replacement</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No*</td>
</tr>
<tr>
<td>Facility required for replacement</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>More than one size required</td>
<td>Likely</td>
<td>Usually</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient unaware of injection</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
</tr>
</tbody>
</table>

* 5 minutes a day × 30 yrs./year
Human TODDD Experiment

- Through 280+ days and 62 measurements
  - All 62 measurements below untreated eye’s
    - Prior to treatment it averaged 0.5mm above untreated eye
  - All 62 measurements below baseline average
  - 1st TODDD thru 184 days = 2.48 mm below
  - 2nd TODDD thru 90 days = 3.44 mm below
  - 3rd TODDD thru 14 days = 4.10 mm below
  - Drug exposure = 15-20% of drops

Major Development Progress

- Demonstrated human comfort and retention
  - Worn continuously 24/7 for 200+ days
  - 10 subjects through 30 days of continuous wear in current clinical (ongoing)
- Developed pilot cast molding manufacturing process
- US and international patents issued and pending for devices and materials processing
- Held pre-IND meeting and discussions with FDA

Will patients accept new Glaucoma drug delivery devices?

- One study out of Singapore looked at patient preferences of new ocular implants
  - 75% of glaucoma patients would trade their eye drops for subconjunctival injection every three months
  - Higher percentages with those using multiple medications
  - 85% may be willing to accept higher costs for alternative treatment method
  - Some willing to pay even double the costs

What Lies Ahead

- Combining these new technologies to other molecules in the pipeline
- These devices could open door to drugs that couldn't be used in a standard drop formulation due to their pharmacokinetics or side effects at peak levels
- Novel delivery system could be used with an IOP monitoring device

Major Development Progress

- 3rd NIH SBIR grant (Phase II-a) $2.6m total
- Optimized materials - in vitro release of therapeutic levels of drugs for over 90 days
- Demonstrated efficacy in 90 day timolol rabbit study
- Lowered IOP 35+% in normotensive dog study
Currently we take IOP measurements weeks or months apart.

Large gaps in data collection
Several new technologies to fill in gaps and provide better IOP readings
- Sensimed Triggerfish
- PRO-IOP
- Icare ONE tonometer

SENSIMED Triggerfish®
- Sensor is a soft disposable silicone contact lens embedding a micro-sensor that captures spontaneous circumferential changes at the corneoscleral area. (1)
- Adhesive SENSIMED Triggerfish® Antenna, which is placed around the eye, receives the information wirelessly from the contact lens. (2)

Contact lens device capable of continuous IOP measurements
- Provides an automated recording of continuous ocular dimensional changes over 24 hours

SENSIMED Triggerfish®
- Contact lens sensor contains strain gauges that measure corneal curvature changes caused by intraocular pressure variations
- Microprocessor and an antenna integrated into the soft contact facilitate wireless powering and communication.
The data is transmitted through a thin flexible cable from the Antenna to the portable recorder. (3)

The portable recorder, worn by the patient, stores the acquired data during the monitoring session. At the end of the recording period, the data is transferred via Bluetooth from the recorder to the software previously installed on the practitioner’s computer. (4)

Collects data during the full physiological 24-hour cycle

Provides the individual IOP-related profile

Reveals currently unavailable information

Enables further treatment personalization for glaucoma patients at risk of progression

Potential use is unclear since it provides relative rather than absolute IOP measurements

May be difficult for some patients to tolerate wearing contact lens for 24 hours

Implandata Ophthalmic Products GmbH (IOP GmbH) is a medical device start-up company, located in Hannover, Germany

PRO-IOP fulfills the requirement for easy and reliable continuous measurement of IOP by the eye doctor or the patient

The video “Telemetric IOP measurement, deciphering glaucoma’s blind spot” was awarded with the 2013 Grand Prize of the ASCRS annual meeting film festival

Pro-IOP eye pressure measurement system consists of an implantable micro sensor, responsible for pressure sensing

External hand held device, which is transferring energy to the micro- sensor telemetrically and which is responsible for data read out and storage

GSM module which can be connected with the hand held device for transfer of measurement data to a database
Database can be accessed by doctor in order to get information about the disease status of patient. Also planned to give patient limited access to data via an App, in order to review data history or allow communication between the eye doctor and the patient.

PRO-IOP
- Delivers direct and real IOP information, expressed in mmHg
- Allows IOP measurement at any chosen cycle, frequency, and repeatability
- Facilitates measurement under patient's normal life situation, not compromising patient's behavior
- Discloses to the eye doctor crucial information regarding patient specific pressure fluctuation and variability, if chosen therapeutic measures work, and on patient therapy adherence
- Designed for easy patient use and can be integrated into telemedicine systems for remote patient management

PRO-IOP
- Good correlation compared to pneumotonometry

PRO-IOP
- Anticipated that device should be durable enough to accurately sense IOP for 10-15 years
- Suitable for stable patients requiring 1-2 measurements a day
- External antenna can be integrated into night mask or spectacle frame if continuous IOP measurements needed
- Integration into telemedicine infrastructure will allow for remote patient management
Icare ONE tonometer

- Developed by Icare Finland Oy for screening and self-monitoring of IOP
- Based on rebound measuring principle in which a magnetized probe is propelled against cornea using a solenoid
- Solenoid detects motion and impact of probe when it touches cornea and rebounds back
- Moving magnet in probe induces voltage in solenoid, and motion parameters are recorded

Icare ONE tonometer

- Main innovation is that it allows patients to self-monitor IOP at home
- Considered to be minimally invasive and accurate, and particularly useful in children
- Patients need to be motivated and able to self-monitor IOP and report readings to doctor
- Cost of tonometer also potential barrier
  - Currently about $1500 for device, plus $2 for replaceable probe

Icare ONE tonometer

- Does not require any calibration or maintenance
- Can be used without topical anesthetic
- Allows patient to self-monitor IOP daily
- Ability to measure IOP outside of clinic hours to detect peaks and fluctuations

Icare ONE tonometer

- Advanced algorithm combined with state of the art software analyzes deceleration and the contact time of the probe while it touches the cornea
- Deceleration and the contact time of the probe change as a function of IOP
- In simple terms, the higher the IOP, the faster the probe decelerates and the shorter the contact time

Summary

- New technologies being developed to better deliver drugs to patients
- Allows for better compliance and dosing
- May be able to individualize treatment plans, so medications aren’t “one size fits all”
- Delivery systems may one day be linked to IOP monitoring systems, like a closed-loop insulin pump