GLAUCOMA DEVICES

In Glaucoma, Devices Go Eye-to-Eye With Drugs

In the treatment of glaucoma, device start-ups began, 10 years ago, to try to fill a void between first-line drugs with compliance issues and end-stage surgeries with their safety and durability limitations. But now, device companies are going head-to-head with drugs as a first-line therapy, hoping to improve glaucoma care and create an enormous device market.

BY MARY STUART

- Glaucoma is a serious disease of interest to VCs and strategic investors because of its sheer size; the disease affects three million people in the US alone.
- Glaucoma is deceptively complicated. On one hand, a single mechanism is implicated: high intraocular pressure (IOP), but IOP and accompanying vision loss vary dramatically among patients.
- While glaucoma has created a drug market worth $4 billion, drugs have several problems, including patient non-compliance, ineffectiveness over time, and inapplicability for certain patients.
- Device companies such as Glaukos are providing physicians with a variety of additional treatment options that are potentially safe and efficacious enough to compete directly with drugs.

The treatment of glaucoma, the second leading cause of blindness in the world, has the hallmark of a clinical field that's somewhat early in its development. There is no clinical consensus regarding preferred therapies, and potential treatments are few and very different from one another. Current glaucoma therapies range from drugs offering maximum safety and minimal efficacy to surgical procedures offering great efficacy but also great risks.

Ten years or so ago, start-up device companies began to see if they might not be able to bring the paradigm of interventional cardiology to glaucoma by introducing less invasive devices that would bring enough efficacy to replace or stave off the morbid surgeries that are typically only reserved for the end stages of a disease. Among the first of these start-ups were **NeoMedix Inc.**, founded in 1993 to develop a minimally invasive device called the *Trabectome*, and **iScience Interventional**, founded in 1999, which borrowed the idea of a catheter from interventional cardiology, creating a minimally invasive entryway to enable a variety of ophthalmic procedures, beginning with glaucoma. (*See Exhibit 1.*)

The pace of innovation increased after the publication, in 2002, of the initial results of the National Eye Institute's Ocular Hypertension Study, which validated the reduction of intraocular pressure as an effective treatment strategy in glaucoma. Venture capital firms were drawn to glaucoma, investing more than $440 million in glaucoma device start-ups over 10 years because of the sheer size of the market – three million patients in the US with open angle glaucoma (the most prevalent kind) and 150,000 new diagnoses each year, with prospects for additional market growth ahead due to the aging population demographics, as the disease tends to affect people over the age of 60. Glaucoma also looked like a space where a tried and true interventional paradigm could be brought to a disease with a known and simple mechanism of action: that of lowering elevated intraocular pressure.

DEVICES GO WHERE ONLY DRUGS WENT BEFORE

Along the way to a new interventional specialty, something unusual happened. Device companies realized that glaucoma has some unique management challenges that give devices the opportunity to do more than just replace morbid end-stage treatments, a relatively small market. **Glaukos Corp.** and other companies that have followed it, including **Transcend Medical Inc.** and **AqueSys Inc.**, believed that a safe and efficacious device could provide a first-line alternative to drugs in patients with mild-to-moderate glaucoma. To demonstrate that it could be done, Glaukos, the first company to advance this strategy, had to blaze new ground in glaucoma treatment: conduct what essentially would be a pre-market approval (PMA) clinical trial.

In a market where all other devices have come out of the 510(k) regulatory process at the FDA, Glaukos mounted the first study in the field of glaucoma devices – maybe even in the entire field of ophthalmology devices – to go through the PMA process using a comparative control. Although not strictly comparing its therapy with drugs, Glaukos chose endpoints that would demonstrate the relative benefits of the device versus drugs.

The company targeted patients with both glaucoma and cata-

racts, and piggybacked its surgical implant onto cataract surgery, lowering the risk for an implanted device. Glaukos conducted a randomized, controlled clinical trial with 239 patients, 116 treated with cataract surgery and the company's *iStent*, while the control group was treated with cataract surgery only. Both groups received glaucoma drugs as needed to manage intraocular pressure. At 12 months follow-up, 72% of the iStent patients met the primary endpoint of intraocular pressure equal to or less than 21 mm Hg (millimeters of mercury, a unit referring to pressure measurements) without the use of anti-glaucoma medications. In the control group, 50% of the patients met that primary endpoint. As a secondary endpoint, Glaukos looked at the percentage of eyes treated that showed an intraocular pressure reduction greater than or equal to 20% from baseline without medication. At 12 months, 66% of the iStent patients' eyes met that goal compared with 48% in the control group.

On July 30, 2010, the Ophthalmic Devices Panel of the FDA voted 7 to 1 that the benefits of the iStent outweigh the risks. The FDA has not yet issued a final determination on the Glaukos device, and the agency said it would like to see five years of continued follow-up data on the 290 pivotal trial patients and may recommend a new prospective 360-patient, five-year post-approval study. Thomas Burns, president and CEO of Glaukos, says, "We are delighted with the panel's finding and its strong support that iStent has established a compelling benefit-to-risk ratio and the panel's broad recognition that additional therapies are needed in the marketplace to effectively manage glaucoma."

THE HIDDEN COMPLICATIONS OF GLAUCOMA

A major factor inhibiting the growth of successful therapies is that clinicians and industry now acknowledge that glaucoma is a deceptively complex disease. As noted, the management of glaucoma revolves around using drugs or surgical strategies to lower intraocular pressure. A physician might determine that a patient should maintain a target intraocular pressure of 18. If the patient comes back and there is progression of the disease, then he or she will lower the target IOP to 16, for example. But there are two enormous complications here. First, while physicians manage the disease by titrating therapy around signs of disease progression with respect to intraocular pressure measurements, there are no

Exhibit 1

Venture Capital Investment In Glaucoma Devices

COMPANY TOTAL RAISED TO DATE SINCE FOUNDING	TECHNOLOGY FOCUS/ INVESTORS
AQUESYS $51 MILLION SINCE 2006	Exact approach not disclosed, but according to company, a device that is broadly adoptable in a 10-minute procedure that does not rely on a hypothesis concerning the source of blockage./Accuitive Medical Ventures, the Carlyle Group, SV Life Sciences, Longitude Capital, and Rho Ventures.
EYETECHCARE $10.6 MILLION SINCE 2008	In contrast to devices increasing outflow for the reduction of IOP, is decreasing inflow with the non-invasive partial destruction of the ciliary bodies using high-intensity focused ultrasound./Credit Agricole Private Equity and CEO-Investissement.
GLAUKOS $90 MILLION SINCE 2001	iStent device restores outflow in physiologic manner, implanted through a tiny hole in the trabecular meshwork and placed in Schlemm's canal. Most advanced glaucoma device targeting a new device segment, was recommended by FDA panel in July 2010./Versant Ventures, Domain Associates, Frazier Healthcare Ventures, InterWest Partners, Fjord Ventures, Montreaux Equity Partners, and OrbiMed Advisors.
ISCIENCE INTERVENTIONAL $71 MILLION SINCE 1999	510(k)-approved platform offers implant-free non-penetrating canaloplasty using *iTrack* flexible microcatheter with an illuminated tip. Canaloplasty involves viscodilation of Schlemm's canal and introducing a suture to distend the trabecular meshwork and the canal. Operates on three different sources of blockage: the trabecular meshwork, Schlemm's canal, and the collector channels./Affinity Capital Management, Johnson & Johnson Development Corp., Clarian Health Ventures, Prism VentureWorks, Three Arch Ventures, De Novo Ventures, and Asset Management.
IMPLANDATA OPHTHALMIC PRODUCTS $886,681 SINCE 2010	Intraocular sensor for continuous monitoring of intraocular pressure for chronic patient management (rather than one-time diagnosis)./High-Tech Gruenderfonds,hannover innovation fonds, and private nvestors.
IVANTIS $14.5 MILLION	Unknown device for glaucoma./New Enterprise Associates.
NEOMEDIX $150 MILLION SINCE 1993	*Trabectome* technology for ab interno version of trabeculecomy. Through a clear corneal incision, the *Trabectome* has an electrocautery tip for removal of a strip of trabecular meshwork and inner wall of Schlemm's canal; no implant is left behind./Private investors.
SENSIMED $11 MILLION SINCE 2003	*TriggerFish* is a disposable contact lens providing improved glaucoma diagnosis through 24-hour IOP monitoring./Wellington Partners, Vinci Captial/Renaissance PME, Blue Ocean Ventures.
TRANSCEND MEDICAL $42 MILLION SINCE 2005	Founded by retinal surgeon Eugene de Juan, is developing ab interno device CyPass, which enters the eye through corneal access, drains to the supra-choroidal space to safely achieve large IOP reductions./Morgenthaler Ventures, Split Rock Partners, HLM Venture Partners, Canaan Partners, Technology Partners, and Latterell Venture Partners.

SOURCE: Elsevier's *Strategic Transactions*

absolute values for safe intraocular pressure. A third of glaucoma patients experience optic nerve damage and vision loss at "normal" intraocular pressure (between 10 and 21 mm Hg), while many people don't get glaucoma with pressures as high as 24 mm Hg. Perhaps 25% of patients who have been diagnosed with the disease and are on therapy still experience disease progression.

The second major complication is the well-studied phenomenon that many patients don't comply with their glaucoma prescriptions. Glaucoma drug regimens consist of drops of one or several drugs placed in one or both eyes, either once or multiple times a day, sometimes with different prescriptions for each eye. This can be complicated, particularly for older patients, and results in many patients not complying with their medical regimen, most commonly because it's difficult to read the fine print on the bottles of medicine and because some medications sting. Perhaps 50% of patients are not compliant within eight months of the initiation of therapy, but this is a disease where compliance is important – 24 hours a day for life – to maintain intraocular pressure within a healthy range.

COMPLIANCE: THE DEAD ELEPHANT IN THE ROOM

In fact, in the requirements for its management, glaucoma is perhaps more like diabetes than any other disease. In both diseases, therapy needs to be titrated to a single parameter; intraocular pressure is the glaucoma equivalent of blood glucose levels. The parameter must be kept within a healthy range at all times throughout a patient's life to avoid fluctuations or spikes that cause long-term damage, and outcomes rest wholly on patient compliance. But the management of glaucoma is unlike diabetes in a few potentially negative ways. First, glaucoma is symptomless, and patients are not always aware of the consequences of taking a holiday from therapy. Second, on a daily basis, patients don't know their levels of intraocular pressure and can't make the connection between compliance and success; finally, in glaucoma there is no surrogate test for overall compliance like the HbA1C test in diabetes. The only marker for success or lack thereof in patients with glaucoma is progressive and irreversible vision loss. One new company, **Implandata Ophthalmic Products GMBH**, has a plan for addressing this information gap, with a continuous monitor for intraocular pressure. (*See sidebar, "Continuous Pressure Monitoring: The Missing Link in Glaucoma Care."*) Such information could one day feed back to patients the information needed to improve compliance.

This lack of compliance, coupled with the personalized nature of glaucoma, means that physicians may not have an accurate picture of the overall pressure management of the patient; and how it relates to disease progression. Do patients get worse because their drugs stop working, or because they aren't complying? Lost vision is never regained, and physicians would like to have many more options for dealing with the individual nature of patients and their disease.

So, while the $4 billion glaucoma drug industry has attracted many innovators, some hoping to offer drugs with novel mechanisms of action, something else is required to get around the compliance problem. (*See "Glaucoma's Changing Of The Guard,"* "The Pink Sheet," *June 28, 2010.*)

Drug delivery devices may make a contribution in this area; devices like punctal plugs, an example of which is the implant developed by ForSight Labs and sold to **QLT Inc.** (*See "From the Foundry, An Incubator Focused on Ophthalmology,"* START-UP, *December 2005.*) Or, one solution might be found in the drug-eluting contact lenses under development by a team led by Daniel Kohane, MD, PhD, a researcher at **Massachusetts General Hospital** for Children and Joseph Ciolino, MD, a corneal surgeon at the **Massachusetts Eye & Ear Infirmary**, which offer potential flexibility in choice of drugs and dosing and the opportunity to correct refractive errors at the same time.

But treating physicians still wish they had many more options for safely lowering intraocular pressure in predictable increments, since today's therapies are so flawed. In the absence of significant evidence to guide surgical decision making, glaucoma physicians will do as much as they possibly can with drugs before entering the quagmire of existing surgical treatments for glaucoma, where the degree of benefit versus the dangerous complications can be murky.

FILLING IN THE RISK/EFFICACY GRID

Glaucoma, like many diseases of aging, is a function of clogging, widely thought to occur in the trabecular meshwork of the eye (although there remains some controversy as to the source of the blockage that causes glaucoma). The ciliary bodies in the eye produce aqueous humor to nourish the front of the eye. In a healthy eye, this fluid is produced at a constant rate – approximately 2.4 microliters per minute – and it exits at a steady flow rate, making its way past the lens, through the pupil, through the angle where the iris and cornea come together, then through the trabecular meshwork, a sieve-like structure that surrounds the iris, after which it finally leaves the eye through a chamber called Schlemm's canal. When the trabecular meshwork becomes clogged with debris or cells so that fluid can't drain out quickly enough, the pressure builds up and presses on the blood vessels that supply the optic nerve, causing damage and the progressive loss of sight.

Glaucoma is treated, in its early stages, with drugs given in the form of eyedrops. Four classes of drugs are used today, alone or in combination with one another, to lower intraocular pressure by either increasing outflow or decreasing inflow. Prostaglandins, of which **Pfizer Inc.**'s $1.7 billion drug *Xalatan* (latanoprost) is an example, relaxes muscles in the eye to ease the outflow of fluids. Beta blockers, alpha agonists and carbonic anhydrase inhibitors decrease the production of aqueous humor. As noted, physicians will prescribe these drugs, most of them in the form of eyedrops, in response to measurements of intraocular pressure and assessments of disease progression. Efficacy depends upon the class of drug or whether it's the first, second, or third one used, but prostaglandins are the most popular drugs and they lower intraocular pressure, on average, about 30% from baseline. (Efficacy of glaucoma treatments is measured by the degree to which they reduce intraocular pressure.)

Device strategies largely focus on increasing outflow, with one exception. (*See sidebar, "EyeCareTech Targets the Other Mechanism in Glaucoma."*) In patients whose glaucoma progresses despite medical therapy, or who can't take drugs for any reason, the next course of therapy might be selective laser trabeculoplasty, or SLT. This is a non-invasive procedure in which a laser is used to target tissue in the trabecular meshwork to increase spacing and improve outflow. There are approximately 250,000 laser trabeculoplasties performed annually in the US, and nearly 80% of patients respond

to SLT, but there is a marked diminution of effect over time to an approximately 50% failure rate at five years.

Traditionally, the next course of treatment has been trabeculectomy, although less invasive 510(k) products have recently entered the market, for example, the canaloplasty procedure of iScience and the Trabectome of NeoMedix noted previously. Trabeculectomy is an invasive ab externo procedure, that is, an outside-in approach to the eye. The surgery creates a new drainage hole whereby the pressure differential inside the eye, which in glaucoma generally exceeds 21 mm Hg, forces the instantaneous flow of fluid from within the eye to the outside, resulting in a zero pressure space underneath the conjunctiva. As part of the procedure, the surgeon creates an episcleral fistula called a bleb, which provides a conduit for the fluid to flow into the episcleral venous system and out into the body.

Trabeculectomy has demonstrated good efficacy, achieving, on average, a 40% reduction in intraocular pressure, but the procedure has a high morbidity rate, still requires the concomitant use of medications and is anxiety-producing for surgeons. Trabeculectomy has a 1 to 2% annual rate of endophthalmitis, an eye infection that can occur any time in the years following the surgery. The formation of a bleb to establish fluid outflow creates early- and late-stage surgical complications and a high incidence of secondary surgical procedures to repair or modify blebs, and there are other formidable complications. The eye can lose too much pressure as a result of the procedure, creating a situation called hypotony, which can cause vision loss and blindness. The eye cannot withstand an excessive pressure drop because the retina requires internal pressure to hold it against the choroid at the back of the eye. In the absence of pressure, the retina can detach, causing retinal maculopathy. Finally, if trabeculectomy fails, the ab externo implantation of an aqueous shunt is a strategy of last resort. This entails the implantation of a fairly large device with a tiny rubber tube that connects from the anterior chamber of the eye to a large plate that creates a space for fluid to drain under the conjunctiva, where fluid can flow out to the bleb. The shunt procedures are associated with high rates of fibrosis, which ends up blocking outflow within several months; high flow rates can also lead to hypotony.

Taken altogether, these disadvantages of current drugs and devices leave clinicians in want of new therapies to individualize the care of patients with this serious and progressive disease. William Link, PhD, a managing director at Versant Ventures, which has backed Glaukos, feels that there is a particular need for devices that enable low-morbidity surgical solutions for glaucoma, thereby avoiding the compliance requirement of drugs. Indeed, he believes, if devices can be developed that are as safe as drugs, they will not need to demonstrate superior efficacy to be adopted in practice. The most desirable quality of a new device for this market will be safety, and that's what Glaukos is banking on in its effort to be the first to market.

GLAUKOS BEGINS TO SHIFT THE MARKET

Because of the morbidity and higher risk-to-benefit ratio of existing procedures and devices for glaucoma, surgeons and other clinicians will generally exhaust all drug options first, before turning to surgical alternatives. Glaukos CEO Thomas Burns says, "There is an existing zero sum mentality based upon perceived safety and risk, which has relied on first-use of drug therapy in mild-to-moderate open angle glaucoma and reserved surgery for more advanced or end-stage patients." That's what Glaukos has set out to change, in crafting its product development and regulatory strategy.

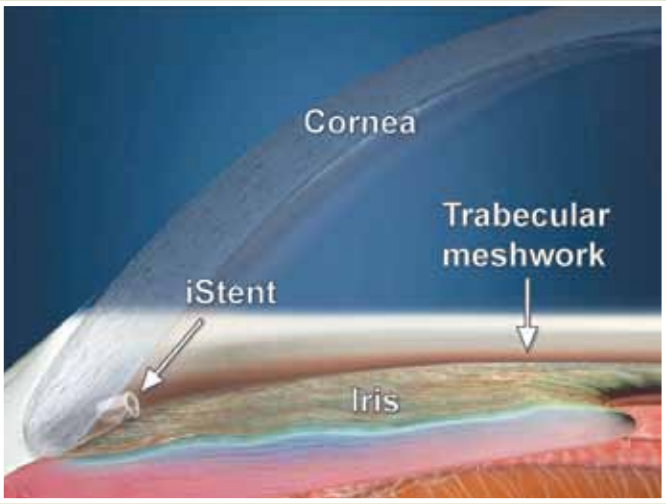
Burns is an ophthalmic industry veteran who joined William Link in 1990 to build Chiron Vision (now part of **Bausch & Lomb Inc.**) in its early days, later leading Eyetech Pharmaceuticals Inc. (since acquired by OSI Pharmaceuticals Inc.) as president, COO, and director. Burns, who joined Glaukos in 2002, shortly after its founding, says "We started with a contrarian premise. We sought to be the first company to pioneer and create a franchise of minimally invasive stents that were so safe and effective that they could be used in place of medication, or to reduce the medication burden in glaucoma, causing a paradigm change in the standard of care."

The company was founded in 2001, with $3 million in venture funding from Versant Ventures and Domain Associates, by venture capitalist Olav Bergheim (then at Domain, now managing director of Fjord Ventures), Richard Hill, MD (an ophthalmologist with the University of California, Irvine at the time and now in private practice), and Mory Gharib, PhD (the Hans W. Liepmann Professor of Aeronautics and Professor of Bio-Inspired Engineering at the California Institute of Technology). To date, the company has raised $90 million in four venture rounds. Its first-generation product is the iStent, a tiny titanium tube. It weighs 60 µg with a bore diameter of 120 µm and is about 1/5,000th of the volume of an ophthalmic aqueous shunt. The company believes that iStent is the smallest medical device that has ever been implanted into the human body.

The iStent is an ab interno device (entirely within the eye with no communication to the outside) implanted through a tiny hole in the trabecular meshwork and placed in the eye's natural drainage ditch, Schlemm's canal. (*See Exhibit 2.*) The

Exhibit 2

iStent Restores Physiologic Outflow



SOURCE: Glaukos Corp.

iStent creates a patent opening into Schlemm's canal by bypassing an impermeable trabecular meshwork and, in so doing, re-establishes physiologic outflow, thereby reducing intraocular pressure into normal ranges. Aqueous humor is directed through collector channels in Schlemm's canal, which feed into the venous system and into the body.

One of the potential clinical advantages of the iStent is that the implant re-establishes normal physiologic outflow through normal physiologic outflow pathways; it doesn't re-route flow artificially to the subconjunctival space. As noted, the latter strategy greatly increases the risks of hypotony, endophthalmitis and bleb-induced complications. The conventional outflow pathway is also governed by a natural back-pressure or resistance that minimizes any potential to induce the hypotony that can occur with other procedures that vent to the subconjunctival space.

The high benefit-to-risk clinical profile is the most important attribute that Glaukos believes its product offers, especially in its initial chosen market: as an alternative to drugs in patients with cataracts and mild-to-moderate glaucoma. In

Continuous Pressure Monitoring: The Missing Link In Glaucoma Care

Physicians responsible for the care of glaucoma patients, in a certain sense, have to operate somewhat blindly. The management of glaucoma is based on keeping a patient's intraocular pressure levels within a range that's healthy for that individual, a determination that's based on tonometry readings in the physician's office and an assessment of a patient's loss of vision. If a clinician detects disease progression, he or she can titrate therapy – choose another dosage, another drug, or a surgical therapy – to achieve even lower levels of intraocular pressure. However, patients' lack of compliance with prescribed drug regimens is so high that physicians can't always be sure that when they're looking at a snapshot of IOP in the office, they're getting a true picture of a patient's overall intraocular pressure management.

It's a well-known and documented phenomenon that patients don't take medications as prescribed, but they might become temporarily compliant in advance of a visit to the doctor, the "white coat" syndrome. Or, they may adhere to the prescribed therapy for a while, then fall off for some period of time, during which intraocular pressure may spike or hover at dangerously high levels, killing off retinal ganglion cells all the while. Pressures may spike while a patient sleeps, but may look normal in the physician's office. Given these variables, it is likely that the physician determining therapy on the basis of periodic intraocular pressure readings will not have all the information necessary to ideally treat the patient. This leaves a major question unanswered for physicians: is disease progression a sign that drugs aren't working or that the patient is not taking them as directed?

The management of glaucoma is actually even more complicated than that. There are no absolute values for safe intraocular pressure. One-third of glaucoma patients experience optic nerve damage and vision loss at "normal" intraocular pressure (between 10 and 21 mm Hg), while many people don't get glaucoma with pressures as high as 24 mm Hg. And one-quarter of glaucoma patients are diagnosed and on therapy, but still experience disease progression.

The mystery that surrounds glaucoma and why it progresses in some patients and not in others may mean that beyond elevated intraocular pressure there are other, unknown mechanisms causing irreversible optic nerve damage. Or, it may simply be that patients don't adhere to therapy, and that episodic pressure measurements in the office are not accurate enough to properly direct therapy.

Implandata Ophthalmic Products GMBH has set out to see what it can do about the latter problem, with an implantable system for continuously monitoring intraocular pressure. The company was founded in 2010 with seed funding of €700,000 (approximately $886,700), although work on the underlying technology began many years earlier at the Fraunhofer-Institut in Munich. Co-founder and managing director Max Ostermeier explains that the project began with tire pressure sensors and a group of collaborating ophthalmologists. Over the course of 10 years or so, researchers tackled the challenges of creating a tiny sensor that would be robust and durable enough to accurately sense intraocular pressures for 10 to 15 years. Fortunately, the eye is less hostile to implants than other parts of the body, says Ostermeier, who notes that the IOP sensor is made of silicone, the material of which intraocular lenses for cataract surgery are made. "We have had sensors implanted in rabbits for two to three years with no issues," he says, noting that long-term stability is crucial in a chronic disease like glaucoma.

The company has completed the design of its sensor, has tested its safety and functionality in animals and humans, and is now aiming for CE mark approval and a market launch, the start-up hopes, in late 2011 or early 2012. Ostermeier describes the sensor as an ASIC (application-specific integrated circuit), which has capacitive pressure membranes responsible for measuring pressure. There is an AD converter on the chip, to convert the analog signal acquired by the pressure membrane into a digital signal, and that digital signal is sent to an external device. An embedded temperature sensor ensures accuracy, since temperature influences pressure levels. The device needs no batteries; the chip is pow-

fact, at the recent FDA Advisory Panel Meeting, the panel concluded that the implant was effective and safe for its intended use, and that the benefit of the device exceeded the risk. This initial market is not insignificant; primary Medicare claims data demonstrate that 20% of the 3.3 million patients in the US who undergo cataract surgery have either concomitant ocular hypertension or glaucoma.

In support of the early treatment of glaucoma patients with iStent, Burns notes that iStent theoretically does not preclude a wide range of therapies as future treatment alternatives or in conjunction with the iStent because the implant procedure spares the conjunctiva, so surgeons will preserve all their existing surgical options if they desire additional future pressure reductions in patients.

Burns describes the iStent as a "foundational therapy" because it provides, "24/7 control of intraocular pressure by re-establishing physiologic outflow and is not subject to the non-adherence to therapy associated with medications." Burns also notes that the mechanism of action of iStent suits it for working alongside medications that increase uveoscleral outflow (prostaglandins) or that reduce aqueous production (beta blockers) to further reduce intraocular pressure.

ered from outside the body and its internal coil receives a magnetic field applied from a hand-held device. The patient holds up the external device, the chip is powered and takes readings, and sends them back out to the external device where they are recorded and displayed. This configuration, which is well suited to one or two measurements a day, should work well for patients who are stable, explains Ostermeier. For patients who are not stable and require continuous monitoring, the external antenna can be integrated into a night mask or the frame of a pair of spectacles, where it will take automatic readings and deliver to the physician a 24-hour profile of a patient's pressure. Implandata will also develop a third component, an interface for uploading the data from the sensor to the doctor's office via internet or cell phone.

Ostermeier emphasizes that the Implandata system does not compete with diagnostic modalities like tonometry, or with diagnostic devices like the *Triggerfish* of **Sensimed AG**, a single-use contact lens that monitors fluctuations in intraocular pressure over 24 hours. (*See "Sensimed AG,"* START-UP, *July 2008*.) Implandata's continuous monitor is designed to give clinicians and patients the information they need for the chronic management of glaucoma.

Since its first-generation device is an intraocular implant, Implandata's target patient population will be those patients who have cataracts and glaucoma, or who are at risk of developing glaucoma as a result of corneaplasty or corneaprosthesis procedures. The device's tiny sensor is foldable and can be inserted in the small incision made for intraocular lenses. The sensor, which is in the form of a ring, is placed in the ciliary sulcus. Piggybacking on a therapeutic surgery eliminates the risk-benefit issues of surgery for a monitoring device, and still gives the company a large patient population to work with. Approximately 15 to 20% of the 3.3 million cataract patients in the US have glaucoma. Many of them could benefit from monitoring because their disease is unstable despite medical therapy.

The company is developing a second-generation extraocular permanent implant, placed under the conjunctiva at the lower outer quadrant, where it won't interfere with future glaucoma surgery procedures done in the upper quadrant of the eye. According to Ostermeier, this less invasive version will ultimately allow a stand-alone outpatient procedure, extending coverage to an even larger proportion of the glaucoma population. The company has demonstrated proof-of-concept for the second-generation device in animals and plans to do its first human studies in 2011.

The appropriate business model for continuous monitoring in any application, whether it is ophthalmic or cardiovascular disease, has yet to be worked out. (*See "Wireless Health: Personalized Medicine Comes to the Device Industry,"* START-UP, *October 2009*.) So for the near future, Ostermeier says Implandata will adopt a hybrid reimbursement model. Ostermeier points out that there are three components to the system: a device that is implanted at the time of cataract surgery, potentially falling under the reimbursement code for cataracts; readings taken from the implant, which might be reimbursable under existing codes for tonometry; and finally, the hand-held device, which patients may be willing to pay for out of pocket.

"What is the utility of our device?" Ostermeier asks. "Doctors need to know, under regular conditions, what is going on in the patient's eye, so they can adjust the patient's therapy, personalize the treatment, and know right away how the patient reacts to medication. Using this device, they'll be able to optimize and personalize therapy, which will eventually result in improved disease outcomes." Ostermeier also points out that the number of patients with glaucoma is expected to increase in the coming years. In 10 to 15 years, doctors will be managing many more patients, he says, and a tool like this, which can eliminate frequent visits to the office for pressure measurements, will help practices be more productive. Finally, Ostermeier says, "If you give patients the opportunity to learn what is going on with their own disease, they might be more compliant."

A FULL RANGE OF TREATMENTS FOR THE FULL SPECTRUM OF PATIENTS

Glaukos is looking to lead a revolution in glaucoma devices and surgery, for which iStent will be only the first application. The company aims to build a franchise of glaucoma therapies for the full range of glaucoma patients from the mildest to the most advanced. Each therapy will have its own benefit-to-risk clinical profile and will be used for glaucoma patients based upon an individual patient's target pressure.

Investigator-sponsored studies are helping to define a role for the new devices as titration therapies to obtain desired reductions in intraocular pressures. Ike Ahmed, MD, a peer-leading glaucoma specialist in Mississauga, Ontario, conducted a study evaluating the use of two or three iStents in combined cataract surgery, the results of which were recently reported at the meeting of the American Society of Cataract and Refractive Surgery in Boston in 2010. Ahmed found significant pressure reductions and reductions in medication burden in both groups at one year. Mean postoperative pressures were approximately 14 mm Hg in both groups. The two-stent group reduced mean medication bur-

EyeCareTech Targets The Other Mechanism In Glaucoma

For patients with glaucoma, there is a single treatment goal: to lower the high intraocular pressure that's ultimately responsible for the death of retinal ganglion cells, damage to the optic nerve, and progressive vision loss. Both drugs and devices accomplish this goal by avoiding the buildup of aqueous humor that pressurizes the eye. Drugs seek to accomplish this one of two ways: by either increasing the outflow or decreasing the production of aqueous humor in the first place. Devices tend to be focused on only increasing outflow by circumventing or opening the blockages that cause fluid buildup. Among device companies, there is one exception. France's **EyeTechCare SA** has devised a non-invasive way of using therapeutic ultrasound to decrease the production of aqueous humor, and as such, it is offering a therapy with a novel mechanism that won't preclude other drug or surgical strategies, and one that might even be able to play alongside drugs in the early stages of glaucoma therapy.

Four years ago, EyeTechCare founder Fabrice Romano was in charge of international marketing for EDAP-TMS, a French company that manufactures ultrasound instruments for urological diseases such as prostate cancer. "I discovered that this high-intensity focused ultrasound (HIFU) was truly amazing – very accurate and very effective. I immediately imagined that an application in ophthalmology was possible," recalls Romano, who already had an extensive background in ophthalmology and microsurgery. Previously, he had served as sales director at Domilens (intraocular lenses and phacoemulsification instruments, now Bausch & Lomb Surgical) from 1989 to 1994.

Romano first met co-founder Philippe Chapuis, EyeTechCare's managing director for industry, while the two were employed at EDAP-TMS in 2005. Chapuis has 13 years of experience in the manufacture of medical equipment and consumables that apply focused ultrasound for therapeutic purposes. The third co-founder, Laurent Farcy, the company's managing director for regulatory and clinical affairs, has 11 years of experience in the field of clinical studies, nine of which involve medical devices.

EyeTechCare has five pending patents (none issued) and will pay a nominal royalty to the **French National Institute for Health (INSERM)**, which helped develop the technology.

The goal of EyeTechCare's new non-invasive therapy is to selectively and partially coagulate and destroy the ciliary bodies responsible for producing aqueous humor. The safety of that concept has already been born out by drugs that lower the production of aqueous humor. Furthermore, says Romano, "We only destroy small parts of the ciliary bodies, a minimum of 40% of the ciliary bodies are preserved, which is sufficient to maintain physiological functioning in the eye." Romano claims that the risk of his company's device is low. "The focal point is precisely in the ciliary bodies. We don't destroy the surrounding structures."

The destruction of ciliary bodies is a strategy that has previously been attempted by laser, but Romano says that lasers have certain limitations that HIFU doesn't. First, lasers depend upon pigment in the ciliary bodies for effectiveness, and don't work in all patients. Second, laser destroys the ciliary bodies with an explosion accompanied by the dispersion of pigment, proteins and other cell debris, which can cause a high degree of inflammation. Ultrasound is effective in every patient, he says, and is gentler. According to Romano, "We only coagulate the tissue, and we preserve the barriers of the cells. We haven't observed any inflammation or pain following the procedure."

EyeTechCare's *EyeOP1* system consists of a console module (similar to a desktop computer) and a single-use disposable device. The sterile device has two major components: a spacer or centering cone placed on the patient's eyeball and a therapy probe, which features six piezoelectric transducers (small components manufactured from a special ceramic that vibrate when subjected to an electric current) that produce HIFU. The console module also contains a high-intensity generator that generates electric power to stimulate the transducers.

Once the spacer is properly centered on the eyeball, the ophthalmologist activates a vacuum system that ensures the spacer is affixed to the eyeball and maintains centering during ultrasound treatment. The therapy probe is then introduced to the spacer. "Treatment lasts one minute, during which time all six transducers are sequentially activated for three seconds each," Romano ex-

den by almost two medications, whereas the three-stent group required no postsurgical medications at all. These mean postoperative baseline pressures are comparable to what can be achieved with trabeculectomy and aqueous shunts with the advantage of a potentially safer procedure.

Glaukos also has two next-generation products in development. To minimize the invasiveness, Glaukos is developing an injectable version of the ab interno iStent called *iStent inject* that, containing two preloaded stents, has the capability of injecting multiple stents from a single 26-gauge applicator through a corneal incision that is less that 0.5 mm long. iStent inject is currently undergoing expanded phase recruitment in an FDA-approved IDE clinical trial.

The second-generation iStent inject clearly begins to take on drugs on their own turf. An injectable device for glaucoma is not a far cry from an injectable drug therapy for that other disease of blindness, age-related macular degeneration (AMD). Patients with AMD routinely undergo in-office injections of *Lucentis* (ranibizumab) on a monthly basis, a model that is so well accepted in ophthalmology that current revenues of Lucentis (marketed by

plains. "All the ultrasound energy is focused in a very small focal area inside the eye."

Each transducer produces two watts of energy. This intensity of ultrasound is between 1,000 and 10,000 times higher than that for traditional ultrasound imaging. "Immediately upon therapy, coagulation occurs within the ciliary bodies, due to the temperature at the focal point, which reaches about 90 degrees Centigrade in one second," Romano says. "As a result, intraocular pressure decreases." Some decrease can be detected the following day, with the full decrease occurring at one week.

A single treatment of the non-invasive therapy should significantly decrease IOP for many years, according to Romano. Normal IOP is considered between 10 and 21mm Hg. "We have already successfully treated patients with IOP as high as 35 or 40 mm Hg, resulting in at least a 30% reduction," he says. "A good result is at least a 20% reduction of IOP, and some of our animal studies have achieved up to a 50% reduction."

The learning curve to use EyeOP1 is "very short," Romano says. "An ophthalmologist will be able to use the system after just a few hours. Ultrasound is not much different than laser." Ultimately, this means offering a treatment that is not limited to the small group of glaucoma surgeons operating in sterile operating rooms, but to general ophthalmologists, as an alternative to the drugs they prescribe.

EyeCareTech conducted its first-in-man clinical trial on four patients in March. With EyeOP1, "IOP dropped about 30% in each of these patients, and treatment was very well tolerated. No adverse events have been observed," Romano notes. "There was also no pain or inflammation." For the study, general anesthesia was used, "but going forward, we will probably use only anesthetic eyedrops," he says.

CE mark for EyeOP1 is expected by yearend, and the company is hoping for a PMA approval in either 2013 or 2014. Initially, EyeCareTech intends to target patients with refractory glaucoma. Romano points out, however, that "surgeons are already seeing the advantages of our technique in terms of efficacy, accuracy, lack of side effects, and ease of use, and are telling us that they would use this technology earlier in treatment. Why not before surgery, even before laser, and after eyedrops?"

Indeed, in the future an argument could be made that EyeOP1 could move up the treatment continuum to possibly become a first-line therapy, alongside drugs. Compared with once or twice daily eyedrops, there is no patient compliance issue with EyeOP1, and the cost is equivalent to only one year of eyedrop therapy. The disposable device will sell for between $500 and $1,000, in addition to the cost of the console module ($20,000 to $30,000). There are existing insurance reimbursement codes in Europe, but for US sales a new DRG may need to be created.

In theory, the mechanism EyeCareTech is employing to lower intraocular pressure might lend itself to longer durability than strategies directed toward increasing outflow. "When you make a hole in the body, with any technology, with or without a stent, the body tends to try to close it up quickly because of the healing process. But when we burn the ciliary body, this tissue is replaced by scar tissue, which is not functional, and it seems to be a permanent state," Romano explains. That's why the company contends that EyeOP1 may result in a more durable treatment. In fact, there are many failures with SLT (selective laser trabeculoplasty), which is also non-invasive, but focused on the goal of increasing outflow. Efficacy also decreases when SLT is repeated.

EyeCareTech is expected to begin European sales by the end of the year, starting in five major countries: France, the United Kingdom, Germany, Italy and Spain. The company will only use a direct sales force in France; in the other four countries, they will rely on a network of distributors.

To date, EyeTechCare has raised $10.6 million in two rounds of financing through several French venture capital firms. The company doesn't anticipate needing any additional capital for another two to three years, at which time funds will be needed to pursue FDA clearance.

Romano emphasizes that there are many companies developing new devices for the treatment of glaucoma, but all of them are following the same strategy of trying to increase outflow with stents, valves and other techniques. "We are offering something very different," he says.

Genentech Inc./Novartis AG) are estimated to exceed $1 billion. An injectable device-therapy for glaucoma might equally offer a simple, office-based procedure, but one in which a single injection might result in long-term control.

Glaukos is also developing a third-generation ab interno device, the *iStent Supra.* The third-generation device relies on a different outflow pathway, the supra-choroidal space, offering a product with the potential to achieve the kinds of potentially large IOP reductions that trabeculectomies and shunts now offer, except with significant safety advantages to these end-stage procedures. The iStent Supra will likely be reserved for patients with more advanced glaucoma, or who need further enhancements to other IOP-reducing therapies.

An injectable device-therapy for glaucoma might offer a simple, office-based procedure, and one in which a single injection might result in long-term control.

Transcend Medical is also developing an implant that bypasses directly to the supra-choroidal space, the *CyPass*. Transcend, which spun out of Forsight Labs, has raised more than $42 million to date from Morgenthaler Ventures, Split Rock Partners, Canaan Partners, Technology Partners, and Latterell Venture Partners. (*See "Transcend Medical Inc.,"* START-UP, *July 2008.*) Transcend is currently investigating the CyPass in clinical trials in patients with glaucoma who are undergoing cataract surgery.

Glaukos has paved the way for clinical adoption of these iStent generations by successfully petitioning the AMA for Category III CPT Codes that will enable widespread reimbursement coverage subsequent to FDA approval. Glaukos secured Category III code 0191T effective July 1, 2008, for intraocular stents implanted in Schlemm's canal and Category III CPT code 0253T, effective January 1, 2011, for intraocular stents implanted into the supra-choroidal space. Companies that follow Glaukos into these markets will be beneficiaries of the groundwork laid by Glaukos.

A DEVICE THAT IMPROVES CLINICIAN AND PATIENT ACCESS

Glaucoma device start-up AqueSys was spun out of the **Innovation Factory** medical device incubator in 2006. (*See "The Innovation Factory: Re-Thinking the Incubator Model*," START-UP, *December 2003.*) AqueSys recently raised a $35 million Series C venture round led by Longitude Capital and Rho Ventures with the participation of the company's existing investors, Accuitive Medical Ventures, the Carlyle Group, and SV Life Sciences. However, company officials are still being very stealthy about its device in development.

CEO Ron Bache, who joined AqueSys after 11 years at ophthalmic surgery company Advanced Medical Optics (now Abbott Medical Optics), says that his company aims to improve patient access to a new therapy by offering a device that can be safely implanted in a broadly adoptable 10-minute procedure. "If we could introduce a technology that demonstrates significant efficacy and is safe and simply performed by the ophthalmic surgeon, we could change the paradigm. Then surgery would not be used as an end-stage treatment, but close to a primary treatment."

AqueSys has entered the field a bit later than some other companies, although it is the product of more than 10 years of research prior to its founding in 2006, a history that has given the company the benefit of learning what works well in glaucoma and what doesn't, says Bache. "A lot of learning has gone on as to the mechanism of action surrounding the blockage in the eye, and there is still some debate about exactly where that blockage is." Several device companies have had to make assumptions based on where the blockage is to bypass it, Bache points out. iScience and Glaukos are opening up Schlemm's canal, for example, although their approaches differ from one another, and Transcend Medical is making use of the supra-choroidal space. But Bache says that based on where AqueSys is restoring drainage, "Our approach is not predicated upon choosing the right blockage in the eye. We bypass all the blockages."

Bache says AqueSys believes it will offer the world's first procedure and technologies to marry the benefits of an ab interno procedure with the pressure reductions of an ab externo procedure like a trabeculectomy, although "in a much safer, broadly adoptable, less traumatic and simpler way." He estimates that AqueSys will be able to achieve IOP reductions on the order of 30 to 40%.

About to begin a clinical trial, AqueSys will initially work with glaucoma surgeons, but in the long term, Bache claims "there is nothing about the procedure or the technology that would preclude it from being done in a setting such as a clean room, by people outside the glaucoma specialty, by primary ophthalmologists." AqueSys will offer a pre-loaded, pre-sterilized device that comes in its inserter. "Our procedure has no more complexity to perform than a standard cataract procedure, which is one of the world's most performed procedures," he says.

The target audience for the AqueSys procedure will be a patient who, Bache says, "for medical or lifestyle reasons seeks less dependence upon medications for IOP control, or those patients who require surgical intervention to achieve their target IOP in a safe and effective manner." That actually sounds like all glaucoma patients, and, indeed, Bache says, "Our goal is that surgeons will choose to perform our procedure due to its efficacy, safety, and adoptability earlier in the patient's treatment regimen, and thus reduce or stop the slowly eroding visual field loss sooner in the patient's life."

AqueSys, like its peers, is spending a great deal of time on reimbursement strategy, still an unknown in this space, "to make sure that the payment for the time and technology is in line with the benefit over time." According to Bache, "We have

a clear line of sight to a time when the use of multiple drugs to control IOP will eventually lose favor to a surgical approach that can achieve the desired efficacy and minimize the compliance, side effects, and cost issues associated with chronic drug use." Bache points out that drugs are expensive; prostaglandins cost $800 to $1,000 per year – for life – and other medications may be added onto that bill, thereby indicating another advantage for a device-based approach.

[The AqueSys] "approach is not predicated upon choosing the right blockage in the eye. We bypass all the blockages."

-Ron Bache

NOTHING IN GLAUCOMA LASTS FOREVER

The recent positive FDA panel review of the Glaukos iStent is only a first step, but it's a giant step in a new direction where device companies are looking to break the dominance of drugs in the treatment of glaucoma. However, the device start-ups looking to enter this market face a skeptical group of physician-customers who rely heavily on clinical data in assessing the potential value of any new therapies and for whom the watchwords have long been, "In glaucoma, nothing works forever." Glaucoma specialists generally expect up to five years worth of data on emerging technologies.

But the FDA panel's findings may indicate that the market will have an opportunity to decide how the various therapeutic approaches will all fit together. Eugene De Juan, MD, a renowned retinal surgeon at the University of California, San Francisco's Medical Center (who is also chairman of the ophthalmic incubator Forsight Labs and a founder of Transcend Medical), agrees: "I interpreted the panel as a strong statement that there needs to be encouragement of this [device-based] approach, and that its usefulness will ultimately be determined within the hands of specialists." What's more, says De Juan, the panel was expressing its belief that the iStent had demonstrated sufficient safety to move into clinical practice, where "the practice of medicine can ultimately determine its value."

It's early, but not too early. Strategic partners are getting ready for this new game. **Nestle SA**'s **Alcon Inc.**, a market leader in glaucoma pharmaceuticals with *Travatan* (travoprost) and *Azopt* (brinzolamide), acquired in late 2009 glaucoma-device manufacture Optonol Ltd. Optonol is selling the 510(k)-cleared *Ex-Press* mini glaucoma shunt, admittedly one of the more traditional, end-stage types of products, but it is Alcon's first product in the glaucoma device space. As the new glaucoma start-ups come to market, it, and perhaps others, will be ready to deal, opening up a new M&A market to go along with these new therapeutic options.

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