

BioCentury

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Product Development

The eyes have it

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Senior Writers**

Continued increases in investment, new targets and expanded delivery options signal growing interest in ophthalmics, resulting in nearly 40 deals since January 2007, led by **Novartis AG's** \$10.4 billion purchase of a 25% stake in **Alcon Inc.**, and over \$370 million in venture financing. Investors believe the sector is ripe for growth due to an aging population, unmet medical needs and increasing interest from large pharmas.

The amount of venture capital going into ophthalmic companies rose from \$123 million in 2004 to \$210 million in 2006. Over the same period, companies with an interest in the eye space raised in excess of \$1.5 billion from all capital market sources (see *Ophthalmic Money Raised*”).

In fact, ophthalmics was not known for pharmaceutical innovation until recent discoveries shifted the field from a surgical specialty toward therapeutics.

“Ophthalmics has traditionally been a realm of surgery. Innovation by surgeons tends to relate to procedures and instruments, not to fundamental, biological pathways of disease,” noted Mark Keating, VP and global head of ophthalmology at Novartis Institutes for Biomedical Research. “One reason why we’ve seen new drugs in glaucoma and anterior chamber disorders such as dry eye is that these have been islands of medicine within traditional ophthalmics. In contrast, there hasn’t been much medicine for the retina.”

In glaucoma, for example, “the first modern drug was timolol from **Merck & Co. Inc.**, which was an outgrowth of their cardiac beta blocker program,” said Alcon spokesperson Doug MacHatton. It was approved for ophthalmic use in 1978.

Next, he said, was the carbonic anhydrase inhibitor class, which includes the generic acetazolamide. After that came the prostaglandin analog class that dominates treatment today.

Novartis, which has been in the ophthalmics business for 25 years, developed Voltaren diclofenac during the 1980s to aid in recovery from cataract surgery. It was one of the first topical NSAIDs.

In 1997, the pharma licensed Vitravene fomivirsin from **Isis Pharmaceuticals Inc.** The antisense product received FDA

approval for CMV retinitis associated with AIDS in 1998.

But according to Samir Shah, global head neuroscience and ophthalmology at Novartis, “Visudyne and Lucentis were the first of the new innovative medical treatments.”

In 2000, the pharma launched Visudyne verteporfin for age-related macular degeneration (AMD). The photodynamic therapy was developed by **QLT Inc.**, but was eclipsed by Lucentis ranibizumab, a Fab fragment against VEGF-A.

In 2003, Novartis licensed rights to Lucentis outside North America from **Genentech Inc.** The product was approved for wet AMD in 2006 in the U.S. and Switzerland and now is approved to treat wet AMD in North America and Europe.

“Robert Kim, now with Novartis, was the senior author on the Lucentis paper in *The New England Journal of Medicine* describing the remarkable success of Lucentis in clinical trials,” Keating said. “Lucentis is the first medicine that actually improves visual acuity.”

Another anti-VEGF therapy, Macugen pegaptanib from **Eyetech Inc.** and **Pfizer Inc.**, came to market first, but does not work as well as Lucentis and has been eclipsed by it in the wet AMD space.

“The real question to be investigated over the next several years is whether ocular diseases like AMD are better treated systemically.”

**Robert Nussenblat,
National Eye Institute**

Exciting science

Researchers in the field point to two seminal events that triggered interest in the biology of ophthalmics.

Patricia D’Amore, senior scientist at **Harvard University’s Schepens Eye Research Institute**, credits colleague Anthony Adamis for his elucidation of angiogenesis and VEGF’s role in diabetic retinopathy in the late 1980s, triggering a surge of interest in a new generation of eye therapeutics.

“Prior to that, ophthalmics was behind the eight ball for a long time, with much of the work being more phenomenological, but angiogenesis put it on the map,” D’Amore said.

Robert Nussenblat, director of immunology at NIH’s **National Eye Institute**, agreed: “VEGF has changed the landscape in terms of funding and translated into something positive for the patient.”

The other key event is the discovery of the role of complement Factor H (CFH) in AMD, made by Josephine Hoh, an

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associate professor at **Yale School of Medicine**, in 2005.

"This breakthrough insight was a factor in my decision to resign from my position as a professor at Harvard Medical School, and from the Howard Hughes Medical Institute, in order to start a new research effort at Novartis in Cambridge focused on ophthalmology," said Keating.

"We're showing complement is a big risk factor for AMD — for complement polymorphisms, the risk is in the 80% range, even more important than age. There's no other example of a population-attributable risk that comes even close," he said. "The question is what is it about complement and the retina? We don't know the answer to that question."

Potentia Pharmaceuticals Inc. has built an early stage pipeline in ocular therapeutics around the role of the complement system. In 2003, the company started investigating the role of macrophages in inflammatory diseases like AMD.

"We were lucky when the genetic studies came out in 2005 because we had been studying the system for a few years," said Cedric Francois, co-founder, president and CEO.

In 2006, Potentia received an exclusive worldwide license from the **University of Pennsylvania** to the Compstatin class of complement-inhibiting peptides to treat ocular diseases.

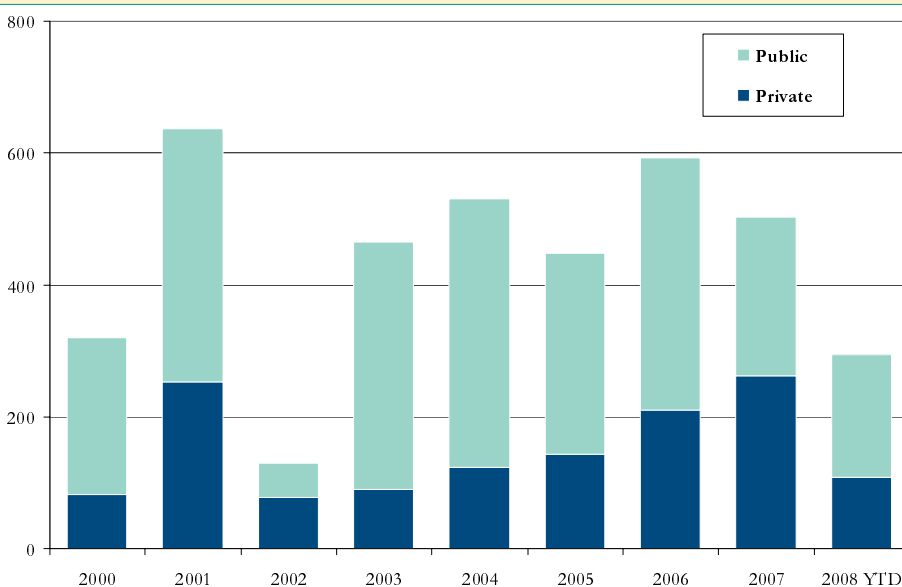
Its lead compound, POT-4, is a synthetic peptide complement 3 (C3) inhibitor in Phase I testing to treat AMD, with data expected in November this year. C3 acts upstream of CFH.

Potentia also has a complement targeting compound in preclinical development to treat glaucoma.

According to Colin Foster, president and CEO of **Ophtherion Inc.**, the complement system is a good therapeutic target for AMD because the absence of CFH function is what leads to activation of the

Ophthalmic money raised

Since 2000, ophthalmic companies have raised at least \$3.9 billion, with \$2.6 billion going to public companies and \$1.3 billion going to private companies. \$M Source: BCIQ: BioCentury Online Intelligence



complement system and the formation of the drusen plaques in these patients.

"When one doesn't have an inhibitor like CFH, [the complement system] takes over at too high a level and leads to the damage of healthy cells," he said.

Foster added that such damage can be inhibited by providing a functional version of CFH.

Moreover, Foster believes the discovery of CFH's role in AMD and its role in the innate immune system demonstrated the systemic nature of ocular diseases and opened the door for new treatment options that not only provide ocular benefits, but also may treat other diseases.

Ophtherion co-founder and CSO Gregory Hageman agreed: "90% of CFH is manufactured in the liver and circulates in the blood stream, making it likely that alterations in CFH are related to other diseases."

Hageman was an author of a 2005

article in the *Proceedings of the National Academy of Sciences* that reported the genetic variations in CFH associated with increased risk for AMD.

Ophtherion has a recombinant form of the protective variant of CFH (rhCFH) in preclinical testing for dry AMD and membranoproliferative glomerulonephritis Type II, an Orphan disease characterized by a combination of AMD-like symptoms and kidney failure, in which dysfunctional CFH also is implicated.

Hageman thinks that in the next year, researchers will begin to link genetic differences in CFH that are associated with AMD to other disease risks like myocardial infarction (MI) and coronary artery disease (CAD).

"Traditional diseases of the eye have been perceived as being exclusively eye-related, with therapeutics developed to treat it locally," Foster told BioCentury.

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“But discovery of CFH and the biology behind it shows us that the disease may be much broader.”

Nussenblat agreed: “The real question to be investigated over the next several years is whether ocular diseases like AMD are better treated systemically.”

Both Nussenblat and D’Amore noted the larger story of the ocular immune environment must be understood before therapeutics can be developed.

“CFH is interesting, but it is an area of immunology that most ophthalmologists don’t know much about,” Nussenblat said. “Over the next few years, the immune system will be looked at and evaluated for its role, but how significant that is and whether it can be translated into something positive for the patient remains to be seen.”

“Attacking complement is a good idea,” D’Amore said, “but we really do not know how these polymorphisms translate into functionality and eye disease.”

While Hageman agreed much work still must be done to fully understand how AMD works and the role of CFH, he said it’s not too early to begin looking into therapeutics.

“Pharmas are pulling things off the shelves that they had tried previously in the complement system, but maybe they weren’t efficacious for the indication,” he said, “and now they are taking a second look at AMD.”

“It is going to be a frenzy; pretty much everybody with a complement inhibitor out there is thinking about AMD,” Potentia’s Francois told BioCentury.

Eyeing new targets

Jean Bennett, senior investigator at University of Pennsylvania’s **Scheie Institute**, hopes to be in the midst of the next wave of innovations with her research on gene therapy for Leber congenital amaurosis (LCA), an early onset retinal disorder that leads to complete vision loss by about the age of three.

Bennett and colleagues have constructed an adenovirus vector containing a functional version of the defective retinal pigment epithelium (RPE65) gene responsible for the disease and injected it into the eyes of three adult patients. Improved vision characterized by improved travel time and reduced mobility errors was reported in one patient within two months

Dry AMD pipeline

Selected compounds in development for dry AMD.

| Company | Product | Description | Status |
|---------------------------------|--|---|---------|
| Neurotech | NT-501 | Encapsulated cell technology to deliver ciliary neurotrophic factor (CNTF) | Ph II |
| Othera | OT-551 | Ophthalmic solution of a small molecule catalytic antioxidant derived from Tempol-H | Ph II |
| Pipex (AMEX:PP) | Zinthionein | Oral zinc-monocysteine complexes | Ph II |
| Sirion | Fenretinide (ST-602) | Synthetic retinoid | Ph II |
| Acucela/ Otsuka (Tokyo:4768) | ACU-4429 | Oral small molecule non-retinoid visual cycle modulator | Ph I |
| Potentia | POT-4 | Synthetic peptide complement C3 inhibitor | Ph I |
| Advanced Cell (OTCBB:ACTC) | Retinal pigment epithelial (RPE) cells | Human stem cell-derived RPE cells | Preclin |
| Ophtherion | rhCFH | Recombinant form of the protective variant of complement factor H (rhCFH) | Preclin |

of injection.

The team published the findings in the May 22 online edition of *The New England Journal of Medicine*. However, a more recent clinical trial to replace the RPE65 gene in three patients did not show an improvement in vision. The trial, conducted by Samuel Jacobsen, professor of ophthalmology at the university and colleagues, was published online in the September edition of *Human Gene Therapy*.

Bennett’s team is beginning to work on Stargardt’s disease, an autosomal recessive form of juvenile macular degeneration. “You have to walk before you can run, but this could be a stepping stone towards larger diseases like AMD,” she said.

Alcon and Novartis also are looking for new targets, and both companies think dry AMD is one of the next hot areas (see “*Dry AMD Pipeline*”).

No therapies are approved for the condition, which involves the accumulation of lipoproteinaceous deposits called drusen. As they accumulate in specific areas of the retina, they cause those areas to essentially die and become atrophied, causing local vision loss (geographic atrophy (GA)), rather than general loss across the macula.

“Many more people have dry AMD than have wet AMD, though it doesn’t cause as much physical dysfunction,” Alcon’s MacHatton noted. “However, it tends to lead to wet AMD. We’re investigating treatments for geographic atrophy for dry AMD. We haven’t disclosed any compounds, which are many years out.”

While the mechanisms of dry AMD

aren’t fully understood, there has been progress in the last few years. Once again, the complement system is a centerpiece.

“A huge thing that’s happened in the last three years in dry AMD is elucidation of the role of complement,” Keating said.

Beyond complement, **Acucela Inc.** is one of the companies tackling a new target. Its ACU-4429 is an oral small molecule non-retinoid visual cycle modulator in Phase I testing to treat dry AMD.

The visual cycle is the process by which light is converted into signals in the eye to produce images. As part of this cycle, the outer portion of photoreceptors undergo phagocytosis to maintain vision. This maintenance can lead to the build-up of N-retinylidene-N-retinylethanolamine (A2E). According to Acucela CEO Ryo Kubota, the accumulation of A2E is strongly correlated with AMD.

Earlier in the visual cycle, trans-retinal is converted to trans-retinol and then back to cis-retinol, which is sent back to the rod cells, where it is conjugated with opsin to form a new rhodopsin molecule. The new rhodopsin molecule starts the visual cycle over again.

ACU-4429 slows the visual cycle by inhibiting the isomerization of trans-retinal to cis-retinol. Kubota believes that slowing the visual cycle will result in less turnover of photoreceptors and hence less accumulation of A2E.

“We chose the isomerization step because it is a highly specific process that does not occur anywhere else in the body,” he said.

Kubota also believes the molecule will

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help slow or eliminate the conversion of dry AMD to wet AMD.

"We know that A2E can trigger the inflammatory process that can lead to vascularization and wet AMD," he told BioCentury.

Sirion Therapeutics Inc. is directly targeting A2E. The company's fenretinide synthetic retinoid, which binds A2E systemically, is in Phase II testing to treat GA associated with dry AMD.

Neurotech Pharmaceuticals Inc. is tackling new targets and a new delivery mechanism with its NT-501. The encapsulated cell technology to deliver ciliary neurotrophic factor (CNTF) is in Phase II testing to treat dry AMD and Phase II/III testing to treat retinitis pigmentosa (RP), with the goal of revitalizing dying photoreceptors and restoring vision. Thus, rather than arrest the visual cycle or bind A2E, CNTF is neuroprotective.

NT-501 contains human retinal cells that express CNTF. About 6,000 cells are loaded into a biodegradable porous polymer capsule that is implanted into the back of the eye. According to President and CEO Ted Danse, "it is a 15-minute procedure that might even be simpler than cataract surgery."

The cells produce CNTF protein, which is secreted through the capsule's porous membrane. Danse thinks the capsule could work for up to two years, which he believes is better than monthly intravitreal injections.

NT-501 has Fast Track and Orphan Drug designations in the U.S. to treat RP.

The company expects top-line data in both indications by 1Q09.

Complementing VEGF

Angiogenesis will remain a hot area. Keating noted that Novartis and Genentech are developing Lucentis for indications including diabetic retinopathy, specifically diabetic macular edema, and retinal vein occlusion. He said other anti-angiogenic targets also will be looked at for the eye.

Ophthotech Corp. is looking to create drugs for use in combination with Lucentis. The company's lead compound, E10030, is an aptamer against platelet derived growth factor (PDGF). It was in-licensed from **OSI Pharmaceuticals Inc.** In February, Ophthotech started Phase I testing of E10030 in combination with Lucentis to treat AMD.

According to President and CEO Samir Patel, "Lucentis is effective at preventing further growth of neo-vascularization, but it doesn't cause significant regression of vascularization."

Patel said preclinical models have shown that blocking both VEGF and PDGF results in vascular regression in the retina.

PDGF plays a role in retinal vascularization through the recruitment of pericytes, which support blood vessel growth in the eye. "If you strip the pericytes, it appears that endothelial cells in their absence are much more sensitive to anti-VEGF," he said.

The company also is looking at combining inhibition of VEGF and complement to treat wet AMD.

ARC1905, an aptamer targeting complement 5 (C5), is in Phase I testing to treat wet AMD. In 2007, the company received an exclusive worldwide license to develop and commercialize **Archemix Corp.**'s aptamers targeting C5 for ophthalmic use.

Patel believes the company's portfolio of in-licensed compounds will work synergistically with Lucentis to treat wet AMD.

Novartis also continues to investigate new targets in wet AMD. Its ACZ885, an antibody against IL-1 beta, is in Phase I testing.

"IL-1 beta antibodies are very potent inhibitors of IL-1 beta and inflammation," Keating noted. "The complement story provides data that inflammation is important in dry and wet AMD, so we're looking at whether going after IL-1 beta will affect AMD."

"Ophthalmics has traditionally been a realm of surgery. Innovation by surgeons tends to relate to procedures and instruments, not to fundamental, biological pathways of disease."

Mark Keating, Novartis

Opportunities in glaucoma

Prostaglandins and beta blockers have been the standard of care for glaucoma for the past decade. But Alcon and **Inspire Pharmaceuticals Inc.** are developing rho kinase inhibitors to treat the disease, which is characterized by the build-up of aqueous humor in the eye leading to increased intraocular pressure (IOP), vision loss and eventual blindness.

The fluid build-up and increased pressure is caused by the breakdown of the eye's drainage system. The aqueous humor is drained from the eye via two systems: the scleral pathway and the trabecular meshwork, with the majority of drainage occurring via the latter.

Traditional prostaglandins like Pfizer's Xalatan latanoprost work by increasing drainage via the scleral pathway. Beta blockers like Merck's timolol reduce pressure by slowing down the aqueous humor production.

Rho kinase inhibitors relax the meshwork.

"It is like a sieve, but over time, the sieve gets clogged up, and rho kinase inhibitors relax the sieve to allow fluids out," R. Kim Brazzell, SVP of ophthalmic R&D at Inspire, told BioCentury.

If rho kinase inhibitors are able to block the underlying mechanism that causes the meshwork to become clogged, Brazzell said the compound and others targeting the kinase could be disease-altering.

Earlier this month, Inspire submitted an IND to begin Phase I trials of its INSI 17548 rho kinase inhibitor to treat glaucoma.

Novartis has its own rho kinase inhibitor, RKI983, in Phase I trials for glaucoma and ocular hypertension.

The pharma also has a topical cannabinoid CBI/CB2 receptor agonist, SAD448, in Phase I trials for ocular hypertension, a risk factor for glaucoma. "This could reduce IOP by two mechanisms: decrease the creation of aqueous humor and increase outflow," Keating said.

Special delivery

The success of drugs like Lucentis has led researchers to look for better drug delivery technologies than intravitreal injection, which can be administered only by retinal specialists and require the patient to be sedated.

EyeGate Pharmaceuticals Inc. is using its iontophoresis
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“90% of CFH is manufactured in the liver and circulates in the blood stream, making it likely that alterations in CFH are related to other diseases.”

Gregory Hageman, Ophtherion

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technology to deliver EGP-437, a dexamethasone phosphate ophthalmic solution, to the front of the eye. The small molecule is in Phase II testing to treat acute anterior uveitis and the company plans to start a Phase II trial to treat dry eye in October.

The technology, which was developed at **Bascom Palmer Eye Institute**, uses simple cell physiology to produce a transitory interference that allows the increased cellular uptake of the therapeutic.

The iontophoresis device sits on top of the eye around the iris and delivers a transitory electric current to the eye. The current opens cellular channels and permits the therapeutic to enter the cells in exchange for a salt molecule.

According to Stephen From, president and CEO of EyeGate, the technology can deliver a variety of drugs to the front or back of the eye, including small molecules, nanoparticles and RNA.

“If we need to penetrate the macula, we will increase the current or leave the device on the eye longer,” he told BioCentury.

Therakine Ltd. has developed a resorbable biopolymer matrix that allows for up to six-months of sustained release of mAbs and large proteins in the eye. The company is interested in partnering the technology with proven biologics that may not have been tried in ophthalmic indications.

“We are talking to firms that have biologics with specific targets to treat ophthalmic disease about putting their drug in our package,” CEO Scott Hampton told BioCentury.

While the packaged biologics still would be administered via an intravitreal injection, Hampton believes the technology will require only two injections per year. “We believe a six-month interval is a lot better than a three-to-six-week interval,” he said.

Therakine also is designing a simpler injector that would allow the diagnosing ophthalmologist to perform the injection.

“Many ophthalmologists are already comfortable with a variety of ocular steroid injections, so a simple injector for a sustained-release anti-inflammatory biologic that does not have many of the side effects of steroids will be an easy conceptual step,” Hampton said.

ESBATech AG also chose to focus on delivery over target discovery. According to CEO Dominik Escher, the company wanted to take out the target risk by focusing on the development of antibody fragments against clinically validated, ophthalmic targets like VEGF and tumor necrosis factor (TNF) alpha.

ESBATech’s lead biologic, ESBA105, is a single-chain antibody fragment against TNF alpha in Phase I testing to treat ophthalmic disease. Because the fragments are relatively small, they are amenable to the company’s eye drop delivery system and can penetrate the tight junctions of the cell epithelium. Escher believes that this will allow the compounds to reach the back of the eye.

As Visudyne has dried up, QLT has taken steps in the past 18 months to restructure its business around its 2007 acquisition of drug delivery company ForSight Newco II Inc. ForSight’s punctal plugs, which act as a dam to keep fluid in the tear duct, have been used for many years to treat dry eye.

QLT intends to use the plugs to deliver therapeutics for front-of-the-eye diseases like glaucoma. The plugs would be inserted into the tear duct to administer drug in a sustained fashion for about 90 days.

The company’s first product, which contains Xalatan, is in Phase II testing to treat glaucoma. Data are expected by year end.

President and CEO Robert Butchofsky believes the plugs will offer compliance advantages over standard eye drops in glaucoma. “There is a huge issue with compliance in topical eye drug medications: about 50% of glaucoma patients do not take the drops beyond six months,” he said.

QLT also believes the plugs will increase efficacy by administering the appropriate dose each time. According to Butchofsky, “drops are inefficient because you lose anywhere from 70-80% of the drug.”

The company plans to have a second formulation in the clinic next year.

“The big pharma’s interest provides an exit route to VCs.”

Graham Boulnois, SV Life Sciences

Ophthalmic dealings

While there have been almost 40 ophthalmics deals since the start of 2007, the Novartis purchase of a 25% stake in Alcon from **Nestle S.A.** is the largest ophthalmics deal ever done (see “*Ophthalmic Deals*”).

“The two groups are complementary from a product and skills perspective,” Shah noted. “We’re strong in the back of the eye. They’re strong in the front of the eye. Back-of-the-eye therapies tend to go to retinal specialists. Front-of-the-eye therapies tend to go to general ophthalmologists. So the segments are pretty complementary.”

According to Keating, Alcon is “very good at development, particularly with respect to anterior chamber therapies — glaucoma, allergy, anti-infectives. Where they have not really aimed is at basic research where you start with genetics and move to biochemistry and try to do something innovative like Lucentis.”

In contrast, he said, “Novartis has strengths in retinal disorders. In the past, we have in-licensed much of the innovation, but now we have a research organization we started not quite three years ago.”

Alcon’s key pipeline product is Retaane anecortave acetate, a modified steroid that inhibits neovascularization in the eye. The company discontinued development of the drug to treat AMD in April, after interim Phase III results showed no effect on the primary endpoint to prevent progression of dry AMD to wet AMD in at-risk patients.

But Alcon plans to continue developing the compound in glaucoma. In March, the company completed a Phase II trial in patients with open-angle glaucoma. Retaane maintained IOP at ≤ 21 mmHg at three months in more than 55% of patients.

By comparison, market leading Xalatan latanoprost, a prostaglandin analog from Pfizer, has been shown to reduce IOP from a baseline of 24-25 mmHg by about 6-8 mmHg when treated for at least six months.

“We have found Retaane reduces
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IOP with an injection once every three or four months,” MacHatton said. “We’re still looking at the right concentration, the right duration of action. We think it’s the most exciting glaucoma treatment out there. It addresses both IOP and compliance with the eye drop regimen.”

In 2007, VCs put over \$261 million into the ophthalmic space; they have added another \$108 million so far this year (see “Venturing into Ophthalmic Space”).

According to Graham Boulnois, partner at SV Life Sciences, “the commercial opportunity was demonstrated by the success of Macugen and Lucentis, which were important in showing people how to think about ophthalmics.”

He added that renewed interest of large pharmas has given VCs more confidence about investing in the space. “The big pharmas’ interest provides an exit route to VCs,” Boulnois said.

Over the past two years, SV Life Sciences has participated in series A financings for **Lux BioSciences Inc.** and Ophthotech, along with a series B round for Neurotech.

Sirion President and CEO Barry Butler believes the interest in ophthalmics will continue to grow due to shifting demographics. “If you look at the population of people over 70, it is expected to double by 2030,” he said, noting that the longer people live, the more likely they are to develop ophthalmic diseases.

Butler also thinks the lower cost of bringing ophthalmics to market makes it an attractive investment. “The target audience is only about 20,000 doctors, so you don’t need as many people in your sales force,” he said.

COMPANIES AND INSTITUTIONS MENTIONED

- Acucela Inc.**, Bothell, Wash.
- Alcon Inc.**, Hünenberg, Switzerland
- Archemix Corp.**, Cambridge, Mass.
- Bascom Palmer Eye Institute**, Miami, Fla.
- ESBATech AG**, Zurich, Switzerland
- EyeGate Pharmaceuticals Inc.**, Waltham, Mass.
- Genentech Inc.** (NYSE:DNA), South San Francisco, Calif.
- Harvard University, Schepens Eye Research Institute**, Boston, Mass
- Inspire Pharmaceuticals Inc.** (NASDAQ:ISPH), Durham, N.C.
- Isis Pharmaceuticals Inc.** (NASDAQ:ISIS), Carlsbad, Calif.
- Lux BioSciences Inc.**, Jersey City, N.J.
- Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.
- National Eye Institute**, Bethesda, Md.
- Nestle S.A.** (SWX:NESN), Vevey, Switzerland
- Neurotech Pharmaceuticals Inc.**, Lincoln, R.I.
- Novartis AG** (NYSE:NVS; SWX:NOVN), Basel, Switzerland
- Ophthotech Corp.**, Princeton, N.J.
- Ophtherion Inc.**, Branford, Conn.
- OSI Pharmaceuticals Inc.** (NASDAQ:OSIP), Melville, N.Y.
- Pfizer Inc.** (NYSE:PFE), New York, N.Y.
- Potentia Pharmaceuticals Inc.**, Louisville, Ky.
- QLT Inc.** (TSX:QLT; NASDAQ:QLTI), Vancouver, B.C.
- Sirion Therapeutics Inc.**, Tampa, Fla.
- Therakine Ltd.**, Cumming, Ga.
- University of Pennsylvania**, Philadelphia, Pa
- University of Pennsylvania, Scheie Institute**, Philadelphia, Pa.
- Yale School of Medicine**, New Haven, Conn.

Ophthalmic deals

Selected deals in the ophthalmic space since 2007; Source: BCIQ: BioCentury Online Intelligence

| Date | Companies | Value [upfront; milestones/royalties] | Description |
|-----------------------|---|---------------------------------------|---|
| Sep 08 | Acucela/Otsuka (Tokyo:4768) | [\$5M; up to \$258M] | Partner to develop a pair of compounds for ophthalmic indications: Acucela’s ACU-4429 for dry age-related macular degeneration (AMD) and potentially other indications such as diabetic retinopathy; and Otsuka’s rebamipide |
| Aug 08 | Eyetechnology/OSI (NASDAQ:OSIP) | [\$0; undisclosed] | OSI employees purchase the assets of the company’s Eyetechnology business to form newco Eyetechnology Inc. which includes OSI’s remaining ophthalmic assets, including U.S. rights to Macugen pegaptanib to treat wet AMD |
| Aug 08 | Asterand (LSE:ATD)/ Allergan (NYSE:AGN) | [\$6.3M; up to \$56M] | Allergan obtains exclusive worldwide rights to undisclosed preclinical small molecule prostaglandin receptor agonists for ophthalmic indications |
| Jul 08 | Alcon (NYSE:ACL)/ Novartis (NYSE:NVS; SWX:NOVN) | \$10.4B cash | Novartis acquires a 25% stake in Alcon from Nestle (SWX:NESN) |
| Jul 08 (proposed acq) | Jerini (Xetra:JI4)/ Shire (LSE:SHP; NASDAQ:SHPGY) | \$516.6M cash | Shire says it will acquire Jerini |
| Jun 08 | Opko (AMEX:OPK)/ Redox | Undisclosed | Opko acquires exclusive worldwide rights to develop and commercialize Doxovir (CTC-96) for ophthalmic indications |
| Jun 08 | MacuSight/Santen (Tokyo:4536; Osaka:4536) | [\$50M; royalties and milestones] | Santen obtains an exclusive license to develop and commercialize an extended-release liquid formulation of sirolimus in Japan and Asia to treat wet AMD and diabetic macular edema (DME). MacuSight retains rights elsewhere. |

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| Date | Companies | Value [upfront; milestones/royalties] | Description |
|--------|---|--|---|
| May 08 | Pipex (AMEX:PP) | Undisclosed | Pipex receives an option to license exclusive worldwide rights to Karl-Georg Schmidt's IP covering Effirma oral flupirtine for ophthalmic diseases, diabetes and diabetes-related indications |
| Apr 08 | arGentis/Southern College of Optometry | Undisclosed | The college grants arGentis rights to ARG103 to treat dry eye in postmenopausal women |
| Apr 08 | Jerini/PR Pharmaceuticals | Undisclosed | Partners will use PR Pharma's drug delivery technologies to develop sustained-release formulations of Jerini's JSM6427 and JPE-1375 to treat AMD |
| Apr 08 | Galapagos (Euronext:GLPG; LSE:GLPG)/ Bausch & Lomb (NYSE:BOL) | [\$400,000; \$50M plus research funding and royalties] | Galapagos grants Bausch & Lomb an exclusive worldwide option to license rights to develop and commercialize undisclosed small molecules for ophthalmic indications |
| Mar 08 | MethylGene (TSX:MYG)/ Otsuka (Tokyo:4768) | [\$6.9M; up to \$50.5M plus royalties] | Partner to develop and commercialize kinase inhibitors to treat ocular diseases, excluding cancer. Upfront includes a \$3M equity investment and \$1.9M in research funding. |
| Mar 08 | Bikam/Dalton | Undisclosed | Dalton will use its medicinal chemistry technology to discover several new classes of compounds against undisclosed Bikam targets for ophthalmic indications |
| Feb 08 | Bridge Pharma/Sirion | Undisclosed | Bridge grants Sirion an exclusive worldwide license to develop and market topical ophthalmic formulations of norketotifen, an anti-inflammatory compound |
| Jan 08 | StemCells (NASDAQ:STEM)/ Oregon Health & Science U | Undisclosed | The university will evaluate StemCell's human neural stem cells (HuCNS-SCs) in a rat model of retinal degeneration |
| Jan 08 | Biogen Idec (NASDAQ:BIIB)/ PDL (NASDAQ:PDLI)/ Ophthotech | Undisclosed | Biogen and PDL grant Ophthotech an exclusive worldwide license to develop and commercialize volociximab (M200) for ophthalmic indications |
| Nov 07 | Fovea/Genzyme (NASDAQ:GENZ) | Undisclosed | Partner to develop gene-related therapies for retinal dystrophies using targets selected by Fovea and Genzyme's gene delivery technologies |
| Nov 07 | CellTran/Ilika | Undisclosed | Partner to develop CellTran's corneal stem cell therapy delivered using plasma polymerization technology |
| Nov 07 | Lantibio/Alcon (NYSE:ACL)/ TRB Chemedica | Undisclosed | Lantibio and TRB grant Alcon exclusive U.S. rights to commercialize Vismed to treat dry eye syndrome |
| Nov 07 | Opko/Ophthalmic Technologies | \$10M stock | Opko acquires the two-thirds of diagnostic company Ophthalmic it does not already own, gaining a diagnostics business to complement its ophthalmic therapeutics |
| Oct 07 | Opko (AMEX:OPK)/Undisclosed | Undisclosed | Opko receives exclusive worldwide rights to civamide to treat dry eye |
| Oct 07 | Ark (LSE:AKT)/ Eyecopharm | Single-digit royalties | Ark will spin out its non-core discovery stage anti-angiogenic peptides and related IP to Eyecopharm, which will develop and commercialize therapeutics to treat eye diseases |
| Oct 07 | ForSight/QLT (TSX:QLT; NASDAQ:QLTI) | [\$42M cash; >\$40M plus royalties] | QLT acquires ForSight, giving it an ocular punctal drug delivery system, which QLT said is capable of delivering compounds to the eye through controlled release to the tear film |
| Sep 07 | Alimera/Emory U | Undisclosed | Alimera receives an exclusive worldwide option to license undisclosed NADPH oxidase inhibitors to treat ophthalmic indications |
| Aug 07 | Archemix/Ophthotech | Undisclosed | Ophthotech receives an exclusive worldwide license to develop and commercialize aptamers targeting complement 5 (C5) to treat wet and dry forms of AMD |
| Aug 07 | Meda (SSE:MEDA)/ MedPointe | \$763.2M cash and stock | Meda acquires MedPointe, gaining the marketed Optivar azelastine, a topical ophthalmic solution of the selective histamine H1 receptor antagonist to treat allergic conjunctivitis |

Ophthalmic Deals,
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| Date | Companies | Value [upfront; milestones/royalties] | Description |
|--------|---|--|---|
| Jul 07 | OSI (NASDAQ:OSIP)/ Ophthotech | Undisclosed | Ophthotech receives rights from OSI's Eyetech subsidiary to an anti-platelet derived growth factor (PDGF) aptamer program that includes E10030, a preclinical compound to treat wet AMD |
| Jul 07 | Pipex (AMEX:PP) | Undisclosed | Pipex receives an exclusive worldwide license to Z-monocys zinc-monocysteine complexes from David Newsome and George Brewer to treat Wilson's disease |
| Jun 07 | SurModics (NASDAQ:SRDX)/ Merck (NYSE:MRK) | [\$20M; \$288M plus royalties] | Merck obtains rights to SurModics' I-variation sustained delivery system for use with triamcinolone acetonide (TA) and selected Merck compounds to treat retinal disease |
| May 07 | CeNeRx/Neuroscienze PharmaNess | Undisclosed | CeNeRx receives exclusive worldwide rights to develop, manufacture and commercialize PharmaNess' cannabinoid portfolio, which includes more than a dozen preclinical compounds to treat pain, glaucoma, CNS-related disorders and obesity |
| Apr 07 | pSivida (NASDAQ:PSDV; ASX:PVA)/ Pfizer (NYSE:PFE) | [Up to \$10M; up to \$155M milestones, plus royalties] | Pfizer receives exclusive worldwide rights to pSivida's controlled-release drug delivery technologies to treat ophthalmic diseases. Upfront includes a \$5M equity investment and a potential \$5M investment. |
| Mar 07 | Acuity/Froptix/eXegenics | NA | Acuity and Froptix reverse merge with shell company eXegenics to form Opko Corp. |
| Mar 07 | International Stem Cell (OTCBB:ISCO)/ U of Calif. | Undisclosed payments | The university will test stem cell lines from the company's preclinical models of macular degeneration and retinitis pigmentosa |
| Mar 07 | Novagali/Topigen | Undisclosed | Novagali receives a license to use Topigen's mRNA-based multi-targeting technology to treat and prevent allergic eye diseases |
| Feb 07 | InSite (AMEX:ISV)/ Pfizer (NYSE:PFE) | Undisclosed | InSite receives exclusive worldwide rights to Pfizer's azithromycin to treat eye infections |
| Jan 07 | MediVas/Pfizer (NYSE:PFE) | Undisclosed | MediVas will apply its biodegradable and biocompatible polymer drug delivery technology to undisclosed Pfizer compounds to treat ophthalmic diseases |
| Jan 07 | Sirion/Laboratoires Théa | Undisclosed | Sirion receives exclusive U.S. rights to develop and commercialize topical ganciclovir to treat viral and superficial eye infections |
| Jan 07 | Fovea/Novartis (NYSE:NVS; SWX:NOVN) | Undisclosed | Fovea receives an exclusive worldwide license to develop and commercialize Novartis' rod-derived cone viability factor (RdCVF) to treat retinal degeneration |
| Jan 07 | arGentis/Southern College of Optometry | Undisclosed | The college grants arGentis exclusive worldwide rights to a patent covering the use of transdermal progesterone to treat dry eye |

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