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# Biotech and pharma companies scramble to exploit lucrative wet AMD market

It may be responsible for only 10% of all age-related macular degeneration cases, but wet AMD has become a prime – and potentially lucrative – target for a number of biotech companies.

Statistics reveal the effect of wet AMD on Europe's growing late middle-aged and elderly population. In particular, the European office of AMD Alliance International predicts that ophthalmologists in the European Union's 25 countries will collectively face about 2.8 million cases of wet AMD within the next decade.

Throughout Europe and across the world, ophthalmologists diagnose an estimated 500,000 new cases of wet AMD per year. Clearly, such statistics create sweet music for any budding entrepreneur who can devise an effective treatment for this enormous and growing market.

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As ophthalmologists well know, the wet form of AMD – unlike that of the more prevalent dry form of AMD – has become a focus for treatment based on treating the abnormal blood vessel growth that characterises the disease. This blood vessel growth – known as “choroidal neovascularisation” – occurs under the centre of the retina. These new blood vessels are prone to bleeding and leakage causing the macula to bulge or lift and distort central vision. A sudden rupture can cause immediate, albeit transitory, blindness.

At present, treatment of wet AMD by means of photodynamic therapy (PDT) has been a popular choice. PDT works by intravenously delivering a light sensitive molecule, “verteporfin,” into the eye which can then be activated by laser. Activation of verteporfin then brings about a cytotoxic

destruction of the new blood vessels associated with progression of wet AMD.

Unfortunately, PDT at best only provides a stabilizing effect on the pathology that derives from the formation of new blood vessels; often, the effect is of a temporary nature. The therapy is not able to prevent the formation of new blood vessels nor is it capable of providing any improvement in vision. Consequently, wet AMD still awaits an effective treatment that can tackle the root cause of the problem – the underlying new blood vessel development.

## Inhibiting angiogenesis

The new blood vessel growth, also referred to as “angiogenesis”, is caused by the expression of a vascular growth factor known by the abbreviation of “VEGF” for vascular endothelial growth factor. Choroidal neovascularisation in the retina, choroid, and iris of the eye, is a major complicating feature among a broad range of ocular disorders. This, as expected, has attracted a lot of attention because if researchers can develop a strategy to prevent neovascularisation for AMD, then such a strategy may also prove useful in treating a whole range of neovascular-related diseases in and outside of the eye.

Many therapeutic rationales focused on treating wet AMD now attempt to interfere in the biological role of VEGF in an effort to interfere with new blood vessel growth. Two relatively new drugs targeting VEGF in the eye are pegaptanib and ranibizumab.

Pegaptanib (Macugen®) is a product of Eyetech Pharmaceuticals and Pfizer. Ranibizumab (Lucentis®) is a product of Genentech and Novartis. Both drugs show encouraging advances in treating wet AMD.

Pegaptanib is an “aptamer,” which is a macromolecule composed of chemically synthesised single stranded nucleic acids of either RNA or DNA. The compound is capable of specifically binding the VEGF165 isoform which when bound is no longer capable of binding to the VEGF receptor and thereby blocks VEGF activity.

Unlike pegaptanib, ranibizumab is an antibody fragment capable of binding all forms of VEGF. This pan-retinal approach may of course have both positive and negative consequences. It is positive in that all VEGF isoforms in the eye can be blocked; however, it is negative if the compound were to leak out of the eye to other parts of the body where new vessel growth were required.

Pegaptanib, which is currently on the market, can bind with very high specificity to its extracellular VEGF target thereby

limiting the ability of VEGF to promote new blood vessel formation. Eyetech, the company currently selling the drug, estimate worldwide sales for 2005 will reach just under \$200 million.

Some researchers believe that the new Lucentis drug may have an edge over Macugen. This is due to the fact that recent Phase III trials with Lucentis have demonstrated a convincing improvement of vision among treated patients. Of course, the devil is in the detail. Both companies continue to exchange blows over which data set is the more realistic and which drug has the better safety profile.

## RNA interference approach

While such squabbles continue, an entirely new class of drugs is emerging which also aim to specifically target VEGF. Popularly referred to as “RNAi” - short for ribonucleic acid interference – this new technology is currently being spearheaded by a variety of biotech players. Two American-based companies, Acuity Pharmaceuticals in Philadelphia, and Sirna in San Francisco, are currently testing first generation drugs in human clinical trials.

Acuity lays claim to be the first company to test RNAi therapeutics in humans in October of 2004 when it targeted VEGF in the retina to treat wet AMD. This was followed shortly by Sirna, which, in November of 2004, initiated Phase I trials with an RNAi compound to target the VEGF receptor mRNA.

Unlike pegaptanib and ranibizumab – which target the VEGF protein – RNAi therapeutics take a step back and aim for the mRNA (messenger ribonucleic acid) targets. Acuity's compound, “Cand5”, targets the mRNA of VEGF itself; Sirna's compound, “Sirna-027,” targets the mRNA of the VEGF receptor to prevent downstream signalling and new blood vessel formation.

Researchers believe that ribonucleic acid interference, or “RNAi” for short, is a biological process that originally evolved to counter viral infections and a number of other enemies. Today, the potential applications for RNAi are so huge that biotechnology investors have collectively invested millions of euro in “RNAi” companies such as Sirna and Acuity.

Aside from the various antibody and RNAi based approaches outlined above, there is a range of treatment strategies now under development with small molecules again aimed at blocking VEGF. These include:

- “Retaane” (anecortave), which is now in a Phase III trial, sponsored by Alcon;

- “Evizon” (squalamine lactate) which has recently completed Phase II trials, sponsored by Genaera.

It is obvious that there is acute interest in developing drugs to treat AMD and the underlying angiogenesis associated with the wet form of AMD. Successful treatment against VEGF in a wet AMD setting will of course open the further opportunity of targeting other diseases associated with undesirable neovascularisation, such as diabetic retinopathy and central vein occlusion.

Market forecasts for the wet AMD space predict a potential multi-billion euro market well into the future which in and of itself will ensure a major focus for companies to continue development programmes in this field.

For more information about ongoing treatment of and research into wet AMD, contact:

Acuity Pharmaceuticals	– <a href="http://www.acuitypharma.com">www.acuitypharma.com</a>
Alcon	– <a href="http://www.alcon.com">www.alcon.com</a>
Eyetech	– <a href="http://www.eyetech.com">www.eyetech.com</a>
Genaera	– <a href="http://www.genaera.com">www.genaera.com</a>
Genentech	– <a href="http://www.gene.com">www.gene.com</a>
Novartis	– <a href="http://www.novartis.com">www.novartis.com</a>
Pfizer	– <a href="http://www.pfizer.com">www.pfizer.com</a>
Sirna	– <a href="http://www.sirna.com">www.sirna.com</a>

## Glossary

**Verteporfin** is a medicine that is activated in the presence of light and oxygen but in their absence has no effects. The drug is routinely used in the photodynamic treatment of eye disorders where it can produce a localised cell killing effect to disrupt new blood vessel growth.

**Cytotoxic** refers to the toxic effects of a substance on the cell.

**VEGF**, vascular endothelial growth factor, is a well studied growth factor responsible for facilitating the growth of new blood vessels.

**Aptamers** are a relatively new type of compound composed of either a double stranded DNA or a single stranded RNA molecule capable of highly specific molecular binding of proteins or metabolites and, as such may prove to be useful tools to block biochemical pathways in a medically relevant context.

**RNAi**, ribonucleic acid interference, refers to a relatively new discovery in which short fragments of RNA, when introduced into cells or tissues, can bring about the shutdown of target genes against which the RNA fragment binds. These short stretches of RNA have been found to be highly potent and effective in halting gene expression leading to their potential value as therapeutic tools in a broad range of diseases from cancers to infections and neurodegenerative disorders.

**mRNA**, or messenger ribonucleic acid, represents the intermediate molecule in the flow of information from DNA to protein. mRNA results from the transcription of specific sequences from DNA and is then used as the template from which proteins are built or “translated”.