**Ask The Experts What It Means – Retina Day 2015**

**The audience posed questions around what scientific language and concepts that were answered by our panel of experts.**

**•** Chair:

o Dr. Andi Skilton, Patient and Public Involvement and Engagement Senior Research Associate

• Panel:

o Professor James Bainbridge, Professor of Retinal Studies and Ophthalmologist

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**Q&A**

**For what conditions will stem cells be effective?**

**What factors determine whether stem cell treatments are likely to be more or less effective in any one specific condition?**

Stem cells are already in use in certain conditions outside of the eye - bone marrow transplant is one. They are also used to resurface the front of the eye. What is more challenging, is to use stem cells to generate nerves, and that is the challenge we face for conditions of the retina.

At the moment, we are identifying situations in which we have the best hope of demonstrating or having an impact on peoples’ sight by targeting the pigment cells underneath the light-sensitive photoreceptor cells. That is where we think we have the best chance of having an impact in the short-term. This is quite challenging because people's sight is not just dependent on those pigment cells but the photoreceptor cells themselves.

We have to find an opportunity where replacing those pigment cells will also enable restoration of normal function or survival of the overlying photoreceptor cells as well, in conditions where both cell types are affected. If we can demonstrate this is possible it would give us the confidence to go on and be more ambitious about the kind of applications that we are going to test.

**What are the priorities for stem cell research?**

**For stem cell treatments, would you say the priority is primarily a commercial decision, or to research conditions that affect the largest number of people, or where you are likely to get the quickest wins for more conditions?**

Ultimately it is all those things, but primarily for us the priority in the first instance, is to prove in principle it is possible to make a difference. The way we can do that the most quickly is by some very carefully controlled and calculated situations, in conditions that don’t necessarily affect lots of people. It is only by showing it might work we can be in a position to expand it to more common conditions which are often more challenging to address.

**What is the difference between genotyping and phenotyping?**

For inherited conditions:

Genotyping is the identification of the defects in the DNA i.e. which gene is affected and what is the problem in that gene. The genotype is the cause.

Phenotyping describes the progression of the condition and provides an understanding how the eye is doing and what is happening in the eye as a whole. The phenotype is the result of the genotype.

**When you have your DNA sequenced, and you are told your genes and the mutations what are the numbers that are referred to and where do they come from?**

The DNA code is given as a sequence of letters. The letters identify the change or fault that has occurred in the alphabet of your DNA, like a mistake in spelling, and the numbers tell you where in this sequence of letters that change has occurred – so it gives you the location of the change in your genetic material. Sometimes this will be a change in both copies of a gene (one inherited from your mother and one from your father) and other times it will change in just one of the copies.

**What is the chances of passing on an inherited retinal condition to a child if one parent has it and the other doesn’t?**

It depends on how it is being inherited. The majority of cases of RP are inherited recessively this means both parents would have to carry the same form of RP, the chances of which are very low about 1%. Two people with different forms RP could have a child not affected by RP.

This trend is not always the case, so it is important to see a doctor to determine how your RP is being inherited to be then able to give you the most reliable genetic counselling information.

**If there are around 200 genes causing retinitis pigmentosa what does that mean for gene therapy?**

For those developing gene therapy, every gene needs to be considered as a new disease and a new therapy needs to be developed for each of them. There are ways around this, which is to try to create therapies to support the eye and make it healthier without tackling the defect.

**What does the term pigmentosa, in retinitis pigmentosa mean?**

Pigmentosa refers to the pigment we see at the back of the eye. Retinitis means inflammation of the retina. Retinitis pigmentosa was originally used by early doctors to describe the appearance of the retina when it looked inflamed and pigmented. We now understand this appearance is often associated with degeneration of the retina as a consequence of inherited retinal disease.

So the terms retinitis pigmentosa, retinal degeneration, inherited retinal degeneration and retinal dystrophy – these all refer to the same group of conditions.

**What is meant by CRB1 positive?**

This is a specific genetic cause of retinitis pigmentosa. There are probably going to be up to 200 different causes of retinitis pigmentosa as a group of conditions. It is also more complicated as genes, like CRB1, will also cause other retinal conditions in addition to retinitis pigmentosa. They will also cause Leber Congenital Amaurosis, which is an earlier onset and more severe form which has similarities to retinitis pigmentosa.

**What is optogenetics?**

This is a technique where you make a different cell in the retina light sensitive. So normally we have the photoreceptor cells and if they don’t work there are more cells in the retina and they are all connected to the brain, but they are not all light sensitive. You can put a molecule in these cells which make them light sensitive, and you get a light response to the brain. Optogenetics might only be used as a last option, similar to the retinal implants that are used. It is an option but normally the first go to idea would be to identify the mutation because the genetic tools to identify which mutation it is are getting better and better, and once the gene defect has been identified gene therapy might be a better option. Optogenetics isn’t as good an option when compared to a proper restoration of the gene in the photoreceptor cells.

Again it matters on the stage of degeneration, where you are in the sequence of progression of the condition over time. In the early stages, drug therapy and gene therapy is potentially most applicable and in later stages it is more about replacing tissue because cells have been lost, so it is stem cell therapy, artificial vision (retinal implants) and optogenetics.

It does make a difference where you are in that pathway and the severity of the condition but there are certainly very exciting avenues in all stages of the condition being explored.

**What is the difference between dry and wet macular degeneration?**

We often talk about them in isolation but there is overlap between them in the sense that if you have wet macular degeneration, you will also have a degree of dry macular degeneration, and if you have dry macular degeneration you can develop the wet form – they are not entirely separate entities.

Wet degeneration is characterised by a sudden loss of vision or disturbance to your central vision because of the development of abnormal blood vessels that grow into the retina and bleed.

Whereas the dry form is a far more slowly progressive condition that progress of years and decades. You start experiencing problems with your straight edge vision, central vision and reading vision in a more slowly progressing fashion.

**What are drusen and what is the significance to sight?**

Drusen is a term used to describe the appearance in the macular of deposits of waste material. Drusen are an early sign, and early feature of age-related macular degeneration (AMD). They are an early indication that someone may be at risk of developing AMD in the future; that may be of the dry form, and that may or may not be complicated by the wet form at some point. Drusen forms part of the progression of AMD and is being addressed as part of the research into that condition.

The relevance of drusen is not clear. It is very likely that they are a marker of the disease and part of the effects of the condition, but it may be that treating the drusen themselves may not have any impact on the condition. There relevance is certainly that they indicate the disease is in progress.

Drusen are typically asymptomatic and are often found in people who have relatively normal sight at the early stages of macular degeneration; so they may have no symptoms at all. They are the sort of thing that may be noticed by the optician who may raise a concern that there may be a risk of developing macular degeneration in the future.

Drusen or drusen-like materials can also be seen in inherited retinal conditions as well. So if you have drusen that doesn’t necessarily mean it is age-related it can be genetic.

**What is a hole in the macular, is it different from macular degeneration?**

This is a separate condition but effects the same part of the retina as macular degeneration; the specialised part of the central retina which we call the macular which is specialised to serve the detailed vision - recognising faces, reading and colour vision. But it is a different disease where the jelly of the eye in front of the retina comes away, as it does for all of us, but it is abnormally attached to the macular, and as it comes away it pulls a hole out of the retina. This is one of the theories.

**Why do 5% of people not respond to macular hole surgery?**

Typically, macular hole effects slightly older people but we don’t understand why it happens to some people and not others. We know that the operation typically fixes the hole in most people. We don’t know for sure why it doesn’t work for everybody; there are some possible reasons one of which is the role of positioning after the surgery, and that is one we are addressing in the trial we heard about earlier on (https://youtu.be/5gau\_KtJeI4).

**What is a Beta-blocker?**

It is a type of the drug that affects a particular part of the nervous system. There are lots of different receptors – components on the surfaces of cells that can be affected by different drugs. These drugs bind to these different parts of the cell and affect a change in the cell. One of the types of drugs that do this is Beta-blockers, these are one of the drops which we use to reduce pressure in the eye.

**What triggers the onset of Stargardt disease?**

There isn’t anything that will have triggered Stargardt disease at a particular age. It varies as to when children will start being symptomatic and that is thought to be due to the variability that we commonly see in inherited retinal diseases and dystrophies. Stargardt disease is particularly variable, and it is across a range of ages that we will see children have problems from five up to 18 years of age; it is very broad, and classically it is in early teenage years.

There will often be a delay in picking Stargardt disease up, it often when they go to school and start doing more visually demanding things it is noted there is a problem. It will often be something that has been building up from early on because this is caused by a genetic fault that has been present right from birth and it takes a period for the detrimental effect of that fault to show itself.

**What is ischemia and why can it happen?**

Ischemia is a deficiency in the circulation. In the retina circulation is very important because it is a very active tissue and a good blood supply is very important. The reasons for poor circulation are many but include high blood pressure and diabetes.

**What is RPE?**

RPE stands for retinal pigment epithelium. It is a very thin layer of cells behind the retina, and it is heavily pigmented. It absorbs all the light that goes straight through the eye to the back. It is very important for the health of the retina because it provides oxygen and nutrients to the photoreceptor cells which don’t have much blood supply themselves and takes away all of the waste. As soon as there is a problem with the RPE (as in AMD or Stargardt disease), that it becomes diseased and dies off the photoreceptor cells directly in contact with the RPE start to suffer as well, and you lose vision in that area of the retina.

**Are there any new therapies in the pipeline, such as stem cell therapy, to improve someone’s vision from retinal detachment?**

Fortunately, retinal detachment can normally be treated quite effectively with surgery to put the retina back into place. There are instances, unfortunately, when the surgery doesn’t work just like in macular hole surgery. People can benefit from additional operations, but occasionally the result can be limited by scarring.

There is a lot of research going on to try to address the impact of that scarring in the retina, and it is hoped that will improve function for those people who don’t benefit. In the meantime, there may be other ways to make the best use of the sight that is preserved including through the use of appropriate illumination and magnifying aids.

**How can I take part in research?**

**What is the best way to ensure you can recognise / be recognised for the most appropriate clinical trials and research and should you exercise caution before proceeding?**

Being on genetic databases is a way to be potentially considered for studies and trials, as is being on the clinical records at a hospital conducting research.

There are many types of research studies available. Some of those studies are with a view to identifying how peoples eye conditions affect them over a period of time, and those are relatively low risk, so there is no need to worry about any side effects. These sort of studies are really important. The main consideration is the amount of time you have available to participate given that some of tests are quite time-consuming.

When it comes to a trial for a new intervention, there are certainly risks associated. Any approved trial will have been through a process of ethical review so an impartial committee will have agreed that the potential benefits of the study to that individual, or to others with the same condition, out-way the risks, although there will be some risk associated with any intervention. It is important to take time to understand these before you make your decision.

You should never have to pay for anything, and you should ensure a study has been through the appropriate regulatory approvals before you consider taking part. Certainly get advice from your doctor.