How do you fix the broken retina?

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Disclosures

• Received Bayer Global Ophthalmology award for my research 2016-2017
What will I cover today?

• The eye in health
• What can go wrong
• Personalized treatment
• Clinical trials
• New treatments
• Questions
The eye is like a camera. Light enters through the front window called the cornea and is fine focused by the lens. The light then travels to the retina which turns light in to electrical signals which travel through the optic nerve to the brain. The macula is important for central vision and functional things such as reading.
The landscape of blindness is changing. About 20 years ago, the main causes of blindness would be dominated by wet macular degeneration and glaucoma. However, with new treatments, these conditions are now becoming treatable. Now, the largest proportion in the developed world is shifting to patients with untreatable inherited retinal disease.
I will use AMD as an example of a degenerative disease. But most adult onset diseases follow the same pattern. They have a pre-symptomatic phase when there is pathology but it is not noticed, a symptomatic phase when there is loss of central vision or difficulty with adjusting to the dark and a later stage where the symptoms worsen and blindness may ensue.
You can already see that compared to normal the just clinical symptomatic eye has a deformed retina with marked activation of complement, one of the major immune system components that cause macular degeneration. Far better to transplant into the healthy retina prior to disease.
Here I show scanning laser ophthalmoscopy which identifies autofluorescence. Normal and healthy retina has a grayish tinge, sick retina is white and dead retina is black. You can see from this patient that in five years the central vision has been lost because of the death of the retina.
So how do we mend the broken retina. The key is to use specific treatments at the right time and this may be different in different diseases. Prevention is always best if possible as it is gradually harder to restore function when the retinal structure is damaged. So let’s focus on early drug treatments.
Why do we have so few drugs to treat our eye diseases. The trouble is that although many compounds may be identified in preclinical studies many of these may be toxic and through trials eventually a tiny amount get accepted for use. The trials take time and go through several phases from phase 1 safety trials to phase 3 and 4 which are larger trials to confirm treatment effect. The cost of all these trials may exceed $1 billion.
What are the approved drugs for the eye that have had the most effect? Two come to mind. Lucentis and Eylea. These are anti vascular endothelial growth factor drugs. These stop a chemical in the eye which causes new blood vessels to grow.
As you can see here a new blood vessel in green is seen. A couple of weeks after treatment the vessel is gone. If left untreated these blood vessels will leak and bleed and cause blindness.
This chart shows the amount of blindness caused by AMD in a region of the UK. The red arrow shows when these drugs were first used. As you can see the amount of blindness caused by wet AMD falls dramatically as soon as the treatments come in to play showing a population wide effect.
What is the future?

• Longer lasting drugs which require less frequent injection

• Trials to develop drops or oral preparations
Let’s next look at the treatments in later stage disease when there is a need to support remaining cells or to replace lost cells. Great progress has now been made.
The knowledge gained from experiments such as Dolly the sheep now allow stem cells to be made from our skin and blood. The chemicals identified in embryos have now been purified and used to turn adult skin cells back into the same type found in embryos.
Stem cells can self renew and differentiate into other cells. They can be found all over the body including on the window of the eye. They can be made by putting chemicals onto skin or blood which open up the cell’s DNA and then transforms them to stem cells.

Stem cell questions

• What are stem cells?
• Where are they found?
• How are they made?
• Why are they useful?
• Have any diseases been treated with stem cells?
They can then be used for disease modelling in a dish, for transplants and for drug screening.
How can stem cells help mend the retina?
We can make the retina from stem cells with the right chemicals and the right timepoints. This follows the time lines of normal development.
Punch biopsy from skin and skin cells growing
Day 0 Stem cells after chemicals were placed on skin
Day 7 early neurons
Day 28 – floating retina with black retinal pigment epithelium cells
Day 50 - after plating these become confluent
You can see that when these cells were transplanted in the human retina they grow and pigment (see red circle)
The cells also make a layer as seen in cross section
Researchers can now also make the neural retina which helps us see and includes photoreceptors.
What other stem cell trials are ongoing?  
Stage I/IIa – side effect trials only

- ES derived RPE for AMD and Stargardt-Astellas
- IPS derived cells for AMD – RIKEN, Japan
- Platform trials in London, Paris and planned in Irvine and USC
- Retinal precursors into the vitreous – Jcyte - Irvine
Let us look at early gene therapy which can also be used to prevent disease progression but can’t be used to bring back lost cells.
What is gene therapy?

• The correction of the effects of genetic defects that lead to disease
• What are the important concepts?

• **Recessive** - usually caused by the lack of a gene
  Replacement

• **Dominant** - Usually caused by the harmful effect of a mutated gene
  Correction
A drug has recently been approved for use in a disease caused by a gene called RPE65. This drug delivers a virus which is injected to the back of the eye and releases a gene which is deficient in some patients. This has allowed patients to see better at night.
What other ongoing late-stage trials are there for gene therapy?

• X-Linked retinoschisis
• Stargardt trial
• Choroideremia

• PDE6B to start shortly
• X-linked retinitis Pigmentosa to start shortly
Looking forward – Gene CORRECTION with CRISPR

1. What is CRISPR?
2. How does CRISPR work?
3. What can we do with CRISPR?
What is CRISPR?

Clustered
Regular
Interspaced
Short
Palindromic
Repeats
CRISPR is a bacterial system that was used to protect bacteria against viruses. It has been adapted for use for gene editing. The CRISPR recognizes certain parts of DNA. It is attached to an enzyme which cuts the DNA. The cut DNA can then be used for editing genes.
Are there any clinical trials with CRISPR?

• No clinical trials as yet but has shown promise in animal models of disease.

• Likely to be the first clinical trials shortly
Summary

• Covered stem cells, gene therapy, drug treatment and clinical trials

• Progress with MORE clinical trials for MORE diseases

• At present difficult to reverse blindness once cells are lost because of the complexity of the retina

• Humans are the key model in the era of personalized medicine to treat personalized genetic disease
What I did not cover

• The importance of visual and social rehabilitation in order to improve the quality of life in visual impairment
Thank you

I am happy to answer any questions