Research into treatments for Usher syndrome

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and why does it seem to be taking so long?

Overview

- Background Information about genes and cells
- Gene Therapy Research
- Stem Cell Therapy Research
- Other types of treatment

- What is the process of getting a new treatment to the patient who needs it?
- Where are we with treatment trials in Usher?

What is a gene?

- An ‘instruction’ made from the chemical, DNA

It tells the body to make something (a protein)

- We have 20,000 pairs of genes in every cell of our bodies
- We have millions and millions of cells

So

- We cannot remove a ‘bad’ gene and replace it with a ‘good’ gene

Usher syndrome

- There are more than 10 different genes that can cause Usher
- A ‘misprint’ (a gene ‘mutation’) in both copies of any one of those 10 genes means that the correct protein is not made in the body
- The protein is needed in cells of the inner ear and in the retina

Gene therapy

Need to:

1. Understand what is wrong
2. Design the treatment
3. Deliver the treatment

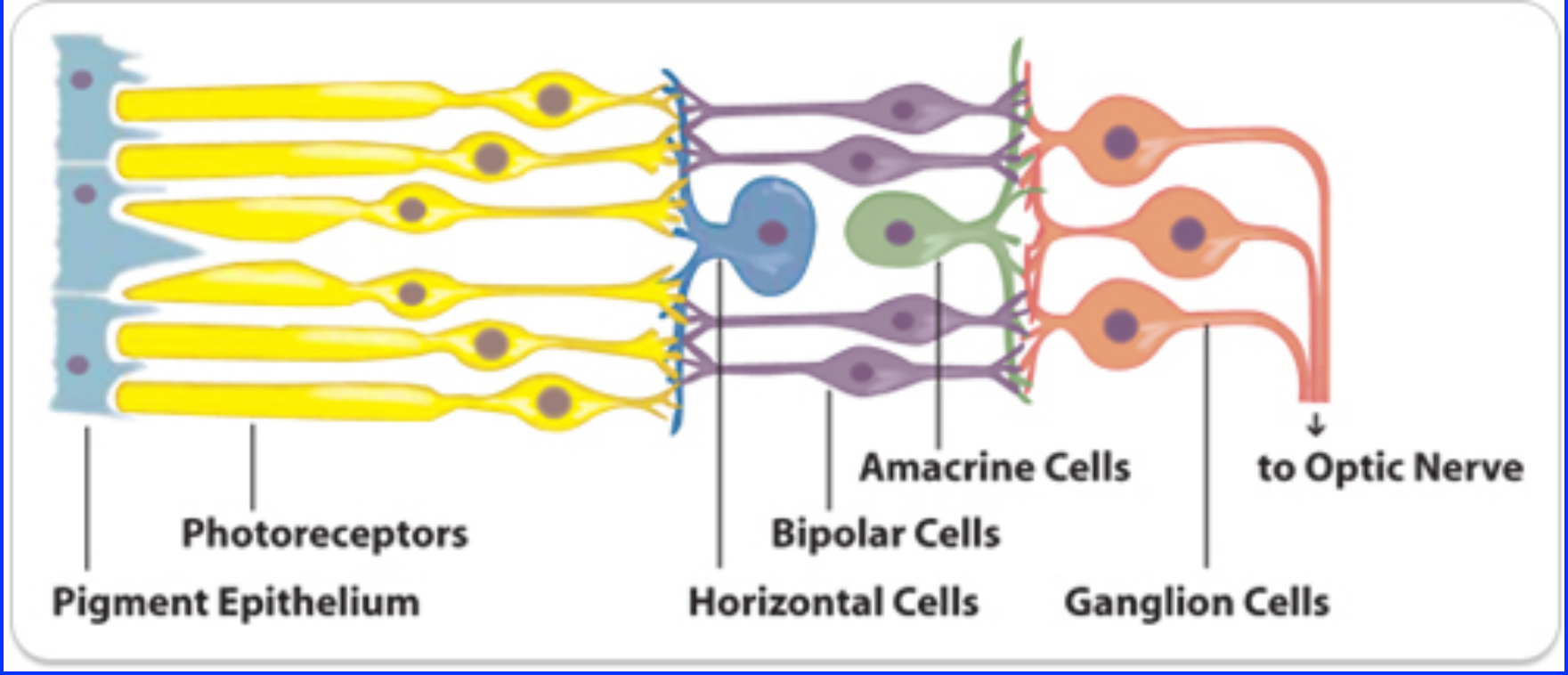
Gene therapy

1. Understand what is wrong
   - Which gene is not working?
   - Where in the retina is it needed?
   - How does it cause retinal cells to die?

Which gene is not working in me?

Subtype	Genes
Type 1	MYO7A USH1C CDH23 PCDH15 USH1G CIB2
Type 2	USH2A GPR98 WHRN
Type 3	USH3A

Where in the retina is it needed?



How does it cause retinal cells to die?

- Animal models (mice, zebrafish) are really helpful for answering these questions
- We cannot get retinal cells or inner ear hair cells easily from people

2. Design the treatment

- Put a new copy of the gene into the cells that need it
- Or just correct the mistake (the ‘misprint’) in the cells that have it

3. Deliver the treatment

We have some of these tools now, as people have been working on them for several decades

- ‘Vectors’ made from inactivated viruses which carry genes into cells
- ‘Gene editing’ tools, which can cut out a mutation and replace it

- This has been done for some other genetic diseases

Gene Therapy

- Challenges
  - We don’t know all the genes yet
  - The Usher genes are really large so delivery is difficult

Stem cell therapy

- We are made up of millions of cells
- Not all cells are the same
- Skin cells get worn out and renew; photoreceptor cells in the retina do not renew

- Stem cells are cells that can renew themselves and
- Can develop into a number of different types of specialized cell. Very useful

Stem cell therapy

- Embryonic stem cells
- Adult stem cells
- Induced pluripotent stem (IPS) cells

  Ordinary adult cells that are 'persuaded' to become stem cells

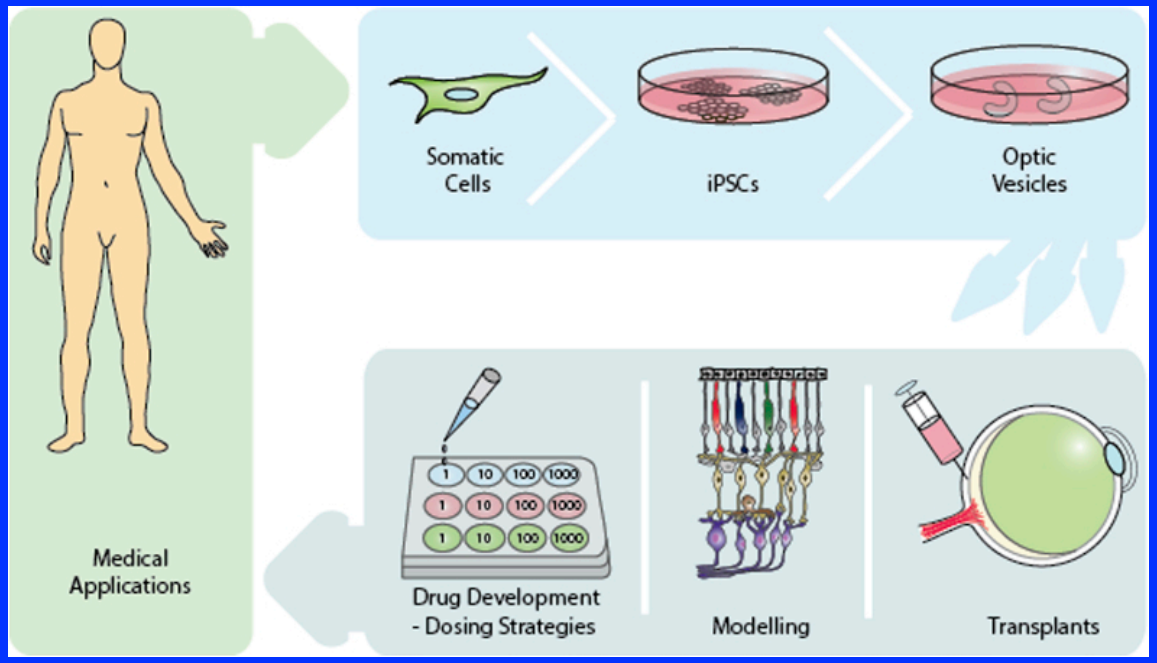
IPS cells

- Adult cells can be re-programmed back to become ‘stem cell-like’
- Take a skin biopsy……grow the skin cells…….re-programme them to become stem cells…….differentiate them into retinal cells

Retinal degenerative diseases and hIPS

- Many retinal degenerative diseases are characterised by dysfunction and/or death of the photoreceptor cells, leading to visual loss and eventually blindness

- Human Induced Pluripotent Stem Cells:



Cosgrove and Zallocchi, 2013
Bonnet and El-Amraoui, 2012
Borooah et al, 2013

Possible uses

1. Obtain cells from patients with genetic disorder and make them into retinal cells
2. Study the cells. Why do they die? Are there drugs that can help them to survive for longer?
3. Manipulate the ‘retinal’ cells from the patient with drugs, or genes, or ‘gene-editing tools’, then transplant the treated cells back into the patient. Care needed!

What is the process of getting new treatments to patients?

Laboratory phase – Phase 0

- Proof of concept
- Have to convince scientific community that intervention and delivery may have an effect in the lab
- No patients involved; cells and animals
- 2-10 years if funding successful

Translational phase

- Safe in animals
- Need pharmaceutical grade therapy – expensive
- Highly regulated – EMEA, HTA (Human Tissue Authority)
- High risk for companies (expensive and may never come to market)
- Millions of pounds

Clinical Trial: Phase 1

- ‘First in man’/ healthy volunteers
- Increasing doses
- Establish dose, maximal tolerated dose
  Recommended dose for the Phase 2 trial
- Is the gene/cell even getting into the tissue at all? Is this feasible?

Phase 2

- test on patients to check safety and efficacy
- Need a validated end point. Retinal thickness in a proportion of patients? In what proportion? Acuity? Am I sure I am measuring something useful? Is my test sensitive?
- If we treat 14 patients and see nothing useful, it is unlikely to be a helpful treatment
- If we see something useful we might expand the numbers of patients

Phase 3

- test drug, which you think is useful, on larger numbers of patients, against ‘standard of care’. Need good measure. Double-blind randomised is gold standard
- ‘Unmet need’ and acceleration if there is no standard of care
- Side effects

Phase 4

- after drug is released for use. Surveillance for long term effects
- Allergic reactions, cancers ….

Where are we with Usher?

- Only 1 Clinical Trial
- UshStat licensed for Phase 1 /2 clinical trials
- Gene therapy trial for USH1B, viral delivery
- Small numbers of adult patients with severe disease
- Who to treat?
- Small or large area?
- How to measure if useful?

UshStat (update from July '14 in Boston)

- 18 patients initially
- Group 1, 3 patients
  - legally blind
  - lowest possible dose
  - Unrecordable ERG

- Group 2, higher dose
- Group 3 /4 will have recordable ERG and better visual fields

- So far (July 2014) treated 4 patients
- Now in Group 2, higher dose.
- No adverse effects

- Treat 1 eye
- Tests every 6 months
- 20 year follow-up
- Talking about *preservation* of vision

Is it doing anything?

- Safety
- Visual acuity
- Retinal exam
- Visual fields
- OCT
- Lab measurements
- Adaptive optics, measure individual cone cells. Can measure their density.
- Treat areas in ‘transitional zone’ outside fovea

Does it work?

What can I do to participate?

- 3 things

- Get on registers
- Keep in touch, stay informed
  - Sense
  - Usher Coalition

What do I need to consider?

- It's a trial so there is always a risk
- It is an unknown treatment
- Scientists and doctors are feeling their way
- Your decision
- You may not be eligible for other trials! You may still be under follow-up
- May be useful to people who come after you
- Not everything has the same validity – there are some unsavoury people out there

- Doctors can advise you
- Organizations can advise you
- Universities/government approved /sponsored

Thank you for your attention!

- Thanks to Professor Jane Sowden and Dr Valentina Di Foggia