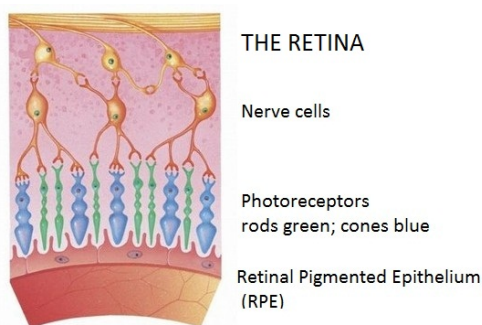




What is the purpose of transplanting retinal cells?

The goal of transplant therapies is to save and restore vision by replacing damaged cells in the retina with new, healthy cells. Currently researchers are working to find ways of replacing two different kinds of cells:

- Retinal pigmented epithelial (RPE) cells
- Photoreceptor cells



Replace RPE Cells to Protect Sight

Retinal pigmented epithelial cells, or RPE cells, are the foundation of the retina. RPE cells process nutrients to feed the retina. In people with age-related macular degeneration (AMD), these cells may be damaged by toxins that build-up over a lifetime. In some types of inherited retinal disorders, these cells are damaged by genetic mutations. Clinical trials are currently testing if replacing RPE cells by transplanting stem-cell derived RPE cells will help the retina function better, prevent further vision loss, and help nourish surviving retinal cells potentially improving vision.

Replace Photoreceptors to Restore Sight

Photoreceptors (rods and cones) are the light sensing cells of the retina. These cells are destroyed in the late stages of retinal disease. If these cells are gone, treatments

that might improve eye function will not be helpful. Only a therapy that would replace these cells (or their function as in the case of retinal prosthetics) will restore sight.

Why transplant cells not the whole retina?

Unfortunately, mature cells in a transplant retina do not grow and make the nerve connections necessary to carry light signals to the brain. Research has shown that less mature cells can make these connections, so scientists began to study ways to use stem cells to grow cells for transplant.

What is a stem cell?

A stem cell is a very basic, unspecialized type of cell. An early human embryo is made up entirely of such cells.

Most of the cells in our body reproduce by dividing. So, for example, as we grow a skin cell on the surface of our body will divide, creating two skin cells. Stem cells are unique. When they divide, the two new daughter cells may become stem cells like their parent, or they may become more specialized cells. It is this remarkable property that allows a human embryo to grow from a blob of unspecialized cells to a baby with many different specialized cells and organs.

Are stem cells only found in embryos?

No. Stem cells are an important part of how the body grows and replenishes itself throughout life. For example, our bone marrow contains stem cells that divide and produce different blood cells as needed. Stem cells in other areas help generate new tissues if our body is damaged by disease or injury. Stem cells in the adult body often

become partially specialized. So for example, stem cells in the liver specialize to only make liver cells. We call these partially specialized stem cells, progenitor cells.

Are there stem cells in the retina?

Yes. Dr. Derek van der Kooy at the University of Toronto, showed that there are stem cells in the human retina. This discovery, which was made in the year 2000, has received much support from Foundation Fighting Blindness (FFB) donors.

Unfortunately, the stem cells and retinal progenitor cells in the human retina, are not functional. They cannot produce new cells when the retina has been damaged. However, Dr. van der Kooy and his team have shown that when these cells are extracted from a human retina, they can be used to produce new retinal cells in a dish in the lab. He and his team study how we might use these cells grown in the lab for transplants into the diseased or damaged eye.

Would it ever be possible to mobilize the retinal stem cells already in the eye so that they produce new retinal cells?

We hope so. Some types of fish and frogs can repair a damaged retina using stem cells in their eyes. If we can understand the genes that control retinal stem cells in these other animals, we might be able to manipulate these cells in humans, enabling them to repair damage to the eye. FFB donors have supported Dr. Vince Tropepe's studies on the genes that mobilize stem cells in fish.

How are stem cells used to make transplant cells?

Stem cells can be grown in the laboratory and then prompted to become the type of retinal cells needed for transplants by using different growth factors and genetic techniques. Cells created in this way can be

injected into the retina. In animal studies, such cells have been able to make complex connections including connections to nerve cells that restore vision.

Different types of cells are needed to treat different conditions. For example, replacing damaged RPE cells might improve vision in people with Stargardt disease or age-related macular degeneration. For people with late stage retinal disease, photoreceptors will be needed to restore sight. The FFB is funding Dr. Gilbert Bernier's research, which has developed a method to produce cone photoreceptors from human stem cells. This discovery provides the foundation for a cone transplantation strategy to restore vision to people who have central vision loss, including people living with AMD, Stargardt disease and retinitis pigmentosa. Dr. Valerie Wallace is currently leading a team project that builds on Dr. Bernier's discovery. Dr. Wallace was recently awarded a prestigious Accelerator Fund from the [Ontario Institute of Regenerative Medicine \(OIRM\)](#). The FFB is a proud partner funder on this project, which is developing a cone transplantation strategy to restore vision to people living with central vision loss. The research team also includes Dr. van der Kooy and Dr. Molly Shoichet, an world expert at using bioengineering to develop better cell delivery methods.

If stem cells can be used to restore sight to animals, what is happening with human trials?

Some human trials have now begun to transplant RPE cells, but not yet photoreceptors. Photoreceptors are more difficult to produce in the laboratory and more difficult to transplant effectively. There are three significant challenges to effective transplant treatments:

To produce large numbers of cells for treatment – Right now most cells used in transplants are produced in research labs. The



process is tremendously complicated, with different technical requirements for each type of cell. Many “recipes” to produce cells are being proposed and patented, but efficiency is still low; we do not yet know the recipes that will be most successful. We hope that Dr. Bernier’s recipe will be a game-changer for producing cone photoreceptors from stem cells. The Centre for Commercialization of Regenerative Medicine in Ontario is playing a lead role to develop ways to scale-up these cell production methods to ensure that Canadian scientists and clinicians will have access to the large volumes of cells that will be needed for clinical trials.

To produce completely pure cultures of cells If retinal cells, either RPE cells or photoreceptors are to be injected into people, we must be confident that the cells injected do not include stem cells or other unwanted cell types. Unwanted cells might grow abnormally. Scientists must be sure that the transplant cells will not increase cancer risk.

To enable newly transplanted cells to integrate with existing cells and make connections – Once the new cells are injected into the eye, they must avoid the body’s defense systems and connect to other retinal cells. This is particularly challenging for photoreceptors cells, which must not only make connections with other cells for nourishment, but must also make connections to nerve cells in order to send light signals to the brain. Unless they can make these connections, the transplanted cells will not be able to restore vision. We know that this is possible in animal studies, but unfortunately such connections are not easily made. The FFB funds research to help solve this problem. In 2015, thanks to funding from the FFB and others, Dr. Brian Ballios made a significant discovery: he demonstrated that using a special biomaterial to deliver stem cells to the eye

significantly increased the success of the transplantation. Previously, the majority of transplantation studies reported very low cell survival (between 0.04% and 8% on average). Dr. Ballios discovered that transplanting cells in a biomaterial significantly increased their survival rates (at best, 16% of cells survived). At the same time, using the biomaterial increased the ability of transplanted cells to integrate and function. Dr. Molly Shoichet supervised Dr. Ballios’s work on this project. She is currently collaborating on Dr. Valerie Wallace’s cone replacement project to determine how biomaterials can best support transplantation.

Where do the stem cells used in retinal research come from?

The earliest studies of stem cell therapies used cells collected from human embryos. These cells are used in some research because they have been studied for longer and more is known about how to grow them. Since Dr. van der Kooy’s discovery of retinal stem cells, he and others around the world have begun using cells gathered from human eyes donated to eye banks. The advantage of these cells is that they are already partly specialized to produce retinal cells; however less is known about the optimal way to grow them.

In 2006, a group of scientists in Japan produced induced pluripotent stem cells (iPSC). These are normal adult cells gathered from the skin or the inside of the cheek that are manipulated in the laboratory to become stem cells. This amazing technology could potentially allow patients to be treated with cells derived from their own body. In 2011, iPSCs were used by a team at Harvard University to make photoreceptor cells, which were then shown to restore some sight to blind mice - proving that cells derived from skin can be used in this way. Dr. Budd Tucker, who was funded by the FFB while he was a post-doctoral scholar is a leader in this field.



Could iPSCs be used to create transplant photoreceptors for inherited retinal conditions?

Inherited retinal diseases occur due to a gene defect. Since all of the cells in our body have the same genes, new photoreceptors grown from the skin cells of a person with inherited disease would have the same mutation that caused the damage. Over time it is likely that these cells would degenerate and vision loss would recur.

If iPSCs prove safe and useful, there are potential solutions to this problem. For example, other types of therapies, such as gene therapies, or gene editing technologies, like CRISPR, might be used to repair the new cells before they are transplanted. For people whose retinal disease developed late in life, unrepaired cells might extend vision for a sufficient time.

What human trials are underway testing retinal transplants?

In September 2014, a team of scientists from the RIKEN institute in Japan began the first human clinical trial of RPE cells made from iPSCs to treat age-related macular degeneration. In addition, a few other human trials are testing RPE cell transplants to improve vision in people with Stargardt disease and age-related macular degeneration (AMD). These conditions were chosen because toxins build up in the RPE in people with these diseases. Some types of retinitis pigmentosa which also damage the RPE could be the focus of future trials.

In October 2014, Advanced Cell Technology (now Ocata Therapeutics) published encouraging results, based on an analysis of 18 patients, who were monitored for an average of almost two years. Half of the treated patients had Stargardt disease and the other half had AMD. So far, the

treatment appears to be safe. Even more exciting is the result that 8 of the 18 patients are showing improved vision!

Are any human clinical trials transplanting photoreceptors?

No, not yet.

What about centres that inject stem cells as treatment?

The idea of stem cells as a potent therapy for incurable diseases has become a powerful one and clearly therapies derived from stem cells have great potential. However many unscrupulous “treatment centres” have been created to take advantage of people’s eagerness for these therapies. These centres offer to inject stem cells at significant cost. These clinics have no evidence that this is effective. **You should never have to pay to be part of a clinical trial!**

However it is possible that direct treatment with some types of stem cells or progenitor cells might have therapeutic value. In 2015, Dr. Henry Klassen, from University of California, Irvine began a clinical trial sponsored by jCyte to evaluate the safety of injecting retinal progenitor cells into the vitreous cavity of patients with late-stage retinitis pigmentosa (RP). ReNeuron is sponsoring a similar clinical trial. In addition to evaluating safety, these trials are testing if transplanted progenitor cells have the ability to protect cone photoreceptors from dying. If successful, the main benefit to people living with RP would be preserving cones and, as a result, saving their remaining high-acuity central vision.

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Updated March 10, 2016: Updated by Dr. Mary Sunderland, Director, Research & Education, Foundation Fighting Blindness; Earlier versions reviewed by Dr. Valerie Wallace, University Health Network and Dr. Carol Schuurmans, University of Calgary.

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