

[MUSIC PLAYING]

DEEPINDER K. What we're going to discuss today are two topics. One is what Dr. Sahel already spoke about, which is the
DHALIWAL: corneal stromal regeneration therapy for corneal scarring, and how we're designing our "first-in-human" clinical trials in the United States. The second topic we'll cover today is corneal endothelial disorders and regeneration.

So first of all, what is the cornea? So the cornea is a clear dome that covers the colored part of the eye. It typically is about a half a millimeter thick, but it's a critically important structure, and really quite beautiful. It should be crystal clear so we can see well. And it really serves to protect the inner eye tissues.

What's interesting is that it provides 2/3 of the eye's focusing power. So it's the cornea that we sculpt when we do laser vision correction. Or when we do LASIK, we just kind of sculpt the cornea in order to improve somebody's vision, if they're nearsighted, for example.

So when you look at the cornea, we have a basic schematic here of the three major cell layers. The outermost is the corneal epithelium. And then 90% of the cornea is actually the stroma. And so we're going to focus on the corneal stroma first. The innermost lining is the endothelium, and we will end our presentation on that cell lining.

So just the basics of vision, a clear cornea is needed for full light entry into the eye. And just as a matter of background, this is the eye, cut in half. And here's the front of the eye, with the cornea allowing light to enter, focusing 2/3 of the light. It then crosses the pupil and then is also refracted or bent by the crystalline lens.

So if this crystalline lens is clear, then, again, all the light is going to go back to the retina. If that crystalline lens is cloudy, that is when a cataract is developing. And light then focuses on the retina, and you have normal vision.

So if you have corneal opacities, you're going to get some distortion or obstruction of the light passage. If you have a mild corneal opacity, you could have some hazy vision. But if you have severe opacities, you will have significant blurred vision, as you can see in that schematic.

Now why does the cornea get hazy? There are so many different reasons why the cornea can get scarred or cloudy. Some common ones that we see are from trauma. You can also have infections. Any infection that is in the cornea will result in a corneal scar. So no matter how successful we are in treating an infection, unfortunately, as the cornea heals, it will heal with a scar.

And so you can see this page, the second picture shows this dense scarring right in the pupil of a patient that slept in their contact lenses. So it's really important to remember contact lens safety. Please, no sleeping in contact lenses.

Herpes virus infection is another common cause of corneal opacity, and then there are some genetic conditions as well. And it's important to note that corneal blindness affects millions of people worldwide. Currently, we don't have any medical therapy for corneal opacities. And in fact, a corneal transplantation is required if we really want to fully treat a corneal opacity.

Now this picture, the first picture right here, is an intraoperative photograph of a corneal transplant being performed. And what we do in surgery is we actually take a trephine, which is like a cookie cutter, if you will, and we basically dissect the central part of the cornea. And then we take donor tissue, and we will then sew it in place.

And you can see here is donor corneal tissue sewn into the rim of host cornea. And these sutures are not dissolvable. We have to remove them in the office. We typically start removing sutures at about a year.

Here's another example of a cloudy cornea from trauma before surgery. And then you can see after surgery, the corneal transplant is clear in the middle and held in place with sutures. So in the US, we're very fortunate because we have a wonderful eye banking system. So we've performed in 2018 about 85,000 corneal transplants.

And again, we are very fortunate in the US. This is not the case globally. Globally, there is a severe shortage of donor material. And really, only 1 out of 70 patients globally can really access high-quality corneal tissue.

Now just because we do a corneal transplant doesn't mean that it's risk free. A full-thickness corneal transplant actually is one of the riskiest procedures that we do because when we remove the entire cornea, there's a risk of bleeding. Even after we put the cornea in place, we always have to worry about graft rejection. This is donor material.

Now we're lucky in ophthalmology that we can use steroid drops, typically, just to be the immunosuppressant. We don't have to use some type of immunosuppressant pills, and things like that, or IVs. We typically can just get away with steroid drops. However, steroid drops can also cause some complications. And we've seen patients develop steroid-induced glaucoma or steroid-induced cataract as a result.

Also, there's complications we also have to worry about with suture infections, donor-related infections or, very sadly, is a patient that might have had a corneal transplant maybe for 20 or 30 years, and then has a fall. And if the fall affects the eye, unfortunately, that wound can really open up quite easily even after 20 or 30 years. The eye is never as strong as it once was. So we know that it's better to avoid a full-thickness corneal transplant if we can.

Now there are also high-risk patients. For example, if you have a history of herpes simplex virus, even if we do a successful corneal transplant, the virus can affect the new corneal transplant as well. Also, there can be cases where a clear graft doesn't necessarily mean you have good vision because you could have high astigmatism as a result.

So what are some alternatives to full-thickness corneal transplant? Luckily, we are developing some surgical innovations, and we can now do partial thickness, or lamellar corneal transplants, even for corneal opacities. And so in Pittsburgh, we are doing deep anterior lamellar keratoplasties. And we're just replacing that scarred area, and we spare the rest of the cornea. The endothelium, we leave in place.

What else can we do? Well, we can replace the entire cornea with an artificial cornea. So that is called a keratoprosthesis. And that is successful in certain cases. But unfortunately, long term, there can be significant issues with extrusion of the device, or even infection.

There is also some research being done in bioengineering with replacement of the scarred cornea with biological substitutes. But what we're really excited about is cell regenerative therapy. And this is actually regenerating the corneal stroma and inducing scar resolution and remodeling, so really curing corneal blindness with the use of stromal stem cells.

And for that exciting topic, I want to now hand over the baton to my co-presenter today, Dr. Gary Yam. And I just want to echo Dr. Sahel's comments. We are thrilled to welcome Gary Yam to our department.

We recruited him from Singapore, and he is just a brilliant scientist with a long history of working on corneal cells for over 15 years, and has many, many wonderful publications. And he's been a great asset to our team. And so without further ado, Gary, I'm going to hand it off to you.

GARY YAM: OK, thank you so much, Deep. Thank you for the nice introduction. Good afternoon, everyone. So I am Gary Yam. So welcome again to this sharing session. So thank you, Deep, for the nice overview on the cornea, and also the diseases causing corneal scarring, and the current treatments, and also their limitations.

Yes, as Deep has mentioned, there has been a demand and a need to look for alternatives to the corneal grafting or the transplantation. And also, we have to find new ways or ideas to maximize, to improve the use of the limited corneal materials. So that means instead of one donor cornea for one patient, we want to-- we hope to maximize the use from one donor to multiple recipients. And this can be achieved by the cell regeneration strategies.

So to develop this kind of cell-based treatment, actually, there are a few things that we need to identify clearly or to work out before we move on to use these cells for the potential clinical applications. So first, we need to have the cells that can be expandable in number. That means that they can generate many more cells for multiple recipients or for multiple treatments.

And then the other thing is that we need the right cell type that express the correct features of the things that we want. For example, in corneal stroma, we need the expressions of the stromal collagen, stromal crystallines, and also some type of proteins that can improve the wound healing to regenerate the normal stromal tissues to reduce the corneal haze and scar formation. And of course, the most important is to give us the clear cornea, that we can restore our visions.

So when the cells are ready to be used in the patients, so the way-- how we administer or how we put the cells to the eye should be safe, easy, and also feasible. So now this is the picture. It's a schematic diagram that shows the human eyeball. So the top transparent front part of the eye is the cornea. So inside the cornea, the corneal stroma occupy the bulk of the overall corneal volume.

And inside the corneal stroma, there is the specific cell type called a corneal stromal keratocyte. Here you can see that they are tiny dots that shows the cells distributing inside the corneal stroma. And these keratocytes are making all the essential proteins for the corneal stromal tissues, stromal functions, and also the transparency of the stroma.

However, these cells are very lazy. They are quite quiet. They do not want to divide. So that's why here and now, right now. But however, on the other hand, in there are populations of stem cells in the peripheral corneal stroma, or we call the limbal stroma. And this type of stem cells actually was identified in our lab in Pittsburgh in 2005 by our previous principal investigator, and also an esteemed vision scientist Prof. James Funderburgh, and also Dr. Du. She is also our PI in our department.

So unfortunately, Jim passed away in November last year. Yeah, this is a big loss to us, and also to the whole world of vision science. So let me say a few words about Jim. I think some of you may know him, so I think you all agree that Jim is a very kind, talented, and knowledgeable person. He worked very hard and had huge contribution in science, especially the corneal cell biology, corneal stromal stem cells, tissue engineering, and also the stem cell therapy studies to treat the corneal scarring. So Jim has done a lot of insightful and exceptional work, and this give us a very wonderful scientific legacy that can impact our life in the future.

So since they identified these corneal stromal stem cells, then actually, now we are calling them the PittStemCells, because it's identified here. So since then, after they identified, the lab has been working on a lot of work that looking at the cell biology, cell behavior, identification, differentiation to keratocytes, and so on. And the most important is that we have been looking at the application of these cells to treat the corneal scarring in different animal models. So today I would like to show you some specific features of these PittStemCells, and also the implication, how these cells [INAUDIBLE] in a corneal wound healing.

So first, the cells exhibit clonal growth, which is the fundamental properties of stem cells. And that means that one stem cells can give a colony of cells that can be over hundreds or thousands of cells without any changes in the cell features. And this can generate many more cells for multiple uses, and also can achieve the one donor to multiple recipients strategy.

And also, these PittStemCells express various stem cell markers showing that they are stem cells. And they can differentiate into the stromal keratocytes the specific cell type inside the corneal stroma. So the differentiated cells shows the specific features of the keratocytes, such they have dendritic or branching morphologies. And they make frequent cell-cell contacts to each other so that they can communicate to each other, forming a so-called cell network that we usually see inside the corneal stroma.

And the cells can express a lot of keratocyte-specific proteins.

And also, very amazing, these PittStemCells can actually block the scar formations when they were put the corneal wound on the mouse model. So for example, like this experiment, there are two group of mice, and the cornea was injured by the deep abrasion. So this is a very severe injury that the cornea usually develops scarring in two to three weeks' time.

So one group of mice were treated with the stem cells and the other not. So after two weeks, the stem cell-treated corneas were quite free of scarring, while the non-treated corneas developed intense scarring. Next, please.

And the stem cells can suppress inflammation, which is very general properties of the mesenchymal stem cells. And in fact, this can lead to much smoother and more successful wound healing with reduced scarring.

And also, very amazing, these PittStemCells can produce a very special scar-free cytokine, which is called a transforming growth factor beta 3, which has been known in the scar-free healing or scarless healing inside the embryo and also in some internal organs of our body.

And also, now in our lab, we are setting up very stringent quality control systems to look for high-quality stem cells with regenerative potential. So now we can know which type of-- which group of cells can regenerate the clear corneas.

And also very interesting is that these stem cells can be stored for a long time without any changes of their qualities. So that means, for example, like this, in this picture, that this shows the cells that have been stored for 10 years in cryostorage. And they still show the clonal growth, and also maintain the differentiation to keratocytes, and their regenerative potential. So that means this method of stem cell banking become attractive and feasible, and we can store these cells for our future use. Next, please.

So all these special features shows that the PittStemCells can induce the stromal tissue regeneration. And from this electron micrograph picture with very high resolutions or magnifications, we can see that the collagen fibrils were properly aligned or well organized in the stem cell-treated corneas, and that that extensive structure here shows the cells.

And this is very different to the disorganized, hardened fibril structures in the scarred corneas. So that means it shows that the stromal are regenerated. And this can help the successful wound healing in the cornea.

So next, I would like to talk about a very exciting clinical trial study using the corneal stromal stem cells that are generated using our Pitt protocol that has been carrying on in LV Prasad Eye Institute in India. Yeah, Deep.

DEEPINDER K. DHALIWAL: Thank you, Gary. So obviously, these stem cells that were discovered in our lab in Pittsburgh were very exciting, and as you saw, these amazing qualities of these stem cells. So Dr. Funderburgh spoke with Virender Sangwan, who is an amazing cornea researcher in India. And Dr. Sangwan was here for one of our Fox Center programs. And he was speaking during one of our Fox Center programs that we had.

And in essence, they came together, and he said, well, we could use these stem cells in India. And Dr. Funderburgh said, OK, why don't you-- why don't we collaborate? So Dr. Sangwan sent Sayan Basu here to Pittsburgh. And the Eye & Ear Foundation actually was instrumental in helping fund Dr. Basu's research for a year.

And so he came to Pittsburgh and learned these techniques, and then went back to India, and actually has done the first human trials with these stem cells in India. So we're very excited. This is the procedure being done by Dr. Basu in India. And there's a scarred cornea. You can see it's being outlined right here.

And this is removing the surface layer of cornea. This is the corneal epithelium being removed. And believe it or not, those are the stem cells. They are in a matrix of thrombin and fibrinogen.

And this is now applied to the cornea, and it's basically just allowed to dry in place. And then a bandage contact lens is placed on top. It's as simple as that. So these stem cells know where to go in the cornea. And they do not need to be injected.

So here are some results from the clinical trial at LV Prasad Eye Institute in India, and there's several examples here. But what I want to draw your attention to is the red highlighted box where one patient with a chronic corneal scar had 2400 vision. Now that is a patient that we would consider legally blind, and he had a chronic corneal scar here. And then after treatment with the stromal stem cells, with the PittStemCells, this patient developed a beautiful cornea with 20/30 vision resulting, so very, very exciting results.

Now we want to bring that information back to the US, so I flew to India and learned from their experience. And we are now in the process of understanding the important aspects of creating a GMP facility for these stem cells, and how to create these protocols. So now I'm going to hand it back to Gary to explain the details.

GARY YAM:

Yes, and right now, now here in our department, we are moving forward to apply these PittStemCells for patient use. And we call it the Funderburgh Corneal Regeneration Project "Pittsburgh Protocol" in remembrance of Jim and his great work in this project.

So we have a development pipeline with three phases in total over a period of three years. So right now, we are-- yes, please, Deep, please-- in the first phase of our pipeline. That is to optimize our cell protocol into a GMP good manufacturing practice, standard operating procedure. So this is to make sure that the cells are well kept in well-controlled conditions that are free of any animal origins, to make sure to eliminate any risk of viral contaminations, and the cells are really good and safe to be used in the patients.

[INAUDIBLE], can you go back? And then we will stringently check these cells for their viability, for their stability, for their differentiation potential in the keratocytes, for their anti-inflammatory effects. And also, we will look for the safety and the treatment efficacy or this treatment efficiency of these cells by doing a lot of animal models using the scarring model and also the stromal degeneration models.

So to move on for the clinical trial, so-- next, please-- we also need to set up germ-free cell culture facilities. And also, this also apply for the stem cell banking. So these kind of cell facilities will follow the high standard of regulatory compliance and the environmental control to minimize the risks and also prevent contamination to the cell products. Next, please.

So in summary, the PittStemCells can regenerate native corneal stroma, restore the stromal functions, and the corneal clarity so at the end, you can restore the visions with reduced need of corneal grafting.

The cell yield is pretty high. It's pretty good, and this can achieve one donor to multiple recipients strategy. And the cells can be applied in fibrin gel eye drops, which is a very simple procedure that can be performed in any regular eye clinics. And also, the cells can be stored for long term, and this makes the stem cell banking become feasible.

And so right now, in Pittsburgh, our CornealRegen Lab in University of Pittsburgh is ready to prepare for the "First-in-Man" clinical trial with these PittStemCells in US for patients with corneal scarring.

OK, so besides this stromal project, we also have very exciting finding in the corneal endothelium. So I would like to hand back to Deep, and then give an overview of this work.

DEEPINDER K.

Thank you. And now for the second part of our presentation, speaking about the corneal endothelium and corneal transparency. So the clarity of the corneal stroma is due to precise spacing and organization of the collagen fibrils and a relative state of dehydration. There is the inner lining, comprised of the corneal endothelium.

DHALIWAL:

And one of the main functions is to actively pump fluid out of the cornea to prevent stromal swelling. This corneal endothelium is actually one layer of cells. And they're hexagonal shaped and tightly packed in a very, very regular pattern.

So if the pump function doesn't work, the cornea gets swollen and gets cloudy, as you can see here. And that's what occurs in Fuchs' endothelial corneal dystrophy. Fuchs' dystrophy is a genetic corneal disease that affects the corneal endothelial cells. And these cells basically die off at a faster rate than normal senescence, or normal attrition. And the vision then becomes cloudy due to corneal swelling.

So you can see in these pictures, the cornea is very, very cloudy. You cannot see the iris or the colored part of the eye very well. When you look at a slit beam, you can see that that slit is actually much thicker than normal.

So we have lots of different surgical treatments for Fuchs' dystrophy that have been very exciting, including DSAEK and DMEK, where we only transplant the corneal endothelial layer. We're no longer doing full-thickness transplants for Fuchs' dystrophy anymore.

Medical therapy is very limited, and that's just with hypertonic drops or ointment. But that's not really a treatment. That's just basically holding-- it's kind of like a Band-Aid until your vision gets bad enough to require surgery.

Now there is a new advance that we've been doing for the past three years, and that's called Descemet stripping only. And that's basically where we just remove the central 4-millimeter zone of Descemet's membrane, with the abnormal endothelium. And we don't place any corneal transplant tissue. So what happens, if you pick the right patient, typically, the corneal endothelium will then migrate, perhaps even divide and kind of rejuvenate, and clear the central cornea. So that is a new advance that we've been doing, but it's for a very selected group of patients.

There are also novel strategies to help patients with Fuchs' dystrophy. And those include some types of medical therapies to improve or sustain corneal endothelial cell survival. There is cell injection therapy that has been wonderfully researched by Dr. Kinoshita in Japan. And he's doing cell injection therapy.

And we want to tell you about another very exciting topic, which is endothelial stem cell regeneration. And for that, I want to hand it back to Dr. Yam.

GARY YAM:

OK, thank you, Deep. Yeah, so there has been several studies looking at the corneal endothelial stem cells. So they might exist in the corneal endothelial periphery. But however, the exact location is still unknown.

So in the past two years, I have been looking at a very special region called the transition zone in the posterior limbus, or on the posterior corneal surface, which is between the corneal endothelium and the trabecular meshwork.

So we have been doing a lot of keratinization study, because this is a very new region that we are looking at. So we have been doing a lot of keratinization study, looking at what kind of cells it contains, how those tissues are structured there, and so on. And so we have a lot of results on that.

But I can tell you that this is very, very thin layers, thin zones. The thickness is only about a quarter of a millimeter thick. But even though, we still can isolate this tissue by microdissections. And we can identify some cells could be the potential stem cells of the endothelium. Next, please. Yeah.

So we can see that these stem cells, these transitional cells, can migrate, can move into the peripheral endothelium. So here, you can see that there are something like multicellular structures that are labeled with the stem cell markers that they may be the stem cells, that they move from the transition zone into the peripheral endothelium. And in the electron micrograph, under high magnification, we can also see that some cells looks like stem cells, with very large nucleus, compared to the very thin peripheral rims.

So then with these stem cells, can we isolate these stem cells and put them in culture? And will these stem cells be able to regenerate into the corneal endothelium? Next, please. So in that case, we have to set up the culture, and we spent quite some time, because nobody has ever done this type of culture with this type of cells before.

So we spent some time to set the culture. And this picture shows the human tissue cell culture that you can see the cells proliferate from a few cells to many, many more cells in 20 days, and even more in subsequent period of time. And this shows the exponential growth of the cells. Next please.

And these cells can regenerate corneal endothelium on the Descemet membrane. That's the original endothelial cells were removed. So here you can see that the cells can settle down well, and then form very nice monolayer, tightly packed monolayers. And they also have-- they're more or less hexagonal in shape. This looks like the corneal endothelial cells. And they also express the typical endothelial cell markers.

So the pattern looks very similar as the native corneal endothelium. So today I'm not going to show you most of the results. But actually, I just show you the very exciting that we can make-- we can regenerate the corneal endothelium on the Descemet membrane. So next, we are planning for future experiment that we are trying to do some functional tests to see if this corneal endothelium that we make from these Tz cells can have the pumping actions that can regulate the stromal hydrations or prevent the stromal edema in the animal cornea.

So we still have a lot of things to do. But with this, hopefully, we'll get some good results from the animal model. And if the results are promising, we'll move on to establish the GMP culture protocol and develop this further into the clinical trial. Next, please.

So in summary, the corneal diseases are treatable. And novel therapies and novel strategies are coming up to improve the treatment outcomes and reduce the reliance on the donor corneal materials. So our work on the corneal endothelial stem cells in the transition zone is very, very exciting. And hopefully, in the foreseeable future, this can be developed into a brand new regenerative therapy for the corneal endothelial diseases.

So thank you very much. And I think all we have shown here is very exciting work. And Deep, do you have anything to add on?

DEEPINDER K. DHALIWAL: Yeah, thank you, Gary. That was phenomenal. It's so exciting that we have this collaboration with clinicians, researchers. But really, honestly, we could not do any of this work without support. And really, the Eye & Ear Foundation has been amazing in support, and as has been mentioned before, the Marstine Family Foundation, Mr. Moufflet, and other organizations have really helped us to expand our research efforts.

And with all these studies, we're excited. We have lots of future potential, and we can't wait to get our studies for the corneal stem cells, especially started right here in the US as well. So thank you, everybody, for listening in this afternoon. We appreciate it.

GARY YAM: Thank you very much. Yeah, thank you very much.

MODERATOR: Well, thank you, all of the speakers. And I'll ask all three of the panelists-- Dr. Sahel, Dr. Yam, and Dr. Dhaliwal-- unmute yourselves here now, and let's get to the questions and answers.

I can tell you personally, when I started over 10 years ago here in this position, I met with Jim and sat down with Jim and learned about what he was doing at that time just in the mouse model. And it made the hair stand up on the back of my neck. It was just tingling in terms of the opportunities.

So that's why we wanted to get involved, and we wanted to help and find ways to get this to be translational. And when Jim sent me the first pictures that came back from India of the patients that were helped, it was-- it's transformative for all of us who want to make a difference and an impact.

So we're very proud of this work. We really want to see it continue. We want to see it really expand, and I want to thank everybody. And I'll highlight again, where Dr. Sahel, when he came on-- now it's been almost four years-- he saw the opportunity to make sure that we get this available to all of you in the US.

So we're open for questions and answers here. I see we already have three that came on while everybody was talking. Please continue to ask questions because I'm sure there's a lot of things you'd like to know. And this is your chance, so please do.

But we do also welcome, if you don't want to ask them now, you can send us an email, which would be in your invitation. You have an email that is available for Mr. Craig Smith. You can send us any questions, of course, at any time. And we welcome you to contact us at any time as well.

So let's start with the first question here. "Can anything in this research be used to correct the scars obtained from radial keratotomy? I am currently suffering the side effects of the surgery done in 1996. It's affecting both my reading and distance vision."

DEEPINDER K. DHALI WAL: So I'll start with that. Just for a background, radial keratotomy was a procedure that we did early in the late '80s, '90s. And it was really done before the [INAUDIBLE] laser was FDA approved. And this was in effort to treat nearsightedness. And basically, we made little incisions in the peripheral cornea. And by doing that, the central cornea flattened, and that corrected nearsightedness.

So the challenge, and what we didn't really understand, is that radial keratotomy is kind of the gift that keeps on giving. And unfortunately, the corneas get flatter and flatter over time. And so you get farsighted.

And this corneal instability that can result is a challenging situation. In order to kind of stabilize the cornea again, something that might be considered is corneal crosslinking, because that would really strengthen the cornea in terms of using these stromal stem cells, the scarring that's there is actually typically helpful because you want the cornea to become stronger.

So this type of therapy wouldn't necessarily, in my mind, erase the incisions that were made. But I'm going to let Gary answer, chime in here. I mean, maybe we could remodel those incisions. I'm not exactly sure because that has not been studied yet. Gary, do you want to chime in? You're on mute, Gary. Do you want to unmute?

MODERATOR: Gary, you're muted. Sorry.

GARY YAM: Yeah, I think I don't have too much information on that because this is a very specific clinical situation. And so far, we just mostly work on the corneal scarring model. So to reconstruct the corneal stroma, yeah, I think we might need some more investigations before we can have more solid answers. Yeah.

MODERATOR: OK. Dr. Sahel or anybody else have any--

JOSE-ALAIN Well, I think, Deep really addressed it. It really depends whether there is a scar that is central. Usually, these
SAHEL: incisions were not performed centrally. So usually, there is no central scar, but maybe it might be the flattening or the change of shape of the cornea.

And I agree that maybe in that case, approaches like crosslinking could be [INAUDIBLE]. I think Vishal Jhanji, who is also in faculty, might be online, so if he has any answer to that, happy to-- I don't know if you could see him, or--

MODERATOR: Jared, if you could unmute him, if he's--

JOSE-ALAIN If he's online. I don't know. Yeah.

SAHEL:

MODERATOR: Yeah. While we're checking on that, I'll get to the second question here, because this is, I think, what everybody-- probably everybody on the line, and everybody is hanging on still, so all of our attendees-- when will any of this be available here in the US? That's probably the million dollar question, right?

JOSE-ALAIN It's more than a million dollar question.

SAHEL:

[LAUGHTER]

The problem is that so the technology is there. The efficiency is clearly established from the Indian study. But to be able to do it in the US, you have to do it using a lot of regulatory guidelines that are protecting the patient. So it's the best interest of everyone.

That's why we decided we need to invest a significant effort. We recruited Isabelle Billig as a manager to really bring this research from the bench to the development stage. And Gary pointed out in the other work that is going on on the manufacturing so that we get into careful fabrication of the self-preparation of the cells and [INAUDIBLE].

But this is making a lot of progress, so we hope we'll be able to get that in the clinic in a couple of years now. The important is that we want this to be done perfectly for patient, no risk, at least no foreseeable risk, because there is nothing without any risk. But we really want to make it as safely as possible.

But we are working very hard on that. And it's more than a million dollars. It's far more than that.

MODERATOR: Yeah. [CHUCKLES] Well, thank you. I think that answered-- and I know we're all working very hard on it. I can tell you that. As a matter of fact, it's not only a priority for Dr. Sahel and his department. But the chancellor of the University of Pittsburgh has also made this particular project, these particular initiatives, a priority for what we're trying to do in changing Pittsburgh in terms of developing technologies for patients.

And we'll get to another question here, "Hi, fascinating stuff. Are there potential use cases of this therapy for treatment of keratoconus? Could the cornea be strengthened, thickened in a similar manner to the process used for corneal scarring?"

JOSE-ALAIN Deep. [CHUCKLES]

SAHEL:

DEEPINDER K. DHALIWAL: Absolutely. I mean, that's the hope. So if we can put these stromal stem cells into the cornea, then they would differentiate into keratocytes. Keratocytes would then allow the cornea to perhaps get thicker, more stable. And it could really change the future.

Now as you know, for keratoconus, we are lucky now that we're diagnosing keratoconus earlier. We are working hard in stabilizing the cornea using corneal crosslinking, which is something that I mentioned before, that is an FDA approved procedure where we use riboflavin drops and UV light therapy to strengthen the cornea, to make it more biomechanically strong. And so that is very, very helpful.

But I want to say one thing that's really important in terms of keratoconus, and that is that we all need to be sure to minimize eye rubbing. So eye rubbing is very much related to progression of keratoconus. And it's not just eye rubbing during the day. So it's also sleeping with pressure on the eyes.

So there's a big initiative that cornea surgeons are undertaking now, and cornea specialists, basically really to educate keratoconic patients, or everybody. Please refrain from eye rubbing or sleeping on your eyes.

And during allergy season, that's really hard. So there is great allergy drops that you can use. But as soon as you start rubbing the eyes, the act of eye rubbing releases histamine. Histamine makes you want to rub your eyes more. so it's a vicious cycle. So the best thing is don't start.

And instead of putting pressure on your eye, you could just pull the eye to the side a little bit like that. And that just takes that little edge off. I know because I have a lot of ocular allergies.

MODERATOR: All right. Well, we have a comment and compliment here, rather than a question. But it says, "Thank you for the exciting development work." This is from Robert Bellizzi, the Corneal Dystrophy Foundation. Well, thank you for that. We're, of course, very excited about that.

More questions here, "How is a corneal disease like Fuchs' diagnosed?"

DEEPINDER K. May I take that one too.

DHALIWAL:

[LAUGHTER]

All right, so this is what I do every day. It's diagnosed by a simple slit lamp exam. You don't need any fancy cameras. You don't have to do any special measurements. You just can have an eye doctor look at your cornea.

And what we see are these little kind of-- they look like little dots, if you will. They're called guttae. And they're actually changes in Descemet's membrane that we see. And it's a very classic picture. So it's really easy to see on slit lamp exam.

Now what the patients notice first is, basically, in early Fuchs' dystrophy, your vision just starts getting blurry. And you're not quite sure why. It could be a cataract. It could be the cornea.

But one classic feature is that early in the morning, a patient with Fuchs' dystrophy, their vision is worse and more cloudy and hazy than it is later in the day. Because overnight, when a Fuchs' dystrophy patient sleeps, the cornea actually gets more swollen. And so in the morning, the cornea is more swollen. Vision is hazier. And then as the day goes on, there's more evaporation that occurs, and the endothelial pump cells can catch up. So the classic symptom is early morning blur that then progresses to blur all day.

MODERATOR: All right, well, thank you. We just have a couple more questions. But we actually have some time. I think if there's a few more questions that would like to come in, that's fine.

This one's interesting. "Can you send patients to India for this surgery?" [CHUCKLES] Well--

JOSE-ALAIN SAHEL: We know of a few people that went to India to get that because they couldn't access that in the US. This is not something that we can organize, and it's not something which would be even approved. So I think it's probably why we think we have to develop the therapy in the US. This is why I made that a top priority and convinced everyone that this is a top priority.

And answering the next question. obviously, this would be paid for. I mean, we've-- all the goal of doing this research is to validate it to really make it an approved therapy so that nobody would have to pay for it. It would be covered by the insurance. It wouldn't be something that people couldn't afford.

MODERATOR: OK. All right, I don't see any more questions, but I know that sometimes means people might want to send them via email. If you have-- I'll give you a second, if anybody wants to type in a question.

But I'll begin thanking everybody, thanking the panelists. I think this was exciting to hear. I, of course, know about the work, but I learn about things every time that we do this. And we did receive another question, which I'll read in a second.

But it's exciting to see it progress, but I also can tell you that the commitment that everybody is making, I know, is genuine. And that is also inspiring. And I know people who are dealing with the problems associated with vision loss can be inspired by the hope that's generated here.

And so the next question is, "What has been the rate of success or outcomes in India?"

JOSE-ALAIN SAHEL: You have the data, Deep?

SAHEL:

DEEPINDER K. DHALIWAL: Yeah, so the final paper with one-year results, I haven't seen the final paper published as yet. And I think that's what we're waiting for. So we are-- it's a work in evolution. It's definitely not 100%. It's higher than 50%, so it's somewhere in that range.

And remember, these are eyes that have significant disease. And I think that as we learn more-- this is an open trial that's happening in India. It's not like this is-- that the results are totally completed yet. So they're still doing the follow-up, et cetera. So we're all actually anxiously awaiting to see the final paper. Gary, do you have any comments on that?

GARY YAM: I heard from the talk in the conference that they are doing five to six patients. Yeah, so-- but I think they are doing many more. Yeah, maybe they just present those that are really exciting finding. Yeah, so actually, I'm also expecting to see their final paper showing all these clinical outcomes that will help us to design further for our clinical trial.

JOSE-ALAIN SAHEL: What we know is that they have done probably more than 85 patients so far. And the understanding is that the range of efficacy, but it's a very diverse population of patients. From what Deep say, it's between 50% and 100%, and 90%-- probably 70% efficiency or better, but to be confirmed by the final paper, which is very impressive because these are scars which couldn't be treated or else. So it's very promising.

I want to add, since I'm speaking, that we should really also credit for the work Martha Funderburgh, the wife of Jim, which I don't know if she's online. But she has been working on that for decades, and very instrumental [INAUDIBLE]. She's the one that brought him to start to work on cornea because she herself had a corneal disease. This is public knowledge now, nothing secret. And she benefited from a graft.

And obviously, [INAUDIBLE] has been working with Jim, and was involved in the work that led to the discovery of the stem cell. So we have a beautiful team here with a lot of new people, but also a long tradition of outstanding work. But more important is we want to deliver that. And I understand the frustration with this not being available in the US. And we are making sure this is happening now.

MODERATOR: OK. Well, we do have one more question. And since we haven't completely closed the hour, we'll take this maybe as our last question. "Is there a point in time with Fuchs' where the stem cell therapy will not work?" Is that something we have an idea about yet?

DEEPINDER K. DHALIWAL: OK, so just to clarify, right now in Fuchs' dystrophy, we are not using stem cell therapy. That is kind of a futuristic goal. For Fuchs' dystrophy, currently, we are using surgical treatments. And that is with DSAEK or DMEK corneal transplants.

So an exciting advance in corneal transplantation is something called selective keratoplasty. So we don't just remove the entire cornea for every single patient. And until maybe 15, 20 years ago is when it shifted. So prior to that, we used to just do that cookie cutter, remove the entire cornea for every single corneal disease. Now we just look at the part of the cornea that is diseased, and we only remove that and transplant that portion.

So in Fuchs' dystrophy, it's simply the endothelial cells with Descemet's membrane that we are removing. And then from the patient, from the donor, we just take that portion of the donor cornea, and then we are able to put that in the patient's eye and unroll it, unscroll it, and put an air bubble in, and there you go. So it's been an incredibly exciting advance in corneal transplantation, really a revolution in corneal transplantation, this endothelial keratoplasty.

Now the other procedure that I spoke about was Descemet stripping only, and that is not a stem cell therapy. That is actually just using your own cells to kind of wake them up from the stem cell niche that's hypothesized to be in that transition zone.

And actually, Dr. Gary Yam has found those cells in the transition zone. So we are thinking that by removing the central 4 millimeters of diseased cornea in Fuchs' dystrophy, we can somehow change the dynamics and allow the endothelial cells to migrate and proliferate and to cover that area. And then the corneas clear up.

And if that's the question, then yes. Not everybody is a candidate for that treatment. And that treatment is done without any donor tissue. There are very specific criteria, and I can just let you know about that.

This Descemet stripping only procedure is indicated for patients that have mainly central disease. So the Fuchs' dystrophy is mainly in the center of the cornea, does not affect the periphery very much at all. In fact, we like to get an endothelial cell count, and we like that to be above 1000 millimeters square.

Now the other thing is you have to have the fellow eye that's functional, because what happens is when we remove the central 4 millimeters in surgery, the cornea actually gets a lot cloudier before it starts clearing up. So you have to have an eye that you can really depend on.

And also, you have to be a patient patient because the visual recovery takes, on average, about seven weeks to get to 20/40 vision. However, in our study where we compared DSO with DMEK, the DMEK guys took less than four weeks to get to 20/40 vision, so it's a lot faster visual recovery.

MODERATOR: And in case this was also where the question was leading, with the potential of what you and Gary are working on with the stem cells that are being researched, do you see or hypothesize any limitations on populations based on the amount of time someone has Fuchs' disease or anything of that nature?

DEEPINDER K. Gary, what do you think?

DHALIWAL:

GARY YAM: I think right now is a bit too early to talk about this at the moment because we are doing most of the things of the individual part of the cells. So once we run into the animal experiments, then we'll know more about the treatment, the effects, the efficacy, and how we put the cells in, and how-- yeah, so I think at that time, we will have more data to answer this question. Yeah.

MODERATOR: OK. That winds up all of our questions. Again, panel, thank you. Attendees, audience, please thank you. Thank you. Almost everybody stayed on to the very end.

And look forward to more. In two weeks, we'll have another webinar coming up. That actually is an otolaryngology on survivorship, a very interesting new way of looking and expanding care for post-surgical patients for head and neck cancer. And then we have more topics in vision, as well as an otolaryngology we'll be doing all through the year. Thank you very much, and everybody, have a wonderful day.

JOSE-ALAIN Thank you. Bye-bye.

SAHEL:

DEEPINDER K. Thank you. Be safe. Stay safe, everyone.

DHALIWAL:

GARY YAM: Goodbye.

JOSE-ALAIN Thank you.

SAHEL: