

(Eberhart Zrenner) So, first of all, I would like to thank very much the organizers for the invitation. I'm very glad and happy to be here. And I will have two topics. Both are about electricity.

Electricity can be used to stimulate neurons and to provide vision. But electricity can also be used to tickle certain cells, to release endogenous growth factors to protect cells from further degeneration. This will be part two of my lecture.

I would like to start with the retina implant and I also would like to thank to Isabelle, because she has given a wonderful introduction already into the different types. The subretinal, epiretinal and the subchoroidal type of electronic implant to restore vision.

We have to be aware that gene therapy and other therapies you learn today, are only applicable in patients, if patients still have cells, if they still have vision to rescue. You can treat only something that is present. If cells are gone, you can't treat them. And the only way presently available to patients, to restore vision in case of blindness or light perception only, or very low vision, extremely low vision are retinal electronic implants. There is nothing else.

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There are two types of implants. The Argus II from Second Sight that you have seen a moment ago and the Alpha AMS from Retinal Implant in Germany. One is epiretinal, the other is subretinal. And I just would like to start with the Alpha AMS which we have developed in Reutlingen and Tübingen, since most recent 20 years old, so to say. These are both on the market and in Germany and other countries, repaid by the public health system. So, the target disease is clear, it is retinitis pigmentosa. You have learned this already about epi- and subretinal.

So, I will go into more details into the subretinal approach. How is it working? Essentially, it is a little camera chip, what we are using, like the one you have in your mobile phone from outside. But inside, it is very different. But the size is the same: 3 mm × 3 mm, it has 1,600 pixels, that is not much in comparison to what cameras have. But Argus II has only 60 pixels. Each of the 1,600 pixels has a photodiode, like the photo cell in the eye. It has an amplifier which amplifies the light point by point. And it has an electrode which forwards amplified current to the bipolar cell layer. Remember, you have these different layers in the cell. All the other layers in retinitis pigmentosa are still functioning pretty well. It's only the photoreceptor layer which is missing function.

That is, what we are doing: we are replacing the natural photoreceptors with artificial technical photoreceptors. And the iris's camera chip, it is in the back of the eye. That's where the photoreceptors had been, when they are still functioning. So it's under the retina. The retina is

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transparent. So, the regular picture through the lens, like in a camera, falls onto the back of the eye, goes through the transparent retina, falls on these 1,600 photodiodes, and an electrical image of this picture is produced and forwarded to bipolar cells.

I just show it to you on the picture, where they are. These are the bipolar cells here. And then, it is processed. So, the processing is a natural processing. There is no computer, like in other approaches which you have to have in the pocket. There is no camera outside in the face. It's all in the eye, it is moving with the eye. And nothing is to be seen outside, except the little coil back behind the ear, like in cochlear implants, where power and signal control is provided. So, it is processed and sent to the optic nerve to the brain. And this has a number of advantages: we can utilize all this remaining network. We can use the fixation of the eye, because if you have a camera outside the goggles. You need to move your head and look, what it is doing, whatever the eyes are doing. But, normally we are used to find objects, where we are looking at.

So, the fact that the implant is right below the phoria, helps us to use this particular pathway from the phoria to the brain to fixate things and to find something, much easier than with the camera outside. And we can use wiggling eye movements, which we normally have, so to say the micro saccades, which help us to refresh the image. If you have a camera outside, you have wiggle the head all of the time in most patients, to refresh the image. If you have the chip under the retina, the normal eye

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movements are helping. Okay, now you have understood how it works. And Dr. Stett in the afternoon will tell you more about the technique, the technology about that. Of course, we need a power supply and other things, which we will see in a moment, like here. So, behind the ear, there is transmitter antenna kept with a magnet. Below the skin, there is a coil that receives the signals from a little box, the patient has in the pocket for its batteries. And you can adjust sensitivity and contrast, like in the old black and white TV.

You may remember football in 1954 you have seen how everything was happening in Basel, no in Switzerland, Bern, Bern, sorry! That was not much to see, but it was as exciting as nowadays with the HDTV. I think, I wasn't there. I heard it on the radio nevertheless. Okay, so then from below, from the implanted coil below the skin, there is a cable that runs from behind the ear, under the skin towards the eye. It enters the eye with a very tiny thin foil, you know, with like in computers, the thin foils with electrical gold wires, printed wires, and it goes into the little camera chip, the AMS, Alpha AMS camera chip, which is implanted under the eye.

The question is now, how to get it there? That is not the greatest place to put something under the retina. And there were many experiments, meanwhile we have operated more than 60 patients and you see them here. So, first a little window is made into the eyeball on the side. You don't see, it is on the side of the eyeball. And then, a little foil, a small foil is advanced through this cut on the

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side, where the muscles are, and advanced to the phoria. So, it is a tunnel which is made in a way. And this foil protects the retina from damage. And then behind the foil, the implant is advanced, so you see, it is elevated a little bit and behind the foil, behind the protected retina, now you see the chip coming forward, until it reaches a place right below the phoria.

There it is, and you see the gold foils in this catch which provide power and control signals. Each of these dots is a pixel. And the size of the visual field is 15 degree. 15 degree is not too much, but you may have had or still have 15 degree of vision and that is pretty good, pretty good to come around, I think, with moving the head and looking. So, 15 degree is not much, but it is absolutely sufficient, even to drive a car actually. Because when you go Porsche on the German highway, these things on the side are going so quickly by, that your visual field is 15 degree or even less. That is why highways are always straight because you may not easily go around corners safely. Okay, that wasn't intended to be discussed.

Okay. Now, what did we do so far? We started in 1995, developed the implants, all the pre-clinical experiments in rats, in pigs in rabbits, until we really understood how everything is working. We did a pilot study with eleven patients. And there was one particular patient: Mika.

He was the first patient, where we put the implant under phoria, before we always had it in the periphery, that was not sharp enough. And he looked on day at his name

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which we had written with chalk on a little black board, 4 centimeters or up to 8 centimeters in height, little white letters on the board.

He was sitting there and saying nothing first. Then he said: „Do you think I am a formula 1 driver?“ So, we asked him, „Why do you think so, that we think that?“ He said, „Mika Häkkinen“, which is a very famous formula 1 driver, „he writes his name like M-I-K-A, the way you have written it.“ „But my name is M-I-I-K-K-A.“ „So, you have made a mistake.“ So, we were very happy about this mistake because this was the really proof, he could see and read properly.

Imagine our joy in 2010, when we learned that the patient told us that we have made a spelling error. That was great. So, we did a few more studies together with other people - Oxford, London, Dresden, Budapest, Hongkong, Singapore - with 29 patients with the wireless chip, the first generation, we call it the IMS. That was very much looking like the present version and it worked pretty well, but it didn't work so long. It was only 9 to 12 months or even less or more in some patients. That is not enough. If you want to have something implanted, you want to have it longer. But there were problems with cable, there was problems with corrosion. But for this time, they had it, the patients were pretty happy.

I show you, what we did with them. And then we developed a new chip. I will tell you at the end: The Alpha AMS, the second generation which I have tested meanwhile

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in 15 patients. It is on the market and that comes at the end. But what first of all: What did we do with the patient? We put them in front of a screen, we show them light, we show them gratings, we show a Landolt ring, you know, this C, where is open, left, right, up, down. So, we learn about visual acuity, learn about light perception.

And then, we do daily life activities. We put a plate on the table, a spoon, a knife, a cup. Then we ask the patient: „What do you see on the table, where is it?“ „How many items on the table, what is it?“ These are the questions. And then, we score. And the score is 0 to 5, actually 5 points, 0 to 4, 0 to 1, 2, 3, 4. If patient sees nothing, it is 0. If he says everything is correct, it is 4. So, what did the patient do? I just tell the outcome of the early study which ended 2013. Roughly 3 quarters of the patients had benefit. Some had very good experiences.

Even reading, telling that there was a Vapiano restaurant in large letters or something like that, or finding the ADAC, which is the German automobile club something like that, but that were just experiences. Some found it useful, but not to that extent like reading. But still finding an object on the table makes a difference from not finding an object of a table. So, you would grab something and your arm, and the hand is in the potato salad. You would like to avoid that, and that helps.

And for a quarter of patients, it was only light source. But also this is helpful, if you see nothing anymore, you are very happy, if you see the window, or a lamp, or a moving

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car light, something like that. In 8 patients, there was no effect because some didn't want to learn very much. It is a bit like skiing, you have to train it properly, and in others, in 4 of them, the implant failed. This is a clinical trial and we learned enormous things from these 29 patients which allowed us to create the next generation.

Still, these 29, just to abbreviate, 72 % reached the primary efficacy endpoint which was significant improvement of activities of daily living and mobility. And 86 reached the secondary efficacy point, like visual acuity of grating vision. So, we were happy, we said: „Okay, let's go on, let's provide something which really can be available to patients.“

That means development, engineering, material sciences, physicists, surgeons, everything had to be improved. I skip something, and we came out with a new subretinal implant Alpha AMS. So, here is the implant, same size with the gold foils. It is implanted the way you know it. It is here with a cable below the skin. And this is a box, the patient has, it has two knobs for brightness and contrast and to switch it on and off, that's all.

And then we started this with 15 patients, just published 2017, results with a Multicentre Trial with a subretinal implant Alpha AMS. And I show you a patient from Oxford who - for the very first time, when it was switched on - looked at the table with the items and she was very touched. So, maybe there is a little - can you give us some audio, please? (video is played)

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She tells us that there is a knife, there is a cup. But you cannot hear it, in a moment.

(woman in the video) Yeah, yeah. Yeah.

(Eberhart Zrenner) And she looks around to find the egg cup.

(woman in the video) Here, I see a cup, that is clear.

(another person in the video) Is it clearer than yesterday? When you were looking?

(Eberhart Zrenner) Okay, and if you look at all these patients together, then we see, if the implant is switched on, which are the green bars, in comparison when the implants are switched off, they are doing much better, significantly better with all the screen tasks over this 12 month period with light perception, with light localization, with seeing the grating acuities, or on the table tasks with finding the items, I just showed. Or also where the items are. They are not so good, what the items are exactly, they may mix a spoon and a knife. But that is probably not so important. I show you a few movies from the patient at home, because the engineers go home to the patients, in the near-vision area. So, the patient looks at a laptop.

(women in the video) Versuchen Sie es mal zu zeichnen.

(Eberhartt Zrenner) Can you like to draw it? So, he nicely

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draws the borders of a square. So, that works. Or another implant, it is the same one, sorry! Grayscale! The patient sits in front of grayscales between white and grey and black. And he describes exactly which way it is around, where are the whites and what is in between, because the vision patients have is blurry, of course. It is low vision, it is 20 over 500, it is not much. But it allows to see a bridge, a car, a scarf or a hat.

And some patients even were able to see others smiling, because the teeth are pretty bright contrast against the face. So, that helps, and now the movie, again. I have problems with the movie. So, plate on the table to find, patient looks around, looks for various items and right away sees it. I skip this one. Okay!

So, now you know the important things you need to know, I think, you may like to hear about the implant. The question is, when can it help to regain some vision? Clearly, it is too late in pigmentosa. But light perception or worse that makes no sense, if you still are able to recognize a face or something to do it. If you are an Usher patient and you have a hearing aid at one side, it is no problem to put a retina implant on the other side. Reading must have been possible earlier in life.

So, the brain develops ability to recognize and if it is not done in the childhood, then it cannot be developed later on. Still some retinal in a layer must be there, no macula holes, optic nerve must still be functioning and of course a proper picture has to go back to the eyes or if you have

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a trauma of the lens or cataract, it has to be first corrected. And no serious systemic disease like infection diseases or so. And we are very grateful to our people who have worked in our teams to develop this in Kiel, in Oxford, Singapore, Budapest, London, Hongkong, Dresden. If you are interested, you can contact any of these centres or ask in Tübingen, in Germany.

This was the first part, the second part is: What can we do to help the neurons in the eye to survive longer? And if you had looked a moment ago very carefully, you may have seen that over the time, a patient became even better a little bit with the power switched off. So, this is an effect of a well-known - and also described by other groups - point, namely that electrically stimulating Müller cells or RPE cells, they do release all kinds of factors that are good for the cells. So, secretion of growth factors, they change the BCL-2 level. And this has been studied in many, many investigations in rats. In a number of studies shown here since 2001. And there are nice reviews that say: „There is a role of electrical stimulation which can help therapy in olphalmic diseases“, published in various archives.

This is an example for the specialists: If you take a rat, you stimulate it with alternative current, very tiny currents, 300 micro Ampère for one hour, the antiapoptotic expression of BCL-2 is measured in Western blot, goes up within six hours. And then in 7 days it wears off again. The apoptotic cells are the ones who provide the death signals to the cells - they go down. Casper3 does nothing

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and growth factors - ciliary derived neurotrophic factor and brain derived neurotrophic factor - after one hour of electrical stimulation of the eye with the electrode, you know, like in the ERG. But not measuring the current, but putting current it into the eye, increases the level of growth factors enormously. And there are clinical trials for various kinds of optic nerve diseases. And we also did a clinical trial in weekly, cause you saw that it keeps active for 7 days.

So, we did a weekly stimulation for 30 minutes for 6 weeks in the first study. And we saw that those who received a certain dose of electricity had an increase in visual field, while those who were sham-treated, so they didn't get a current, they had a slight decrease. And also lower dose had a decrease.

Then we did a second study in 52 RP patients randomized over one year in 3 groups. And it turned out they had very similar effects. Also, especially the electroretinogram, the b-wave increased and implicit time shortens. Then we did a multi-centric study with this device in 105 patients. And again 2 years, 30 minutes a week, we saw in the stimulated eye a significant increase in the best corrected visual acuity. Not in all patients and this with many treatments, like glaucoma, it lowers the pressure, but it doesn't help all the patients. So, there is - the device is not shown here.

So, how does it work? It is called OkuStim, it is like glasses. But instead of lenses, you have tiny fine, little spider-

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web wire, electrical conducting. You put that onto the eye. The spiderweb type wire is in the lower lid, and you have a box that provides the current, where you put the plug-in to, and you sit there for half an hour. You may get a little bit of tickling, the eye may be a little bit dry for one or two days afterwards. So, you get some regular wetting drops into the eye. So, we learned that it has in clinical trials significant improvement. It is safe and well tolerated by patients and the German health insurance has now acknowledged that it has potential benefit.

We think, that is a very important point that the German healthcare system - that was difficult to get - says: „Let’s to do on the expense of the taxpayer in Germany a big trial with 250 people and look on the long-term effect.“ So, we hope that in the next 2, 3 years, we will be able to get these 200, 250 patients cost-free for the patients into the trial, financed by the German healthcare system. That’s where we are.

Finally, I would like to show you our new hospital, new clinic. Only one in Germany, we are a full-fledged research institute with 110 researchers within the same building with a hospital with 72 beds. And in the same building with an ENT department. So, we have a special Usher clinic Wednesdays. Katarina Stingl, my senior physician, is running it together with Anke Tropitzsch. And if you are interested, I have put here the e-mail, where you can write to Katarina, if you want to join this special clinic for Usher patients and other rare diseases that affect eye and ear together. Thank you very much for your attention!

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I was speaking a little bit slowly and overdoing it for two minutes. And if you have questions, I will be there during lunch. Thank you! (applause)