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Inflammatory Eye Disease Transcript

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Inflammatory Eye Disease

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What I would like to do today is to address the matter of ocular inflammatory disease. It can occur as a consequence of a number of things, and it is by far the number one cause of blindness worldwide. It may be because of infection of the cornea, it may be because of trauma and loss of the eye, it can even be as a consequence of cancer, and finally, the thing that you will hear a considerable amount tonight about, it may be because of autoimmunity. Although the primary goal is to speak this evening about ocular inflammation, time does not permit really speaking about the panoply of functional diseases to the eye that can destroy vision.

I'm going to focus, in just a moment, on inflammation internally, inside the eye or uveitis, but there are many examples of an external inflammatory diseases, which occurs as a consequence of the immune system losing its ability to discriminate between self and non-self and to begin to attack conjunctiva and subsequently cornea.

What is this uveitis? What is its importance? What is the history of its therapy, and what does the future hold?

It is inflammation of the uvea, from the Latin word meaning 'grape'. The Ancients thought that the inner vascular layer of the eye, sandwiched between the white outside wall or sclera and the innermost aspect, the retina, looked similar to a grape, purplish, and then from the Greek origins, 'itis', meaning anything that is inflamed, so inflammation of the uvea. Other general terms in the past include ophthalmia and flegmoni.

This uvea is comprised of three basic structures or organs. One is the iris - most people will be quite familiar with that; the coloured part of the eye. If you were to look at the front of the eye with the cornea, the chamber filled with aqueous humor behind that, and the coloured part of the eye, the iris is that with the pupil within it. Behind that is another structure making up the uveal tract. It is called the ciliary body. This, with its little finger-like projections, is responsible for producing all the aqueous humor that we will ever have throughout our entire lives. And then finally, the middle layer of the sandwich, between sclera and retina, is the choroids. So, the iris, ciliary body, and choroid make up the uveal tract.

But what is the importance of this inflammatory disease called uveitis? It is, unequivocally, the third leading cause of preventable blindness in all developed societies. Perhaps many of you might not have even heard the word 'uveitis' before, which might be surprising since it is this great cause of blindness. We will probably know the names of other causes of blindness, so why is it that uveitis has been left out? It continues to blind people even sixty years after the introduction of steroid therapy, with 12.3 million cases in the United States at any one time, 45,000 new cases every year, and it accounts for about 10% of the blindness in the USA. In the USA it costs people \$242.6 million every year. So it is the third leading cause of preventable blindness in developed countries, including the United Kingdom.

Uveitis does its dirty work slowly but surely through secondary disorders, namely, the production, for example, of glaucoma, and through that, blindness. The glaucoma was the blinding final step, but it was the uveitis that caused the glaucoma. Similarly, it can cause just the reverse. It can cause such destruction of the ciliary body that that aqueous humour fluid that is produced, minute by minute, stops and then the globe collapses, like a collapsed basketball that the air has been let out of, or it can cause damage to the retina. It can cause damage to structures that are critical for good vision. The eye cannot tolerate what the skin or the joints might tolerate. Small amounts of inflammation over a sufficient time will cause damage to the optic nerve of the macula, the seeing part of the retina, such that holes may develop in the retina or membranes may develop on its surface or destruction of the nerve may occur. All of these ways in which people go blind from uveitis are operative right now, right this minute, as we sit here this evening here in London.

It is one of the great problems of uveitis that there are excellent therapies out there for it, but that they are insufficiently brought to the table. In the United States, the United Kingdom and across the developed world, there are therapies that can stop uveitis, but they are simply not as wide-spread as they should be. The consequence is that, over the years, if one follows large collections of patients of uveitis, up to a third of them will be blind by the time 25 to 30 years has gone by.

I am going to regress now back to consider a little bit of the history of the therapy for this disease. The Ebers Papyrus, coming from about 1500 BC, is the earliest document from which we find evidence of uveitis being spoken about and therapy being applied to it. Some of the seminal early work came from the UK, and in particular from MacKenzie in the mid-1800s, but if we go back to the oldest known existing ophthalmic document in the world, currently in residence at the New York Academy of Medicine, we find the Edwin Smith Surgical Papyrus, which is based, among other things, on writings from the time of 2600-2700 BC. This describes inflammatory conditions of the eye, including what we presume now to be uveitis, and, even back as far as that, physicians with special interest in the eye were identifiable.

As a matter of fact, Pepi-Ankh-Or-Iri, the physician to the Pharaoh at that time was the most ancient identifiable ophthalmologist called the Royal Oculist. His other title was Palace Eye Physician and Guardian of the Anus. It may seem strange now to have a connection between the eye and the anus, but the prescribing of purgatives for treating various ailments, including uveitis, became fashionable as far back as then and remained fashionable up until the middle part of the Nineteenth Century.

Additional therapies evolving through time included employment of poultices and solutions and a hundred of the 237 medication recipes in the Ebers Papyrus - almost half of them - were for the treatment of eye disease. Some of the things that were prescribed included elements such as zinc, antimony, copper, aloe, yellow and red ochre, myrrh, ink powder, and then, in the Roman period, in around the second century BC, marijuana or cannabis came to the fore, as did opium and other plant extracts. But cathartics and enemas were still part of the treatment paradigm.

In the Byzantine period, between the 4th and 15th centuries AD, they used opium, milk, honey, oil and other sorts of things that could be made into poultices. It is also in this period that we see, for the first time, blood-letting. It was blood-letting that took hold and stayed with us for a while, but there also continued to be the administration of antidotes via the anus, which continues to be a fascination for them.

In the modern period, namely the 15th Century to the present, Scarpa described something interesting in 1806:

'A strong countrywoman, 35 years old, was brought into the hospital in April 1796, on account of violent, acute ophthalmia in both her eyes, with great tumefaction of the eyelids, redness of the conjunctiva, pain, and fever.'

So she was in great distress, with this tremendous inflammation, a constriction of the pupil, and a layering of pus by blood cells in the inferior aspect of the anterior chamber. But he goes on to describe what he did about this:

'I took away blood abundantly from the arm, foot, and also locally by means of leeches applied near both the angles of the eyes, and I also purged her.'

She got better, perhaps in spite of his attempts to cure her, but possibly as a consequence of his ministrations to her.

Other sorts of herbs and other attempted cures were also present in this period. These included, emollient herbs boiled in milk; quince seed mucilage; and bags of tepid mallows. There was also

a technique that was imported from Asia - blistering therapy. It was imagined to draw poisons out the body. Heated bottles would be placed at various places, and as the heated bottles would cool, they would create a vacuum inside, which would then suck skin up into the bottle and produce blisters.

You may wonder as to the sanity of these old methods of treatment for these illnesses, but let me assure you, ladies and gentlemen, that 100 years from now, someone will be standing here giving a talk and saying the same thing about the things that I am going to tell you we are doing today.

As an interesting aside, you might be interested to know that Louis Braille, the inventor of the communication system that all around the world now embrace for those who are profoundly visually impaired, was blinded as a consequence of uveitis. His particular form of uveitis is called sympathetic ophthalmia, occurring as a consequence of injury to one eye, and that eye suffering inflammation and damage to vision, but then the other eye starting in with sympathising inflammation in the same way.

In 1830 MacKenzie, a British physician, instituted the dilation of the pupil with tincture of belladonna. I do not know if it is actually true or not, but it is said that the plant belladonna got its name from the fact that Italian women in a prior century,

particularly those from Venice, had taken to putting extracts of a common plant into each eye prior to going out to an important social function. It would dilate the pupils which made them attractive to men. It is a fact that pupils dilate when you are looking at something that is pleasing to you, and they realised that back then, and so the men would appreciate that appearance, and the plant, by the by, took on the name that the men would use in describing those women, 'bella donna'. It became in widespread use for dilating the pupil because dilating the pupil gives the patient very rapid relief of the excruciating pain that she or he is having as a consequence of the intraocular inflammation and spasm of the ciliary body that occurs.

But at the same time as this, in the middle of the 1800s, blood-letting, purging and blister therapy are still employed. But by 1900, something new has come along: fever therapy. This took about half a century to realise what was this mechanism of action, but the adoption of fever into the patient, through a variety of techniques, was found to be therapeutically helpful in resolving inflammatory problems, including uveitis. The fever could be induced by intramuscular injections of milk, and subsequently with typhoid protein. Both of these had to be done on successive occasions.

This use of fever therapy would sometimes prove to be fatal and it was still in use even in the 1950's. At the Massachusetts Eye and Ear Infirmary, where one of Professor Ayliffe's former teachers and one of my colleagues, Dr Charles Regan, was still on faculty when Professor Ayliffe was with us for a year. Dr Charles Regan would tell stories about how, when he was a resident physician in training at the Massachusetts Eye Infirmary, he and other residents would draw the unpleasant duty of sitting by the patient's bedside throughout the night after fever therapy had been induced to monitor them carefully because fatalities could occur as a consequence of fever going too high and fever seizures occurring. The fevers had to be done in succession at least three times to be effective, and typhoid protein was employed once it became available.

It eventually became clear that fever therapy was having its effect as a consequence of the induction of an endogenous hormone. This hormone was called a cortisol, HCTH-generating cortisol, and it was left then to Dr Hensch to develop that molecule artificially, to produce it and to begin using it in humans with rheumatoid arthritis. So, the first publication in the use of systemic corticosteroids in the treatment of patients was by Hensch in 1949. It came as effectively a miracle: people with rheumatoid arthritis who were wheelchair-bound rose from their chairs and walked, even ran, and climbed stairs. It was an amazing advance.

Dan Gordon, Professor at Cornell University in New York City, began making eye drops out of this. He did experiments on rabbits, and then began treating patients. In 1950, this revolutionised the care of patients with ocular inflammatory disease. People who would suffer for a month before finally getting some relief were made better inside of a week as a consequence of Dan Gordon's elixir containing steroid.

However, it took less than a year for Hensch, and subsequently Gordon, to recognise that there was a dark side to the steroid miracle as well. We all know that every medicine known to man has possible side effects. Well, with corticosteroids, side-effects are absolutely and categorically guaranteed; no one escapes the side effects of steroids. When used long enough, everyone will have one or more complications from their use, and with respect to the drops, the most notable complication is development of cataracts and, secondarily glaucoma, and tertiarily, increased susceptibility of infection. It is a hideous drug; it is a wonderful drug. We dance with the devil that we know, but try to use him to our own ends without actually getting taken straight to Hades.

A Spanish ophthalmologist, Roda Perez, from Madrid, was the first to try something different from cortico-steroids in the care of patients with ocular inflammation. Roda Perez worked with rheumatologists at one of the universities in Madrid, where a drug, nitrogen mustard, that had been developed in the chemical warfare of mustard gas in World War I. It had been worked with and experimented with and developed into a drug to treat inflammatory disease and cancer. Their work with patients with uveitis, published in the Spanish Journal of Ophthalmology in 1952, regrettably, even though the cases were wonderful success stories, was effectively hidden from the rest of the world. Not too many people in the UK and Europe, nor in the United States or Japan, read the Spanish Journal of Ophthalmology, and as a consequence, this work was basically hidden from view.

A person named Vernon Wong, working at the National Institute of Health in Bethesda, Maryland, independent to Roda Perez's work, conceived of the same sort of strategy. The medication that he employed, back in 1965, was named Methotrexate and it is still with us today. Today it is one of our favourites for dealing with not only ocular inflammation but also arthritis and psoriasis.

Others followed, from the United States, from Australia, from Lebanon, and from Switzerland and elsewhere, and now, it is very clear, and very clearly established in peer-reviewed literature that the prevalence of vision disability and blindness, secondary uveitis, has not measurably changed in the past forty years, in spite of the effectiveness and, when used correctly, the safety of these immune-modulatory drugs like Methotrexate and derivatives of nitrogen mustard.

But how can that possibly be? How can it be that these therapies are there and functioning wonderfully, and yet instances of uveitis has remained the same since their introduction?

Sadly, perhaps the main reason is that the vast bulk of ophthalmologist training programmes around the globe are stuck in second gear. They only know steroids. Very few Departments of Ophthalmology have recruited onto their faculties an ocularimmunologist who can teach the residents, and because they do not have such a person, most ophthalmologists completing their residency training programme have never been exposed to uveitis patient management with anything other than steroids.

So, what do you suppose those newly-qualified eye doctors are going to do when they go out into practice and they see their patients with uveitis? Of course, they are going to treat those patients with steroids, and therefore nothing will change. Just as the prevalence of blindness, secondary uveitis, has not changed in the past forty years, so too, I predict, it will not change in the next forty years, unless this phenomenon changes. I can speak all I wish about this matter; it will change nothing; I can publish my textbook and give my courses and train my fellows. It makes no difference at all. The only thing that has any actual chance of changing this is the hope that more chairmen in departments of ophthalmology around the world recognising that this is a problem and they will then actively recruit ocularimmunologists onto their faculty, who can not only help take care of the uveitis patients here and now, but also train the next generation and the generation after that on how to take care of patients correctly.

Now, rheumatologists learned this lesson the hard way before we did. They learned that starting with steroids or aspirin first, and then NSAID after that, and reserving immune-modulatory therapy for patients with advanced disease, was resulting in progressive joint damage and great disability. Early employment of steroid sparing IMT or immune-modulatory therapy, so called disease modifying agents, results in vastly superior outcomes, and that is now well-recognised and embraced by the rheumatologic community at large. And, by the way, speaking of those poisons and how dangerous they are, the rheumatologists, and we as well, have recognised that, used correctly, the side effects of such medicine is actually less than the chronic use of corticosteroid therapy.

So the battle cry throughout the world of rheumatology has become: the mission is remission. I believe that ophthalmologists can and should learn from the rheumatologists, and the battle cry for ophthalmologists taking care of patients with ocular inflammatory disease should also become: the mission is remission. The eye is so much less tolerate and forgiving of chronic inflammation than is the joint, and so we should embrace this model even more vigorously than do the rheumatologists. Allowing flare-ups and low-grade chronic inflammation leads to loss of vision. We do not have to continually re-learn that lesson. That lesson is well-established and should be learnable by open-minded people.

So where are we today? With respect to immune-modulatory therapy, clear evidence for safety and effectiveness in saving vision in selected populations with uveitis patients, doomed to a life of blindness without such therapy, is very abundant, very clear and solid evidence. There is also clear evidence for insufficient employment of such therapy by ophthalmologists worldwide.

In my view, if this is to change, the future should be as is outlined here, with an increased emphasis on education by the sub-speciality learned societies, like the International Uveitis Study Group, the International Ocular Inflammation Society, the American Uveitis Society, and the so-called Uveitis Sub-Speciality Day that occurs at the Ophthalmology Annual Meeting. These things are being done, thankfully. These societies are putting much more emphasis on prosthelytising and getting the information disseminated amongst the world's ophthalmologists.

There should be an increased emphasis on recruitment of fellowship trained ocular immunologists on Departments of Ophthalmology. This is the key, in my judgement, and this is not currently being done. Part of the reason that this is not being done is because of ignorance, and part of the reason is because some department heads see the uveitis specialist as simply a money-loser. They figure that they are going to be like a pathologist or a neural-ophthalmologist - they cannot really earn enough to not be a drain on the department. That is categorically incorrect, and yet, it is a commonly held belief in the minds of department chairs, who, as you probably know, are increasingly sensitive about their department finances,

with finances being so much more difficult year by year.

We also need new initiatives by big pharmaceutical companies, like the Merck Sharp & Dohmes of the world and the Novartis of the world, on clinical trials of medications capable of affecting the immune system and ocular inflammatory disease, including uveitis. I am very happy to tell you that, in the past two years, we are starting to see this. They have not done this because of goodness of their hearts; they have done this because uveitis is now recognised as a so-called orphan disease, and so so-called fast-tracking rules exist for bringing drugs to market for so-called orphan diseases. So they are not going to have to invest the multiple millions of dollars that they typically have to invest in drug development through clinical trials.

Basic tissue, cellular and molecular research on the causes and the mechanisms of ocular inflammatory eye tissue disease is also necessary. There is far too little of this being done at the moment. This is not theoretical, pie-in-the-sky type research that goes nowhere. This is stuff that can have real clinical applicability and can be life-changing.

Also needed is basic research on the immune system and mechanisms of regulation, with the emphasis on mechanisms of regulation. I will return to this idea of regulation shortly, so please take note of this point.

Now, let me share with you a couple of my ophthalmological fantasies. The first is that it is possible during my lifetime to re-educate the immune system so that the person's own immune system, instead of being autoimmune, with the white cells becoming confused and turning against the person's own tissues, mistaking them for foreign material and attacking them in an attempt to kill it, one can re-train the immune system so that it regulates itself correctly.

In fact, we are doing this now through the kinds of therapy that we have spoken about up to this point. We have very large numbers of patients who are cured of their ocular-inflammatory disease, whether it be cicatricial pemphigoid, necrotizing scleritis or chronic uveitis. These patients are curable and they need not be on drugs throughout their entire lives, and the reason for that is because of this: it is quite clear that the immune system is malleable. It is amenable to re-training.

We are currently doing it in unbelievably crude ways, through the use of systemic chemotherapy

and autoimmune-modulatory therapy. I am not using IMT, or immune-modulatory therapy, to control somebody's uveitis; I am using it to cure them. There is a huge difference. Anybody can use medication for life and keep things by-and-large under control. That is not my goal. My goal is to re-train the immune system. I do not always succeed, but we succeed in a very large percentage of instances - upwards of 70% of our patients are ultimately off-drug, in remission, five, ten, twenty years later.

Now, the first step of course is to get them in remission, off steroids. If one can make it to there, then you have basically won the game. That person is not going to go blind. But the ultimate goal is: in remission, long-term, eventually they are taken off the medication and they stay in remission, off all drugs. That is the goal, and we are accomplishing that in a high proportion of patients, but it is very crude, and so what I would really like to do is to identify the target molecule or molecules involved in uveitis, and then re-train the immune system in ways that I am going to share with you now.

I mentioned the blinding disease known as cicatricial pemphigoid earlier on, where the patient's white blood cells become confused, we do not know why but they begin to produce antibody against one of the proteins in this tissue, called conjunctiva. Conjunctiva is what gets red and gives you a pink eye when you get a bout of conjunctivitis. But in addition to covering the white part of the eye, it also lines the inner aspect of the upper and lower eyelid. Chronic inflammation, caused by this autoimmune disease causes scarring and shrinking of conjunctiva, the formation of bands of scar tissue, clipping off or closing off oil glands and tear gland ducts, so that profound eye dryness, corneal damage, blood vessel in-growth into the cornea occur. I mentioned that the immune system gets confused and starts to make antibodies against a protein in the conjunctiva, and we know what that protein is now, as a consequence of about twenty years of basic research. The molecule that is targeted in this autoimmune process that causes blindness in patients who are not treated with systemic chemotherapy lies in the basal epithelial cell, underlying stroma.

Specifically, we now know that it is something called the Beta-4 sub-unit of Alpha-6 Beta-4 integrin. We see in tests that stricken patients produce an antibody that it ought not produce, and that antibody is sticking at this basement membrane, and we believe that it is sticking on Beta-4 peptide and causing trouble. We do not know the details of the trouble that it is causing. It could be a number of things, but one possibility is that, by sticking there, it causes a dissociation amongst various components of this attachment complex, and, as a consequence of that, inflammatory chemicals are produced, and

as a consequence of that, a whole army of inflammatory cells are called into the battlefield and they amplify the process, producing more and more inflammation.

There is one more piece and knowing that means everything, if one has a fantasy of re-inducing immunologic tolerance in people with pemphigoid. Because now you know what the target antigen is, and then, if you could just take that and re-educate the patient's white blood cells that this is a friend, not a foe, then you could re-regulate that patient's immune system without the use of chemicals.

So, how do we re-educate the blood cells? Well, first, one has to actually get some white blood cells from the patient. That is easy - you take some blood and then you get rid of the red blood cells. Furthermore, you can use so-called antibodies that stick to certain cell surface molecules that allow you to stick the whole collection of white blood cells through a machine called a cell-sorter, and by using electrical tricks with an antibody hook to this cell surface molecule, different cell types can be identified, and by using electrical tricks, one can sort the cells as they come through this pathway. Once a cell that contains one of those molecules on the surface level is seen by the detection system, an electrical charge can be placed across two plinths, causing the cell to deflect slightly, and with enough cell surface markers, one can sort that person's white blood cells into a whole panoply of sub-types of white blood cells, and specifically, we want the sub-type that contains the surface marker that is typical for regulatory or suppressor.

This is rather complex but I hope that I have reduced it to the point that it is not overwhelming and that it is understandable. White blood cells are the immune system. They are made up of many different types and sub-types. We can identify them, we can isolate them, and once we have a collection of regulatory lymphocytes from the patient as pemphigoid, we can then put it in a Petri dish, along with the target auto-antigen, the Beta-4 peptide, and a couple of other things in a recipe, like TGF-Beta, that encourage this population of T-cells to become tolerant and, frankly, suppressive of all the other kinds of attack things that the immune system is trying to do. We cultivate Suppressor T-cell regulation, which is specific to the auto-antigen that previously has been the target of an autoimmune response in this patient being blinded by this autoimmune disease, we expand them, feed them, nurse them, and then transfuse them back into the patient. All of this is not Jules Verne type fantasy: it is something that I expect to see accomplished during my lifetime.

Now, these re-educated regulatory T-cells regulate or suppress the aggressive cells, thereby abrogating the autoimmune attack on the eye without the need of any chemotherapy whatsoever. No drugs. One has simply re-set, re-educated, the immune system.

That was fairly complicated. However, there is a really easy alternative. The problem with this one will be getting permission from institutional review boards.

It all stems from the work of a British zoologist who was awarded the Nobel Prize in Physiology or Medicine in 1960 for his work on the immunology of the eye, Sir Peter Medawar. I suspect everyone sitting here understands that the eye is special - as is the brain and the testicle: there are various areas that are immunologically privileged. Immune responses do not occur in those areas the same way they do in skin, for example. Medawar, in his experiments, found that if you put skin or other foreign material into the anterior chamber of a rabbit, it was not instantly rejected; whereas if you put that skin from another animal, sewed it onto the rabbit's skin, the immune system of the rabbit would almost immediately reject that transplant. Now, his work led to the concept of immunologically privileged sites, the eye being one such site, and immunologic tolerance in such sites. This is, after all, why corneal transplants are so routinely accepted, without systemic immune suppression, as opposed to kidneys, which are rejected without such immuno-suppressive chemotherapy.

Medawar's work resulted in about sixty years' worth of research in this whole area, and for the subject of the latter part of this evening's talk, the most important of that work came from Boston, from Baruj Benacerraf, who identified a unique population of white blood cells called regulatory or suppressor lymphocytes. You have already heard about them. If one takes protein and injects it into the skin, it will produce a flagrant inflammatory response. It will also immunise the person against that protein, so that if you then come back two weeks later and do a very tiny injection in the other arm, there will be a huge inflammatory response in that arm. If you do the same thing into the anterior chamber of the eye, that person who has been so inoculated in the anterior chamber with foreign protein does not develop a big inflammatory response, nor do they develop the so-called delayed type reaction when you come back and stick the protein in the skin two weeks later. Instead, anterior chamber inoculation of that foreign material has resulted in the development of an incredible population of regulatory or suppressor T-lymphocytes, and these are the things that are responsible for Medawar's observations. These are the things that are responsible for cornea transplant tolerance. It is not the absence of lymphatics or immunologic

ignorance that allows the person to maintain a clear transplant after corneography. It is an active process driven by regulator t-cells, this suppressor t-cell group that I introduced you to earlier.

So, might one be able then to induce immunologic tolerance in a patient with autoimmune disease by inoculating that patient in the anterior chamber of the eye with the protein against which the autoimmune reaction has developed? Could I take a patient with pemphigoid, isolate the Beta-2 peptide? In fact, one can even just buy these genes, as they have been cloned and you can purchase them. Could I take Beta-2 peptide and stick it in the anterior chamber of a patient with pemphigoid and induce immunologic tolerance all over again for that person, as if when they were first born?

Well, that is one of my fantasies - that is my favourite fantasy. This is because it would be so easy. They will be difficult though from the standpoint of the experimentation and institutional regulator boards. But this same kind of thinking should certainly be applied to animal models of disease. There is no good animal model of pemphigoid, but there are animal models of uveitis.

To summarise, this disease that I have focused on this evening, uveitis, is a potentially blinding eye problem. It is a problem of enormous epidemiologic and economic importance, and it is vastly under-appreciated. Excellent therapy exists today for it, yet far too ophthalmologists avail themselves and their patients of such therapy. The prescriptions for progress that I see are, first and foremost, training more ocularimmunologists, who can then, in turn, train residents in training so that they, in turn, know that there is more to treating a disease of the eye than just the use of corticosteroids. Research dedicated to uveitis, especially the identification of relevant targets, could be then exploited to induce tolerance, and, finally, continued research dedicated to the immune system and to regulation of it.

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