

**TRANSCRIPT OF
THE #MDPEOPLE GROUP SESSION
WITH DR. KENT SMALL**

10/28/99

(Edited for length and clarity)

Dan: Dr. Kent Small is a Professor of Ophthalmology at the Jules Stein Eye Institute at the UCLA School of Medicine. In addition to his work at Jules Stein, he conducts genetic research for cone dystrophy and other forms of MD. Dr. Small, welcome, and thank you for being our guest on MDForum. Before I open the floor to questions, please tell us a little more about your background and the work you are doing.

Dr. Small: Thank you. My background began in medicine as a clinician. However, I learned the skills and power of molecular genetic research and now have experience in both clinical trials, as well as basic science research.

Dan: I enjoyed hearing the speech which you presented at the recent Visions '99 Conference in Los Angeles, and I am grateful that you have accepted my invitation to discuss some of those topics with us today. The floor is now open for questions.

Joan: I have some questions regarding Cone-Rod dystrophy. Are there any studies involving individuals with Cone/Rod Dystrophy? If so, how do we become part of the study?

Dr. Small: Yes, there are many molecular genetic studies of cone rod dystrophy. Cone rod dystrophy appears to be a very heterogeneous group of diseases with several different genetic loci and genes involved. If there is a family history of cone rod dystrophy, then it is possible to become part of the gene mapping studies. If there is no family history, then your DNA could be used in candidate gene analysis studies. We are involved in both types of studies here, as well as other centers here in the U.S. and abroad.

Alan: What is your opinion concerning the viability of acupuncture with regard to dry MD?

Dr. Small: Alan, it is my opinion that there is no repeatable scientific data or information to suggest that there is any therapeutic benefit to acupuncture. I would be happy to review any such information that anyone has published in a scientific peer review journal if you would like my opinion specifically about that.

Nan: Are herbal antioxidants beneficial to the slowing of progression of M.D., specifically taurine and grape seed extract?

Dr. Small: There is a serious lack of scientific data suggesting that herbal medicines or supplements can significantly slow the progression of macular degeneration. This is in part because this field has not been approached in a scientifically meaningful way overall. Therefore, the short answer to your question is, "We don't know," because there is no data of value. Again, I am open to reviewing any scientific peer review article addressing these issues. However, until there is a significant body of

medicines or supplements can significantly slow the progression of macular degeneration. This is in part because this field has not been approached in a scientifically meaningful way overall. Therefore, the short answer to your question is, "We don't know," because there is no data of value. Again, I am open to reviewing any scientific peer review article addressing these issues. However, until there is a significant body of data, I do not recommend that my patients take vitamin supplements of any kind for their macular degeneration. I will say, I have colleagues whom I respect who take a different position on this. I recommend that my patients eat dark green leafy vegetables for their antioxidants.

Dan: What about lutein and zeaxanthin, specifically? There have been some positive results in small studies.

Dr. Small: Regarding lutein and zeaxanthin, the data come from the study suggesting that the consumption of dark green leafy vegetables is beneficial in macular degeneration. I am not yet aware of a clinical study showing specific documentation that lutein and zeaxanthin are beneficial. There is some circumstantial evidence, however.

Judy: For a "dry" eye suddenly turning "wet," would you recommend the PDT clinical trials as opposed to photocoagulation laser? Is time of any urgency?

Dr. Small: I just returned from the American Academy of Ophthalmology meeting where photo dynamic therapy (PDT) and transpupillary thermotherapy (TTT) were discussed. It does appear that PDT and TTT may have a significant role in the management of wet macular degeneration. The PDT data are currently being examined by the FDA for possible release and use by the public. Some physicians are using TTT outside of a research protocol. PDT is currently being used only under a stricter research protocol. Regarding dry macular degeneration treatments, other than dark leafy green vegetables, there is not much in the way of treatment. However, there is a new procedure being investigated where drusen (small yellow bumps under the macula) can be lightly treated by laser. The early data from this trial suggests that this may help prevent the wet form of macular degeneration from developing and rarely may even improve the vision slightly.

Dan: What is your opinion on TTT?

Dr. Small: The early data regarding TTT looks encouraging, as well. Remember, in most of these trials, we look to see which group lost the least amount of vision. This showed that typically both the control and the treated group still lose vision. Therefore, "encouraging" usually means being successful at limiting the amount of vision loss.

Joan: Regarding gene therapy, the death of Jesse Gelsinger in the UPenn OTC study: can you assess the impact on gene therapy in general?

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Dan: How close are we to gene replacement therapy in humans? Do you agree with the general opinion that this will be the direction from which a cure will come?

Dr. Small: I believe we will see clinical trials using gene therapy within approximately five years. I personally am very hopeful about the strategies, in that the basic root cause of the disease is being addressed, rather than dealing with managing the late complications such as wet macular degeneration. One problem I see with gene therapy at this time is that large pharmaceuticals will not be willing to participate in custom designing of the therapeutics. Currently a different therapeutic agent will have to be custom-made for each individual.

Sadonya: Do you have any thoughts about micro-current stimulation?

Dr. Small: I would like to see scientific peer review data showing its efficacy. I really cannot recommend such alternative treatments without more information. Again, I would be happy to review any such data if it is even available.

Judy: How urgent is it to get some type of treatment for a wet eye? A day, week, month?

Dr. Small: Wet macular degeneration can develop and progress very rapidly. In research studies, a fluorescein angiogram is ideally performed within 72 hours. However, because our current standard of care and treatment options are limited, being evaluated within a few days to a week rarely makes any practical differences in the outcome. If a patient has a new onset of symptoms consistent with wet macular degeneration, I try to examine as soon as is conveniently possible for them and advise them not to panic.

Nan: Several years ago, I read of fetal tissue transplants being used. Is this still being done and, if so, what is the result?

Dr. Small: Your session with Dr. Gouras probably addressed the transplantation issues. My interpretation of the data regarding a retinal or retinal pigment epithelial transplantation is that there is much work yet to be done.

Pam: What treatment or research do you think gives us the highest hope for the future, and on what timescale?

Dr. Small: This is not a simple question. My highest hope for a treatment or cure lies in the realm of gene therapy or, better stated, gene directed therapy. Unfortunately, I think this is also the "longest row to hoe." I will be surprised if there are any "quick fixes" in the near future. In the meantime, we're frustrated with our attempts at managing the disease, but not curing the late complications, such as wet macular degeneration. I applaud all scientific endeavors in managing and treating MD. I predict that several different types of modalities will be needed in order to control and manage this debilitating disease. Regarding wet macular

with our attempts at managing the disease, but not curing the late complications, such as wet macular degeneration. I applaud all scientific endeavors in managing and treating MD. I predict that several different types of modalities will be needed in order to control and manage this debilitating disease. Regarding wet macular degeneration, I view it somewhat like treating a cancer. It may require several different types of treatments in combination, such as chemotherapy (anti-angiogenic drugs which are currently under investigation), radiation therapy, surgery, photodynamic therapy, and genetic manipulation.

Jonathan: Recently, two people wrote to the List that MD can result in fluid accumulating behind the retina and affecting vision. Is this condition common?

Dr. Small: You are referring to wet macular degeneration. New, but abnormal, blood vessels grow under the macula and can leak serum or plasma or blood. Wet macular degeneration is less common than dry macular degeneration, but has a more sudden and serious effect on the vision.

Robert: How many research groups seem to be in a position to commence clinical trials of gene replacement for Stargardt's in the foreseeable future? How about for other ocular genetic diseases such as RP?

Dr. Small: A friend and colleague, Bill Hauswirth, Ph.D. at the University of Florida, is actively working on this problem, primarily with retinitis pigmentosa. I have heard that he may be considering going into clinical trials for the p23h mutation in rhodopsin patients. Dr. Bennett's group at the University of Pennsylvania is also quite active in this field. In order to test gene therapy, a good animal model is first needed. The current animal models, developed by Dr. Travis at Southwest Medical Center in Dallas, have some technical difficulties so far, which may slow the trials in macular degeneration.

Dan: Along these same lines, how does the recently-discovered ABCR gene mutation relate to both Stargardt's and ARMD?

Dr. Small: Thank you for asking. A large international consortium was formed to answer this question. I am a member of that consortium. Dr. Allikmets, the head of the consortium, found that the ABCR gene mutations most definitely accounts for some age related macular degeneration. The current estimates are around 5-8 percent. There is no question that ABC mutations account for a large percentage of Stargardt's disease.

Joan: Apparently, there is no eye like a human eye. Dr. Gouras spoke of using designer mice. What animal models are being used in retinal gene therapy research? Is there any movement toward using transgenic eyes?

Dr. Small: The mechanisms by which ABCR mutations cause macular degeneration are currently being elucidated. Mice are probably the best studied, but there are also dogs and cats which are now known to contain spontaneously occurring mutations causing their retinas to degenerate. There are animal models which have been created through genetic manipulations. Again, mice are most commonly used for a variety of reasons. A colleague of mine has also created a pig with retinitis pigmentosa. Pigs' eyes probably most closely resemble non-primate's

which have been created through genetic manipulations. Again, mice are most commonly used for a variety of reasons. A colleague of mine has also created a pig with retinitis pigmentosa. Pigs' eyes probably most closely resemble non-primate's eyes. This pig (as well as the mice) with retinitis pigmentosa mutations was created primarily for the purpose of having an animal model to begin therapeutic trials. Without animal models to test treatment modalities on, it would be impossible and unethical to go on the human trials. This is particularly true when dealing with genetic manipulation.

Jonathan: Earlier you referred to MD as a "debilitating disease." Am I correct in inferring that fatigue often accompanies MD?

Dr. Small: When I referred to macular degeneration has being a debilitating disease, I meant visually debilitating. Macular degeneration is not known to affect any other organ systems. Fatigue is not something that normally accompanies macular degeneration. If you are experiencing fatigue, you need to work with your internist to find cause.

Judy: At this moment in time, PDT only prolongs vision for a short period. Why bother going through it all when this disease just keeps on ravaging the eye? PDT is a Band-Aid solution, don't you agree?

Dr. Small: The one-year data on PDT does show that most patients require re-treatment. However, the need for re-treatment decreases after each subsequent re-treatment. Without longer-term follow-up, it is difficult to know. I agree with you that all of our current treatments for wet macular degeneration are Band-Aids for a bad situation. However, the PDT data does appear to be better than doing nothing. I share your frustration, which is expressed between the lines of your question.

Robert: What is the nature of the technical problems, which you mentioned have been encountered in animal models for gene therapy?

Dr. Small: Ideally one wants an animal model which shows a severe manifestations of the disease early in life. The mouse model created by Dr. Travis shows very mild to minimal changes in the retina which will make it more difficult to see a therapeutic response.

Robert: Mice don't exactly have foveas!

Dr. Small: You are correct, in that mice do not have a macula. That does not seem to be a major problem with the mouse model for Stargardt disease, however.

Dan: As a final statement from you, Doctor, what would be the most important thing for us to remember as we continue to watch for new treatments and preventions?

While we are waiting for Doctor Small's reply, I want to thank everyone for attending the session. This has been our highest turnout yet, with 16 people attending. The transcript of this session will be posted tomorrow in "The Clinic" on the [MD Support web site](#).

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attending the session. This has been our highest turnout yet, with 16 people attending. The transcript of this session will be posted tomorrow in "The Clinic" on the [MD Support web site](#).

Dr. Small: In response to Dan, we're all frustrated by macular degeneration: the clinician, the researcher, and--most importantly--the patients and their families. This frustration and "search for a quick fix" sometimes causes us to look in the wrong places. The psychology behind this is somewhat similar to the fear, anxiety, and frustrations experienced by a cancer patient and their families, as well as by the physicians taking care of them. It is unlikely, based on the biology of the disease, that there will be a simple or quick fix.

If you hear something on the news that sounds too good to be true, it probably is. When you hear about "breakthroughs" or new treatments, first look at the source. Ask yourself, "Were the results which were presented generated scientifically?" The scientific process is often long and arduous. Without using the scientific process, the information is mere hearsay, testimonial, anecdotal, or worse. Only after the data has undergone a rigorous scientific review by other scientists and tested in a repeatable fashion by others can progress be made.

Dan: That is the reality of the disease, Doctor, and I think we are all prepared for it.

Dr. Small: I realize that this is not what you really want to hear, but I think it is best for you to be informed and not to be led astray.

Dan: Thank you for spending time with us today. You have been very enlightening.

Dr. Small: Thank you for allowing me to participate.

Dan: This ends our session, and I hope to see everyone again next time.