Inflammation in Early AMD
October 26, 2016
Transcript of Teleconference with Gerard "Jerry" Lutty, PhD, and Imran Bhutto, MD, PhD

Please note: This Chat was edited for clarity and brevity.

MICHAEL BUCKLEY: Hello, I am Michael Buckley with BrightFocus Foundation. Welcome to today’s BrightFocus Chat, “Inflammation in Early AMD.” We would like to welcome our speakers today, Gerard “Jerry” Lutty, PhD., and Imran Bhutto, MD, PhD, of the Wilmer Eye Institute at Johns Hopkins University.

If today is your first time joining us, welcome to the BrightFocus Chat, and thank you. Let me take a moment to tell you a little bit about BrightFocus and what we will do today. BrightFocus funds some of the top scientists in the world. We support research that is trying to find cures for macular degeneration, glaucoma, and Alzheimer’s. We share the latest news from these scientists with families impacted by these diseases. We have a number of free publications and plenty of materials on our website, www.BrightFocus.org. We also have information on every research grant that we fund, if you are interested in learning more about our scientists and their work. BrightFocus Chats, like the one today, are another way of sharing information from the world of research with families that are impacted by macular degeneration.

Now let’s turn to Dr. Bhutto and Dr. Lutty. Thank you for joining us today. Research that you have been working on really helps us better understand AMD, and some of the questions we get most frequently are from people that are looking in the form of new treatments. So before we turn to that, let’s start with a very basic question for both of you: What inspired you to be an AMD researcher?
DR. LUTTY: My two mentors at Johns Hopkins paved the way to study AMD. One of them was Bernie Hochheimer, who designed the cameras that allowed us to look better at the eye and eventually look at the choroid—the two tissues that Imran and I specialize in. My second mentor was Arnall Patz, who was an angiogenesis early pioneer—angiogenesis being the growth of new blood vessels. So, as I began to study choroid, I first studied its development and then how it deteriorated in diseases like AMD. I am driven to find a cure because of the fact that my mother had wet AMD in both eyes when she passed away.

DR. BHUTTO: When I completed my MD and started as a general ophthalmologist, I started my research, as well. I went to Japan for my PhD in ophthalmology, and my focus was to attempt to interpret the normal and pathologic features of the choroid, especially in small animals such as rats and mice. It seems these small animals are considered to be a useful experimental model for several choroid diseases and because it’s easy to treat small animals.

When I started my research at the time I met Jerry Lutty, and his interest in choroid inspired me. As I just mentioned, I was in Japan, I had only the opportunity to study on small animals. In Jerry Lutty’s lab, they are extensively studying the human donor eyes. I found that AMD is a really devastating disease in humans, which inspired me to join Jerry Lutty’s lab. It has now been 15 years that we have been working together on researching human donor eyes diagnosed with AMD.

MICHAEL BUCKLEY: Well that’s great, thank you so much for the two of you. It’s really interesting to hear your motivations, and we at BrightFocus appreciate you dedicating your careers to this disease. Dr. Bhutto, when you mentioned a minute ago how AMD is so debilitating, you’re exactly right. It seems to affect daily life, daily tasks such as reading, driving, identifying things, faces that you may see across the room or across the street, watching television and navigating stairs—it just seems it really cuts to the core of daily life. Before we get into some topics of inflammation, would one of you be able to provide a very basic idea of what causes AMD?
DR. LUTTY: I don’t think we really know what causes AMD, but we do know the risk factors, things that make people prone to have AMD. The first factor is genetics, our understanding of which is a very new development. We now have a series of 12 genes that, if they are mutated, people that have that mutation or change in the gene code have a propensity to get AMD.

The second biggest risk factor is smoking. Smoking is incredibly destructive, not just to lungs but to other tissues in the body, because of its many toxins. And what we also found can be causal for AMD is cardiovascular disease. So many of the subjects that we have studied in cadaver eyes, as Imran mentioned, have some sort of cardiovascular disease or hypertension. So we think that having poor blood supply to the eye, and especially to the choroid, really affects the choroid and may lead to age-related macular degeneration.

MICHAEL BUCKLEY: Thank you for that overview. Today’s topic has to deal with inflammation. For a lot of us, inflammation is a word that we associate with sports injuries in the knee or elbow. Can you tell us a little about inflammation that’s related to AMD and why it is so important to developing AMD?

DR. LUTTY: Inflammation is actually the body’s response not just to injury, as you mentioned, but to foreign substances or organisms; and of course smoking is a foreign substance, and in inflammation the white blood cells becomes activated, so your immune system becomes activated, and they respond to the injury or the foreign material by releasing molecules that activate other parts of the immune system and its cells.

In choroid, there are two kinds of white blood cells: mast cells and macrophages. A mast cell is a cell that is a first responder—with a bee sting, snake bite, or poison ivy, the cells that respond first to that are mast cells. They become activated and release a lot of materials into the environment. The second inflammatory cell in the choroid is a macrophage. These cells migrate to foreign particles or dying cells and actually devour those cells for material. We have found in our studies,
too, that not only are mast cells activated, but macrophages are activated in the AMD choroid.

MICHAEL BUCKLEY: Thank you. Is inflammation a risk for both dry and wet AMD?

DR. LUTTY: Yes, we have found that both cells activated in both diseases, and Imran has done several studies where he looked at the proteins that were in choroid and retina, and he finds a lot of inflammatory proteins.

DR. BHUTTO: Yes, the scientific term is CRP reactive protein, which we found very significantly elevated levels of CRPs in AMD choroid, and at the same time, we also see the complement factor age was declined. We have also found the complements like C3A, C5A were significantly accumulated in AMD choroids.

MICHAEL BUCKLEY: I understand your research has looked at antioxidants. A lot of us who use newspapers, TV, and the internet hear a lot about antioxidants. Could you tell us how this is important to eye health?

DR. LUTTY: Sure. First of all, an antioxidant is something that your body can make in defense of reactive oxygen radicals. Oxygen radicals are molecules that have an extra negative or positive charge, and that makes them reactive. So if they bump into another molecule, they can actually change that molecule so it doesn’t work. If they bump into the membrane of a cell, they can cause that membrane to not work correctly or actually open up, releasing the contents of the cell. So, again, it’s hard not to talk about smoking, as smoking has a lot of oxygen radicals in it and oxygen-radical-generating molecules. Your body makes several antioxidants; these are molecules that will destroy the oxygen radicals, but as you age, you make less of those. That is why, a while ago, the AREDS study looked at antioxidants that were taken to see if they would affect progression of AMD, and indeed there was a slight protection against the progression of AMD. I also would point out that those were supplements, but eating healthy, such as green vegetables
and fruits, will give you antioxidants. You don’t have to necessarily take a pill, but the pill bolsters the antioxidants in your blood.

MICHAEL BUCKLEY: Thank you. I want to take a question about antioxidants that just came in from John from Minnesota. He is wondering about the specific composition of AREDS [supplements], such as lutein. So if Dr. Bhutto or Dr. Lutty could elaborate on what is in AREDS when someone’s looking for that at the store, what should guide them?

DR. LUTTY: I think we are on the third formula in relation of AREDS and antioxidants, right Imran? So, the original AREDS formulation perhaps wasn’t the best grouping of antioxidants, and one that was in there was quickly removed in AREDS2, and that’s beta-carotene. Beta-carotene was found to be associated with cancer in smokers that took beta-carotene supplements. Recently, they have taken out some of the original antioxidants and they’ve added lutein and zeaxanthin. These are natural antioxidants, and they occur in the macula, which is in the retina and is the site where AMD is most devastating. Macula are the center of vision, and when you look into your eye you will see this yellowish color in the macula, which is the presence of lutein and zeaxanthin. So now that new AREDS formula, when you look on the shelf, it will say “new AREDS formula plus lutein and zeaxanthin.” That seems to be the one that’s favored at this point in time.

MICHAEL BUCKLEY: Great, thank you. Because that information is so important, it will be included with the transcript of this call, which will be available on our website at www.BrightFocus.org. I also want to let people know that we provide several materials on macular degeneration that are free both online and in print. We have one in particular called Macular Degeneration: Essential Facts, and that spells out the AREDS2 recommendation for the supplement formula. This free publication can be sent out to you if you call us at any time toll-free at 1-800-437-2423.

We got a question about smoking: This caller is wondering if the risks continues even after you stop smoking. The impact of smoking, does that continue to be a risk factor even after you’ve stopped?
DR. LUTTY: It is, but the risk factor becomes reduced when you have years away from smoking.

DR. BHUTTO: We studied the human donor choroid, and we found in past smokers that histopathological changes are there, so I believe it continues affecting even after someone has stopped smoking for a while.

But it is additives, so if you stop then, you’re not adding in any more of the chemicals or harming the tissue any further, so it certainly is good to quit. I know the audience is looking for recommendations, and another recommendation in cardiovascular disease would be gentle exercise that is recommended for seniors. That will reduce cardiovascular disease and increase circulation to all tissues, including circulation to the eye. Basically, you want to keep your blood moving.

MICHAEL BUCKLEY: That’s really great advice. We hear a lot about healthy aging, but I think it’s one of those things that people might not always know what it means or why it’s important. As you and the audience may know, BrightFocus also funds Alzheimer’s disease research, and it’s really interesting to see the broad benefits across diseases of not smoking, a good diet, and remaining physically active. A question for the two of you—when you look down the road at the type of research that you’re working on, do you think it’s possible this could lead to future treatments for AMD?

DR. LUTTY: We hope so. I’ll let Imran go further on the mast cell story, and then I’ll pipe in on therapies that result from our findings.

DR. BHUTTO: With BrightFocus Foundation’s support, we recently have studied the human choroid diagnosed with AMD. Just to mention, AMD has been clinically subdivided into three stages: early, intermediate, and advanced. Advanced has two subtypes: wet or exudative. The other is the geographic atrophy (GA). I won’t go into details about this, but we had all three clinically diagnosed AMD donor eyes, and we have aged controls that had no evidence of AMD. So we studied the choroids of these human donor eyes and looked at the number of mast cells—the total numbers in the degenerative mast cells—and found the mast cells were significantly increased in choroidal areas in all forms of AMD: early, dry,
or wet. The areas where we had the greatest numbers of degenerative mast cells also had loss of choriocapillaries. Choriocapillaries is the choroidal vasculature that supplies the nutrients to the outer retina. These increased numbers of mast cells in the degranulation we observed in AMD choroids, suggested that the mast cells degeneration should be contributing to the pathogenesis of AMD.

DR. LUTTY: Mast cells are interesting because, as I mentioned, its simple things like poison ivy that can cause the mast cells to get activated and degranulate the way Imran said. It happens also in the front of the eye when a person encounters an allergen in the environment, the white part of their eye becomes very red. That redness is because mast cells have degranulated, releasing their contents. There are drugs that can be used to stop the mast cells from degranulation, and they are used in that case, which is called conjunctivitis. We will, in the future, look at some of these drugs, some of which are actually generic, so we could advance pretty quickly to using them in humans. But right now Imran is developing an animal model that will tell us how important a mast cell degranulation is in making the eye look like an AMD eye. Once we have that model, we can start to evaluate these drugs and say whether they should perhaps go to clinic or not.

MICHAEL BUCKLEY: We are getting some great questions in from our listeners. Before we turn to some of the questions that have just come in, I would like to remind people of a resource from BrightFocus, a nice simple card that can fit into your coat pocket or bag titled Top 5 Questions to Ask Your Eye Doctor, which helps you prepare ahead of time—a simple front-and-back card. You can call 1-800-437-2423, and we will be happy to mail it out.

So, Dr. Bhutto and Dr. Lutty, a few questions, and I’ll let you pick who would like to answer them. One caller is asking whether flossing your teeth can prevent inflammation that might be harmful to the eye.

DR. LUTTY: I don’t know that—they are talking about the importance of your biome gut, which, of course, your mouth leads to your gut, but no one has looked at that in relation to AMD.
MICHAEL BUCKLEY: Our next question, getting back to smoking: “What about cigar smoke, does that also contain oxidants that you talked about a few minutes ago?”

DR. LUTTY: Absolutely, but the saving grace is that a lot of cigar smokers do not inhale. If you inhale cigars, they are just as bad as cigarettes.

MICHAEL BUCKLEY: Good to know. Another caller has heard that Caucasian women are at greater risk of AMD. She is wondering if that is true and, if so, why?

DR. LUTTY: That is true, and we actually do not know why that is. It is very interesting that African-Americans and Africans very rarely get AMD. There is a pigmentation propensity for AMD, which there have been many studies to look at. Imran, would you like to add to that?

DR. BHUTTO: Yes, like Jerry said, Caucasians have a lack of melanin—these are the dark pigmented substance in eyes. In Caucasians, they are lacking that, which is most likely the reason that Caucasians are at a higher risk than African-Americans.

MICHAEL BUCKLEY: What about the gender difference?

DR. LUTTY: Well, females live longer than males. I didn’t mention this before, but age is probably the second-greatest risk factor.

DR. BHUTTO: I think the latest research doesn’t show significant differences. I think both genders are equally affected.

MICHAEL BUCKLEY: Does this vary by exposure to environmental factors, like sun and other factors that we could control, or just a function of where we live in the world?

DR. LUTTY: That is an excellent question, I think where you live in the world is more related to maybe eating fish and eating a healthy diet as opposed to eating a lot of red meat. People who have a dominant fish diet have a lesser incidence of AMD. There was a great study done at Johns Hopkins in terms of light exposure done by Shelia West, who
looked at watermen, guys who worked on the Chesapeake Bay on fishing boats, who are exposed to huge amounts of sunlight. She compared their eyes and their eye disease to miners, who for at least 8 hours a day see no light whatsoever. The hypothesis was that the people exposed to light would have more AMD than the miners. That did not turn out to be true. There was a difference in one small thing, it was pigmented cells that move onto the cornea—they were more prominent in watermen. So light exposure, although it makes sense because it can induce oxidative stress, the experimental studies have not been able to link it to AMD.

MICHAEL BUCKLEY: That is interesting. Another question is related to fish and other foods. We have someone from Connecticut wondering, “Is it possible to decrease inflammation through simple herbs: turmeric, garlic, black pepper, etc.?“ Do any of those have impact on inflammation?

DR. LUTTY: Well, nutraceutical people would say yes, all of those have antioxidant effects, so it probably is a good idea. The one problem is, how much do you take? There haven’t been serious medical studies on those, so it becomes a recommendation of wise people in countries where those herbs are raised who have determined through the years what and how much you should take in.

MICHAEL BUCKLEY: A caller wanted to get back to some of the research and how it could lead to new drugs and treatments down the line. We get a lot of questions from people who receive injections. Would there be a different delivery method for potential new drugs that doesn’t involve injections?

DR. LUTTY: The drugs we are thinking about may be used topically or orally, that’s definitely a possibility. However, the drug companies do not like oral administration because the drug goes everywhere. There are some new ideas that say we can target the exact activated cells. We work with a group of medical engineers who specialize in a nanoparticle called a dendrimer, they have put dyes and drugs on these dendrimers, and we put them intravenously into animals that have had injury to their eye. Very interestingly, the tissues that took up the dendrimer were the
activated macrophages that I mentioned earlier. So we are hopeful that that may be a way to deliver drugs to the cells that seem to be activated—that you can take orally or an intravenous dose every month or so because the drug seems to be retained for a long time in the cells.

MICHAEL BUCKLEY: That is interesting. Leonard from New Jersey is wondering if there is any research going on about how we can restore vision that has been lost to AMD.

DR. LUTTY: There are two approaches. One is mechanical, where they put a photodiode array—basically a light-sensing chip—on the retina and have it rigged so that the impulses from that go to the neurons. Unfortunately, they have not engineered a chip that has enough pixels in it that you can actually see or find objects. You can see light and dark and a door or no door. But that is the best they have done so far. That is one approach, and that research is ongoing. There are several companies trying to make a better chip.

In our institute and around the country, there are many who are taking a second approach, which is stem cells—not necessarily embryonic stem cells, now we can make stem cells that are circulating your body, so they would be from your own set of precursors so you wouldn’t have an immune response to them. Imran and I have done some work in making those cells into blood vessel progenitors, and we’ve actually seen them go to blood vessels that have died and repopulate them. So we actually are going to try such experiments on our models for geographic atrophy where the choroidal blood vessels are prominently missing to see if those cells will home to those areas and maybe remake the choriocapillaris, which are the small blood vessels of the choroid. Our colleagues are looking at using those cells and making them into retinal-pigment epithelial cells, which are the pigmented bottom cells of retina and also photo receptors. That is a look into the future, like the chip. This is active research that is going on in both directions, so there is hope that could regenerate parts of the eye someday.

MICHAEL BUCKLEY: That is great! That is a very encouraging answer that gives us a lot of hope for the future. Before we wrap up, are there
any final bits of advice that you could give to people who have AMD or who care for someone who does?

DR. LUTTY: In terms of your health and delaying AMD, we talked about the important things like don’t smoke, do exercise, and taking antioxidant formulation is a very good idea.

I will also ask people to donate their eyes so people like us can move forward in research. That is done in most states by simply checking a box on the back of your driver’s license or state-issued identification.

DR. BHUTTO: Jerry nicely covered the important points. Taking antioxidants or an anti-inflammatory formulation can help in the progression of AMD, and I would advise, as Jerry said, to exercise and improve your lifestyle.

MICHAEL BUCKLEY: Well, thank you. This has been very helpful and a great opportunity to hear what’s new in research and how that carries over into people’s daily lives and their future. I would like to conclude by thanking Dr. Bhutto and Dr. Lutty for sharing their research for us today and answering a lot of great questions. We make this call available in both a transcript on our website, which can also be mailed out to you free of charge, as well as an audio file on iTunes and SoundCloud. We were very fortunate to get a lot of very good specific advice today that will be in the transcript but also in our publication Macular Degeneration: Essential Facts, which you can receive free of charge by calling 1-800-437-2423.

Looking forward to our next Chat, we are going to be very relevant to the seasons. For most of us in this country, the days are getting shorter and nights longer and darker. That is what we are going to look at on our next Chat, on November 30, 2016, as we head into the holiday season, and look at the impact of short days and long nights and how low light and other challenges of this time of year impact your vision health and your overall health and daily lives. To register call 1-800-437-2423. We hope that you can join us.
Dr. Bhutto and Dr. Lutty, thank you for being so helpful today and also for dedicating your careers in trying to improve sight for people all over the world. It’s really wonderful work. We want to thank you for all that you do.

**DR. BHUTTO:** Thank you. I especially want to thank BrightFocus for supporting our research. It is really a great support, and thank you for having us.

**MICHAEL BUCKLEY:** Our pleasure. To our listeners, thank you for joining us, you can always visit us on our website at www.BrightFocus.org or call toll-free at 1-800-437-2423. On behalf of everyone at BrightFocus, thank you very much.
Useful Resources and Key Terms

BrightFocus Foundation: 1-800-437-2423 or visit us at www.BrightFocus.org. Available resources include:

- Information on research funded by BrightFocus
- Amsler grid
- Macular Degeneration: Essential Facts
- Safety and the Older Driver
- The Top Five Questions to Ask Your Eye Doctor
- Clinical Trials: Your Questions Answered
- BrightFocus funded work of Dr. Bhutto and Dr. Lutty

Other resources related to this call—
- Wilmer Eye Institute http://www.Hopkinsmedicine.org/Wilmer
- Information on the AREDS and AREDS2 supplements
  - BrightFocus article “Are You Getting What You Need from Your AREDS Supplements?”
  - NIH’s National Eye Institute FAQ for patients

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