A PEEK AT THE COMPLEMENT PATHWAY


Experts share what we have learned so far, and how it might impact clinical practice–soon.

AN INTERVIEW WITH PETER K. KAISER, MD, AND CHARLES C. WYKOFF, MD, PHD

The complement pathway has been a hot topic in retina research for years. As several programs work their way through phase 3 trials, it may become increasingly relevant for the clinic. *Retina Today* sat down with two experts in the field, Peter K. Kaiser, MD, and Charles C. Wykoff, MD, PhD, to find out what all the fuss is about.

Retina Today: How has our understanding of the complement pathway evolved over the years?

Peter K. Kaiser, MD: The complement system, part of our innate immune system, is conserved across species and is designed to combat bacteria and foreign invaders. There are three activation pathways. The classical pathway is activated by antibodies binding to bacteria, initiating the cascade producing C3- and C5-convertase that leads to the formation of membrane attack complex (MAC) on the bacterial surface or activation of macrophages and inflammasomes via C3a and C5a. The MAC produces open pores in the cell membrane, thereby killing the bacteria.

The lectin pathway is similar, except you don't need antibodies. The body simply recognizes epitopes on a bacterial surface, which initiates the same cascade.

The most interesting pathway is the alternative pathway because our body was smart enough to say, "I don't know what I'm going to be up against, so, I'm going to constantly activate the complement cascade, and place activated C3b, which is called opsonization, on everything I see." And then the body inactivates the C3b through complement factor H (CFH) and complement factor I (CFI) to protect host cells from being damaged by the system.

We've always known that inflammation plays a role in AMD. Genome-wide association studies first identified that mutations in the gene coding CFH were associated with an increased risk of macular degeneration. Since then, other parts of the complement cascade have been identified to increase the risk. But more importantly, histopathologic staining around drusen, geographic atrophy (GA), and choroidal neovascularization reveals multiple components from the complement cascade. But we don't know which pathway is most involved. Researchers started to test the theory that blocking complement factors could slow AMD, and they attacked complement using drugs from cancer and other indications. Those studies weren't designed to test the drugs for ophthalmic use, and many of them failed. In addition, large prospective phase 3 studies with a complement factor D inhibitor, lampalizumab (Genentech/Roche), didn't meet their primary endpoints.

That really made us question whether we should attack complement. Maybe it was too late in the process, and we needed to do it earlier, or maybe we weren't attacking it in the right place. But since then, we have discovered newer drugs that have had better results.

RT: Why should busy retina surgeons brush up on the complement pathway now?

Charles C. Wykoff, MD, PhD: GA remains the largest unmet need in most retina clinics across the United States. We have nothing to treat this disease, and multiple studies have failed. Currently, all of the programs in late-stage human trials that are promising involve selective inhibitors of different steps within the complement cascade.

It's important that physicians understand the mechanisms of action of these therapies that are likely to be clinically available in a few years. However, while retina specialists are familiar with the mechanisms of action of anti-VEGF drugs and some of the nuances between VEGF-A, other VEGF family members, and the different VEGF receptors, the complement cascade is much more complicated.

The complement cascade involves the interaction of dozens of membrane-bound and fluid-phase proteins that are produced both in the liver and locally within the eye. Furthermore, many of the key molecules cleaved during complement propagation, including C3 and C5, have breakdown products with multiple physiologic functions. From a basic biology perspective, even the scientists working on elucidating the nuances of each of these molecules are clear

that we don't understand everything about the complement pathway. We are developing new therapies within an incomplete body of knowledge. Nonetheless, it's important that physicians understand the key molecules and mechanisms that we are targeting because these medicines will likely become relevant to clinical practice in the near future.

RT: Which therapeutics are showing promise?

Dr. Wykoff: The ultimate goal is to prevent the development of GA before it begins, but for now, the molecules in late-stage development are all attempting to slow the progressive enlargement of areas of GA. One trial program, GATHER, involves avacincaptad (Zimura, Iveric Bio), an inhibitor of C5 cleavage. The first pivotal trial studying avacincaptad, GATHER1, was positive, and the ongoing phase 3 GATHER2 trial is anticipated to have data this year.

The other program involves pegcetacoplan (Apellis Pharmaceuticals), an inhibitor of C3 cleavage. Pegcetacoplan was studied in the FILLY phase 2 trial, and in 2021, 1-year data was presented from the phase 3 DERBY and OAKS trials, which involved 1,258 patients; in OAKS, pegcetacoplan met the primary endpoint and in DERBY pegcetacoplan did not meet the primary endpoint.

There are other ongoing trial programs as well, including programs aiming to inhibit the MAC, C1Q in the classical pathway, complement factor D (one of which is an oral formulation), and additional C3 inhibitors; finally there are programs aiming to increase the down-regulators of the pathway, including CFH and CFI.

As incredibly promising as these trials are, their objectives may be disheartening for some patients; many patients with GA want to see better, especially those with foveal involvement. But the reality is that the therapeutics in phase 3 trials appear to be able to slow GA progression, probably not stop it all together, at least within the time frame of the studies to date. We are interested to see, as we treat these patients consistently for longer periods of time, if the differential between no treatment and treatment will grow.

Overall when considering the current data from both avacincaptad and pegcetacoplan, it appears that inhibition of the complement cascade at C3 or C5 leads to a slowing of GA growth by about 15% to 30%, with a greater reduction observed among patients with extrafoveal lesions, a phenotype well-recognized to be associated with a more rapid rate of GA growth than lesions that involve the fovea.

RT: What are some of the challenges researchers face?

Dr. Kaiser: Our regulatory environment only allows us to get a drug approved that prevents photoreceptor loss, which in this case means preventing GA growth. We know that the complement cascade is involved early in AMD, but proving that these molecules prevent photoreceptor loss requires a considerably longer study. You need to take patients with intermediate AMD, for example, and prove that they don't develop GA. This study would take 2 or 3 years.

Both of the drugs currently in phase 3 have shown that they can prevent the progression of incomplete retinal pigment epithelial (RPE) and outer retinal atrophy (iRORA) to complete RPE and outer retinal atrophy (cRORA), or GA. They also can prevent progression from intermediate AMD to iRORA or cRORA. Thus, it appears that both drugs, even though their primary outcomes have nothing to do with iRORA or conversion of drusen into iRORA, have a mechanism of action that works earlier than what is being tested in phase 3 clinical trials, which hopefully means we will start to treat patients earlier if these drugs get approved.

In addition, companies will hopefully develop longer-acting agents in the future. One company is using gene therapy to deliver recombinant CFI, which should help patients with the mutation have lifelong treatment against AMD. We know that complement inhibition is not an episodic type of treatment, it's going to be lifelong. The first step is getting a treatment to work, and the second area of intense research now is looking at ways to make that last longer, much longer.

RT: What are you most excited about as research continues for therapies targeting the complement pathway?

Dr. Kaiser: Complement modulation is an incredibly exciting avenue. We have a massive unmet need, and we are finally starting to see something that appears to work. The teaching has always been that there's no treatment for GA, which is true right now. But we hope to change that soon. ■

CHARLES C. WYKOFF, MD, PHD

- Director of Research, Retina Consultants of Texas/Retina Consultants of America, Houston, Texas; Deputy Chair for Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, Houston, Texas
- ccwmd@retinaconsultantstexas.com
- Financial disclosure: Research Grants/Scientific Advisor (Apellis, Iveric, Gyroscope, NGM)

PETER K. KAISER, MD

- Chaney Family Endowed Chair in Ophthalmology Research; Professor of Ophthalmology, Cleveland Clinic Lerner College of Medicine; staff surgeon in the vitreoretinal department at the Cole Eye Institute, Cleveland Clinic; founding director of the Digital Optical Coherence Tomography Reading Center at the Cole Eye Institute, all in Cleveland, Ohio
- pkkaiser@gmail.com
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