An old drug finds new purpose against retinal neovascularization

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Layton Smith, Ph.D. Credit: Sanford Burnham Prebys Medical Discovery Institute (SBP)

Researchers at Sanford Burnham Prebys Medical Discovery Institute (SBP) have found that the anti-malaria drug amodiaquine inhibits the apelin receptor protein, which helps drive the vascularization behind diabetic retinopathy, wet age-related macular degeneration (AMD) and other conditions. Because the drug has been approved to treat malaria for decades, it could move relatively quickly through the pipeline to help patients. The study was published in the journal *PLOS ONE*.

"We have a receptor that has no relationship to the malarial bug— - it just happens that this compound interacts with the receptor and turns it off," says associate professor Layton Smith, Ph.D., director, Drug Discovery Florida, and senior author of the paper. "This could be an enormous benefit. Wet AMD is the leading cause of blindness in the Western world, affecting millions of people."

Wet AMD, and similar conditions, are often treated with drugs that inhibit the VEGF protein, which promotes angiogenesis or blood vessel growth. These drugs can preserve sight, but do not work for all patients.

"They're great drugs, if you respond to them," says Smith. "But 30 percent of patients don't respond at all. Over time, many people lose their responsivity."

While using high-throughput chemical screening to identify small molecule compounds that boost apelin activity, Smith and colleagues were intrigued to find several that prevented the protein from activating the APJ receptor, a critical link in the apelin pathway.

The team knew apelin plays a role in embryonic blood vessel development. Unfortunately, the protein can be mistakenly turned on to cause aberrant vessel growth in adulthood. As a result, finding a good apelin inhibitor could be quite useful. One molecule that proved especially effective against apelin was amodiaquine, which has been

used for decades to prevent malaria.

"People take amodiaquine around the world for malarial prophylaxis," says Smith. "It was an interesting idea that we could come up with a new, non-VEGF- based therapy for these eye diseases."

In the study, amodiaquine suppressed blood vessel formation through both the apelin and VEGF pathways. In addition, the compound reversed vascular eye damage in animal models. Further study showed the compound blocked the receptor's function in a unique way: Instead of occupying the site to which apelin binds to activate the receptor, amodiaquine binds to another area, likely changing its conformation and thus inhibiting apelin's ability to turn it on and drive blood vessel growth.

One of the advantages of re-tasking an existing drug is that its safety profile is already established. Amodiaquine is well- tolerated, though it does cause liver toxicity over time. Smith believes this may not be a problem when treating eye disease, as the compound could be administered exclusively in the eye rather than being given systemically.

Because the drug is so well known, it could potentially take a streamlined path to patients. Since safety tests have already been done, a drug company would only have to prove its efficacy.

In addition to studying the existing drug, chemists on the team tweaked the amodiaquine molecule to make it even more effective. However, because these alterations created a distinct compound, any trial sponsors would have to prove its safety, extending the regulatory process.

Amodiaquine could be used by itself, but Smith and his team are curious to see if it works with existing anti-VEGF treatments.

"We want to know if there's synergy," says Smith. "These VEGF

inhibitors are quite expensive, but we might be able to use less of them in combination with amodiaquine, or a similar small molecule, which are inexpensive by comparison."

Provided by Sanford Burnham Prebys Medical Discovery Institute