AMD PIPELINE UPDATES: A DIFFERENT WAY OF THINKING ABOUT THE COMPLEMENT CASCADE

A new layout of the complement cascade highlights the major changes to this year's two-sided poster.

BY PETER K. KAISER, MD

We may look back on 2023 as a breakthrough year. After decades of research and a handful of almost-there drug candidates, the US Food and Drug Administration determined that two different treatments for geographic atrophy (GA) were safe and effective. Rather than holding our patients' hands as they marched toward inevitable vision loss, we retina specialists may be able to avert devastating vision loss in a significant number of patients.

But researchers aren't satisfied with only two options. Dozens of other pipeline candidates remain under investigation for the treatment of GA, many of them complement inhibitors like the approved treatments, pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izervay, Iveric Bio). We lack the depth of experience to know whether complement inhibition will ultimately prove to be the best long-term approach to GA therapy. But for now, we have a breakthrough—and we'll take it.

With all the focus on dry AMD and GA, it's easy to forget that seismic shifts have come (or are coming) in wet AMD therapy. The era of biosimilars has arrived, and we should expect more biosimilar candidates under investigation to clear regulatory hurdles in the coming years. Real-world evidence of the safety and efficacy of dual inhibition therapy with faricimab (Vabysmo, Genentech/Roche) has shown that this approach works. To that end, we dedicated significant space in this year's pipeline update to educating readers on multitarget therapies that were recently approved or are under investigation. The next age of wet AMD therapy may very well rely on simultaneous inhibition of several targets, and the data researchers publish in the coming years will inform the viability of this approach. ■

Remember that the drugs listed in this poster are not exhaustive. If there is a drug that you think we should include in next year's poster, email us at cdeming@bmctoday.com.

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RETINA PIPELINE 2024
A VIEW INTO ONGOING INNOVATION
WET AMD

If you would like to submit an addition for next year's poster, please email Peter K. Kaiser, MD, at pkkaiser@gmail.com and Cara Deming at cdeming@bmctoday.com.

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RT Retina Today

Extracellular VEGF Pathways

VEGF: PIGF, C, B, A

- pegaptanib *(Bausch + Lomb)* FDA APPROVED
- ranibizumab *(Genentech/Roche)* FDA APPROVED
- Port Delivery System with ranibizumab *(Genentech/Roche)*

biosimilars:
- Xlucane *(Bausch + Lomb)*
- ranibizumab-nuna *(Samsung/Biogen)* FDA APPROVED
- PF582 *(Pfenex)*
- ranibizumab-eqrn *(Formycon/Coherus)* FDA APPROVED
- ranibizumab-razumab *(Intas)*
- SJP-0133 *(Senju Pharma)*
- LUBT010 *(Lupin)*
- Ongavia *(Teva Pharmaceuticals)*
- BCD100 *(BIOCND/Qilu)*
- CKD-701 *(Chong Jun Dang)*

- bevacizumab OFF-LABEL

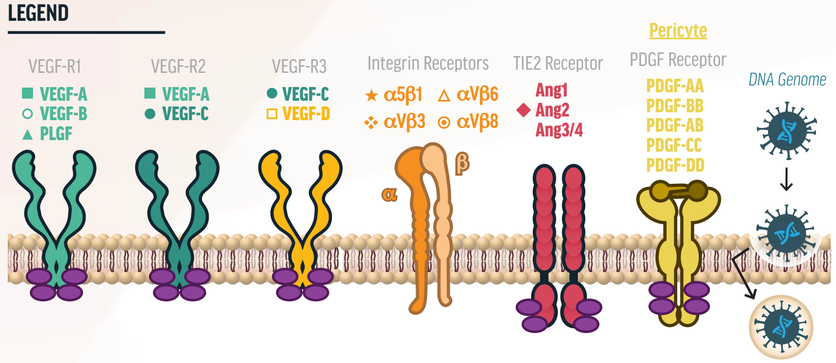
biosimilars:
- bevacizumab-vikg *(Outlook Therapeutics)*
- HLX04-O *(Hengenix Biotech)*
- TAB014 *(Zhaoke Ophthalmology)*
- CT-P16 *(Celltrion)*
- HLX04-O *(Shanghai Henlius Biotech)*
- Alymsys *(Amneal Pharmaceuticals/mAbxience)*
- AK-3008 *(Anhui Anke Biotechnology)*
- MIL-60 *(Beijing Mabworks Biotech)*

- brolucizumab *(Novartis)* FDA APPROVED
- abicipar pegol *(Molecular Partners)*
- KNP-301 *(Kanaph Therapeutics)*
- tarcocimab tedromer *(Kodiak Sciences)*
- aflibercept *(Regeneron)* FDA APPROVED
- High-dose aflibercept *(Regeneron)* FDA APPROVED

biosimilars:
- ALT-L9 *(Alteogen/Kissei)*
- M710 *(Mylan/Momentra)*
- SB15 *(Samsung)*
- CHS-2020 *(Coherus)*
- SOK583A1 *(Sondoz/Novartis)*
- ABP 938 *(Amgen)*
- OT-702 *(Ocumension Therapeutics/Shandong Boan)*
- FY203 *(Formycon/BioEq)*
- CT-P42 *(Celltrion)*
- AVT-06 *(Alvotech)*

- conbercept *(Kanghong Biotech)* CDE APPROVED
- conbercept *(Kanghong Biotech)*
- OPT-302 *(Opthea)*

LEGEND



TIE2 Activation Pathways

- faricimab *(Genentech/Roche)* FDA APPROVED
- BI 836880 *(Boehringer Ingelheim)*
- RO-101 *(RevOpsis)*
- ASKG-712 *(AffaMed, AskGene Pharma)*
- ABP-201 *(AbPro)*

Gene Therapy

- RGX-314 *(Regenxbio, AbbVie)*
- ADVM-022 *(Adverum Biotechnologies)*
- 4D-150 *(4D Molecular Therapeutics)*
- EXG-102-031 *(Exogenesis Bio)*

Integrin Pathways

- PAN risuteganib *(Allegro Ophthalmics/Senju Pharma)*
- AG-73305 *(Allgenesis Biotherapeutics)*
- AXT107 *(AsclepiX Therapeutics)*

Other Pathways

- CVX-51401 *(CavtheRx)* – **Caveolin Modulator**
- APX3330 *(Ocuphire Pharma)* – **Ref-1 Inhibitor**
- EXN407 *(Exonate)* – **SRPK1 Inhibitor**
- aganirsen *(Gene Signal)* – **Inhibition of Insulin Receptor Substrate 1 (IRS-1)**
- PL9654 *(Palatin)* – **Melanocortin Receptor Agonist**
- UBX1325 *(Unity Biotechnology)* – **Bcl-xL inhibitor**
- EOM147 *(EOM Pharmaceuticals)* – **Squalamine analog**

MULTI-TARGETS FOR WET AMD

The earliest iterations of approved treatments for wet AMD blocked VEGF-A, soon to be followed by an option that blocked VEGF-A, VEGF-B, and PlGF. Despite efforts to show the safety and efficacy of other approaches, no drug approved for the treatment of wet AMD relied on a method other than VEGF and PlGF inhibition—that is, until the approval of faricimab (Vabysmo, Genentech/Roche) in January 2022.

Here's some of the latest news on multitargeted therapy for wet AMD.

VEGF/Ang-2 inhibition seeks to counter upregulation of Ang-2, which has been implicated in vascular leakage, inflammation, and neovascularization in wet AMD.[1] Faricimab is the only therapeutic agent approved for this approach, but researchers continue to evaluate other drug candidates leveraging dual inhibition of VEGF and Ang-2.

VEGF-C/D inhibition has been evaluated in a phase 2b study.[2] Current formulations and approaches use intravitreal injection therapy that occurs alongside conventional anti-VEGF or anti-VEGF/Ang-2 treatment. In phase 2b, patients with wet AMD who received high-dose OPT-302 (Opthea) and ranibizumab (Lucentis, Genentech) gained significantly more letters than those who received monotherapy (14.2 vs 10.8 letters, $P = .01$).[2]

Integrin inhibition has the potential to be used as a primary therapy, an adjunctive therapy, or as a treatment for patients whose disease has not responded to other treatments.[3] The integrins $\alpha5\beta1$, $\alpha v\beta3$, and $\alpha v\beta5$ are among the targets under investigation by researchers evaluating various pipeline candidates.

1. Canonica J, Foxton R, Garrido MG, et al. Delineating effects of angiopoietin-2 inhibition on vascular permeability and inflammation in models of retinal neovascularization and ischemia/reperfusion. *Front Cell Neurosci*. 2023;17:1192464.
2. Jackson TL, Slakter J, Buyse M, et al; Opthea Study Group Investigators. A randomized controlled trial of OPT-302, a VEGF-C/D inhibitor for neovascular age-related macular degeneration. *Ophthalmology*. 2023;130(6):588-597.
3. Bhatwadekar AD, Kansara V, Luo Q, Ciulla T. Anti-integrin therapy for retinovascular diseases. *Expert Opin Investig Drugs*. 2020;29(9):935-945.

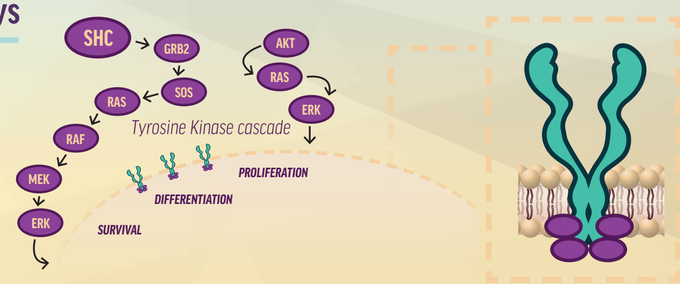
Tyrosine Kinase Inhibition

The tyrosine kinase cascade is activated when VEGF binds to its receptor, and may be effective at interacting with VEGF receptors 1, 2, and 3,[1] and some of the TKIs in the retina pipeline have been used in the oncologic space.[2] So far, trials assessing the safety and efficacy of TKIs have evaluated approaches that include intravitreal, oral, and microparticle-based sustained delivery methods.[1]

1. Wolf AT, Harris A, Oddone F, Siesky B, Verticchio Vercellin A, Ciulla TA. Disease progression pathways of wet AMD: opportunities for new target discovery. *Expert Opin Ther Targets*. 2022;26(1):5-12.
2. Jackson TL, Boyer D, Rosenfeld PJ. Oral Tyrosine kinase inhibitors for neovascular age-related macular degeneration. *JAMA Ophthalmol*. 2019;137(7):854-855.

Tyrosine Kinase Inhibitor (TKI) Pathways

- OTX-TKI/axitinib *(Ocular Therapeutix)*
- GB-102/sunitinib *(Graybug Vision)*
- PAN 90806/CP-547,632 *(PanOptica)*
- CLS-AX/axitinib *(Clearside Biomedical)*
- EYP-1901/vorolanib *(EyePoint Pharmaceuticals)*
- AIV007 *(AiViva Biopharma)*
- Lenvatinib *(Merck/Eisai)*



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RETINA PIPELINE 2024
A VIEW INTO ONGOING INNOVATION
DRY AMD

1 Suppress Inflammation

Targeting the Complement Cascade

1. **ANX007** *(Annexon)* – **C1q Inhibition**
2. **Pegcetacoplan** *(Apellis)* – **C3 Inhibition** FDA Approved
3. **CB-2782-PEG** *(Catalyst Biosciences)* – **C3 Protease**
4. **NGM621** *(NGM Biotherapeutics)* – **C3 Inhibition**
5. **AMY106** *(Amyndas Pharmaceuticals)* – **C3 Inhibition**
6. **SLN501** *(Silence Therapeutics/Mallinckrodt Pharmaceuticals)* – **siRNA vs C3**
7. **PRO657** *(Mosaic/Ocular Therapeutix)* – **C3 Inhibition**
8. **iPTACOPAM** *(Novartis)* – **Bb Inhibition**
9. **AGN-151151** *(AbbVie)* – **C5 Inhibition**
10. **cEMDISIRAN** *(Alnylam Pharmaceuticals)* – **siRNA C5 mRNA Inhibiton**
11. **KNP-302** *(Kanaph Therapeutics)* – **C3b and CD59 Inhibition**
12. **Avacincaptad pegol** *(Iveric Bio)* – **C5 Inhibition** FDA Approved
13. **ALXN1720** *(Alexion)* – **C5 Inhibition**
14. **PASylated Nomacopan** *(Akari Therapeutics)* – **Bispecific Inhibition of C5 & LTB4**
15. **JNJ-1887** *(Janssen)* – **MAC Inhibition Gene Therapy**
16. **Ionis-FB-LRx** *(Ionis/Roche)* – **Complement Factor B Inhibition**
17. **ALXN2040** *(Alexion Pharmaceuticals/AstraZeneca)* – **Complement Factor D Inhibition**
18. **BCX9930** *(BioCryst Pharmaceuticals)* – **Complement Factor D Inhibition**
19. **sFH GTx** *(Aevitas Therapeutics)* – **Complement Factor H Gene Therapy**
20. **CFH GTx** *(Syncona)* – **Complement Factor H Gene Therapy**
21. **GEM103** *(Gemini Therapeutics)* – **Recombinant Complement Factor H Therapy**
22. **AAV.SFH** *(Aevitas)* – **Short-Form Complement Factor H Gene Therapy**
23. **AVD-104** *(Aviceda Therapeutics)* – **Complement Factor H Activation**
24. **CB-4332** *(Catalyst)* – **Recombinant Complement Factor I**
25. **PPY 988** *(Gyroscope Therapeutics/Novartis)* – **Complement Factor I Gene Therapy**
26. **OMS721** *(Omeros)* – **Blocks MASP-2**
27. **OMS906** *(Omeros)* – **Blocks MASP-3**
28. **KNP-301** *(Kanaph Therapeutics)* – **Blocks C3b/Anti-VEGF**
29. **IBI302** *(Innovent Biologics)* – **sCR1 Inhibition/Anti-VEGF**
30. **NM5072** *(NovelMed)* – **Properdin Inhibition**

TMi-018 *(Translatum Medicus Inc)* – **Blocks M1 Transcriptome Expression**

2 Reduce Toxic By-Product Accumulation

Prevents Amyloid Aβ Oligomer Assembly
GAL-101 *(Galimedix Therapeutics/Iacta)*
ALZ-801 *(Alzheon)*
VUTRISIRAN *(Alnylam Pharmaceuticals)* – **siRNA TTR Silencer**

3 Visual Cycle Modulation

ALK-001 *(Alkeus Pharmaceuticals)*

4 Stem Cells

Human Embryonic Stem Cells (hESCs)
OpRegen *(Lineage Cell Therapeutics, Genentech/Roche)*
CPCB-RPE1 Implant *(Regenerative Patch Technologies)*
MA09-hRPE *(Astellas Pharma)*
hESC RPE Sheets *(Pfizer)*
HLS001 Cell Sheets *(Sumitomo Dainippon Pharma)*
Umbilical Stem Cells (hUTCs)
Human Umbilical Stem Cells *(jCyte)*

5 Other Approaches

Inflammasome Inhibition
kamuvudine *(Inflammasome Therapeutics)*
Xiflam *(OcuNexus Therapeutics)*

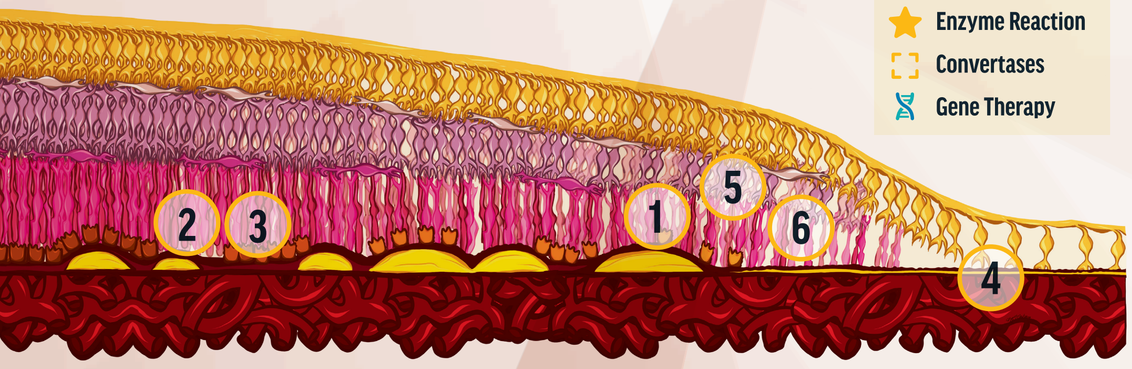
Matrix Modulation
doxycycline *(Galderma Labs)*

Other Mechanisms
OCU410 *(Ocugen)* – **Gene Therapy Delivers RORA Anti-inflammatory Protein**
CT1812 *(Cognitive Therapeutics)* – **Selective σ-2 Antagonist**

6 Neuroprotection

Repair Mitochondrial Dysfunction/Oxidative Stress
elamipretide *(Stealth Biotherapeutics)*
risuteganib *(Allegro Ophthalmics)*
photobiomodulation *(LumiThera)*
Oculogenex – **Gene Therapy to Reduce Oxidative Stress**

LEGEND
- Enzyme Reaction
- Convertases
- Gene Therapy



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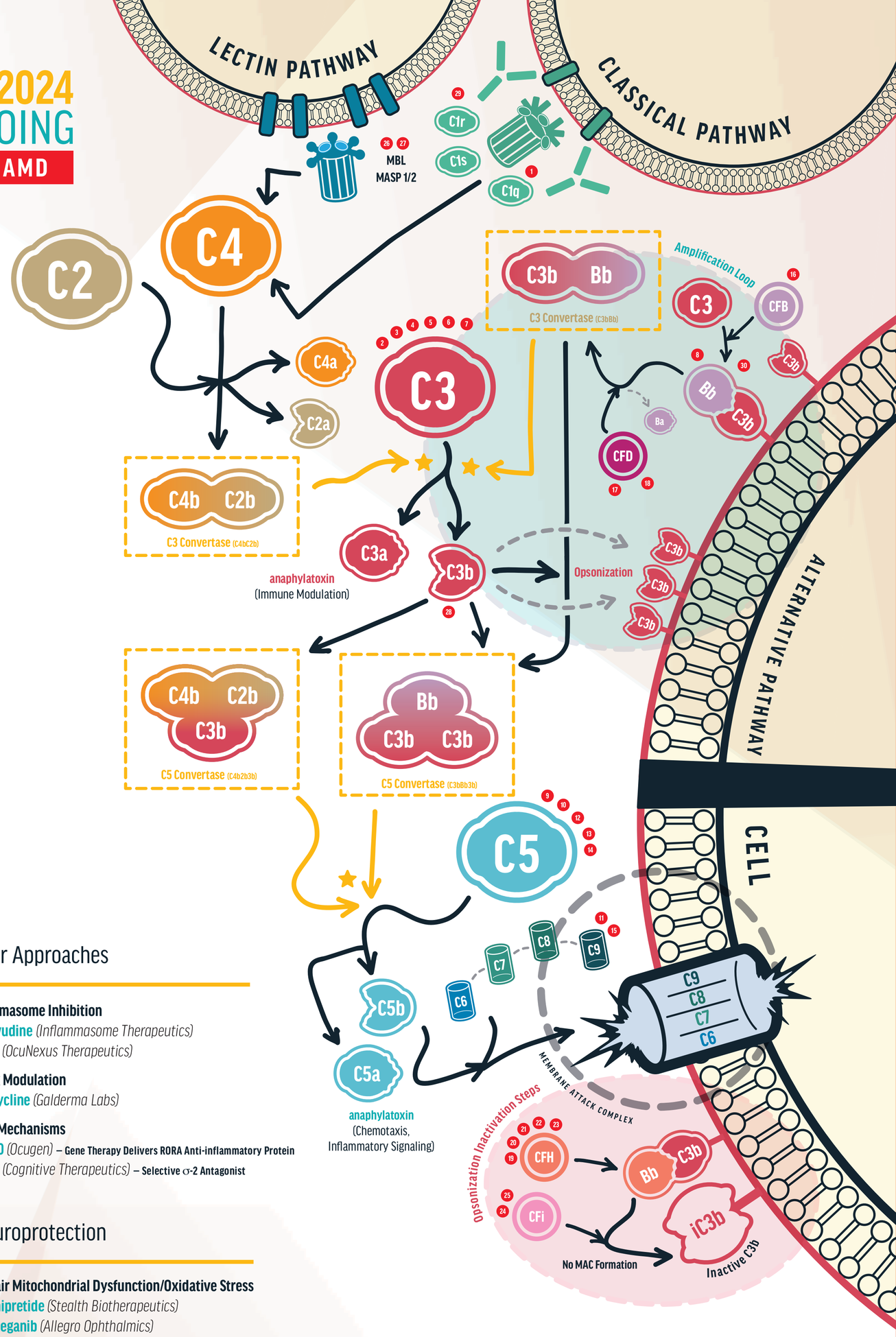

Gene Therapy: A Potential One-Time Treatment for GA

Five gene therapy–based investigational interventions seek to inhibit MAC formation, either via upregulation of CFH or CFI (leading to inactive C3b) or via increased production of CD59 (a cell surface protein that inhibits MAC formation).[1] The exact routes of administration remain under investigation.

Two other investigation gene therapies use a strategy outside of the complement pathway. OCU410 (Ocugen) aims to deliver RORα (or *RORA*) proteins, which have been implicated in controlling inflammation.[2] Oculogenex seeks to reduce oxidative stress via gene therapy, using a mechanism that has not yet been widely articulated.

COMPLEMENT INHIBITION
- **JNJ-1887** *(Janssen)* – **MAC Inhibition Gene Therapy**
- **sFH GTx** *(Aevitas Therapeutics)* – **Complement Factor H Gene Therapy**
- **CFH GTx** *(Syncona)* – **Complement Factor H Gene Therapy**
- **AAV.SFH** *(Aevitas)* – **Short-Form Complement Factor H Gene Therapy**
- **PPY 988** *(Gyroscope Therapeutics/Novartis)* – **Complement Factor I Gene Therapy**

PROTEIN DELIVERY
- **OCU410** *(Ocugen)* – **Gene Therapy Delivers RORA Anti-inflammatory Protein**

NEUROPROTECTION
- **Oculogenex** – **Gene Therapy to Reduce Oxidative Stress**

1. Khan H, Aziz AA, Sulahria H, et al. Emerging treatment options for geographic atrophy (GA) secondary to age-related macular degeneration. *Clin Ophthalmol.* 2023;17:321-327.
2. Nejati Moharrami N, Bjørkøy Tande E, et al. RORα controls inflammatory state of human macrophages. *PLoS One.* 2018;13(11):e0207314.