Where do we stand

- Anti-VEGF intravitreal injection is the current gold standard for neovascular AMD treatment
- Even with regular injection, 20% lose vision, 60% do not gain 3 or more letters on ETDRS chart
- Anti-VEGF stops permeability but doesn’t stop the progression of the disease. 50% of patients develop submacular scar even with regular injection
- Real world patients are under treated
How to Improve

- Increase Efficacy
- Decrease Injection Frequency

Current anti-VEGF agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macugen (Pegabtanib)</td>
<td>Synthetic RNA based oligonucleotide targeting VEGF₁₆₅</td>
<td>December 2004</td>
</tr>
<tr>
<td>Avastin (Bevacizumab)</td>
<td>Humanized monoclonal IgG₁ antibody against VEGF</td>
<td>February 2004 for metastatic colorectal cancer Used off-label for nAMD</td>
</tr>
<tr>
<td>Lucentis (Ranibizumab)</td>
<td>Humanized monoclonal IgG₁ antibody fragment against VEGF</td>
<td>June 2006</td>
</tr>
<tr>
<td>Eylea (Aflibercept)</td>
<td>VEGF-trab, recombinant protein formed by fusing second domain of VEGF receptor 1 with third domain of VEGF receptor 2 to the Fc portion of human IgG1</td>
<td>November 2011</td>
</tr>
</tbody>
</table>
Phases of clinical trials

- Phase 1 (safety phase)
- Phase 2 (Efficacy phase)
- Phase 3 (comparison against gold standard)
- Phase 4 (Post marketing surveillance)

New Anti-VEGF molecules

- Anti-VEGF + Tie 2 receptor modulator
- Anti-VEGF + Anti-PDGF
- Sustained release treatments
- Topical treatments
New Anti-VEGF molecules

Anti-VEGF + Tie 2 receptor modulator

Sustained release treatments

Anti-VEGF + Anti-PDGF

Topical treatments

Brolucizumab (Novartis)

- What's new?
  In Maintenance phase injection is every 3 months
- Mechanism:
  Humanized single chain antibody fragment for VEGF-A
- Results:
  Phase 3 study ongoing
  HAWK and HARRIER trials
  Brolucizumab 6mg is non inferior to aflibercept 2mg at 1 year according to press release in June 2017
Abicipar pegol (Allergan)

- What’s new?
  In Maintenance phase injection is every 3 months
- Mechanism:
  synthetic protein that block all isoforms of VEGF-A
- Results:
  phase 3 study ongoing
  Phase 3 will compare Abicipar at 2 month interval, Abicipar at 3 month interval and ranibizumab at monthly interval

OPT-302 (Opthea)

- What’s new?
  Anti-VEGF C and D
- Results:
  phase 2 study ongoing
  In Phase 1 study, higher efficacy when combined with ranibizumab than ranibizumab monotherapy.
New Anti-VEGF molecules

Anti-VEGF + Tie 2 receptor modulator

Sustained release treatments

Anti-VEGF + Anti-PDGF

Topical treatments

New Anti-VEGF molecules

Anti-VEGF + Tie 2 receptor modulator

Sustained release treatments

Anti-VEGF + Anti-PDGF

Topical treatments
Anti platelet derived growth factor (Anti-PDGF)

- PDGF promotes recruitment, maturation and survival of pericytes.
- Pericytes cover the endothelial cells of capillaries and can secrete VEGF-A by paracrine signalling, thereby providing anatomical and physiological barriers to anti-VEGF A.
- combination of Anti-VEGF and Anti-PDGF can enhance efficacy of Anti-VEGF A.

DE-120 (Santen Pharma)

- What’s new?
  Single molecule with anti-VEGF A and anti-PDGF activity
- Results:
  Phase 2 ongoing
  Compare DE-120 monotherapy to combination therapy with aflibercept
X-82 (Tyrogenex)

- What’s new?
  Oral anti-PDGF and anti-VEGF A
- Results:
  phase 2 ongoing
  compare X-82 with as needed aflibercept to aflibercept fixed dose.

New Anti-VEGF

- Anti-VEGF + Tie 2 receptor modulator
- Sustained release treatments
- Anti-VEGF + Anti-PDGF
- Topical treatments
New Anti-VEGF

Anti-VEGF + Tie 2 receptor modulator

Sustained release treatments

Anti-VEGF + Anti-PDGF

Topical treatments

Tie 2 receptor modulator

- Tie 2 receptors are expressed on endothelial cells. Their activation results in stabilization of vasculature and limiting permeability.

- Angiopoietin-1 (Ang-1) is a ligand that activates the receptor. Angiopoietin -2 (Ang-2) is a competitive antagonist to Ang-1.

- The enzyme vascular endothelial protein tyrosine phosphatase (VE-PTP) inactivates the receptor.
**Nesvacumab (Regeneron)**

- **What’s new?**
  Ang-2 inhibitor

- **Results:**
  phase 2 ongoing
  Compare combination between aflibercept and nesvacumab to aflibercept monotherapy

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**RG7716 (Roche)**

- **What’s new?**
  Bispecific antibody against Ang-2 and VEGF-A

- **Results:**
  phase 2 ongoing
  Phase 2 compares ranibizumab monotherapy, RG7716 monotherapy and combination between them
New Anti-VEGF

- Anti-VEGF + Tie 2 receptor modulator
- Anti-VEGF + Anti-PDGF

Sustained release treatments
Topical treatments
**PAN-90806 (PanOptica)**

- **What’s new?**
  - VEGF-A inhibitor eye drop
- **Results:**
  - **finished phase 1**
    In phase 1, monotherapy was tried in 50 naïve patients and results were comparable to those of currently available anti-VEGF therapies

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**LHA510 (Alcon)**

- **What’s new?**
  - eye drops, anti-VEGF A
- **Results:**
  - **phase 2 ongoing**
    Phase 2 will investigate whether addition of LHA510 to ranibizumab injection would decrease the injection frequency
Squalamine Lactate (Ohr Pharmaceutical)

- What's new?
  - eye drops, prevent signaling of receptors VEGF-1, VEGF-2, PDGF, b-FGF

- Results:
  - phase 3 ongoing
  - In phase 2: combination with ranibizumab showed VA benefit for lesion size <10mm²
New Anti-VEGF

Anti-VEGF + Tie 2 receptor modulator
Anti-VEGF + Anti-PDGF
Sustained release treatments
Topical treatments

Ranibizumab port delivery system (Genetech)

- What's new?
  Nonbiodegradable port fixed to the sclera with a reservoir filled in the office

- Results:
  phase 2 ongoing
  Phase 1 results showed that it improved VA to a greater degree than monthly ranibizumab at 12 mth follow up
  Endophthalmitis and vitreous hemorrhage are side effects
### Intravitreal depot injections

<table>
<thead>
<tr>
<th>Agent</th>
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<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogel anti-VEGF depot (Ocular Theraputix)</td>
<td>biodegradable hydrogel contain anti-VEGF A particles</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>ENV1305 (Envisia Therapeutics)</td>
<td>nanoparticles containing VEGF-A inhibitors</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Durasert (pSvidia corp)</td>
<td>bioerodible implant contain TKI that inhibits VEGF-A and PDGF</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>GB-102 (GrayBug Vision)</td>
<td>TKI against VEGF-A and PDGF. erodable nanoparticles that slowly degrade and remain away from visual axis</td>
<td>Pre-clinical</td>
</tr>
</tbody>
</table>

### Gene therapy

- The eye is a good site for gene therapy due to accessibility, tight blood ocular barrier, immune privileged site.
- Non harmful viruses are used as conduits for genetic material.
- Current viruses used are adeno associated virus (AAV) and lentivirus
AVA-101 (Ocular Biofactory)

- What’s new?
  AAV injected subretinal after PPV produce anti-VEGF A continuously
- Results:
  phase 2 finished
  In phase 2 no significant difference in VA was obtained at 1 year when AVA-101 was added to PRN ranibizumab. Difference in rescue injections was not large (2 vs. 4)

RGX-314 (Regenexbio)

- What’s new?
  AAV8 carrying genes for anti-VEGF expression. Delivered subretinal after PPV
- Results:
  phase 1 started in 2017
Retinostat (Oxford Biomedica)

- What’s new?
  EIAV encoding endostatin and angiostatin delivered subretinal after PPV

- Results:
  finished phase 1
  21 patients with advanced nAMD poorly responsive to anti-VEGF A were treated with Retinostat. At 1 year, only 1 patient showed reduction of retinal fluid compared to baseline

References


Thank you!