A novel oral plasma kallikrein (PKal) inhibitor KV123833 blocks VEGF-mediated retinal vascular hyperpermeability in a murine model of retinal edema (#3464)

Nivetha Murugesan, Allen C. Clermont, Louise J. Rushbrooke, Peter A. Robson, Robrecht Thoonen, Stephen J. Pethen, Sally L. Hampton & Edward P. Feener
Diabetic Macular Edema (DME)

- Approximately 900,000 patients in the United States have active DME and are at serious risk of vision loss\(^1\)
- DME is caused by breakdown of the blood-retinal barrier resulting in the leakage of fluid and circulating proteins into the neural retina\(^2\)

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Source: (1) Zhang X et al. JAMA. 2010;304(6):649-656; (2) Duh et al, JCI Insight 2017, July 20, 2(14)
40% of Eyes with DME have Minimal Visual Improvement in Response to Ranibizumab at 12 weeks

- Post hoc analysis of Protocol I: Early and Long-term responses

Mean BCVA response among stratified ranibizumab treated eyes *

<table>
<thead>
<tr>
<th>Mean Change: 12 weeks</th>
<th>Eyes</th>
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<tbody>
<tr>
<td>15.2 letters</td>
<td>37%</td>
</tr>
<tr>
<td>(126 of 340)</td>
<td></td>
</tr>
<tr>
<td>6.9 letters</td>
<td>23%</td>
</tr>
<tr>
<td>(79 of 340)</td>
<td></td>
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<tr>
<td>-0.3 letters</td>
<td>40%</td>
</tr>
<tr>
<td>(135 of 340)</td>
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Plasma Kallikrein and VEGF do not Correlate in DME Vitreous

- Not all DME patients have increased VEGF
- All patients show increased PKal

Mainly PKal increased
VEGF & PKal increased

DME Patients with high PPK and low VEGF

The Kallikrein Kinin System

~50µg/ml in plasma

Contact Activation System

Tissue kallikrein (hK1)

Prekallikrein

FXIIa

FXII

Plasma kallikrein

Contact

Activation

System

Inactive fragments

ACE,NEP

[des-Arg9]-bradykinin

Bradykinin (1–9)

Kininase I

ACE,NEP

LK

HiK

BK1-Rec

BK2-Rec

Inflammation & Edema

Plasma Kallikrein Mediates Retinal Vascular Permeability and Edema Induced by Multiple Triggers

<table>
<thead>
<tr>
<th>Factors implicated in triggering macular edema:</th>
<th>% Reduction in retinal vascular permeability/edema with:</th>
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<tbody>
<tr>
<td></td>
<td>Plasma Kallikrein Inhibitor</td>
</tr>
<tr>
<td>Diabetes/Hyperglycemia</td>
<td>-83%(^1)</td>
</tr>
<tr>
<td>Inflammation (TNF(\alpha))</td>
<td>-52%(^3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-70%(^4)</td>
</tr>
<tr>
<td>Hemorrhage (carbonic anhydrase)</td>
<td>-81%(^5)</td>
</tr>
<tr>
<td>VEGF</td>
<td>-57%(^3)</td>
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VEGF increases Plasma Kallikrein levels in the Retina


Green – endothelial cells (CD31)
Red – plasma prekallikrein (PPK)
Plasma Prekallikrein contributes to VEGF-induced Retinal Edema in Mice

- Knock-out of plasma prekallikrein reduced retinal edema triggered by intravitreal injection of VEGF
- Plasma kallikrein activity mediates, in part, the edematous effects of VEGF on the retina

KV123833: Pharmacological Profile

- MW: < 500 daltons
- Human Pkal Ki: 3nM
- > 500 fold selectivity vs. serine proteases
- Solubility: >500 µg/ml (aqueous and gastric fluid)
- Oral bioavailability: 36% (rats)

<table>
<thead>
<tr>
<th>Species PKal</th>
<th>KV123833 IC$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>11.0nM ± 6.2</td>
</tr>
<tr>
<td>Mouse</td>
<td>14.8nM ± 5.7</td>
</tr>
<tr>
<td>Rat</td>
<td>17.5nM ± 8.4</td>
</tr>
</tbody>
</table>
Ex-Vivo Assay to Measure Plasma Kallikrein Activity in Whole Plasma

Dextran sulfate-stimulated kininogen (HK) cleavage in undiluted human plasma

- KV123833 is protective against HK cleavage in undiluted human plasma
Plasma and Retina exposure of KV123833 following systemic administration in mice using Alzet 1003D osmotic pumps

- VEGF increases retinal exposure of circulating KV123833

**Plasma Exposure**

**Retinal Exposure**

[Graph showing plasma and retinal exposure of KV123833 and VEHICLE]
Systemically administered PKi inhibitor KV123833 reduces VEGF-induced RVP in mice

- KV123833: 1.92 mg/kg/day (2mg/ml in 10% PEG400/90% PBS (v/v))
- 1003D Alzet pumps inserted s.c. in mice
Oral Pharmacokinetics of KV123833 in mice

- Oral gavage of 45 mg/kg KV123833 in mice maintains plasma exposure over 137 ng/ml for about 9 hours

Mean Plasma Exposure ofKV123833 (ng/mL)
Orally administered PKal inhibitor KV123833 is protective against VEGF-induced retinal leakage in mice

- GAVAGE 1 (VEH/833)
- IVT VEGF/PBS
- GAVAGE 2 (VEH/833)
- GAVAGE 3 (VEH/833)
- EVANS BLUE
- Retina & Plasma collection
- Retinal EB assay

- Nominally 50mg/kg bid (in 10% DMSO/10% Cremophor/80% H2O)
Conclusions

- Orally administered PKal inhibitor KV123833 is highly protective against VEGF-induced retinal edema in mice.

- Intravitreal injection of VEGF increases retinal exposure of circulating KV123833 suggesting that retinal vascular hyper-permeability increases drug distribution to the retina.

- Previous work has implicated plasma kallikrein in mediating VEGF-independent DME.

- This current study suggests that oral PKal inhibitors may also provide an opportunity to reduce the edematous effects of VEGF in DME.
Diabetic Retinopathy

- Retina ischemia
- Breakdown of the BRB, leaky microaneurysms, retinal hemorrhages

- VEGF
- Plasma Kallikrein system

Anti-VEGF therapies

Anti-PKal Therapies
- IVT injection KVD001
- Oral PKal Inhibitor

Diabetic Macular Edema
Study of the Intravitreal Plasma Kallikrein Inhibitor, KVD001, in Subjects With Center-Involving Diabetic Macular Edema (ciDME)

- Approximately 123 patients who have discontinued treatment with anti-VEGF therapy and who still have significant edema and reduced visual acuity
- Sham-controlled, double-masked clinical trial will evaluate two doses
- Efficacy endpoints include best corrected visual acuity (BCVA), central subfield thickness (CST), and the diabetic retinopathy severity scale (DRSS)
- ClinicalTrials.gov Identifier: NCT03466099