Supplemental Figure Legends

Supplemental Figure 1. Expression of ANGPTL4 in patients with nvAMD.

(**A** and **B**) Aqueous levels of ANGPTL4 in treatment-naïve patients with active nvAMD (i.e., nvAMD patients who have never received anti-VEGF therapy; nvAMD UnTx; A) or patients with nvAMD previously treated with anti-VEGF therapy 12 or more weeks prior to sample collection (nvAMD Recurrent; B) compared to patients with nvAMD and non-AMD (Control) patients. NOTE: Red circle identifies patient sample not displayed in Figure 3B to adequately demonstrate the variability within the nvAMD samples. Kruskal-Wallis with Dunn's multiple comparisons test, *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001. NS, not significant.

Supplemental Figure 2. Chemical structure of rBEAQ polymer for *in vivo* delivery of siRNA.

Chemical structures for R groups of rBEAQ polymer.

Supplemental Tables

Supplemental Table 1. Baseline characteristics of TEP/M and Control patients whose aqueous samples were used for ELISAs.

Characteristic	q4 (n=10)	q6-8 (n=9)	q10-12 (n=6)	Weaned (n=13)	Control (n=39)
Mean Age (yr)	76.2 ± 1.6	78.6 ± 3.0	81.2 ± 1.9	82.5 ± 2.4	70.0 ± 1.5
Female % (#)	60% (6)	56% (5)	83% (5)	77% (10)	56% (22)
Pseudophakic % (#)	90% (9)	89% (8)	33% (2)	85% (11)	23% (9)

Abbreviation: n, sample size; yr, years; q4, TEP/M patients who required treatment with anti-VEGF therapy every 4 weeks at the end of their first year of treatment; q6-8, TEP/M patients who required treatment with anti-VEGF therapy every 6-8 weeks at the end of their first year of treatment; q10-12, TEP/M patients who required treatment with anti-VEGF therapy every 10-12 weeks at the end of their first year of treatment weeks; Weaned, TEP/M patients who were weaned off treatment with anti-VEGF therapy for 30 weeks or longer at the end of their first year of treatment; and ELISA, enzyme-linked immunoassay. Values displayed as mean ± standard error of the mean.

Supplemental Table 2. Performance characteristics of each angiogenic mediator alone and in combination when used to predict patients who were likely to require continuous monthly treatment vs those who required intermittent treatment and those who were able to be weaned.

Angiogenic Factor	Sensitivity	Specificity	AUC
VEGF	0.833	0.529	0.696
ANGPTL4	0.909	0.679	0.802
ANGPT2	0.714	0.454	0.513
VEGF + ANGPT2	0.595	0.743	-
VEGF + ANGPTL4	0.758	0.849	-
ANGPTL4 + ANGPT2	0.649	0.825	-

Abbreviations: AUC, area under curve; VEGF, vascular endothelial growth factor; ANGPTL4, angiopoietin-like 4; ANGPT2, angiopoietin 2.

Supplemental Table 3. Patient Characteristics for aqueous samples.

Patient Characteristic	Control (N=38)	nnvAMD (N=12)	nvAMD Untreated (N=20)	nvAMD Recurrent (N=20)	nvAMD First Treatment§ (N=12)	*P*
Mean Age in Years ± SD	65.6 ± 11.8	76.1 ± 5.7	81.0 ± 5.5	80.6 ± 10.6	78.1 ± 6.6	<0.0001
Males – no. (%)	18 (47)	5 (42)	5 (25)	5 (25)	6 (50)	0.28
Pseudophakic – no. (%)	0 (0)	0 (0)	16 (80)	13 (65)	7 (58)	<0.0001
Prior vitrectomy – no. (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–
DM – no. (%)	0 (0)	3 (25)	5 (25)	4 (20)	5 (42)	0.005
CVD[a] – no. (%)	27 (71)	7 (58)	17 (85)	19 (95)	10 (83)	0.09

nnvAMD, non-neovascular age-related macular degeneration. nvAMD, neovascular age-related macular degeneration. DM, diabetes mellitus. CVD, cardiovascular disease.
§Includes unique samples from the same eyes of 8 patients from the nvAMD untreated group.
[a]Includes any patient with a history of hypertension, hypercholesterolemia, coronary artery disease, or cerebral vascular accident.

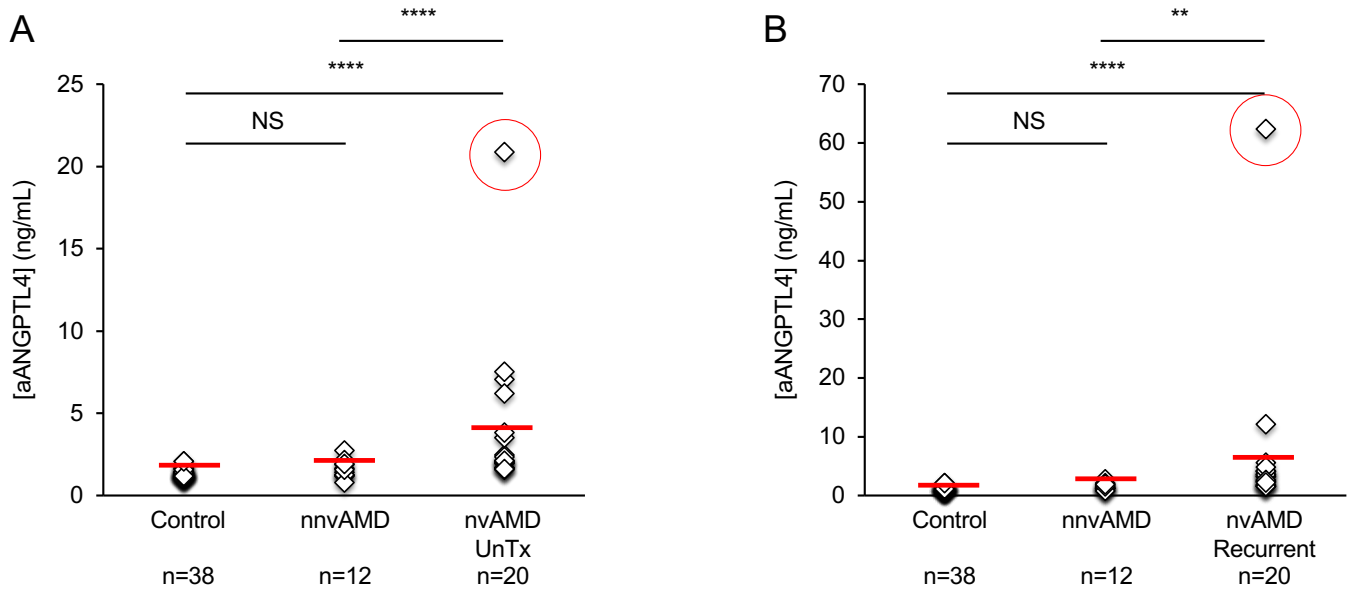
Supplemental Table 4. Primer sequences for Real-Time (RT)-PCR

	Gene		Sequence (5'to 3')
Mouse			
	Angptl4	Forward	TTGGTACCTGTAGCCATTCC
		Reverse	GAGGCTAAGAGGCTGCTGTA
	Vegf	Forward	CTTATACAGGAATGGAGGCTGT
		Reverse	TTCACCTGACAGGATTGGATAAT
	PPIA	Forward	AGCATACAGGTCCTGGCATC
		Reverse	TTCACCTTCCCAAAGACCAC
	Hif1a	Forward	GCACGGGCCATATTCATGTC
		Reverse	CACGTCATGGGTGGTTTCTTG

Supplemental Table 5. Antibodies used in this study.

Name	Company	Species	Catalog Number	dilution	Marker or Applications
HIF-1α	Gene Tex	rabbit	GTX127309	1:200 or 1:1000	WB
HIF-1α	Novus	mouse	NB-100-105	1:500	IF
HIF-1α	abcam	rabbit	Ab2185	1:500	IHC
β-Actin	Cell signaling	rabbit	4967	1:5000	WB
GAPDH	sigma	mouse	G8795	1:10000	WB
Isolectin GS IB4	Thermo Fisher		I21413	1:200	IF
CD31	R&D	goat	AF3628	1:1000	IF
VEGF	Santa Cruz	rabbit	Sc-152	1:1000	IHC/IF
ANGPTL4	abcam	rabbit	Ab115798	1:400	IHC/IF
Nrp1	abcam	Rabbit	Ab81321	1:1000	WB
Nrp2	Santa Cruz	Mouse	Sc13117	1:1000	WB
2° antibodies	Invitrogen			1:1000	IF
2° antibodies	Dako			1:100	IHC

Supplemental Figure 1



Supplemental Figure 2