**Figure EV1. Validation of cremastranone's inhibition of FECH.**

A 5-Aminolevulinic acid (5-ALA)-induced protoporphyrin IX (PPIX) buildup in HRECs after cremastranone treatment. *P = 0.0201; **P = 0.0012; ***P = 0.0006 relative to no cremastranone control, ANOVA with Dunnett's post hoc tests (n = 3 per group).

B Partial rescue of cremastranone's inhibition of HREC proliferation with 5-ALA, an inducer of heme biosynthesis. HRECs treated with DMSO only are shown as 100% proliferation control. *P = 0.046; ****P = 0.0006, ANOVA with Tukey's post hoc tests (n = 3 per group).

C Cremastranone does not bind iron as determined in an iron chelation assay; EDTA and deferoxamine are positive controls. ****P = 0.0001; ***P = 0.0003 relative to DMSO control, ANOVA with Dunnett's post hoc tests (n = 2 per group).

Data information: Representative figures from at least three independent experiments. Graphs show mean ± SEM.
Figure EV2. Effects of FECH inhibition on HRECs.

A  Time course of the effect of FECH siRNA on proliferation of HRECs. The % proliferation calculated are with respect to proliferation with negative control siRNA.

B  FECH knockdown does not induce apoptosis, as assessed by TUNEL (red). Staurosporine (1 μM) is a positive control.

C  FECH knockdown does not induce apoptosis, as assessed by activated caspase-3 immunostaining (red). Staurosporine (1 μM) is a positive control.

D  Apoptosis of HRECs after treatment with different doses of NMPP as assessed by TUNEL assay. ns, not significant; ****P = 0.0001 as compared with no treatment group, ANOVA with Tukey’s post hoc tests. Staurosporine (SP) is positive control.

E  Washout of NMPP reverses antiproliferative effects. HRECs were treated for 48 h with the indicated concentrations of NMPP; then, drug was removed and proliferation assessed 24 and 48 h later by AlamarBlue.

F  Apoptosis of HRECs after treatment with different doses of griseofulvin as assessed by TUNEL assay. ns, not significant; ****P = 0.0001 as compared with no treatment group, ANOVA with Tukey’s post hoc tests.

G  Washout of griseofulvin reverses antiproliferative effects. HRECs were treated for 48 h with the indicated concentrations of griseofulvin; then, drug was removed and proliferation assessed 24 and 48 h later by AlamarBlue.

Data information: Representative figures from at least three independent experiments. Graphs show mean ± SEM, n = 3. Scale bars = 1 mm.
Figure EV3. Effects of FECH inhibition on Rf/6a choroidal endothelial cells.

A The effect of NMPP, a specific inhibitor of FECH activity, on in vitro proliferation was measured using an AlamarBlue assay (n = 3 per dose).

B Ability of NMPP-treated Rf/6a cells to form tubular structures in Matrigel was monitored and analyzed using ImageJ. **P = 0.0002; ****P = 0.0001 compared to DMSO-treated sample, ANOVA with Dunnett’s post hoc tests (n = 6 per group).

C The effect of griseofulvin on in vitro proliferation was measured using an AlamarBlue assay (n = 3 per dose).

D Ability of griseofulvin-treated Rf/6a cells to form tubular structures in Matrigel was monitored and analyzed using ImageJ. *P = 0.018; ***P = 0.0002 compared to DMSO-treated sample, ANOVA with Dunnett’s post hoc tests (n = 6 per group).

Data information: Representative figures from at least three independent experiments. Graphs show mean ± SEM. Scale bars = 1 mm.
Figure EV4.
Figure EV4. *FECH* knockdown or inhibition has no significant effects on proliferation of other ocular or macrovascular cell types.

A Effect of *FECH* knockdown on proliferation of ARPE-19 retinal pigment epithelial cells. ns, non-significant, *P* > 0.05, two-tailed unpaired Student’s *t*-test.
B Effect of *FECH* knockdown on proliferation of 92-1 uveal melanoma cells. ns, non-significant, *P* > 0.05, two-tailed unpaired Student’s *t*-test.
C Effect of *FECH* knockdown on proliferation of human umbilical vein endothelial cells (HUVECs). ns, non-significant, *P* > 0.05, two-tailed unpaired Student’s *t*-test.
D Effect of NMPP on proliferation of ARPE-19 cells.
E Effect of NMPP on proliferation of 92-1 cells.
F Effect of griseofulvin on proliferation of HUVECs.
G Effect of griseofulvin on proliferation of ARPE-19 cells.
H Effect of griseofulvin on proliferation of 92-1 cells.
I Effect of griseofulvin on proliferation of HUVECs.
J Effect of NMPP on proliferation of Y-79 retinoblastoma cells.
K Effect of griseofulvin on proliferation of Y-79 cells.
L Effect of NMPP on proliferation of human brain microvascular endothelial cells (BMECs).
M Effect of griseofulvin on proliferation of BMECs.

Data information: Graphs show mean ± SEM, *n* = 3. Representative figures from three experiments are shown in (A, B, and C). Source data are available online for this figure.

Figure EV5. Oral griseofulvin’s systemic effects and combination with anti-VEGF therapy.

A Oral griseofulvin treatment did not significantly change mouse weights during the experimental time course. *P* > 0.05, two-way repeated measures ANOVA with Tukey’s post hoc tests (*n* = 10 mice per group).
B Griseofulvin increased liver weights as expected with these treatments, confirming drug intake and systemic metabolism. *** *P* = 0.0001 and 0.002 versus vehicle, ANOVA with Dunnett’s post hoc tests (*n* = 6 mice per group).
C Intravitreal griseofulvin in combination with anti-VEGF<sub>164</sub> therapy in L-CNV. Treatment with indicated single agents and combinations. ** *P* = 0.0011 versus vehicle; *** *P* = 0.0002, <0.0001, 0.0001, versus vehicle, left to right, respectively, ANOVA with Tukey’s post hoc tests. All other comparisons were non-significant (*n* = 6–10 mice per group).

Data information: Graphs show mean ± SEM.