

Supplementary Materials for
**Synergistically acting agonists and antagonists of G protein–coupled
receptors prevent photoreceptor cell degeneration**

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Table S1. Retinal gene sets significantly altered in response to bright light exposure in *Abca4^{-/-}Rdh8^{-/-}* mice.

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Figure S1

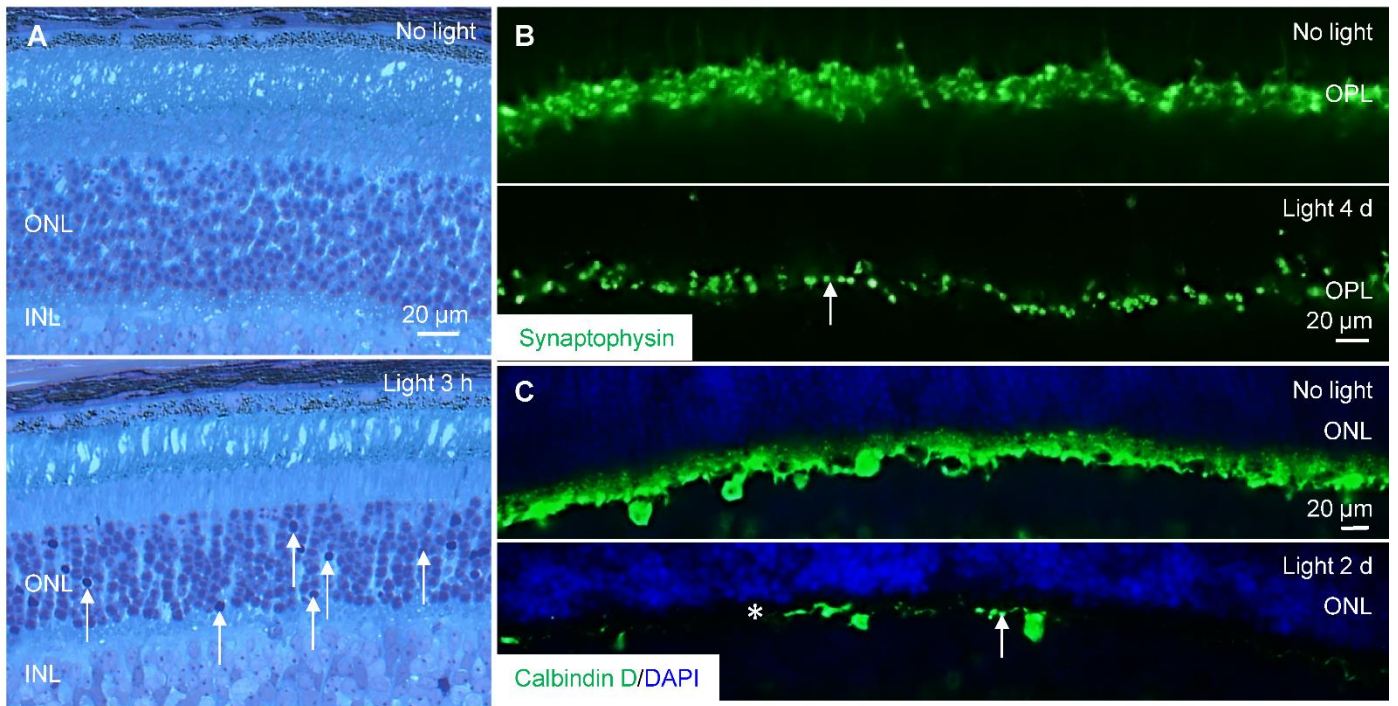


Figure S1. *Abca4*^{-/-}*Rdh8*^{-/-} mice exposed to bright light exhibit pyknosis of photoreceptor cells, diminished synaptophysin in the OPL, and altered horizontal cell morphology. (A). Retinal thick sections from pigmented *Abca4*^{-/-}*Rdh8*^{-/-} mice unexposed to bright light (No light) and 3 h after light exposure (Light 3 h) were stained with toluidine blue and examined by light microscopy. White arrows indicate pyknotic photoreceptor cells. Scale bar: 20 μ m. (B, C) Albino *Abca4*^{-/-}*Rdh8*^{-/-} mice were exposed to bright light at 10,000 lux for 1 h. Retinal cryosections were prepared from mice unexposed to bright light and at indicated times after light exposure, i.e. 2 d (Light 2d) and 4 d (Light 4d). Immunohistochemistry was performed to assess the expression of synaptophysin (B) and calbindin D (C). ONL: outer nuclear layer; OPL: outer plexiform layer. White arrows in B and C indicate representative areas in the OPL with diminished expression of synaptophysin and calbindin D, respectively. Asterisks in C identify areas where calbindin D immunoreactivity was not readily detected. Scale bar: 20 μ m.

Figure S2

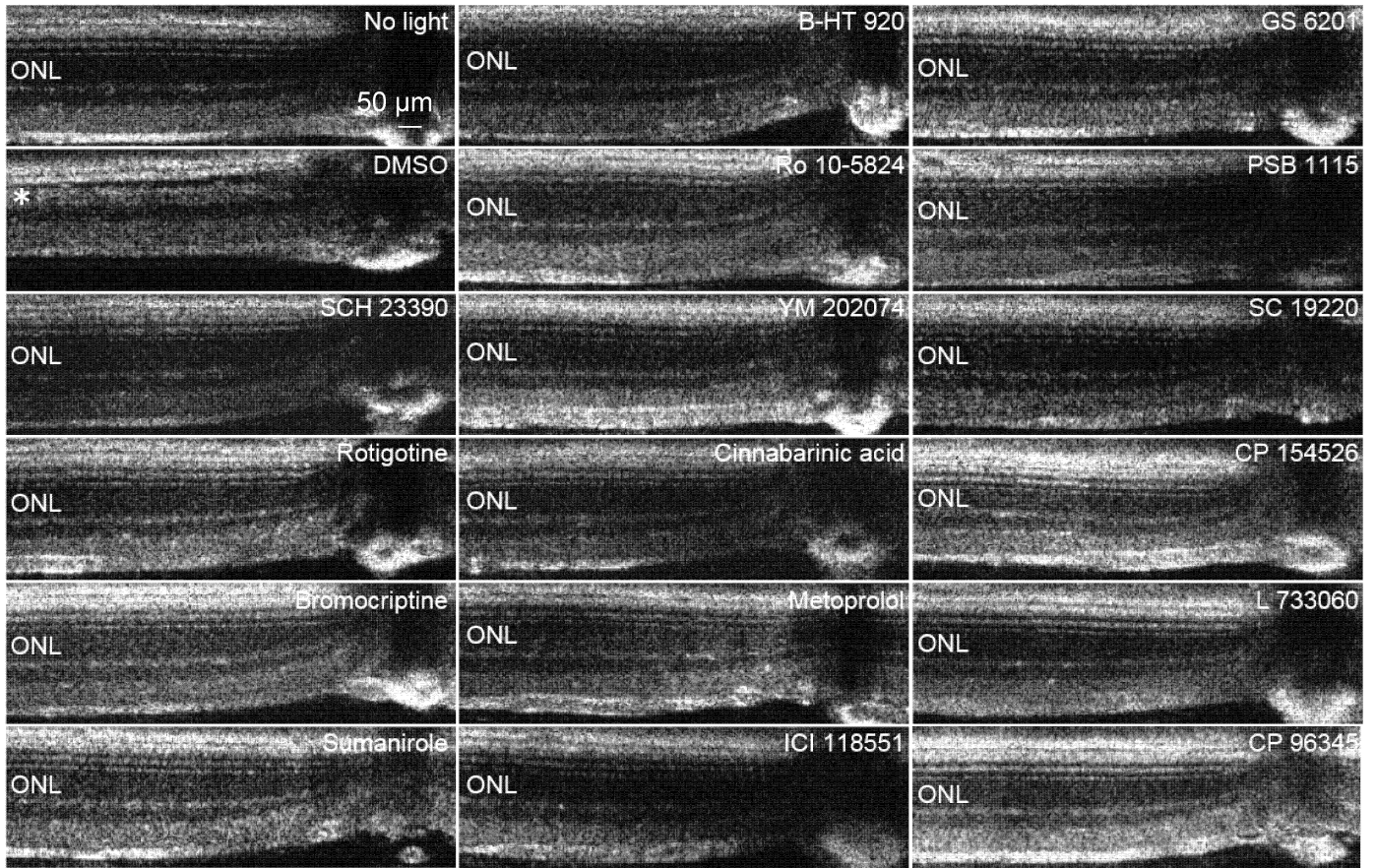


Figure S2. Pharmacological pretreatments targeting different GPCRs preserve retinal structure in bright light-exposed *Abca4*^{-/-}*Rdh8*^{-/-} mice. OCT imaging was performed to examine retinal structures in *Abca4*^{-/-}*Rdh8*^{-/-} mice either unexposed to bright light, or with light exposure after pretreatment with either DMSO or the compounds indicated in **Table 2** that modulate the activity of GPCRs. ONL: outer nuclear layer. Asterisk marks severely attenuated ONL. OCT was performed 7 days after bright light.

Figure S3

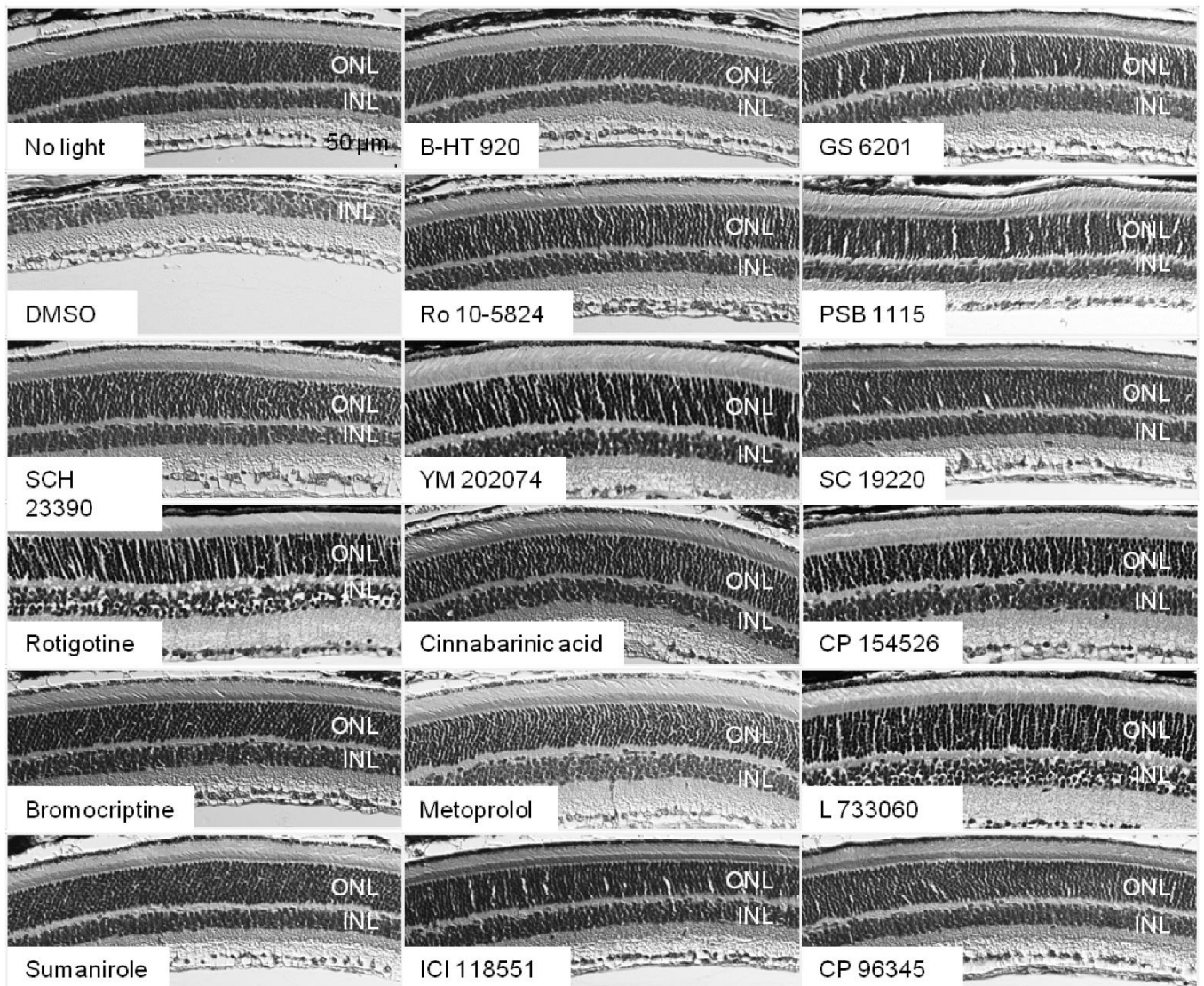


Figure S3. Variable preservation of retinal morphology by pharmacological pretreatments targeting different GPCRs in bright light-exposed *Abca4*^{-/-}*Rdh8*^{-/-} mice. H&E staining of paraffin sections of eyes from *Abca4*^{-/-}*Rdh8*^{-/-} mice was performed either without light exposure, or 14 days after bright light exposure and pretreatment with either DMSO or the indicated compounds listed in **Table 2**. ONL: outer nuclear layer; INL: inner nuclear layer. Scale bar: 50 µm.

Figure S4

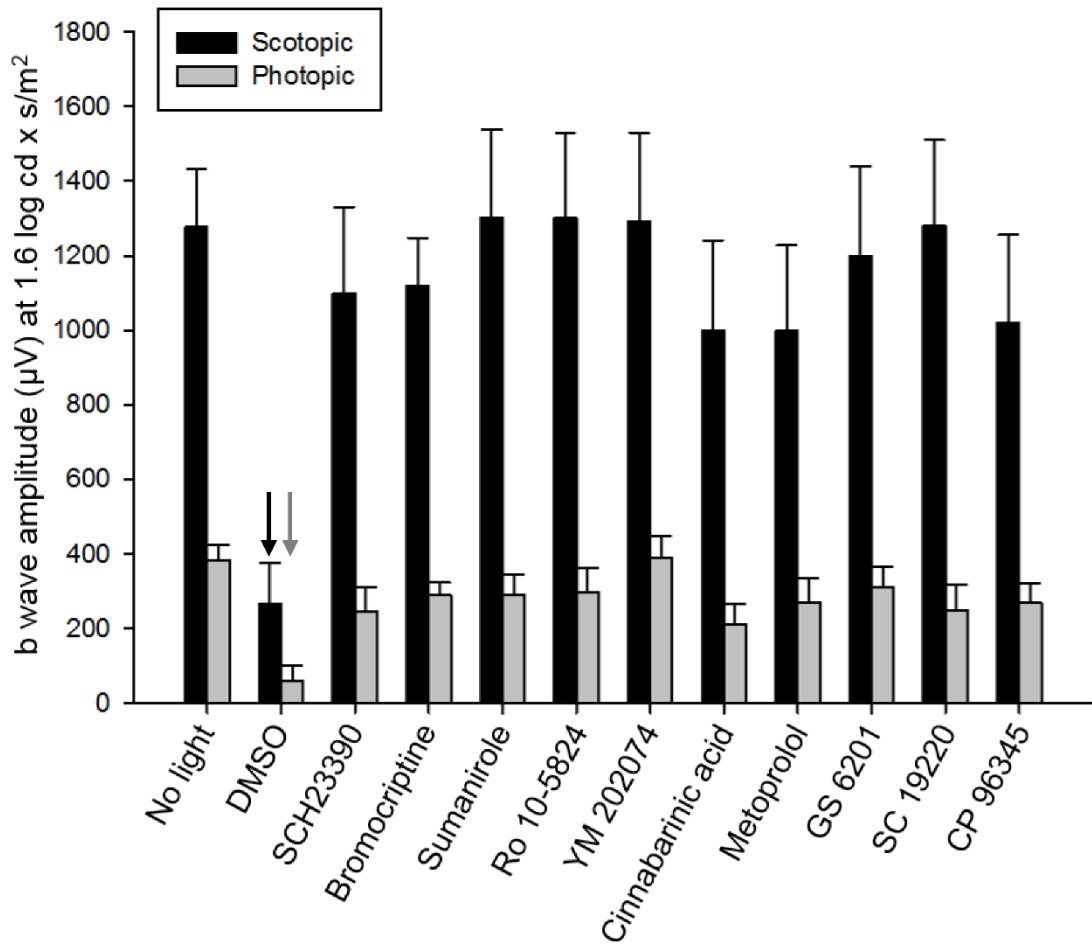


Figure S4. Pharmacological pretreatment affecting various GPCRs preserves retinal function in bright light-exposed *Abca4^{-/-}Rdh8^{-/-}* mice. ERG analyses of retinal function were performed in *Abca4^{-/-}Rdh8^{-/-}* mice either unexposed to bright light, or with light exposure and pretreatment with either DMSO or the indicated compounds listed in **Table 2**. Black and grey arrows highlight the decreased scotopic and photopic b wave amplitudes, respectively, in light-exposed, DMSO-treated mice. ERG was performed 10 days after bright light exposure.

Figure S5

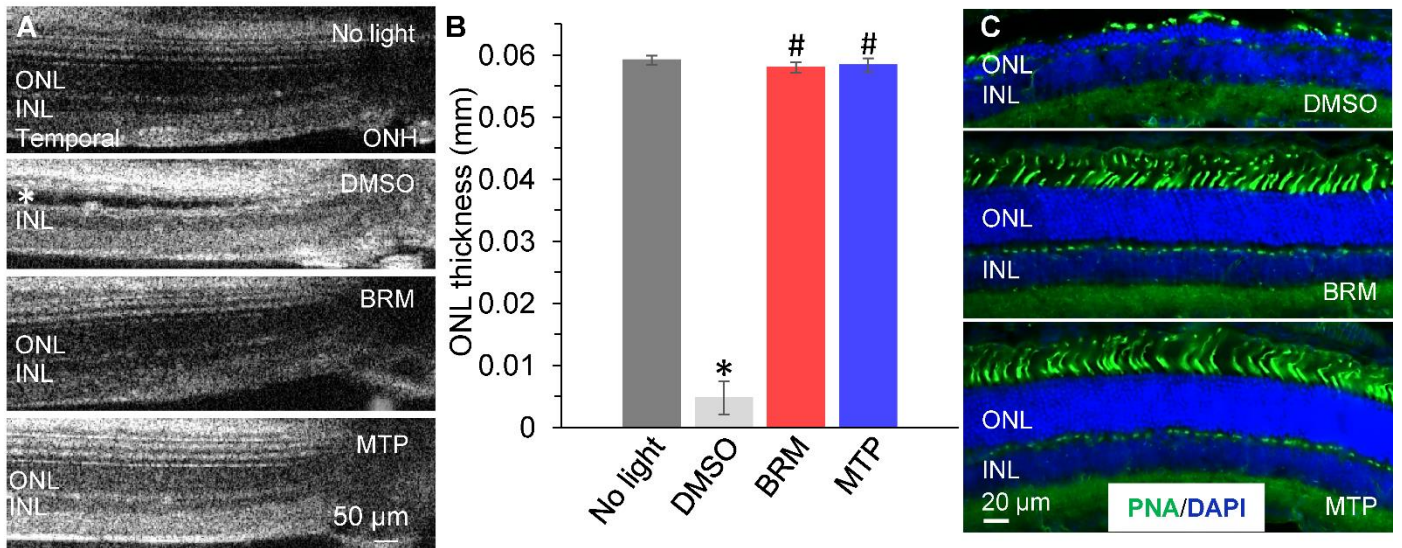


Figure S5. BRM or MTP pretreatment protects retinas of BALB/c mice from bright light-induced degeneration. (A) BALB/c mice were pretreated as indicated, and exposed to bright light. OCT imaging was performed 7 d later to examine retinal structures either unexposed to bright light, exposed to bright light and pretreated with DMSO, exposed to bright light and pretreated with BRM at 2.5 mg/kg bw (BRM), or exposed to bright light and pretreated with MTP at 10 mg/kg bw (MTP). (B) ONL thickness was measured in OCT images 0.45 mm away from the ONH in the temporal retina. * Compared to No light, $P < 0.05$; # Compared to DMSO, $P < 0.05$. ONH: optic nerve head; ONL: outer nuclear layer; INL: inner nuclear layer. Asterisk indicates reduced ONL thickness. (C) Retinal expression of PNA (green) along with DAPI counterstaining (blue) was examined in cryosections collected from light-exposed BALB/c mice pretreated with either DMSO, BRM or MTP. Scale bar; 20 μ m.

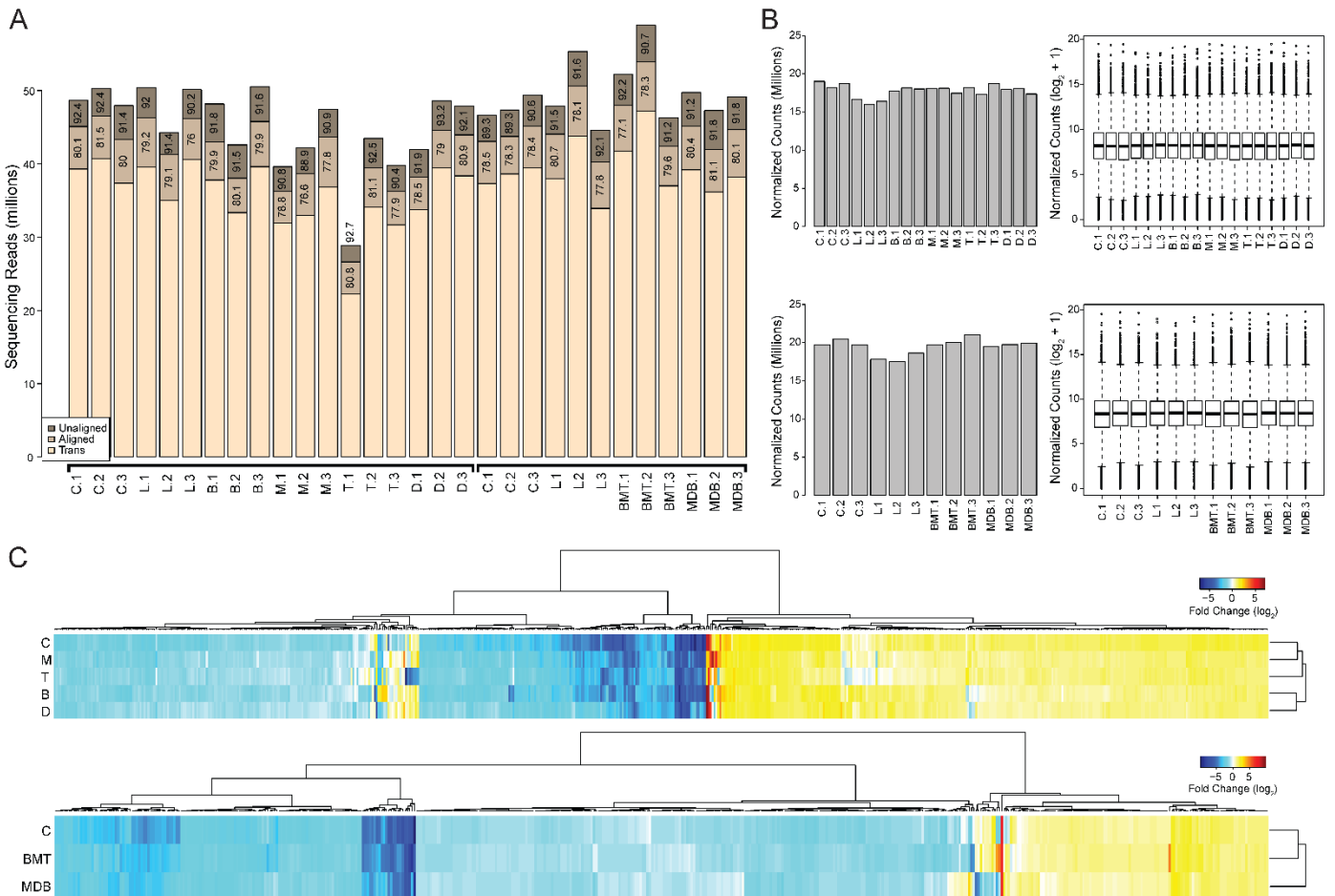
Figure S7

Figure S6. Transcriptome analysis of the retina. Sequencing depth and alignment statistics for the RNA-seq experiment performed for retinal samples collected from *Abca4^{-/-}Rdh8^{-/-}* mice unexposed to bright light (C), light-exposed mice pretreated with DMSO vehicle control (L), or BRM (B), MTP (M), TAM (T), DOX (D), BMT (B+M+T) and MDB (B+M+D). Doses used for retinal transcriptome analyses of the mice receiving mono treatment were: 1 mg/kg bw for BRM, 10 mg/kg bw for MTP, 2.5 mg/kg bw for TAM and 10 mg/kg bw for DOX. Doses for combined treatment with B+M+T were 0.1 mg/kg bw for BRM, 1 mg/kg bw for MTP and 0.05 mg/kg bw for TAM. Doses for combined treatment with B+M+D were 0.1 mg/kg bw for BRM, 1 mg/kg bw for MTP and 1 mg/kg bw for DOX. (A) Trans indicates the number of reads mapping to the known gene annotation. Aligned are the amounts of intronic and intergenic reads mapping to the genome. Unaligned are the number of reads not successfully aligned. (B) Shown also are the normalized count values and distribution after normalization of the mono pretreatments (upper) and combination pretreatments (lower). (C) Clustering of the fold change values is evident from the differential expression analysis of the mono pretreatments (upper) and combination pretreatments (lower).

Figure S7

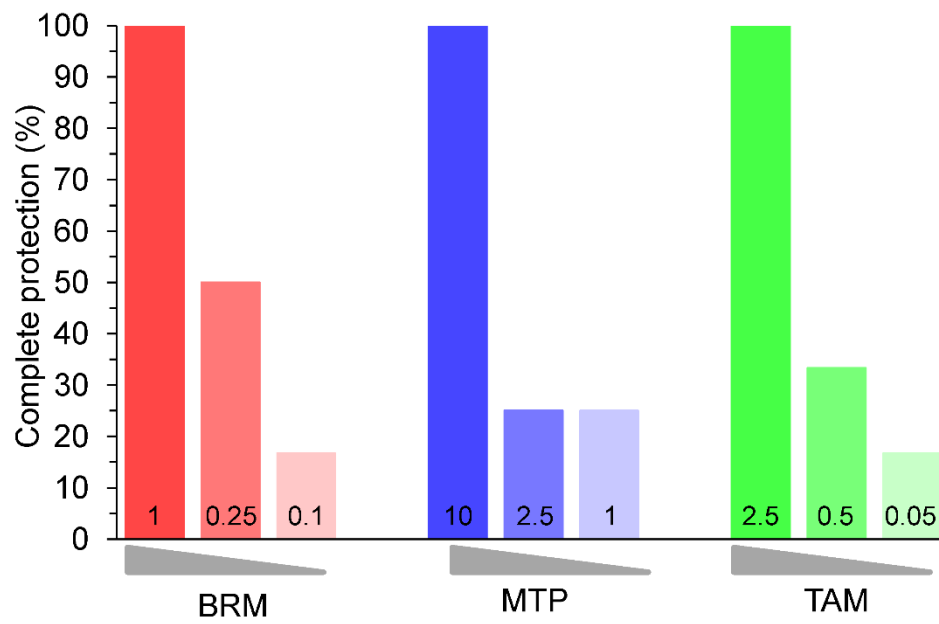


Figure S7. Dose-dependent protection of retinal morphology in *Abca4*^{-/-}*Rdh8*^{-/-} mice by BRM, MTP, and TAM pretreatment. *Abca4*^{-/-}*Rdh8*^{-/-} mice pretreated with different doses of BRM, MTP, and TAM were exposed to bright light. OCT imaging was performed 7 d after light exposure. The percentage of complete retinal protection is summarized for each treatment delivered at the dose indicated.

Figure S8

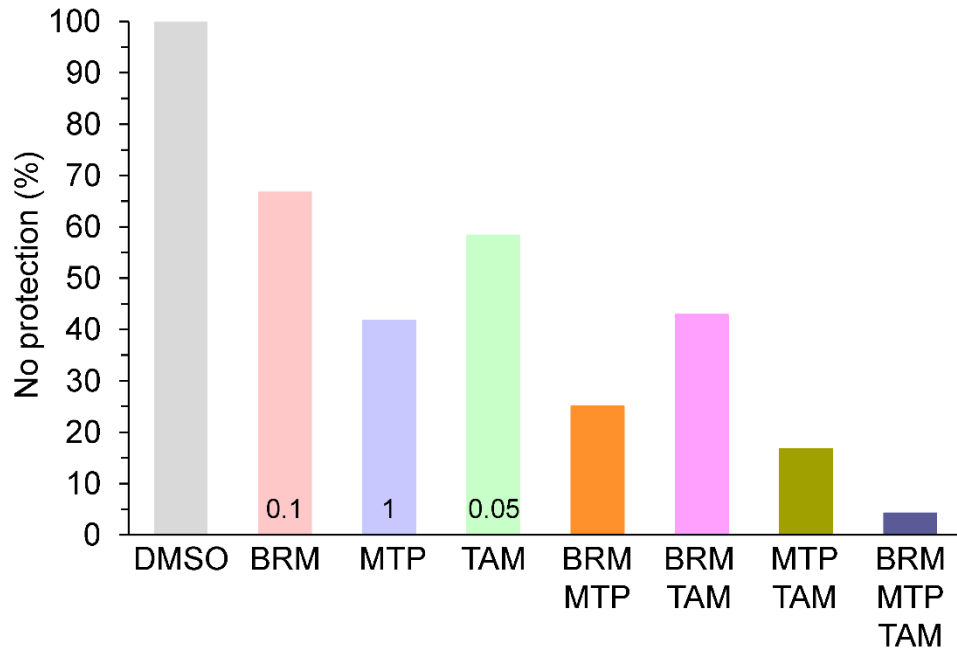


Figure S8. Combined pretreatments improve retinal morphological protection against bright light-exposed in *Abca4^{-/-}Rdh8^{-/-}* mice. Either BRM, MTP, or TAM was administered individually at a sub-effective dose to *Abca4^{-/-}Rdh8^{-/-}* mice or in a combined pretreatment consisting of two or three of these compounds, each at its sub-effective dose. This was followed by exposure to bright light and OCT imaging performed 7 d later. Percentages of mice manifesting no protection of retinal structures were calculated for each condition. Doses for either mono or combined pretreatments were 0.1 mg/kg bw, 1 mg/kg bw, and 0.05 mg/kg bw for BRM, MTP and TAM, respectively.

Figure S9

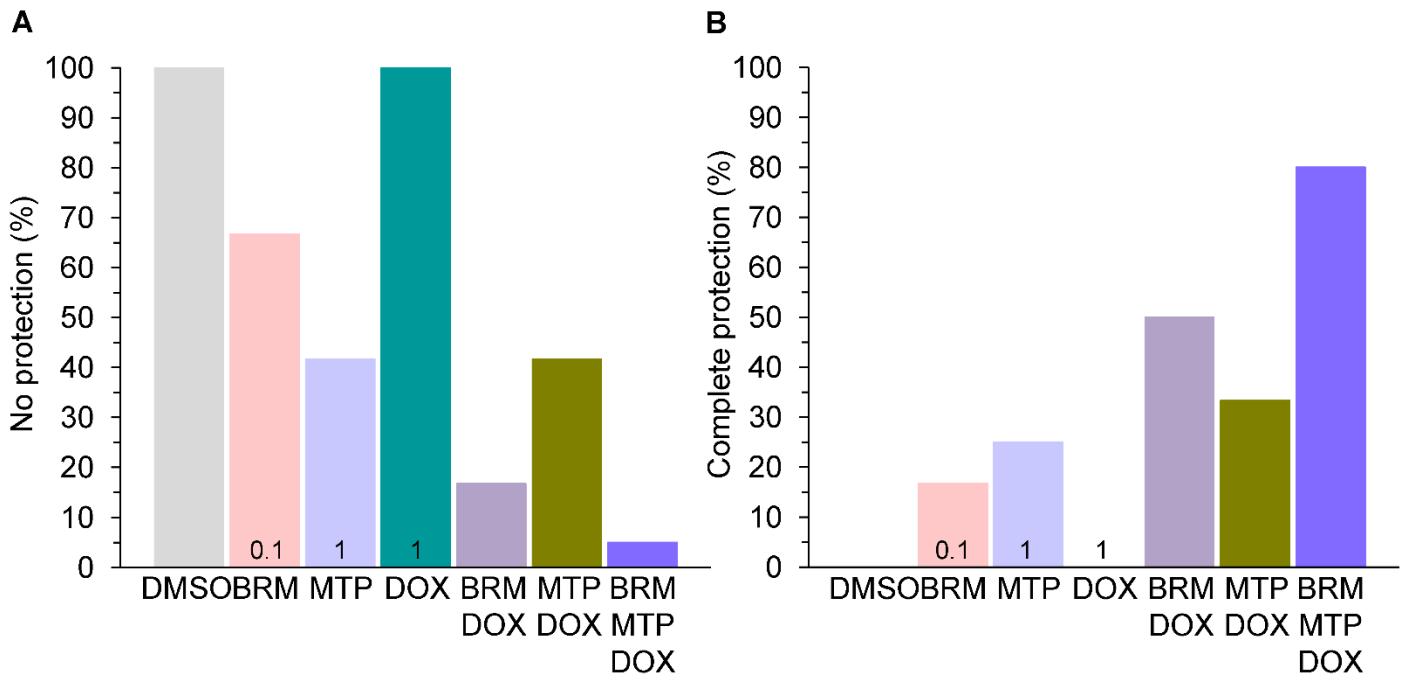


Figure S9. Combined treatments with subeffective doses of individual drugs exhibit improved retinal morphological protection in bright light-exposed *Abca4*^{-/-}*Rdh8*^{-/-} mice. BRM, MTP, or DOX was individually administered at a sub-effective dose or together with one or two other compounds, each delivered at a sub-effective dose, to *Abca4*^{-/-}*Rdh8*^{-/-} mice prior to bright light exposure. OCT imaging was performed 7 d after light exposure. The percentage of mice manifesting either (A) no protection or (B) complete protection of retinal structure is summarized for each treatment. Doses in all conditions were 0.1 mg/kg bw, 1 mg/kg bw, and 1 mg/kg bw for BRM, MTP and DOX, respectively.

Figure S10

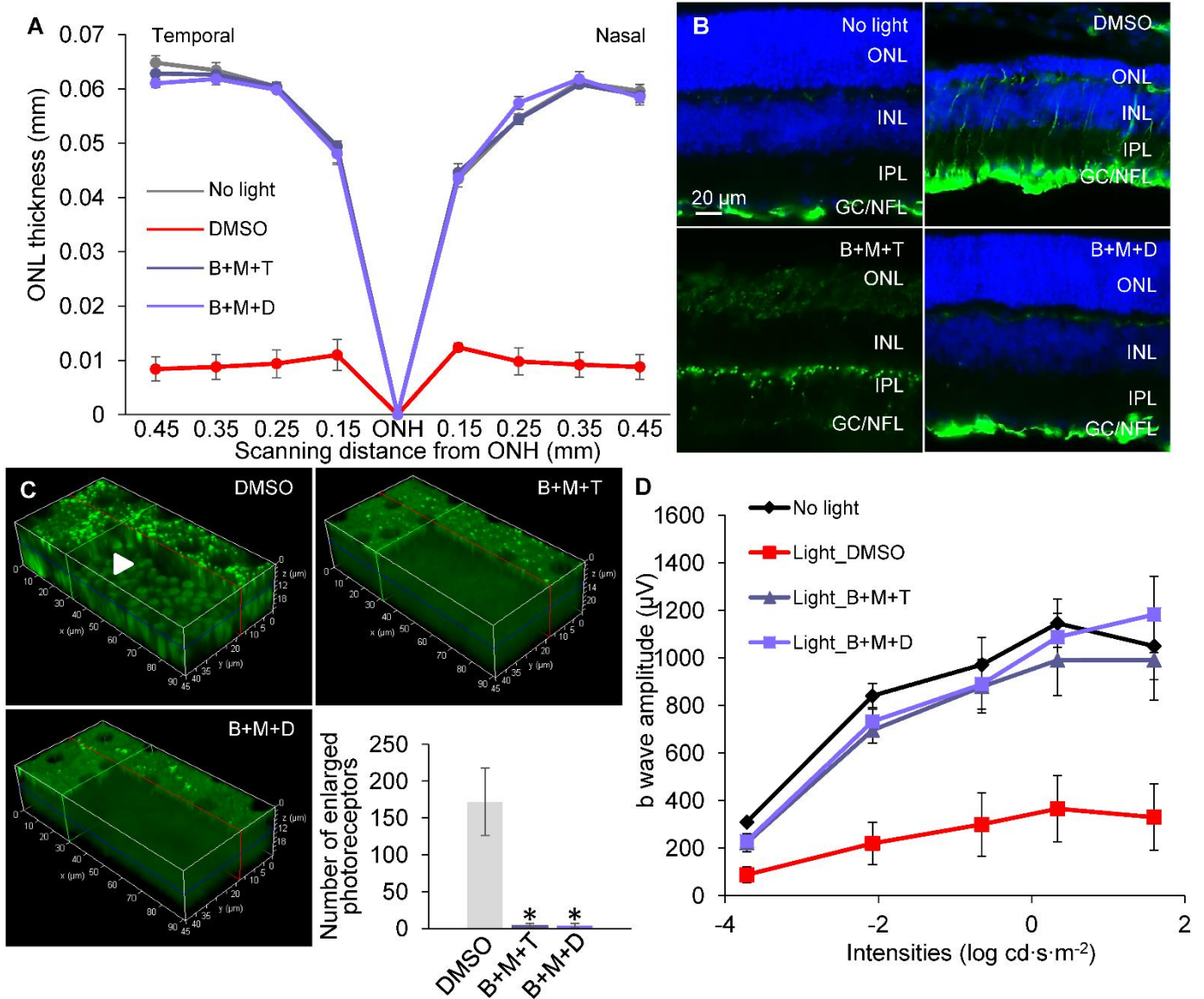


Figure S10. Combined pretreatments protect retinas of BALB/c mice from bright light-induced photoreceptor degeneration. BALB/c mice were exposed to bright light after pretreatment with DMSO, a combination of either BRM (0.1 mg/kg bw), MTP (1 mg/kg bw) and TAM (0.05 mg/kg bw) (B+M+T) or a combination of BRM (0.1 mg/kg bw), MTP (1 mg/kg bw) and DOX (1 mg/kg bw) (B+M+D). **(A)** OCT imaging of BALB/c mice was performed 7 days following exposure to bright light. Thicknesses of the ONL were measured from the OCT images. ONH: optic nerve head; ONL: outer nuclear layer; INL: inner nuclear layer. **(B)** Cryosections were prepared from BALB/c mice either unexposed to bright light or 2 weeks after bright light exposure. Retinal GFAP staining (green) was then determined by immunohistochemistry with DAPI counterstaining (blue). ONL: outer nuclear layer; INL: inner nuclear layer; IPL: inner plexiform layer; GC: ganglion cell; NFL: nerve fiber layer. Scale bar: 20 µm. **(C)** TPM imaging was performed 3 days after light exposure to examine the changes in photoreceptors; enlarged photoreceptors were quantified. White arrowhead indicates an enlarged photoreceptor cell. # Compared to DMSO, $P < 0.05$, $n = 5$. **(D)** ERG examinations were performed 10 days after light exposure and the changes in scotopic b wave amplitudes were analyzed after ERG recordings.

Table S1. Retinal gene sets significantly altered in response to bright light exposure in *Abca4^{-/-}Rdh8^{-/-}* mice. Gene expression in the retinas from *Abca4^{-/-}Rdh8^{-/-}* mice exposed to bright light was compared to the gene expression in the retinas from mice that had not been exposed to bright light.

Gene set name	NES ^a	NOM <i>P</i> value ^b
CYTOKINE-CYTOKINE RECEPTOR INTERACTION	2.499941	0
P53 SIGNALING PATHWAY	2.294004	0
OSTEOCLAST DIFFERENTIATION	2.254599	0
JAK-STAT SIGNALING PATHWAY	2.226176	0
TOLL-LIKE RECEPTOR SIGNALING PATHWAY	2.14331	0
LEISHMANIASIS	2.114414	0
RHEUMATOID ARTHRITIS	2.106262	0
MEASLES	2.09881	0
INFLUENZA A	2.080741	0
HEPATITIS C	1.949769	0
CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)	1.907339	0
PROTEASOME	1.84367	0
APOPTOSIS	1.834949	0
MAPK SIGNALING PATHWAY	1.812699	0
RIG-I-LIKE RECEPTOR SIGNALING PATHWAY	1.786783	0
TUBERCULOSIS	1.731797	0
REGULATION OF ACTIN CYTOSKELETON	1.68178	0
PATHWAYS IN CANCER	1.542123	0.001311
CYTOSOLIC DNA-SENSING PATHWAY	1.853622	0.001667
AXON GUIDANCE	1.604034	0.002813
GAP JUNCTION	1.681527	0.003053
TOXOPLASMOSIS	1.663511	0.003106
CHEMOKINE SIGNALING PATHWAY	1.615531	0.004219
MALARIA	1.849309	0.00531
CELL CYCLE	1.631867	0.005806
CELL ADHESION MOLECULES (CAMS)	1.64954	0.006051
LEUKOCYTE TRANSENDOTHELIAL MIGRATION	1.63332	0.006098
PATHOGENIC ESCHERICHIA COLI INFECTION	1.607625	0.013514
T CELL RECEPTOR SIGNALING PATHWAY	1.54441	0.015337
MELANOMA	1.561813	0.017268
ANTIGEN PROCESSING AND PRESENTATION	1.594037	0.017742
PANCREATIC CANCER	1.62309	0.020472
BLADDER CANCER	1.573655	0.025042
B CELL RECEPTOR SIGNALING PATHWAY	1.524973	0.026359
TGF-BETA SIGNALING PATHWAY	1.479011	0.027994
EPITHELIAL CELL SIGNALING IN HELICOBACTER PYLORI INFECTION	1.436208	0.031204
PHAGOSOME	1.444337	0.032593
PROSTATE CANCER	1.441207	0.033588
MINERAL ABSORPTION	1.461418	0.03413
FOCAL ADHESION	1.407668	0.034722
NATURAL KILLER CELL MEDIATED CYTOTOXICITY	1.467622	0.035144
NEUROACTIVE LIGAND-RECEPTOR INTERACTION	1.389158	0.036309
RENAL CELL CARCINOMA	1.419761	0.037258
NEUROTROPHIN SIGNALING PATHWAY	1.361332	0.047026

PHOTOTRANSDUCTION	-2.71384	0
OXIDATIVE PHOSPHORYLATION	-1.78353	0
PARKINSON'S DISEASE	-1.3712	0.015432
GLYCOSYLPHOSPHATIDYLINOSITOL(GPI)-ANCHOR BIOSYNTHESIS	-1.54824	0.021898
ETHER LIPID METABOLISM	-1.51432	0.033981
ABC TRANSPORTERS	-1.52816	0.041363

^aNES: normalized enrichment score.

^bNOM *P* value: nominal *P* value.

Table S2. Retinal gene sets beneficially regulated by BRM pretreatment. Gene expression in the retinas from DMSO-treated light-exposed *Abca4^{-/-}Rdh8^{-/-}* mice was compared to the gene expression in the retinas from BRM-pretreated light-exposed mice.

Gene set name	NES ^a	NOM <i>P</i> value ^b
INFLUENZA A	2.316076	0
CYTOKINE-CYTOKINE RECEPTOR INTERACTION	2.311251	0
OSTEOCLAST DIFFERENTIATION	2.292695	0
TOLL-LIKE RECEPTOR SIGNALING PATHWAY	2.20026	0
JAK-STAT SIGNALING PATHWAY	2.190011	0
HEPATITIS C	2.172245	0
LEISHMANIASIS	2.067241	0
TUBERCULOSIS	2.06043	0
P53 SIGNALING PATHWAY%KEGG	2.059358	0
MEASLES	2.041737	0
RIG-I-LIKE RECEPTOR SIGNALING PATHWAY	2.030246	0
CYTOSOLIC DNA-SENSING PATHWAY	1.996471	0
RHEUMATOID ARTHRITIS	1.964366	0
CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)	1.928461	0
MAPK SIGNALING PATHWAY	1.697178	0
APOPTOSIS	1.74725	0.001808
CELL CYCLE	1.725497	0.001828
CHEMOKINE SIGNALING PATHWAY	1.665321	0.001873
T CELL RECEPTOR SIGNALING PATHWAY	1.781596	0.003831
MALARIA	1.811571	0.004158
TOXOPLASMOSIS	1.596552	0.007859
RIBOSOME BIOGENESIS IN EUKARYOTES	1.518271	0.012146
PROTEASOME	1.577355	0.017442
NOD-LIKE RECEPTOR SIGNALING PATHWAY	1.556338	0.023346
ANTIGEN PROCESSING AND PRESENTATION	1.601986	0.024668
PYRIMIDINE METABOLISM	1.465657	0.025926
VIBRIO CHOLERAEE INFECTION	1.503147	0.037328
BLADDER CANCER	1.467256	0.04142
B CELL RECEPTOR SIGNALING PATHWAY	1.474744	0.041502
PHAGOSOME	1.403161	0.047957
PHOTOTRANSDUCTION	-2.42237	0
PROTEIN DIGESTION AND ABSORPTION	-1.88516	0
OXIDATIVE PHOSPHORYLATION	-1.52288	0.010799
ECM-RECEPTOR INTERACTION	-1.47	0.032538
PARKINSON'S DISEASE	-1.37642	0.043981
BILE SECRETION	-1.41742	0.046316

^a NES: normalized enrichment score.

^b NOM *P* value: nominal *P* value.

Table S3. Retinal gene sets beneficially affected by MTP pretreatment. Gene expression in the retinas from DMSO-treated light-exposed *Abca4*^{-/-}*Rdh8*^{-/-} mice was compared to the gene expression in the retinas from MTP-pretreated light-exposed mice

Gene set name	NES ^a	NOM <i>P</i> value ^b
CYTOKINE-CYTOKINE RECEPTOR INTERACTION	2.298575	0
HEPATITIS C	2.114615	0
JAK-STAT SIGNALING PATHWAY	2.091388	0
LEISHMANIASIS	2.05127	0
MEASLES	2.051036	0
TOLL-LIKE RECEPTOR SIGNALING PATHWAY	2.04943	0
P53 SIGNALING PATHWAY	2.038268	0
INFLUENZA A%KEGG	2.020124	0
OSTEOCLAST DIFFERENTIATION	2.007467	0
PROTEASOME	1.898456	0
RHEUMATOID ARTHRITIS	1.858606	0
CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)	1.847138	0
CELL CYCLE	1.671191	0
MAPK SIGNALING PATHWAY	1.653268	0
REGULATION OF ACTIN CYTOSKELETON	1.614068	0.001232
PHAGOSOME	1.671424	0.001346
RIG-I-LIKE RECEPTOR SIGNALING PATHWAY	1.83438	0.001464
MALARIA	1.759778	0.001621
TUBERCULOSIS	1.730178	0.002646
PATHOGENIC ESCHERICHIA COLI INFECTION	1.656261	0.002954
CYTOSOLIC DNA-SENSING PATHWAY	1.761675	0.003049
NEUROTROPHIN SIGNALING PATHWAY	1.538862	0.005057
APOPTOSIS	1.614587	0.005525
LEUKOCYTE TRANSENDOTHELIAL MIGRATION	1.69688	0.005563
MINERAL ABSORPTION	1.654049	0.008104
PATHWAYS IN CANCER	1.418722	0.010381
ANTIGEN PROCESSING AND PRESENTATION	1.650826	0.010448
TOXOPLASMOSIS	1.535752	0.010825
CELL ADHESION MOLECULES (CAMS)	1.624701	0.011511
GAP JUNCTION	1.481687	0.015131
BLADDER CANCER	1.568963	0.016641
FOCAL ADHESION	1.410039	0.017456
CHEMOKINE SIGNALING PATHWAY	1.448831	0.024204
T CELL RECEPTOR SIGNALING PATHWAY	1.432076	0.025956
ECM-RECEPTOR INTERACTION	1.497648	0.026316
MELANOMA	1.472294	0.030523
SHIGELLOSIS	1.504511	0.030856
B CELL RECEPTOR SIGNALING PATHWAY	1.47098	0.032689
LYSOSOME	1.393048	0.033854
EPITHELIAL CELL SIGNALING IN HELICOBACTER PYLORI INFECTION	1.451014	0.034188
AMOEBIASIS	1.482668	0.035765
PROSTATE CANCER	1.412496	0.039161

PHOTOTRANSDUCTION	-2.74171	0
OXIDATIVE PHOSPHORYLATION	-1.40455	0.019084
FRUCTOSE AND MANNOSE METABOLISM	-1.56356	0.019553
GLUTAMATERGIC SYNAPSE	-1.33414	0.025926

^a NES: normalized enrichment score.

^b NOM *P* value: nominal *P* value.

Table S4. Retinal gene sets beneficially affected by TAM pretreatment. Gene expression in the retinas from DMSO-treated light-exposed *Abca4*^{-/-}*Rdh8*^{-/-} mice was compared to the gene expression in the retinas from TAM-pretreated light-exposed mice

Gene set name	NES ^a	NOM <i>P</i> value ^b
CYTOKINE-CYTOKINE RECEPTOR INTERACTION	2.287917	0
PROTEASOME	1.989326	0
P53 SIGNALING PATHWAY	1.980445	0
JAK-STAT SIGNALING PATHWAY	1.953612	0
CYTOSOLIC DNA-SENSING PATHWAY	1.915203	0
MEASLES	1.886409	0
OSTEOCLAST DIFFERENTIATION	1.878713	0
TOLL-LIKE RECEPTOR SIGNALING PATHWAY	1.833643	0
HEPATITIS C	1.83041	0
RIG-I-LIKE RECEPTOR SIGNALING PATHWAY	1.798662	0
INFLUENZA A	1.795979	0
REGULATION OF ACTIN CYTOSKELETON	1.69899	0
MAPK SIGNALING PATHWAY	1.527737	0
PATHWAYS IN CANCER	1.504636	0.001242
FOCAL ADHESION	1.582052	0.001357
LEISHMANIASIS	1.814122	0.001582
AXON GUIDANCE	1.583195	0.002725
LEUKOCYTE TRANSENDOTHELIAL MIGRATION	1.704037	0.002882
RIBOSOME BIOGENESIS IN EUKARYOTES	1.640137	0.002894
PATHOGENIC ESCHERICHIA COLI INFECTION	1.767884	0.003021
RIBOSOME	1.631069	0.004367
PHAGOSOME	1.641816	0.00438
ANTIGEN PROCESSING AND PRESENTATION	1.728092	0.004702
TUBERCULOSIS	1.515861	0.006935
RHEUMATOID ARTHRITIS	1.656786	0.008
VIBRIO CHOLERAE INFECTION	1.625489	0.010836
APOPTOSIS	1.599561	0.011364
CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)	1.560899	0.011412
GAP JUNCTION	1.538637	0.012766
NEUROTROPHIN SIGNALING PATHWAY	1.439027	0.014144
CHEMOKINE SIGNALING PATHWAY	1.394057	0.019947
BLADDER CANCER	1.552929	0.022876
TOXOPLASMOSIS	1.476038	0.023916
SHIGELLOSIS	1.502287	0.025758
ECM-RECEPTOR INTERACTION	1.488929	0.026194
COLLECTING DUCT ACID SECRETION	1.587351	0.027687
EPITHELIAL CELL SIGNALING IN HELICOBACTER PYLORI INFECTION	1.517176	0.030347
CELL CYCLE	1.38958	0.031208

BACTERIAL INVASION OF EPITHELIAL CELLS	1.425374	0.035874
NATURAL KILLER CELL MEDIATED CYTOTOXICITY	1.41612	0.036819
COLORECTAL CANCER	1.391793	0.043027
N-GLYCAN BIOSYNTHESIS	1.390149	0.046899
MINERAL ABSORPTION	1.47998	0.049459
PHOTOTRANSDUCTION	-2.78218	0
OLFACTORY TRANSDUCTION	-1.73251	0.017073

^a NES: normalized enrichment score.

^b NOM *P* value: nominal *P* value.

Table S5. Retinal gene sets beneficially affected by DOX pretreatment. Gene expression in the retinas from DMSO-treated light-exposed *Abca4^{-/-}Rdh8^{-/-}* mice was compared to the gene expression in the retinas from DOX-pretreated light-exposed mice

Gene set name	NES ^a	NOM <i>P</i> value ^b
CYTOKINE-CYTOKINE RECEPTOR INTERACTION	2.421621	0
P53 SIGNALING PATHWAY	2.182522	0
HEPATITIS C	2.104995	0
INFLUENZA A	2.096623	0
MEASLES	2.025816	0
TOLL-LIKE RECEPTOR SIGNALING PATHWAY	1.985675	0
OSTEOCLAST DIFFERENTIATION	1.944466	0
CYTOSOLIC DNA-SENSING PATHWAY	1.903977	0
RHEUMATOID ARTHRITIS	1.892949	0
LEISHMANIASIS	1.892227	0
ANTIGEN PROCESSING AND PRESENTATION	1.781439	0
REGULATION OF ACTIN CYTOSKELETON	1.579483	0.001724
JAK-STAT SIGNALING PATHWAY	1.759936	0.00173
RIG-I-LIKE RECEPTOR SIGNALING PATHWAY	1.82371	0.001812
APOPTOSIS	1.754144	0.001866
CELL CYCLE	1.658268	0.001869
MALARIA	1.89198	0.001938
CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)	1.658659	0.003571
TUBERCULOSIS	1.674743	0.005396
MAPK SIGNALING PATHWAY	1.548901	0.006689
LEUKOCYTE TRANSENDOTHELIAL MIGRATION	1.569841	0.008772
PORPHYRIN AND CHLOROPHYLL METABOLISM	1.684691	0.008993
BLADDER CANCER	1.637299	0.011173
CHEMOKINE SIGNALING PATHWAY	1.405576	0.017986
TOXOPLASMOSIS	1.512747	0.021277
TGF-BETA SIGNALING PATHWAY	1.488449	0.021858
CELL ADHESION MOLECULES (CAMs)	1.512765	0.022727
VIBRIO CHOLERAЕ INFECTION	1.509372	0.02583
T CELL RECEPTOR SIGNALING PATHWAY	1.450954	0.026415
NATURAL KILLER CELL MEDIATED CYTOTOXICITY	1.502091	0.026978
PHAGOSOME	1.418228	0.034545
RIBOSOME BIOGENESIS IN EUKARYOTES	1.427248	0.034602
MINERAL ABSORPTION	1.447369	0.049116
PHOTOTRANSDUCTION	-2.74511	0
PARKINSON'S DISEASE	-1.54818	0

OXIDATIVE PHOSPHORYLATION	-1.63641	0.002232
HUNTINGTON'S DISEASE	-1.3618	0.023913
ALZHEIMER'S DISEASE	-1.36465	0.034642
GLYCOSAMINOGLYCAN BIOSYNTHESIS - CHONDROITIN SULFATE	-1.48782	0.044715

^a NES: normalized enrichment score.

^b NOM *P* value: nominal *P* value.

Table S6. Significantly altered retinal gene sets as a result of bright light exposure in *Abca4*^{-/-}*Rdh8*^{-/-} mice. Gene expression in the retinas from *Abca4*^{-/-}*Rdh8*^{-/-} mice exposed to bright light was compared to the gene expression in the retinas of mice that had not been exposed to bright light. These data were obtained from an independently repeated set of experiments that provided the controls for the retinal transcriptome analyses of mice that received combined treatments.

Gene set name	NES ^a	NOM <i>P</i> value ^b
OSTEOCLAST DIFFERENTIATION	2.229871	0
CYTOKINE-CYTOKINE RECEPTOR INTERACTION	2.180506	0
HEPATITIS C	2.12151	0
INFLUENZA A	2.105985	0
TOLL-LIKE RECEPTOR SIGNALING PATHWAY	2.09756	0
JAK-STAT SIGNALING PATHWAY	2.079457	0
MEASLES	2.047953	0
LEISHMANIASIS	2.041105	0
RIG-I-LIKE RECEPTOR SIGNALING PATHWAY	2.029745	0
CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)	2.001642	0
CYTOSOLIC DNA-SENSING PATHWAY	1.901548	0
APOPTOSIS	1.876382	0
TUBERCULOSIS	1.852426	0
MAPK SIGNALING PATHWAY	1.775217	0
ANTIGEN PROCESSING AND PRESENTATION	1.763592	0
CHEMOKINE SIGNALING PATHWAY	1.713428	0
B CELL RECEPTOR SIGNALING PATHWAY	1.737553	0.00125
RHEUMATOID ARTHRITIS	1.81068	0.001376
TOXOPLASMOSIS	1.682618	0.002404
LEUKOCYTE TRANSENDOTHELIAL MIGRATION	1.627085	0.003727
P53 SIGNALING PATHWAY	1.718236	0.003906
INSULIN SIGNALING PATHWAY	1.532373	0.004598
NEUROTROPHIN SIGNALING PATHWAY	1.605815	0.005688
PRION DISEASES	1.670822	0.005755
SHIGELLOSIS	1.642595	0.006369
T CELL RECEPTOR SIGNALING PATHWAY	1.609217	0.007344
CHRONIC MYELOID LEUKEMIA	1.563919	0.007435
PATHWAYS IN CANCER	1.423846	0.008333
REGULATION OF ACTIN CYTOSKELETON	1.425106	0.009772
PROTEASOME	1.568564	0.010038
TYPE II DIABETES MELLITUS	1.59443	0.012146
ACUTE MYELOID LEUKEMIA	1.566775	0.013924
AMYOTROPHIC LATERAL SCLEROSIS (ALS)	1.540152	0.014103
ADIPOCYTOKINE SIGNALING PATHWAY	1.56679	0.016291
DORSO-VENTRAL AXIS FORMATION	1.642545	0.016296

MALARIA	1.573381	0.027356
THYROID CANCER	1.550927	0.027941
WNT SIGNALING PATHWAY	1.457934	0.028868
PANCREATIC CANCER	1.479344	0.030113
PATHOGENIC ESCHERICHIA COLI INFECTION	1.497784	0.030872
TGF-BETA SIGNALING PATHWAY	1.464963	0.032298
BASE EXCISION REPAIR	1.509695	0.036061
CELL CYCLE	1.359097	0.044118
DILATED CARDIOMYOPATHY	1.420122	0.04534
GNRH SIGNALING PATHWAY	1.418318	0.047679
PHOTOTRANSDUCTION	-2.70085	0
OXIDATIVE PHOSPHORYLATION	-1.33032	0.036232

^a NES: normalized enrichment score.

^b NOM *P* value: nominal *P* value.

Table S7. Retinal gene sets beneficially affected as a result of combined pretreatment with BRM, MTP, and TAM. Gene expression in the retinas from DMSO-treated light-exposed *Abca4^{-/-}Rdh8^{-/-}* mice was compared to the gene expression in the retinas from light-exposed mice pretreated with BRM, MTP, and TAM.

Gene set name	NES ^a	NOM <i>P</i> value ^b
INFLUENZA A	2.143801	0
OSTEOCLAST DIFFERENTIATION	2.14301	0
CYTOKINE-CYTOKINE RECEPTOR INTERACTION	2.126632	0
TOLL-LIKE RECEPTOR SIGNALING PATHWAY	2.102577	0
MEASLES	1.991847	0
P53 SIGNALING PATHWAY	1.981955	0
JAK-STAT SIGNALING PATHWAY	1.973431	0
HEPATITIS C	1.964715	0
LEISHMANIASIS	1.945592	0
CYTOSOLIC DNA-SENSING PATHWAY	1.857026	0
PATHOGENIC ESCHERICHIA COLI INFECTION	1.83432	0
APOPTOSIS	1.81466	0
TOXOPLASMOSIS	1.683499	0
MAPK SIGNALING PATHWAY	1.671156	0
PATHWAYS IN CANCER	1.504963	0
CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)	1.790724	0.001202
RIG-I-LIKE RECEPTOR SIGNALING PATHWAY	2.039497	0.001299
TUBERCULOSIS	1.601844	0.002345
VIRAL MYOCARDITIS	1.682111	0.002717
RHEUMATOID ARTHRITIS	1.706822	0.006793
DORSO-VENTRAL AXIS FORMATION	1.689233	0.008415
PROTEASOME	1.604089	0.01005
CHEMOKINE SIGNALING PATHWAY	1.566392	0.010274
NEUROTROPHIN SIGNALING PATHWAY	1.45211	0.011403
ANTIGEN PROCESSING AND PRESENTATION	1.68035	0.012162
LEUKOCYTE TRANSENDOTHELIAL MIGRATION	1.529136	0.013699
B CELL RECEPTOR SIGNALING PATHWAY	1.55796	0.015385
CHRONIC MYELOID LEUKEMIA	1.512632	0.015951
MALARIA	1.642832	0.016517

PHAGOSOME	1.484726	0.016867
AXON GUIDANCE	1.487379	0.017026
INSULIN SIGNALING PATHWAY	1.458486	0.020737
PRION DISEASES	1.596309	0.021645
ACUTE MYELOID LEUKEMIA	1.539761	0.023591
SHIGELLOSIS	1.434921	0.031095
CELL CYCLE	1.396446	0.031432
NOTCH SIGNALING PATHWAY	1.48805	0.033333
ADIPOCYTOKINE SIGNALING PATHWAY	1.455296	0.03607
REGULATION OF ACTIN CYTOSKELETON	1.361143	0.04102
PORPHYRIN AND CHLOROPHYLL METABOLISM	1.455169	0.041547
AMYOTROPHIC LATERAL SCLEROSIS (ALS)	1.447752	0.042308
THYROID CANCER	1.46991	0.048091
PHOTOTRANSDUCTION	-2.78328	0
PARKINSON'S DISEASE	-1.29663	0.021583
OXIDATIVE PHOSPHORYLATION	-1.3763	0.022901
OLFACTORY TRANSDUCTION	-1.60694	0.025806

^a NES: normalized enrichment score.

^b NOM *P* value: nominal *P* value.

Table S8. Retinal gene sets beneficially affected as a result of combined pretreatment with BRM, MTP, and DOX. Gene expression in the retinas from DMSO-treated light-exposed *Abca4^{-/-}Rdh8^{-/-}* mice was compared to the gene expression in the retinas from light-exposed mice pretreated with BRM, MTP, and DOX.

Gene set name	NES ^a	NOM <i>P</i> value ^b
OSTEOCLAST DIFFERENTIATION	2.303482	0
TOLL-LIKE RECEPTOR SIGNALING PATHWAY	2.212396	0
HEPATITIS C	2.167976	0
INFLUENZA A	2.111236	0
CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)	2.054227	0
CYTOKINE-CYTOKINE RECEPTOR INTERACTION	2.042606	0
LEISHMANIASIS	1.990311	0
JAK-STAT SIGNALING PATHWAY	1.91761	0
TUBERCULOSIS	1.899948	0
MEASLES	1.89661	0
APOPTOSIS	1.888334	0
RIG-I-LIKE RECEPTOR SIGNALING PATHWAY	1.844952	0
MAPK SIGNALING PATHWAY	1.828108	0
RHEUMATOID ARTHRITIS	1.758656	0
CHEMOKINE SIGNALING PATHWAY	1.668104	0.001449
T CELL RECEPTOR SIGNALING PATHWAY	1.570795	0.0016
CYTOSOLIC DNA-SENSING PATHWAY	1.68831	0.001686
NEUROTROPHIN SIGNALING PATHWAY	1.561962	0.004451
P53 SIGNALING PATHWAY	1.68567	0.006483
TOXOPLASMOSIS	1.54663	0.012048
ERBB SIGNALING PATHWAY	1.483864	0.012658
INSULIN SIGNALING PATHWAY	1.439256	0.017991
PROTEASOME	1.4892	0.019704
PATHOGENIC ESCHERICHIA COLI INFECTION	1.548095	0.021595

TYPE II DIABETES MELLITUS	1.560293	0.021703
ANTIGEN PROCESSING AND PRESENTATION	1.536125	0.024221
AMYOTROPHIC LATERAL SCLEROSIS (ALS)	1.532355	0.025641
B CELL RECEPTOR SIGNALING PATHWAY	1.54414	0.028007
PANCREATIC CANCER	1.456896	0.034596
ADIPOCYTOKINE SIGNALING PATHWAY	1.460983	0.035032
PHAGOSOME%KEGG	1.385304	0.039695
EPITHELIAL CELL SIGNALING IN HELICOBACTER PYLORI INFECTION	1.467262	0.044343
AMINOACYL-TRNA BIOSYNTHESIS	1.439216	0.046358
CELL CYCLE	1.388515	0.046377
GNRH SIGNALING PATHWAY	1.4003	0.047546
PHOTOTRANSDUCTION	-2.31083	0
PROTEIN DIGESTION AND ABSORPTION	-2.03409	0
ECM-RECEPTOR INTERACTION	-1.68148	0.005168
GLUTATHIONE METABOLISM	-1.62617	0.012376
PROXIMAL TUBULE BICARBONATE RECLAMATION	-1.68127	0.015945
FOCAL ADHESION	-1.40136	0.016077
PROPANOATE METABOLISM	-1.50335	0.025943
SMALL CELL LUNG CANCER	-1.45885	0.033537
ALDOSTERONE-REGULATED SODIUM REABSORPTION	-1.48797	0.049261

^a NES: normalized enrichment score.

^b NOM *P* value: nominal *P* value.