

age-related retinal diseases (18, 19). Oxidative changes in the ageing RPE predisposes AMD by triggering altered mitochondrial metabolism, impaired intracellular RPE processing pathways (autophagy, phagolysosome and protein trafficking) and senescence, all tractable pathways that cross-regulate and also determine appropriate immune responses (20-24). Inflammatory responses can be initiated by pathogen-induced reactive oxygen species (ROS) through signalling transduction pathways mediated by Toll-like receptors (TLRs) (25-27), which detect a variety of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Nevertheless, excessive or persistent TLR-mediated inflammation disrupts cell and tissue homeostasis.

The magnitude of inflammatory responses is balanced by tonic inhibitory mechanisms, including Interleukin 1 receptor-associated kinase-M (IRAK-M), encoded by *IRAK3 gene*, a unique IRAK family member that lacks kinase activity and serves as an anti-inflammatory molecule (28). IRAK-M suppresses TLRs or Interleukin 1 receptor (IL-1R)-transduced inflammation cascade by impeding the uncoupling of IRAK1/4 from IRAK-MyD88 complex (Myddosome) (28-30). Dysregulated IRAK signalling contributes to metabolic insulin resistance in diabetes and obesity (30, 31). IRAK-M expression is downregulated in monocytes and adipose tissues of obese subjects, associated with exaggerated oxidative stress, elevated systemic inflammation and features of metabolic syndrome (31). It was previously found that IRAK-M was expressed in a murine RPE cell line and the expression was reduced by wortmannin (a PI3K inhibitor) or following a prolonged period of culture when the cells demonstrated increased mitochondrial superoxide and impaired autophagy (13). However, the expression, role, and significance of the regulation of IRAK-M in retinal health and diseases have not been defined.

Summary

The present inventors have identified that IRAK-M expression within the RPE in human and mouse retinas declines with age and oxidative stress. Data mining of an RNA-Seq study further divulged lower IRAK-M expression in AMD eyes than those from age-matched controls. Immunohistochemistry staining analysis of human eye sections additionally confirmed the decline of ocular IRAK-M expression with age and AMD. The decreased IRAK-M expression may undermine ability to maintain RPE function and health. For example, IRAK-M knockout mice developed outer retinal and RPE pathology, and this was accentuated following oxidative insult. The present inventors have showed that augmentation of IRAK-M expression provided protection to the RPE and retina. By introducing human IRAK-M transgene to mouse RPE, mitochondrial activity was retained and cell survival under oxidative stress was promoted. The present inventors have also shown the prevention of AMD-like phenotype in two animal models (i.e., prevention of light-induced retinal damage (LIRD) in wild-type mice and prevention of age-related retinal damage in IRAK-M knockout mice).

Accordingly, the disclosure relates to an agent for increasing IRAK-M expression in a target cell and/or increasing IRAK-M activity in a target cell, for use in a method of treatment or prophylaxis of macular degeneration in a subject.

5 IRAK-M in a target cell may be increased by introducing exogenous IRAK-M to a target cell. Thus, the agent may be an IRAK-M polypeptide or a nucleic acid encoding IRAK-M. The following examples relate to approaches for increasing IRAK-M in a target cell by introducing exogenous IRAK-M to a target cell.

10 In one aspect, the present disclosure provides for a use of a nucleic acid in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid comprises a nucleic acid sequence encoding IRAK-M and wherein the nucleic acid is capable of driving expression of IRAK-M in a target cell. In an example of the disclosure, provided is a nucleic acid for use in a method of treatment or prophylaxis of macular degeneration in a subject. The
15 nucleic acid may comprise a nucleic acid sequence encoding IRAK-M. The nucleic acid may be capable of driving expression of IRAK-M in a target cell.

In some examples, a promoter is operably linked to the nucleic acid sequence. The promoter may be an RPE-specific promoter. The RPE-specific promoter may be selected from the group consisting of
20 a RPE65 promoter, a NA65 promoter, a VMD2 promoter (also known as Best1 promoter), and a Synpiii promoter. In alternative examples, the promoter is a ubiquitous promoter. The ubiquitous promoter may be selected from the group consisting of a CMV promoter, a CAG promoter, a GAPDH promoter, a UbiC promoter, and an EF-1 α promoter. In other examples, the promoter is the native promoter for *IRAK3* or a functional fragment thereof.

25 In some examples, IRAK-M expression is increased in the target cell comprising the nucleic acid compared to an equivalent cell not comprising the nucleic acid. Autophagic flux may be maintained or increased in the target cell comprising the nucleic acid compared to an equivalent cell not comprising the nucleic acid. Mitochondrial activity may be maintained or increased in the target cell comprising
30 the nucleic acid compared to an equivalent cell not comprising the nucleic acid. Proinflammatory cytokine production may be reduced in the target cell comprising the nucleic acid compared to an equivalent target cell not comprising the nucleic acid. The proinflammatory cytokines may be selected from the group consisting of GM-CSF and MCP-1.

35 The nucleic acid may be suitable for integration into the genome of the target cell by an RNA-guided endonuclease system. The RNA-guided endonuclease may be a CRISPR-Cas system.

In some examples, the nucleic acid is DNA. The nucleic acid may be an episome. In some examples, the nucleic acid is a plasmid or a minicircle. In some examples, the nucleic acid is RNA.

40 The nucleic acid may be messenger RNA or circular RNA.

In some examples, the nucleic acid is delivered to a target cell via a non-viral carrier. The non-viral carrier may be selected from the group consisting of nanoparticles, liposomes, cationic polymer, and calcium phosphate particles.

5 In some examples, the nucleic acid is delivered to a target cell via a viral vector. The viral vector may be selected from the group consisting of an adeno-associated virus vector, an adenovirus vector, a retrovirus vector, an orthomyxovirus vector, a paramyxovirus vector, a papovavirus vector, a picornavirus vector, a lentivirus vector, a herpes simplex virus vector, a vaccinia virus vector, a pox virus vector, an anellovirus vector, and an alphavirus vector.

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The nucleic acid may be a viral vector genome. The viral vector genome may be selected from the group consisting of an adeno-associated virus vector genome, an adenovirus vector genome, a retrovirus vector genome, an orthomyxovirus vector genome, a paramyxovirus vector genome, a papovavirus vector genome, a picornavirus vector genome, a lentivirus vector genome, a herpes simplex virus vector genome, a vaccinia virus vector genome, a pox virus vector genome, an anellovirus vector genome, and an alphavirus vector genome.

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The macular degeneration may be age-related macular degeneration (AMD). The age-related macular degeneration (AMD) may be dry AMD. In some examples, the dry AMD is selected from the group consisting of early dry AMD, intermediate dry AMD, and advanced dry AMD.

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The target cell may be a cell of the retina or the choroid. In some examples, the target cell is a cell of the retina. The target cell may be a cell of the ganglion cell layer (GCL), the inner plexiform layer (IPL), the inner nuclear layer (INL), the outer plexiform layer (OPL), the outer nuclear layer (ONL), the photoreceptor outer segment (POS), or the retinal pigmental epithelium (RPE). In some examples, the target cell is a cell of the RPE.

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The target cell may be a myeloid cell. The myeloid cell may be a retinal myeloid cell. In some examples, the target cell is a CD11b+ myeloid cell.

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The nucleic acid may be administered intraocularly, intravitreally, subretinally, or periocularly to a subject. In some examples, the nucleic acid is administered subretinally. The nucleic acid may be administered by injection or infusion. In some examples, the nucleic acid is administered by subretinal injection. In some examples, the subject is human. The subject may be affected by or at risk of developing macular degeneration.

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In some examples, the nucleic acid sequence encodes a polypeptide comprising an amino acid sequence having at least 60% sequence identity to the amino acid sequence of SEQ ID NO: 1. In some examples, the nucleic acid sequence encodes a functional polypeptide. The nucleic acid sequence may encode a polypeptide capable of preventing dissociation of IRAK-1 and/or IRAK-4

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from MyD88 in a target cell. The nucleic acid sequence may encode a polypeptide capable of preventing formation of an IRAK-1-TRAF6 complex.

In another aspect, the present disclosure provides for a use of a vector virion in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the vector virion comprises a nucleic acid comprising a nucleic acid sequence encoding IRAK-M and wherein the nucleic acid is capable of driving expression of IRAK-M in a target cell. In another example, provided is a vector virion for use in a method of treatment or prophylaxis of macular degeneration in a subject, the vector virion comprising the nucleic acid described herein.

In some examples, IRAK-M expression is increased in the target cell comprising the vector virion compared to an equivalent cell not comprising the vector virion. Autophagic flux may be maintained or increased in the target cell comprising the vector virion compared to an equivalent cell not comprising the vector virion. Mitochondrial activity may be maintained or increased in the target cell comprising the nucleic acid compared to an equivalent cell not comprising the vector virion. Proinflammatory cytokine production may be reduced in the target cell comprising the vector virion compared to an equivalent target cell not comprising the vector virion. The proinflammatory cytokines may be selected from the group consisting of GM-CSF and MCP-1.

The vector virion may be selected from the group consisting of adeno-associated virus, adenovirus, retrovirus, orthomyxovirus, paramyxovirus, papovavirus, picornavirus, lentivirus, herpes simplex virus, vaccinia virus, pox virus, anellovirus, and alphavirus. In some examples, the vector virion is an adeno-associated virus (AAV). The AAV may be selected from the group consisting of AAV type 1 (AAV-1), AAV type 2 (AAV-2), AAV type 3 (AAV-3), AAV type 4 (AAV-4), AAV type 5 (AAV-5), AAV type 6 (AAV6), AAV type 7 (AAV-7), AAV type 8 (AAV-8), and AAV type 9 (AAV9). In some examples, the AAV is AAV2. In some examples, the AAV is AAV8.

The vector virion may be administered intraocularly, intravitreally, subretinally, or periocularly to a subject. In some examples, the vector virion is administered subretinally. The vector virion may be administered by injection or infusion. In some examples, the vector virion is administered by subretinal injection. In some examples, the subject is human. The subject may be affected by or at risk of developing macular degeneration.

In some examples, the vector virion comprises a nucleic acid sequence encoding a polypeptide comprising an amino acid sequence having at least 60% sequence identity to the amino acid sequence of SEQ ID NO: 1. The vector virion may comprise a nucleic acid sequence encoding a polypeptide capable of preventing dissociation of IRAK-1 and/or IRAK-4 from MyD88 in a target cell. The vector virion may comprise a nucleic acid sequence encoding a polypeptide capable of preventing formation of an IRAK-1-TRAF6 complex.

In a further aspect, the present disclosure provides for a use of an IRAK-M polypeptide in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject. A further example provides an IRAK-M polypeptide for use in a method of treatment or prophylaxis of macular degeneration in a subject. In some examples, the polypeptide comprises an amino acid sequence having at least 60% sequence identity to the amino acid sequence of SEQ ID NO: 1.

The polypeptide may be capable of preventing dissociation of IRAK-1 and/or IRAK-4 from MyD88 in a target cell. The polypeptide may be capable of preventing formation of an IRAK-1-TRAF6 complex.

In some examples, the polypeptide further comprises a cell penetrating peptide (CPP). In some examples, the polypeptide further comprises a peptide-based cleavable linker (PCL). The CPP may be conjugated to the N-terminus of the PCL. The amino acid sequence having at least 60% sequence identity to the amino acid sequence of SEQ ID NO: 1 may be conjugated to the C-terminus of the PCL. In some examples, the PCL is a peptide sequence that is cleavable by cathepsin D.

Autophagic flux may be maintained or increased in the target cell comprising the polypeptide compared to an equivalent cell not comprising the polypeptide. Mitochondrial activity may be maintained or increased in the target cell comprising the polypeptide compared to an equivalent cell not comprising the polypeptide. Proinflammatory cytokine production may be reduced in the target cell comprising the polypeptide compared to an equivalent target cell not comprising the polypeptide. The proinflammatory cytokines may be selected from the group consisting of GM-CSF and MCP-1.

In a further aspect, the present disclosure provides for a use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising: a) a nucleic acid sequence encoding an RNA-guided endonuclease; b) a nucleic acid sequence encoding a guide RNA complementary to a target sequence associated with an insertion site in the genome of the target cell and capable of directing said RNA-guided endonuclease to said target sequence; and c) a nucleic acid sequence encoding IRAK-M, wherein the nucleic acid sequence encoding IRAK-M is capable of driving expression of IRAK-M in a target cell of the subject and wherein the nucleic acid system is suitable for directed insertion of the nucleic acid sequence encoding IRAK-M at the insertion site in the genome of the target cell. In an example of the disclosure, a nucleic acid system is provided comprising one or more nucleic acids, comprising:

- a) a nucleic acid sequence encoding an RNA-guided endonuclease;
 - b) a nucleic acid sequence encoding a guide RNA complementary to a target sequence associated with an insertion site in the genome of the target cell and capable of directing said RNA-guided endonuclease to said target sequence; and
 - c) a nucleic acid sequence encoding IRAK-M,
- for use in a method of treatment or prophylaxis of macular degeneration in a subject. The nucleic acid sequence encoding IRAK-M is capable of driving expression of IRAK-M in a target cell of the subject and the nucleic acid system is suitable for directed insertion of the nucleic acid sequence encoding IRAK-M at the insertion site in the genome of the target cell.

The nucleic acid sequence encoding IRAK-M may be flanked by 5' homology arm and a 3' homology arm. In some examples, the 5' homology arm is homologous to a DNA sequence 5' of the target sequence from the insertion site and the 3' homology arm is homologous to a DNA sequence 3' of the target sequence from the insertion site. The nucleic acid sequence encoding IRAK-M may further
5 comprise a 5' flanking sequence comprising a target sequence and a 3' flanking sequence comprising a target sequence. In some examples, the 5' flanking sequence is 5' of the 5' homology arm and the 3' flanking sequence is 3' of the 3' homology arm.

10 In alternative examples, the nucleic acid sequence encoding IRAK-M is flanked by a 5' target sequence and a 3' target sequence. The 5' target sequence and the 3' target sequence may be identical to target sequence from an insertion site in the genome.

In some examples, the one or more nucleic acids are one or more viral vector genomes. The one or more viral vector genomes may be one or more adeno-associated virus vector genomes.

- 5 Further provided is a viral vector system comprising the nucleic acid system as described herein. In some examples, the viral vector system is an adeno-associated virus vector system.

Another example provides a pharmaceutical composition comprising a nucleic acid, a vector virion, a polypeptide, a nucleic acid system, or a viral vector system as described herein. In some examples,
10 the pharmaceutical composition is formulated for ocular delivery.

IRAK-M expression may be increased by increasing endogenous IRAK-M expression in a target cell. Thus, the agent may be capable of increasing endogenous IRAK-M expression. The following examples relate to agents capable of increasing endogenous IRAK-M expression in a target cell.

15 In a further aspect, the present disclosure provides for a use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising: a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to one or more transcriptional
20 activators; and b) a nucleic acid sequence encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject. Accordingly, provided is a nucleic acid system comprising one or more nucleic acids, comprising:

- 25 a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to one or more transcriptional activators; and
b) a nucleic acid sequence encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence,
30 for use in a method of treatment or prophylaxis of macular degeneration in a subject, where the nucleic acid system increases IRAK-M expression in a target cell of the subject.

The transcriptional activator may be VP64.

35 In a further aspect, the present disclosure provides for a use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising: a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease; and b) a nucleic acid sequence

encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein said guide RNA further comprises an aptamer capable of specifically binding to a transcriptional activator, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject. Accordingly, provided is a nucleic acid system comprising one or more nucleic acids, comprising:

a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease; and

b) a nucleic acid sequence encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein said guide RNA further comprises an aptamer capable of specifically binding to a transcriptional activator, for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

In a further aspect, the present disclosure provides for a use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising: a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease; b) a nucleic acid sequence encoding an RNA binding protein fused to one or more transcriptional activators; and c) a nucleic acid sequence encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein said guide RNA further comprises an RNA aptamer capable of specifically binding to the RNA binding protein, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject. An example of the disclosure, also provides a nucleic acid system comprising one or more nucleic acids, comprising:

a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease;

b) a nucleic acid sequence encoding an RNA binding protein fused to one or more transcriptional activators; and

c) a nucleic acid sequence encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein said guide RNA further comprises an RNA aptamer capable of specifically binding to the RNA binding protein,

for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

The one or more transcriptional activators may be selected from the group consisting of VP64, p65 and HSF1. The RNA aptamer may be capable of binding to an RNA binding protein dimer. The RNA binding protein may be MS2. In some examples, the deactivated RNA-guided endonuclease is fused to an additional transcriptional activator. The additional transcriptional activator may be VP64.

In a further aspect, the present disclosure provides for a use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising: a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to an epitope repeat array comprising one or more epitopes; b) one or more nucleic acid sequences encoding an epitope binding molecule fused to one or more transcriptional activators, wherein said epitope binding molecule is capable of specifically binding to an epitope of the epitope repeat array; and c) a nucleic acid sequence encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject. A further example provides a nucleic acid system comprising one or more nucleic acids, comprising:

a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to an epitope repeat array comprising one or more epitopes;

b) one or more nucleic acid sequences encoding an epitope binding molecule fused to one or more transcriptional activators, wherein said epitope binding molecule is capable of specifically binding to an epitope of the epitope repeat array; and

c) a nucleic acid sequence encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence,

for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

The epitope binding molecule may comprise a nuclear localisation sequence (NLS). The epitope binding molecule may be an antibody or antibody-like molecule. In some examples, the one or more transcriptional activators are selected from the group consisting of VP64, p65 and Rta.

- 5 The one or more nucleic acids may be one or more viral vector genomes. The one or more viral vector genomes may be one or more adeno-associated virus vector genomes.

In a further aspect, the present disclosure provides for a use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject,
 10 wherein the nucleic acid system comprises one or more nucleic acids, comprising: a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to one or more DNA demethylating agents; and b) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene and capable of directing
 15 said RNA-guided endonuclease to said target sequence, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject. Another example provides a nucleic acid system comprising one or more nucleic acids, comprising:

- a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to one or more DNA demethylating agents; and
 20 b) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene, and capable of directing said RNA-guided endonuclease to said target sequence,
 for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the
 25 nucleic acid system increases IRAK-M expression in a target cell of the subject.

In a further aspect, the present disclosure provides for a use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising: a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease; and b) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein said guide RNA further comprises an aptamer capable of specifically binding to a DNA demethylating agent, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject. Further provided is a nucleic acid system comprising one or more nucleic acids, comprising:

a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease; and

b) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene, and capable of directing said RNA-guided endonuclease to said target sequence, wherein said guide RNA further comprises an aptamer capable of specifically binding to a DNA demethylating agent, for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

In a further aspect, the present disclosure provides for a use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising: a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease; b) a nucleic acid sequence encoding an RNA binding protein fused to one or more DNA demethylating agents; c) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein said guide RNA further comprises an RNA aptamer capable of specifically binding to the RNA binding protein, for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject. An example provides a nucleic acid system comprising one or more nucleic acids, comprising:

a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease;

b) a nucleic acid sequence encoding an RNA binding protein fused to one or more DNA demethylating agents;

c) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene, and capable of directing said RNA-guided endonuclease to said target sequence, wherein said guide RNA further comprises an RNA aptamer capable of specifically binding to the RNA binding protein,
 5 for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

The RNA aptamer may be capable of binding to an RNA binding protein dimer. The RNA binding protein may be MS2. In some examples, the deactivated RNA-guided endonuclease is fused to an additional transcriptional activator.
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In a further aspect, the present disclosure provides for a use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising: a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to an epitope repeat array comprising one or more epitopes; b) one or more nucleic acid sequences encoding an epitope binding molecule fused to one or more DNA demethylating agents, wherein said epitope binding molecule is capable of specifically binding to an epitope of the epitope repeat array; and c) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject. A further example provides a nucleic acid system comprising one or more nucleic acids,
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 25 comprising:

a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to an epitope repeat array comprising one or more epitopes;

b) one or more nucleic acid sequences encoding an epitope binding molecule fused to one or more DNA demethylating agents, wherein said epitope binding molecule is capable of specifically binding to an epitope of the epitope repeat array; and
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c) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene, and capable of directing said RNA-guided endonuclease to said target sequence,

for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.
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The epitope binding molecule may comprise a nuclear localisation sequence (NLS). The epitope binding molecule may be an antibody or antibody-like molecule.

5 In some examples, the DNA demethylating agent is TET1. In some examples, the DNA demethylating agent is LESD1.

The one or more nucleic acids may be one or more viral vector genomes. The one or more viral vector genomes may be one or more adeno-associated virus vector genomes.

10 Also provided is a viral vector system comprising the nucleic acid systems as described herein. In some examples, the viral vector system is an adeno-associated virus vector system.

15 An alternative targeted approach for increasing endogenous expression of IRAK-M in a target cell may use a nucleic acid binding molecule (e.g., nucleic acid binding portion) capable of binding to a target sequence.

In a further aspect, the present disclosure provides for a use of a nucleic acid in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid comprises a nucleic acid sequence encoding a fusion protein, the fusion protein comprising: (a) a
20 nucleic acid binding molecule capable of binding to a target sequence in the promoter or regulatory sequences of the *IRAK3* gene; and (b) one or more transcriptional activators, wherein the fusion protein is capable of increasing IRAK-M expression in a target cell of the subject, optionally wherein the transcriptional activator is the transactivation domain, VP64. Thus, an example provides a nucleic acid comprising a nucleic acid sequence encoding a fusion protein, the fusion protein comprising:

25 a) a nucleic acid binding molecule capable of binding to a target sequence in the promoter or regulatory sequences of the *IRAK3* gene; and

b) one or more transcriptional activators,

for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the fusion protein is capable of increasing IRAK-M expression in a target cell of the subject.

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An example of the disclosure provides a nucleic acid system comprising:

a) a nucleic acid sequence encoding a fusion protein, wherein the fusion protein comprises (i) a nucleic acid binding molecule capable of binding to a target sequence in the promoter or regulatory sequences of the *IRAK3* gene and (ii) an epitope repeat array; and

35 b) one or more nucleic acid sequences encoding an epitope binding molecule fused to one or more transcriptional activators, wherein said epitope binding molecule is capable of specifically binding to an epitope of the epitope repeat array,

for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system is capable of increasing IRAK-M expression in a target cell of the subject.

5 In a further aspect, the present disclosure provides for a use of a nucleic acid in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid comprises a nucleic acid sequence encoding a fusion protein, the fusion protein comprising: a) a nucleic acid binding molecule capable of binding to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene; and b) one or more DNA demethylating agents, wherein the fusion
10 protein is capable of increasing IRAK-M expression in a target cell of the subject. A further example provides a nucleic acid sequence encoding a fusion protein, the fusion protein comprising:
a) a nucleic acid binding molecule capable of binding to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene; and
15 b) one or more DNA demethylating agents,

for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the fusion protein is capable of increasing IRAK-M expression in a target cell of the subject.

Also provided is a nucleic acid system comprising:

- 5 a) a nucleic acid sequence encoding a fusion protein, wherein the fusion protein comprises (i) nucleic acid binding molecule capable of binding to (1) a target sequence in the promoter sequence for the *IRAK3* gene, (2) a target sequence in the regulatory sequences for the *IRAK3* gene or (3) a target sequence in the *IRAK3* gene and (ii) an epitope repeat array; and
- 10 b) one or more nucleic acid sequences encoding an epitope binding molecule fused to one or more DNA demethylating agents, wherein said epitope binding molecule is capable of specifically binding to an epitope of the epitope repeat array,
- 15 for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system is capable of increasing IRAK-M expression in a target cell of the subject.
- 15 The nucleic acid binding molecule may be a TAL effector repeat array or a zinc finger array.

The transcriptional activator may be the transactivation domain, VP64.

- 20 The DNA demethylating agent may be a DNA demethylating enzyme or a fragment thereof. In further examples, the DNA demethylating agent is the catalytic domain of TET1. In some examples, the DNA demethylating agent is TET1. In some examples, the DNA demethylating agent is LESD1.

- 25 Another example provides a small molecule for use in a method of treatment or prophylaxis of macular degeneration in a subject, where the small molecule increases endogenous IRAK-M expression in a target cell of the subject.

- 30 The molecule may reduce DNA methylation in the promoter sequence for the *IRAK3* gene, the regulatory sequence for the *IRAK3* gene and/or in the *IRAK3* gene sequence. In some examples, the small molecule is EPZ-6438. In some examples, the small molecule is azacytidine.
- 30 In some examples, the small molecule is ibudilast.

- 35 The small molecule may enhance the transcription-activating activity of a factor (such as a polypeptide) that promotes transcription from the *IRAK3* promoter. In some examples, the small molecule is a glucocorticoid. In some examples, the small molecule is cortisol.

The small molecule may reduce the N⁶-methyladenosine (m⁶A) modification of IRAK-M mRNA transcripts, which reduces the mRNA degradation and increases IRAK-M expression. In some examples, the small molecule is a METTL3 inhibitor. In some examples, the small molecule is

STM2457. In some examples, the small molecule is Cpd-564. In some examples, the small molecule is UZH2.

A further example provides a nucleic acid for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid increases endogenous IRAK-M expression in a target cell of the subject.

In some examples, the nucleic acid inhibits METTL3 expression. The nucleic acid may be capable of binding to a target sequence in METTL3 mRNA and downregulating it, thereby increasing IRAK-M expression.

A further example provides a peptide or polypeptide for use in a method of treatment or prophylaxis of macular degeneration in a subject, where the peptide or polypeptide increases endogenous IRAK-M in a target cell of the subject.

The peptide or polypeptide may activate ERK1/2 and/or activate PI3K and Akt1. In some examples, the peptide or polypeptide is adiponectin. In some examples, the peptide or polypeptide is globular adiponectin.

In some examples, IRAK-M expression is increased in the target cell comprising the agent capable of increasing endogenous IRAK-M expression compared to an equivalent cell not comprising the agent. Autophagic flux may be maintained or increased in the target cell comprising the agent capable of increasing endogenous IRAK-M expression compared to an equivalent cell not comprising the agent. Mitochondrial activity may be maintained or increased in the target cell comprising the nucleic acid compared to an equivalent cell not comprising the agent capable of increasing endogenous IRAK-M expression. Proinflammatory cytokine production may be reduced in the target cell comprising the agent compared to an equivalent target cell not comprising the agent. The proinflammatory cytokines may be selected from the group consisting of GM-CSF and MCP-1.

Alternatively, or additionally, IRAK-M activity could be increased in a target cell. Thus, the agent may be capable of increasing IRAK-M activity. The following example relate to increasing IRAK-M activity in a target cell.

The agent may promote IRAK-M binding to IRAK-1 and/or IRAK-4. Alternatively, or additionally, the agent may promote IRAK-M binding to MyD88.

A small molecule for use in a method of treatment or prophylaxis of macular degeneration in a subject is provided, where the small molecule increases IRAK-M activity in a target cell of the subject.

The small molecule is capable of stimulating guanylate cyclase (GC), thereby increasing cellular cGMP. In some examples, the small molecule is nitric oxide (NO) donor. In some examples, the small molecule is nitric oxide. In some examples, the small molecule is riociguat. Alternatively, the small molecule may be cGMP.

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Further provided is a peptide or polypeptide for use in a method of treatment or prophylaxis of macular degeneration in a subject, where the peptide or polypeptide increases IRAK-M activity in a target cell of a subject. In some examples, the agent is a polypeptide.

10 The peptide or polypeptide may promote IRAK-M binding to IRAK-1. In some examples, the peptide or polypeptide is α -MSH or a fragment thereof.

In some examples, IRAK-M activity is increased in the target cell comprising the agent capable of increasing IRAK-M activity compared to an equivalent cell not comprising the agent. Autophagic flux may be maintained or increased in the target cell comprising the agent capable of increasing IRAK-M activity compared to an equivalent cell not comprising the agent. Mitochondrial activity may be maintained or increased in the target cell comprising the nucleic acid compared to an equivalent cell not comprising the agent capable of increasing IRAK-M activity. Proinflammatory cytokine production may be reduced in the target cell comprising the agent capable of increasing IRAK-M activity compared to an equivalent target cell not comprising the agent capable of increasing IRAK-M activity. The proinflammatory cytokines may be selected from GM-CSF and MCP-1.

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The macular degeneration may be age-related macular degeneration (AMD). The age-related macular degeneration (AMD) may be dry AMD. In some examples, the dry AMD is selected from the group consisting of early dry AMD, intermediate dry AMD, and advanced dry AMD.

The target cell may be a cell of the retina or the choroid. In some examples, the target cell is a cell of the retina. The target cell may be a cell of the ganglion cell layer (GCL), the inner plexiform layer (IPL), the inner nuclear layer (INL), the outer plexiform layer (OPL), the outer nuclear layer (ONL), the photoreceptor outer segment (POS), or the retinal pigmental epithelium (RPE). In some examples, the target cell is a cell of the RPE.

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The target cell may be a myeloid cell. The myeloid cell may be a retinal myeloid cell. In some examples, the target cell is a CD11b+ myeloid cell.

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In a further aspect, the present disclosure provides for a use of a pharmaceutical composition in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the composition comprises the nucleic acid, the vector virion, the IRAK-M polypeptide, the nucleic acid system, or the nucleic acid as described herein, optionally wherein the pharmaceutical composition is formulated for ocular delivery. A further example provides a pharmaceutical composition comprising one or more of the agents as described herein. In some examples, the pharmaceutical composition is formulated for ocular delivery.

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The disclosure includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

Summary of the Figures

Embodiments and experiments illustrating the principles of the invention will now be discussed with reference to the accompanying figures in which:

Figure 1. IRAK-M is predominantly expressed by RPE in the retina and its expression is reduced with age and in AMD.

(A&B) Representative confocal images of human retinal sections from a 20-year-old donor (without recorded ocular disease) demonstrate a predominant immunopositivity of IRAK-M at the pigmented RPE layer (anti-RPE65 stain). DAPI and anti-Rhodopsin were used to stain nuclei and photoreceptor outer segments (POS), respectively. (C&D) Representative confocal images of retinal sections of adult mice showing IRAK-M immunostaining largely colocalized with RPE65. (E&F) Representative western blotting and densitometry quantification demonstrate reduced levels of IRAK-M expression with old age in human RPE/choroidal lysates (E, n=4-6) and mouse RPE lysates (F, n=4-6). (G) Data mining of transcriptome data (GSE99248) shows significantly decreased IRAK-M mRNA level in RPE/Choroid/Sclera of AMD donors, compared to age-matched normal donors. Antisense RNA of IRAK-M showed an insignificant increase in AMD samples (n=7-8).

Figure 2. *In vitro* oxidative treatment downregulates IRAK-M expression in RPE cells.

(A) A human RPE cell line (ARPE-19) was treated with various concentrations of a prooxidant, paraquat (PQ), for up to 72h. LDH release demonstrate dose-dependent cytotoxic effect of PQ after 72h (n=3-4). (B) A sub-toxic concentration of PQ (0.25mM) was used to stress ARPE-19 and led to diminished IRAK-M expression in ARPE19 cells after 72h (Western blot), which is accompanied by (C) increased secretion of pro-inflammatory cytokines HMGB1 (EIA, n=4-6), IL-18 and GM-CSF, and decreased anti-inflammatory cytokine IL-11 (multiplex cytokine array, n=4). (D) LDH cytotoxicity assay demonstrates sub-toxic doses of PQ on human iPSC-derived RPE after 72h treatment (n=5). (E) Western blot shows downregulated IRAK-M expression by 72h treatment of subtoxic PQ (0.25-0.5mM). LDH assay (F, n=3-6) and representative western blot (G) show curtailed IRAK-M expression in human primary RPE cell culture by 72h treatment of sub-toxic PQ (0.25mM).

Figure 3. *In vivo* oxidative insults leads to declined IRAK-M level in the RPE.

Retinal oxidative stresses were induced in C57BL/6J mice by either fundus-light induction (100kLux for 20min, A-C) or intravitreal administration of PQ (2μl at 1.5mM, D-F). Western blot analyses of IRAK-M expression in RPE lysate on day 7 post oxidative damage (A&D, n=4 or 5). Representative funduscopy and OCT images obtained on day 14 demonstrate appearance of retinal lesions (red arrows, B&E) and a surrogate of cell loss as demonstrated by reduced thickness of outer retina (light model, C, n=8) or both outer and inner retina (PQ model, F, n=9-11).

Claims

1. Use of a nucleic acid in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid comprises a nucleic acid sequence encoding IRAK-M and wherein the nucleic acid is capable of driving expression of IRAK-M in a target cell.
2. The use according to claim 1, wherein a promoter is operably linked to the nucleic acid sequence, optionally wherein the promoter is selected from the group consisting of a CMV promoter, a Best1 promoter, and the native promoter for *IRAK3* or a functional fragment thereof.
3. The use according to any one of the preceding claims, wherein:
 - (i) autophagic flux is maintained or increased in the target cell comprising the nucleic acid compared to an equivalent cell not comprising the nucleic acid;
 - (ii) mitochondrial activity is maintained or increased in the target cell comprising the nucleic acid compared to an equivalent cell not comprising the nucleic acid; and/or
 - (iii) proinflammatory cytokine production is reduced in the target cell comprising the nucleic acid compared to an equivalent target cell not comprising the nucleic acid.
4. The use according to any one of the preceding claims, wherein the nucleic acid is delivered to a target cell via a viral vector, optionally wherein the viral vector is selected from the group consisting of an adeno-associated virus vector, an adenovirus vector, a retrovirus vector, an orthomyxovirus vector, a paramyxovirus vector, a papovavirus vector, a picornavirus vector, a lentivirus vector, a herpes simplex virus vector, a vaccinia virus vector, a pox virus vector, an anellovirus vector, and an alphavirus vector.
5. The use according to any one of the preceding claims, wherein the nucleic acid is a viral vector genome, optionally wherein the viral vector genome is selected from the group consisting of an adeno-associated virus vector genome, an adenovirus vector genome, a retrovirus vector genome, an orthomyxovirus vector genome, a paramyxovirus vector genome, a papovavirus vector genome, a picornavirus vector genome, a lentivirus vector genome, a herpes simplex virus vector genome, a vaccinia virus vector genome, a pox virus vector genome, an anellovirus vector genome, and an alphavirus vector genome.
6. The use according any one of the preceding claims, wherein the macular degeneration is age-related macular degeneration (AMD), optionally dry AMD.
7. The use according any one of the preceding claims, wherein the target cell is a cell of the retina or the choroid, optionally wherein the target cell is a cell of the RPE.

8. The use according any one of the preceding claims, wherein the nucleic acid is to be administered intraocularly, intravitreally, subretinally, or periorcularly to a subject, optionally wherein the nucleic acid is to be administered by subretinal injection.
9. The use according to any one of the preceding claims, wherein the nucleic acid sequence encodes a polypeptide comprising an amino acid sequence having at least 60% sequence identity to the amino acid sequence of SEQ ID NO: 1; and/or wherein the nucleic acid sequence encodes a polypeptide capable of preventing dissociation of IRAK-1 and/or IRAK-4 from MyD88 in a target cell.
10. Use of a vector virion in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the vector virion comprises a nucleic acid comprising a nucleic acid sequence encoding IRAK-M and wherein the nucleic acid is capable of driving expression of IRAK-M in a target cell.
11. The use according to claim 10, wherein a promoter is operably linked to the nucleic acid sequence, optionally wherein the promoter is selected from the group consisting of a CMV promoter, a Best1 promoter, and the native promoter for *IRAK3* or a functional fragment thereof.
12. The use according to claim 10 or claim 11, wherein:
 - (i) autophagic flux is maintained or increased in the target cell comprising the vector virion compared to an equivalent cell not comprising the vector virion;
 - (ii) mitochondrial activity is maintained or increased in the target cell comprising the vector virion compared to an equivalent cell not comprising the vector virion; and/or
 - (iii) proinflammatory cytokine production is reduced in the target cell comprising the vector virion compared to an equivalent target cell not comprising the vector virion.
13. The use according to any one of claims 10 to 12, wherein the nucleic acid is suitable for integration into the genome of the target cell by an RNA-guided endonuclease system.
14. The use according to any one of claims 10 to 13, wherein the vector virion is selected from the group consisting of adeno-associated virus, adenovirus, retrovirus, orthomyxovirus, paramyxovirus, papovavirus, picornavirus, lentivirus, herpes simplex virus, vaccinia virus, pox virus, anellovirus, and alphavirus.
15. The vector virion for use according to claim 14, wherein the vector virion is an adeno-associated virus (AAV) optionally wherein the AAV is selected from the group consisting of AAV type 1 (AAV-1), AAV type 2 (AAV-2), AAV type 3 (AAV-3), AAV type 4 (AAV-4), AAV type 5 (AAV-5), AAV type 6 (AAV-6), AAV type 7 (AAV-7), AAV type 8 (AAV-8), and AAV type 9 (AAV-9).

16. The use according any one of claims 10 to 15, wherein the macular degeneration is age-related macular degeneration (AMD), optionally dry AMD.
17. The use according any one of claims 10 to 16, wherein the target cell is a cell of the retina or the choroid, optionally wherein the target cell is a cell of the RPE.
18. The use according any one of claims 10 to 17, wherein the vector virion is to be administered intraocularly, intravitreally, subretinally, or periorcularly to a subject, optionally wherein the vector virion is to be administered by subretinal injection.
19. The use according to any one of claims 10 to 18, wherein the nucleic acid sequence encodes a polypeptide comprising an amino acid sequence having at least 60% sequence identity to the amino acid sequence of SEQ ID NO: 1; and/or wherein the nucleic acid sequence encodes a polypeptide capable of preventing dissociation of IRAK-1 and/or IRAK-4 from MyD88 in a target cell.
20. Use of an IRAK-M polypeptide in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject.
21. The use according to claim 20, wherein the IRAK-M polypeptide comprises an amino acid sequence having at least 60% sequence identity to the amino acid sequence of SEQ ID NO: 1; and/or wherein the IRAK-M polypeptide is capable of preventing dissociation of IRAK-1 and/or IRAK-4 from MyD88 in a target cell.
22. The use according to claim 20 or claim 21, wherein the IRAK-M polypeptide further comprises a cell penetrating peptide (CPP).
23. The use according to any one of claims 20 to 22, wherein:
 - (i) autophagic flux is maintained or increased in the target cell comprising the IRAK-M polypeptide compared to an equivalent cell not comprising the IRAK-M polypeptide;
 - (ii) mitochondrial activity is maintained or increased in the target cell comprising the IRAK-M polypeptide compared to an equivalent cell not comprising the IRAK-M polypeptide; and/or
 - (iii) proinflammatory cytokine production is reduced in the target cell comprising the IRAK-M polypeptide compared to an equivalent target cell not comprising the IRAK-M polypeptide.
24. Use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising:
 - a) a nucleic acid sequence encoding an RNA-guided endonuclease;

b) a nucleic acid sequence encoding a guide RNA complementary to a target sequence associated with an insertion site in the genome of the target cell and capable of directing said RNA-guided endonuclease to said target sequence; and

c) a nucleic acid sequence encoding IRAK-M,
wherein the nucleic acid sequence encoding IRAK-M is capable of driving expression of IRAK-M in a target cell of the subject and wherein the nucleic acid system is suitable for directed insertion of the nucleic acid sequence encoding IRAK-M at the insertion site in the genome of the target cell.

25. Use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising:

a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to one or more transcriptional activators; and

b) a nucleic acid sequence encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence,
wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

26. Use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising:

a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease; and

b) a nucleic acid sequence encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein said guide RNA further comprises an aptamer capable of specifically binding to a transcriptional activator,
wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

27. Use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising:

a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease;

b) a nucleic acid sequence encoding an RNA binding protein fused to one or more transcriptional activators; and

c) a nucleic acid sequence encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein said guide RNA further comprises an RNA aptamer capable of specifically binding to the RNA binding protein,
wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

28 The use according to claim 27, wherein:

- (i) the RNA aptamer is capable of binding to an RNA binding protein dimer;
- (ii) the RNA binding protein is MS2; and/or
- (iii) the deactivated RNA-guided endonuclease is fused to an additional transcriptional activator.

29. Use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising:

- a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to an epitope repeat array comprising one or more epitopes;
 - b) one or more nucleic acid sequences encoding an epitope binding molecule fused to one or more transcriptional activators, wherein said epitope binding molecule is capable of specifically binding to an epitope of the epitope repeat array; and
 - c) a nucleic acid sequence encoding a guide RNA complementary to a target sequence in the promoter or regulatory sequences for the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence,
- wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

30. The use according to claim 29, wherein the epitope binding molecule comprises a nuclear localisation sequence (NLS); and/or wherein the epitope binding molecule is an antibody or antibody-like molecule.

31. Use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising:

- a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to one or more DNA demethylating agents; and
 - b) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence,
- wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

32. Use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising:

- a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease; and
- b) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene and capable of directing said RNA-guided

endonuclease to said target sequence, wherein said guide RNA further comprises an aptamer capable of specifically binding to a DNA demethylating agent, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

33. Use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising:

- a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease;
- b) a nucleic acid sequence encoding an RNA binding protein fused to one or more DNA demethylating agents;
- c) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein said guide RNA further comprises an RNA aptamer capable of specifically binding to the RNA binding protein, for use in a method of treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

34. The use according to claim 33, wherein:

- (i) the RNA aptamer is capable of binding to an RNA binding protein dimer;
- (ii) the RNA binding protein is MS2; and/or
- (iii) the deactivated RNA-guided endonuclease is fused to an additional DNA demethylating agent.

35. Use of a nucleic acid system in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid system comprises one or more nucleic acids, comprising:

- a) a nucleic acid sequence encoding a deactivated RNA-guided endonuclease fused to an epitope repeat array comprising one or more epitopes;
- b) one or more nucleic acid sequences encoding an epitope binding molecule fused to one or more DNA demethylating agents, wherein said epitope binding molecule is capable of specifically binding to an epitope of the epitope repeat array; and
- c) a nucleic acid sequence encoding a guide RNA complementary to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene and capable of directing said RNA-guided endonuclease to said target sequence, wherein the nucleic acid system increases IRAK-M expression in a target cell of the subject.

36. The use according to claim 35, wherein the epitope binding molecule comprises a nuclear localisation sequence (NLS); and/or wherein the epitope binding molecule is an antibody or antibody-like molecule.

37. The use according to claim 35 or claim 36, wherein the DNA demethylating agent is TET1 or LESD1.

38. The use according to any one of claims 35 to 37, wherein the one or more nucleic acids are one or more viral vector genomes, optionally wherein the one or more viral vector genomes are one or more adeno-associated virus vector genomes.

39. Use of a nucleic acid in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid comprises a nucleic acid sequence encoding a fusion protein, the fusion protein comprising:

(a) a nucleic acid binding molecule capable of binding to a target sequence in the promoter or regulatory sequences of the *IRAK3* gene; and

(b) one or more transcriptional activators,

wherein the fusion protein is capable of increasing IRAK-M expression in a target cell of the subject, optionally wherein the transcriptional activator is the transactivation domain, VP64.

40. Use of a nucleic acid in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the nucleic acid comprises a nucleic acid sequence encoding a fusion protein, the fusion protein comprising:

a) a nucleic acid binding molecule capable of binding to (i) a target sequence in the promoter sequence for the *IRAK3* gene, (ii) a target sequence in the regulatory sequences for the *IRAK3* gene or (iii) a target sequence in the *IRAK3* gene; and

b) one or more DNA demethylating agents,

wherein the fusion protein is capable of increasing IRAK-M expression in a target cell of the subject.

41. The use according to claim 40, wherein the DNA demethylating agent is TET1 or LESD1.

42. The use according to claim 40 or claim 41, wherein the nucleic acid binding molecule is a TAL effector repeat array; and/or wherein the nucleic acid binding molecule is zinc finger array.

43. The use according to any one of claims 40 to 42, wherein the nucleic acid is delivered to a target cell via a viral vector; and/or wherein the nucleic acid is a viral vector genome.

44. Use of a pharmaceutical composition in the manufacture of a medicament for the treatment or prophylaxis of macular degeneration in a subject, wherein the composition comprises the nucleic acid according to any one of claims 1 to 9, the vector virion according to any one of claims 10 to 19, the IRAK-M polypeptide according to any one of claims 20 to 23, the nucleic acid system according to any

one of claims 24 to 38, or the nucleic acid according to any one of claims 39 to 43, optionally wherein the pharmaceutical composition is formulated for ocular delivery.