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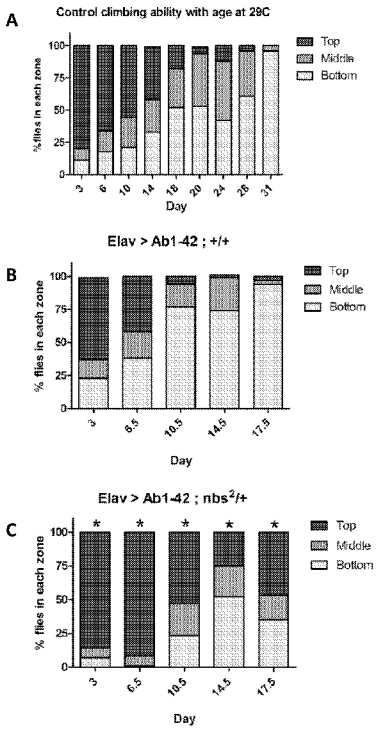
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(54) Title: TREATMENT OF NEUROLOGICAL PATHOLOGIES WITH INHIBITORS OF DNA DAMAGE REPAIR

Figure 1



(57) Abstract: The present invention provides an inhibitor of DNA damage signalling and repair for use in treating or preventing a neurological pathology and a neuro-regenerative compound comprising an inhibitor of DNA damage signalling and repair attached to a nanoparticle and/or a cell targeting peptide.

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TREATMENT OF NEUROLOGICAL PATHOLOGIES WITH INHIBITORS OF DNA DAMAGE REPAIR

Field of Invention

The invention relates to treating or preventing neurological pathologies. Methods of treatment of neurological pathologies are also provided, as are compounds and compositions for use in such methods.

Background to the Invention

The extremely limited regenerative capacity of injured CNS axons leads to permanent functional neurological deficits after optic nerve, spinal cord and brain injury. Consequently, enabling axon regeneration after trauma or a disease is a major challenge in neuro-regenerative medicine. Over the past several decades, many groups have investigated the basis of regenerative failure in the hope of developing strategies to stimulate the re-growth of axons and restore neurological function. Nevertheless, a therapy promoting functional improvements is not available. The optic nerve has been widely studied as a model system for insights into mechanisms that regulate axon regeneration after central nervous system injury. Following optic nerve damage in adult mammals, retinal ganglion cells (RGC) normally fail to regenerate their axons, resulting in blindness in patients who suffer from neurodegenerative diseases such as glaucoma or who have sustained traumatic injury to the optic nerve.

There are also currently no effective therapies that reliably slow or prevent late-onset forms of neurodegeneration. Current therapies are generally aimed at ameliorating symptoms or ameliorating consequences of neuronal loss e.g. dopamine agonists in Parkinson's disease; cholinesterase inhibitors or NMDA antagonists in Alzheimer's disease. Recently monoclonal antibodies targeted to the beta amyloid peptide have shown some efficacy in slowing the decline in cognitive ability in phase 3 trials of patients with mild Alzheimer's disease (e.g., solanezumab). Solanezumab acts as a peripheral sink to deplete amyloid-beta levels. However, the effect is mild. Early onset inherited forms of neurodegeneration are almost always monogenic, recessively inherited disorders. As a consequence, these are in theory amenable to enzyme replacement therapy or gene therapy approaches where the causal mutation is known.

However, to date there are still no effective therapies to any neurodegenerative conditions that will prevent or slow disease progression.

In view of the lack of effective treatments currently available there is a need to provide therapies to promote neuro-regeneration and to treat or prevent neurodegeneration.

Radio- and chemo-therapeutic agents damage targeted cells by introducing strand breaks to the DNA. If these breaks are repaired incorrectly (or not repaired at all) a cell will often die in the next mitosis. Radio- or chemo-sensitising compounds comprising a nanoparticle, a DNA repair inhibitor and a nuclear localisation signal element (NLS) are known from WO 2013/179014. The nanoparticle is engulfed into cancer cells, carrying with it the DNA repair inhibitor and the NLS. Once within the cell the NLS targets the compound to the nucleus where the DNA repair inhibitor acts to inhibit the repair of strand breaks induced by the radio- or chemo-therapy. The compounds thereby enhance cancer cell killing by chemo- or radio-therapy.

Description

In direct contrast to the effect of DNA repair inhibitors on cancer cells, the Inventors have recognised that inhibition of DNA damage signalling or repair in damaged neurons surprisingly leads to an unprecedented amount of neural survival and axon outgrowth, previously not observed for any other axon growth-promoting molecule. Similarly, inhibition of the early stages of the signalling pathway involved in detection of DNA damage slows neurodegeneration. This approach does not attempt to ameliorate the consequences of neuronal pathology (such as reductions in cholinergic neurotransmission, leaking of glutamate neurotransmitter or reductions in dopamine). Rather, it is neuroprotective; preventing or slowing the rate of neural loss.

The present invention therefore provides an inhibitor of DNA damage signalling and repair for use in treating or preventing neurological pathologies. Preferably, the inhibitor of DNA damage signalling and repair treats, prevents or slows neurodegeneration and/or promotes neuro-regeneration, for example, by promoting

neuron survival and axonal growth after injury and/or trauma and slowing or preventing pathology in neurodegeneration, respectively.

As described herein an inhibitor of DNA damage signalling and repair refers to an inhibitor of one or more pathways involved in signalling and repairing damage to DNA, such as double strand breaks (DSBs) or other types of DNA damage. These pathways form a network known as the DNA damage response (DDR). DDR is a signal transduction pathway that implicates different factors depending on the type of damage and/or the cell cycle phase. DNA damage is initially detected by sensor proteins such as MRN (MRE11-RAD50-NSB1) or PARP1 (Poly(ADP-ribose) Polymerase 1). These sensors recruit apical kinases Ataxia telangiectasia mutated (ATM), or Rad3-related (ATR). The signal is further amplified and results in repair (by diverse mechanisms), cell cycle arrest and/or apoptosis. DSBs are repaired by two main mechanisms: homologous recombination (HR) and non-homologous-end-joining (NHEJ). HR involves mediators such as BRCA2, RAD51 and PALB2. NHEJ brings into play proteins such as DNA dependent kinase catalytic subunit (DNA-PKcs), Ku70/80, Ligase IV and XRcc4.

The inhibitor of DNA damage signalling and repair may be an inhibitor of any one or more component of the DDR. The inhibitor may inhibit a protein that senses DNA damage. In particular the inhibitor may be an inhibitor of the MRN complex and/or PARP-1. The inhibitor may be an inhibitor a kinase recruited by a sensor of DNA damage, such as ATM kinase and/or ATR kinase. The inhibitor may inhibit HR, for example by inhibiting one or more of BRCA2, RAD51 or PALB2. The inhibitor may be an inhibitor of NHEJ, such as an inhibitor of the Ku complex, DNA PKcs, Ligase IV or XRcc4. The inhibitor may inhibit DNA winding or unwinding, for example by inhibiting topoisomerase I or topoisomerase II. Preferably the inhibitor of DNA damage signalling and repair is an inhibitor of the MRN complex, such as an inhibitor of one or more of Mre11, Rad50 or Nbs1, or an inhibitor of the Ku complex, such as an inhibitor of Ku70 or Ku80.

Such inhibitors of DNA damage signalling and repair are generally known in the art and the skilled person can identify additional suitable inhibitors by routine methods.

The MRN complex is known to be extremely highly conserved between species and is present in mammals including humans. MRN inhibitors such as Mirin are known from e.g., Shibata *et al* 2014. Other inhibitors of the MRN complex are as described in Example 4 of the present application. The inhibitor of the MRN complex may be a peptide. For example the MRN inhibitor may be KEESLADDL. The inhibitor of DNA damage signalling and repair may be an inhibitor of the Ku complex, such as EGGDVDDLLDMI.

Suitable DNA damage signalling and repair inhibitors include peptides, small molecules or antibodies. The inhibitor may be selected from one or more of NU10125, 1,5-IQD, Lymparza, Talaoparib, Valiparib, Rucaparib, Niraparib, INO-1011, E7016, CEP-9722, KU55933, LY294002, caffeine, torin2, KU60019, KU59403, CP466722, Mirin, wortmannin, V821, V822/VX970, Schisandrin B, PI-124, PI-103, NVP-BEZ 235, ETP-46464, AZ-20, AZD6738, PFM39, PFM01, PFM03, NU7441, Etoposide, ICRF-193, F11782, Camptothecin, NU7026, KU0060648, ICO5 compounds, OK-1035, SU11752, vanillin, NK314, CC-115, GRN163L, L189, SCR7, salvianolic acid B, lithospermic acid, 2-O-feruloyl tartaric acid, DIDS, halenaquinone/xestoquinone, B02, RI-1/RI-2 and IBR2/IBR120.

The inhibitor of DNA damage signalling and repair may be attached to a nanoparticle and/or to a cell targeting peptide, such as a cell type specific targeting peptide or a cell penetrating peptide, optionally via a linker. The cell targeting peptide may be a nuclear localisation signal (NLS) element. The presence of an NLS assists in targeting the inhibitor to the nucleus of the cell, thereby assisting in localisation of the inhibitor of DNA damage signalling and repair close to the DNA.

The NLS may be, for example, an adenoviral or SV40 NLS, or a synthetic sequence such as M4 targeting sequence. The M4 targeting sequence may be KKKKKKGGRGDMFG. The adenoviral NLS may be GGFSTSLRARKA.

Any suitable naturally occurring or synthetic NLS may also be used. Synthetic NLS are generally known in the art. The M4 targeting sequence from the above is a synthetic peptide, the Adenoviral NLS is a naturally occurring targeting sequence.

The nanoparticles are typically metal nanoparticles, such as transition metal particles. These include gold, platinum or palladium, or mixtures thereof. The nanoparticles are typically below 100 nm, typically 1-50 nm, 5-30 nm or 10-15 nm in diameter.

The nanoparticle and/or cell targeting peptide may be attached via generally known systems onto the inhibitor of DNA damage signalling and repair. For example, a linker moiety having affinity for a metal nanoparticle may be utilised. Such linker moieties include thio-containing linkers, such as thioctic acid, gold binding peptide 1 (Brown, 1997), 3R-GBP1 which contains 3 repeat sequence of MHGKTQATSGTIQS (Tamerler *et al*) which binds to both gold and platinum surfaces, CALNN peptide (Lévy R, J. *et al*, 2004) and glutathione.

The inhibitor of DNA damage signalling and repair may be attached to two or more cell targeting peptides, which may be the same or different. For example, the two or more cell targeting peptides may be two M4 targeting NLS elements, two adenoviral NLS elements, or one M4 targeting NLS and one adenoviral NLS. The inhibitor of DNA damage signalling and repair may be attached to three or more or four or more cell targeting peptides.

In embodiments of the invention two or more inhibitors of DNA damage signalling and repair may be attached to a nanoparticle and/or cell targeting peptide. The inhibitors of DNA damage signalling and repair may be the same or different. For example, two NBS1 inhibitors, two Mre11 inhibitors, two Rad50 inhibitors or one NBS1 inhibitor and one Mre11 or one Rad50 inhibitor may be attached to a nanoparticle and/or NLS.

The invention also provides a neuro-regenerative compound comprising an inhibitor of DNA damage signalling and repair attached to a nanoparticle and/or cell targeting peptide, such as an NLS, optionally attached via one or more linker moieties.

As described herein a neuro-regenerative compound refers to a compound capable of stimulating neuronal survival and neuro-regeneration, for example by stimulating survival and axon outgrowth, and/or capable of preventing or inhibiting neurodegeneration, for example by slowing the rate of neural loss.

The inhibitor of DNA damage signalling and repair and cell targeting peptide may be separately attached to the nanoparticle, optionally via a linker moiety. That is, the inhibitor and cell targeting peptide may be attached to separate parts of the nanoparticle. Alternatively, the inhibitor of DNA damage signalling and repair may be attached to the nanoparticle, for example, via a linker moiety, and the cell targeting peptide may be attached to the inhibitor of DNA damage signalling and repair (for example as a fusion protein/peptide) or attached to a different part of the linker moiety, for example as a pendant moiety. Alternatively the cell targeting peptide may be attached to the nanoparticle, for example via a linker moiety, and the inhibitor of DNA damage signalling and repair may be attached to the cell targeting peptide, or to the linker moiety (for example as a pendant moiety).

The present invention also provides compositions comprising a neuro-regenerative compound and/or an inhibitor of DNA damage signalling and repair in combination with one or more pharmaceutically acceptable carriers or diluents.

The inhibitor of DNA signalling damage and repair and compounds or compositions of the invention may be used as a medicament, for example for use in treating or preventing a neurological pathology such as a neurodegenerative disease or an injury to the central and/or peripheral nervous system. The neurological pathology may be glaucoma, spinal cord or traumatic brain injury, Alzheimer's, Huntington's, Parkinson's disease, dementia with Lewy bodies, frontal temporal dementia, amyotrophic lateral sclerosis or mild cognitive impairment. In particular, inhibitors of

DNA damage signalling and repair and compounds or compositions of the invention may be used to treat eye related diseases (such as glaucoma, optic neuritis or direct penetrating injuries), brain or spinal cord injuries (especially where CNS axon regeneration is critical to function and a reasonable standard of normal life) and neurodegenerative conditions (such as Alzheimer's, Huntington's and Parkinson's disease). The inhibitors of DNA damage signalling and repair and compounds or compositions of the invention preferably treat, prevent or slow neurodegeneration and/or promote neuro-regeneration, for example, by promoting neuron survival and axonal growth after injury and/or trauma and slowing or preventing pathology in neurodegeneration, respectively.

Without being bound by theory, neurological pathologies, such as neurodegenerative conditions, share common features including early synaptic changes preceding loss of neurons and dysregulation of autophagy, suggesting that the inhibitors of DNA damage signalling and repair may be effective in treating all forms of neurodegeneration. For late-onset neurodegenerative conditions such as Alzheimer's disease, vascular dementia or Parkinson's disease, treatment with inhibitors of DNA damage signalling and repair, compounds or compositions of the present invention may slow disease progression though its neuroprotective effect. This may be particularly effective for patients with mild or early forms of neurodegeneration. If the onset of disease can be predicted, for example by the use of biomarkers, the inhibitors of DNA damage signalling or repair could be administered to patients at a pre-symptomatic stage.

For neurodegenerative syndromes displaying genetic anticipation, e.g. Huntington's disease, inhibitors of DNA damage signalling and repair, compounds or compositions of the present invention could be administered before pathology is evident in a patient because the age of onset of pathology can be predicted. For disorders such as multiple sclerosis, inhibitors of DNA damage signalling and repair, compounds or compositions of the present invention may slow or prevent long-term degeneration, while for inherited forms of neurodegeneration, children or younger siblings with a genetic diagnosis could benefit from treatment. Treatment may also slow pathology in

older patients displaying pathology. Treatment may also prevent or slow the development of cognitive impairment and neurodegeneration following traumatic brain injury.

Methods of treating or preventing a neurological pathology in a subject comprising administering a therapeutically effective amount of an inhibitor of DNA damage signalling and repair or a compound or composition according to the invention to a subject in need thereof are also provided. A therapeutically effective acceptable amount of the inhibitor of DNA damage signalling and repair or a compound or composition according to the invention is preferably an amount sufficient to slow neurodegeneration, stabilise symptoms of the pathology and/or to improve or prevent worsening of symptoms, such as loss of cognition.

Compounds of the invention may include one or more surface targeting moieties capable of being specifically attached to a target cell, such as a neuron. That moiety may, for example, be a ligand of a receptor found the surface of the target cell. Such compounds can provide targeted delivery of the inhibitor of DNA damage signalling and repair. The inhibitor of DNA damage signalling and repair, compound or composition may be administered intravenously, intramuscularly, intraperitoneally, transdermally or orally. Neurological pathologies affecting the brain may be treated, for example, by perfusion through the skull beyond the blood-brain barrier.

Brief Description of the Drawings

The invention will now be described by way of example only by reference to the following figures:

Figure 1: shows the protection of neural function in a Drosophila model of Alzheimer's disease. A shows standard neurological function as measured by climbing ability; ability decreases with age. B shows that expression of the human β-amyloid 1-42 peptide ($A\beta_{1-42}$) causes climbing ability to be impaired more rapidly. C shows that in flies expressing $A\beta_{1-42}$ and heterozygous for a null allele of nbs (nbs^2), neural activity was supported and climbing ability was maintained.

Figure 2 shows that a reduction in MRN levels prevents cell death in a Huntington's disease model in Drosophila. A shows the progression of pathology in the eyes of flies carrying either an expansion of 16 glutamines (Htt-16Q) or 128 glutamines (Htt-128Q), the latter reflecting the disease-causing allele seen in human Huntington's disease. Loss of the red pigmentation in the compound eye occurs after several weeks of Htt-128Q expression, indicating a loss of cells internally. The Htt-16Q construct has no effect. B shows that if the Htt128Q protein is expressed in a fly that is heterozygous for a null allele of the Rad50 gene ($Rad50^{EP50}/+$) the red pigmentation of the eye is largely maintained after 42 days.

Figure 3 shows that Mre11/Rad50/NBS1 (MRN) complex inhibition via the NBS1 subunit stimulates neuro-regeneration of retinal ganglion cells (RGC). A shows immuno-stained RGC treated and untreated *ex vivo* cultures. Cilliary Neurotrophic Factor (CNTF) was used as a positive control. Plain uncoated gold nanoparticles were used as a control to exclude any stimulatory effect of gold itself. The arrows indicate neuronal growth. B, C and D show quantitative analysis of major neuro-regeneration indicators after treatment with NBS1 inhibiting peptide: mean RGC survival, mean axon growth initiation and mean axon/neurite length.

Figure 4 shows that Mre11/Rad50/NBS1 (MRN) complex inhibition via the Mre11 exonuclease subunit stimulates neuro-regeneration of RGC. A shows representative images of immuno-stained RGC treated and untreated *ex vivo* cultures. The arrows indicate axonal growth. B, C and D show quantitative analysis of major neuro-regeneration indicators after treatment with Mirin: mean RGC survival, mean axon growth initiation and mean axon/neurite length.

Figure 5 shows immunofluorescence analysis of DNA damage in regenerating neurons. Green focal staining (Alexa488) for histone γ-H2AX is the indicator for DNA damage. Blue staining (DAPI) shows nuclei and red staining (Texas red - β3 tubulin) identifies regenerating neuronal cell bodies. A shows regenerating RGCs in an *in vitro* culture system. B shows regenerating dorsal root ganglion cells (DRGN) *in*

vivo. In both cases the regenerating neurons show the presence of DNA damage, with virtually no damage signal detected in surrounding non-neuron satellite cells (glia, astrocytes, etc).

Figure 6 shows that inhibition of multiple DNA double strand break detection and repair pathway components by small molecule inhibitors stimulates neuro-regeneration of retinal ganglion calls (RGC). The panels show immuno-stained RGC treated and untreated *ex vivo* cultures. Cilliary Neurotrophic Factor (CNTF) was used as a positive control.

Figure 7 shows quantitative analysis of major neuro-regeneration indicators after inhibition of multiple DNA double strand break detection and repair pathway components by small molecule inhibitors - mean RGC survival, mean axon growth initiation and mean axon/neurite length.

Figure 8 shows that circadian periodicity of flies is extended by the Abeta 1-42 peptide in a *Drosophila* model of Alzheimer's disease. The effect on circadian periodicity is suppressed in flies expressing Abeta 1-42 peptide that are also heterozygous for a NBS null allele. Error bars indicate SEM. Asterisks indicate significance at $p<0.01$.

Figure 9 shows that expression of glutamine expanded Htt (HttQ128) in the adult nervous system leads to a rapid decline in climbing ability that is suppressed in flies heterozygous for a null NBS allele. Error bars indicate SEM.

Figure 10 shows a model of Alzheimer's disease and fronto-temporal dementia in which expression of human 2N4R Tau in the adult nervous system of flies leads to a rapid decline in climbing ability that is suppressed in flies heterozygous for a null NBS allele (Figure 10A). Error bars indicate SEM. Expression of human 2N4R Tau in the adult nervous system leads to a decline in non-stimulated speed of movement. Treatment of Tau-expressing flies with an MRE11 inhibitor (Compound A) suppresses the decline in mean speed over time (Figure 10B). Error bars indicate

SEM. Asterisks indicate significance at $p<0.05$. Detail of mean speed in 1 min bins of Tau-expressing flies treated with compound A and control flies on day 5 is shown in Figure 10C. Errors bars indicate SEM. The solid lines indicate the mean over the entire 1 hr period.

Figure 11 shows that inhibitors A and B promote positive effects similar to mirin and greater than the positive controls on axon regeneration, increasing neurite outgrowth (Figure 11A), mean neurite length (Figure 11B) and the proportion of DRGN with neurites (Figure 11C).

Examples

Example 1 - Protection of neural function in a Drosophila model of Alzheimer's disease.

A published model of human Alzheimer's disease was used to test the neuroprotective effect of reducing MRN complex activity. A dimeric, aggregation-prone form of the human β-amyloid 1-42 peptide ($A\beta_{1-42}$) associated with Alzheimer's disease was expressed pan-neurally in adult flies. Expression was restricted to the adult nervous system to prevent potentially confounding effects of expression on nervous system development.

Methodology: the standard UAS-GAL4 system was used to control expression of the $A\beta_{1-42}$ peptide with the standard Elav-GAL4C155 line used to direct pan-neural expression. A temperature-sensitive form of the GAL4 repressor, GAL80 (tsGAL80) was included to prevent expression of the $A\beta_{1-42}$ peptide in embryonic, larval or pupal developmental stages. Flies were developed at the permissive temperature (18°C) until eclosion as adults then shifted to the restrictive temperature (29°C). At 29°C tsGAL80 no longer represses GAL4 and allows expression of the $A\beta_{1-42}$ peptide.

Detailed description of the genetics:

Driver line: Elav-$GAL4^{C155}$; tsGAL80

Virgin females of this line were used in all crosses. Female progeny were tested for climbing ability.

Control: w^{1118}. Used in part A.

$A\beta_{1-42}$ line: a UAS-construct expressing a dimer of human $A\beta_{1-42}$ peptide separated by a flexible 12-amino acid linker to promote aggregation. A leader sequence ensures secretion. See Speretta *et al*, 2012.

nbs^2: a null allele of *nbs*, the Drosophila orthologue of NBS1/NBN.

Results: See Figure 1. **A:** Flies were tested for general neural function using a standard negative geotaxis assay. Flies tapped to the base of an empty plastic vial immediately attempt to climb back up. Flies are allowed to climb for 30 s and the number scored in each of three zones up the vial then recorded. As flies age climbing ability is progressively impaired. This is used as a standard method of testing neural function.

B: When the $A\beta_{1-42}$ peptide is expressed in adult neurons, climbing ability is impaired more rapidly than in controls. **C:** In flies heterozygous for a null allele of nbs (nbs^2), neural activity is supported and climbing ability is maintained. A χ^2 test indicates significantly different performance at each age tested.

Example 2: a reduction in MRN levels prevents cell death in a Huntington's disease model in Drosophila.

A published Drosophila model of Huntington's disease was used to test the strategy of reducing MRN activity to slow pathology. The flies express human Huntingtin protein (Htt) carrying either an expansion of 16 glutamines (Htt-16Q) or 128 glutamines (Htt-128Q), the latter reflecting the disease-causing allele seen in human Huntington's disease.

Methodology: the standard UAS-GAL4 system was used to drive expression of the Htt constructions in the developing and adult eye. The GMR-gal4 driver was used. Expression was maintained for 42 days at 25°C.

Explanation of the genotypes:

w^{1118} Wild-type control for the GMR-gal4 driver.

$Rad50^{EP1}/+$	Flies heterozygous for a null Rad50 allele. No expression of Htt-128Q. Control for any effects of the heterozygous Rad50 allele.
UAS-Htt-128Q	Flies expressing Htt-128Q in the eye under the control of the GMR-gal4 driver. See Lee *et al*, 2004.
$Rad50^{EP1}/+$; UAS-Htt-128Q	Expression of Htt-128Q in the eye in a flies heterozygous for the Rad50 allele.

Results: See Figure 2. **A**: Both construct Htt-16Q and Htt-128Q were expressed in the developing and adult eye. Loss of the red pigmentation in the compound eye occurs after several weeks of Htt-128Q expression indicating a loss of cells internally. The Htt-16Q construct has no effect. **B**: If the Htt-128Q protein is expressed in a fly that is heterozygous for a null allele of the Rad50 gene ($Rad50^{EP50}/+$) the red pigmentation of the eye is largely maintained after 42 days.

Example 3 - Mre11/Rad50/NBS1 (MRN) complex inhibition via the NBS1 subunit and via Mre11 exonuclease stimulates neuro-regeneration of retinal ganglion cells (RGC).

Methods and results: See Figure 3: NBS1 inhibitory peptide coated gold nanoparticles (GNP) efficiently stimulate all aspects of neuro-regeneration in RGC. Panel A: Representative pictures of immuno-stained RGC treated and untreated *ex vivo* cultures. Plain uncoated gold nanoparticles had been used as a control to exclude the possibility that nanogold itself has a stimulatory effect. Several MRN complex unrelated peptides had been also tested with no stimulation observed (data not shown). The arrows indicate axonal growth.

Panels B,C,D: Quantitative analysis of major neuro-regeneration indicators after treatment with an NBS1 inhibitory peptide: mean RGC survival, mean axon growth initiation and mean axon/neurite length. Cilliary Neurotrophic Factor (CNTF) is a benchmark positive control commonly used in neuro-regeneration studies (used at maximum effect titrated concentration). *** = $P<0.0001$, ANOVA.

See Figure 4. Mre11 exonuclease inhibitor Mirin very efficiently stimulates all aspects of neuro-regeneration in retinal ganglion cells (RGC). Panel A: Representative pictures of immuno-stained RGC treated and untreated *ex vivo* cultures. The arrows indicate axonal growth.

Panels B,C,D: A quantitative analysis of major neuro-regeneration indicators after treatment with Mirin: mean RGC survival, mean axon growth initiation and mean axon/neurite length. Cilliary Neurotrophic Factor (CNTF) is a benchmark positive control commonly used in neuro-regeneration studies (used at maximum effect titrated concentration). *** = P<0.0001, ANOVA.

Example 4 - MRN inhibitory constructs have been designed as follows:

Single peptide designs:

Peptide ID	Peptide sequence	Peptide function
3408	CALNNKKKKKKGGRGDMFGKEESLADDL	Gold attachment - M4 targeting - NBS1 inhibiting
3410	CALNNGGFSTSLRARKAKEESLADDL	Gold attachment - Adenoviral NLS - NBS1 inhibiting
6267	CALNNGGFSTSLRARKAEGGDVDDLLDMI	Gold attachment - Adenoviral NLS - Ku80 inhibiting
6268	CALNNEGGDVDDLLDMIGGFSTSLRARKA	Gold attachment - Ku80 inhibiting - Adenoviral NLS

Dual-peptide designs:

Peptide ID	Peptide sequence	Peptide function	
3408+3410	CALNNKKKKKKGGRGDMFGKEESLADDL CALNNGGFSTSLRARKAKEESLADDL	Gold attachment - M4 targeting - NBS1 inhibiting Gold attachment - Adenoviral NLS - NBS1 inhibiting	Dual targeting
3408+6267	CALNNKKKKKKGGRGDMFGKEESLADDL CALNNGGFSTSLRARKAEGGDVDDLLDMI	Gold attachment - M4 targeting - NBS1 inhibiting Gold attachment - Adenoviral NLS - Ku80 inhibiting	Dual targeting & inhibition
3408+6268	CALNNKKKKKKGGRGDMFGKEESLADDL CALNNEGGDVDDLLDMIGGFSTSLRARKA	Gold attachment - M4 targeting - NBS1 inhibiting Gold attachment - Ku80 inhibiting - Adenoviral NLS	Dual targeting & inhibition
3410+6267	CALNNGGFSTSLRARKAKEESLADDL	Gold attachment - Adenoviral NLS - NBS1 inhibiting	

	CALNNGGFSTSLRARKAE GGDVDDLLDMI	Gold attachment - Adenoviral NLS - Ku80 inhibiting	Dual inhibition
3410+6268	CALNNGGFSTSLRARKAK EESLADDL CALNNEGGDVDDLLDMIG GFSTSLRARKA	Gold attachment - Adenoviral NLS - NBS1 inhibiting Gold attachment - Ku80 inhibiting - Adenoviral NLS	Dual inhibition
3412+3414	CALNNKKKKKKGGRGDM FG CALNNKEESLADDL	Gold attachment - M4 targeting Gold attachment - NBS1 inhibiting	Separate targeting & inhibition
3416+3414	CALNNKEESLADDL CALNNGGFSTSLRARKA	Gold attachment - NBS1 inhibiting Gold attachment - Adenoviral NLS	Separate targeting & inhibition
3412+6270	CALNNKKKKKKGGRGDM FG CALNNEGGDVDDLLDMI	Gold attachment - M4 targeting Gold attachment - Ku80 inhibiting	Separate targeting & inhibition
3416+6270	CALNNGGFSTSLRARKA CALNNEGGDVDDLLDMI	Gold attachment - Adenoviral NLS Gold attachment - Ku80 inhibiting	Separate targeting & inhibition

Multiple-peptide designs:

Peptide ID	Peptide sequence	Peptide function	
3412+3414 +6270	CALNNKKKKKKGGRGDM FG CALNNKEESLADDL CALNNEGGDVDDLLDMI	Gold attachment - M4 targetting Gold attachment - NBS1 inhibiting Gold attachment - Ku80 inhibiting	Single targeting & dual inhibition
3416+3414 +6270	CALNNKEESLADDL CALNNGGFSTSLRARKA CALNNEGGDVDDLLDMI	Gold attachment - NBS1 inhibiting Gold attachment - Adenoviral NLS Gold attachment - Ku80 inhibiting	Single targeting & dual inhibition
3412+3416 +3414+62 70	CALNNKKKKKKGGRGDM FG CALNNKEESLADDL CALNNGGFSTSLRARKA CALNNEGGDVDDLLDMI	Gold attachment - M4 targetting Gold attachment - NBS1 inhibiting Gold attachment - Adenoviral NLS Gold attachment - Ku80 inhibiting	Dual targeting & inhibition

Example 5 - DNA repair inhibitors for neuron regeneration

Methods: Inhibitors 1-7 were coated on gold nanoparticles and applied to *ex vivo* rat RGC cultures.

NU 7441 (Tocris Cat No: 3712)	10mg coded INHIBITOR 1	
1mM	0.4225mg/ml	stock solution in DMSO
Camptothecin (Tocris Cat No: 1100)	25mg coded INHIBITOR 2	
1mM	0.34835mg/ml	stock solution in DMSO
MIRIN (Tocris Cat No: 3190)	10mg coded INHIBITOR 3	
1mM	0.23376mg/ml	stock solution in DMSO
KU 55933 (Tocris Cat No: 3544)	10mg coded INHIBITOR 4	
1mM	0.39999mg/ml	stock solution in DMSO
NU 1025 (Tocris Cat No: 1401)	10mg coded INHIBITOR 5	
1mM	0.17617mg/ml	stock solution in DMSO
L189 (Tocris Cat No: 3561)	10mg coded INHIBITOR 6	
1mM	0.25079mg/ml	stock solution in DMSO

VE 821 (Selleckchem.com Cat No: S8007) coded INHIBITOR 7
About 100µl at 100mM ATR inhibitor

Typical responses of most adult central nervous system (CNS) neurons to injury is that the few ganglion cells surviving the injury trauma fail to regenerate their axons, resulting in permanent loss of function. Growth failure of injured CNS axons is attributed to both limited neurotrophic factor (NTF) supply/NTF receptor expression, and an abundance of axon growth inhibitory molecules within scar and mature projection pathways. Growth failure may be explained if either NTF supply is scarce,

and/or growth is overwhelmed by prolonged exposure to axon growth inhibitory ligands. CTNF stimulates axonal growth in RGC cultures.

Results: See Figures 6 and 7. Inhibitory peptide coated nanoparticles efficiently stimulate all aspect of neuro-regeneration in RGC. Figure 6 shows representative pictures of immuno-stained RGC treated and untreated *ex vivo* cultures. CTNF was used as a positive control. Axonal growth can be seen in RGC cultures treated with inhibitors 1-7 or CTNF. Figure 7 shows quantitative analysis of major neuro-regenerative indicators after treatment with inhibitors 1-7: mean RGC survival, mean axon growth initiation and mean axon/neurite length.

Example 5 - Description of the Drosophila model of Alzheimer's disease.

Methods: Circadian periodicity was determined essentially as described (Rosato and Kyriacou, 2006). The tandem Abeta 1-42 dimer (Speretta *et al*, 2012) was expressed in clock neurons under the control of Timeless-Gal4. Flies were maintained in on a 12 hr light-dark cycle for 3 days then in constant darkness for 6 days. Activity was determined for males flies using standard TriKinetics DAM monitors.

Genotypes:
Control: Tim-Gal4 / +
Abeta: Tim-Gal4 / UAS-Abeta 1-42 12 linker ; +/+
Abeta ; nbs1: Tim-Gal4 / UAS-Abeta 1-42 12 linker ; nbs1/+

Results: See Figure 8. Expression of Abeta 1-42 peptide extends the circadian periodicity of flies. This is suppressed in flies heterozygous for a NBS null allele. Error bars indicate SEM. Asterisks indicate $p<0.01$

Example 6 - Description of the Drosophila model of Huntington's disease

Methods: Methods were carried out as per example 1 and utilised the same lines described in examples 1 (ElavC155 driver) and 2 (UAS-HttQ128). A Glutamine-

expanded form of human Htt with 128 glutamines (HttQ128) was expressed specifically in adult neurons under the control of Elav-Gal4. Expression was restricted to adult neurons by use of tsGal80. Flies were developed at 18 °C to prevent expression and shifted to 29 °C upon adult eclosion.

Neural activity was quantified using a standard negative geotaxis climbing assay.

Genotypes:
Elav-Gal4 / w1118 ; ; UAS-HttQ128 /+ vs. Elav-Gal4 / w1118 ; ; UAS-HttQ128, nbs1 / +

Results: See Figure 9. Data are presented as the percentage of flies in the upper zone after 30 secs. Flies per genotype. Expression of glutamine expanded Htt (HttQ128) in the adult nervous system leads to a rapid decline in climbing ability that is suppressed in flies heterozygous for a null NBS allele. Error bars indicate SEM.

Example 7 - Description of the Drosophila model of Alzheimer's disease and Frontotemporal dementia

Human 2N4R Tau (Povellato *et al.* 2013) was expressed specifically in adult neurons under the control of Elav-Gal4. Expression was restricted to adult neurons by use of tsGal80. Flies were developed at 18 °C to prevent expression and shifted to 29 °C upon adult eclosion.

Methods: Neural activity in Figure 9 was quantified using a standard negative geotaxis climbing assay as for Figures 1 and 8, and presented as the percentage of flies in the upper zone after 30 secs. In Figure 2B neural activity was quantified as the mean speed of a non-startled or stimulated cohorts of 40 male flies using DART software (Faville et al, 2015).

Genotypes:

A: Elav-Gal4/w1118 ; tsGal80/+ ; UAS-2N4R Tau/+ vs. Elav-Gal4/w1118 ; tsGal80/+ ; UAS-2N4R Tau, nbs1/+
B&C: Elav-Gal4/Y ; tsGal80/+ ; UAS-2N4R Tau/+

Compound treatments:
100 μM MRE11 inhibitor compound A or 1% DMSO as vehicle control were added to molten fly food at 55 °C. Flies were maintained on compound A or 1% DMSO from eclosion.

Results: See Figure 10.
A: Expression of human 2N4R Tau in the adult nervous system leads to a rapid decline in climbing ability that is suppressed in flies heterozygous for a null NBS allele. Error bars indicate SEM.
B: Expression of human 2N4R Tau in the adult nervous system leads to a decline in non-stimulated speed of movement. Treatment of Tau-expressing flies with an MRE11 inhibitor (Compound A) suppresses the decline in mean speed over time. Error bars indicate SEM. Asterisks indicate significance at $p<0.05$.
C: Detail of mean speed in 1 min bins of Tau-expressing flies treated with compound A and control flies on day 5. Errors bars indicate SEM. The solid lines indicate the mean over the entire 1 hr period.

Example 8 - Axon regeneration promoted by new inhibitors

Methods: Primary dorsal root ganglion neurons (DRGN) were dissociated from adult Sprague-Dawley rats and cultured in supplemented Neurobasal-A (Ahmed *et al.*, 2005). The inhibitors were titrated to obtain the optimal concentration and added to cultures on day 1. Cultures were incubated at 5% CO_2 and at 37°C for 3 days prior to fixing cells in paraformaldehyde and immunostaining for βIII-tubulin (marker of neurons and their axons). Images were collected randomly using a Zeiss fluorescent microscope and Axiovision Software (Version 4.) (Carl Zeiss) was used to measure the length of the longest neurite (Ahmed *et al.*, 2005). The proportion of DRGN with neurites was also counted.

Results: See Figure 11. The results show that the new inhibitors promote positive effects similar to mirin and greater than the positive controls on axon regeneration, increasing neurite outgrowth (Figure 11A), mean neurite length (Figure 11B) and the proportion of DRGN with neurites (Figure 11C).

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Speretta *et al.* Expression in Drosophila of tandem amyloid β peptides provides insights into links between aggregation and neurotoxicity. J Biol. Chem. 287; 20748-54, 2012

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Claims

1. An inhibitor of DNA damage signalling and repair for use in treating or preventing a neurological pathology.

2. An inhibitor of DNA damage signalling and repair for use according to claim 1, wherein the neurological pathology is a neurodegenerative disease.

3. An inhibitor of DNA damage signalling and repair for use according to claim 1, wherein the neurological pathology is an injury to the nervous system.

4. An inhibitor of DNA damage signalling and repair for use according to any of claims 1 to 3, wherein the neurological pathology is selected from one or more of glaucoma, spinal cord injury, traumatic brain injury, vascular dementia, multiple sclerosis, Alzheimer's disease, Huntington's disease, Parkinson's disease, dementia with Lewy bodies, frontal temporal dementia, amyotrophic lateral sclerosis and mild cognitive impairment.

5. An inhibitor of DNA damage signalling and repair for use according to any of claims 1 to 4, wherein the inhibitor of DNA damage signalling and repair is an inhibitor of one or more of the MRN complex, the Ku complex, PARP-1, ATM kinase, ATR kinase, DNA PKcs, topoisomerase I, topoisomerase II, BRCA2, RAD51 or PALB2.

6. An inhibitor of DNA damage signalling and repair for use according to claim 5, wherein the inhibitor of DNA damage signalling and repair is an inhibitor of one or more of Mre11, Rad50, Nbs1, Ku70, Ku80, LigaseIV and Xrcc4.

7. An inhibitor of DNA damage signalling and repair for use according to any of claims 1 to 6, wherein the inhibitor of DNA damage signalling and repair is selected from one or more of a peptide, a small molecule or an antibody.

8. An inhibitor of DNA damage signalling and repair for use according to any of claims 1 to 7, wherein the inhibitor of DNA damage signalling and repair is selected from one or more of NU10125, 1,5-IQD, Lymparza, Talaoparib, Valiparib, Rucaparib, Niraparib, INO-1011, E7016, CEP-9722, KU55933, LY294002, caffeine, torin2, KU60019, KU59403, CP466722, Mirin, wortmannin, V821, V822/VX970, Schisandrin B, PI-124, PI-103, NVP-BEZ 235, ETP-46464, AZ-20, AZD6738, PFM39, PFM01, PFM03, NU7441, Etoposide, ICRF-193, F11782, Camptothecin, NU7026, KU0060648, ICO5 compounds, OK-1035, SU11752, vanillin, NK314, CC-115, GRN163L, L189, SCR7, salvianolic acid B, lithospermic acid, 2-O-feruloyl tartaric acid, DIDS, halenaquinone/xestoquinone, B02, RI-1/RI-2 and IBR2/IBR120.

9. An inhibitor of DNA damage signalling and repair for use according to any of claims 1 to 8, wherein the inhibitor of DNA damage signalling and repair is attached to a nanoparticle and/or a cell targeting peptide.

10. An inhibitor of DNA damage signalling and repair for use according to claim 9, comprising two or more cell targeting peptides attached to the nanoparticle and/or inhibitor of DNA damage signalling and repair, optionally attached via linker moieties.

11. An inhibitor of DNA damage signalling and repair for use according to claim 9 or 10, comprising two or more inhibitors of DNA damage signalling and repair attached to the nanoparticle and/or cell targeting peptide, optionally attached via linker moieties.

12. A neuro-regenerative compound comprising an inhibitor of DNA damage signalling and repair attached to a nanoparticle and/or a cell targeting peptide.

13. A compound according to claim 12, comprising two or more cell targeting peptides.

14. A compound according to claim 12 or 13, comprising two or more inhibitors of DNA damage signalling and repair.

15. A composition comprising an inhibitor of DNA damage signalling and repair and/or a compound according to any of claims 12 to 14, in combination with one or more pharmaceutically acceptable carriers or diluents.

16. A compound according to any of claims 12 to 14 or a composition according to claim 15 for use as a medicament.

17. A compound or composition according to claim 16, for use in treating or preventing a neurological pathology.

18. A method of treating or preventing a neurological pathology in a subject comprising administering a therapeutically effective amount of an inhibitor of DNA damage signalling and repair and/or a compound according to any of claims 12 to 14 and/or a composition according to claim 15 to a subject in need thereof.

19. A compound or composition for use according to claim 17 or a method of treatment according to claim 18, wherein the neurological pathology is selected from one or more of glaucoma, spinal cord injury, traumatic brain injury, vascular dementia, multiple sclerosis, Alzheimer's disease, Huntington's disease, Parkinson's disease, dementia with Lewy bodies, frontal temporal dementia, amyotrophic lateral sclerosis and mild cognitive impairment.

Figure 1

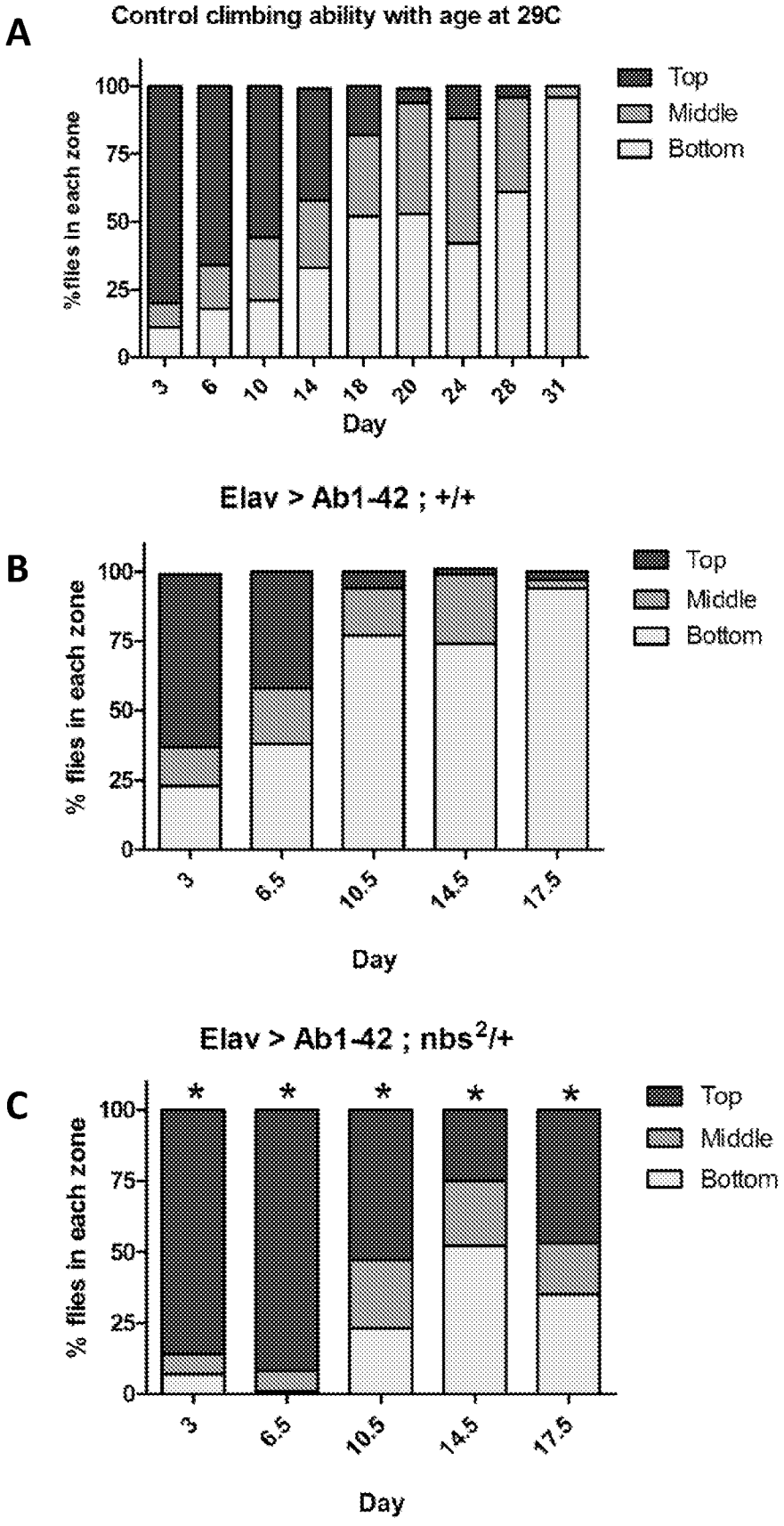

A
Control climbing ability with age at 29C
% flies in each zone
100
75
50
25
0
3
6
10
14
18
20
24
28
31
Day
Top
Middle
Bottom
Elav > Ab1-42 ; +/+
B
% flies in each zone
3
6.5
10.5
14.5
17.5
Day
Top
Middle
Bottom
Elav > Ab1-42 ; nbs2/+
C
*
% flies in each zone
Day
Top
Middle
Bottom

Figure 2

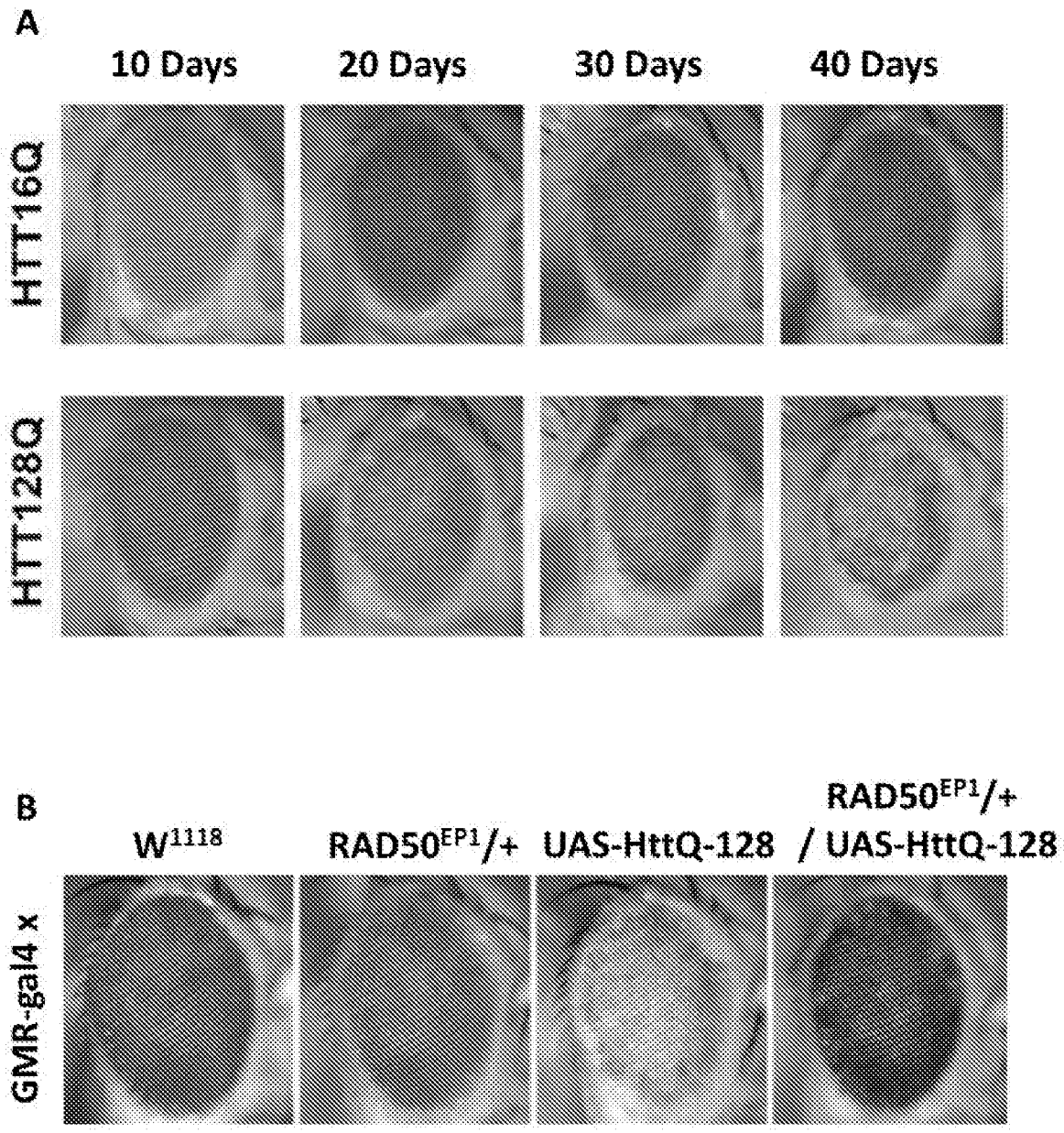

A
10 Days
20 Days
30 Days
40 Days
HTT16Q
HTT128Q
B
W1118
RAD50EP1/+
UAS-HttQ-128
RAD50EP1/+ / UAS-HttQ-128
GMR-gal4 x

Figure 3

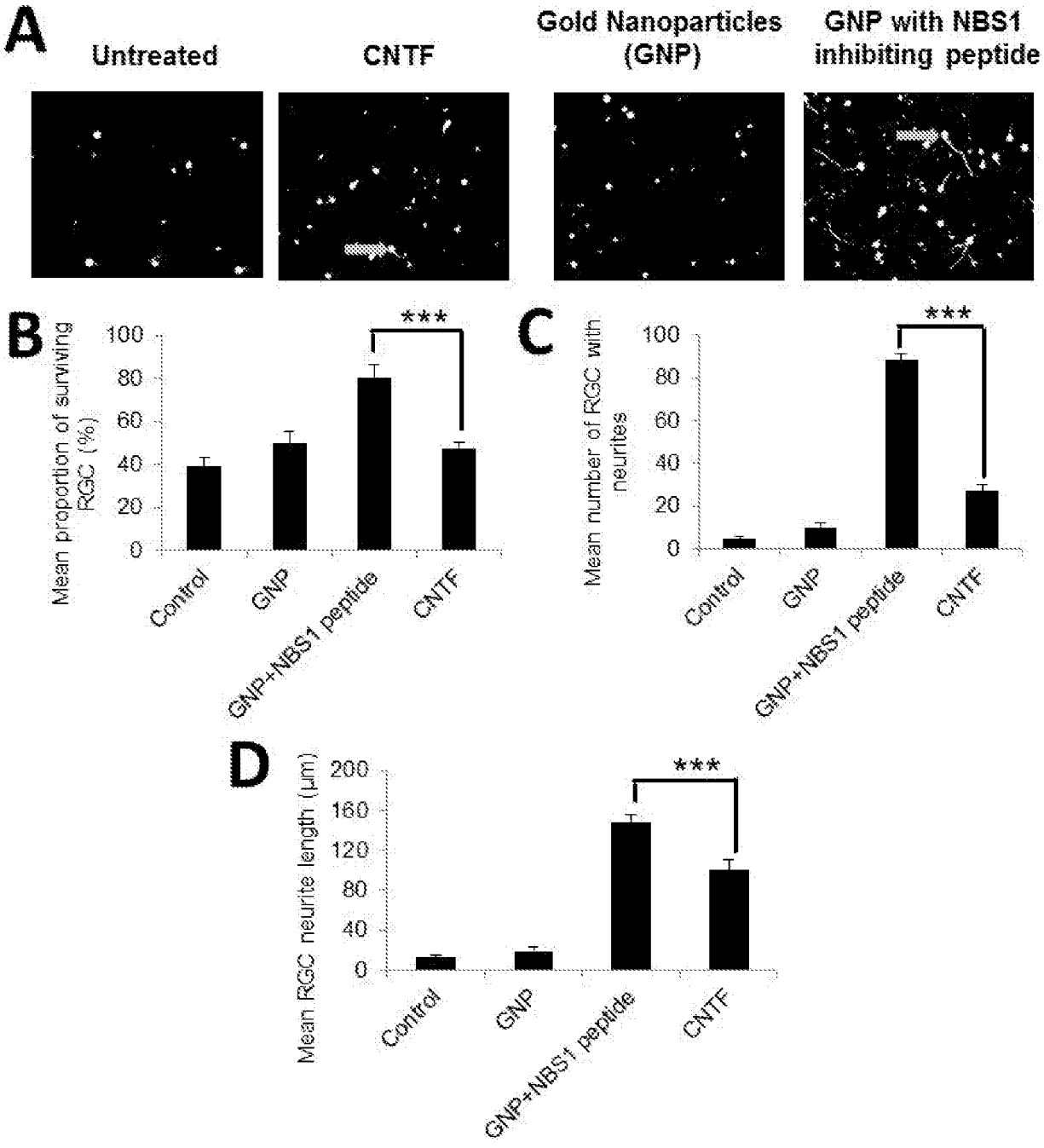

A
Untreated
CNTF
Gold Nanoparticles (GNP)
GNP with NBS1 inhibiting peptide
B
Mean proportion of surviving RGC (%)
100
80
60
40
20
0
***
Control
GNP
GNP+NBS1 peptide
CNTF
C
Mean number of RGC with neurites
100
80
60
40
20
0
***
Control
GNP
GNP+NBS1 peptide
CNTF
D
Mean RGC neurite length (µm)
200
160
120
80
40
0
***
Control
GNP
GNP+NBS1 peptide
CNTF

Figure 4

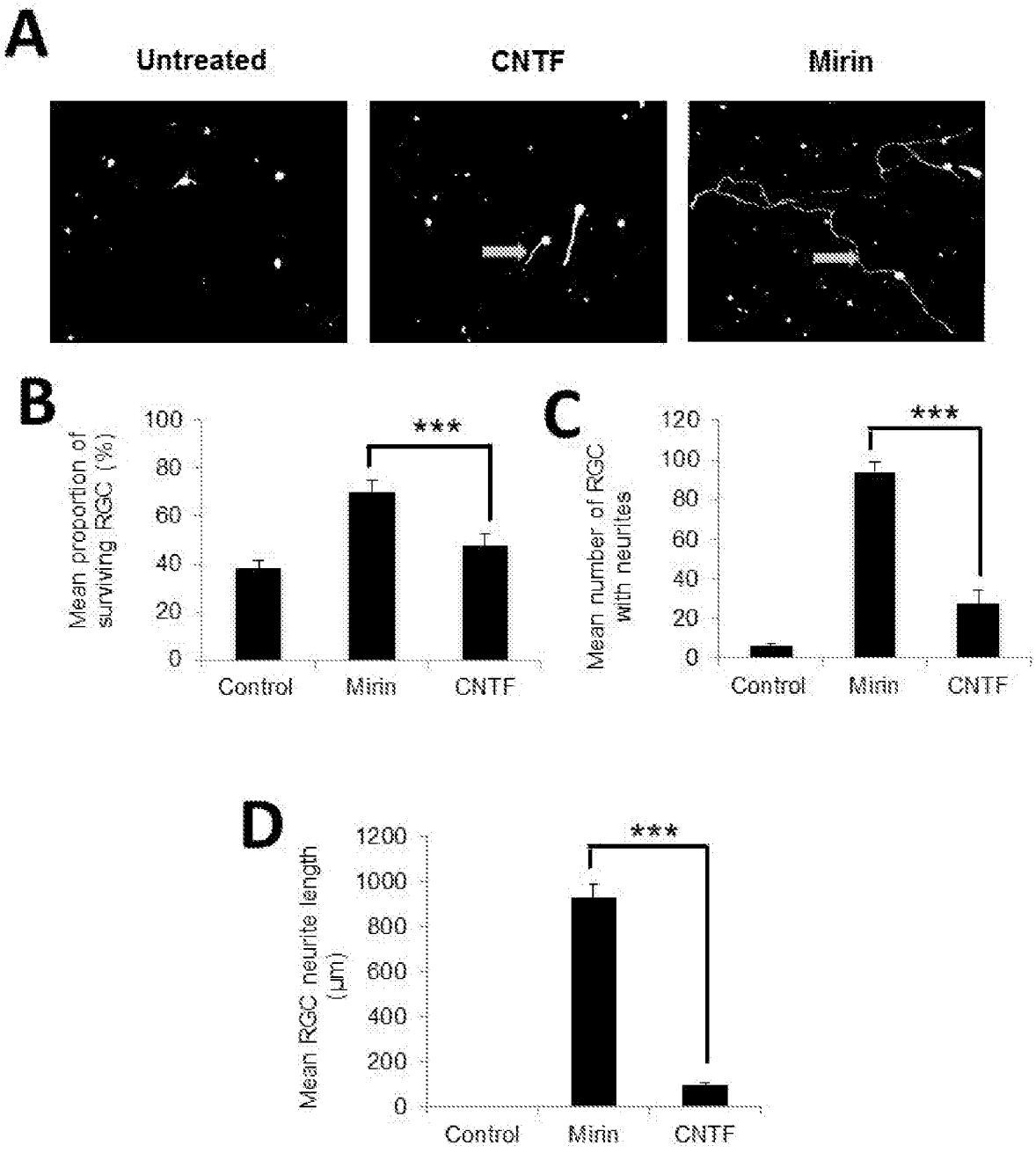
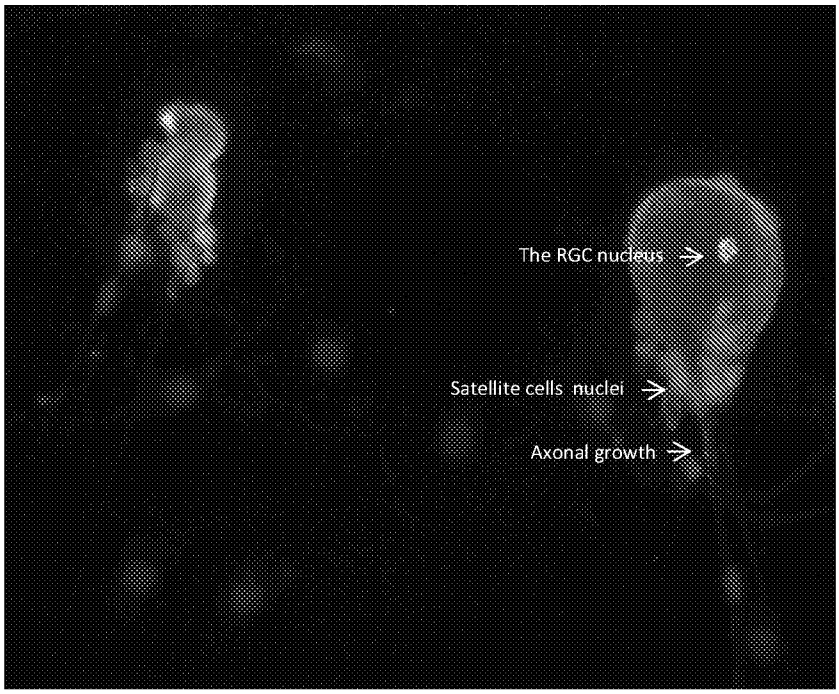

A
Untreated
CNTF
Mirin
B
Mean proportion of surviving RGC (%)
100
80
60
40
20
0
***
Control
Mirin
CNTF
C
Mean number of RGC with neurites
120
100
80
60
40
20
0
***
Control
Mirin
CNTF
D
Mean RGC neurite length (µm)
1200
1000
800
600
400
200
0
***
Control
Mirin
CNTF

Figure 5

A


The RGC nucleus
Satellite cells nuclei
Axonal growth

B

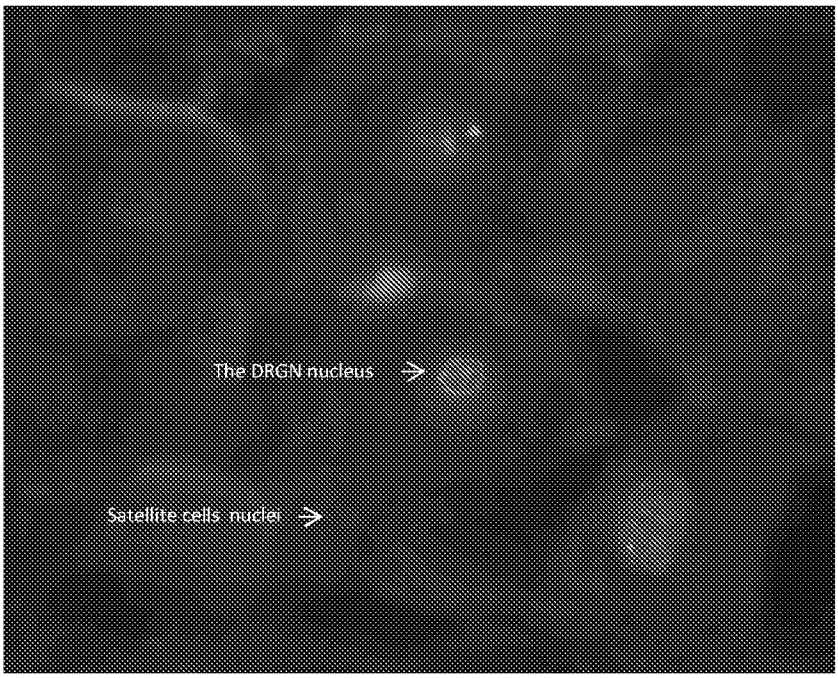

The DRGN nucleus
Satellite cells nuclei

Figure 6

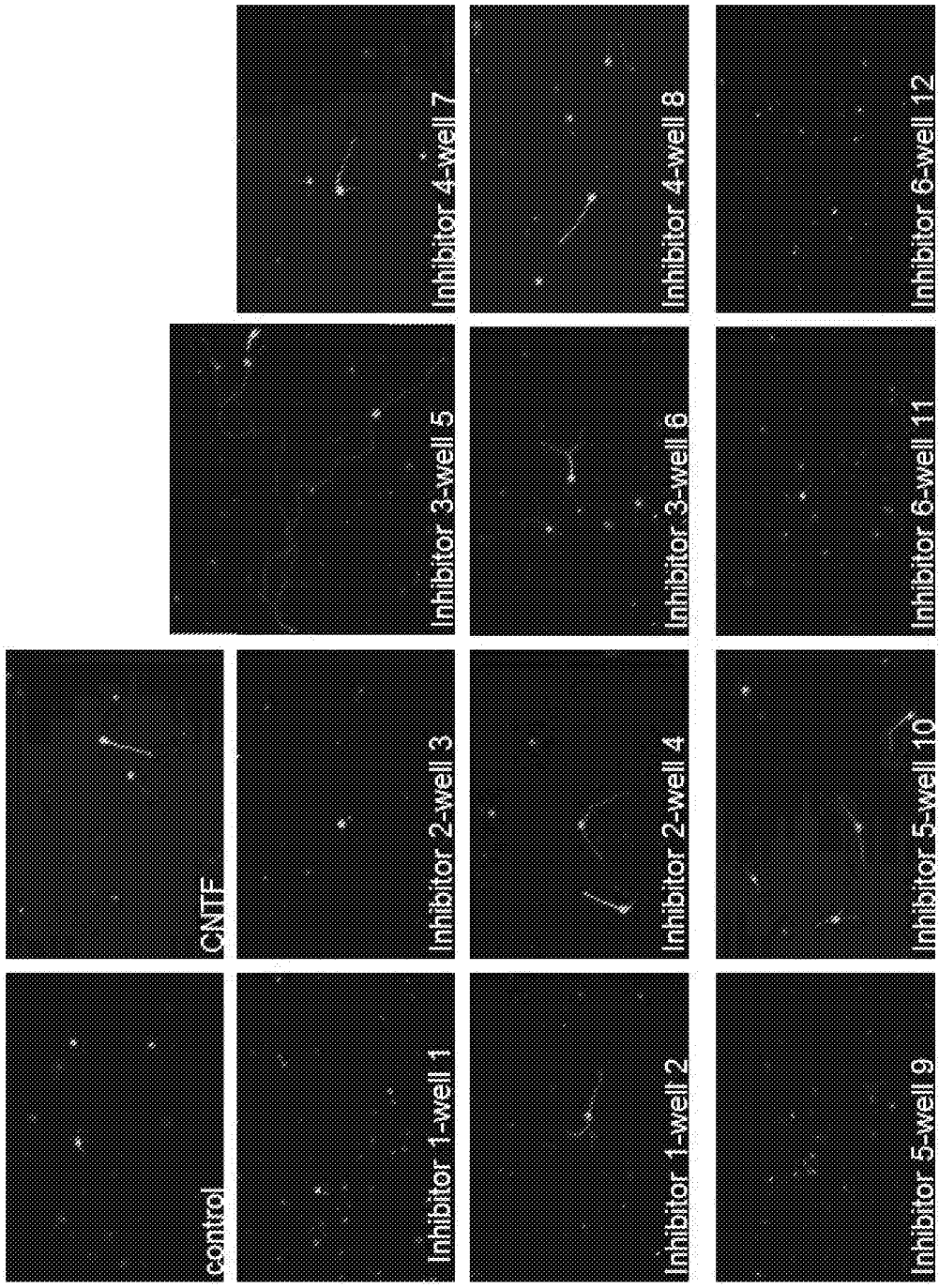

control
CNTF
Inhibitor 1-well 1
Inhibitor 2-well 3
Inhibitor 3-well 5
Inhibitor 4-well 7
Inhibitor 1-well 2
Inhibitor 2-well 4
Inhibitor 3-well 6
Inhibitor 4-well 8
Inhibitor 5-well 9
Inhibitor 5-well 10
Inhibitor 6-well 11
Inhibitor 6-well 12

Figure 7

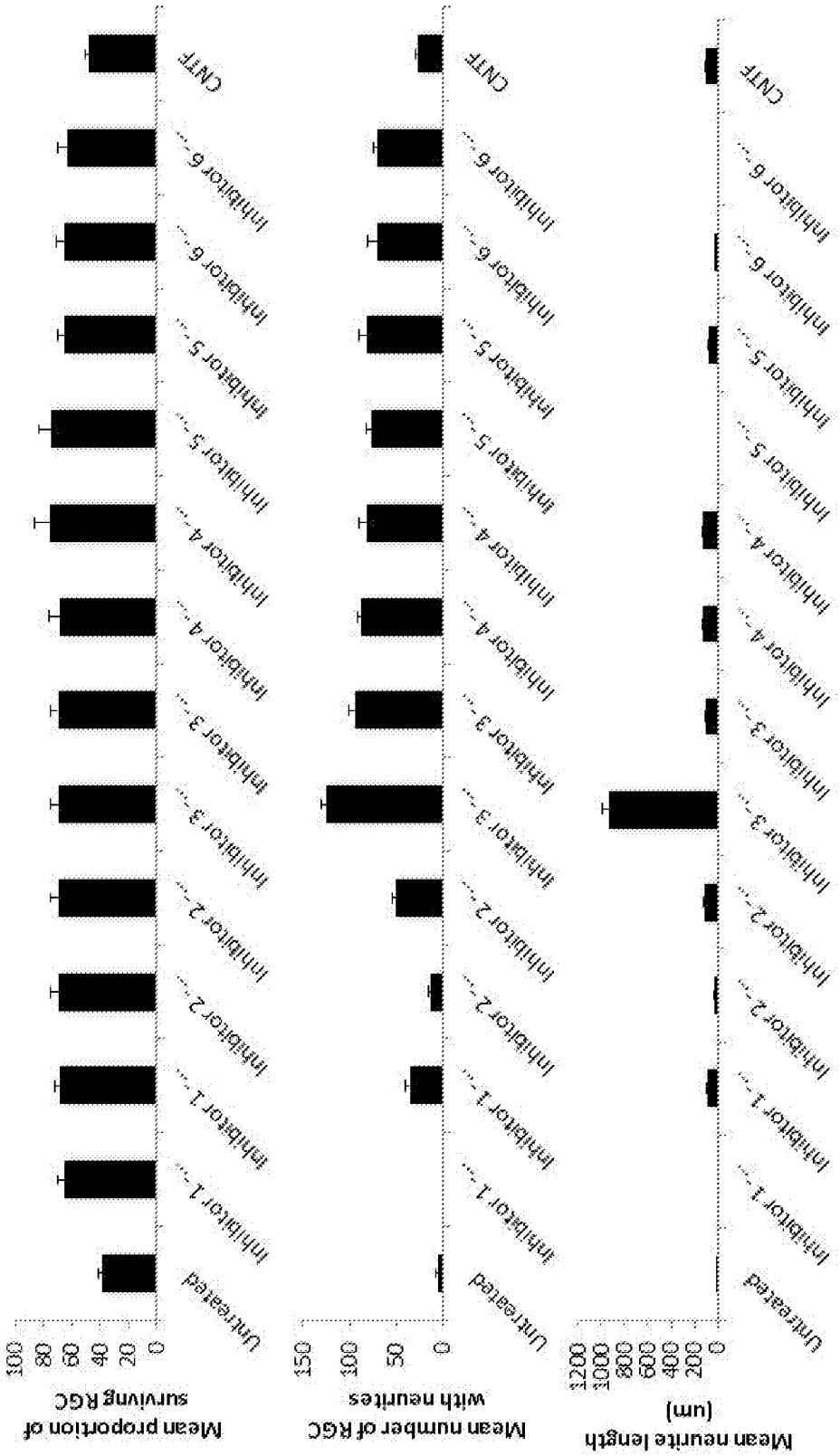

Mean proportion of surviving RGC
100
80
60
40
20
0
Untreated
Inhibitor 1 ...
Inhibitor 1 ...
Inhibitor 2 ...
Inhibitor 2 ...
Inhibitor 3 ...
Inhibitor 3 ...
Inhibitor 4 ...
Inhibitor 4 ...
Inhibitor 5 ...
Inhibitor 5 ...
Inhibitor 6 ...
Inhibitor 6 ...
CNTF
Mean number of RGC with neurites
150
100
50
0
Untreated
Inhibitor 1 ...
Inhibitor 1 ...
Inhibitor 2 ...
Inhibitor 2 ...
Inhibitor 3 ...
Inhibitor 3 ...
Inhibitor 4 ...
Inhibitor 4 ...
Inhibitor 5 ...
Inhibitor 5 ...
Inhibitor 6 ...
Inhibitor 6 ...
CNTF
Mean neurite length (um)
1200
1000
800
600
400
200
0
Untreated
Inhibitor 1 ...
Inhibitor 1 ...
Inhibitor 2 ...
Inhibitor 2 ...
Inhibitor 3 ...
Inhibitor 3 ...
Inhibitor 4 ...
Inhibitor 4 ...
Inhibitor 5 ...
Inhibitor 5 ...
Inhibitor 6 ...
Inhibitor 6 ...
CNTF

Figure 8

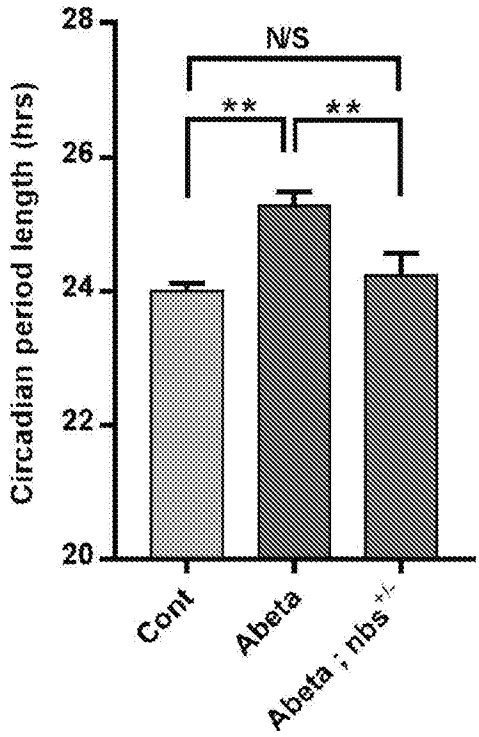


Figure 9

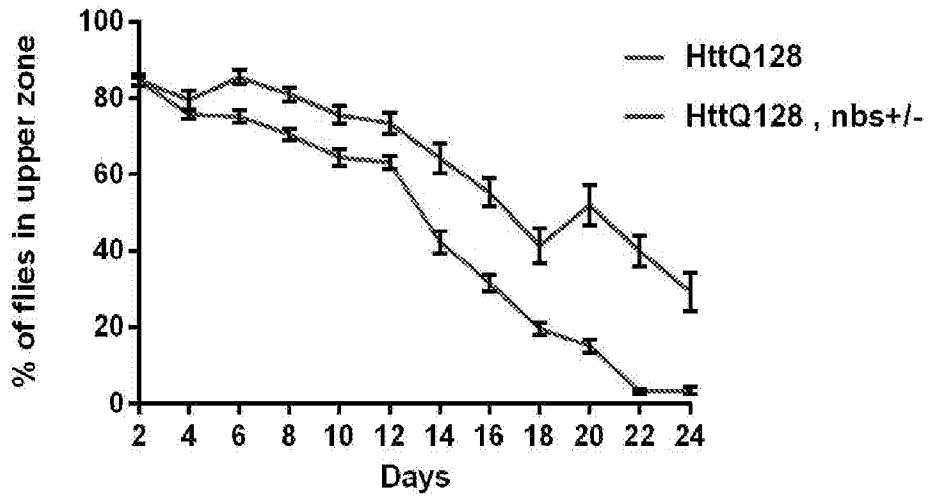


Figure 10

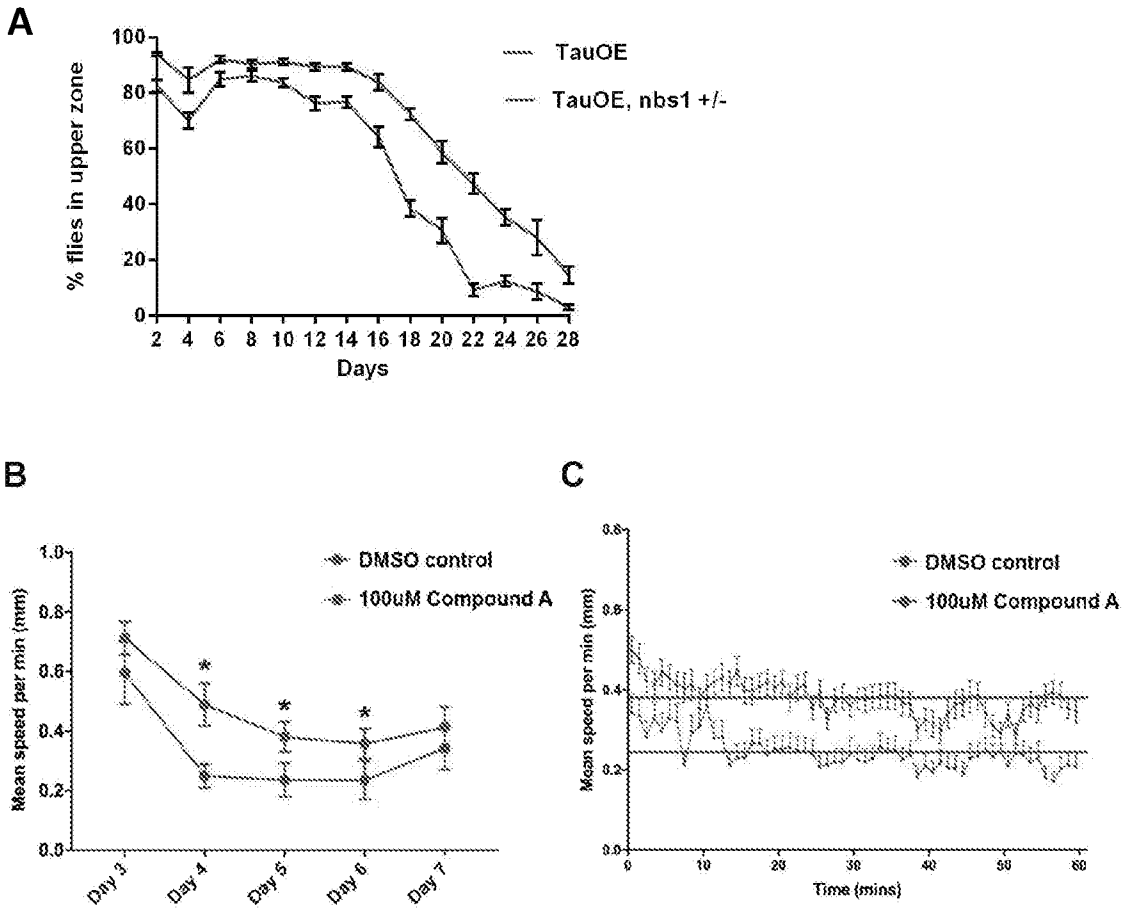
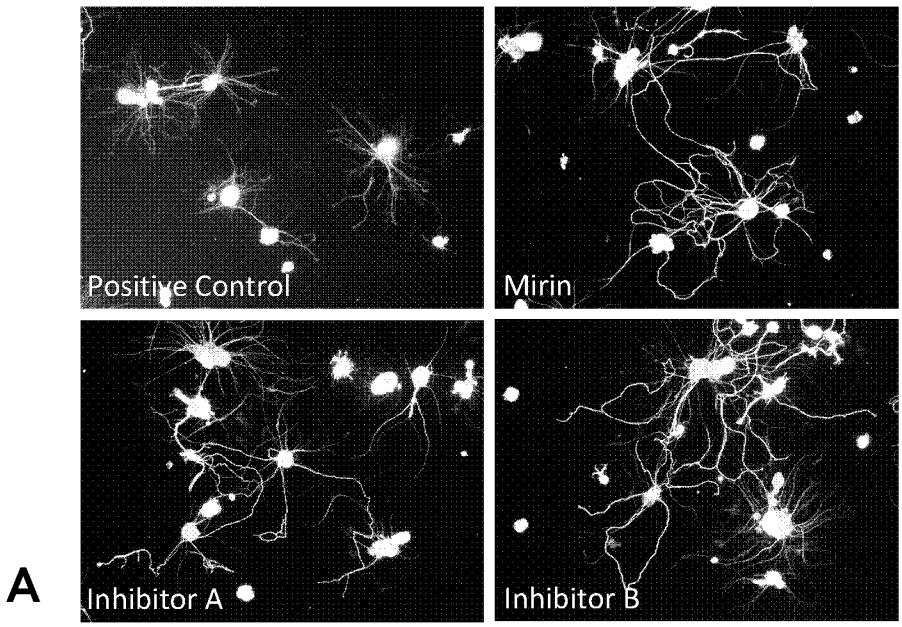
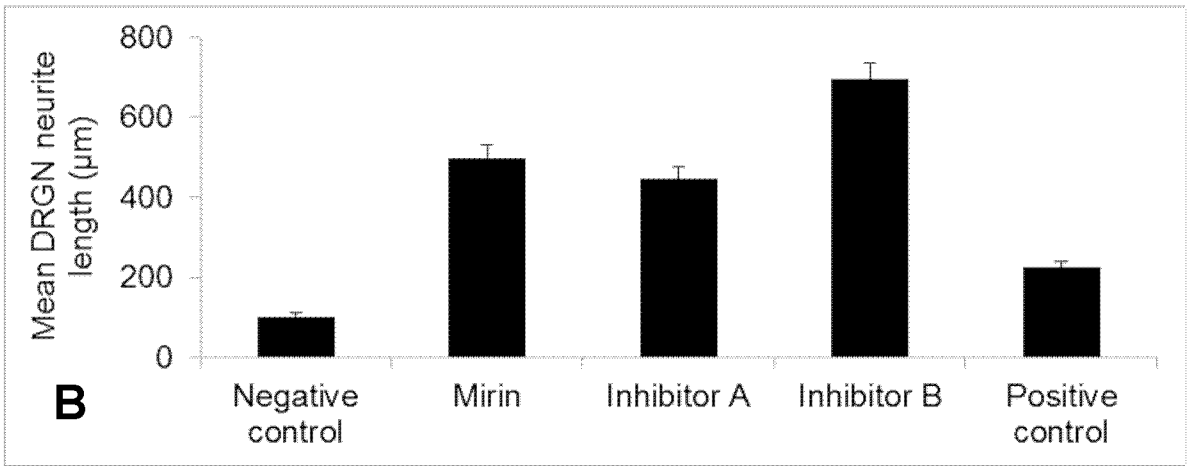

A
% flies in upper zone
Days
TauOE
TauOE, nbs1 +/-
B
Mean speed per min (mm)
DMSO control
100uM Compound A
Day 3
Day 4
Day 5
Day 6
Day 7
C
Mean speed per min (mm)
DMSO control
100uM Compound A
Time (mins)

Figure 11


Positive Control
Mirin
Inhibitor A
Inhibitor B
A


Mean DRGN neurite length (µm)
800
600
400
200
0
Negative control
Mirin
Inhibitor A
Inhibitor B
Positive control
B


Mean proportion of DRGN with neurites (%)
100
80
60
40
20
0
Negative control
Mirin
Inhibitor A
Inhibitor B
Positive control
C

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2017/051400

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/16 A61K31/454 A61P25/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/031536 A1 (UNIV NORTHEASTERN [US]) 5 March 2015 (2015-03-05) claims 61-70 page 14	1-5, 7-11, 17-19

X	WO 2013/179014 A1 (UNIV BIRMINGHAM [GB]) 5 December 2013 (2013-12-05)	1-11, 17-19
Y	claims 1-21	1-11, 17-19

X	WO 99/11649 A2 (GUILFORD PHARM INC [US]) 11 March 1999 (1999-03-11) claims 1-23	1-5, 7-11, 17-19

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 August 2017	03/11/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schnack, Anne

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANTONELLA CARDINALE ET AL: "PARP-1 Inhibition Is Neuroprotective in the R6/2 Mouse Model of Huntington's Disease", PLOS ONE, vol. 10, no. 8, 7 August 2015 (2015-08-07) , page e0134482, XP055397236, DOI: 10.1371/journal.pone.0134482	1-5, 7-11, 17-19
Y	abstract	1-11, 17-19

X	MARTIRE SARA ET AL: "PARP-1 involvement in neurodegeneration: A focus on Alzheimer's and Parkinson's", MECHANISMS OF AGEING AND DEVELOPMENT, vol. 146, 13 April 2015 (2015-04-13), pages 53-64, XP029130660, ISSN: 0047-6374, DOI: 10.1016/J.MAD.2015.04.001	1-5, 7-11, 17-19
Y	the whole document	1-11, 17-19

X	BOGDAN A. STOICA ET AL: "PARP-1 Inhibition Attenuates Neuronal Loss, Microglia Activation and Neurological Deficits after Traumatic Brain Injury", JOURNAL OF NEUROTRAUMA., vol. 31, no. 8, 15 April 2014 (2014-04-15) , pages 758-772, XP055397285, US ISSN: 0897-7151, DOI: 10.1089/neu.2013.3194	1-5, 7-11, 17-19
Y	abstract	1-11, 17-19

X	BARANES K ET AL: "Conditional inactivation of the NBS1 gene in the mouse central nervous system leads to neurodegeneration and disorganization of the visual system", EXPERIMENTAL NEUROLOGY, ELSEVIER, AMSTERDAM, NL, vol. 218, no. 1, 1 July 2009 (2009-07-01), pages 24-32, XP026170113, ISSN: 0014-4886, DOI: 10.1016/J.EXPNEUROL.2009.03.026 [retrieved on 2009-04-01] abstract	1-11, 17-19

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BRANDON J. LAMARCHE ET AL: "The MRN complex in double-strand break repair and telomere maintenance", FEBS LETTERS., vol. 584, no. 17, 22 July 2010 (2010-07-22), pages 3682-3695, XP055397295, NL ISSN: 0014-5793, DOI: 10.1016/j.febslet.2010.07.029 page 4 - page 5	1-11, 17-19
X	MADABHUSHI RAM ET AL: "DNA Damage and Its Links to Neurodegeneration", NEURON, CELL PRESS, US, vol. 83, no. 2, 16 July 2014 (2014-07-16), pages 266-282, XP029035654, ISSN: 0896-6273, DOI: 10.1016/J.NEURON.2014.06.034 the whole document	1-11, 17-19
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Y	DENIS VELIC ET AL: "DNA Damage Signalling and Repair Inhibitors: The Long-Sought-After Achilles' Heel of Cancer", BIOMOLECULES 2013, vol. 5, no. 4, 1 December 2015 (2015-12-01), pages 3204-3259, XP055397226, ISSN: 2218-273X, DOI: 10.3390/biom5043204 the whole document	1-11, 17-19
X	TAKUYA TAMURA ET AL: "Ku70 Alleviates Neurodegeneration in Drosophila Models of Huntington's Disease", PLOS ONE, vol. 7, no. 1, 7 November 2011 (2011-11-07), XP055397323, DOI: 10.1371/annotation/e436994f-3b22-4b35-bd29 -49992f64a584 *Discussion*	1-11, 17-19

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	X.-H. LU ET AL: "Targeting ATM ameliorates mutant Huntingtin toxicity in cell and animal models of Huntington's disease", SCIENCE TRANSLATIONAL MEDICINE, vol. 6, no. 268, 24 December 2014 (2014-12-24), pages 268ra178-268ra178, XP055298355, ISSN: 1946-6234, DOI: 10.1126/scitranslmed.3010523 abstract --- JOGHATAIE M T ET AL: "Protective effect of caffeine against neurodegeneration in a model of Parkinson's disease in rat: behavioral and histochemical evidence", PARKINSONISM AND RELATED DISOR, ELSEVIER SCIENCE, OXFORD, GB, vol. 10, no. 8, 1 December 2004 (2004-12-01), pages 465-468, XP004638390, ISSN: 1353-8020, DOI: 10.1016/J.PARKRELDIS.2004.06.004 abstract ---	1-5, 7-11, 17-19
X		1-5, 7-11, 17-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2017/051400

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-11, 17-19

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-11, 17-19

An inhibitor of DNA damage signalling and repair for use in treating or preventing a neurological pathology.

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2. claims: 12-16

A neuro-regenerative compound comprising an inhibitor of DNA damage signalling and repair attached to a nanoparticle and/or a cell targeting peptide. First medical use of such compound.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2017/051400

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015031536 A1	05-03-2015	EP 3038600 A1	06-07-2016
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