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(54) Title: REDUCTION OF AGING-INDUCED TYPE I INTERFERON SIGNALING AT THE BRAIN'S CHOROID PLEXUS OR WITHIN THE CNS FOR TREATMENT OF DISEASE OR INJURY OF THE CNS

(57) Abstract: An agent that reduces type I IFN activity at the choroid plexus or within the CNS for use in treating a disease, disorder, condition or injury of the CNS is provided.



**REDUCTION OF AGING-INDUCED TYPE I INTERFERON SIGNALING AT THE
BRAIN'S CHOROID PLEXUS OR WITHIN THE CNS FOR TREATMENT OF
DISEASE OR INJURY OF THE CNS**

5 FIELD OF THE INVENTION

The present invention relates in general to methods and compositions for treating a disease, disorder, condition or injury of the Central Nervous System (CNS), including restoration of cognitive function, by reducing the level of aging-induced type I interferon signaling.

BACKGROUND OF THE INVENTION

10 One of the mysteries of brain senescence is to what extent it is influenced by aging of other body tissues (1, 2). Recent studies have suggested that age-related changes in both circulating soluble factors (3-5) and peripheral immunity (6) are involved in this process. Nevertheless, given the fact that the mammalian central nervous system (CNS) is secluded behind barriers from directly interacting with the blood circulation (7), the underlying
15 mechanism remains unclear.

The choroid plexus (CP), an epithelial monolayer that forms the blood-cerebrospinal fluid barrier (B-CSF-B) and produces the CSF, serves as a neuro-immunological interface in shaping brain function in health and pathology by integrating signals from the brain with signals coming from the circulation (6, 8-11). We envisioned that understanding how CP activity is altered in
20 aging might lead to identification of strategies to attenuate age-associated decline in brain function.

WO 2014/037952 discloses methods of treating disease, disorder, condition or injury of the Central Nervous System (CNS) by activation of the choroid plexus.

25 US Patent Application No. 61/951,783 discloses methods and compositions for treating disease, disorder, condition or injury of the CNS by reducing the level and/or activity of regulatory T cells (Tregs) in the circulation.

There remains a need for alternative and efficient methods for maintaining a young phenotype of the CP in order to facilitate CNS tissue maintenance and repair.

SUMMARY OF INVENTION

30 In one aspect, the present invention provides a method for treating a disease, disorder, condition or injury of the Central Nervous System (CNS) comprising administering to an individual in need thereof an agent that reduces type I interferon (IFN) activity at the choroid plexus or within the CNS.

BRIEF DESCRIPTION OF DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

5 **Figs. 1A-D** show that there is a type I interferon expression program in the aging CP. (**A-B**) mRNA abundance of type I and type II IFN-dependent genes in the CP of aged animals, presented as fold change relative to expression in young mice CPs (n=10 mice per group; bars represent mean $\pm$ SEM; *, P < 0.05; **, P < 0.01; ***, P < 0.001; Student's t test for each pair; data are representative of at least three independent experiments performed). (**C**) Representative
10 images of brain sections of young and aged mice, immunostained for Claudin-1 (marking epithelial tight junctions; in green), and either CXCL10 or ICAM1 (in red) (Scale bar, 25 μ m). (**D**) Representative micrographs of immunohistochemical staining for IRF7 in young and aged mice, and for IRF7 and IFN- β in young and aged human postmortem CPs (Scale bar, 50 μ m).

Fig. 2 shows a Venn diagram of IFN type I (α and β), II (IFN- γ), and III -dependent genes
15 (as defined by the "Interferome" database) within the gene cluster (IX) that shows increased expression in the aged CP.

Figs. 3A-C show that signals from the cerebrospinal fluid, but not from the blood circulation, have an effect on type I IFN-dependent genes in the CP. (**A-B**) mRNA expression of type I IFN-dependent genes, *ifit1* and *irf7* (**A**) and the type II IFN-dependent gene, *ccl11* (**B**) in
20 the CP of parabiotic mice (n=6-8 mice per group). (**C**) mRNA expression of *ifit1* and *irf7* in primary cultures of CP cells treated with PBS or CSF aspirated from young (3 months old) or aged (22 months old) mice (n=4-5 per group). Throughout the figure, bars represent mean $\pm$ SEM; *, P < 0.05; **, P < 0.01; ***, P < 0.001; one-way ANOVA with Newmann-Kleus post-hoc test.

25 **Fig. 4** depicts *ifit1* and *irf7* mRNA expression in primary cultures of CP cells treated with PBS or a mixture of pro-inflammatory cytokines (TNF- α , IL-1 β and IL-6) (n=4 per group; bars represent mean $\pm$ SEM; ***, P < 0.001; Student's t test).

Figs. 5A-M show that premature cognitive decline occurs in adult mice lacking IFN- γ signaling. Transgenic mice lacking IFN- γ -receptor (*IFN- γ R*^{-/-}) and mice lacking IFN- γ
30 expression by CD4⁺ T cells (*Tbx21*^{-/-}) were repeatedly tested for their hippocampal-dependent spatial memory. (**A-B**) Performance of *IFN- γ R*^{-/-} compared to aged-matched wild type (WT) in the RAWM task. *IFN- γ R*^{-/-} mice did not show changes in cognitive performance at the age of 6 months (**A**), but did show reduced learning at 9 months of age (**B**) (n=10 per group; bars represent mean $\pm$ SEM, and the average number of errors per group per day; two-way repeated-

measures ANOVA with Bonferroni post-hoc test). (C) At 9 months of age *IFN- γ ^{-/-}* mice showed reduced spatial memory relative to age-matched WT mice, measured in the NLR task, shown as percentage preference to the relocated object on the testing day (n=10 per group; bars represent mean $\pm$ SEM; **, P < 0.01; one-way ANOVA with Newmann-Kleus post-hoc). (D-E) Performance of *Tbx21*^{-/-} mice compared to aged-matched wild type (WT) in the RAWM task. *Tbx21*^{-/-} mice did not show changes in cognitive performance at the age of 9 months (D), but did show reduced learning at 12 months of age (E) (n=10 per group; bars represent mean $\pm$ SEM, and the average number of errors per group per day; two-way repeated-measures ANOVA with Bonferroni post-hoc test). (F) At 12 months of age *Tbx21*^{-/-} showed reduced spatial memory relative to age-matched WT mice, measured in the NLR task, shown as percentage preference to the relocated object on the testing day (n=10 per group; bars represent mean $\pm$ SEM; *, P < 0.05; **, P < 0.01; one-way ANOVA with Newmann-Kleus post-hoc). (G, H) Average swimming speed of 9 month old *IFN- γ ^{-/-}* (G), 12 month old *Tbx21*^{-/-} (H), and age matched WT mice (n=10 per group; bars represent mean $\pm$ SEM; Student's t test) (I) Representative images of DCX (red) and BrdU (green) immunostaining on hippocampal sections of 9 month old *IFN- γ ^{-/-}* and WT mice (scale bar, 50 μ m). (J-K) Quantification of DCX⁺ (J) and BrdU⁺ (K) newly-born neurons in the hippocampal dentate gyrus (DG) of 9 month old *IFN- γ ^{-/-}* and aged-matched WT mice (n=3 per group; bars represent mean $\pm$ SEM; *, P < 0.05; Student's t test). (L) mRNA transcript levels of *cxcl10* and *icam1* in the CP epithelium of 9 month old *IFN- γ ^{-/-}* and WT mice (n=8; bars represent mean $\pm$ SEM; *, P < 0.05; ***, P < 0.001; Student's t test). (M) FACS analysis of leukocytes (CD45⁺), T cells (TCR β ⁺), and CD4 T cells (TCR β ⁺/CD4⁺) in the CSF of 9 month old *IFN- γ ^{-/-}* and WT mice (n=6-7 per group; *, P < 0.05; **, P < 0.01; Student's t test).

Fig. 6 depicts a schematic presentation of premature functional brain aging in mice lacking IFN- γ signaling. Schematic explanation of the results presented in Fig. 5, showing cognitive decline during adulthood in *IFN- γ ^{-/-}* (dashed line), *Tbx21*^{-/-} (dotted line) and WT mice (continuous line). Gradual “wear and tear” of the brain tissue accumulates throughout life and contributes to functional brain aging. Cognitive ability and adult hippocampal neurogenesis drop when such accumulation exceeds a certain threshold, beyond which the brain can no longer reverse or contain the intrinsic damage (at around 18-22 months of age in WT C57BL/6 mice) (1-3). Circulating immune cells have been shown to contribute to the maintenance of neurogenesis and spatial learning and memory abilities in adulthood (4-7), likely by restoration of brain homeostasis (8, 9). IFN- γ at the CP plays a critical role in mediating CNS immune surveillance, leukocyte recruitment to the CNS following acute injury (10), and for maintaining

local levels of IL-4 under control, therefore indirectly supporting brain function (8) (see also: fig. 10). Taken together with those observations, the premature functional brain aging in mice that lack type II IFN in the circulation (*Tbx21*^{-/-} mice, at 12 months of age) or are unable to respond to it (*IFN-γR*^{-/-} mice, at 9 months of age) (fig. 5), could be the outcome of continuous failure to restore homeostasis of the brain parenchyma. All together, these observations suggest that type II IFN-dependent processes become crucial for maintaining brain function at this critical time point.

Figs. 7A-E show that CP function is restored after neutralization of the age-induced type I IFN response in the brain. **(A-B)** *ifit1*, *irf7* **(A)**, and *bdnf* and *igf1* **(B)** mRNA expression in CP epithelial cells cultured for 24h with murine IFN-β (n=4 per group; bars represent mean ± SEM; *, P < 0.05; ***, P < 0.001, Student's t test). **(C)** *ifit1* and *irf7* mRNA expression in the CP 3 days after α-IFNAR or IgG control i.c.v. administration. **(D-E)** *bdnf* and *igf1* **(D)** and *ccl11* **(E)** mRNA expression in the CP 7 days after α-IFNAR or IgG control i.c.v. administration (n=6-7 per group). Throughout the figure, bars represent mean ± SEM; *, P < 0.05; one-way ANOVA with Newmann-Kleus post-hoc test.

Fig. 8 shows immunohistochemical staining of BDNF (in red) and epithelial marker E-Cadherin (in green) (scale bar, 50μm).

Figs. 9A-F show that brain function is restored after neutralization of the age-induced type I IFN response in the brain. **(A)** Performance of “cognitively unimpaired” and “cognitively impaired” aged mice in the NLR task (n=5-18 per group). **(B)** Performance of α-IFNAR and control IgG injected cognitively-impaired aged mice in the NLR task (n=5-6 per group). **(C-D)** Analysis of the hippocampal dentate gyrus (DG) of α-IFNAR or control IgG i.c.v.-injected “cognitively impaired” aged mice, and of young and aged “cognitively unimpaired” mice, 14 days after treatment (n=4-6 per group). Quantification of hippocampal DCX and BrdU labeled newly-born neurons (notably, in this experiment, young mice showed significantly higher numbers of DCX and BrdU labeled cells, 16832±873 and 4403±51, respectively) **(D)**; *il-10* mRNA expression in the hippocampus **(D)**. **(E-F)** Quantification **(E)**, and representative images **(F)**, of GFAP and IBA-1 staining intensity in hippocampal brain sections immunostained for GFAP (in red), IBA-1 (in green), and Hoechst nuclear staining (in blue) (scale bar, 50μm). Throughout the figure, bars represent mean ± SEM; *, P < 0.05; **, P < 0.01; one-way ANOVA with Newmann-Kleus post-hoc test.

Fig. 10 depicts a proposed model illustrating aging-associated changes at the CP and their effects on brain function: (1) In young mice, balanced amounts of stromal IFN-γ and IL-4 maintain CP function (neurotrophic factor production and CNS immunosurveillance). (2) During

aging, this balance is skewed towards IL-4, triggering the CP to produce CCL11 and reduce leukocyte trafficking, thus affecting brain function. (3) Parenchymal-derived signals from the aged brain induce a type I IFN response program in the CP, which affects CP function and negatively regulates brain plasticity. (4) In heterochronic parabiosis settings, the mixed
5 circulation modulates the local cytokine balance of the CP of young parabionts, inducing local CCL11 expression. (5) In the aged heterochronic parabionts, type II IFN-dependent activation of the CP for CNS immunosurveillance is induced, whereas CCL11 expression is maintained. (6) Neutralizing IFN-I signaling from the CSF by i.c.v administration of α -IFNAR antibody partially restores CP function and brain plasticity.

10

DETAILED DESCRIPTION OF THE INVENTION

It has been found in accordance with the present invention that in aged mice and humans, the choroid plexus (CP), an epithelial interface between the brain and the circulation, shows a type I interferon (IFN-I)-dependent expression profile, often associated with anti-viral responses
15 (Example 1). This signature was induced by brain-derived signals present in the cerebrospinal fluid of aged mice (Example 2). Blocking IFN-I signaling within the brain of cognitively-impaired aged mice, using IFN-I receptor neutralizing antibody, led to partial restoration of cognitive function and hippocampal neurogenesis (Example 5), and reestablished IFN-II-dependent CP activity, lost in aging. Our data identify a chronic aging-induced IFN-I signature at
20 the CP, and demonstrate its negative influence on brain function (Examples 3 and 4), suggesting a potential therapeutic target for attenuating age-related cognitive decline.

The CP has been reported to undergo significant changes during aging, including atrophy and reduced secretory activity (19). Recent studies have attributed to the CP a key role in the ongoing dialogue between the brain and the circulating immune system, and indicated that a
25 delicate cytokine balance locally regulates its function. Specifically, basal levels of IFN- γ and IL-4 at the CP were shown to maintain CNS immunosurveillance and CP neurotropic factor expression (6, 10); a shift in this local cytokine equilibrium in aging involving excessive IL-4 and insufficient IFN- γ levels, was demonstrated to induce epithelial expression of CCL11 (6), with negative consequences to brain plasticity (3) (**Fig. 10**). Here, we identified type I IFN as a
30 novel player in this local cytokine balance, which negatively influences CP function.

Though originally identified by their anti-viral properties, type I IFNs have important roles in attenuating inflammation, both outside and inside the CNS (24-26). Nevertheless, we found that blocking IFN-I signaling in the brain of aged mice, not only partially restored cognitive function but also attenuated age-related chronic neuroinflammation. It is thus possible that IFN-I

response program at the aged CP represents a physiological mechanism evoked to mitigate age-related neuroinflammation, and when this process persists, it negatively affects adult neurogenesis and spatial learning and memory, at least in part by interfering with IFN-II activity in the CP and brain parenchyma, needed for immune-mediated active resolution of neuroinflammation (9) (**Fig. 10**). Such a detrimental influence of IFN-I in CNS function was also found in patients suffering from diseases in which cerebral levels of IFN-I are increased (25), and in chronic inflammatory diseases in which type I IFNs are therapeutically administered, often accompanied by neurological and neuropsychiatric complications (27). Thus, neutralizing the response to type I IFNs within the CNS might provide an approach to reverse or slow down age-related cognitive decline.

Thus, in one aspect, the present invention provides a method for treating a disease, disorder, condition or injury of the CNS comprising administering to an individual in need thereof an agent that reduces type I IFN activity at the choroid plexus or within the CNS.

In another aspect, the present invention provides an agent that reduces type I IFN activity at the choroid plexus or within the CNS for use in treating a disease, disorder, condition or injury of the CNS.

The term "type I IFN activity" as used herein refers to the activity elicited by an agent capable of binding to and activating the cell surface receptor complex IFN- α/β receptor (IFNAR) also referred to herein as type I IFN receptor. IFNAR consists of two subunits: IFNAR1 and IFNAR2 and has a wide variety of specific ligands: IFN- α (and its 13 subtypes: IFNA1, IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFNA8, IFNA10, IFNA13, IFNA14, IFNA16, IFNA17, IFNA21); IFN- β 1; IFN β 3; IFN- ϵ , IFN- κ , IFN- τ , and IFN - ζ . Reduction of the IFNAR activity may be achieved either by inhibiting the receptor by preventing binding of, and/or activation by, a specific ligand by e.g. competitive, uncompetitive, or non-competitive reversible inhibition or irreversible inhibition at the extracellular part of the receptor; inhibiting IFNAR-ligand production; interfering with downstream intra-cellular signal-transduction, i.e. interfering with the JAK-STAT signaling pathway; or inhibiting or reducing IFNAR subunit(s) expression.

Assays for measuring type I interferon IFN activity *in vitro* are well-known in the art. For example, induction of IFN-I-dependent gene expression as disclosed herein below, or as taught by Feng et al. (29) may be measured.

As exemplified in Example 4, the agent that reduces type I IFN activity may be an antagonist to the type I IFN receptor, such as a neutralizing antibody specific to the type I IFN receptor. Other agents may be selected from known antagonists to the type I IFN receptor such as a soluble decoy IFN-I receptor, a type I IFN antagonist selected from a viral protein such as

influenza virus NS1 protein, a paramyxovirus V protein (e.g. mumps virus V protein or human parainfluenza virus 2 V protein), a Sendai virus C protein, respiratory syncytial virus NS1 or NS2 protein, or Ebola virus VP35 protein (e.g. 38); a molecule capable of interfering with type I IFN receptor signal transduction pathway selected from a statin such as atorvastatin (29), or a splice variant of IFN regulatory factor-3 (IRF3), known as splice variant IRF3-nirs3 (30), which inhibits IFN- β response, or an agent activating or coupling ITAM-coupled β 2 integrins and Fc γ R; a molecule capable of interfering with type I IFN receptor-ligand production, such as hydroxychloroquine, which is inhibiting IFN- α production (31); or a nucleic acid molecule encoding an antibody or viral IFNAR antagonist or IRF3-nirs3.

The agent may further be selected from an IFN- α antagonist; an IFN- β antagonist; or an agent reducing type I IFN activity by reducing type I IFN receptor expression at the choroid plexus or in the CNS selected from (a) an artificial siRNA or shRNA molecule comprising a nucleic acid sequence being complementary to a sequence within a nucleic acid sequence encoding the type I IFN receptor or IFN- β ; or a glycoside such as bufalin (32).

siRNA or shRNA molecule capable of inhibiting or reducing type I IFN receptor expression are well known (e.g. 33, 34 incorporated by reference as if fully disclosed herein). In certain embodiments, the siRNA molecule is a double stranded RNA of 20-24 base pairs in length with phosphorylated 5' ends and hydroxylated 3' ends with two overhanging nucleotides. The siRNA or shRNA may be chosen to target the IFNAR1 gene (Entrez Gene ID, 3454; UniGene ID Hs. 529400), at exon 7 at any position, for example at position 987, 988, 992, 1043, 1056; at exon 8 at any position, for example at position 1114, 1130, 1131, 1135, 1186 or 1199; or exon 11 at any position, for example at position 2734 or 667.

The nucleic acid molecule encoding an antibody or viral IFNAR antagonist, IRF3-nirs3, siRNA or shRNA may be comprised within a viral vector. The vector may be used for transferring the nucleic acid to a host cell; it optionally may comprise a viral capsid or other materials for facilitating entry of the nucleic acid into the host cell and/or replication of the vector in the host cell.

The IFN- α antagonist may be selected from the known IFN- α 2b antagonist peptides SP-7 (SLSPGLP; SEQ ID NO: 1), FY-7 (FSAPVRY; SEQ ID NO: 2) (35), KP-7 (KNVHPPP; SEQ ID NO: 3) or IR-7 (IRPDTPR; SEQ ID NO: 4) (36).

In particular, the neutralizing antibody specific to the type I IFN receptor is a human antibody.

Any of the above-mentioned agents may be administered by any method and route routinely used to provide agents to the choroid plexus or the CNS, such as, but not limited to, intracerebroventricular or intrathecal injection.

Since according to the findings of the present invention, inhibition of type I IFN activity
5 restores cognitive function and induces or improves neurogenesis (Example 5), the agent or method of the present invention may be utilized for treating a disease, disorder or condition of the CNS selected from the group consisting of a neurodegenerative disease, disorder or condition selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease; primary progressive multiple sclerosis; secondary
10 progressive multiple sclerosis; a retinal degeneration disorder selected from the group consisting of age-related macular degeneration and retinitis pigmentosa; anterior ischemic optic neuropathy; glaucoma; uveitis; depression; stress; autism, schizophrenia and Rett syndrome; in particular Alzheimer's disease. It may also be used for treating an injury of the CNS selected from spinal cord injury, closed head injury, blunt trauma, penetrating trauma, hemorrhagic
15 stroke, ischemic stroke, cerebral ischemia, optic nerve injury, myocardial infarction, organophosphate poisoning and injury caused by tumor excision.

The use of the agent in treating as disclosed above may improve CNS motor and/or cognitive function and it may alleviate age-associated loss of cognitive function, for example age-associated loss of cognitive function occurring in subjects free of a diagnosed disease or
20 resulting from acute stress. The use of the agent in treating as disclosed above may also induce or increase neurogenesis in the diseased or injured CNS.

The terms "cognition", "cognitive function" and "cognitive performance" are used herein interchangeably and are related to any mental process or state that involves but is not limited to learning, memory, creation of imagery, thinking, awareness, reasoning, spatial ability, speech
25 and language skills, language acquisition and capacity for judgment attention. Cognition is formed in multiple areas of the brain such as hippocampus, cortex and other brain structures. However, it is assumed that long term memories are stored at least in part in the cortex and it is known that sensory information is acquired, consolidated and retrieved by a specific cortical structure, the gustatory cortex, which resides within the insular cortex.

30 In humans, cognitive function may be measured by any know method, for example and without limitation, by the clinical global impression of change scale (CIBIC-plus scale); the Mini Mental State Exam (MMSE); the Neuropsychiatric Inventory (NPI); the Clinical Dementia Rating Scale (CDR); the Cambridge Neuropsychological Test Automated Battery (CANTAB) or the Sandoz Clinical Assessment-Geriatric (SCAG). Cognitive function may also be measured

indirectly using imaging techniques such as Positron Emission Tomography (PET), functional magnetic resonance imaging (fMRI), Single Photon Emission Computed Tomography (SPECT), or any other imaging technique that allows one to measure brain function.

5 An improvement of one or more of the processes affecting the cognition in a patient will signify an improvement of the cognitive function in said patient, thus in certain embodiments improving cognition comprises improving learning, plasticity, and/or long term memory. The terms "improving" and "enhancing" may be used interchangeably.

The term "learning" relates to acquiring or gaining new, or modifying and reinforcing, existing knowledge, behaviors, skills, values, or preferences.

10 The term "plasticity" relates to synaptic plasticity, brain plasticity or neuroplasticity associated with the ability of the brain to change with learning, and to change the already acquired memory. One measurable parameter reflecting plasticity is memory extinction.

The term "memory" relates to the process in which information is encoded, stored, and retrieved. Memory has three distinguishable categories: sensory memory, short-term memory, 15 and long-term memory.

The term "long term memory" is the ability to keep information for a long or unlimited period of time. Long term memory comprises two major divisions: explicit memory (declarative memory) and implicit memory (non-declarative memory). Long term memory is achieved by memory consolidation which is a category of processes that stabilize a memory trace after its 20 initial acquisition. Consolidation is distinguished into two specific processes, synaptic consolidation, which occurs within the first few hours after learning, and system consolidation, where hippocampus-dependent memories become independent of the hippocampus over a period of weeks to years. In another aspect, the present invention provides an agent that reduces type I IFN activity at the choroid plexus or within the CNS as defined herein above, for use in treating 25 a disease, disorder, condition or injury of the CNS.

In a further aspect, the present invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an agent that reduces type I IFN activity at the choroid plexus or within the CNS as defined herein above, for treating a disease, disorder, condition or injury of the CNS.

30 It is to be understood that all embodiments described for a certain aspect, in this case the method for treatment, such as the specific agents that may be used in the method, or the specific diseases that may be treated by the method, apply also to the other aspects of the present invention.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

5 The following exemplification of carriers, modes of administration, dosage forms, etc., are listed as known possibilities from which the carriers, modes of administration, dosage forms, etc., may be selected for use with the present invention. Those of ordinary skill in the art will understand, however, that any given formulation and mode of administration selected should first be tested to determine that it achieves the desired results.

10 Methods of administration include, but are not limited to, parenteral, e.g., intravenous, intraperitoneal, intramuscular, subcutaneous, mucosal (e.g., oral, intranasal, buccal, vaginal, rectal, intraocular), intrathecal, topical and intradermal routes. Administration can be systemic or local. In certain embodiments, the pharmaceutical composition is adapted for oral administration.

15 The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the active agent is administered. The carriers in the pharmaceutical composition may comprise a binder, such as microcrystalline cellulose, polyvinylpyrrolidone (polyvidone or povidone), gum tragacanth, gelatin, starch, lactose or lactose monohydrate; a disintegrating agent, such as alginic acid, maize starch and the like; a lubricant or surfactant, such as magnesium stearate, or sodium
20 lauryl sulphate; and a glidant, such as colloidal silicon dioxide.

For oral administration, the pharmaceutical preparation may be in liquid form, for example, solutions, syrups or suspensions, or may be presented as a drug product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g.,
25 sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g.,
30 pregelatinized maize starch, polyvinyl pyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well-known in the art.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

5 The compositions may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multidose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing
10 agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen free water, before use.

The compositions may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

15 For administration by inhalation, the compositions for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by
20 providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin, for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The invention will now be illustrated by the following non-limiting examples.

EXAMPLES

25 Materials and Methods

Animals. Males of the following mouse strains were used: 3 month old C57BL/6 (The Jackson Laboratory or the Animal Breeding Centre of the Weizmann Institute of Science), C57BL/6 aged mice (National Institute on Ageing, Weizmann Institute of Science colony, or Harlan Laboratories, Netherlands), B6.129 IFN- γ R1-knockout (*IFN- γ R^{-/-}*) (The Jackson
30 Laboratory), and Tbx21-knockout (*Tbx21^{-/-}*) mice (The Jackson Laboratory). Mice were housed under specific pathogen-free conditions, under a 12 h light-dark cycle, and all behavioral tests were conducted during the dark hours. All experiments conformed to the regulations formulated by either the Weizmann Institutional Animal Care and Use Committee, or the Veterans Affairs Palo Alto Committee on Animal Research.

Paraffin embedded sections of human CP. Postmortem non-CNS-disease human brain sections were obtained from the Thomas Willis Oxford Brain Collection (TWIBC) with informed consent and Ethics Committee approval (TW220).

Parabiosis. Parabiosis was performed as previously described (11). Briefly, mirror-image incisions at adjacent flanks on each mouse were made through the skin; shorter incisions were made through the abdominal wall, after which the peritoneal cavities of the parabionts were sutured together. Elbow and knee joints were sutured together to facilitate ease of movement, and the skin was stapled (9-mm autoclip, Clay Adams). Parabionts were given subcutaneous injections of Baytril (antibiotic) and Buprenorphine as directed for pain, and monitored during recovery, providing 0.9% saline i.p. as needed for hydration. Parabionts from each pair were simultaneously transcardially perfused with PBS before tissues were dissected, snap-frozen on dry ice, and stored at -80°C.

Intracerebroventricular (i.c.v.) injections. Neutralizing antibody to IFNAR1 (mouse anti-mouse IFNR1 Ab clone MAR1-5A3, eBioscience) (10µg) or mouse IgG1 κ isotype control (clone MG1-45, BioLegend) (10µg) were injected i.c.v. (0.4 mm posterior to the bregma, 1.0 mm lateral to the midline and 2.0 mm in depth from the brain surface), as described (12).

Cerebrospinal fluid collection. CSF was collected using the cisterna magna puncture technique, as previously described (10). Briefly, anesthetized mice were placed on a stereotactic instrument and sagittal incision of the skin was made inferior to the occiput. Subcutaneous tissue and muscle were separated, and a capillary was inserted into the cisterna magna through the dura mater, lateral to the arteria dorsalis spinalis. Approximately 9-16 µl of CSF could be aspirated from an individual mouse.

Tissue collection and RNA purification. Mice were perfused with Phosphate-buffered saline (PBS) to the left heart ventricle prior to tissue collection. Choroid plexus (from third, fourth and lateral ventricles), hippocampus (from both hemispheres), thymus, right lung, single lobe of liver, spleen, colon, and cervical, mesenteric and inguinal lymph nodes were collected, snap-frozen on dry ice and stored at -80°C. Bone marrow was flushed from single femur and tibia with PBS, centrifuged, and stored at -80°C. Total RNA from the choroid plexus was extracted with the RNA MicroPrep kit (Zymo Research). Total RNA of the remaining organs was extracted with TRI reagent (MRC, Cincinnati, OH) and purified from the lysates using the RNeasy kit (Qiagen).

RNA-sequencing. Total RNA (100 ng per sample) was heat-fragmented at 94°C for 5 min into fragments with an average size of 300 nucleotides (NEBNext Magnesium RNA Fragmentation Module), and the 3' polyadenylated fragments were enriched by selection on

poly-dT beads (Dynabeads, Invitrogen). The RNA was reverse transcribed to cDNA using smart-scribe RT kit (Clontech). Illumina compatible adaptors were added using NEB Quick ligase (New England Biolabs), and the DNA library was amplified by PCR using P5 and P7 Illumina compatible primers (IDT). DNA concentration was measured by Qubit DNA HS, and the quality of the library was analyzed by TapeStation (Agilent).

Pre-processing of RNA-sequencing data. DNA libraries were sequenced on Illumina HiSeq-1500 with an average of 5.6 million reads per sample in the multi-organ analysis, and 9.4 million reads for the parabiotic CP analysis. After alignment and counting the number of unique-molecules using molecular identifiers (UMI) (13), an average of 2 million aligned reads per sample in the multi-organ analysis and 5.7 million aligned and unified reads per sample in the parabiotic CP analysis were obtained. All reads were aligned to the mouse reference genome (mm9, NCBI 37) using the TopHat aligner algorithm (14). Raw expression levels of the genes were calculated using Scripture (15), an *ab initio* software for transcriptome reconstruction. Data were then normalized with DESeq (16) based on the negative binomial distribution and a local regression model. For the transcriptome analysis of aged and young mice tissues (not shown), we applied a log2 transformation, averaged the duplicates, filtered by max>5 and subtracted average of "Young" from the "Old" values to obtain the fold-change expression, and discarded differences lower than 1. Finally, we clustered by K-means (20 clusters) using Squared Euclidean distance as the correlation metrics. For the transcriptome analysis of CPs of parabiotic partners (not shown), we applied a log2 transformation, averaged the duplicates, filtered by max>3 to obtain fold-change by subtracting the average of "young isochronic" values from all samples and discarded values lower than 0.75. A final filtering consisted of removal of genes (raw in the data matrix) for which raw data values in at least 10 out of the 12 samples were equal to zero. Finally, we clustered by K-means (10 clusters) using Squared Euclidean distance as the correlation metrics. The heat maps were generated using GEN-E software (<http://www.broadinstitute.org/cancer/software/GENE-E/index.html>).

Gene Ontology (GO) Enrichment analysis. GO was performed using *Gorilla* software (<http://cbl-gorilla.cs.technion.ac.il/>), in which gene symbols within clusters (as a target set) and a complete gene list (as a background set) were imported.

cDNA synthesis and real-time quantitative PCR. mRNA (1 µg) was converted to cDNA using High Capacity cDNA Reverse Transcription Kit (Applied Biosystems). The expression of specific mRNAs was assayed using fluorescence based real-time quantitative PCR (qPCR). qPCR reactions were performed using Fast SYBR Green PCR Master Mix (Applied Biosystems) in triplicates for each sample. Peptidylprolyl isomerase A (PPIA) or hypoxanthine

guanine phosphoribosyltransferase (HPRT) were chosen as reference genes according to their stability in the target tissue. The amplification cycles were 95°C for 5 sec, 60°C for 20 sec, and 72°C for 15 sec. At the end of the assay, a melting curve was constructed to evaluate the specificity of the reaction. All quantitative real-time PCR reactions were performed and analyzed using the StepOne Plus Real-Time PCR System (Applied Biosystems) with the comparative Ct method.

The following primers were used:

ppia forward, 5'-AGCATACAGGTCCTGGCATCTTGT-3' (SEQ ID NO: 5), and reverse, 5'-CAAAGACCACATGCTTGCCATCCA-3' (SEQ ID NO: 6);

hprt forward, 5'-GCTATAAATTCTTTGCTGACCTGCTG-3' (SEQ ID NO: 7), and reverse, 5'-AATTACTTTTATGTCCCCTGTTGACTGG-3' (SEQ ID NO: 8);

ifnβ forward, 5'-CTGGCTTCCATCATGAACAA-3' (SEQ ID NO: 9), and reverse, 5'-AGAGGGCTGTGGTGGAGAA-3' (SEQ ID NO: 10);

ifit1 forward, 5'-CTTTACAGCAACCATGGGAGAG-3' (SEQ ID NO: 11), and reverse, 5'-TCCATGTGAAGTGACATCTCAG-3' (SEQ ID NO: 12);

irf7 forward, 5'-GCACTTTCTTCCGAGAACTGG-3' (SEQ ID NO: 13), and reverse, 5'-CCTGCTGACAAGTCTTGCC-3' (SEQ ID NO: 14);

cxcl10 forward, 5'-AACTGCATCCATATCGATGAC-3' (SEQ ID NO: 15), and reverse, 5'-GTGGCAATGATCTCAACAC-3' (SEQ ID NO: 16);

ccl17 forward, 5'-GTACCATGAGGTCACCTTCAG-3' (SEQ ID NO: 17), and reverse, 5'-GACAGTCAGAAACACGATGG-3' (SEQ ID NO: 18);

icam1 forward, 5'-AGATCACATTCACGGTGCTGGCTA-3' (SEQ ID NO: 19), and reverse, 5'-AGCTTTGGGATGGTAGCTGGAAGA-3' (SEQ ID NO: 20);

ccl11 forward, 5'-CATGACCAGTAAGAAGATCCC-3' (SEQ ID NO: 21) and reverse, 5'-CTTGAAGACTATGGCTTTCAGG-3' (SEQ ID NO: 22);

bdnf forward, 5'-CCTGCATCTGTTGGGGAGAC-3' (SEQ ID NO: 23), and reverse, 5'-GCCTTGTCCTGGACGTTTA-3' (SEQ ID NO: 24);

igf1 forward, 5'-CCGGACCAGAGACCCTTTG-3' (SEQ ID NO: 25) and reverse, 5'-CCTGTGGGCTTGTTGAAGTAAAA-3' (SEQ ID NO: 26).

Immunohistochemistry and immunofluorescence. Tissue processing and immunohistochemistry were performed on paraffin embedded sectioned mouse (6 μm thick) and human (10 μm thick) brains. For IRF-7 and IFN-β staining, primary rabbit-anti-IRF7 (1:100 LifeSpan Biosciences) or rabbit-anti-IFN-β (1:100 LifeSpan Biosciences) antibodies were applied. Next, slides were incubated for 10 min with 3% H₂O₂, and secondary biotin-conjugated

anti-rabbit antibody was used, followed by biotin/avidin amplification with Vectastain ABC kit (Vector Laboratories). Subsequently, DAB (3, 3'-diaminobenzidine) substrate (Zytomed kit) was applied; slides were dehydrated and mounted with xylene-based mounting solution (Leica Biosystems). For immunofluorescent staining, the following primary antibodies were used: rat-anti-BrdU (1:100, Serotec); goat anti-DCX (1:50 Santa Cruz); goat anti-CXCL10 (1:50, R&D Systems); rat anti-ICAM-1 (1:100, Abcam); rabbit anti-Claudin-1 (1:100, Invitrogen); rabbit anti-BDNF (1:100, Alomone labs); rabbit anti-IBA-1 (1:300; Wako); rabbit-anti-GFAP (1:100, Dako); mouse anti-E-cadherin (1:100, Invitrogen, with use of Mouse on Mouse (M.O.M.) Basic Kit (Vector Labs)). For BrdU staining, slides were additionally incubated in 2N HCl for 30 min at 37°C, transferred to borate buffer (pH=8.5) and incubated at room temperature for another 10 min before incubation with blocking solution. Secondary antibodies included: Cy2/Cy3/biotin-conjugated donkey anti-rabbit/rat antibodies (1:200; all from Jackson Immuno Research). The slides were exposed to Hoechst for nuclear staining (1:2000; Invitrogen Probes) for 30 seconds. Two negative controls were routinely used in immunostaining procedures, staining with isotype control antibody followed by secondary antibody, and staining with secondary antibody alone. For microscopic analysis, a fluorescence microscope (Nikon Eclipse 80i) was used. The fluorescence microscope was equipped with a digital camera (DXM 1200F; Nikon) and with 20× NA 0.50 and 40× NA 0.75 objective lenses (Plan Fluor; Nikon). Recordings were made on postfixed tissues at 24°C using acquisition software (NIS-Elements, F3). Images were cropped, merged, and optimized using Photoshop CS6 13.0 (Adobe), and were arranged using Illustrator CS5 15.1 (Adobe). For quantification of staining intensity, total cell and background fluorescence was measured using ImageJ software (NIH), and intensity of specific staining was calculated, as previously described (17).

BrdU administration and quantification of BrdU and DCX positive cells. BrdU was injected intraperitoneally (75mg/kg body weight) once daily for 7 days, and mice were sacrificed 12 hours after the last injection. To estimate the total number of BrdU-positive and DCX-positive cells in the brain, the paraffin sections of hippocampus were stained, and the BrdU-positive and DCX-positive cells in the subgranular zone of the dentate gyrus were counted and multiplied accordingly to estimate the total number of BrdU-positive and DCX-positive cells in the entire dentate gyrus.

Primary culture of choroid plexus cells. CP cultures were prepared as previously described (8, 10). Briefly, the CP tissue excised from PBS-perfused animals was dissociated in 0.25% trypsin by shaking (20' at 37°C) and pipetting, then centrifuged, washed and plated (~250,000 cells/well) in 24-well plates in culture medium for epithelial cells (DMEM/HAM's

F12 (Invitrogen Corp)), supplemented with 10% Fetal Calf Serum (Sigma-Aldrich), 1 mM l-glutamine, 1 mM sodium pyruvate, 100 U/ml penicillin, 100 mg/ml streptomycin, 5µg/ml insulin, 5ng/ml sodium selenite, 20 µM arabinofuranosyl cytidine (Ara-C) and 10ng/ml EGF) at 37°C, 5% CO₂. After 24 hours, the medium was changed, and the cells were either left untreated, or treated with either 1000 U IFN-β (Merc Milipore), a mixture of pro-inflammatory cytokines: TNF-α (100ng/ml), IL-1β (100 ng/ml) and IL-6 (10 ng/ml) (all from Peprotech) for 24h, or with cerebrospinal fluid collected from young (3 month old) or aged (22 month old) animals, diluted 1:1 with culture medium for 8 hours. RNA isolation was performed with RNA MicroPrep kit (Zymo Research) according to the manufacturer's protocol.

Radial Arm Water Maze. The radial-arm water maze (RAWM) test was performed as previously described (18). Briefly, the goal arm location (containing a platform submerged 1.5 cm below the water surface) remained constant for a given mouse, whereas the start arm was changed during each trial. Within the testing room, only distal visual shape and object cues were available to the mice to aid in location of the platform. On day 1, mice were trained for 15 trials, with alternating visible and hidden platform, while on day 2, mice were trained for 15 trials with the hidden platform only. Entry into an incorrect arm or remaining for more than 15 seconds in the same, incorrect arm or the central area was scored as an error. The number of errors was determined, and the escape latency to the platform was measured on every trial. The data were analyzed as the mean of errors or escape latencies for training blocks, each spanning three consecutive trials. Swimming speed was measured using EthoVision automated tracking system (Noldus). Animals subject to the second RAWM testing were trained in the same arena with new visual cues and different platform location relative to the first test.

Novel Location Recognition (NLR) Test. NLR was performed as previously described (19). Briefly, mice were placed in a grey, square box (50 cm x 50 cm x 50 cm) with visual cues on the walls. On the training day, mice were given four sessions of 6 minutes; during the first session, mice were allowed to explore the arena without objects, and in the following three trials, two objects of different color, shape and texture were present (training, day 1). After 24 h, mice were returned to the arena, in which one of the objects was placed in a new location (testing day, day 2). Time spent exploring each object on each day was manually scored using EthoVision tracking system (Noldus), and percentage preference for the displaced object was calculated for each animal, for each day, by dividing the time spent exploring the displaced object by the total exploration time of both objects and multiplying the result by 100%, according to the formula: Percentage preference=((displaced object exploration time)/(displaced object exploration time + non-displaced object exploration time))*100%. Generally, the result of the calculation was

approx. 50% on day 1 (training) and 60-80% on day 2 for “cognitively unimpaired” mice. Tested mice were considered having “impaired memory” when the difference between the percentage preference on day 1 (training) and day 2 (test) was lower than 10% ([percentage preference on day 2 – day 1] < 10%), and “unimpaired memory” was defined as [percentage preference on day 2 – day 1] > 10%. On average, 70% of aged (~22 month old) C57BL/6 WT mice tested in NLR manifested “impaired memory”, in accordance with previous observations (20). Animals subject to the second NLR testing were trained and tested in the same arena with new visual cues, different objects and object locations relative to the first test.

Flow cytometry sample preparation and analysis. CSF was collected as described above. Samples were stained with Alexa-700 conjugated anti-CD45.2, FITC conjugated anti-TCR β , and PE conjugated anti-CD4 according to the manufacturer’s protocol (BD Pharmingen and eBioscience). Cells were analyzed on an LSRII cytometer (BD Biosciences) using FACSDiva and FlowJo software. Unstained control was used to identify the population of interest and to exclude others.

Statistical analysis. Data were analyzed using the Student’s t test to compare between two groups. One-way ANOVA was used to compare several groups, and Newman–Keuls post-hoc procedure was used for follow-up pairwise comparison of groups after the null hypothesis was rejected ($P < 0.05$). Data from behavioral tests were analyzed using two-way repeated-measures ANOVA, and Bonferroni post-hoc procedure was used for follow-up pairwise comparison. Results are presented as means $\pm$ SEM. In the graphs, y-axis error bars represent SEM. Statistical calculations were performed using Prism 5.01 software (GraphPad Software). All histology and behavioral experiments were conducted in a randomized and blinded fashion.

Example 1. The expression profile of aged choroid plexus is unique relative to other aged organs.

To determine whether aging of the CP reflects aging of the brain and other body tissues, we systematically characterized mRNA expression profile of young (3-month old) and aged (22-month old) mice by RNA-sequencing. Whereas all examined organs from aged mice showed increased expression of mRNA transcripts associated with age-related processes, such as “immune response” (p -value=2.66E-05; cluster XIX; **fig. 2A** and Table 1), the aged CP exhibited an expression profile corresponding to “type I interferon (IFN-I) response” (p -value=4.25E-07; cluster IX; **Fig. 2A-B**), classically associated with anti-viral activity (12). To exclude a non-age-related effect, such as viral infection, we confirmed the increased expression of IFN-I-dependent genes (e.g. interferon regulatory factor 7 (*irf7*), interferon-beta 1 (*ifn β*), and

interferon-induced protein with tetratricopeptide repeats 1 (*ifit1*) by real-time quantitative PCR (qPCR) in aged mice received from different animal centers (**Fig. 1A**). Closer examination by qPCR and immunohistochemical staining showed that whereas IFN-I-associated gene expression was increased in the aged CP, expression of type II IFN (IFN- γ)-dependent genes (*10*) (e.g. intercellular adhesion molecule 1 (*icam1*), interferon gamma-induced protein 10 (*cxcl10*), and chemokine (C-C motif) ligand 17 (*ccl17*)) was decreased (**Fig. 1B, 1C**). Immunohistochemical staining of brain sections of young and aged mice, as well as postmortem brain sections from non-CNS-diseased young and aged humans, showed an age-associated increase of IFN- β and IRF-7 at the CP (**Fig. 1D**), and indicated that this effect is conserved among species.

Table 1. Top five gene ontology (GO) terms significantly enriched in each cluster.

Cluster	GO term	Description	P-value	FDR q-value
I	GO:0033555	multicellular organismal response to stress	6.49E-04	1.00E+00
	GO:2000021	regulation of ion homeostasis	8.14E-04	1.00E+00
III	GO:0007223	Wnt signaling pathway, calcium modulating pathway	1.67E-04	6.33E-01
	GO:0018149	peptide cross-linking	2.80E-04	7.05E-01
	GO:0035567	non-canonical Wnt signaling pathway	2.80E-04	5.28E-01
	GO:0009653	anatomical structure morphogenesis	8.25E-04	1.00E+00
	GO:0044767	single-organism developmental process	9.79E-04	1.00E+00
IV	GO:0006631	fatty acid metabolic process	3.23E-07	2.44E-03
	GO:0019752	carboxylic acid metabolic process	3.71E-07	1.40E-03
	GO:0044255	cellular lipid metabolic process	8.36E-07	2.11E-03
	GO:0032787	monocarboxylic acid metabolic process	1.86E-06	3.51E-03
	GO:0043436	oxoacid metabolic process	2.42E-06	3.65E-03
V	GO:0001822	kidney development	1.13E-04	8.57E-01
	GO:0006023	aminoglycan biosynthetic process	3.36E-04	1.00E+00
	GO:0006024	glycosaminoglycan biosynthetic process	3.36E-04	8.47E-01
	GO:0031123	RNA 3'-end processing	4.28E-04	8.08E-01
VI	GO:0009067	aspartate family amino acid biosynthetic process	2.89E-04	1.00E+00
VII	GO:0016568	chromatin modification	7.30E-06	5.52E-02
	GO:0006325	chromatin organization	9.17E-06	3.46E-02
	GO:0016570	histone modification	1.77E-05	4.46E-02
	GO:0016569	covalent chromatin modification	2.22E-05	4.19E-02
	GO:0051276	chromosome organization	9.56E-05	1.44E-01
VIII	GO:0032695	negative regulation of interleukin-12 production	9.29E-04	1.00E+00
IX	GO:0034340	response to type I interferon	4.25E-07	3.21E-03
	GO:0035456	response to interferon-beta	1.67E-06	6.31E-03
	GO:0035455	response to interferon-alpha	2.08E-06	3.93E-03
	GO:0071357	cellular response to type I interferon	1.69E-05	1.83E-02
	GO:0009615	response to virus	1.68E-04	1.41E-01
XI	GO:0046483	heterocycle metabolic process	9.71E-04	1.00E+00

Table 1. Top five gene ontology (GO) terms significantly enriched in each cluster.

Cluster	GO term	Description	P-value	FDR q-value
	GO:0006139	nucleobase-containing compound metabolic process	9.99E-04	1.00E+00
XII	GO:0008156	negative regulation of DNA replication	2.99E-04	1.00E+00
	GO:0043547	positive regulation of GTPase activity	8.01E-04	1.00E+00
XIII	GO:0032271	regulation of protein polymerization	6.36E-04	1.00E+00
XIV	GO:0003341	cilium movement	1.62E-04	1.00E+00
	GO:0030031	cell projection assembly	5.58E-04	1.00E+00
XV	GO:0000280	nuclear division	1.04E-05	7.83E-02
	GO:0007067	mitosis	1.04E-05	3.91E-02
	GO:0048285	organelle fission	2.07E-05	5.22E-02
	GO:0051301	cell division	3.16E-04	5.96E-01
	GO:0048704	embryonic skeletal system morphogenesis	4.31E-04	6.52E-01
XVI	GO:0008272	sulfate transport	3.69E-04	1.00E+00
	GO:0006281	DNA repair	4.29E-04	1.00E+00
	GO:0000086	G2/M transition of mitotic cell cycle	4.53E-04	1.00E+00
	GO:0031572	G2 DNA damage checkpoint	4.53E-04	8.56E-01
	GO:0007017	microtubule-based process	6.34E-04	9.59E-01
XVII	GO:0032787	monocarboxylic acid metabolic process	1.67E-06	1.26E-02
	GO:0044281	small molecule metabolic process	5.92E-06	2.23E-02
	GO:0006629	lipid metabolic process	8.94E-06	2.25E-02
	GO:0044699	single-organism process	1.12E-05	2.11E-02
	GO:0006631	fatty acid metabolic process	1.34E-05	2.02E-02
XVIII	GO:0000186	activation of MAPKK activity	1.66E-04	1.00E+00
XIX	GO:0002376	immune system process	1.38E-07	1.04E-03
	GO:0050896	response to stimulus	3.30E-06	1.25E-02
	GO:0006955	immune response	2.66E-05	5.03E-02
	GO:0002252	immune effector process	3.90E-05	5.90E-02
	GO:0050776	regulation of immune response	5.10E-04	2.75E-01
XX	GO:0034620	cellular response to unfolded protein	2.51E-07	1.90E-03
	GO:0030968	endoplasmic reticulum unfolded protein response	2.51E-07	9.50E-04
	GO:0035967	cellular response to topologically incorrect protein	1.24E-06	3.11E-03
	GO:0006986	response to unfolded protein	9.27E-06	1.75E-02
	GO:0035966	response to topologically incorrect protein	1.37E-05	2.06E-02

Clusters that were not found to be significantly enriched (II and X) do not appear in the table.

Example 2. The local IFN- γ response of the CP is modulated by the circulation, age-associated IFN-I signaling is induced by factors emitted from the brain.

Because the CP epithelium is exposed from its apical side to brain-derived signals, via the CSF, and from its basal side to peripheral signals, via the circulation (13), we investigated which of these compartments induces the transcriptional signature of the aged CP. To differentially

Table 2. Top five gene ontology (GO) terms significantly enriched in each individual cluster.

Cluster	GO term	Description	P-value	FDR q-value
II	GO:0000375	RNA splicing, via transesterification reactions	1.07E-04	9.13E-01
	GO:0000377	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile	4.86E-04	1.00E+00
	GO:0000398	mRNA splicing, via spliceosome	4.86E-04	1.00E+00
III	GO:0006875	cellular metal ion homeostasis	1.80E-05	7.66E-02
	GO:0050900	leukocyte migration	3.83E-05	6.51E-02
	GO:0048870	cell motility	6.36E-05	6.00E-02
	GO:0016477	cell migration	1.96E-04	1.19E-01
	GO:0007155	cell adhesion	3.17E-04	1.42E-01
IV	GO:0097435	fibril organization	3.74E-05	3.17E-01
	GO:0001525	angiogenesis	7.35E-05	2.08E-01
	GO:0048646	anatomical structure formation involved in morphogenesis	1.25E-04	2.66E-01
	GO:0038084	vascular endothelial growth factor signaling pathway	4.60E-04	4.89E-01
	GO:0043206	extracellular fibril organization	5.70E-04	5.38E-01
V	GO:0022603	regulation of anatomical structure morphogenesis	1.94E-04	1.00E+00
	GO:0043535	regulation of blood vessel endothelial cell migration	4.33E-04	1.00E+00
	GO:0045664	regulation of neuron differentiation	5.33E-04	1.00E+00
	GO:0030644	cellular chloride ion homeostasis	6.16E-04	1.00E+00
	GO:0055064	chloride ion homeostasis	6.16E-04	1.00E+00
VI	GO:0009615	response to virus	6.96E-12	5.91E-08
	GO:0035456	response to interferon-beta	1.78E-06	8.40E-04
	GO:0034340	response to type I interferon	3.77E-06	1.52E-03
	GO:0032481	positive regulation of type I interferon production	1.56E-05	6.04E-03
	GO:0035458	cellular response to interferon-beta	3.05E-05	1.13E-02
VII	GO:0050731	positive regulation of peptidyl-tyrosine phosphorylation	4.31E-06	3.66E-02
	GO:0050730	regulation of peptidyl-tyrosine phosphorylation	1.30E-05	5.51E-02
	GO:0042531	positive regulation of tyrosine phosphorylation of STAT protein	8.41E-05	2.38E-01
	GO:0042509	regulation of tyrosine phosphorylation of STAT protein	2.08E-04	4.43E-01
	GO:0046427	positive regulation of JAK-STAT cascade	3.35E-04	5.69E-01
VIII	GO:0045087	innate immune response	3.41E-05	2.90E-01
	GO:0052547	regulation of peptidase activity	1.19E-04	5.04E-01
	GO:0051707	response to other organism	4.30E-04	9.13E-01
	GO:0098542	defense response to other organism	4.35E-04	7.40E-01
	GO:0006955	immune response	5.67E-04	8.02E-01

Table 2. Top five gene ontology (GO) terms significantly enriched in each individual cluster.

Cluster	GO term	Description	P-value	FDR q-value
IX	GO:0034470	ncRNA processing	5.19E-05	4.41E-01
	GO:0006396	RNA processing	3.19E-04	1.00E+00
	GO:0008203	cholesterol metabolic process	4.11E-04	1.00E+00
	GO:0016125	sterol metabolic process	4.11E-04	8.73E-01
X	GO:0031111	negative regulation of microtubule polymerization or depolymerization	6.02E-04	1.00E+00
	GO:0031016	pancreas development	9.46E-04	1.00E+00
III and VIII together	GO:0007155	cell adhesion	2.25E-06	1.91E-02
	GO:0022610	biological adhesion	3.24E-06	1.38E-02
	GO:0050900	leukocyte migration	6.40E-05	7.76E-02
	GO:0006955	immune response	4.47E-04	1.90E-01
	GO:0030595	leukocyte chemotaxis	8.52E-04	2.68E-01
Cluster I was not found to be significantly enriched				

examine these effects, we made use of parabiosis settings, in which young and aged mice are surgically connected to share vasculature. Under these settings, there is a bi-directional, though not symmetric, effect on hippocampal neurogenesis and cognitive function between young and aged heterochronic parabionts (3, 4). Transcriptome and qPCR analyses revealed that whereas the circulation of aged mice failed to induce expression of IFN-I-dependent genes in the CP of young heterochronic partners, it did affect IFN-II-dependent gene expression (**Fig. 3A** and Table 2 (clusters III and VIII)), including reduced expression of homing and trafficking determinants needed for physiological leukocyte entry via the CP to the CSF (10), and increased expression of the chemokine CCL11 (**Fig. 3B**), which was shown to impair brain plasticity(3), and its expression by the CP is induced by the cytokine interleukin (IL)-4 when local IFN- γ is reduced in aging (6). Under the same experimental setting, young circulation failed to reverse the expression program of IFN-I-dependent genes in the aged CP (**Fig. 3A-B**), yet affected IFN- γ -regulated genes (10); notably, CCL11 expression by the CP of the aged heterochronic parabionts was not affected by the young circulation, further substantiating its indirect local suppression by IFN- γ (6). These results indicated that the IFN-II expression program at the CP could be partially modulated by factors derived from the circulation, whereas IFN-I in this compartment might be induced by factors emitted from the aged brain. To test whether aged mice CSF can affect IFN-I response at the CP, we exposed primary cultures of CP epithelial cells from young mice to CSF aspirated from either aged or young mice and found that the CSF of aged, but not of young animals, could induce IFN-I-dependent gene expression (**Fig. 3C**). This response was recapitulated when epithelial cells of the CP were treated with a mixture of pro-inflammatory

cytokines that accumulate in the brain during aging and neurodegeneration (14) (**fig. 4**). These results suggested that in the aged CP, the induced IFN-I response, and the reduced IFN-II response, are controlled by signals present in the aged CSF, and in the circulation, respectively.

5 Example 3. Impaired ability to respond to IFN- γ , or reduced IFN- γ production by T cells, is sufficient to cause premature cognitive decline and lower hippocampal neurogenesis in adulthood.

IFN-II has an essential role in CP function (10), and its diminished levels in this compartment were associated with brain aging (6). Follow up of transgenic mice deficient in
 10 IFN-II signaling, including IFN- γ receptor knockout (*IFN- γ R^{-/-}*) mice (which lack the ability to directly respond to IFN- γ) and *Tbx21*^{-/-} mice (which lack Tbx21, a transcription factor critical for the control of IFN- γ production in CD4⁺ T cells (15)), revealed that these mice developed spatial learning and memory deficits (**fig. 5A to H**), and reduced hippocampal neurogenesis during adulthood (**fig. 6I to K**). Brain function decline in *IFN- γ R^{-/-}* mice was accompanied by impaired
 15 CP activity in supporting leukocyte trafficking to the CSF (**fig. 5L to M**). These results indicated that impaired ability to respond to IFN- γ , or reduced IFN- γ in the circulation, could lead to premature cognitive decline and restrict hippocampal neurogenesis in adulthood (**fig. 6**). These findings, together with the apparent inverse relation between type I and type II IFN expression programs in the aged CP (**Fig. 1, 3**), and the fact that chronically activated IFN-I signaling was
 20 shown to interfere with IFN-II-dependent resolution of inflammation outside the CNS (16-18), prompted us to examine whether chronic IFN-I in the aged CP could affect brain function, and if so, whether it involves interfering with local IFN-II-dependent activities.

25 Example 4. *In vivo* neutralization of the response to type I IFNs in aged mice partly restores CP function and expression levels of IFN- γ -regulated genes to that of young mice.

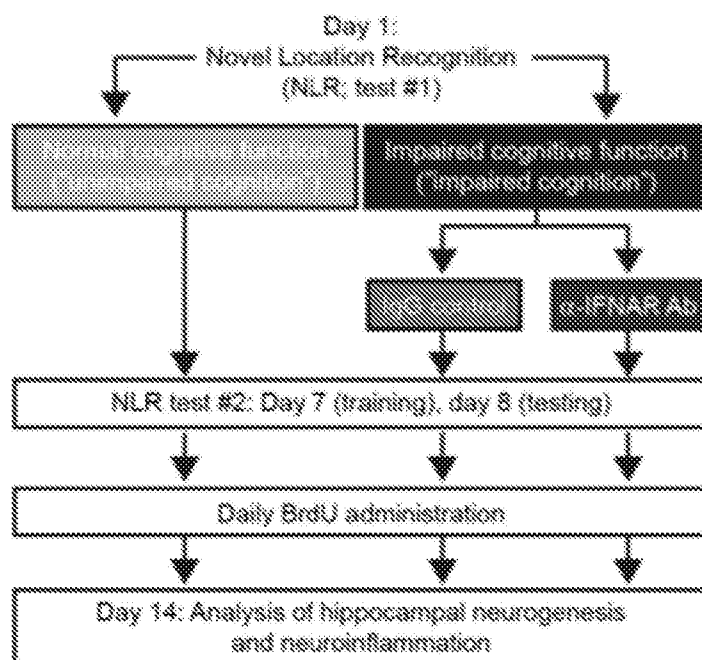
To test whether aging-induced IFN-I response in the CP might influence brain function, we examined both the direct effect of the major IFN-I cytokine, IFN- β , on CP epithelial cells of young mice, and that of the neutralization of IFN-I responses in the brain of aged mice. Exposure of CP epithelial cells to IFN- β induced the classical “anti-viral” response (**Fig. 7A**), and resulted
 30 in reduced expression of insulin-like growth factor (*igf1*) and brain derived neurotrophic factor (*bdnf*) (**Fig. 7B**), two CP-secreted molecules that support neuronal growth, differentiation and survival (11, 19). Intracerebroventricular (i.c.v.) administration of IFN-I receptor-neutralizing antibody (α -IFNAR) to the CSF of aged mice blocked IFN-I response program at the CP (**Fig. 7C**), and led to restoration of the IFN-II-regulated genes, *igf1* and *bdnf* (**Fig. 7D, fig. 8**), and of

ccl11 expression (**Fig. 7E**), to levels similar to those found in the CP of young mice. These results showed that neutralizing IFN-I response within the brain affected CP function, and suggested that IFN-II response in the aged CP is suppressed by chronically elevated IFN-I.

5 Example 5. Blocking the type I IFN response in the CNS of aged mice attenuates age-related neuroinflammation and partially reverses age-related decline in brain function.

To further test whether *in vivo* neutralization of IFN-I in aging could restore brain function, we assessed spatial learning and memory abilities and hippocampal neurogenesis, two independent measurements of brain function and plasticity (20) (**Scheme I**).

Scheme I. Illustration of the experimental design.



- 10 Because age-associated cognitive decline varies across individuals, we first scored aged mice for their learning and memory, using the novel location recognition (NLR) test, in which mice are freely exploring two objects within an arena, and the time of exploration of each object is measured (21). After 24 hours, one of the objects is relocated. Under these conditions, cognitively-unimpaired mice spent more time exploring the displaced object (**Fig. 9A**).
- 15 Cognitively-impaired aged mice were i.c.v. injected with either α-IFNAR or control IgG, and tested again a week after for their cognitive performance. Cognitively-impaired aged mice treated with α-IFNAR spent more time exploring the relocated object, whereas exploration preference of control IgG-injected mice was not changed (**Fig. 9B**). Subsequently, mice of all groups were administered with 5-bromo-2'-deoxyuridine (BrdU) for detection of newly-formed
- 20 cells in the hippocampus (22). The number of newly-born neurons, stained for BrdU and

Doublecortin (DCX), was increased in the α -IFNAR-treated group (**Fig. 9C**); enhanced hippocampal neurogenesis to a similar extent in aged mice was correlated with improved cognitive function (3, 4). We also examined the hippocampal parenchyma for the effect on neuroinflammation, which detrimentally affect adult neurogenesis (23), and found increased mRNA expression of the anti-inflammatory cytokine, IL-10 (**Fig. 9D**), and a marked decrease in astrogliosis and microgliosis (**Fig. 9E, F**) in the α -IFNAR-treated group.

REFERENCES

1. A. M. Stranahan, M. P. Mattson, *Nat Rev Neurosci* **13**, 209-216 (2012).
2. M. Yeoman, G. Scutt, R. Faragher, *Nat Rev Neurosci* **13**, 435-445 (2012).
3. S. A. Villeda *et al.*, *Nature* **477**, 90-94 (2011).
- 5 4. S. A. Villeda *et al.*, *Nat Med* **20**, 659-663 (2014).
5. L. Katsimpardi *et al.*, *Science* **344**, 630-634 (2014).
6. K. Baruch *et al.*, *Proc Natl Acad Sci U S A* **110**, 2264-2269 (2013).
7. R. M. Ransohoff, B. Engelhardt, *Nat Rev Immunol* **12**, 623-635 (2012).
8. K. Baruch, M. Schwartz, *Brain Behav Immun* **34**, 11-16 (2013).
- 10 9. M. Schwartz, K. Baruch, *EMBO J* **33**, 7-22 (2014).
10. G. Kunis *et al.*, *Brain* **136**, 3427-3440 (2013).
11. A. M. Falcao *et al.*, *Front Cell Neurosci* **6**, 34 (2012).
12. J. M. Gonzalez-Navajas, J. Lee, M. David, E. Raz, *Nat Rev Immunol* **12**, 125-135 (2012).
- 15 13. C. Johanson *et al.*, *Toxicol Pathol* **39**, 186-212 (2011).
14. K. M. Lucin, T. Wyss-Coray, *Neuron* **64**, 110-122 (2009).
15. S. J. Szabo *et al.*, *Science* **295**, 338-342 (2002).
16. E. B. Wilson *et al.*, *Science* **340**, 202-207 (2013).
17. R. M. Teles *et al.*, *Science* **339**, 1448-1453 (2013).
- 20 18. J. R. Teijaro *et al.*, *Science* **340**, 207-211 (2013).
19. D. F. Emerich *et al.*, *Bioessays* **27**, 262-274 (2005).
20. W. Deng, J. B. Aimone, F. H. Gage, *Nat Rev Neurosci* **11**, 339-350 (2010).
21. A. M. Oliveira, T. J. Hemstedt, H. Bading, *Nat Neurosci* **15**, 1111-1113 (2012).
22. H. van Praag *et al.*, *Nature* **415**, 1030-1034 (2002).
- 25 23. C. T. Ekdahl *et al.*, *Proc Natl Acad Sci U S A* **100**, 13632-13637 (2003).
24. R. C. Axtell, L. Steinman, *Immunity* **28**, 600-602 (2008).
25. M. J. Hofer, I. L. Campbell, *Cytokine Growth Factor Rev* **24**, 257-267 (2013).
26. M. Prinz *et al.*, *Immunity* **28**, 675-686 (2008).
27. M. Wichers, M. Maes, *Int J Neuropsychopharmacol* **5**, 375-388 (2002).
- 30 28. Park Man-Seong, Megan L. Shaw, Jorge Muñoz-Jordan, Jerome F. Cros, Takaaki Nakaya, Nicole Bouvier, Peter Palese, Adolfo García-Sastre, and Christopher F. Basler (2003) Newcastle Disease Virus (NDV)-Based Assay Demonstrates Interferon-Antagonist Activity for the NDV V Protein and the Nipah Virus V, W, and C Proteins. *J Virol*. Jan 2003; 77(2): 1501-1511.

29. Feng X, Han D, Kilaru BK, Franek BS, Niewold TB, Reder AT. (2012) Inhibition of Interferon-beta Responses in Multiple Sclerosis Immune Cells Associated With High-Dose Statins *Arch Neurol.* 69(10):1303-9.
30. Marozin S, Altomonte J, Stadler F, Thasler WE, Schmid RM, Ebert O (2008) Inhibition of the IFN-beta response in hepatocellular carcinoma by alternative spliced isoform of IFN regulatory factor-3. *Mol Ther.* 16(11):1789-97.
31. Sacre K, Criswell LA and JM McCune (2012) Hydroxychloroquine is associated with impaired interferon-alpha and tumor necrosis factor-alpha production by plasmacytoid dendritic cells in systemic lupus erythematosus. *Arthritis Research & Therapy*, 14:R15542.42
32. Ye J, Chen S and Maniatis T. (2011) Cardiac glycosides are potent inhibitors of interferon- β gene expression. *Nat Chem Biol.* 7(1):25-33.
33. Damdinsuren, B., Nagano, H., Wada, H., Noda, T., Natsag, J., Marubashi, S., Miyamoto, A., Takeda, Y., Umeshita, K., Doki, Y., *et al.* (2007). Interferon alpha receptors are important for antiproliferative effect of interferon-alpha against human hepatocellular carcinoma cells. *Hepatology* 37, 77-83.
34. Schirmer, S.H., Bot, P.T., Fledderus, J.O., van der Laan, A.M., Volger, O.L., Laufs, U., Bohm, M., de Vries, C.J., Horrevoets, A.J., Piek, J.J., *et al.* (2010) Blocking interferon {beta} stimulates vascular smooth muscle cell proliferation and arteriogenesis. *J Biol Chem* 285, 34677-34685.
35. Tian W, Bai G and Yang W (2006) Antagonist peptides of human interferon- α 2b isolated from phage display library inhibit interferon induced antiviral activity. *Acta Pharmacologica Sinica* 27 (8): 1044–1050.
36. Zhang et al. (2008) Identification of antiviral mimetic peptides with interferon α -2b-like activity from a random peptide library using a novel functional biopanning method. *Acta Pharmacol Sin* 2008 May; 29 (5): 634–640).

CLAIMS

1. An agent that reduces type I IFN activity at the choroid plexus or within the CNS for use in treating a disease, disorder, condition or injury of the CNS.
2. The agent according to claim 1, selected from:
 - 5 (i) an antagonist to the type I IFN receptor selected from a neutralizing antibody specific to the type I IFN receptor; a soluble decoy IFN-I receptor, a type I IFN antagonist selected from a viral protein such as influenza virus NS1 protein, a paramyxovirus V protein (e.g. mumps virus V protein or human parainfluenza virus 2 V protein), a Sendai virus C protein, respiratory syncytial virus NS1 or NS2
 - 10 protein, or Ebola virus VP35 protein;
 - (ii) a molecule capable of interfering with type I IFN receptor signal transduction pathway selected from a statin such as atorvastatin, a splice variant of IFN regulatory factor-3 (IRF3) splice variant IRF3-nirs3 or an agent activating or coupling ITAM-coupled $\beta 2$ integrins and Fc γ R;
 - 15 (iii) a molecule capable of interfering with type I IFN receptor-ligand production, such as hydroxychloroquine;
 - (iv) a nucleic acid molecule encoding an antagonist of (i) or IRF3-nirs3 of (ii);
 - (v) an IFN- α antagonist;
 - (vi) an IFN- β antagonist; or
 - 20 (vii) an agent reducing type I IFN activity by reducing type I IFN receptor expression at the choroid plexus or in the CNS selected from (a) an artificial siRNA or shRNA molecule comprising a nucleic acid sequence being complementary to a sequence within a nucleic acid sequence encoding the type I IFN receptor or IFN- β ; or (b) a glycoside such as bufalin.
- 25 3. The agent according to claim 2, wherein said IFN- α antagonist of (v) is selected from IFN- $\alpha 2b$ antagonist peptides SP-7 (SLSPGLP), FY-7 (FSAPVRY), KP-7 (KNVHPPP) or IR-7 (IRPDTPR).
4. The agent according to claim 2, wherein said antagonist to the type I IFN receptor of (i) is a neutralizing antibody specific to the type I IFN receptor.
- 30 5. The agent according to any one of claims 1 to 4, wherein the agent is administered by intracerebroventricular or intrathecal injection.

6. The agent according to any one of claims 1 to 5, for use in treating a disease, disorder or condition of the CNS selected from the group consisting of a neurodegenerative disease, disorder or condition selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease; primary progressive multiple sclerosis; 5 secondary progressive multiple sclerosis; a retinal degeneration disorder selected from the group consisting of age-related macular degeneration and retinitis pigmentosa; anterior ischemic optic neuropathy; glaucoma; uveitis; depression; stress; autism, schizophrenia, and Rett syndrome.
7. The agent according to claim 6, for use in treating Alzheimer's disease.
8. The agent according to any one of claims 1 to 5, for use in treating an injury of the CNS 10 selected from spinal cord injury, closed head injury, blunt trauma, penetrating trauma, hemorrhagic stroke, ischemic stroke, cerebral ischemia, optic nerve injury, myocardial infarction, organophosphate poisoning and injury caused by tumor excision.
9. The agent according to any one of claims 1 to 5, wherein said treating improves CNS motor and/or cognitive function.
- 15 10. The agent according to claim 9, for use in alleviating age-associated loss of cognitive function.
11. The agent according to claim 10, wherein said age-associated loss of cognitive function occurs in subjects free of a diagnosed disease
12. The agent according to claim 9, for use in alleviating loss of cognitive function resulting 20 from acute stress.
13. The agent according to any one of claims 8 to 12, wherein said cognitive function is learning, memory or both.
14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an agent that reduces type I IFN activity at the choroid plexus or within the CNS for use in treating 25 a disease, disorder, condition or injury of the CNS.

Fig. 1A

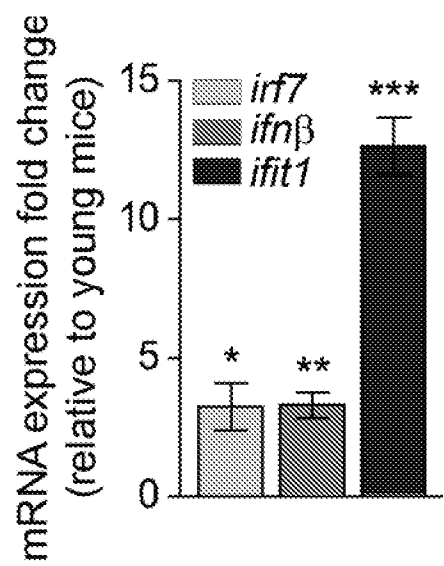


Fig. 1B

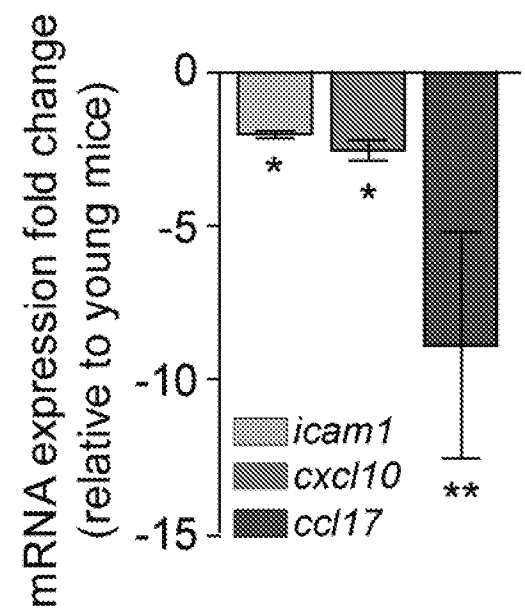


Fig. 1C

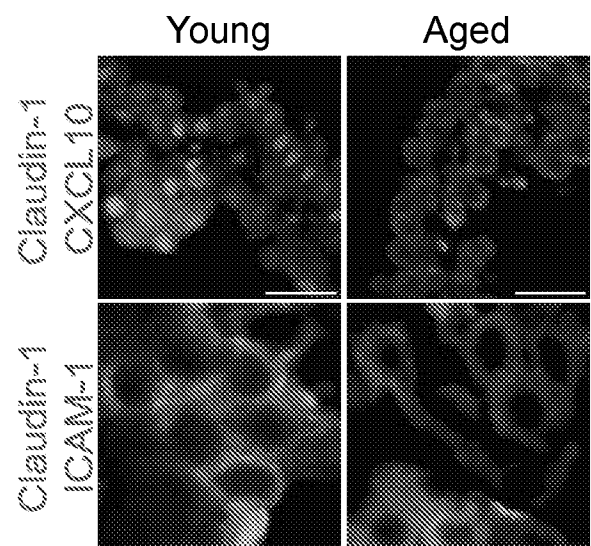


Fig. 1D

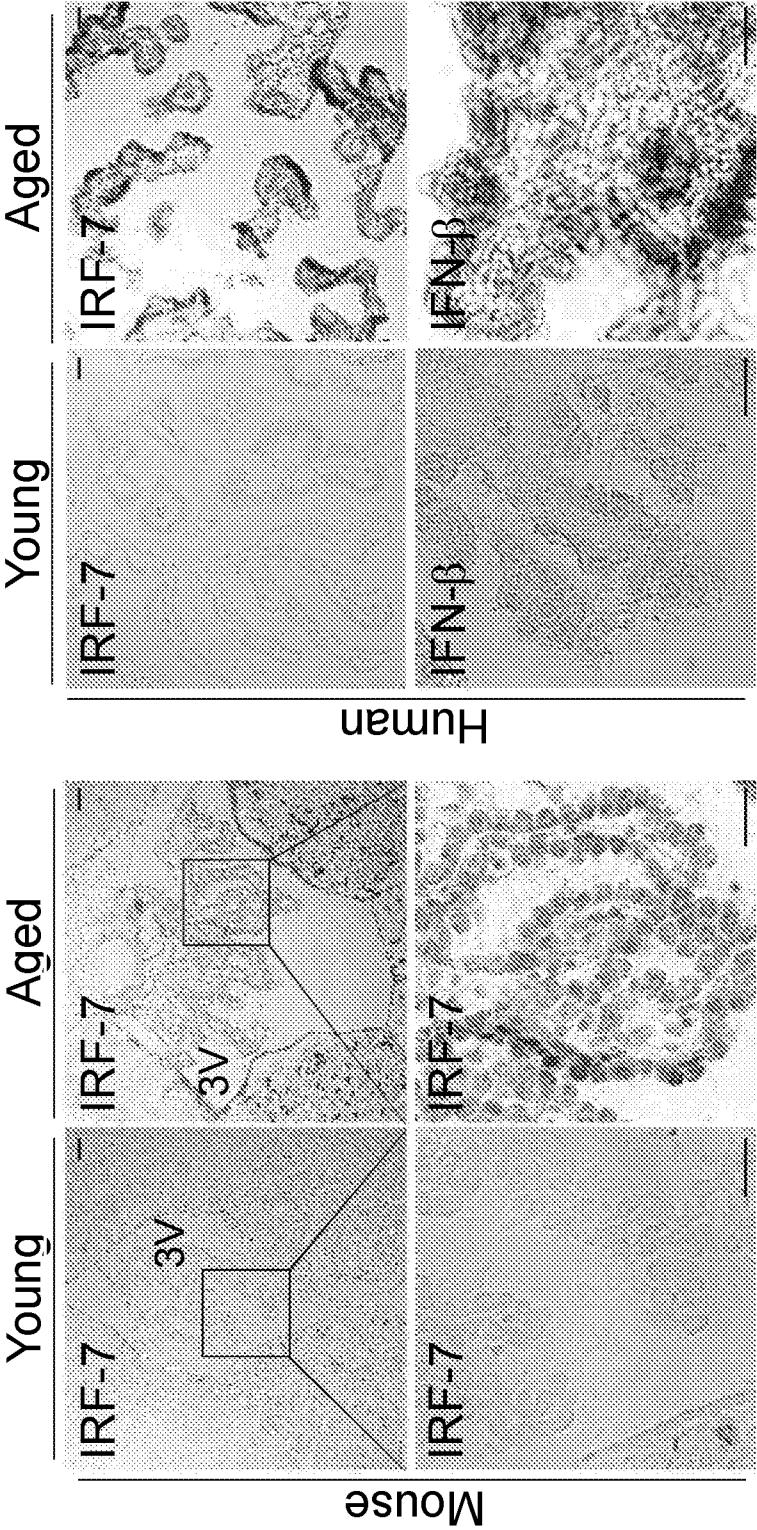


Fig. 2

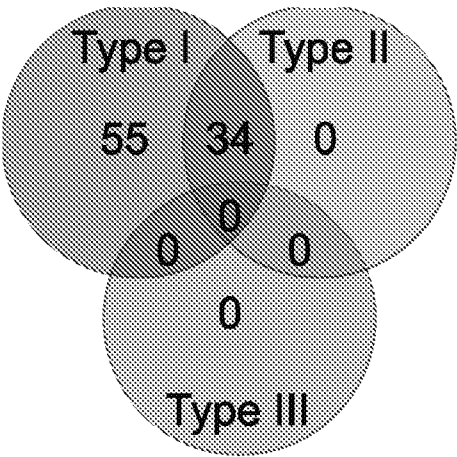


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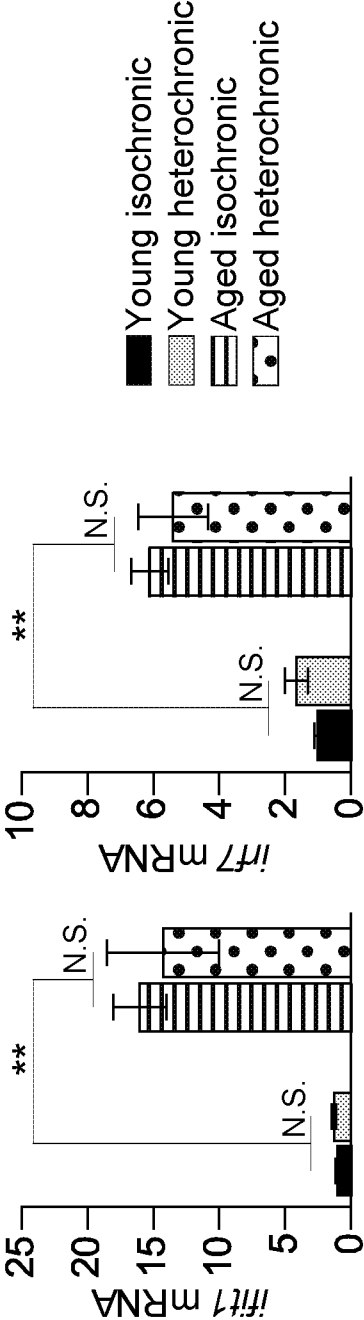


Fig. 3B

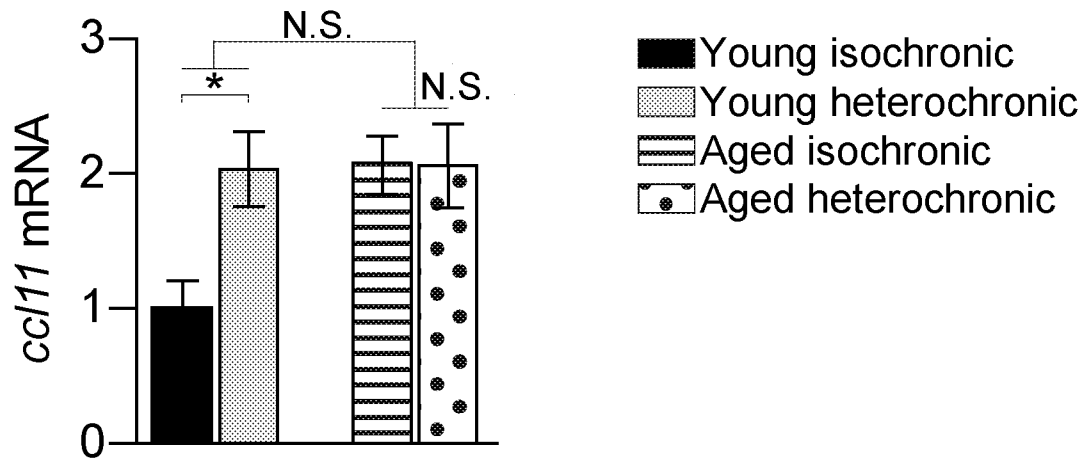
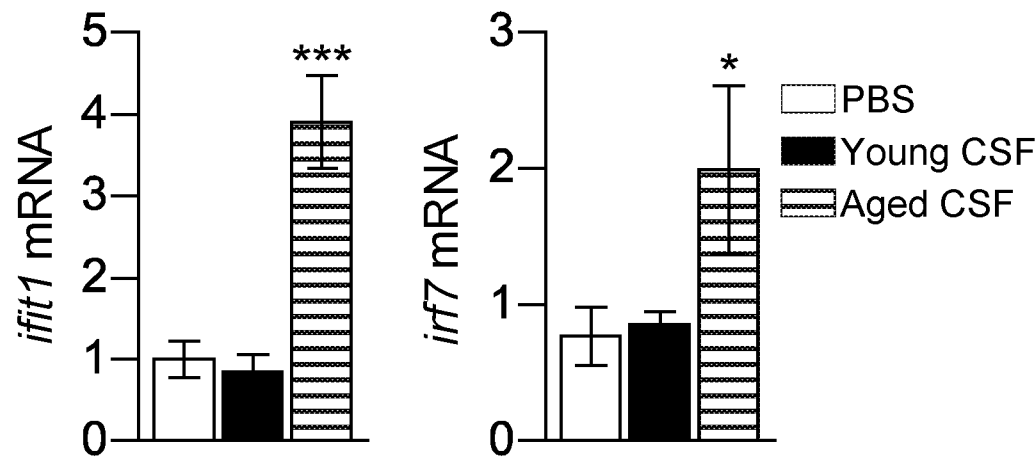


Fig. 3C



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Fig. 4

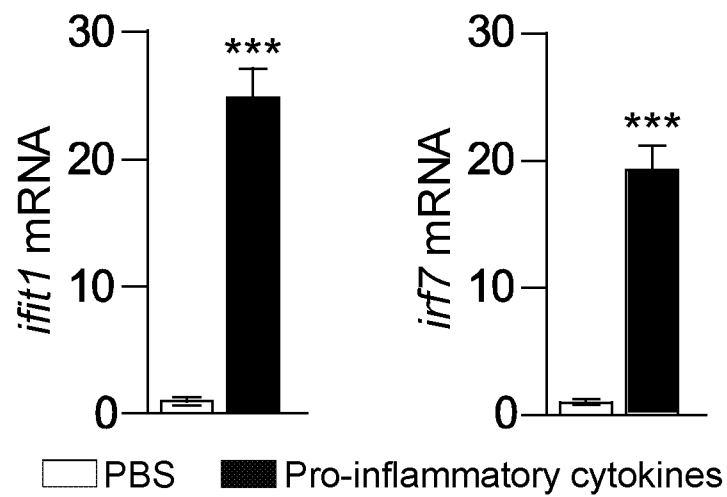


Fig. 5A

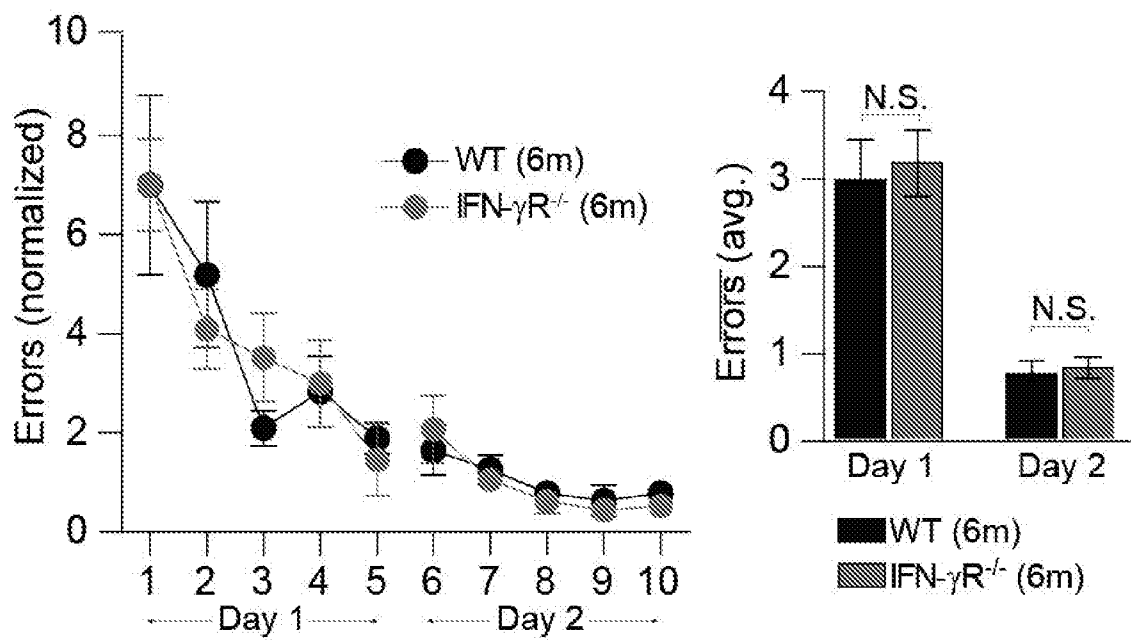


Fig. 5B

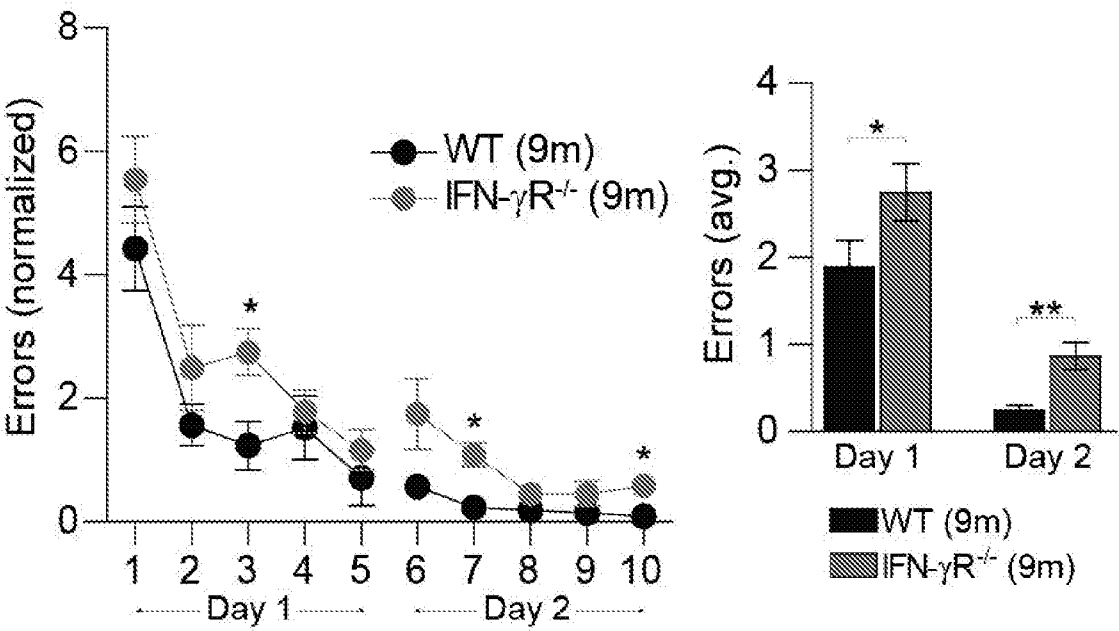
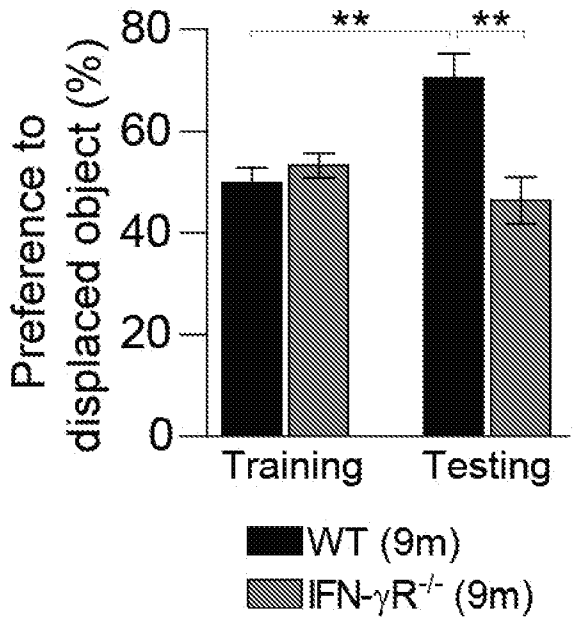


Fig. 5C



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Fig. 5D

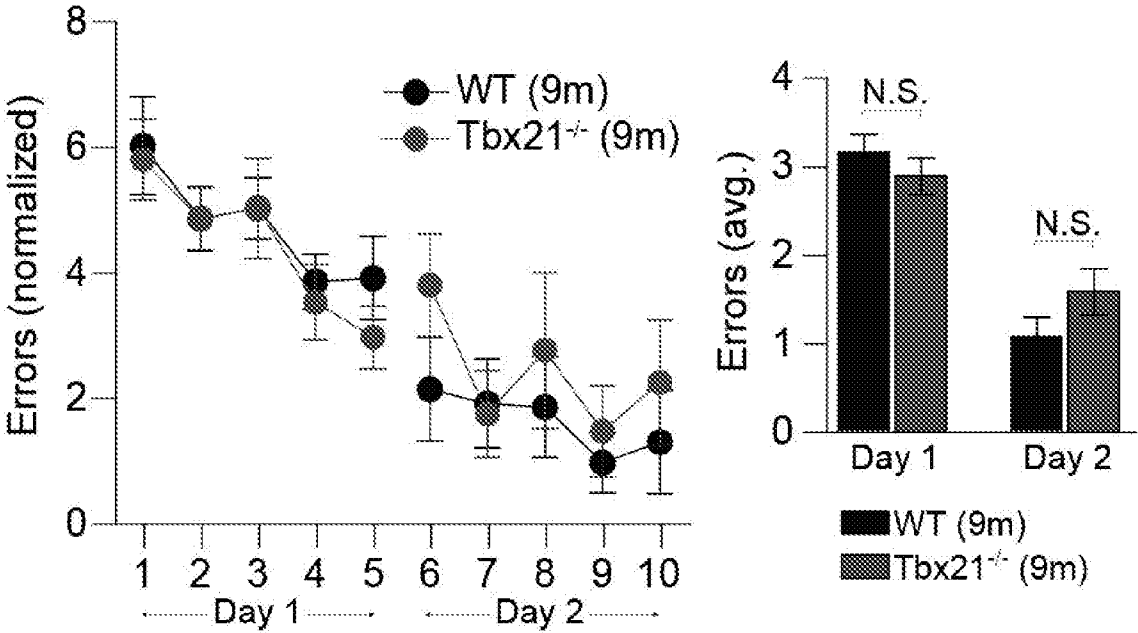


Fig. 5E

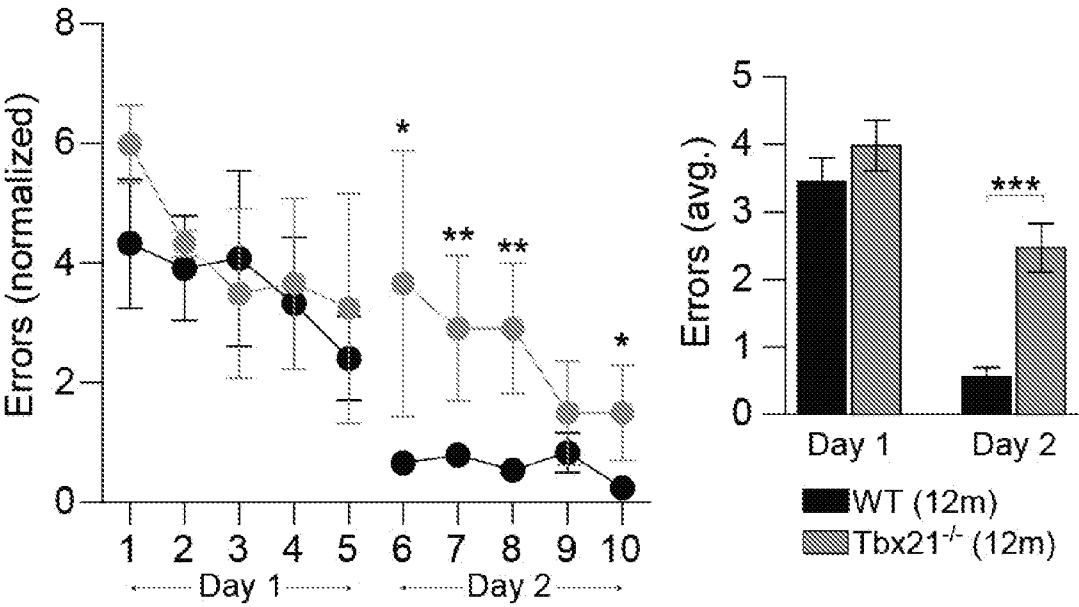


Fig. 5F

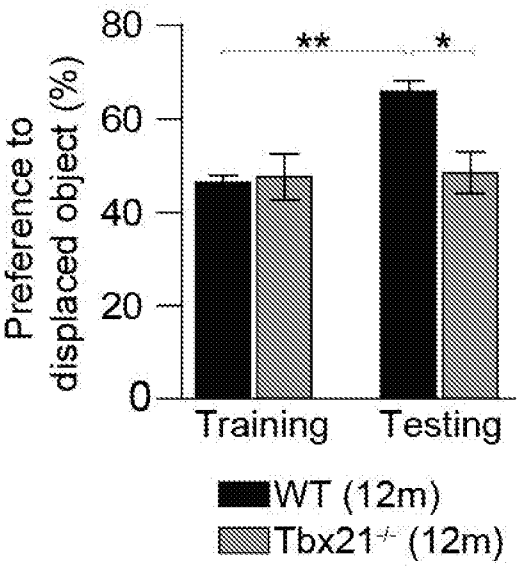


Fig. 5G

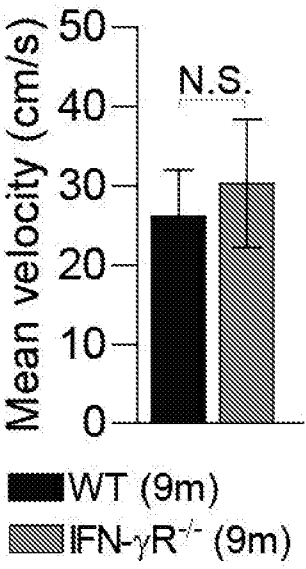


Fig. 5H

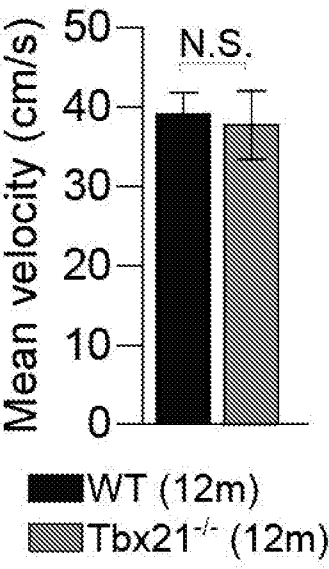


Fig. 5I

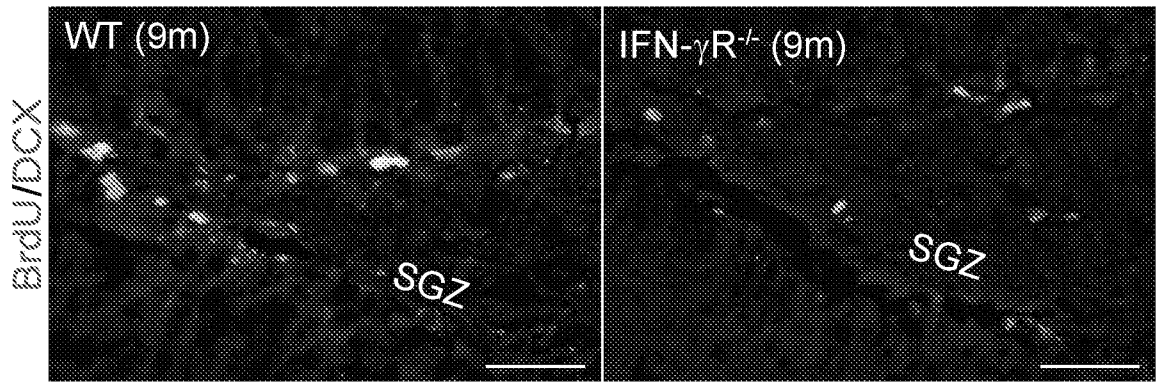


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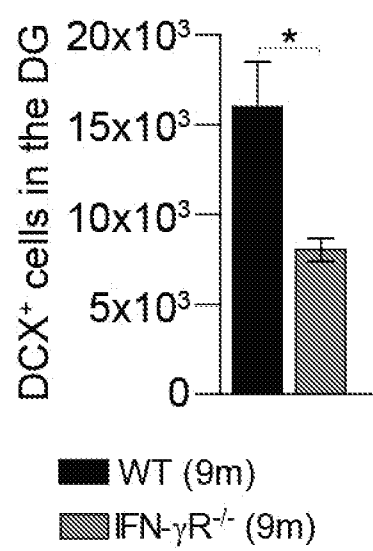
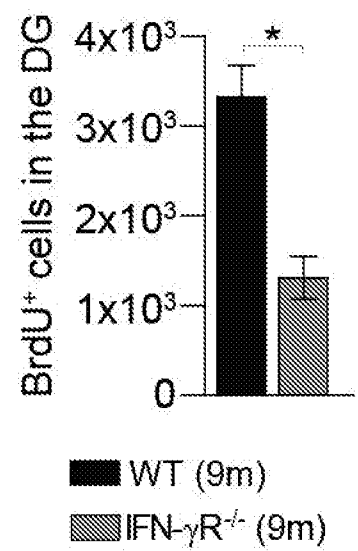


Fig. 5K



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Fig. 5L

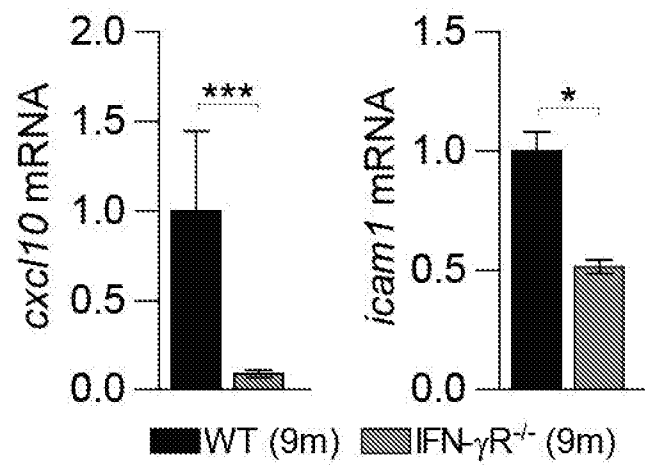


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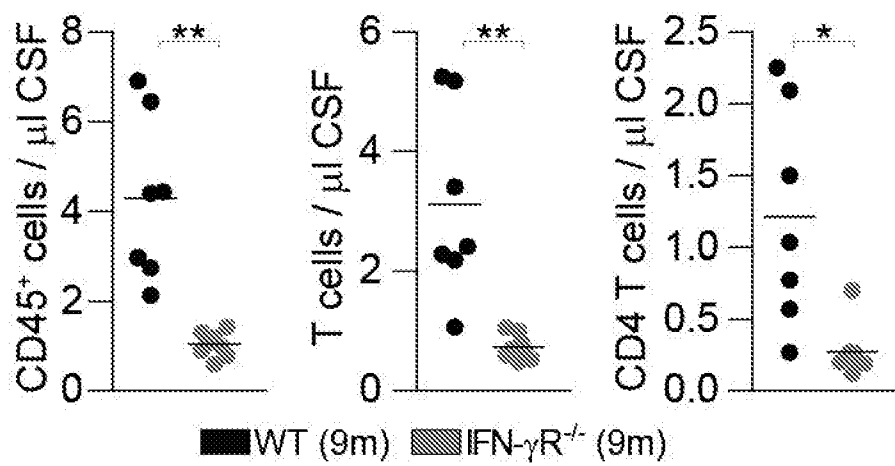


Fig. 6

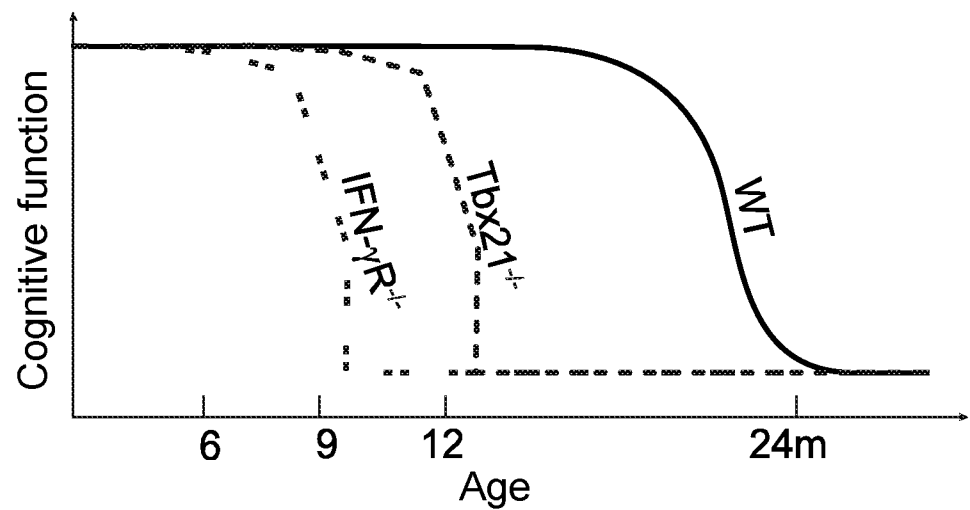


Fig. 7A

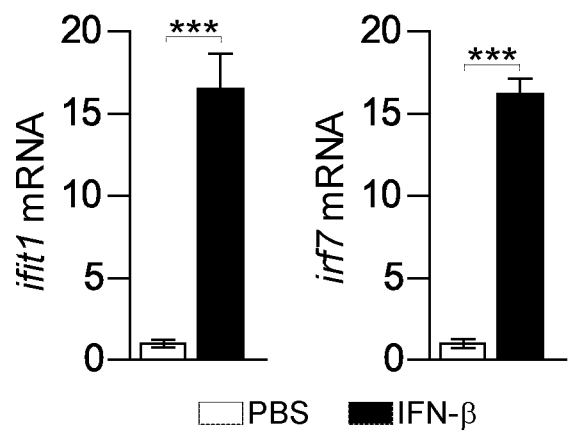


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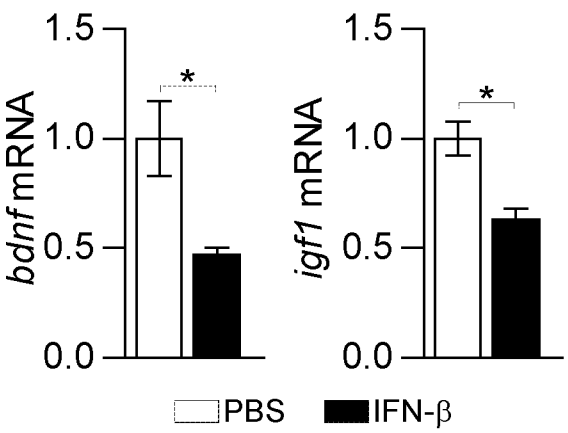


Fig. 7C

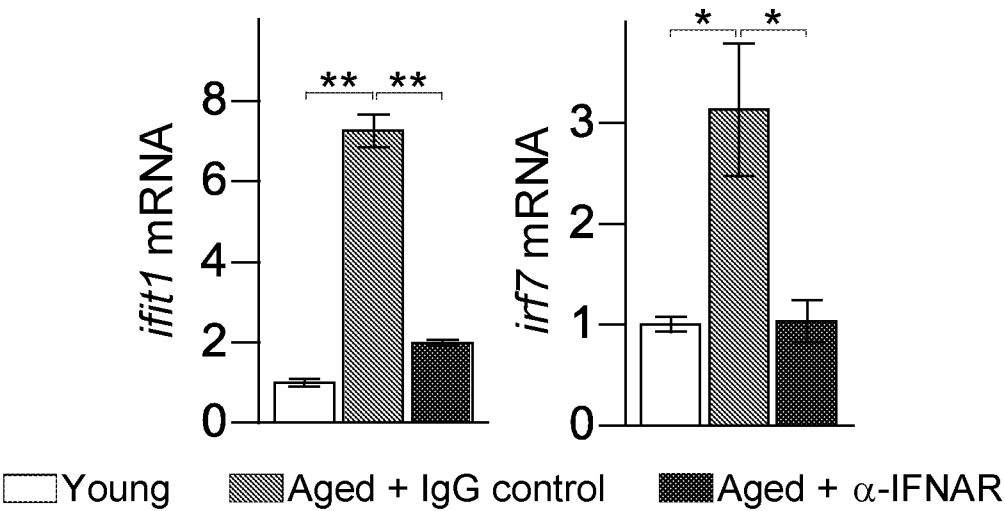


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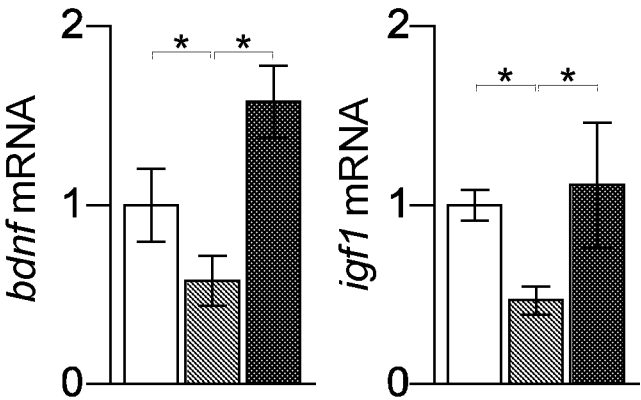
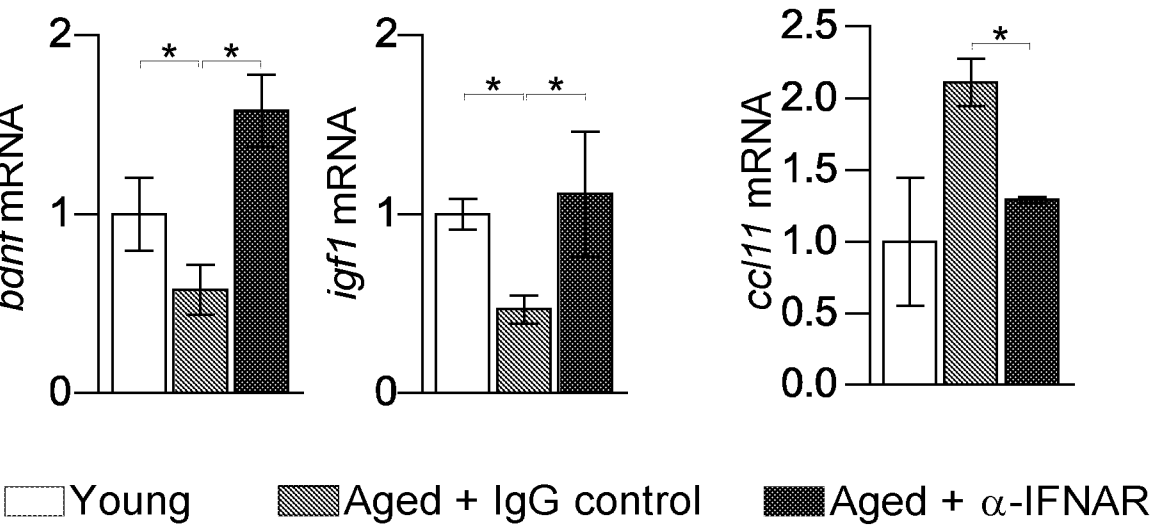


Fig. 7E



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Fig. 8

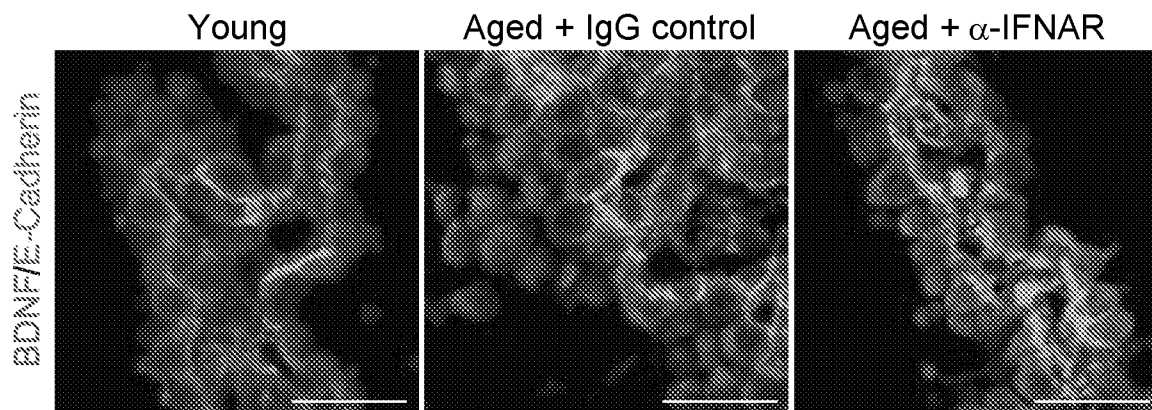
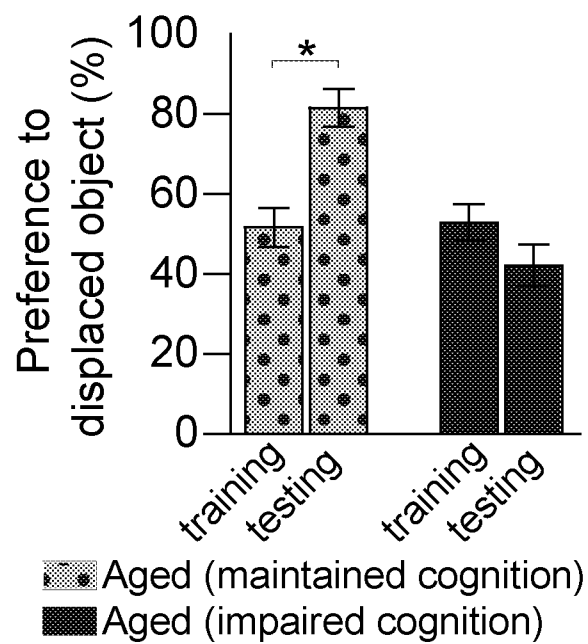


Fig. 9A



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Fig. 9B

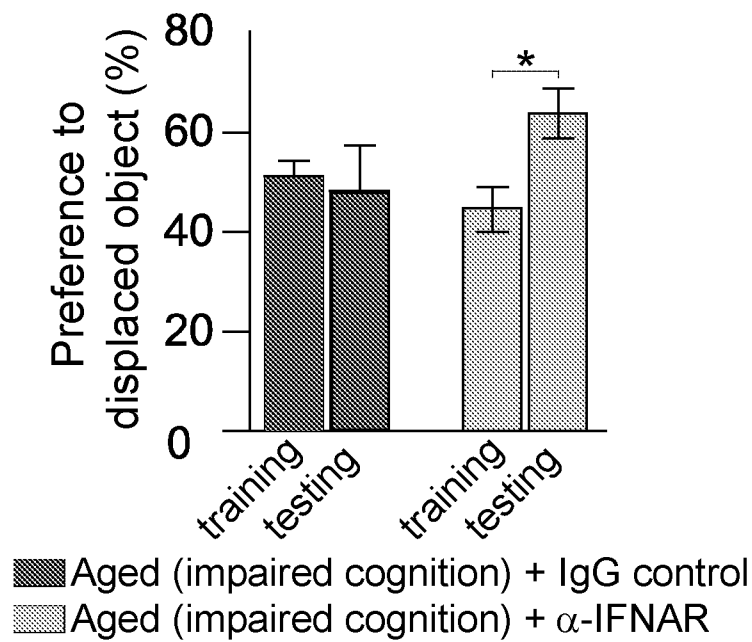
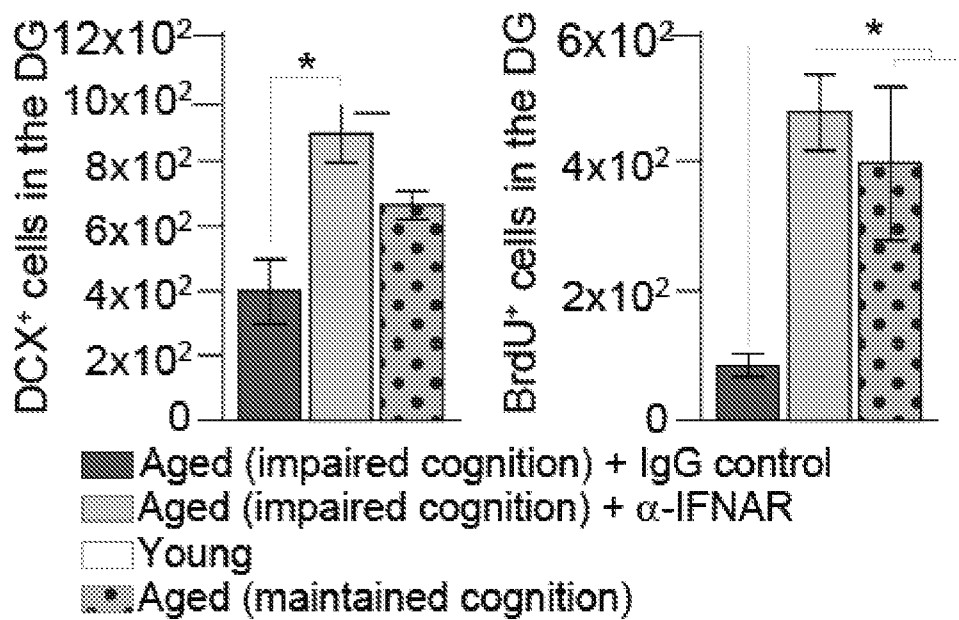


Fig. 9C



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Fig. 9D

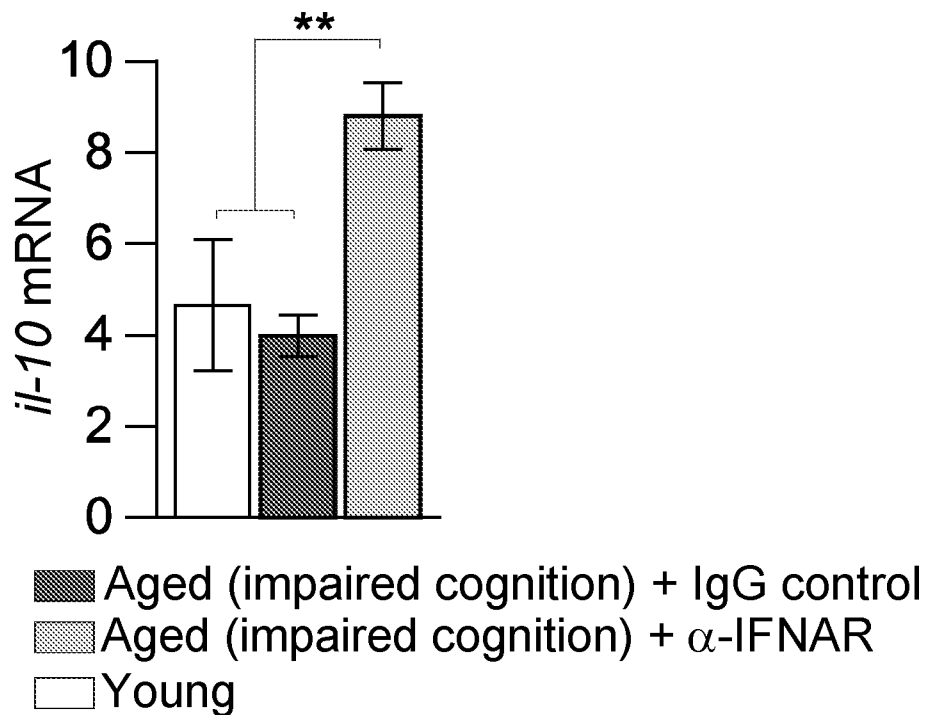


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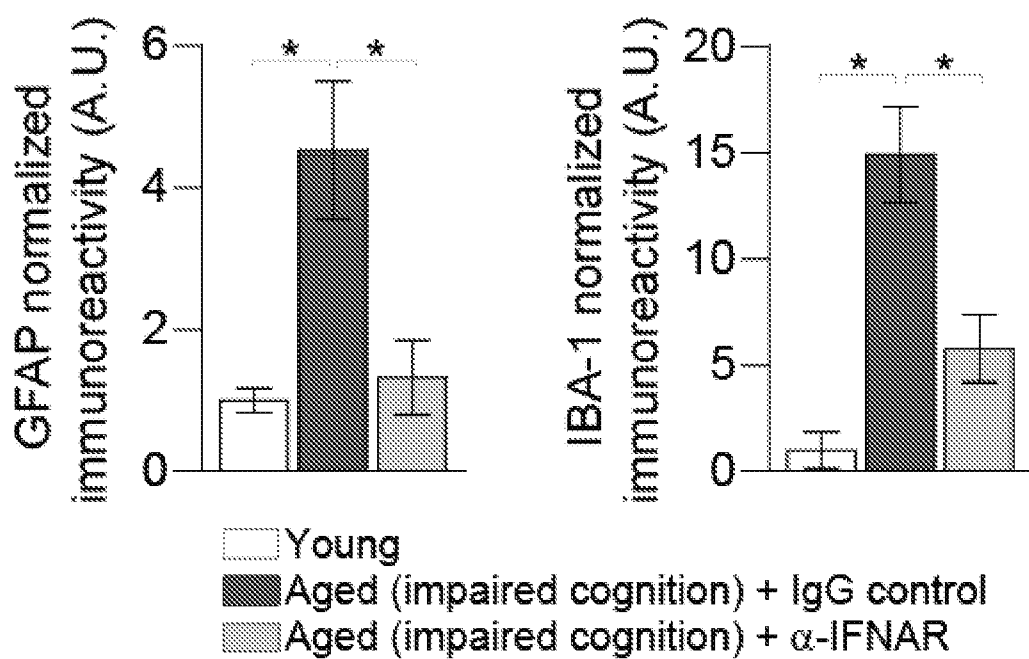
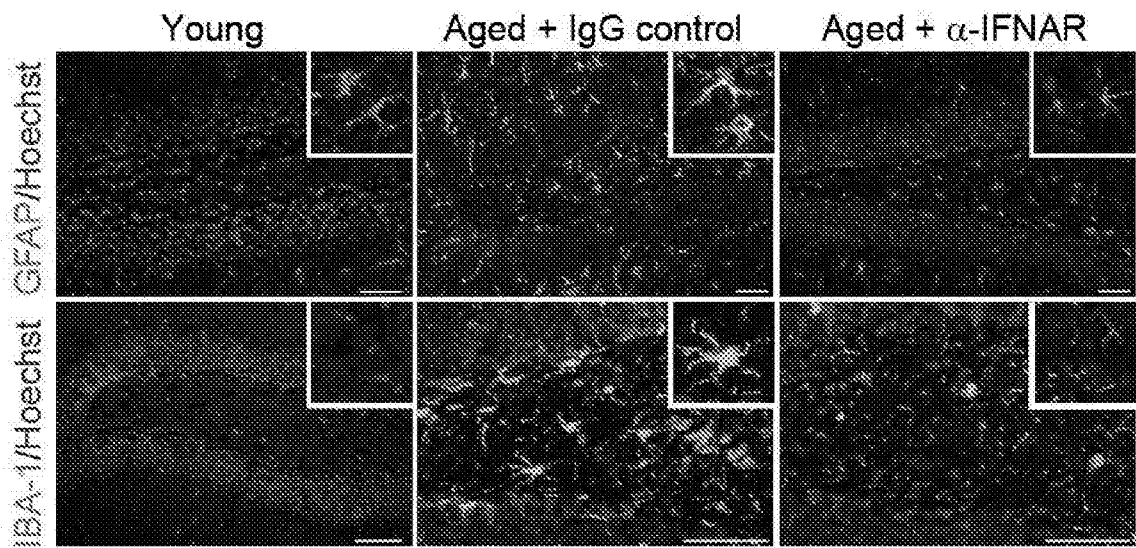
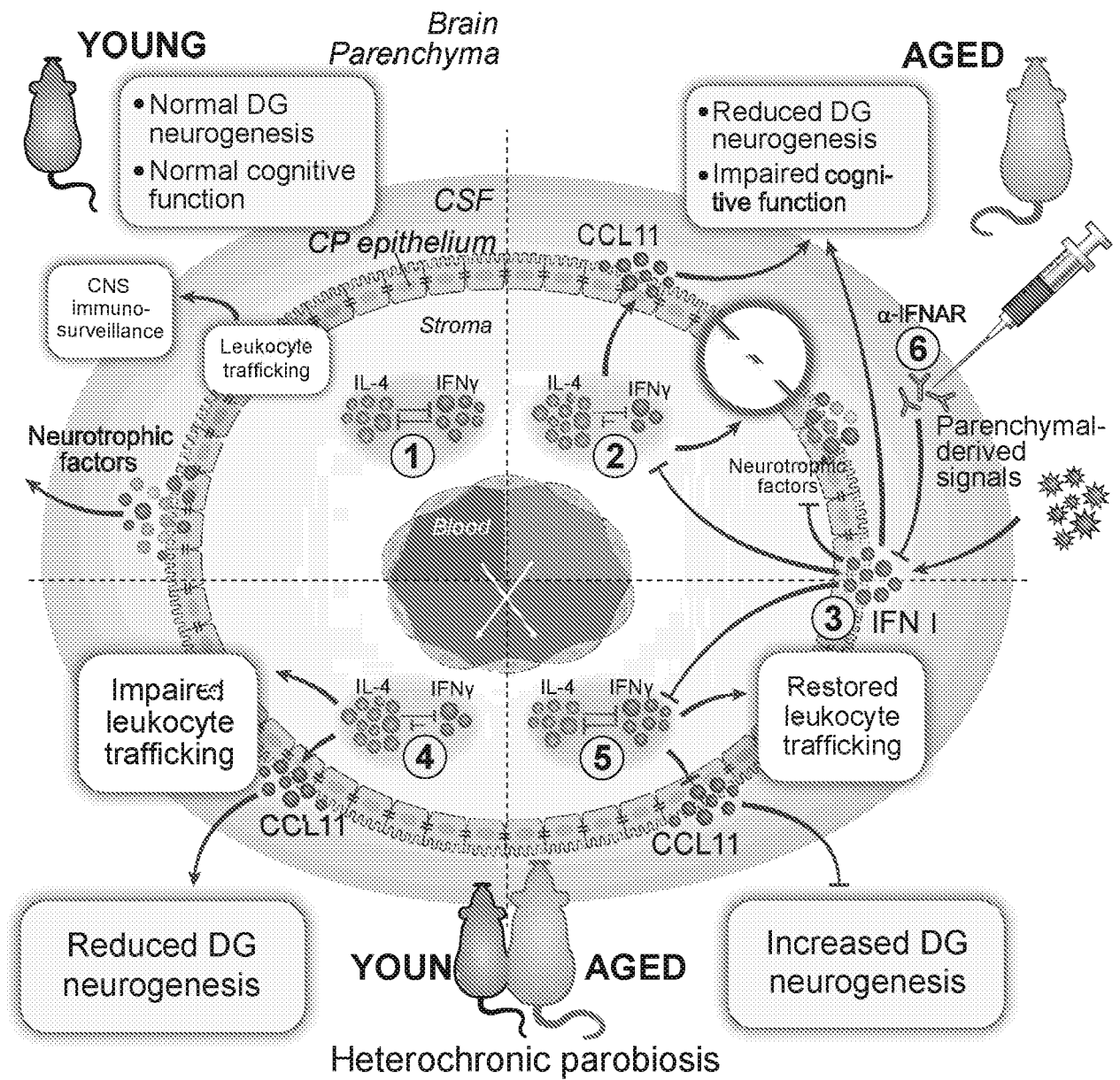


Fig. 9F



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Fig. 10



INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2015/050726

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K38/04 A61K31/40 A61K31/4706 A61K31/585 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 A61P 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, WPI Data, EMBASE								
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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.						
A	QI ZHANG ET AL: "Identification of antiviral mimetic peptides with interferon [alpha]-2b-like activity from a random peptide library using a novel functional biopanning method", ACTA PHARMACOLOGICA SINICA, vol. 29, no. 5, 1 May 2008 (2008-05-01), pages 634-640, XP055221057, US, CN ISSN: 1671-4083, DOI: 10.1111/j.1745-7254.2008.00755.x the whole document ----- -/--	1-14						
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.								
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "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						
20 October 2015		28/10/2015						
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Schnack, Anne						

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2015/050726

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a. ☒ forming part of the international application as filed:
- ☒ in the form of an Annex C/ST.25 text file.
- ☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
- ☐ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
- ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No

PCT/IL2015/050726

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WANG TIAN ET AL: "Antagonist peptides of human interferon-[alpha]2b isolated from phage display library inhibit interferon induced antiviral activity", ACTA PHARMACOLOGICA SINICA, vol. 27, no. 8, 1 August 2006 (2006-08-01) , pages 1044-1050, XP055221060, US, CN ISSN: 1671-4083, DOI: 10.1111/j.1745-7254.2006.00351.x the whole document	1-14
X,P	K. BARUCH ET AL: "Aging-induced type I interferon response at the choroid plexus negatively affects brain function", SCIENCE, vol. 346, no. 6205, 21 August 2014 (2014-08-21), pages 89-93, XP055211098, ISSN: 0036-8075, DOI: 10.1126/science.1252945 the whole document	1-14
X,P	KUNIS GILAD ET AL: "Immunization with a Myelin-Derived Antigen Activates the Brain's Choroid Plexus for Recruitment of Immunoregulatory Cells to the CNS and Attenuates Disease Progression in a Mouse Model of ALS.", 22 April 2015 (2015-04-22), THE JOURNAL OF NEUROSCIENCE : THE OFFICIAL JOURNAL OF THE SOCIETY FOR NEUROSCIENCE 22 APR 2015, VOL. 35, NR. 16, PAGE(S) 6381 - 6393, XP009186702, ISSN: 1529-2401 the whole document	1-14
X	WO 2012/068630 A1 (UNIV MELBOURNE [AU]; UNIV MONASH [AU]; CRACK PETER [AU]; HERTZOG PAUL) 31 May 2012 (2012-05-31) paragraphs [0016] - [0022], [0038] - [0044], [0062] - [0064], [0078] example 14 claims 1-15	1-14
X	WO 97/03691 A1 (MAROUN LEONARD E [US]) 6 February 1997 (1997-02-06) page 5, line 30 - page 10, line 30 claims 1-21	1-14
	-/--	

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2015/050726

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TAYLOR JULIET M ET AL: "Type-1 interferon signaling mediates neuro-inflammatory events in models of Alzheimer's disease", NEUROBIOLOGY OF AGING, vol. 35, no. 5, 29 October 2013 (2013-10-29), pages 1012-1023, XP028608066, ISSN: 0197-4580, DOI: 10.1016/J.NEUROBIOLAGING.2013.10.089 the whole document -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IL2015/050726

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012068630 A1	31-05-2012	WO 2012068630 A1	31-05-2012
		WO 2012068636 A1	31-05-2012

WO 9703691 A1	06-02-1997	AU 6459596 A	18-02-1997
		CA 2226911 A1	06-02-1997
		US 5780027 A	14-07-1998
		US 2003021764 A1	30-01-2003
		US 2005013813 A1	20-01-2005
		WO 9703691 A1	06-02-1997
