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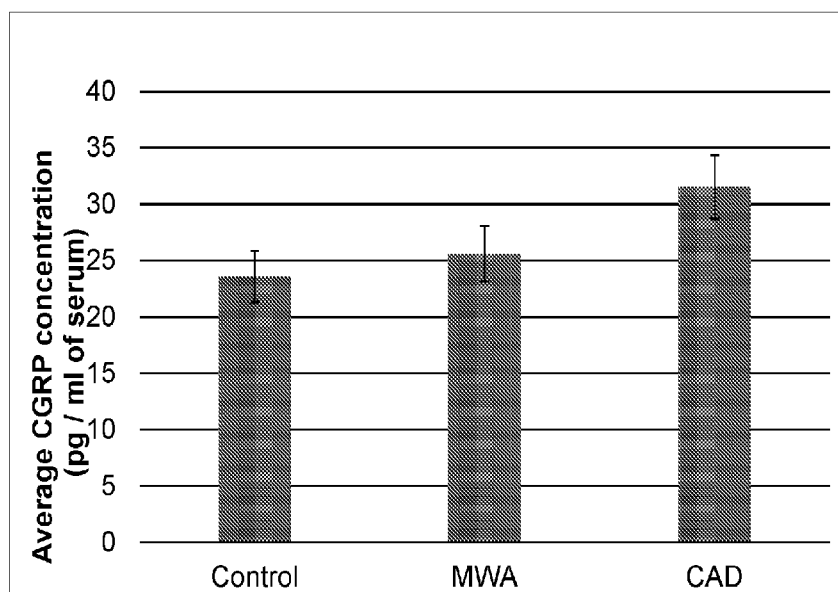
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(54) Title: METHODS AND MATERIALS FOR TREATING LEUKODYSTROPHIES

FIG. 1



(57) Abstract: This document relates to methods and materials for treating a leukodystrophy (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CADASIL). For example, one or more calcitonin gene-related peptide (CGRP) inhibitors can be administered to a mammal having, or at risk of developing, CADASIL to treat the mammal.

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METHODS AND MATERIALS FOR TREATING LEUKODYSTROPHIES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Patent Application Serial No. 62/787,594, filed on January 2, 2019. The disclosure of the prior application is
5 considered part of (and is incorporated by reference in) the disclosure of this application.

BACKGROUND

1. Technical Field

This document relates to methods and materials for treating a leukodystrophy such as cerebral autosomal dominant arteriopathy with subcortical infarcts and
10 leukoencephalopathy (CADASIL). For example, one or more calcitonin gene-related peptide (CGRP) inhibitors can be administered to a mammal having, or at risk of developing, CADASIL to treat the mammal.

2. Background Information

CADASIL (or CADASIL syndrome) is an autosomal dominant disorder caused by
15 a variant (mutation) in the *NOTCH3* gene. The *NOTCH3* gene gives the body instructions to make the Notch3 receptor protein needed for normal function and survival of vascular smooth muscle cells. Mutations in *NOTCH3* cause the body to make an abnormal protein, thus impairing the function and survival of vascular smooth muscle cells and causing these cells to self-destruct. The loss of vascular smooth muscle cells in
20 the brain causes blood vessel damage that leads to the characteristic features of CADASIL (*Genetics Home Reference (GHR)*, May 2013; available online at ghr.nlm.nih.gov/condition/cerebral-autosomal-dominant-arteriopathy-with-subcortical-infarcts-and-leukoencephalopathy). Currently, there is no cure or effective treatment for CADASIL, and current treatments options are only supportive and depend on the
25 symptoms (*NINDS CADASIL Information Page. National Institute of Neurological Disorders and Stroke (NINDS)*, 2017; available online at ninds.nih.gov/disorders/cadasil/CADASIL.htm).

SUMMARY

This document provides methods and materials related to treating a
30 leukodystrophy such as CADASIL. For example, this document provides methods and

materials for using one or more CGRP inhibitors (*e.g.*, erenumab) to treat a mammal having, or at risk of developing, CADASIL. In some cases, a mammal having, or at risk of developing, CADASIL can be treated with a composition including one or more CGRP inhibitors to reduce or eliminate one or more symptoms of CADASIL (*e.g.*, migraine headaches, small subcortical strokes, and/or vascular dementia). In some cases, a mammal having, or at risk of developing, CADASIL can be treated with a composition including one or more CGRP inhibitors to slow the progression of CADASIL within the mammal.

CADASIL is characterized clinically by migraine headaches, small subcortical strokes, and vascular dementia. Migraines are typically the first symptom to appear, often years before patients develop strokes and more than a decade before patients develop dementia. The ability to treat CADASIL patients (*e.g.*, CADASIL patients in the early stages of the disease, such as the migraine phase of the disease) provides a unique and unrealized opportunity to delay or even prevent the emergence of strokes and vascular dementia in those CADASIL patients.

In general, one aspect of this document features methods for treating a mammal having a leukodystrophy. The methods can include, or consist essentially of, administering a composition including a CGRP inhibitor to a mammal to reduce one or more symptoms of said leukodystrophy in the mammal. The mammal can be a human. The leukodystrophy can be CADASIL. The composition can be administered to the mammal during a migraine phase of CADASIL. The one or more symptoms of CADASIL can be migraine headaches, small subcortical strokes, and/or vascular dementia. The CGRP inhibitor can be an antibody. The CGRP inhibitor can be a small molecule. The CGRP inhibitor can specifically bind CGRP. The CGRP inhibitor can specifically bind a CGRP receptor. The CGRP inhibitor can be erenumab. The composition can include from about 70 mg to about 140 mg of the CGRP inhibitor. The composition can be administered to the mammal once a month. The composition can be administered to the mammal by subcutaneous injection (*e.g.*, subcutaneous injection to the abdomen, thigh, or upper arm of the mammal).

In another aspect, this document features methods for slowing the progression of a leukodystrophy. The methods can include, or consist essentially of, administering a composition including a CGRP inhibitor to a mammal identified as having a leukodystrophy. The mammal can be a human. The leukodystrophy can be CADASIL.

The composition can be administered to the mammal during a migraine phase of CADASIL. The one or more symptoms of CADASIL can be migraine headaches, small subcortical strokes, and/or vascular dementia. The CGRP inhibitor can be an antibody. The CGRP inhibitor can be a small molecule. The CGRP inhibitor can specifically bind CGRP. The CGRP inhibitor can specifically bind a CGRP receptor. The CGRP inhibitor can be erenumab. The composition can include from about 70 mg to about 140 mg of the CGRP inhibitor. The composition can be administered to the mammal once a month. The composition can be administered to the mammal by subcutaneous injection (*e.g.*, subcutaneous injection to the abdomen, thigh, or upper arm of the mammal).

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used to practice the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 contains a graph showing average CGRP concentrations in patients with CADASIL (CAD), patients with migraine with aura (MWA), and control patients.

DETAILED DESCRIPTION

This document provides methods and materials related to treating CADASIL. For example, this document provides methods and materials for using one or more CGRP inhibitors (*e.g.*, erenumab) to treat a mammal having, or at risk of developing, CADASIL.

In some cases, a mammal having, or at risk of developing, CADASIL can be treated with a composition including one or more CGRP inhibitors to reduce or eliminate one or more (*e.g.*, one, two, three, four, five or more) symptoms of CADASIL. Examples of symptoms of CADASIL include, without limitation, migraine headaches (*e.g.*,

migraine headaches with aura), strokes (*e.g.*, small subcortical strokes), cognitive impairment (*e.g.*, vascular dementia), psychiatric problems (*e.g.*, mood disturbances such as apathy and depression), seizures, white matter lesions retinal disease, cerebral microbleeds, and cerebral atrophy.

5 In some cases, a mammal having, or at risk of developing, CADASIL can be treated with a composition including one or more CGRP inhibitors to reduce or eliminate leukoaraiosis in the mammal. For example, administering one or more CGRP inhibitors to a mammal having, or at risk of developing, CADASIL can be effective to reduce or eliminate leukoaraiosis in the mammal, thereby reducing or eliminating one or more (*e.g.*,
10 one, two, three, four, five or more) symptoms of CADASIL (*e.g.*, small subcortical strokes and/or vascular dementia) in the mammal.

 In some cases, a mammal having, or at risk of developing, CADASIL can be treated with a composition including one or more CGRP inhibitors to reduce or eliminate small vessel infarcts in the mammal. For example, administering one or more CGRP
15 inhibitors to a mammal having, or at risk of developing, CADASIL can be effective to reduce or eliminate small vessel infarcts in the mammal, thereby reducing or eliminating one or more (*e.g.*, one, two, three, four, five or more) symptoms of CADASIL (*e.g.*, small subcortical strokes and/or vascular dementia) in the mammal.

 For example, administering one or more CGRP inhibitors to a mammal having, or
20 at risk of developing, CADASIL can be effective to improve the function and/or survival of one or more vascular smooth muscle cells in the mammal.

 For example, administering one or more CGRP inhibitors to a mammal having, or at risk of developing, CADASIL can be effective to reduce or eliminate granular deposits in the smooth muscle of small blood vessels in the mammal.

25 In some cases, a mammal having, or at risk of developing, CADASIL can be treated with a composition including one or more CGRP inhibitors to slow the progression of CADASIL within the mammal. For example, administering one or more CGRP inhibitors to a mammal having early stage CADASIL (*e.g.*, a migraine phase of CADASIL) can be effective to slow the progression of CADASIL. In some cases,
30 slowing the progression of CADASIL can delay or eliminate the development of one or more symptoms associated with later stages of CADASIL such as strokes (*e.g.*, small subcortical strokes) and cognitive impairment (*e.g.*, vascular dementia).

In some cases, a mammal having, or at risk of developing, CADASIL can be treated with a composition including one or more CGRP inhibitors to reduce or eliminate neuroinflammation in the mammal.

When treating a mammal having, or at risk of developing, CADASIL as described
5 herein (*e.g.*, by administering one or more CGRP inhibitors), the mammal can be any appropriate mammal. In some cases, a mammal can be an adult mammal (*e.g.*, a human 18 years of age or older). Examples of mammals that can be treated using a composition containing one or more CGRP inhibitors as described herein include, without limitation, humans, non-human primates such as monkeys, dogs, cats, horses, cows, pigs, sheep,
10 mice, and rats. In some cases, a composition containing one or more CGRP inhibitors can be administered to a human having, or at risk of developing, CADASIL to treat the human.

In some cases, the methods described herein also can include identifying a mammal as having, or as being at risk of developing, CADASIL. Examples of methods
15 for identifying a mammal as having, or as being at risk of developing, CADASIL include, without limitation, physical examination, laboratory tests (*e.g.*, for elevated levels of CGRP in a sample, such as blood or saliva, obtained from the mammal), imaging tests (*e.g.*, MRI for identifying leukoaraiosis, small vessel infarcts, and/or white matter lesions), genetic tests (*e.g.*, genetic tests for one or more mutations in the *NOTCH3* gene),
20 electron microscopy of a skin biopsy, and/or immunohistochemical analysis of skin biopsy. In cases where the presence of an elevated level of CGRP in a sample obtained from a mammal is used to identify that mammal as having or as being at risk of developing CADASIL, an elevated level of CGRP can be any level that is higher than a level of CGRP typically observed in a sample (*e.g.*, a control sample) from one or more
25 mammals (*e.g.*, humans) that do not have CADASIL. Control samples can include, without limitation, samples from healthy mammals and mammals having migraine with aura. In some cases, an elevated level of CGRP can be a level that is greater than about 25 pg/mL as measured in blood (*e.g.*, in plasma and/or in serum). For example, when a blood sample (*e.g.*, a plasma sample and/or a serum sample) from a mammal contains
30 from about 25 pg/mL to about 42 pg/mL of CGRP (*e.g.*, from about 25 pg/mL to about 40 pg/mL, from about 25 pg/mL to about 38 pg/mL, from about 25 pg/mL to about 35 pg/mL, from about 25 pg/mL to about 33 pg/mL, from about 25 pg/mL to about 31 pg/mL, from about 25 pg/mL to about 30 pg/mL, from about 25 pg/mL to about 28

pg/mL, from about 27 pg/mL to about 42 pg/mL, from about 30 pg/mL to about 42 pg/mL, from about 32 pg/mL to about 42 pg/mL, from about 35 pg/mL to about 42 pg/mL, from about 38 pg/mL to about 42 pg/mL, from about 28 pg/mL to about 40 pg/mL, from about 30 pg/mL to about 38 pg/mL, from about 32 pg/mL to about 35 pg/mL, from about 28 pg/mL to about 32 pg/mL, from about 30 pg/mL to about 35 pg/mL, or from about 32 pg/mL to about 38 pg/mL of CGRP), the mammal can be identified as having or as being at risk of developing CADASIL. Once identified as having, or as being at risk of developing, CADASIL, a mammal can be administered or instructed to self-administer one or more CGRP inhibitors described herein (*e.g.*,
 10 erenumab).

A composition containing one or more (*e.g.*, one, two, three, four, five or more) CGRP inhibitors can include any appropriate CGRP inhibitor(s). A CGRP inhibitor can inhibit CGRP expression or CGRP activity. In some cases, a CGRP inhibitor can target a CGRP (*e.g.*, an α -CGRP and/or a β -CGRP). In some cases, a CGRP inhibitor can target a
 15 CGRP receptor (*e.g.*, a calcitonin receptor-like (CALCRL) receptor). For example, a CGRP inhibitor can target an unassociated CALCRL receptor or can target a CALCRL receptor associated with a receptor activity-modifying protein (RAMP; *e.g.*, RAMP1 or RAMP3). A CGRP inhibitor can be any type of molecule. Examples of molecules that be used as a CGRP inhibitor include, without limitation, nucleic acid molecules designed
 20 to induce RNA interference (*e.g.*, a siRNA molecule or a shRNA molecule), antisense molecules, miRNAs, antibodies (*e.g.*, monoclonal antibodies), and small molecules (*e.g.*, non-peptide small molecules) that can reduce or eliminate CGRP expression or CGRP function. In some cases, a CGRP inhibitor can be readily designed based upon the nucleic acid and/or polypeptide sequences of CGRP. Examples of CGRP inhibitors that
 25 can be used as described herein (*e.g.*, to treat a mammal having, or at risk of developing, CADASIL) include, without limitation, erenumab (AMG-334; also known as AimovigTM), eptinezumab (ALD403), fremanezumab (TEV-48125), galcanezumab (LY2951742), BI 44370 TA (BI 44370), MK-3207, olcegepant (BIBN-4096BS), rimegepant (BMS-927711), SB-268262, telcagepant (MK-0974), and ubrogepant. In
 30 some cases, a composition containing one or more CGRP inhibitors can include erenumab.

In some cases, a composition containing one or more (*e.g.*, one, two, three, four, five or more) CGRP inhibitors can include the one or more CGRP inhibitor(s) as the sole

active ingredient in the composition that is effective against one or more symptoms of CADASIL.

In some cases, a composition containing one or more (*e.g.*, one, two, three, four, five or more) CGRP inhibitors also can include one or more (*e.g.*, one, two, three, four, 5 five or more) additional active agents (*e.g.*, therapeutic agents) in the composition that are effective against one or more symptoms of CADASIL.

In some cases, a mammal having, or at risk of developing, CADASIL being treated as described herein (*e.g.*, by administering one or more CGRP inhibitors) also can be treated with one or more (*e.g.*, one, two, three, four, five or more) additional 10 therapeutic agents. A therapeutic agent used in combination with one or more CGRP inhibitors described herein can be any appropriate therapeutic agent. Examples of therapeutic agents that can be used in combination with one or more CGRP inhibitors described herein include, without limitation, antiplatelet agents (*e.g.*, aspirin, dipyridamole, and clopidogrel), blood pressure reducing agents (*e.g.*, chlorthalidone), 15 cholesterol lowering agents (*e.g.*, statins such as atorvastatin), and anti-migraine agents. In some cases, the one or more additional therapeutic agents can be administered together with the one or more CGRP inhibitors (*e.g.*, in a composition containing one or more CGRP inhibitors and containing one or more additional therapeutic agents). In some cases, the one or more (*e.g.*, one, two, three, four, five or more) additional therapeutic 20 agents can be administered independent of the one or more CGRP inhibitors. When the one or more additional therapeutic agents are administered independent of the one or more CGRP inhibitors, the one or more CGRP inhibitors can be administered first, and the one or more additional therapeutic agents administered second, or vice versa.

In some cases, a composition containing one or more CGRP inhibitors can be 25 formulated into a pharmaceutically acceptable composition for administration to a mammal having, or at risk of developing, CADASIL. For example, one or more CGRP inhibitors can be formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. Pharmaceutically acceptable carriers, fillers, and vehicles that can be used in a pharmaceutical composition described herein include, 30 without limitation, saline, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen

phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol (PEG; *e.g.*, PEG400), sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat.

5 In some cases, when a composition containing one or more CGRP inhibitors is administered to a mammal having, or at risk of developing, CADASIL, the composition can be designed for oral or parenteral (including subcutaneous, intramuscular, intravenous, and intradermal) administration to a mammal having, or at risk of developing, CADASIL. Compositions suitable for oral administration include, without
10 limitation, liquids, tablets, capsules, pills, powders, gels, and granules. Compositions suitable for parenteral administration include, without limitation, aqueous and non-aqueous sterile injection solutions that can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient. In some cases, a composition containing one or more CGRP inhibitors can be formulated
15 for administration by subcutaneous injection (*e.g.*, subcutaneous injection the abdomen, thigh, or upper arm).

 A composition containing one or more CGRP inhibitors can be administered to a mammal having, or at risk of developing, CADASIL in any appropriate amount (*e.g.*, dose). Effective amounts can vary depending on the route of administration, the age and
20 general health condition of the subject, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents, and the judgment of the treating physician. An effective amount of a composition containing one or more CGRP inhibitors can be any amount that can treat a mammal having, or at risk of developing, CADASIL (*e.g.*, can reduce or eliminate one or more symptoms of CADASIL such as
25 migraine headaches, small subcortical strokes, and/or vascular dementia in the mammal) without producing significant toxicity to the mammal. For example, an effective amount of erenumab can be from about 70 milligrams (mg) to about 140 mg (*e.g.*, from about 70 mg to about 130 mg, from about 70 mg to about 120 mg, from about 70 mg to about 110 mg, from about 70 mg to about 100 mg, from about 70 mg to about 90 mg, from about 70
30 mg to about 80 mg, from about 80 mg to about 140 mg, from about 90 mg to about 140 mg, from about 100 mg to about 140 mg, from about 110 mg to about 140 mg, from about 120 mg to about 140 mg, from about 130 mg to about 140 mg, from about 80 mg to about 130 mg, from about 90 mg to about 120 mg, from about 100 mg to about 110 mg, from

about 80 mg to about 100 mg, or from about 100 mg to about 120 mg) administered once a month. The effective amount can remain constant or can be adjusted as a sliding scale or variable dose depending on the mammal's response to treatment. Various factors can influence the actual effective amount used for a particular application. For example, the frequency of administration, duration of treatment, use of multiple treatment agents, route of administration, and severity of the CADASIL in the mammal being treated may require an increase or decrease in the actual effective amount administered.

A composition containing one or more CGRP inhibitors can be administered to a mammal having, or at risk of developing, CADASIL in any appropriate frequency. The frequency of administration can be any frequency that can treat a mammal having, or at risk of developing, CADASIL (*e.g.*, can reduce or eliminate one or more symptoms of CADASIL such as migraine headaches, small subcortical strokes, and/or vascular dementia in the mammal) without producing significant toxicity to the mammal. For example, the frequency of administration can be from about once a week to about once a month, from about twice a month to about once a month, or from about once a month to about every other month. In some cases, a composition containing one or more CGRP inhibitors can be administered once a month. The frequency of administration can remain constant or can be variable during the duration of treatment. As with the effective amount, various factors can influence the actual frequency of administration used for a particular application. For example, the effective amount, duration of treatment, use of multiple treatment agents, and route of administration may require an increase or decrease in administration frequency.

A composition containing one or more CGRP inhibitors can be administered to a mammal having, or at risk of developing, CADASIL for any appropriate duration. An effective duration for administering or using a composition containing one or more CGRP inhibitors can be any duration that can treat a mammal having, or at risk of developing, CADASIL (*e.g.*, can reduce or eliminate one or more symptoms of CADASIL such as migraine headaches, small subcortical strokes, and/or vascular dementia in the mammal) without producing significant toxicity to the mammal. For example, the effective duration can vary from several months to several years or to a lifetime. In some cases, the effective duration can range in duration from about 10 years to about a lifetime. Multiple factors can influence the actual effective duration used for a particular treatment.

For example, an effective duration can vary with the frequency of administration, effective amount, use of multiple treatment agents, and route of administration.

In certain instances, a course of treatment can be monitored. In some cases, methods described herein also can include monitoring the severity or progression of CADASIL in a mammal. Any appropriate method can be used to monitor the severity or progression of CADASIL in a mammal. For example, one or more symptoms of CADASIL (*e.g.*, migraine headaches, small subcortical strokes, and/or vascular dementia) can be assessed using any appropriate methods and/or techniques, and can be assessed at different time points. In cases where a symptom of CADASIL is a migraine headache, the migraine headache can be assessed using standardized migraine scales like the Migraine Disability Scale (MIDAS). In cases where a symptom of CADASIL is stroke (*e.g.*, small subcortical stroke) or vascular dementia, the stroke (*e.g.*, small subcortical stroke) or vascular dementia can be assessed using brain MRI (*e.g.*, brain MRI focusing on features of small vessel disease such as the extent of white matter ischemic changes, lacunar infarcts, and cerebral microbleeds). In some cases, methods described herein also can include monitoring a mammal being treated as described herein for toxicity. The level of toxicity, if any, can be determined by assessing a mammal's clinical signs and symptoms before and after administering a known amount of a particular composition. It is noted that the effective amount of a particular composition administered to a mammal can be adjusted according to a desired outcome as well as the mammal's response and level of toxicity.

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

EXAMPLES

Example 1: Serum Concentrations of CGRP in Patients with CADASIL

Patients with CADASIL have an elevated serum concentration of calcitonin gene-related peptide (CGRP) when compared against healthy control subjects and patients with known migraine with aura.

Methods:

Twenty patients with genetically diagnosed or phenotypically confirmed CADASIL are compared against 10 healthy controls and 20 patients (50 total patients)

with chronic migraine with aura, diagnosed by a headache specialist. Patients are previously evaluated by the Neurology department at Mayo Clinic Florida. Venous samples are obtained through the cubital veins by laboratory personnel. Serum samples are drawn and analyzed per the below instructions.

5 *Collection Procedure*

1) Collect blood in an EDTA aprotinin vacutainer. (Heparinized tubes are not used.)

2) Gently invert the tube 8-10 times, and let tube sit in an upright position for 15-30 minutes at room temperature to allow the blood to clot.

10 3) Label sample with appropriate study code.

4) Centrifuge blood at 1,600xg for 15 minutes at 4 °C.

5) Recover plasma with transfer pipette.

6) Place ~0.5 mL of plasma into each cryovial tube.

7) Clearly label the amount in each tube.

15 8) Label each aliquot with appropriate study code and date of collection. No identifying information is included on the label that researchers will see aside from a study ID.

9) Freeze plasma at -80°C until ready to ship.

Shipping Procedure

20 Samples are shipped on dry ice using overnight shipping. The serum does not thaw during transport.

Subjects

The subject population includes 50 patients (children, adults, and groups) as follows: adults with CADASIL, adults as healthy controls, and adults with chronic
25 migraine with aura.

Inclusion criteria:

- Age $\geq$ 18 years old, known diagnosis of CADASIL or history of migraine

Exclusion Criteria:

- Under the age of 18 years old

- Patients with competing intracerebral pathology (e.g. history of intracerebral hemorrhage, multiple sclerosis)
- Use of migraine abortive agent within 1 week of serum collection
- Significant cardiac disease with impaired ejection fraction
- Pregnancy or breastfeeding

Example 2: Serum Calcitonin Gene-Related Peptide Concentrations in CADASIL patients

Methods

Up to 40 patients with genetically diagnosed or phenotypically confirmed CADASIL were compared against 40 healthy controls and 40 patients (120 total patients) with chronic migraine with aura, diagnosed by a headache specialist. Venous samples were obtained through the cubital veins by laboratory personnel. Serum samples were drawn and analyzed for CGRP levels.

Results

20 patients with CADASIL, 20 patients with migraine with aura, and 10 healthy controls were included (Table 1).

Table 1. CADASIL CGRP Analysis.

Diagnosis	Study ID	Age	Gender	Sample number	Ave CGRP conc in pg/mL of serum
CADASIL	CAD-1	64	Male	CAD-1	12.6
CADASIL	CAD-2	52	Male	CAD-2	24.9
CADASIL	CAD-3	69	Male	CAD-3	23.2
Migraines with Aura	CAD-4	56	Female	CAD-4	15.0
Migraines with Aura	CAD-5	48	Male	CAD-5	19.6
Control	CAD-6	65	Female	CAD-6	14.3
Migraines with Aura	CAD-7	42	Male	CAD-7	7.9
Migraines with Aura	CAD-8	47	Female	CAD-8	24.9
Migraines with Aura	CAD-9	53	Female	CAD-9	14.7
Migraines with Aura	CAD-10	59	Male	CAD-10	14.7
CADASIL	CAD-11	57	Male	CAD-11	28.8
Migraines with Aura	CAD-12	58	Female	CAD-12	18.7
Migraines with Aura	CAD-13	31	Female	CAD-13	20.6
Control	CAD-14	64	Female	CAD-14	28.1

Control	CAD-15	66	Male	CAD-15	26.8
Control	CAD-16	57	Male	CAD-16	26.8
Control	CAD-17	51	Female	CAD-17	10.0
Control	CAD-18	24	Male	CAD-18	20.1
CADASIL	CAD-19	60	Male	CAD-19	21.6
CADASIL	CAD-20	58	Female	CAD-20	16.6
Migraines with Aura	CAD-21	51	Female	CAD-21	27.4
CADASIL	CAD-22	50	Female	CAD-22	14.3
Control	CAD-23	84	Female	CAD-23	28.8
CADASIL	CAD-24	63	Male	CAD-24	26.8
Control	CAD-25	46	Female	CAD-25	29.5
Control	CAD-26	86	Female	CAD-26	28.8
Control	CAD-27	73	Female	CAD-27	22.6
Migraines with Aura	CAD-28	62	Female	CAD-28	23.2
CADASIL	CAD-29	36	Female	CAD-29	21.1
CADASIL	CAD-30	47	Male	CAD-30	23.2
Migraines with Aura	CAD-31	40	Female	CAD-31	34.0
CADASIL	CAD-32	34	Male	CAD-32	33.2
CADASIL	CAD-33	73	Female	CAD-33	38.4
CADASIL	CAD-34	53	Female	CAD-34	52.5
Migraines with Aura	CAD-35	38	Female	CAD-35	27.4
CADASIL	CAD-36	60	Male	CAD-36	46.5
Migraines with Aura	CAD-37	34	Female	CAD-37	40.3
Migraines with Aura	CAD-38	28	Female	CAD-38	24.9
Migraines with Aura	CAD-39	31	Female	CAD-39	32.4
Migraines with Aura	CAD-40	40	Female	CAD-40	20.6
Migraines with Aura	CAD-41	36	Female	CAD-41	20.6
Migraines with Aura	CAD-42	62	Female	CAD-42	28.8
Migraines with Aura	CAD-43	44	Female	CAD-43	53.8
Migraines with Aura	CAD-44	51	Female	CAD-44	42.3
CADASIL	CAD-45	72	Female	CAD-45	46.5
CADASIL	CAD-46	49	Female	CAD-46	34.0
CADASIL	Roch-7	82	Female	ROCH-7	46.5
CADASIL	Roch-8	65	Female	ROCH-8	29.5
CADASIL	Roch-14	37	Female	ROCH-14	47.7
CADASIL	Roch-15	63	Female	ROCH-15	42.3

Mean CGRP levels found among the CADASIL group was 31.5 pg/mL, among migraine with aura group was 25.6 pg/mL, and among the controls was 23.6 pg/mL

5 (Figure 1).

Example 3: Treating a Human having CADASIL

A human identified as having CADASIL is administered one or more CGRP inhibitors (*e.g.*, erenumab). After administration of a CGRP inhibitor, the severity of migraine headaches, small subcortical strokes, and/or vascular dementia in the human is
5 reduced.

Example 4: Slowing the Progression of CADASIL in a Human

A human identified as having CADASIL is administered one or more CGRP polypeptide inhibitors (*e.g.*, erenumab) during the migraine phase of CADASIL. After administration of a CGRP inhibitor, the development of small subcortical strokes and/or
10 vascular dementia in the human is delayed or eliminated.

OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims.
15 Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method for treating a mammal having a leukodystrophy, wherein said method comprises administering a composition comprising a calcitonin gene-related peptide (CGRP) inhibitor to said mammal to reduce one or more symptoms of said leukodystrophy in said mammal.
2. The method of claim 1, wherein said mammal is a human.
3. The method of any one of claims 1-2, wherein said leukodystrophy is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).
4. The method of claim 3, wherein said composition is administered to said mammal during a migraine phase of said CADASIL.
5. The method of any one of claims 3-4, wherein said one or more symptoms of CADASIL are selected from the group consisting of migraine headaches, small subcortical strokes, and vascular dementia.
6. The method of any one of claims 1-5, wherein said CGRP inhibitor is an antibody.
7. The method of any one of claims 1-5, wherein said CGRP inhibitor is a small molecule.
8. The method of any one of claims 1-7 wherein said CGRP inhibitor specifically binds CGRP.
9. The method of any one of claims 1-7, wherein said CGRP inhibitor specifically binds a CGRP receptor.
10. The method of claim 9, wherein said CGRP inhibitor is erenumab.

11. The method of any one of claims 1-10, wherein said composition comprises from about 70 mg to about 140 mg of said CGRP inhibitor.
12. The method of any one of claims 1-11, wherein said composition is administered to said mammal once a month.
13. The method of any one of claims 1-12, wherein said composition is administered to said mammal by subcutaneous injection.
14. The method of claim 13, wherein said subcutaneous injection is administered to the abdomen, thigh, or upper arm of said mammal.
15. A method for slowing the progression of a leukodystrophy, wherein said method comprises administering a composition comprising a calcitonin gene-related peptide (CGRP) inhibitor to a mammal identified as having said leukodystrophy.
16. The method of claim 15, wherein said mammal is a human.
17. The method of any one of claims 15-16, wherein said leukodystrophy is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).
18. The method of claim 17, wherein said composition is administered to said mammal during a migraine phase of said CADASIL.
19. The method of any one of claims 15-18, wherein said CGRP inhibitor is an antibody.
20. The method of any one of claims 15-18, wherein said CGRP inhibitor is a small molecule.

21. The method of any one of claims 15-20, wherein said CGRP inhibitor specifically binds CGRP.
22. The method of any one of claims 15-20, wherein said CGRP inhibitor specifically binds a CGRP receptor.
23. The method of claim 22, wherein said CGRP inhibitor is erenumab.
24. The method of any one of claims 15-23, wherein said composition comprises from about 70 mg to about 140 mg of said CGRP inhibitor.
25. The method of any one of claims 15-24, wherein said composition is administered to said mammal once a month.
26. The method of any one of claims 15-25, wherein said composition is administered to said mammal by subcutaneous injection.
27. The method of claim 26, wherein said subcutaneous injection is administered to the abdomen, thigh, or upper arm of said mammal.

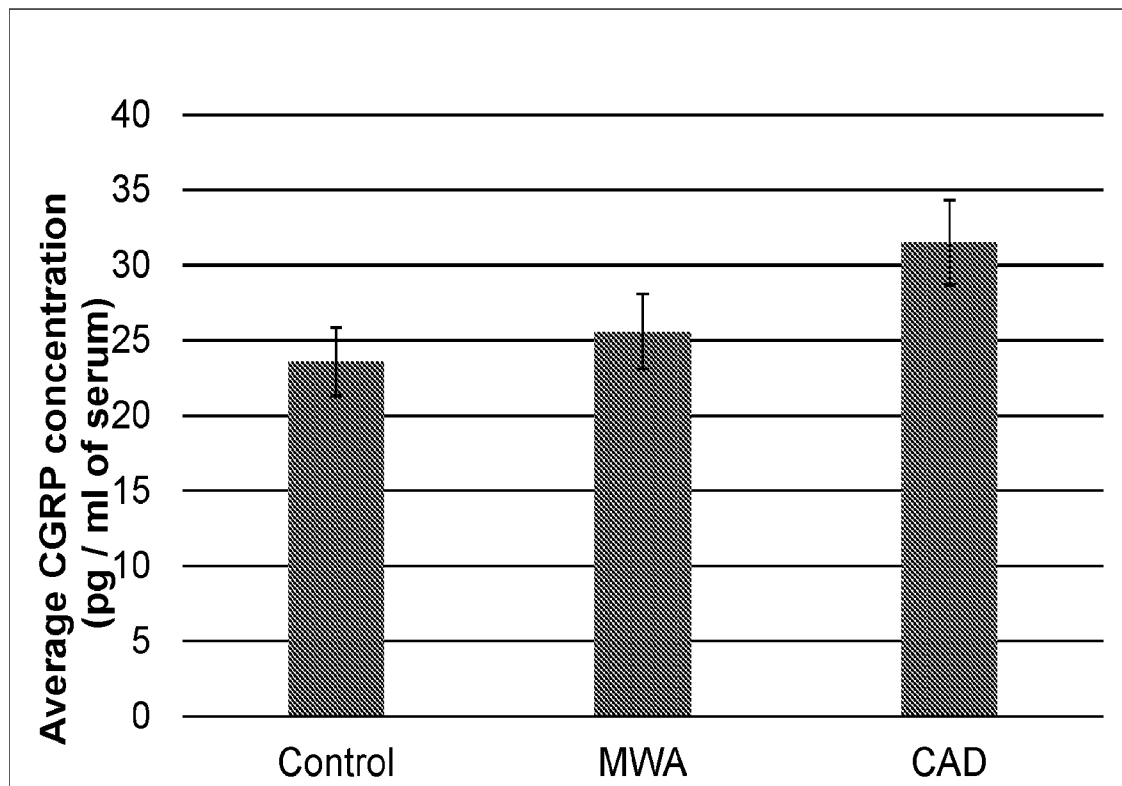


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2019/068731

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.: 5-14, 19-27
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:

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 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.:

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2019/068731

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/519; A61K 38/16; A61P 25/28; C07K 14/00; C07K 14/47; C07K 14/705 (2020.01)

CPC - A61K 31/7076; A61K 38/00; A61K 45/06; A61K 47/6811; A61K 47/6851; A61K 47/6871 (2020.02)

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)

See Search History document

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

USPC - 424/139.1; 530/350 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	WO 2018/119001 A1 (FRED HUTCHINSON CANCER RESEARCH CENTER) 28 June 2018 (28.06.2018) entire document	1, 2, 15, 16 ----- 3, 4, 17, 18
Y	US 2017/0119899 A1 (THE JOHNS HOPKINS UNIVERSITY et al) 04 May 2017 (04.05.2017) entire document	3, 4, 17, 18
Y	WO 2007/076336 A1 (ELI LILLY AND COMPANY et al) 05 July 2007 (05.07.2007) entire document	4, 18
A	BOHM et al. "Migraine Headache: Updates and Future Developments," Mayo Clinic Proceedings, 01 November 2018 (01.11.2018), Vol. 93, Iss. 11, Pgs. 1648-1653. entire document	1-4, 15-18
A	ERDENER et al. "Modelling Headache and Migraine and its Pharmacological Manipulation," British Journal of Pharmacology, 25 February 2014 (25.02.2014), Vol. 171, Iss. 20, Pgs. 4575-4594. entire document	1-4, 15-18
A	MAASSENVANDEBRINK et al. "Calcitonin Gene-Related Peptide (Receptor) Antibodies: An Exciting Avenue for Migraine Treatment," Genome Medicine, 22 February 2018 (22.02.2018), Vol. 10, Iss. 10, Pgs. 1-3. entire document	1-4, 15-18

☐ 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

23 February 2020

Date of mailing of the international search report

12 MAR 2020

Name and mailing address of the ISA/IIS

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