PTO/SB/05 (08-08)
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U.S. Patent and Trademark Office. U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	**2159.3210002/JMC/MRG/U-S**
First Inventor	**Matvey E. LUKASHEV**
Title	**Treatment for Multiple Sclerosis**
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (e.g., PTO/SB/17)
2. ☐ **Applicant claims small entity status.** See 37 CFR 1.27.
3. ☒ **Specification** [*Total Pages* 38]
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. ☒ **Drawing(s)** (*35 U.S.C. 113*) [*Total Sheets* 4]
5. **Oath or Declaration** [*Total Sheets* 2]
   a. ☐ Newly executed (original or copy)
   b. ☒ A copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☒ **Application Data Sheet.** See 37 CFR 1.76
7. ☐ **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape Table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission**
   (if applicable, items a. – c. are required)
   a. ☐ Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☒ Paper
   c. ☐ Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents**
P.O. Box 1450
Alexandria VA 22313-1450

ACCOMPANYING APPLICATION PARTS

9. ☐ **Assignment Papers** (cover sheet (PTO-1595) & document(s))
   Name of Assignee **Biogen Idec MA Inc.**
10. ☐ **37 CFR 3.73(b) Statement** *(when there is an assignee)* ☐ **Power of Attorney**
11. ☐ **English Translation Document** *(if applicable)*
12. ☒ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☒ Copies of foreign patent documents, publications, & other information
13. ☒ **Preliminary Amendment**
14. ☐ **Return Receipt Postcard** (MPEP 503)
    (Should be specifically itemized)
15. ☐ **Certified Copy of Priority Document(s)**
    (if foreign priority is claimed)
16. ☐ **Nonpublication Request** under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. ☒ Other: **Authorization under 37 CFR 1.136(a)(3)**
    See 1 in Addendum

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 12/526,296

Prior application information: *Examiner* John D. ULM *Art Unit:* 1649

19. CORRESPONDENCE ADDRESS

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Addendum

1. Authorization to Permit Access to Application by Participating Offices (PTO/SB/39);
2. Certification and Request for Prioritized Examination Under 37 C.F.R. § 1.102(e);
3. Request for Transfer of a Computer Readable Form Under 37 CFR 1.821(e);
4. First Supplemental Information Disclosure Statement;
5. Second Supplemental Information Disclosure Statement;
6. Third Supplemental Information Disclosure Statement.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/SB/424 (12-11)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Matvey E. LUKASHEV	Nonprovisional Application Number (if known):	To be assigned
Title of Invention:	Treatment for Multiple Sclerosis (As Amended)		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☑ **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed oath or declaration under 37 CFR 1.63 is filed with the application.

II. ☐ **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature Marsha A. Rose	Date 2/12/2012
Name (Print/Typed) Marsha A. Rose	Practitioner Registration Number 58,403

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

☑ *Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: *To be assigned*
LUKASHEV *et al.*	Art Unit: *To be assigned*
Appl. No.: To be assigned	Examiner: *To be assigned*
(*Continuation of Appl. No. 12/526,296; § 371(c) Date: January 13, 2011*)	Atty. Docket: 2159.3210002/JMC/MRG/U-S
Filed: Herewith	
For: **Treatment for Multiple Sclerosis (As Amended)**	

Authorization to Treat a Reply as Incorporating an Extension of Time Under 37 C.F.R. § 1.136(a)(3)

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

The U.S. Patent and Trademark Office is hereby authorized to treat any concurrent or future reply that requires a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. The U.S. Patent and Trademark Office is hereby authorized to charge all required extension of time fees to our Deposit Account No. 19-0036, if such fees are not otherwise provided for in such reply.

Respectfully submitted,

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APPLICATION DATA SHEET

Electronic Version v14
Stylesheet Version v14.1

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Title of Invention:	Treatment for Multiple Sclerosis
Application Type:	regular, utility
Attorney Docket Number:	2159.3210002/JMC/MRG/U-S

Botanic Information:

Publication Information:
Suggested Figure for Publication -
Suggested Classification -
Suggested Technology Center -
Total Number of Drawing Sheets - 4

Representative Information:

Domestic Priority Information:

This is a Continuation of US application number 12/526,296, having a § 371(c) date of 2011-01-13, now pending.

US application number 12/526,296, having a § 371(c) date of 2011-01-13, is the National Stage of international application number PCT/US2008/001602, filed 2008-02-07, which claims the benefit of US provisional application number 60/888,921, filed 2007-02-08.

Foreign Priority Information:

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COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **Treatment for Multiple Sclerosis (as amended)**, the specification of which:

[] is attached hereto.
[] was filed on _____ as Application No. _____.
[x] was filed as PCT International Application No. PCT/US2008/001602, filed on February 7, 2008, and as amended herewith in U.S. Application No. 12/526,296, which is the national stage entry of PCT/US2008/001602 and having a § 371(c) date of January 13, 2011.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim the benefit under Title 35, United States Code, §119(e)(1) of any United States provisional application(s) listed below:

U.S. Serial No.	Filing Date	Status
60/888,921	**February 8, 2007**	**Expired**

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Serial No.	Filing Date	Status

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Country	Application No.	Filing Date	Priority Claimed
			[ ] Yes [ ] No

Combined Declaration and Power of Attorney

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

All Attorneys and Agents associated with

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Direct all telephone calls to John M. Covert at telephone number (202) 772-8673.

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☒ For Assigned Inventions: I understand that the purpose of making this appointment is to permit prosecution of patent applications for the above-identified invention for the benefit of my assignee, and that this appointment does not create a personal attorney-client relationship between me and these appointees.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

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November 15, 2013

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60/888,921 8 February 2007 (08.02.2007) US

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Published:
— *without international search report and to be republished upon receipt of that report*

(54) Title: NRF2 SCREENING ASSAYS AND RELATED METHODS AND COMPOSITIONS

(57) Abstract: Provided are certain methods of screening, identifying, and evaluating neuroprotective compounds useful for treatment of neurological diseases, such as, e.g., multiple sclerosis (MS). The compounds described upregulate the cellular cytoprotective pathway regulated by Nrf2. Also provided are certain methods of utilizing such compounds in therapy for neurological disease, particularly, for slowing or reducing demyelination, axonal loss, or neuronal and oligodendrocyte death.

WO 2008/097596 A2

Nrf2 SCREENING ASSAYS AND RELATED METHODS AND COMPOSITIONS

[0001] Provided are certain compounds for treating neurological diseases, including demyelinating neurological diseases, such as, e.g., multiple sclerosis.

[0002] Multiple sclerosis (MS) is an autoimmune disease with the autoimmune activity directed against central nervous system (CNS) antigens. The disease is characterized by inflammation in parts of the CNS, leading to the loss of the myelin sheathing around neuronal axons (demyelination), loss of axons, and the eventual death of neurons, oligodenrocytes and glial cells.

[0003] An estimated 2,500,000 people in the world suffer from MS. It is one of the most common diseases of the CNS in young adults. MS is a chronic, progressing, disabling disease, which generally strikes its victims some time after adolescence, with diagnosis generally made between 20 and 40 years of age, although onset may occur earlier. The disease is not directly hereditary, although genetic susceptibility plays a part in its development. Relapsing-remitting MS presents in the form of recurrent attacks of focal or multifocal neurologic dysfunction. Attacks may occur, remit, and recur, seemingly randomly over many years. Remission is often incomplete and as one attack follows another, a stepwise downward progression ensues with increasing permanent neurological deficit.

[0004] Although various immunotherapeutic drugs can provide relief in patients with MS, none is capable of reversing disease progression, and some can cause serious adverse effects. Most current therapies for MS are aimed at the reduction of inflammation and suppression or modulation of the immune system. As of 2006, the available treatments for MS reduce inflammation and the number of new episodes but not all have an effect on disease progression. A number of clinical trials have shown that the suppression of inflammation in chronic MS rarely significantly limits the accumulation of disability through sustained disease progression, suggesting that neuronal damage and inflammation are independent pathologies. Promoting CNS remyelination as a repair mechanism and otherwise preventing axonal loss and

neuronal death are some of the important goals for the treatment of MS. For a comprehensive review of MS and its current therapies, see, e.g., McAlpine's Multiple Sclerosis, by Alastair Compston et al., 4th edition, Churchill Livingstone Elsevier, 2006.

[0005] "Phase 2 enzymes" serve as a protection mechanism in mammalian cells against oxygen/nitrogen species (ROS/RNS), electrophiles and xenobiotics. These enzymes are not normally expressed at their maximal levels and, their expression can be induced by a variety of natural and synthetic agents. Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor responsible for the induction of a variety of important antioxidant and detoxification enzymes that coordinate a protective cellular response to metabolic and toxic stress.

[0006] ROS/RNS are most damaging in the brain and neuronal tissue, where they attack post-mitotic (i.e., non-dividing) cells such as glial cells, oligodendocytes, and neurons, which are particularly sensitive to free radicals. This process leads to neuronal damage. Oxidative stress has been implicated in the pathogenesis of a variety of neurodegenerative diseases, including ALS, Alzheimer's disease (AD), and Parkinson's disease (PD). For review, see, e.g., van Muiswinkel et al., Curr. Drug Targets CNS--Neurol. Disord., 2005, 4:267-281. An anti-oxidative enzyme under control of Nrf2, NQO1 (NAD(P)H dehydrogenase, quinone (1), was recently reported to be substantially upregulated in the brain tissues of AD and PD subjects (Muiswinkel et al., Neurobiol. Aging, 2004, 25: 1253). Similarly, increased expression of NQO1 was reported in the ALS subjects' spinal cord (Muiswinkel et al., Curr. Drug Targets--CNS. Neurol. Disord., 2005, 4:267-281) and in active and chronic lesions in the brains of patients suffering from MS (van Horssen et al., Free Radical Biol. & Med., 2006, 41 311-311). These observations indicate that the Nrf2 pathway may be activated in neurodegenerative and neuroinflammatory diseases as an endogenous protective mechanism. Indeed, most recently, it has been reported that induced activation of Nrf2-dependent genes by certain cyclopenanone-based compounds (NEPP) counters the toxic effects of metabolic inhibition and ROS/RNS production in

the brain and protects neurons from death in vitro and in vivo (see Satoh et al., PNAS, 2006, 103(3):768-773).

[0007] Additionally, many publications have reported neuroprotective effects of compounds in natural plant-derived compounds ("phytochemicals"), including α-tocopherol (vitamin E), lycopene (tomatoes), resveratrol (red grapes), sulforaphane (broccoli), EGCG (green tea), etc. For review, see Mattson and Cheng, Trends in Neurosci., 2006, 29(11):632-639. Originally, the action of these compounds was attributed to their anti-oxidant properties. However, while most anti-oxidants are effective only at high concentrations, at least some of these compounds appear to exert neuroprotective effects at much lower doses. Emerging evidence suggests that these compounds may exert their neuroprotective effects by activating cellular stress-response pathways, including the Nrf2 pathway, resulting in the upregulation of neuroprotective genes. However, the exact mechanism of action of these compounds remains poorly understood.

[0008] To date, more than 10 different chemical classes of inducers of Nrf2 pathway have been identified including isothiocyanates and their thiol addition products, dithiocarbamates, as well as 1,2-dithiole-3-thiones, trivalent arsenic derivatives (e.g., phenyl arsenoxide), heavy metals, certain conjugated cyclic and acyclic polyenes (including porphyrins, chlorophyllins, and chlorophyll), and vicinal dimercaptans. These inducers have few structural similarities. They are mostly electrophiles, and all can react chemically with thiol groups by alkylation, oxidation, or reduction, suggesting that the intracellular sensor for inducers is likely to contain very highly reactive (cysteine) thiols. The inducers can modify thiol groups by a variety of mechanisms including: alkylation (Michael addition acceptors, isothiocyanates, quinones); oxidation (e.g., peroxides and hydroperoxides); and direct reaction with thiol/disulfide linkages (e.g., vicinal dithiols such as 1,2-dimercaptopropanol, lipoic acid). These diverse response mechanisms provide plasticity for cellular responses to a variety of electrophilic and oxidant stressors.

[0009] Provided are methods that comprise at least one of the following methods:

1) methods of screening for at least one new candidate compound for treating a neurological disease;
2) methods of evaluating neuroprotective properties of at least one drug candidate for treating a neurological disease;
3) methods of comparing (e.g., for bioequivalence) at least two pharmaceutical compositions which comprise fumaric acid derivatives;
4) methods of treating a neurological disease by administering to the subject in need thereof at least one compound that is partially structurally similar to DMF or MMF; and
5) methods of treating a neurological disease by a combination therapy that comprises administration of at least one first compound that upregulates the Nrf2 pathway and at least one second compound that does not upregulate the Nrf2 pathway.

[0010] In some embodiments, the neurological disease is a neurodegenerative disease such as, for example, ALS, Parkinson's disease, Alzheimer's disease, and Huntington's disease. In some embodiments the neurological disease is MS or another demyelinating neurological disease.

[0011] In some embodiments, the methods 1-3 further comprise:

a) contacting a cell with the test compound, and
b) determining whether the Nrf2 pathway is upregulated in the cell.

In some embodiments, the methods may further comprise:

c) determining whether the test compound slows or prevents demyelination, axonal loss, and/or neuronal death, and/or
d) selecting the test compound as a candidate for treating neurodegeneration in a neurological disease if 1) the Nrf2 pathway is upregulated and 2) demyelination, axonal loss, and/or neuronal death are/is prevented or slowed.

[0012] In some embodiments, the methods 1-3 comprise contacting a cell with at least one test compound and determining whether the Nrf2 pathway is upregulated in the cell. In such methods, an upregulation of the Nrf2 pathway above a threshold

(e.g., by at least 30% over a control) indicates that the at least one compound has at least one biological property beneficial in treating a neurological disease (e.g., neuroprotective properties). In some embodiments, the upregulation of the Nrf2 pathway is assessed (in vivo and/or in vitro) by at least one of the following:

i) expression levels of endogenously produced and/or exogenously introduced Nrf2;
ii) subcellular localization and/or nuclear translocation of Nrf2;
iii) expression levels and/or activity of one or more genes under control of Nrf2 (e.g., endogenous NQO1) or an Nrf2-regulated reporter gene in an artificial reporter construct;
iv) levels of Nrf2 binding to the Nrf2-binding DNA element ARE;
v) stability of Nrf2/Keap1 complexes; and
vi) modification (e.g., alkylation) levels of Keap1 and/or at least one other Nrf2/Keap1-associated proteins.

[0013] In some embodiments of methods 1-3, the compounds that are being screened, evaluated, or compared comprise at least one member of at least one of the following classes of compounds: mild alkylating agents, Michael addition acceptors, and compounds that are metabolized upon administration to Michael addition acceptors. In some embodiments, the Michael addition acceptor has the structure of Formula I, II, III, or IV set forth below.

[0014] In some embodiments method 1 comprises:

a) contacting a cell with a plurality of test compounds,
b) determining whether the Nrf2 pathway is upregulated in the cell, and
c) selecting from the plurality of compounds at least one compound that upregulates the Nrf2 pathway,

wherein an upregulation of the Nrf2 pathway by the selected at least one compound indicates that the selected at least one compound may be useful for treating a neurological disease. The plurality of compounds may be represented, e.g., by a combinatorial chemical library, and the method may be performed, e.g., by high-throughput screening.

[0015] In some embodiments method 2 comprises:

a) contacting a cell with the at least one drug or drug candidate, and

b) determining whether the Nrf2 pathway is upregulated in the cell, wherein an upregulation of the Nrf2 pathway by the at least one drug or drug candidate indicates that the at least one drug or drug candidate is useful for neuroprotection in treating a human having a neurological disease.

[0016] In some embodiments method 3 comprises:

a) contacting a cell with a first composition comprising at least one test compound, and

b) comparing the level of Nrf2 pathway upregulation in the cell by the at least one test compound to the corresponding level of the Nrf2 pathway upregulation in a control cell treated with a second composition comprising at least one of DMF and MMF.

[0017] In some embodiments of method 3, the test compound is fumaric acid, a salt thereof, or a fumaric acid derivative. In some embodiments, the first composition comprises DMF, MMF, or both. In some embodiments, the dose and/or the formulation of the first composition differs from the dose and/or the formulation of the second composition.

[0018] In some embodiments, method 3 further comprises:

c) comparing at least one pharmacokinetic parameter (e.g., serum-half-life) of the first and the second compositions.

[0019] In some embodiments method 4 comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound having Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF).

[0020] In some embodiments method 4 provides a method of slowing or preventing neurodegeneration in a patient in need thereof, by administering the compound in an amount and for a period of time sufficient to slow or prevent demyelination, axonal loss, and/or neuronal death, e.g., by at least 30% relative to a control.

[0021] In some embodiments method 5 comprises:

a) administering to the mammal a therapeutically effective amount of at least one first compound that upregulates the Nrf2 pathway, and

b) administering a therapeutically effective amount of at least one second compound that does not upregulate the Nrf2 pathway.

[0022] In some embodiments of method 5, the at least one first compound, used in step (a), is a compound of Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF); and the at least one second compound, which is used in step (b), is an immunosuppressive or an immunomodulatory compound that does not upregulate the Nrf2 pathway (e.g., by more than 30% over a control).

[0023] In some embodiments method 5 comprises administering to the mammal a therapeutically effective amount of a compound of Formula I, II, III, or IV.

[0024] In some embodiments of methods 1-5, the at least onecompound being screened, identified, evaluated, or used for treating a neurological disorder is not fumaric acid or its salt, or a fumaric acid derivative (e.g., DMF or MMF).

[0025] Other features and embodiments of the invention will be apparent from the following description and the claims.

BRIEF DESCRIPTION OF THE FIGURES

[0026] Figure 1 demonstrates that DMF and MMF are activators of Nrf2 at concentrations within clinical exposure range (cells in culture).

[0027] Figure 2 shows results of RNAi experiments.

[0028] Figure 3 shows evidence of Nrf2 activation by DMF and MMF In vivo.

[0029] Figure 4 shows evidence of Nrf2 activation by DMF and MMF In vivo.

[0030] Fumaric acid esters, such as DMF, have been proposed for treatment of MS (see, e.g., Schimrigk et al., Eur. J. Neurol., 2006, 13(6):604-10; Drugs R&D, 2005, 6(4):229-30).

[0031] Provided are, among other things, means for identifying compounds with a new therapeutic modality useful in at least one of multiple neurological indications and, optionally, complementary to other drugs for the treatment of a neurological disease, including a number of currently used immunomodulators.

[0032] DMF is a member of a large group of anti-oxidant molecules known for their cytoprotective and anti-inflammatory properties. These molecules also share the property of the Nrf2 pathway activation. Thus, the finding that DMF activates the Nrf2 pathway in conjunction with the neuroprotective effects of DMF further offers a rationale for identification of structurally and/or mechanistically related molecules that would be expected to be therapeutically effective for the treatment of neurological disorders, such as, e.g., MS.

[0033] Certain terms are defined in this section; additional definitions are provided throughout the description.

[0034] The terms "activation" and "upregulation," when used in reference to the Nrf2 pathway, are used interchangeably herein.

[0035] The terms "disease" and "disorder" are used interchangeably herein.

[0036] The term "a drug for treating a neurological disease" refers to a compound that has a therapeutic benefit in a specified neurological disease as shown in at least one animal model of a neurological disease or in human clinical trials for the treatment of a neurological disease.

[0037] The term "neuroprotection" and its cognates refer to prevention or a slowing in neuronal degeneration, including, for example, demyelination and/or axonal loss, and/or, neuronal and/or oligodendrocyte death. Neuroprotection may occur through several mechanisms, e.g., through reducing inflammation, providing neurotrophic factors, scavenging free radicals, etc. As used herein, a compound is considered neuroprotective if it (1) upregulates the Nrf2 pathway above a certain threshold and (2) provides neuroprotection, regardless of possible other mechanisms of action.

[0038] The terms "treatment," "therapeutic method," "therapeutic benefits," and the like refer to therapeutic as well as prophylactic/preventative measures. Thus, those in need of treatment may include individuals already having a specified disease and those who are at risk for acquiring that disease.

[0039] The terms "therapeutically effective dose" and "therapeutically effective amount" refer to that amount of a compound which results in at least one of prevention

or delay of onset or amelioration of symptoms of a neurological disorder in a subject or an attainment of a desired biological outcome, such as reduced neurodegeneration (e.g., demyelination, axonal loss, and neuronal death) or reduced inflammation of the cells of the CNS.

[0040] In one aspect, provided are methods of evaluating neuroprotective properties of test compounds, including the following methods:

1) methods of screening for new candidate compounds that may be useful for treating a neurological disease;
2) methods of evaluating neuroprotective properties of drugs and candidates that are used or proposed for treating a neurological disease;
3) methods of comparing (e.g., for bioequivalence) two or more pharmaceutical compositions which contain fumaric acid derivatives;

[0041] In some embodiments, methods 1-3 may comprise:

a) contacting a cell with the test compound,
b) determining whether the Nrf2 pathway is upregulated in the cell,

and, in some embodiments, additionally performing the following step(s):

c) determining whether the test compound slows or prevents demyelination, axonal loss, and/or neuronal death, and/or
d) selecting the test compound as a candidate for treating neurodegeneration in a neurological disease if 1) the Nrf2 pathway is upregulated and 2) demyelination, axonal loss, and/or neuronal death are/is prevented or slowed.

Method 1

[0042] In some embodiments the methods of screening for a candidate compound for treating a neurological disease comprise:

a) contacting a cell with a plurality of test compounds,
b) determining whether the Nrf2 pathway is upregulated in the cell, and
c) selecting from the plurality of compounds at least one compound that upregulates the Nrf2 pathway,

wherein an upregulation of the Nrf2 pathway by the selected at least one compound indicates that the selected at least one compound may be useful for treating a neurological disease. For example, the plurality of compounds may be represented by a combinatorial chemical library, and the screening method may be performed by a high-throughput screening as described in, e.g., High-Throughput Screening in Drug Discovery (Methods and Principles in Medicinal Chemistry), by Jörg Hüser (ed.), John Wiley & Sons (2006).

[0043] Combinatorial libraries of compounds are also described in, e.g., Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries (Tetrahedron Organic Chemistry) Ian Salusbury (ed.), Elsevier (1998); Combinatorial Libraries: Synthesis, Screening and Application Potential (Library Binding), by Riccardo Cortese (ed.), Walter de Gruyter (1995). The libraries of compounds may be, for example, quinone libraries and other libraries as described in Mittoo, Comb. Chem. & High Throughput Screen, 2006, 9:421-423.

[0044] In some embodiments, the at least one compound or plurality of compounds being screened and/or selected comprises at least one compound selected from at least one of the following groups of compounds: mild alkylating agents, Michael addition acceptors or compounds that are metabolized to Michael addition acceptors, including compounds of Formulas I, II, III, or IV.

[0045] In some of the embodiments, the at least one compound is selected from fumaric acid, its salts, and fumaric acid derivatives.

Method 2

[0046] Also provided are methods of evaluating neuroprotective properties of at least one drug or drug candidate for treating at least one neurological disease. Such methods comprise:

a) contacting a cell with the at least one drug or drug candidate, and

b) determining whether the Nrf2 pathway is upregulated in the cell,

wherein the upregulation of the Nrf2 pathway by the at least one drug or drug candidate indicates that the at least one drug or drug candidate is neuroprotective in treating a human having a neurological disease.

[0047] In some embodiments, the upregulation of the Nrf2 pathway by the at least one drug or drug candidate indicates that the at least one drug or drug candidate has at least one activity selected from slowing demyelination, slowing the loss of axons, and slowing the rate of neuronal death.

[0048] In some embodiments, the method of evaluating at least one drug or drug candidate comprises an additional step:

c) evaluating demyelination, loss of axons, and/or neuronal death.

[0049] In some embodiments, steps a) and c) are performed in vivo in at least one model of a neurological disease, e.g., as described below.

[0050] In other embodiments, particularly those in which the neurological disease is multiple sclerosis or another demyelinating disease, the evaluated at least one drug or drug candidate for a neurological disease is chosen from the following: FTY720 (2-(4-octylphenethyl)-2-aminopropane-1,3-diol; Novartis); anti-IL12 antibody (e.g., ABT-874; Abbott Laboratories); GSK683699 (GSK/Tanabe); NeuroVax (Immune Response Corp.; Darlington, Curr. Opin. Mol. Ther., 2005, 7(6):598-603); anti-CCR2 antibody (e.g., MLN 1202; Millennium); interferon β-1a (e.g., Avonex®; Biogen Idec); anti-α4-integrin antibody (e.g., Tysabri®; Biogen Idec/Elan); anti-CD20 antibody (e.g., Rituxan® (Biogen Idec/Genentech); TV 5010 (Teva); NBI-788 (Neurocrine); MBP8298 (BioMS (see Warren et al., Eur. J. Neurol., 2006, 13(8):887-95); Mylinax (Oral Cladribine; 2-chlorodeoxyadenosine; Serono/IVAX); Teriflunomide ((Z)-2-cyano-N-(4-(trifluoromethyl)phenyl)-3-hydroxybut-2-enamide; Sanofi-Aventis); Temsirolimus (Wyeth); Laquinimod (5-chloro-N-ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-N-phenylquinoline-3-carboxamide; Active Biotech/Teva); and interferon tau (Tauferon; Pepgen).

[0051] In some embodiments, the at least one drug or drug candidate being evaluated is at least one compound selected from at least one class selected from a mild alkylating agent, a Michael addition acceptor, and a compound that is metabolized to a Michael addition acceptor, including compounds of Formulas I, II, III, or IV.

[0052] In some of the embodiments, the compound is fumaric acid, its salt, or a fumaric acid derivative.

Method 3

[0053] Also provided are methods of comparing (e.g., for bioequivalence) at least two pharmaceutical compositions. Such methods comprise:

a) contacting a cell with at least one first composition comprising a test compound, and

b) comparing the level of the Nrf2 pathway upregulation in the cell by the test compound to the corresponding level of the Nrf2 pathway upregulation in a cell treated with at least one second composition ("comparator composition") comprising DMF, MMF, or both.

[0054] In some embodiments, substantially dissimilar levels of upregulation by the at least one first and at least one second compositions indicate that the compositions are not bioequivalent.

[0055] In some embodiments, the test compound is fumaric acid, its salt thereof, a fumaric acid derivative, or mixtures thereof. In some embodiments, the first composition comprises at least one of DMF, MMF, and both DMF and MMF. In some embodiments, the dose and/or the formulation of the at least one first composition differs from the dose and/or the formulation of the at least one second composition. The at least one first composition may be a controlled release composition such as, e.g., compositions described in WO 2006/037342.

[0056] In some embodiments, the method further comprises and additional step:

c) comparing at least one pharmacokinetic parameter of the at least one first and the at least one second compositions.

[0057] Pharmacokinetic parameters and methods for evaluating the same are well known and are described in, e.g., Pharmacokinetics, Second Edition (Drugs and the Pharmaceutical Sciences) by Milo Gibaldi et al. (eds.), Informa Healthcare (1982). Examples of such pharmacokinetic parameters that can be evaluated include serum half-life, clearance, and volume distribution.

[0058] In some embodiments, substantially dissimilar pharmacokinetic parameter(s) of the a least one first and at least one second compositions indicate that the compositions are not bioequivalent.

[0059] In some embodiments, the test compound being evaluated is a mild alkylating agent, and more specifically, a Michael addition acceptor, or a compound that is metabolized to a Michael addition acceptor.

[0060] In some of the embodiments, the test compound is fumaric acid or its salt, or a fumaric acid derivative.

[0061] Also provided are methods of treating a mammal who has or is at risk for developing a neurological disease, including the following methods:

4) methods of treating a neurological disease by administering to the subject in need thereof at least one compound that is partially structurally similar to DMF or MMF (including compounds selected using methods 1-3 described above) ; and
5) methods of treating a neurological disorder by a combination therapy that includes administration of a first compound that does not upregulate the Nrf2 pathway and a second compound that upregulates the Nrf2 pathway.

Method 4

[0062] Also provided are methods of treating a neurological disease by administering to the subject in need thereof at least one compound that is at least partially structurally similar to DMF and/or MMF.

[0063] In some embodiments of method 4, a method of treating a mammal who has or is at risk for a neurological disease is provided. The methods comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound which has Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF).

[0064] In some embodiments of method 4, a method of slowing or preventing neurodegeneration (more specifically, e.g., demyelination, axonal loss, and/or neuronal death) in a subject in need thereof, by administering the at least one compound in an amount and for a period of time sufficient to do at least one of slow or

prevent demyelination, slow or prevent axonal loss, and alow or prevent neuronal death, e.g., by at least 30%, 50%, 100% or higher over a control over a period of at least 5, 10, 12, 20, 40, 52, 100, or 200 weeks, or more.

Method 5

[0065] Also provided are methods of treating a mammal having a neurological disease by combination therapy. In some embodiments such methods comprise:

a) administering to the mammal a therapeutically effective amount of at least one first compound that upregulates the Nrf2 pathway, and
b) administering a therapeutically effective amount of at least one second compound that does not upregulate the Nrf2 pathway.

[0066] In some of embodiments of method 5, the at least one first compound, used in step (a), is a compound of Formula I, II, III, or IV, e.g., DMF or MMF; and the at least one second compound, which is used in step (b), is an immunosuppressive or an immunomodulatory compound that does not upregulate the Nrf2 pathway (e.g., by more than 30%, 50%, 100% over a control).

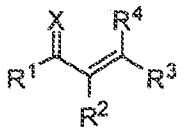
[0067] In some embodiments of method 5, the method comprises administering to the mammal a therapeutically effective amount of a compound of Formula I, II, III, or IV.

[0068] In method 5, the at least one first compound and the at least one second compound may be administered concurrently (as separate compositions or a mixed composition) or consecutively over overlapping or non-overlapping intervals. In the sequential administration, the at least one first compound and the at least one second compound can be administered in any order. In some embodiments, the length of an overlapping interval is more than 2, 4, 6, 12, 24, or 48 weeks, for example.

[0069] Michael addition acceptors generally include olefins or acetylenes conjugated to an electron withdrawing group, such as carbonyl containing groups, thiocarbonyl containing groups, cyano, sulfonyl, sulfonamido, amido, formyl, keto, and nitro. Exemplary carbonyl groups include carboxylic acid esters and carboxylic acid.

[0070] In some embodiments of methods 1-5, the at least one compound being screened, identified, evaluated, or used for treating a neurological disorder is selected from a mild alkylating agent, aMichael addition acceptor, and a compound that is metabolized to a Michael addition acceptor.

[0071] In some embodiments, the Michael addition acceptor has the structure of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is O; S; C(R)(C_{1-12})alkyl; or C(R)(C_{2-12})alkenyl, wherein R is H, (C_{1-12})alkyl or (C_{2-12})alkenyl;

R^1, R^2, R^3 and R^4 are independently selected from: H; OH; O^-; CO_2H, CO_2^-; SH; S^-; SO_2H, SO_2^-; (C_{1-24})alkyl; (C_{1-24})alkenyl; (C_{6-50})aryl, CO_2(C_{1-24})alkyl; SO_2(C_{1-24})alkyl; CO_2(C_{1-24})alkenyl; SO_2(C_{1-24})alkenyl; CO_2Y, wherein Y is psoralen-9-yl, retinyl, alpha-tocopherol, calciferyl, corticostreoid-21-yl or monosaccarid-ω-yl; (C_{1-24})alkoxy; (C_{1-24})alkenyloxy; (C_{6-50})aryloxy; (C_{1-24})alkylthio; (C_{1-24})alkenylthio; (C_{6-50})arylthio, amino; amido; arylalkyl; cyano; nitro; sulfonyl; sulfoxido; sulfonamido; formyl; keto; and D and L natural or unnatural amino acids; or any two of X, R^1, R^2 and R^3, and R^4 may be joined together to form a cyclic moiety; and wherein the alkyl, alkoxy, alkenyl, alkenyloxy, aryl and aryloxy groups may be optionally substituted with at least one group chosen from halogen (F, Cl, Br, or I), OH, (C_{1-4})alkoxy, nitro and cyano.

[0072] In some embodiments, the at least one Michael addition acceptor has the structure of Formula I, with the following provisos:

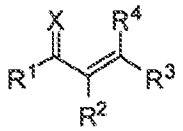
R^1 is selected from: H; OH; O^-; CO_2H, CO_2^-; SH; S^-; SO_2H, SO_2^-; (C_{1-24})alkyl; (C_{1-24})alkenyl; (C_{6-50})aryl; CO_2(C_{1-24})alkyl; SO_2(C_{1-24})alkyl; CO_2(C_{1-24})alkenyl; SO_2(C_{1-24})alkenyl; CO_2Y, wherein Y is psoralen-9-yl, retinyl, alpha-tocopherol, calciferyl, corticostreoid-21-yl or monosaccarid-ω-yl; (C_{1-24})alkoxy; (C_{1-24})alkenyloxy; (C_{6-50})aryloxy; (C_{1-24})alkylthio; (C_{1-24})alkenylthio; (C_{6-50})arylthio;

arylalkyl; amino; amido; cyano; nitro; sulfonyl, sulfoxido; sulfonamido; formyl, keto; and D or L natural or unnatural amino acids; and wherein the alkyl, alkoxy, alkenyl, alkyenyloxy, aryl and aryloxy groups may be optionally substituted with at least one group chosen from halogen (F, Cl, Br, or I), OH, (C_{1-4})alkoxy, nitro and cyano;

R^2 is selected from: H; CO_2H; CO_2^-; SO_2H; SO_2^-; (C_{1-24})alkyl; (C_{1-24})alkenyl; (C_{6-50})aryl; CO_2(C_{1-24})alkyl; SO_2(C_{1-24})alkyl; CO_2(C_{1-24})alkenyl; SO_2(C_{1-24})alkenyl; CO_2Y, wherein Y is psoralen-9-yl, retinyl, alpha-tocopherol, calciferyl, corticostreoid-21-yl or monosaccarid-ω-yl; (C_{1-24})alkoxy; (C_{1-24})alkenyloxy; (C_{6-50})aryloxy; (C_{1-24})alkylthio; (C_{1-24})alkenylthio; (C_{6-50})arylthio, amido; arylalkyl; cyano; nitro; sulfonyl, sulfoxido, sulfonamido; formyl, keto; and D or L natural or unnatural amino acids; wherein the alkyl, alkoxy, alkenyl, alkyenyloxy, aryl and aryloxy groups may be optionally substituted with at least one group chosen from halogen (F, Cl, Br, or I), OH, (C_{1-4})alkoxy, nitro and cyano; and

R^3 and R^4 are independently selected from: H; CO_2H; CO_2^-; SO_2H; SO_2^-; (C_{1-24})alkyl; (C_{1-24})alkenyl; (C_{6-50})aryl; CO_2(C_{1-24})alkyl; SO_2(C_{1-24})alkyl; CO_2(C_{1-24})alkenyl; SO_2(C_{1-24})alkenyl; CO_2Y, wherein Y is psoralen-9-yl, retinyl, alpha-tocopherol, calciferyl, corticostreoid-21-yl or monosaccarid-ω-yl; (C_{1-24})alkoxy; (C_{1-24})alkenyloxy; (C_{6-50})aryloxy; (C_{1-24})alkylthio; (C_{1-24})alkenylthio; (C_{6-50})arylthio; amido; arylalkyl; cyano; nitro; cyano; nitro; sulfonyl; sulfoxido; sulfonamido; formyl; and keto; wherein the alkyl, alkoxy, alkenyl, alkyenyloxy, aryl and aryloxy groups may be optionally substituted with at least one group chosen from halogen (F, Cl, Br, or I), OH, (C_{1-4})alkoxy, nitro and cyano.

[0073] In some embodiments, the at least one Michael addition acceptor has the structure of Formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

X is selected from O; S; C(R)(C_{1-12})alkyl; and C(R)(C_{2-12})alkenyl, wherein R is selected from H; (C_{1-12})alkyl; and (C_{2-12})alkenyl; and R^1, R^2, R^3, and R^4

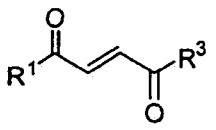
are independently selected from: H; OH; O^-; CO_2H; CO_2^-; (C_{1-12})alkyl; (C_{1-12})alkenyl; and $CO_2(C_{1-12})$alkyl;

or any two of X, R^1, R^2 and R^3 may be joined together to form a cyclic moiety.

[0074] In some embodiments of the compounds of Formulae I-IV, the pharmaceutically acceptable salt is a salt of a metal (M) cation, wherein M can be an alkali, alkaline earth, or transition metal such as Li, Na, K, Ca, Zn, Sr, Mg, Fe, or Mn.

[0075] In some embodiments of methods 1-5, the compounds of Formula I include fumaric acid, its salts, and fumaric acid derivatives.

[0076] In some embodiments, the at least one compound of Formula I has the structure of Formula III:



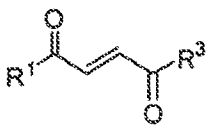
(III),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^3 are independently selected from OH; O^-; (C_{1-24})alkoxy; (C_{1-24})alkenyloxy; (C_{6-50})aryloxy; psoralen-9-yloxy; retinyloxy; alpha-tocopheroloxy; calciferyloxy; corticostreoid-21-yloxy; monosaccarid-ω-yloxy; amino; and a D or L natural or unnatural amino acid; and wherein at least one of the the (C_{1-24})alkoxy; (C_{1-24})alkenyloxy; and (C_{6-50})aryloxy groups may be optionally substituted with at least one group chosen from halogen (F, Cl, Br, or I), OH, (C_{1-4})alkoxy, nitro and cyano.

[0077] Compounds wherein at least one of R^1 and R^3 is derived from a natural or unnatural D or L amino acid are described in U.S. Application Serial Nos. 10/433,295, paragraphs 10 to 11 and 18-28, and 11/421,083, which are incorporated herein by reference.

[0078] In some embodiments, the compound of formula (I) has the structure of Formula IV:



(IV),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^3 are independently selected from OH; O^-; (C_{1-24})alkoxy; allyloxy; vinyloxy; (C_{6-50})aryloxy; psoralen-9-yloxy; retinyloxy; alpha-tocopheroloxy; calciferyloxy; corticostreoid-21-yloxy; monosaccarid-ω-yloxy; amino; and a D or L natural or unnatural amino acid; and wherein at least one of the the (C_{1-24})alkoxy, allyloxy, vinyloxy, and (C_{6-50})aryloxy may be optionally substituted with at least one group chosen from Cl, F, I, Br, OH, (C_{1-4})alkoxy, nitro, and cyano.

[0079] In some embodiments, the "fumaric acid derivative" is chosen from the compounds of Formula III, compounds of Formula IV and the following:

1) fumaric acid amides derived from natural and unnatural amino D or L acids, as described in U.S. Patent Application Serial Nos. 10/433,295, paragraphs 10 to 11 and 18-28, and 11/421,083.

2) a carbocyclic or oxacyclic fumaric acid oligomer as described in U.S. Patent Application Serial No. 10/511,564, paragraphs 15-44; and

3) a glycerol or alkane diol or polyol derivative of fumaric acid as described in U.S. Patents Nos. 4,851,439, 5,149,695, 5,451,667, at cols. 2-4.

[0080] In some embodiments, "fumaric acid derivative" is one or more dialkyl fumarates (e.g., DMF), mono alkyl fumarates (MMF) or salts thereof.

[0081] In some of the embodiments of methods 1-5, the at least one compound being screened, evaluated, compared or used for treating a neurological disorder is not fumaric acid or its salt, or a fumaric acid derivative (e.g., DMF or MMF).

[0082] Nrf2 (Nuclear Factor-E2-related factor 2; for sequence of the Nrf2, see Accession No. AAB32188) is a transcription factor that, upon activation by oxidative stress, binds to the antioxidant response element (ARE), and activates transcription of Nrf2-regulated genes. This pathway has been well characterized for its role in hepatic detoxification and chemoprevention through the activation of phase II gene expression. ARE-regulated genes may also contribute to the maintenance of redox homeostasis by serving as endogenous anti-oxidant systems. At present, the list of Nfr2-regulated genes contains over 200 genes encoding proteins and enzymes involved in detoxification and antioxidant response (Kwak et al., J. Biol. Chem., 2003, 278:8135) such as, e.g., HO-1, ferritin, glutathione peroxidase,

glutathione-S-transferases (GSTs), NAD(P)H:quinone oxidoreductases, now commonly known as nicotinamide quinone oxidoreductase 1 (NQO1; EC 1.6.99.2; also known as DT diaphorase and menadione reductase), NQO2, g-glutamylcysteine synthase (g-GCS), glucuronosyltransferase, ferritin, and heme oxygenase-1 (HO-1), as well as any one of the enzymes proteins listed in Table 1 in Chen & Kunsch, Curr. Pharm. Designs, 2004, 10:879-891; Lee et al., J. Biol. Chem., 2003, 278(14):12029-38, and Kwak, supra.

[0083] Accordingly, in some embodiments, the at least one Nrf2-regulated gene which is used to assess the activation of the Nrf2 pathway is selected from a phase II detoxification enzyme, an anti-oxidant enzyme, an enzyme of the NADPH generating system, and Nrf2 itself. Examples of the phase II detoxification enzymes include NQO1, NQO2, GST-Ya, GST-pi, GST-theta 2, GST-mu (1,2,3), microsomal GST 3, catalytic y-GCS, regulatory-GCS, microsomal epoxide hydrolase, UDP-glucuronosyltransferase, transaldolase, transketolase, and drug-metabolizing enzyme. Examples of the anti-oxidant enzymes include HO-1, ferritin (L), glutathione reductase, glutathione peroxidase, metallothionein I, thioredoxin, thioredoxin reductase, peroxiredoxin MSP23, Cu/Zn superoxide dismutase, and catalase. Examples of the enzymes of the NADPH generating system include malic enzyme, UDP-glucose dehydrogenase, malate oxidoreductase, and glucose-6-phosphate dehydrogenase.

[0084] The antioxidant response element (ARE, also referred to as the electrophile response element (EpRE), GRE1, ARE4, and StREb) is a *cis*-acting DNA regulatory element with a core nucleotide sequence of 5'-TGA(C/T/G)NNNGC-3' (SEQ ID NO:1) (Rushmore et al., J. Biol. Chem., 1991, 266(18):11632-9; see also Nioi et al., Mutation Res., 2004, 555:14-171).

[0085] Accordingly, in some embodiments, the DNA sequence of the ARE element, to which Nrf2 binds (whether the former is a part of an endogenous gene or an artificial construct), comprises the core ARE sequence TGA(C/T/G)NNNGC (SEQ ID NO:2) or the ARE consensus sequence (G/A)TGA(C/T/G)NNNGC(A/G) (SEQ ID

NO:3). In further specific embodiments, the ARE sequence comprises any one of the "minimal enhancer" sequences shown in Table 1.

[0086] In some embodiments, the ARE sequence further comprises at least one of corresponding 5'- and 3'-USR sequences as shown in Table 1. In some embodiments, the ARE sequence comprises the sequence GTGANNNNGCA (SEQ ID NO:4), or more particularly, the mouse (NNNN=gtcg) or human (NNNN=ctca) versions thereof.

Table 1

Species	Gene	Element	5'-USR	Minimal enhancer	3'-USR	SEQ ID NO
mouse	nqo1	ARE	agTCAca	GTGAgtcgGCA	aaattt	SEQ ID NO:5
rat	NQO1	ARE	agTCAca	GTGACttgGCA	aaatct	SEQ ID NO:6
human	NQO1	ARE	agTCAca	GTGACtcaGCA	gaatct	SEQ ID NO:7
mouse	gsta1	EpRE	gcTAAtg	GTGACaaaGCA	actttc	SEQ ID NO:8
rat	GSTA2	ARE	gcTAAtg	GTGACaaaGCA	actttc	SEQ ID NO:9
mouse	gsta3	ARE	ctcAggc	ATGACattGCA	tttttc	SEQ ID NO:10
rat	GSTP1	GPE1	agTCAct	ATGATtcaGCA	acaaaa	SEQ ID NO:11
human	GCLC	ARE4	ccTCccc	GTGACtcaGCG	ctttgt	SEQ ID NO:12
human	GCLM	EpRE	gaagAca	ATGACtaaGCA	gaaatc	SEQ ID NO:13
mouse	ho1	StREb	cccAAcc	ATGACacaGCA	taaaag	SEQ ID NO:14
ARE 'core'...				TGACnnnGC		SEQ ID NO:15
ARE consensus ...				TAAnn ATGACnnnGCA C G T G	aaaa tttt	SED ID NO:16

[0087] A current model of Nrf2 function is as follows. Under basal conditions, Nrf2 is sequestered in the cytoplasm to the actin-bound Kelch-like ECH-associated

protein 1 (Keap1; Accession No. NP_987096 for human Keap1), a Cullin3 ubiquitin ligase adaptor protein. More specifically, the N-terminal domain of Nrf2, known as Neh2 domain, is thought to interact with the C-terminal Kelch-like domain of Keap1. In response to xenobiotics or oxidative stress, Nrf2 is released from the Keap1/Nrf2 complex, thereby promoting nuclear translocation of Nrf2 and concomitant activation of ARE-mediated gene transcription. Keap1 function, in turn, requires association with Cullin3, a scaffold protein that positions Keap1 and its substrate in proximity to the E3 ligase Rbx1, allowing the substrate (Nrf2) to be polyubiquitinated and thus targeted for degradation. The exact mechanism of how the Keap1/Nrf2 complex senses oxidative stress is not fully understood. Human Keap1 contains 25 cysteine residues that were hypothesized to function as sensors of oxidative stress; 9 of the cysteines are thought to be highly reactive (Dinkova-Kostova et al., PNAS, 2005, 102(12):4584-9). It was theorized but is not relied on for the purposes of this invention that alkylation of cysteins leads to a conformational change, resulting in the liberation of Nrf2 from Nrf2/Keap1/Cullin3 complexes, followed by nuclear translocation of the liberated Nrf2.

[0088] In some embodiments, methods 1-3 described herein comprise contacting a cell with at least one test compound and determining whether the Nrf2 pathway is upregulated in the cell. In such methods, an upregulation of the Nrf2 pathway above a threshold (e.g., by at least 30%, 50%, 100%, 200%, 500% over a control) indicates that the at least one compound has certain biological properties beneficial in treating a neurological disease (e.g., neuroprotective properties).

[0089] The ability of a compound to activate the Nrf2 pathway can be determined by one or more in vitro and in vivo assays, including, e.g., the following assays described below.

[0090] i) Expression *levels of Nrf2*--The sequence of the promoter region of the *nrf2* gene (−1065 to −35) has been published, for example, in Chan et al., PNAS, 1996, 93:13943-13948. One may use an artificially constructed expression construct containing the Nrf2 promoter element and an artificial reporter gene. Alternatively, one may use PCR or Northern blotting to determine expression levels of Nrf2 mRNA, or Western blotting to determine Nrf2 protein levels. Exemplary procedures for

determining expression levels of Nrf2 are described in Kwak et al., Mol. Cell. Biol. 2002, 22(9):2883-2892 and Kwak et al., Mol. Med., 2001, 7:135-145. Antibodies against Nrf2 are can be produced by methods known in the art and are commercially available from, for example, StressGen. Accordingly, in some embodiments, the Nrf2 pathway is activated so that the expression levels of Nrf2 are increased by, for example, at least 30%, 50%, 100%, 200%, 500% or more as compared to the non-activated state.

[0091] ii) *Subcellular localization and/or nuclear translocation of Nrf2*-- Such assays include cell staining, or analysis of cytoplasmic versus nuclear cell extracts. For example, a Nrf2-green fluorescence protein (GFP) fusion protein construct can be made and introduced into cells and visualized as described in, e.g., Kraft et al., J. Neurosci., 2004, 24, 1101-1112; and Satoh et al., PNAS, 2006, 103(3):768-773. Accordingly, in some embodiments, the Nrf2 pathway is activated so that the ratio between cytomplasmic and nuclear Nrf2 is elevated by, for example, at least 30%, 50%, 100%, 200%, 500% or more as compared to the non-activated state.

[0092] iii) *Expression levels and/or activity of one or more genes under the control of Nrf2*--Such genes under the control of Nrf2 include endogenous or artificially introduced reporter genes in reporter constructs introduced into cells. For example, expression levels of endogenous or exogenously introduced NQO1 may be determined as described in the Examples. Alternatively, a reporter gene construct with one or more ARE sites operably linked to a reporter gene (e.g., luceferase or GFP) can be made, as described in, e.g., Satoh et al., PNAS, 2006, 103(3):768-773. Expression levels of an Nrf-2 induced gene product can be measured at the protein (e.g., by Western blotting or enzymatic activity assays) or at the mRNA levels (e.g., by PCR). Methods for performing RT-PCT are described in, e.g., Calabrese et al., J. Neurosci. Res., 2005, 79:509-521 for HO-1, in Wierinckx et al., J. Neuroimmunology, 2005, 166:132-143 for NQO1. Methods for measuring enzymatic activity of NQO1, using for example, menadione as a substrate, are described in Dinkova-Kostova et al., PNAS, 2001, 98:3404-09 or by Prochaska et al., Anal. Biochem., 1988, 169:328-336. Methods for measuring GST activity, using for example, 1-chloro-2,4-dinitrobenzene as

a substrate, are described in Ramos-Gomez et al., J. Neurosci., 2004, 24(5):1101-1112 and Habig et al., 1974, J. Biol. Chem., 219, 7130-7139. Methods for measuring HO-1 activity are described in, e.g., in Calabrese et al., 2005, J. Neurosci. Res., 79:509-521. Accordingly, in some embodiments, the Nrf2 pathway is activated so that the expression levels and/or activity of the gene produced are increased by, for example, at least 30%, 50%, 100%, 200%, 500% or more as compared to the non-activated state.

[0093] iv) *Levels of Nrf2 binding to ARE*--For example, such assays may utilize electromobility shift assays (EMSA) and Chromatin Immununoprecipitation (ChIP) assay, as described in, e.g., Satoh et al., PNAS, 2006, 103(3):768-773 and Kwak et al., Mol. Cell Biol., 2002, 22(9):2883-2892. Accordingly, in some embodiments, the Nrf2 pathway is activated so that the level of Nrf2 binding to ARE is increased by, for example, at least 30%, 50%, 100%, 200%, 500% or more as compared to the non-activated state.

[0094] v) *The stability of Nrf2/Keap1 complexes*--Such assay may include analysis of immunoprecipitated complexes with Nrf2 and/or Keap1 or other Nrf2/Keap1-associated proteins as described in, e.g., Satoh et al., PNAS, 2006, 103(3):768-773. Anti-Keap1 antibodies can be produced using methods known in the art and are available commercially from, for example, Santa Cruz Biotechnology. Accordingly, in some embodiments, the Nrf-2 pathway is activated so that the stability of Nrf2/Keap1 complexes is increased by, for example, at least 30%, 50%, 100%, 200%, 500% or more as compared to the non-activated state.

[0095] vi) *Modification (e.g., alkylation levels) of Keap1 and other Nrf2/Keap1-associated proteins*--Such assays may include mass spectrometric analysis of immunoprecipitated Keap1, using techniques as described in, e.g., Dinkova-Kostova et al., PNAS, 2005, 102(12):4584-9 and Gao et al., J. Biol. Chem., on-line pub. Manuscript M607622200. In some embodiments, the Nrf-2 pathway is activated so that the level of Keap1 and other Nrf2/Keap1-associated proteins is increased by, for example, at least 30%, 50%, 100%, 200%, 500% or more as compared to the non-activated state.

[0096] Alkylating capacity of a compound can be assessed using recombinant Keap1, by a competition reaction with 5,5'-dithiobis(2-nitrobezoic acid) (DTNB) as described in, e.g., Gao et al., J. Biol. Chem., on-line pub. Manuscript M607622200.

[0100] In some embodiments, the cell being contacted with at least one test compound is a neuron or a neuronal cell line. In some embodiments, the cell being contacted with the at least one test compound is selected from a colon carcinoma cell line (e.g., DLD1), a neuroblastoma cell line (e.g., SkNSH or IMR32), and a primary monocyte. The cell may be a cell in culture (in vitro) or be inside of an animal (in vivo).

[0101] Cell viability, and in particular, neuronal viability can be assessed in vivo or in vitro using any suitable method, including methods as described in the Examples. For example, neuronal viability can be assessed using an MTT assay after exposure of neuronal cell cultures to cytotoxic levels of glutamate as described in, e.g., Shih et al., J. Neurosci., 2005, 25(44):10321-35. Additionally, cell viability may also be assessed in assays in which cell death is induced by oxidative damage, for example, by the addition of glucose oxidase to astrocyte cell cultures, as described in, e.g., Calabrese et al., J. Neurosci. Res., 2005, 79:509-521. In vivo assays may be performed as described in, e.g., Misgeld, Histochem. Cell Biol., 2005, 124:189-196.

[0102] The amount of the reporter gene expressed can be determined by any suitable method. Expression levels, at the RNA or the protein level, can be determined using routine methods. Expression levels are usually scaled and/or normalized per total amount of RNA or protein in the sample and/or a control, which is typically a housekeeping gene such as actin or GAPDH. RNA levels are determined by quantitative PCR (e.g., RT-PCR), Northern blotting, or any other method for determining RNA levels, e.g., as described in Cloning: A Laboratory Manual, by Sambrook et al. (eds.), 2nd ed., Cold Spring Harbor Laboratory Press, 1989; Lodie et al., Tissue Eng., 2002, 8(5):739-751); or as described in the Examples. Protein levels are determined using, Western blotting, ELISA, enzymatic activity assays, or any other method for determining protein levels as described in, e.g., Current Protocols in Molecular Biology, by Ausubel et al. (eds.), John Wiley and Sons, 1998.

[0103] Expression levels may also be determined using reporter gene assays in cell/tissue extracts or by tissue or whole-animal imaging. In addition to MRI, tissue imaging on living animals can be performed by fluorescence detection (Hoffman Lancet Oncol., 2002 3:546-556; Tung et al., Cancer Res., 2000, 60:4953-4958), bioluminescence detection (Shi et al., PNAS, 2001, 98:12754-12759; Luke et al., J. Virol., 2002, 76:12149-12161; and U.S. Patent Nos. 5,650,135 and 6,217,847), positron emission tomography (Liang et al., Mol. Ther., 2002, 6:73-82, near-infrared fluorescence (Tung et al., Cancer Res., 2000, 60:4953-4958), or X-ray imaging (Hemminki et al., J. Nat. Cancer Inst., 2002, 94:741-749).

[0104] A neurological disease in methods 1-5 above can be a neurodegenerative disease such as, for example, ALS, Parkinson's disease, Alzheimer's disease, and Huntington's disease. The neurological disease can also be multiple sclerosis (MS), or other demyelinating diseases of the central or peripheral nervous system. In some embodiments the form of MS in methods 1-5 is selected from: relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and malignant MS (Marburg Variant).

[0105] The subject being treated or administered the compound as per methods described herein, is a mammal in need thereof, such as a subject in need of neuroprotection, including a subject who has or is at risk for developing a demyelinating and another specified neurodegenerative disease. The subject is mammalian, and can be a rodent or another laboratory animal, e.g., a non-human primate. In some embodiments, the subject is human.

[0106] Neurodegenerative diseases are described in, for example, Neurodegenerative Diseases: Neurobiology, Pathogenesis and Therapeutics, M. Flint Beal, Anthony E. Lang, Albert C. Ludolph, Cambridge University Press (July 11, 2005). Examples of neurological diseases suitable for the methods described herein include neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, and Huntington's disease. Other examples include demyelinating neurological disease including, in addition to MS, the following diseases: acute haemorrhagic leucoencephalomyelitis, Hurst's disease, acute

disseminated encephalomyelitis, optic neuritis, Devic's disease, spinal cord lesions, acute necrotizing myelitis, transverse myelitis, chronic progressive myelopathy, progressive multifocal leukoencephalopathy (PML), radiation myelopathy, HTLV-1 associated myelopathy, monophasic isolated demyelination, central pontine myelinolysis, and leucodystrophy (e.g., adrenoleucodystrophy, metachromatic leucodystrophy, Krabbe's disease, Canavan's disease, Alexander's disease, Pelizaeus-Merbacher disease, vanishing white matter disease, oculodentodigital syndrome, Zellweger's syndrome), chronic inflammatory demyelinating polyneuropathy (CIDP), acute inflammatory demyelinating polyneuropathy (AIDP), Leber's optic atrophy, and Charcot-Marie-Tooth disease.

[0107] Additional examples of diseases suitable for the methods described herein include polyneuritis and mitochondrial disorders with demyelination. These disorders may be co-presented with, and possibly aggravated by diabetes, e.g., insulin-dependent diabetes mellitus (IDDM; type I diabetes), or other diseases.

[0108] A test compound may be further assayed in an animal model of MS, known as Experimental Autoimmune Encephalomyelitis (EAE) (Tuohy et al., J. Immunol., 1988, 141:1126-1130, Sobel et al. J. Immunol., 1984, 132:2393-2401, and Traugott, Cell Immunol., 1989 119:114-129). Chronic relapsing EAE provides a well established experimental model for testing agents that would be useful for the treatment of MS. The mouse EAE is an induced autoimmune demyelinating disease with many similarities to human MS in its clinical manifestations. In both EAE and MS, clinical disease is associated with blood-brain barrier (BBB) dysfunction, infiltration of central nervous system by mononuclear cells (mainly macrophages and T lymphocytes, and serum products), and demyelination (Baker et al. J. Neuroimmunol., 1990, 28:261; Butter et al., J. Neurol. Sci., 1991, 104:9; Harris et al., Ann. Neurol., 1991, 29:548; Kermonde et al., Brain, 1990, 113:1477).

[0109] Clinical signs of MS and demyelinating pathology in EAE result from immunization with CNS myelin proteins or peptides (e.g., MBP, PLP, and MOG) under Th1 conditions (direct immunization model), or by adoptive transfer of CNS antigen-specific Th1 cells (adoptive transfer model) (Ben-Nun et al., Eur. J. Immunol.,

1981, 11:195-199; Ando et al., Cell Immunol., 1989, 124:132-143; Zamvil et al., Nature, 1985, 317:355-358; Zamvil et al., Ann. Rev. Immunol., 1990, 8:579-621). For example, in the SJL mouse model of EAE, immunization with the CNS peptide PLP 139-151 or adoptive transfer of PLP-specific Th1 cells results in a disease course consisting of an acute phase with loss of tail tone on day 10 to day 12, followed by hind limb paralysis and CNS mononuclear cell infiltration (Tuohy et al., J. Immunol., 1988, 141:1126-1130, Sobel et al., J. Immunol., 1984, 132:2393-2401, and Traugott, Cell Immunol., 1989, 119:114-129). Resolution of clinical signs and recovery occurs on day 20 to day 25 and the animals may undergo several more relapses less severe than the initial phase. EAE has been used to evaluate new therapeutic approaches to T-cell-mediated autoimmune disease because of the clinical and histopathological similarities to the human demyelinating MS.

[0110] The ability of a compound to slow or prevent neurodegeneration (including demyelination and neuronal death) can be assessed in the EAE model or another animal model, including for example, Thieler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease, murine hepatitis virus (MHV), Semliki Forest Virus, or Sindbis virus as described in, e.g., Ercoli et al., J. immunol., 2006, 175:3293-3298.

[0111] A compound may be optionally tested in at least one additional animal model (see, generally, Immunologic Defects in Laboratory Animals, eds. Gershwin et al., Plenum Press, 1981), for example, such as the following: the SWR X NZB (SNF1) mouse model (Uner et al., J. Autoimmune Disease, 1998, 11(3):233-240), the KRN transgenic mouse (K/BxN) model (Ji et al., Immunol. Rev., 1999, 69:139); NZB X NZW (B/W) mice, a model for SLE (Riemekasten et al., Arthritis Rheum., 2001, 44(10):2435-2445); the NOD mouse model of diabetes (Baxter et al., Autoimmunity, 1991, 9(1):61-67), etc.); or mouse models of multiple sclerosis (see, e.g., Linker et al., Eur. J. Immunol., 2002, 8(6):620-624, and Eugster et al., Nat. Med., 1999, 29:626-632; and Gold et al., Brain, 2006, 129:1953-1971).

[0112] Preliminary doses, for example, as determined in animal tests, and the scaling of dosages for human administration is performed according to art-accepted

practices. Toxicity and therapeutic efficacy can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. In some embodiments compositions that exhibit large therapeutic indices are used.

[0113] The therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (i.e., the concentration of the therapeutic compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture assays or animal models. Levels in plasma may be measured, for example, by ELISA or HPLC. The effects of any particular dosage can be monitored by a suitable bioassay. Examples of dosages are: about 0.1 x IC_{50}, about 0.5 x IC_{50}, about 1 x IC_{50}, about 5 x IC_{50}, 10 x IC_{50}, about 50 x IC_{50}, and about 100 x IC_{50}.

[0114] The data obtained from the in vitro assays or animal studies can be used in formulating a range of dosages for use in humans. Therapeutically effective dosages achieved in one animal model can be converted for use in another animal, including humans, using conversion factors known in the art (see, e.g., Freireich et al., Cancer Chemother. Reports, 1966, 50(4):219-244 and Table 2 for Equivalent Surface Area Dosage Factors).

Table 2

To: / From:	Mouse (20 g)	Rat (150 g)	Monkey (3.5 kg)	Dog (8 kg)	Human (60 kg)
Mouse	1	1/2	1/4	1/6	1/12
Rat	2	1	1/2	1/4	1/7
Monkey	4	2	1	3/5	1/3
Dog	6	4	3/5	1	1/2
Human	12	7	3	2	1

[0115] In some embodiments the dosage of such compounds lies within a range of circulating concentrations that include the ED_{50} with little or no toxicity. In some embodiments the dosage varies within this range depending upon the dosage form employed and the route of administration utilized. Generally, a therapeutically effective amount may vary with the subject's age, condition, and sex, as well as the severity of the medical condition in the subject. Examples of pharmaceutically acceptable dosages for compounds described herein are from 1 µg/kg to 25 mg/kg, depending on the compounds, severity of the symptoms and the progression of the disease. The appropriate therapeutically effective doses can be selected by a treating clinician and in some embodiments range approximately from 1 µg/kg to 20 mg/kg, from 1 µg/kg to 10 mg/kg, from 1 µg/kg to 1 mg/kg, from 10 µg/kg to 1 mg/kg, from 10 µg/kg to 100 µg/kg, from 100 µg to 1 mg/kg. Additionally, certain specific dosages are indicated in the Examples.

[0116] For DMF or MMF, an effective amount can range from 1 mg/kg to 50 mg/kg (e.g., from 2.5 mg/kg to 20 mg/kg or from 2.5 mg/kg to 15 mg/kg). Effective doses will also vary, as recognized by those skilled in the art, dependent on route of

administration, excipient usage, and the possibility of co-usage with other therapeutic treatments including use of other therapeutic agents. For example, an effective dose of DMF or MMR to be administered to a subject orally can be from about 0.1 g to 1 g per pay, 200 mg to about 800 mg per day (e.g., from about 240 mg to about 720 mg per day; or from about 480 mg to about 720 mg per day; or about 720 mg per day). For example, the 720 mg per day may be administered in separate administrations of 2, 3, 4, or 6 equal doses.

[0117] The dosage may be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment. The compositions may be given as a bolus dose, to maximize the circulating levels for the greatest length of time after the dose. Continuous infusion may also be used after the bolus dose.

[0118] In some embodiments, compositions used in the methods described herein further comprise a pharmaceutically acceptable excipient. As used herein, the phrase "pharmaceutically acceptable excipient" refers to any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions. The pharmaceutical compositions may also be included in a container, pack, or dispenser together with instructions for administration.

[0119] A pharmaceutical composition is formulated to be compatible with its intended route of administration. Methods to accomplish the administration are known in the art. "Administration" is not limited to any particular delivery system and may include, without limitation, parenteral (including subcutaneous, intravenous, intramedullary, intraarticular, intramuscular, or intraperitoneal injection), rectal, topical, transdermal, or oral (for example, in capsules (e.g., as, poweder, granules, microtablet, micropellets, etc.), suspensions, or tablets). Examples of some of formulations containing DMF and/or MMF are given in, e.g., US Patents Nos. 6,509,376, and 6,436,992.

[0120] Administration to an individual may occur in a single dose or in repeat administrations, and in any of a variety of physiologically acceptable salt forms, and/or with an acceptable pharmaceutical carrier and/or additive as part of a pharmaceutical composition. Physiologically acceptable salt forms and standard pharmaceutical formulation techniques and excipients are well known to persons skilled in the art.

[0121] The following Examples are intended for illustrative purposes and do not limit the inventions claimed.

EXAMPLES

Example 1

[0122] Human colon carcinoma DLD1 cells were treated with DMF or MMF at indicated concentrations (5, 15, or 50 μM) for 16 hours, rinsed with PBS, and harvested into reducing SDS sample buffer. The lysates were subjected to SDS PAGE and the separated proteins were electrophoretically transferred onto nitrocellulose membranes for Western blot analysis. To detect Nrf2 and NQO1, the membranes were incubated with the respective primary antibodies overnight at 4°C, washed, and incubated with peroxidase-conjugated secondary antibodies followed by the chemiluminescent peroxidase substrate. Detection of the target protein band luminescence and image acquisition were done using CCD-equipped imaging station Kodak2000R. The results shown in Figure 1, demonstrate that DMF and MMF are potent activators of Nrf2 at concentrations within clinical exposure range.

Example 2

[0123] DLD1 cells were grown in MEM supplemented with 10% fetal bovine serum. The cells were transfected with the indicated siRNA's using the Lipofectamine reagent (Invitrogen) according to the manufacturer's instructions and 30 hrs later stimulated with 30 μM DMF for 40 hours. The cells were harvested and processed for Western blotting analysis of Nrf2 and NQO1 levels as described in Example 1. Sources and

the identity of reagents used in Examples 1 and 2 are specified Table 3 below:

	Target	Reagent	Source/Sequence	Vendor
Primary Antibody	Nrf2	Nrf2 (T-19)	goat polyclonal antibody	Santa Cruz Biotechnology
	Keap1	Keap1 (E-20)	goat polyclonal antibody	Santa Cruz Biotechnology
	NQO1	NQO1 (A180)	mouse monoclonal antibody	Santa Cruz Biotechnology
	GAPDH	Anti-GAPDH	mouse monoclonal antibody	Ambion
Secondary antibody	anti-mouse	HRP-Mouse IgG	sheep	Amersham Biosciences
	anti-rabbit	HRP-Rabbit IgG	donkey	Amersham Biosciences
	anti-Goat	HRP-Goat IgG	Bovine	Santa Cruz Biotechnology
siRNA	Nrf2	Nrf2-2	UCAUUGAACUGC UCUUUGGUU (antisense) (SEQ ID NO:17)	Dharmacon
	Keap1	Keap1-1	GAAUUAAGGCGG UUUGUCCUU (antisense) (SEQ ID NO:18)	Dharmacon

[0124] The results are shown in Figure 2 (for ease of representation, the image of the Western blot is turned upside down). The results demonstrate that DMF-induced upregulation of NQO1 requires Nrf2 and can be mimicked by activation of

Nrf2 through repression of Keap1. Therefore, DMF acts as an Nrf2 agonist causing cellular accumulation of Nrf2 and Nrf2 target gene expression.

Example 3

[0125] For induction of EAE, mice received s.c. injections in the flanks and tail base of 50 µg MOG 35–55 peptide in PBS emulsified in an equal volume of complete Freund's adjuvant (CFA) containing Mycobacterium tuberculosis H37RA (Difco, Detroit MI, USA) at a final concentration of 0·5 mg/ml. Two injections of pertussis toxin (List Biological Laboratories Inc., California, USA; 200 ng per mouse i.p) were given on days 0 and 2.

[0126] DMF and MMF was diluted in 200 µl 0·08% Methocel/H_2O as vehicle and administered by oral gavage starting from day 3 post immunization (p.i) until termination. Each treatment group consisted of 8 animals: vehicle alone as a negative control, 5 mg/kg body weight DMF twice a day, 15 mg/kg body weight DMF twice a day, 15 mg/kg body weight MMF twice a day. The compounds were obtained via Fumapharm AG. Oral gavage was used to ensure exact dosing and to avoid compound degradation.

[0127] Spinal cord tissues were fixed in 4% paraformaldehyde and embedded in paraffin. Slides were deparaffinized and rehydrated in graded alcohol solutions. Antigen retreival was performed by immersing the slides in 10 mM Citrate, pH 6.0 for 20 minutes in a pressure cooker at 120 C (Pascal, Dako Cytomation).

[0128] Immunohistochemistry was performed using the Dako autostainer as follows. Endogenous peroxidase was quenched by a 10 minute incubation in 3% H_2O_2 / Methanol. The rabbit anti Nrf2 antibody C-20 (sc-722, Santa Cruz Biotechnology) was added at a 1:250 dilution in Dako Diluent with Background Reducing Components (Dako # S3022) C-20 antibody was detected using the Envision anti rabbit labeled polymer-HRP (Dako #K4003) and DAB (Vector Labs #SK-4100) was used as the chromogenic substrate. Morphometric analysis of Nrf2 immunostaining was performed using ImageJ software from NIH (http://rsb.info.ih.gov/ij/).

[0129] The resuluts, shown in Figures 3 and 4, demonstrate MMF and DMF activation of Nrf2 in vivo.

* * *

[0130] All publications and patent documents cited herein are incorporated by reference in their entirety. To the extent the material incorporated by reference contradicts or is inconsistent with the present specification, the present specification will supersede any such material.

CLAIMS

1. A method of evaluating neuroprotective properties of at least one test compound, the method comprising:

a) contacting a cell with the at least one test compound,

b) determining whether the Nrf2 pathway is upregulated in the cell,

c) determining whether the at least one test compound slows or prevents at least one of demyelination, axonal loss, and neuronal death, and

d) selecting the test compound as a candidate for treating neurodegeneration in a neurological disease if 1) the Nrf2 pathway is upregulated and, optionally,

e) further determining whether at least one of demyelination, axonal loss, and neuronal death are prevented or slowed by the compound.

2. The method of claim 1, wherein the neurological disease is a demyelinating disease.

3. The method of claim 2, wherein the demyelinating disease is multiple sclerosis.

4. The method of claim 1, wherein the cell in step a) is contacted with a plurality of test compounds.

5. The method of claim 1, wherein the Nrf2 pathway upregulation is determined by the levels of expression or activity of NQO1.

6. The method of claim 1, wherein the Nrf2 pathway is upregulated by at least 30% as indicated by one or more of the following parameters:

i) expression levels of at least one of endogenously produced and exogenously introduced Nrf2;
ii) at least one of subcellular localization and nuclear translocation of Nrf2;
iii) the expression level of at least one gene under control of Nrf2;
iv) the level of Nrf2 binding to the Nrf2-binding DNA element ARE;
v) the stability of Nrf2/Keap1 complexes; and
vi) modification levels of at least one protein selected from Keap1 and other Nrf2/Keap1-associated proteins.

7. The method of claim 6, wherein the at least one gene under control of Nrf2 is an Nrf2-regulated reporter gene in an artificial reporter construct.

8. The method of claim 1, further comprising comparing the level of Nrf2 pathway upregulation by the at least one test compound with the level of Nrf2 pathway upregulation by at least one comparator compound.

9. The method of claim 8, wherein the at least one comparator compound is selected from dimethyl fumarate and monomethyl fumarate.

10. The method of claim 1, wherein the at least one test compound has the structure of Formula I.

11. The method of claim 1, wherein the at least one test compound is selected from fumaric acid, its salts, and fumaric acid derivatives.

12. The method of claim 1, wherein the at least one test compound is chosen from FTY 720, ABT-874, GSK683699, NeuroVax, MLN 1202, interferon γ, Tysabri™, Rituxan, TV 5010, NBI-788, MBP8298, Cladribine, Teriflunomide, Temsirolimus, and Laquinimod.

13. A method of treating a mammal having a neurological disease, comprising:

a) selecting a test compound according to the method of any one of claims 1-10, and

b) administering the selected test compound a mammal in need thereof, thereby treating neurodegeneration in the mammal.

14. A method of treating a mammal having a neurological disease by combination therapy, the method comprising:

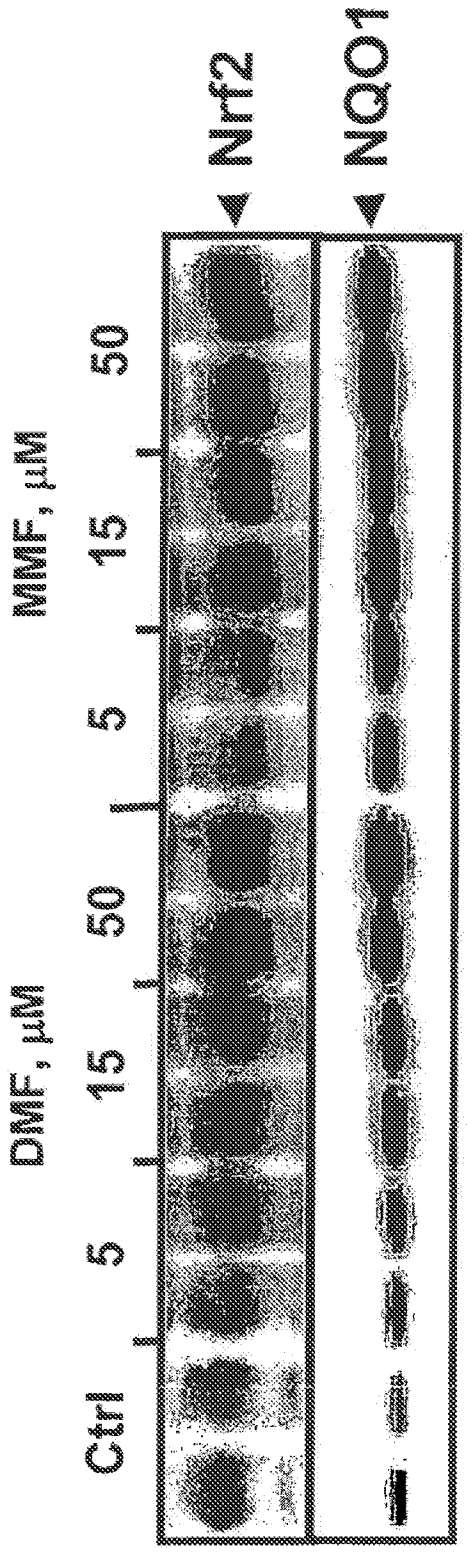
a) administering to the mammal a therapeutically effective amount of at least one first compound that upregulates the Nrf2 pathway, and

b) administering a therapeutically effective amount of at least one second compound that does not upregulate the Nrf2 pathway.

15. The method of claim 14, wherein the at least one first compound is selected from fumaric acid, its salts, and fumaric acid derivatives.

16. The method of claim 13 or 14, wherein the neurological disease is a demyelinating disease.

17. The method of claim 16, wherein the demyelinating disease is multiple sclerosis.



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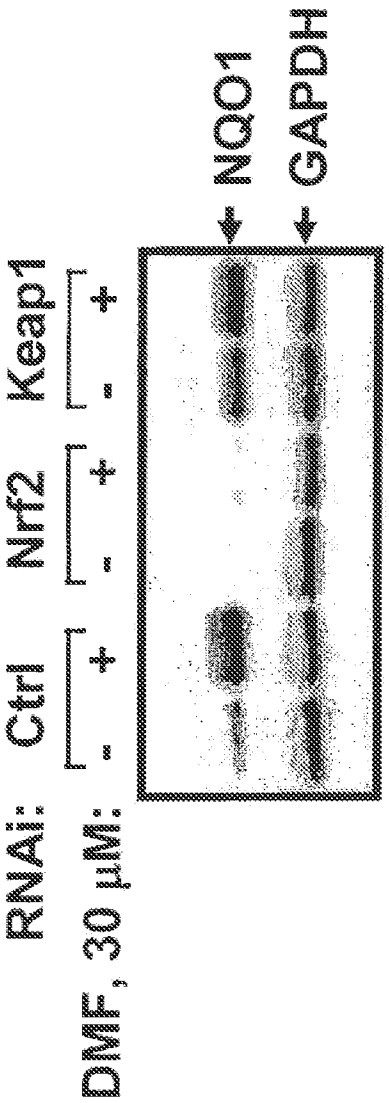

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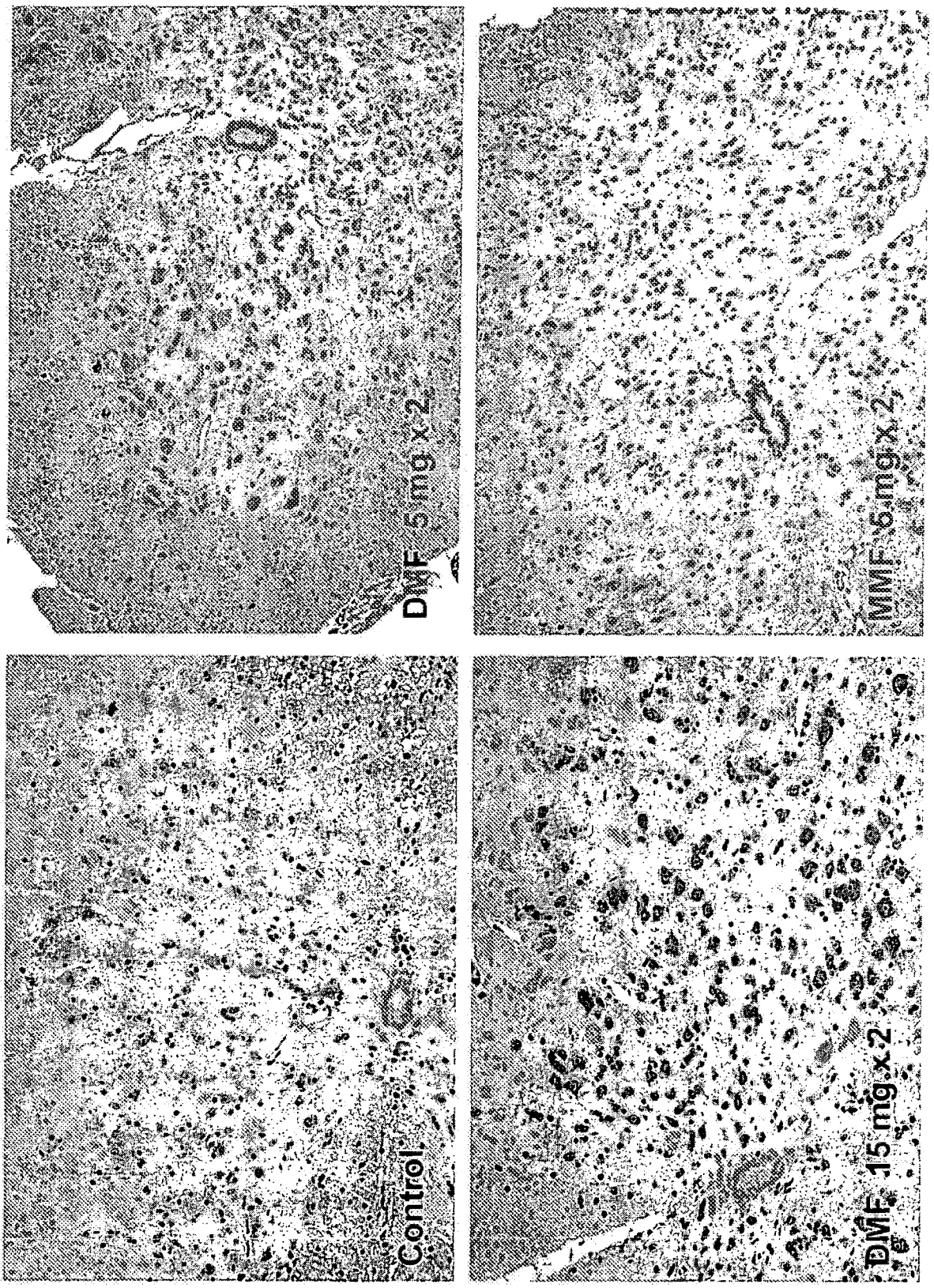

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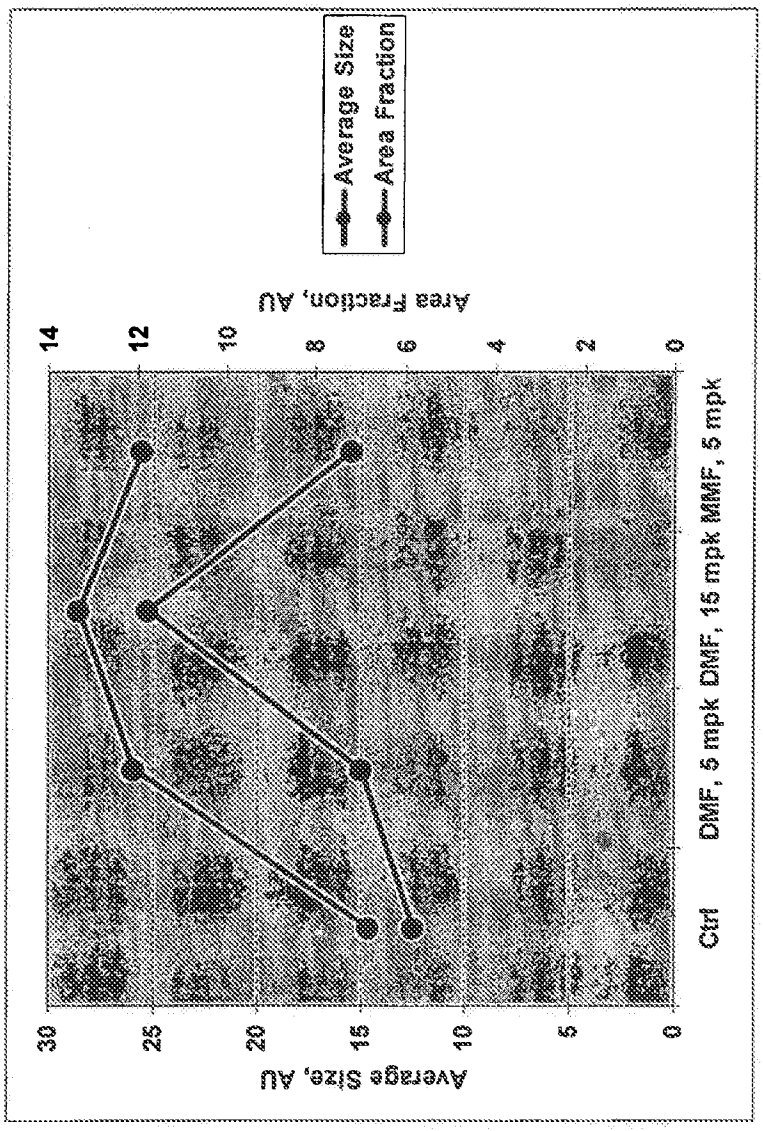
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Figure 4

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PTO/SB/93 (03-10)
Approved for use through 02/28/2013. OMB 0651-0024
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REQUEST FOR TRANSFER OF A COMPUTER READABLE FORM UNDER 37 CFR 1.821(e)

Application No.:	To be assigned	First Named Inventor:	Matvey E. LUKASHEV
Filing Date:	February 13, 2012	Attorney Docket No.:	2159.3210002/JMC/MRG/U-S
Title of the Invention:	Treatment for Multiple Sclerosis (As Amended)		

The sequence information in the paper copy or PDF file of the Sequence Listing filed:

- ☑ herewith;
- ☐ as part of the originally-filed specification of this application;
- ☐ as a separate amendment filed on _____;

for the above identified application, is identical to the sequence information in the

- ☐ only
- ☑ last filed
- ☐ other (specify second, third, fourth, etc.) _____

computer readable form which was filed on August 7, 2009,

in application number 12/526,296 filed January 13, 2011 (§ 371(c) Date)

This computer readable form was compliant with 37 CFR 1.821-1.825, and applicant hereby requests that it be used as the computer readable form for the present application, in accordance with 37 CFR 1.821(e).

The above referenced paper copy or PDF file of the Sequence Listing contains no new matter.

A sequence listing text file submitted via EFS-Web that complies with the requirements of 37 CFR 1.824(a)(2)-(6) and (b) (i.e., is a compliant sequence listing ASCII text file), serves as both the paper copy required by 37 CFR 1.821(c) and the CRF required by 37 CFR 1.821(e). If a user submits a compliant sequence listing ASCII text file via EFS-Web, the U.S. Patent and Trademark Office will not carry out a request to use a compliant computer readable "Sequence Listing" that is already on file for another application pursuant to 37 CFR 1.821(e) but will use the sequence listing submitted with the application as originally filed via EFS-Web.

It is understood that upon the transfer of a copy of the computer readable form to this application, the U.S. Patent and Trademark Office will update the copy of the computer readable form to reflect the application number and filing date for this application.

Signature Marsha A. Rose	Date 2/13/2012
Name (Print/Typed) Marsha A. Rose	Registration Number 58,403

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: *To be assigned*
LUKASHEV *et al.*	Art Unit: *To be assigned*
Appl. No.: *To be assigned*	
(*Continuation of Appl. No. 12/526,296,*	
§ 371(c) Date: January 13, 2011)	Examiner: *To be assigned*
Filing Date: Herewith	Atty. Docket: 2159.3210002/JMC/MRG/U-S
For: **Treatment for Multiple Sclerosis (As Amended)**	

Preliminary Amendment Under 37 C.F.R. § 1.115

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

In advance of prosecution, Applicants submit the following amendments and remarks.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks and Arguments begin on page 6 of this paper.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1-17. (Cancelled)

18. (New) A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof, and (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof is about 480 mg per day.

19. (New) The method of claim 18, wherein the pharmaceutical composition is administered in the form of a tablet, a suspension, or a capsule.

20. (New) The method of claim 18, wherein the therapeutically effective amount is administered in separate administrations of 2, 3, 4, or 6 equal doses.

21. (New) The method of claim 20, wherein the therapeutically effective amount is administered in separate administrations of 2 equal doses.

22. (New) The method of claim 20, wherein the therapeutically effective amount is administered in separate administrations of 3 equal doses.

23. (New) The method of claim 18, wherein the pharmaceutical composition consists essentially of dimethyl fumarate and one or more pharmaceutically acceptable excipients.

24. (New) The method of claim 18, wherein the pharmaceutical composition consists essentially of monomethyl fumarate and one or more pharmaceutically acceptable excipients.

25. (New) The method of claim 18, wherein the pharmaceutical composition is administered to the subject for at least 12 weeks.

26. (New) The method of claim 23, wherein the therapeutically effective amount is administered to the subject in 2 equal doses.

27. (New) The method of claim 26, wherein the therapeutically effective amount is administered to the subject for at least 12 weeks.

28. (New) A method of treating a subject in need of treatment for multiple sclerosis consisting essentially of orally administering to the subject about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

29. (New) The method of claim 28, wherein about 480 mg of dimethyl fumarate per day is administered to the subject.

30. (New) The method of claim 29, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.

31. (New) The method of claim 29, wherein the dimethyl fumarate is administered in separate administrations of 3 equal doses.

32. (New) A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of dimethyl fumarate and (b) one or more pharmaceutically acceptable excipients, wherein

the therapeutically effective amount of dimethyl fumarate is about 480 mg per day.

33. (New) The method of claim 32, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.

34. (New) The method of claim 18, wherein the expression level of NQO1 in the subject is elevated after administering to the subject the therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

35. (New) The method of claim 28, wherein the expression level of NQO1 in the subject is elevated after administering to the subject about 480 mg per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

36. (New) The method of claim 32, wherein the expression level of NQO1 in the subject is elevated after administering to the subject the therapeutically effective amount of dimethyl fumarate.

Remarks

Upon entry of the foregoing amendment, claims 18-36 are pending in the application, with claims 18, 28, and 32 being the independent claims.

Claims 1-17 are sought to be cancelled without prejudice or disclaimer thereof. New claims 18-36 are sought to be added. Support for claims 18-36 is set forth in Section I below.

I. Summary of the Claimed Subject Matter

The claimed invention is generally directed to methods of orally treating multiple sclerosis (MS). MS is a chronic disease for which only a limited number of disease-modifying treatment options are currently available, most of which are administered by injection. Only one disease-modifying oral drug has been approved in the United States and that has only recently been approved. In addition, not all MS drugs are indicated for every MS patient. Furthermore, patients must carefully weigh the risks associated with each drug at a given disease state. It is very clear that additional medications are needed to provide better life quality and reduced risk of disability for MS patients. Oral MS medications with favorable safety profiles are particularly desired. Applicants' invention satisfies this desire.

Applicants disclose a method for treating a neurological disease with at least one fumaric acid derivative, including dimethyl fumarate (DMF) or monomethyl fumarate (MMF), as "method 4" in paragraph [0009], lines 9-11 and paragraphs [0062-0063] of the specification. The application discloses that *"[i]n some embodiments the neurological disease is MS or another demyelinating neurological disease."*

(Specification, p. 4, paragraph [0010]) (emphasis added). Applicants also discussed a MS animal model, Experimental Autoimmune Encephalomyelitis (EAE), in paragraphs [0108] and [0109], as well as Example 3. Therefore, MS is supported in the application.

Additionally, Applicants disclose that DMF and/or MMF are effective in treating MS. For example, DMF and MMF are listed as specific examples of neuroprotective compounds. (Specification, p. 13, paragraph [0063].) Specifically, the specification indicates that

> [i]n some embodiments of method 4, a method of treating a mammal who has or is at risk for a neurological disease is provided. The methods comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound which has Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF).

(*Id.*) As such, DMF and MMF are specifically named in the application as compounds effective in treating neurological diseases such as MS. Furthermore, the dosages disclosed in paragraph [0116] of the application refer to the specific compounds "DMF" and "MMF". Accordingly, Applicants teach that DMF and MMF are effective in treating MS.

Applicants also disclose that orally administering 480 mg per day of DMF and/or MMF is effective in treating MS. (Specification, p. 30, paragraph [0116].) Specifically, the specification discloses that

> [a]n effective dose of DMF or MMR [sic] to be administered to a subject orally can be from about 0.1 g to 1 g per pay [sic], 200 mg to about 800 mg per day (e.g.,

> from about 240 mg to about 720 mg per day; or **from about 480 mg to about 720 mg per day**; or about 720 mg per day).

(*Id.*) (emphasis added). Because Applicants teach 480 to 720 mg/day, and further disclose this dosage range as the most narrow range, it is clear that Applicants describe orally administering 480 mg DMF daily to treat MS. *See, e.g., In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976).

The specification further discloses that the daily dose of DMF and/or MMF can be administered in 2, 3, 4, or 6 equal doses. *See, e.g.*, Specification, pp. 29-30, paragraph [0116] ("[F]or example, the 720 mg per day may be administered in separate administrations of 2, 3, 4, or 6 equal doses.") It is clear from the entire paragraph [0116] that, although the above citation from the specification refers to 720 mg/day as an example, the disclosure of multiple separate administrations equally applies to other dosages, *e.g.*, the 480 mg/day dose.

The specification further discloses that the expression level of NQO1 is elevated in *vivo* after administration of DMF or MMF. *See, e.g.*, original claims 1, 5, and 11; p. 2, paragraph [0006]; pp. 4-5, paragraph [0012]; pp. 22-23, paragraph [0092]; p. 31, paragraph [0122], Example 1, Figure 1; p. 31-32, paragraph [0123], Example 2, Figure 2.

Accordingly, Applicants disclose treating a subject with MS by orally administering 480 mg/day DMF and/or MMF to the subject.

Applicants' claimed method involves the oral administration of a specific daily dose of about 480 mg/day of dimethyl fumarate (DMF) and/or monomethyl fumarate (MMF) (the physiologically active metabolite of DMF). The claimed method has been

proven effective for the treatment of MS in human patients in two large-scale Phase 3 clinical studies (further discussed herein below). Quite surprisingly, it was found in those clinical studies that the 480 mg/day dose is just as effective in treating MS as a higher dose of 720 mg/day DMF. This is especially unexpected given the results of a Phase 2 clinical study in which a dose of 720 mg/day DMF, but not a 360 mg/day DMF dose, was found to be effective.

II. Patentability of the Claimed Invention

The prior art teaches that certain autoimmune diseases (*e.g.*, MS) can be treated with fumarates (*e.g.*, DMF). *See e.g.*, U.S. Patent Publication No. 2003/0018072 to Joshi *et al.* ("Joshi") and Schimrigk *et al.*, *European Journal of Neurology* 2006, 13(6):604-610 ("Schimrigk"). However, the prior art does not teach or suggest a dose consisting essentially of about 480 mg/day of DMF and/or MMF. Needless to say, the prior art does not mention the efficacy of the 480 mg/day dose.

As mentioned above, it is unexpected that the dose of about 480 mg/day DMF was similarly effective compared to the higher dose of about 720 mg/day. The evidence of these unexpected results are provided in a declaration under 37 CFR § 1.132 of Katherine T. Dawson, M.D. ("Declaration") previously filed on October 13, 2011, in U.S. Patent Application No. 12/526,296, submitted herewith as Exhibit 1.

Biogen Idec MA Inc. ("Biogen Idec"), the assignee of the current application, recently completed two pivotal Phase 3 placebo-controlled, double-blind, clinical studies, "the DEFINE study" and "the CONFIRM study", which evaluated the investigational oral drug candidate BG-12 (DMF as the only active ingredient) to treat relapsing-remitting MS (RRMS).

Results of the DEFINE study are depicted in Figures 4-11 and Table 2 of the Declaration. The results of the DEFINE study indicate that the dose of 480 mg/day unexpectedly demonstrated significant efficacy on MS disease activity as measured by the key clinical and MRI disease activity endpoints. (Declaration, pages 11-18, Figures 4-11; and page 20, Table 2.) Even more unexpected was the magnitude of the treatment effect. Given that the dose typically impacts the efficacy, it was quite surprising that the 480 mg/day dose demonstrated similar efficacy to the higher 720 mg/day dose on both clinical and MRI measures of MS disease activity – with a *high level of statistical significance*. (*Id.* at page 19, paragraphs 13-15; and page 20, Table 2.)

Furthermore, the results of the second Phase 3 study (CONFIRM) support the first Phase 3 study. See Exhibit 2, which states "[r]esults of the CONFIRM study showed that 240 mg of BG-12, administered either twice a day (BID) or three times a day (TID), demonstrated significant efficacy and favorable safety and tolerability profiles. Further analyses of the CONFIRM study are ongoing . . . ."

Therefore, the results of the DEFINE and CONFIRM studies indicate that the 480 mg/day DMF dose demonstrates efficacy in the DEFINE study, meeting all measured endpoints with a high level of statistical significance. (*See* Declaration, page 16, paragraph 16; *see* Exhibit 2.) Not only was the 480 mg/day DMF dose efficacious, but the 480 mg/day dose surprisingly demonstrated similar effectiveness on clinical and MRI measures of MS disease activity as 720 mg/day DMF. (*See* Declaration, page 15, paragraph 15.)

III. The Unexpected Results Must Be Given Substantial Weight: There is a Nexus Between the Supported Claims 18-36 and the Unexpected Results of the DEFINE and CONFIRM Studies

Unexpected results of the claimed invention do not need to be included in the specification for an Examiner to consider them. The MPEP at 716.01(b) states that "[t]o be given substantial weight in the determination of obviousness or nonobviousness, evidence of secondary considerations must be relevant to the *subject matter as claimed*, and therefore the examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations." (emphasis added). Thus, according to the MPEP, the Examiner must consider whether there is a nexus between the ***claimed invention*** and the unexpected results.

As mentioned above, the application teaches and fully supports the claimed invention of treating MS using DMF and/or MMF at a dose of 480 mg/day. Thus, the data from the DEFINE and CONFIRM clinical studies, which flow inherently from the claimed invention, must be given substantial weight when considering the patentability of claims 18-36.

IV. Summary

Based on the reasons set forth above, Applicants respectfully submit that the present claims are patentable.

Conclusion

Prompt and favorable consideration of this Preliminary Amendment is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Marsha A. Rose

Marsha A. Rose
Attorney for Applicants
Registration No. 58,403

Date: 2/13/2012

1100 New York Avenue, N.W.
Washington, D.C.20005-3934
(202) 371-2600

1481215_1.DOCX

Substitute for form 1449/PTO

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	*To be assigned*
Filing Date	Herewith
First Named Inventor	Matvey E. LUKASHEV
Art Unit	*To be assigned*
Examiner Name	*To be assigned*
Attorney Docket Number	2159.3210002/JMC/MRG/U-S

U.S. PATENT DOCUMENTS

Examiner initials*	Cite No.[1]	Document Number: Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	FP51	DE 25 30 372 A1	01-13-1977	Schweckendiek, Walter, Dr.		
	FP52	DE 26 21 214 A1	11-17-1977	Koronis GmbH, Chemisch-Pharmazeutische Präparate		
	FP53	DE 28 40 498 B1	08-02-1979	Schweckendiek, Walter, Dr.		

1476787_1.DOCX

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or notcitation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Doc Code: PD.TO.AUTH
Document Description: Authorization to access Appl. by Trilateral Office

PTO/SB/39 (07-09)
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P.O. Box 1450, Alexandria, VA 22313-1450

COMPLETE IF KNOWN	
Application Number	To be assigned
Filing Date	Herewith
First Named Inventor	Matvey E. LUKASHEV
Attorney Docket Number	2159.3210002/JMC/MRG/U-S
Title (Required)	Treatment for Multiple Sclerosis (As Amended)

The undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified patent application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h).

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the above-identified application with respect to: 1) the above-identified patent application-as-filed; 2) any foreign application to which the above-identified patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified patent application; and 3) any U.S. application-as-filed from which benefit is sought in the above-identified patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

This written authorization should be submitted prior to the filing of a subsequent foreign application, in which priority is claimed to the above-identified patent application, with any intellectual property office (e.g., the EPO, JPO, KIPO, or DAS Accessing Office). However, if applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified patent application is filed to have access to the above-identified patent application, this written authorization should not be filed.

No fee will be charged under 37 CFR 1.19(b)(1) for providing a participating intellectual property office with an electronic copy of the above-identified patent application.

This form must be signed by an authorized party in accordance with 37 CFR 1.14(c).

Marsha A. Rose	2/13/2012
Signature	Date
Marsha A. Rose	(202) 371-2600
Printed or Typed Name	Telephone Number
Attorney for Applicants	58,403
Title	Registration Number, if applicable

This collection of information is required by 37 CFR 1.14(h). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process an application). Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

1474802

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449/PTO				*Complete if Known*	
THIRD SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*				Application Number	*To be assigned*
				Filing Date	Herewith
				First Named Inventor	Matvey E. LUKASHEV
				Art Unit	*To be assigned*
				Examiner Name	*To be assigned*
Sheet	1	of	1	Attorney Docket Number	2159.3210002/JMC/MRG/U-S

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
	NPL328	LANGNER, A., *et al.*, "Results of a Phase II Study of a Novel Oral Fumarate, BG00012, in the Treatment of Severe Psoriasis," European Congress on Psoriasis, October 21-24, 2004, Paris, France	
	NPL329	LANGNER, A., *et al.*, "The Efficacy and Safety of a Novel Oral Formulation of Dimethylfumarate, BG00012, in Patients with Severe Psoriasis: Results of a Phase 2 Dose-Finding and Safety Extension Study," 3rd Spring Symposium of the European Academy of Dermatology and Venerology (EADV), 2005, Sofia, Bulgaria	
	NPL330	LANGNER, A., *et al.*, "Oral Fumarate for the Treatment of Severe Forms of Psoriasis: Results of a Phase II Clinical Study," 2nd Spring Symposium of the European Academy of Dermatology and Venerology (EADV) April 29-May 1, 2004, Budapest, Hungary	
	NPL331	LANGNER, A., *et al.*, "Effects of a Novel Oral Fumarate, BG00012, in Patients with Severe Psoriasis: Results of a Phase 2 Study," 13th Congress of the European Academy of Dermatology and Venerology (EADV), November 17-21, 2004, Florence, Italy	
	NPL332	LANGNER, A., *et al.*, "Efficacy and Safety of a New Oral Formulation of Fumaric Acid Ester for the Treatment of Moderate to Severe Psoriasis," 10th International Psoriasis Symposium, June 10-13, 2004, Toronto, Canada	
	NPL333	'T HART *et al.*, "Modelling of multiple sclerosis: lessons learned in a non-human primate," *The Lancet Neurology 3(10):588-597,* Elsevier Ltd. (2004)	
	NPL334	Office Action mailed July 13, 2011, in U.S. Application No. 12/526,296, Lukashev *et al.*, § 371(c) Date: January 13, 2011	
	NPL335	Office Action mailed December 15, 2011, in U.S. Application No. 12/526,296, Lukashev *et al.*, § 371(c) Date: January 13, 2011	
	NPL336	"Efficacy and Safety Study of Oral BG00012 with Active Reference in Relapsing-Remitting Multiple Sclerosis (CONFIRM)," ClinicalTrials.gov, accessed at http://www.clinicaltrials.gov/ct2/show/NCT00451451?term=bg00012&rank=8, first received on March 21, 2007, 4 pages	

1476793_1.DOCX

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.
[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	Treatment for Multiple Sclerosis
First Named Inventor/Applicant Name:	Matvey E. LUKASHEV
Filer:	Marsha A. Rose/Erin Miller
Attorney Docket Number:	2159.3210002/JMC/MRG/U-S
Filed as Large Entity	

Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	380	380
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Request for Prioritized Examination	1817	1	4800	4800
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- early, voluntary, or normal	1504	1	300	300
Processing Fee, except for Provis. apps	1808	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**6480**

Electronic Acknowledgement Receipt

EFS ID:	12062982
Application Number:	13372426
International Application Number:	
Confirmation Number:	5998
Title of Invention:	Treatment for Multiple Sclerosis
First Named Inventor/Applicant Name:	Matvey E. LUKASHEV
Customer Number:	53644
Filer:	Marsha A. Rose/Erin Miller
Filer Authorized By:	Marsha A. Rose
Attorney Docket Number:	2159.3210002/JMC/MRG/U-S
Receipt Date:	13-FEB-2012
Filing Date:	
Time Stamp:	20:56:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$6480
RAM confirmation Number	7068
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		2159_3210002_Transmittals.pdf	9107980 399c6ab409183eea5d082989ecc311eb4f7dde6e	yes	74

Multipart Description/PDF files in .zip description

Document Description	Start	End
Miscellaneous Incoming Letter	1	3
Transmittal of New Application	4	5
TrackOne Request	6	6
Authorization for Extension of Time all replies	7	7
Application Data Sheet	8	10
Oath or Declaration filed	11	12
Abstract	13	13
Specification	14	47
Claims	48	50
Drawings-only black and white line drawings	51	54
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Preliminary Amendment	62	62
Specification	63	63
Claims	64	66
Applicant Arguments/Remarks Made in an Amendment	67	73
Authorization to access Appl. by Trilateral Office	74	74

Warnings:

Information:

2		2159_3210002_IDS.pdf	11542820 52509b3af6d8ed3defc2e3ba9227626097f46c53	yes	75

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal Letter	1	6
Information Disclosure Statement (IDS) Form (SB08)	7	7
Transmittal Letter	8	18
Information Disclosure Statement (IDS) Form (SB08)	19	25
Information Disclosure Statement (IDS) Form (SB08)	26	55
Transmittal Letter	56	63
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Information Disclosure Statement (IDS) Form (SB08)	65	68
Transmittal Letter	69	74
Information Disclosure Statement (IDS) Form (SB08)	75	75

Warnings:

Information:

3	Non Patent Literature	NPL328_Langner_2004.pdf	442101 0eda15f90f2366826d8ce9b3f81642d2a31c5720	no	4

Warnings:

Information:

4	Non Patent Literature	NPL329_Langner.pdf	71864 87d8cd80562b4d6bbe2c3c0bf346828625da994a	no	4

Warnings:

Information:

5	Non Patent Literature	NPL330_Langner.pdf	504989 7e1b1d0e979bfeee755ac3b424c93a58761704b4	no	3

Warnings:

Information:

6	Non Patent Literature	NPL331_Langner_2004.pdf	443315 ef5aac34c39d9ced672ae35671dcec1d6b610ab5	no	4
Warnings:					
Information:					
7	Non Patent Literature	NPL332_Langner_2004.pdf	439432 11130bb67991122895a8813b443ea110e478eace	no	4
Warnings:					
Information:					
8	Non Patent Literature	NPL333_Hart_2004.pdf	1707370 f3ae7e96a970dd501c57186151b0f707535e76b9	no	10
Warnings:					
Information:					
9	Non Patent Literature	NPL334_OA_12526296.pdf	294656 aa5dead73b64cbc0d235832ebe5e4a0780e65e42	no	8
Warnings:					
Information:					
10	Non Patent Literature	NPL335_FOA_12526296.pdf	339180 0b10f24ae2624953ca32d3d50966af03904f1edc	no	9
Warnings:					
Information:					
11	Non Patent Literature	NPL336_CONFIRM_2007.pdf	215299 2bd45de0988f040079653df7a9f16a6c67a748d7	no	4
Warnings:					
Information:					
12	Fee Worksheet (SB06)	fee-info.pdf	40068 16e2286fe3e5f19a2607f1a93c1a624fea7b98b5	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	25149074	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

MARSHA A. ROSE
DIRECTOR
(202) 772-8692
MROSE@SKGF.COM

Sterne Kessler Goldstein Fox
ATTORNEYS AT LAW

February 13, 2012

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Re: U.S. Non-Provisional Utility Patent Application under 37 C.F.R. § 1.53(b)
(Continuation of Appl. No. 12/526,296; § 371(c) Date: January 13, 2011)
Appl. No. To be assigned; Filed: Herewith
For: **Treatment for Multiple Sclerosis (As Amended)**
Inventors: LUKASHEV *et al.*
Our Ref: 2159.3210002/JMC/MRG/U-S

Sir:

The following documents are transmitted herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Utility Patent Application Transmittal Form (PTO/SB/05);

2. Online Credit Card Payment Authorization for $6,480.00 to cover:

   $1,250.00 Patent Application fees (including basic filing, search, and examination fees);

   $4,800.00 Prioritized Examination Fee;

   $300.00 Publication Fee; and

   $130.00 Processing Fee.

3. Certification and Request for Prioritized Examination Under 37 C.F.R. § 1.102(e);

4. Authorization to Treat a Reply As Incorporating An Extension of Time Under 37 C.F.R. § 1.136(a)(3);

5. U.S. Utility Patent Application entitled:

   Treatment for Multiple Sclerosis (As Amended)

   and naming as inventors:

Matvey E. LUKASHEV and Gilmore O'NEILL

the application consisting of:

a. An Application Data Sheet (37 C.F.R. § 1.76);

b. Copy of an executed combined Declaration and Power of Attorney filed in U.S. Application No. 12/526,296;

c. A specification containing:

i. 34 pages of description prior to the claims;

ii. 3 pages of claims (17 claims);

iii. a one (1) page abstract;

d. 4 sheets of drawings (Figures 1-4); and

e. Sequence listing;

6. Request for Transfer of a Computer Readable Form Under 37 C.F.R. § 1.821(e);

7. Preliminary Amendment Under 37 C.F.R. § 1.115;

8. Authorization to Permit Access to Application by Participating Offices (PTO/SB/39);

9. Information Disclosure Statement (IDS);

10. IDS Form PTO/SB/08a (1 page);

11. First Supplemental Information Disclosure Statement;

12. First Supplemental IDS Form PTO/SB/08a (7 pages);

13. First Supplemental IDS Form PTO/SB/08b (30 pages);

14. Second Supplemental Information Disclosure Statement;

15. Second Supplemental IDS Form PTO/SB/08a (1 page);

16. Second Supplemental IDS Form PTO/SB/08b (4 pages);

17. Third Supplemental Information Disclosure Statement; and

18. Third Supplemental IDS Form PTO/SB/08b (1 page) with 9 accompanying documents (NPL328-NPL336).

The above-listed documents are filed electronically through EFS-Web.

Fee payment is provided through online credit card payment. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Marsha A. Rose

Marsha A. Rose
Attorney for Applicants
Registration No. 58,403

MRG/U-S:enm
Enclosures

1474804_1.DOCX

Equivalent of Form PTO/SB/08a (07-09)

Substitute for form 1449/PTO	Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*	Application Number	*To be assigned*
	Filing Date	Herewith
	First Named Inventor	Matvey E. LUKASHEV
	Art Unit	*To be assigned*
	Examiner Name	*To be assigned*
Sheet 1 of 1	Attorney Docket Number	2159.3210002/JMC/MRG/U-S

U.S. PATENTS AND PUBLISHED U.S. PATENT APPLICATIONS

Examiner Initials	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Issue or Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US-			
		US-			
		US-			
		US-			
		US-			
		US-			

Note: Copies of the U.S. Patent Documents are not Required in IDS filed after October 21, 2004

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[6]
		WO 2007/005879 A2	01-11-2007	BISWAL, ET AL.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation[6]
		SCHIMRIGK, ET AL., "Oral fumaric acid esters for the treatment of active multiple sclerosis: an open-label, baseline-controlled pilot study", European Journal of Neurology, vol. 13, no. 6, XP-002496537, pages 604-610, (June 2006)	
		WIERINCKX, ET AL., "Detoxication enzyme inducers modify cytokine production in rat mixed glial cells", Journal of Neuroimmunology, Elsevier Science Publishers BV, XX, vol. 166, no. 1-2, XP-005000427, pages 132-143 (September 1, 2005)	

Examiner Signature		Date Considered	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: LUKASHEV *et al.* Appl. No.: To be assigned (*Continuation of Appl. No. 12/526,296; § 371(c) Date: January 13, 2011*) Filed: Herewith For: **Treatment for Multiple Sclerosis (As Amended)**	Confirmation No.: *To be assigned* Art Unit: *To be assigned* Examiner: *To be assigned* Atty. Docket: 2159.3210002/JMC/MRG/U-S

First Supplemental Information Disclosure Statement

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Listed on accompanying IDS Forms PTO/SB/08a equivalent and/or PTO/SB/08b equivalent are documents that may be considered material to the patentability of this application as defined in 37 C.F.R. §1.56, and in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.97 and 1.98.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

Applicants have checked the appropriate boxes below.

☐ 1. Statement under 37 C.F.R. 1.704(d). Each item of information contained in this Information Disclosure Statement was first cited in a communication from a foreign patent office in a counterpart application and this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty days prior to the filing of this information disclosure statement.

☒ 2. Filing under 37 C.F.R. § 1.97(b). This Information Disclosure Statement is being filed within three months of the date of filing of a national application other than a continued prosecution application (CPA), OR within three months of the date of entry of the national stage as set forth in 37 C.F.R. § 1.491 in an international application, OR before the mailing date of a first Office Action on the merits OR before the mailing of a first Office Action after the filing of a request for continued examination under 37 C.F.R. § 1.114. No statement or fee is required.

☐ 3. Filing under 37 C.F.R. § 1.97(c). This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection, or Notice of Allowance, or an action that otherwise closes prosecution in the application.

☐ a. Statement under 37 C.F.R. § 1.97(e)(1). I hereby state that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. Statement under 37 C.F.R. § 1.97(e)(2). I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ c. Attached is our PTO-2038 Credit Card Payment Form in the amount of $180.00 in payment of the fee under 37 C.F.R. § 1.17(p).

☐ 4. Filing under 37 C.F.R. § 1.97(d) This Information Disclosure Statement is being filed more than three months after the U.S. filing date and after the mailing date of a Final Rejection or Notice of Allowance, but on or before payment of the Issue Fee. Enclosed find our PTO-2038 Credit Card Payment Form in the amount of $180.00 in payment of the fee under 37 C.F.R. § 1.17(p); in addition:

☐ a. Statement under 37 C.F.R. § 1.97(e)(1). I hereby state that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. Statement under 37 C.F.R. § 1.97(e)(2). I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ 5. The document(s) was/were cited in a search report by a foreign patent office in a counterpart foreign application. Submission of an English language version of the search report that indicates the degree of relevance found by the foreign office

is provided in satisfaction of the requirement for a concise explanation of relevance. 1138 OG 37, 38 and MPEP 609.04(a)(III).

☒ 6. A concise explanation of the relevance of the non-English language documents appears below in accordance with 37 C.F.R. § 1.98(a)(3).

Document **FP1**, **JP 54-80439 A**, is in the Japanese language. An English language abstract of document FP1 is cited as document **NPL1** and submitted herewith.

Document **FP2**, **EP 0 188 749 A2**, is in the German language. Document **US3** is believed to be an English-language equivalent of document FP2.

Document **FP4**, **EP 0 312 697 A2**, is in the German language. Document **US4** is believed to be an English-language equivalent of document FP4.

Document **FP5**, **DE 38 34 794 A1**, is in the German language. An English language abstract of document FP5 is cited as document **NPL2** and submitted herewith.

Document **FP6**, **EP 0 518 388 A2**, is in the German language. Document **US4** is believed to be an English-language equivalent of document FP6.

Document **FP7**, **JP 6-345644 A**, is in the Japanese language. An English language abstract of document FP7 is cited as document **NPL3** and submitted herewith.

Document **FP9**, **JP 8-99906 A**, is in the Japanese language. An English language abstract of document FP9 is cited as document **NPL4** and submitted herewith.

Document **FP13**, **JP 9-221428 A**, is in the Japanese language. An English language abstract of document FP13 is cited as document **NPL5** and submitted herewith.

Document **FP15**, **WO 97/48405 A1**, is in the Russian language. An English language abstract of document FP15 is cited as document **NPL6** and submitted herewith.

Document **FP19**, **DE 197 21 099 A1**, is in the German language. Document **US14** is believed to be an English-language equivalent of document FP19.

Document **FP23**, **RU 2 189 813 C1**, is in the Russian language. An English language abstract of document FP23 is cited as document **NPL7** and submitted herewith.

Document **FP25**, **WO 2005/027899 A1**, is in the German language. An English language abstract of document FP25 is cited as document **NPL8** and submitted herewith.

Document **FP37**, **CN 1125141 A**, is in the Chinese language. An English language abstract of document FP37 is cited as document **NPL292** and submitted herewith.

Document **NPL28**, **Dücker and Pfeiff**, is in the German language. An English language abstract of document NPL28 can be found on the face page of the publication.

Document **NPL31**, **Fliegner and Spiegel**, is in the German language. An English language abstract of document NPL31 can be found on the face page of the publication.

Document **NPL48**, **Hunziker and Schmidli**, is in the German language. It is believed that document **NPL47** is a partial English language translation of document NPL48.

Document **NPL163**, **Gutzmer *et al.***, is in the German language. An English language abstract of Document NPL163 is cited as document **NPL164** and submitted herewith.

Document **NPL165**, **Hagedorn *et al.***, is in the German language. An English language abstract of document NPL165 can be found on the face page of the publication.

Document **NPL187**, **Roodnat *et al.***, is in the German language. An English language abstract of document NPL187 can be found on the face page of the publication.

Document **NPL191**, **Schilling and Schopf**, is in the German language. An English language abstract of document NPL191 can be found on the face page of the publication.

Document **NPL198**, **Van Loenen *et al.***, is in the Dutch language. An English language abstract of document NPL198 can be found on the face page of the publication.

Document **NPL202**, **Wanscher and Sørensen**, is in the Danish language. An English language abstract of document NPL202 can be found on the page 6357 of the publication.

Document **NPL210**, *Immunmodulation durch Fumaderm. Das richtungsweisende Konzept*, is in the German language. It is believed that document **NPL211** is a partial English language translation of document NPL210.

Document **NPL215**, **Bayard *et al.***, is in the German language. An English language abstract of document NPL215 can be found on the face page of the publication.

Document **NPL234**, "Klinische Studie mit Fumaderm® als magensaftresistente Mikrotabletten," the first three pages are in the German language. An English language translation of pages 1-3 of document NPL234 can be found on pages 4-6 of the same document.

Document **NPL247**, **Peeters *et al.***, is in the Dutch language. An English language abstract of document NPL247 can be found on the last page of the publication.

Document **NPL257**, **Stangel *et al.***, is in the German language. An English language abstract of document NPL257 can be found on page 215 of the publication.

Document **NPL258**, **Stühlinger *et al.***, is in the German language. An English language abstract of document NPL258 can be found on the face page of the publication.

☐ 7. Copies of the documents are submitted. However, in accordance with 37 C.F.R. § 1.98(a)(2), no copies of U.S. patents and patent application publications cited as documents US1-US40 on the attached IDS Forms are submitted.

☒ 8. Copies of documents FP1-FP50 and NPL1-NPL293 were cited by or submitted to the Office in an IDS that complies with 37 C.F.R. § 1.98(a)-(c) in Application No. 12/526,296, with a § 371(c) date of January 13, 2011, which is relied upon for an earlier filing date under 35 U.S.C. § 120. Thus, copies of these documents are not attached. 37 C.F.R. § 1.98(d).

☒ 9. It is expected that the examiner will review the prosecution and cited art in the parent application no. 12/526,296 in accordance with MPEP 2001.06(b), and indicate in the next communication from the office that the art cited in the earlier prosecution history has been reviewed in connection with the present application.

☒ 10. In accordance with the Federal Circuit decision in *Dayco Prods., Inc. v. Total Containment, Inc.* 329 F.3d 1358 (Fed. Cir. 2003), Applicants submit herewith Office Actions from the co-pending U.S. Patent Application Nos. 09/194,862, §

371(c) date July 8, 1999; 09/402,103, § 371(c) date September 27, 1999; 09/743,978, § 371(c) date January 17, 2001; 09/831,620, § 371(c) date May 10, 2001; 10/148,858, § 371(c) date May 28, 2002; 10/197,077, filed July 17, 2002; 11/765,563, filed June 20, 2007; 11/765,578, filed June 20, 2007; 12/405,661, filed March 17, 2009; and 12/405,665, filed March 17, 2009, as documents **NPL269-NPL291**.

The identification of these Office Actions is not to be construed as a waiver of secrecy as to those applications now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination.

It is respectfully requested that the Examiner initial and return a copy of the enclosed IDS Forms, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Marsha A. Rose
Attorney for Applicants
Registration No. 58,403

Date: 2/3/2012

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Substitute for form 1449/PTO				Complete if Known	
SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	*To be assigned*
				Filing Date	Herewith
				First Named Inventor	Matvey E. LUKASHEV
(Use as many sheets as necessary)				Art Unit	*To be assigned*
				Examiner Name	*To be assigned*
Sheet	1	of	4	Attorney Docket Number	2159.3210002/JMC/MRG/U-S

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
	NPL294	Memorandum of Meeting Minutes for the meeting held on August 30, 2006, between attendees from the FDA and Biogen Idec regarding the End of Phase 2 for application PIND 73,061, BG00012	
	NPL295	ALTMEYER, P. and NÜCHEL, C., "Systemtherapie der Psoriasis," *Dtsch. med. Wschr. 121*:1605-1607, Georg Thieme Verlag, Germany (1996)	
	NPL296	English language translation of ALTMEYER, P. and NÜCHEL, C., "Systemtherapie der Psoriasis," *Dtsch. med. Wschr. 121*:1605-1607, Georg Thieme Verlag, Germany (1996)	
	NPL297	ALTMEYER, P. and NÜCHEL, C., "Systemische Therapie der Psoriasis," *T&E Dermatologie 27*:380-382, 384, Reed Elsevier Deutschland, Germany (1997)	
	NPL298	English language translation of ALTMEYER, P. and NÜCHEL, C., "Systemische Therapie der Psoriasis," *T&E Dermatologie 27*:380-382, 384, Reed Elsevier Deutschland, Germany (1997)	
	NPL299	COMPSTON, A., *et al.*, "The person with multiple sclerosis: a prospectus," in *McAlpine's Multiple Sclerosis, 4th Edition*, p. 803-810, Compston, A., *et al.*, eds., Elsevier Inc., China (2006)	
	NPL300	KRAFT, A.D., *et al.*, "Nuclear Factor E2-Related Factor 2-Dependent Antioxidant Response Element Activation by *tert*-Butylhydroquinone and Sulforaphane Occurring Preferentially in Astrocytes Conditions Neurons against Oxidative Insult," *J. Neurosci. 24(5)*:1101-1112, Society for Neuroscience, United States (2004)	
	NPL301	MALIPIERO, U., *et al.*, "Myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis is chronic/relapsing in perforin knockout mice, but monophasic in Fas- and Fas ligand-deficient *lpr* and *gld* mice," *Eur. J. Immunol. 27(12)*:3151-3160, WILEY-VCH Verlag GmbH, Germany (1997)	
	NPL302	MCDONALD, W.I., *et al.*, "Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis," *Ann. Neurol. 50(1)*:121-127, Wiley-Liss, Inc., United States (2001)	
	NPL303	MISGELD, T., "Death of an axon: studying axon loss in development and disease," *Histochem. Cell Biol. 124*:189-196, Springer-Verlag, Germany (2005)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.
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SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*				Application Number	*To be assigned*
				Filing Date	Herewith
				First Named Inventor	Matvey E. LUKASHEV
				Art Unit	*To be assigned*
				Examiner Name	*To be assigned*
Sheet	2	of	4	Attorney Docket Number	2159.3210002/JMC/MRG/U-S

NON PATENT LITERATURE DOCUMENTS			
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	NPL304	MROWIETZ, U., "Nephrotoxische Wirkung durch Fumarsäure," *Der Hautarzt 51*:615, Springer-Verlag, Germany (2000)	
	NPL305	English language translation of MROWIETZ, U., "Nephrotoxische Wirkung durch Fumarsäure," *Der Hautarzt 51*:615, Springer-Verlag, Germany (2000)	
	NPL306	NOSEWORTHY, J., *et al.*, "The treatment of symptoms in multiple sclerosis and the role of rehabilitation," in *McAlpine's Multiple Sclerosis, 4th Edition*, p. 701-728, Compston, A., *et al.*, eds., Elsevier Inc., China (2006)	
	NPL307	NOSEWORTHY, J., *et al.*, "Disease-modifying treatments in multiple sclerosis," in *McAlpine's Multiple Sclerosis, 4th Edition*, p. 729-802, Compston, A., *et al.*, eds., Elsevier Inc., China (2006)	
	NPL308	RIEMEKASTEN, G., *et al.*, "Strong Acceleration of Murine Lupus by Injection of the SmD1$^{83\text{-}119}$ Peptide," *Arthritis & Rheum. 44(10)*:2435-2445, Wiley-Liss, Inc., United States (2001)	
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	NPL310	English language translation of SADJAK, A., *et al.*, "Nephrotoxische Wirkung von Fumarsäurederivaten," *Dtsch. med. Wschr. 116(12)*:478, Georg Thieme Verlag, Germany (1991)	
	NPL311	English language translation of German Patent Publication No. DE 25 30 372 A1	
	NPL312	English language translation of German Patent Publication No. DE 26 21 214 A1	
	NPL313	English language translation of German Patent Publication No. DE 28 40 498 B1	

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SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 4

Complete if Known	
Application Number	*To be assigned*
Filing Date	Herewith
First Named Inventor	Matvey E. LUKASHEV
Art Unit	*To be assigned*
Examiner Name	*To be assigned*
Attorney Docket Number	2159.3210002/JMC/MRG/U-S

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	NPL314	BALASUBRAMANIAM, P., *et al.*, "Fumaric acid esters in severe psoriasis, including experience of use in combination with other systemic modalities," *Br. J. Dermatol. 150*:741-746, British Association of Dermatologists, England (2004)	
	NPL315	FFRENCH-CONSTANT, C., "Pathogenesis of multiple sclerosis," *Lancet 343(8892)*:271-275, The Lancet Ltd., England (1994)	
	NPL316	GHORESCHI, K., *et al.*, "A molecule solves psoriasis? Systemic therapies for psoriasis inducing interleukin 4 and Th2 responses," *J. Mol. Med. (Berl.) 81(8)*:471-480, Springer-Verlag, Germany (2003)	
	NPL317	HARTUNG, H.-P., *et al.*, "Circulating adhesion molecules and inflammatory mediators in demyelination: A review," *Neurology 45(6)(Suppl. 6)*:S22-S32, Advanstar Communications Inc., United States (1995)	
	NPL318	LEE, J.-M., *et al.*, "Nrf2, a multi-organ protector?" *FASEB J. 19(9)*:1061-1066, Federation of American Societies for Experimental Biology, United States (2005)	
	NPL319	LOEWE, R., *et al.*, "Dimethylfumarate Inhibits Tumor-Necrosis-Factor-Induced CD62E Expression in an NF-κB-Dependent Manner," *J. Invest. Dermatol. 117*:1363-1368, The Society for Investigative Dermatology, United States (2001)	
	NPL320	SORMANI, M.P., *et al.*, "Clinical trials of multiple sclerosis monitored with enhanced MRI: new sample size calculations based on large data sets," *J. Neurol. Neurosurg. Psychiatry 70*:494-499, British Medical Association, England (2001)	
	NPL321	TRAUGOTT, U., *et al.*, "Multiple Sclerosis Distribution of T Cells, T Cell Subsets and Ia-positive Macrophages in Lesions of Different Ages," *J. Neuroimmunol. 4*:201-221, Elsevier Science Publishers, Netherlands (1983)	
	NPL322	TRAUGOTT, U. and LEBON, P., "Multiple Sclerosis: Involvement of Interferons in Lesion Pathogenesis," *Ann. Neurol. 24(2)*:243-251, American Neurological Association, United States (1988)	
	NPL323	WALSH, M.J. and TOURTELLOTTE, W.W., "Temporal Invariance And Clonal Uniformity Of Brain And Cerebrospinal IgG, IgA, And IgM in Multiple Sclerosis," *J. Exp. Med. 163*:41-53, Rockefeller University Press, United States (1986)	

Examiner Signature		Date Considered	

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 4

Complete if Known	
Application Number	*To be assigned*
Filing Date	Herewith
First Named Inventor	Matvey E. LUKASHEV
Art Unit	*To be assigned*
Examiner Name	*To be assigned*
Attorney Docket Number	2159.3210002/JMC/MRG/U-S

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume number, publisher, city and/or country where published	T[2]
	NPL324	"BG 12 BG 00012, BG 12/Oral Fumarate, FAG-201, Second-Generation Fumarate Derivative – Fumapharm/Biogen Idec," *Drugs in R&D 6(4)*:229-230, Adis Data Information BV, New Zealand (2005)	
	NPL325	"Efficacy and Safety of BG00012 in MS," ClinicalTrials.gov, accessed at http://www.clinicaltrials.gov/ct2/show/NCT00168701?term=bg00012&rank=3, accessed on September 19, 2008, 3 pages	
	NPL326	"Efficacy and Safety of Oral BG00012 in Relapsing-Remitting Multiple Sclerosis (DEFINE)," ClinicalTrials.gov, accessed at http://www.clinicaltrials.gov/ct2/show/NCT00420212?term=bg00012&rank=1, accessed on September 19, 2008, 4 pages	
	NPL327	"Biogen Idec Announces Positive Top-Line Results from Second Phase 3 Trial Investigating Oral BG-12 (Dimethyl Fumarate) in Multiple Sclerosis," accessed at http://www.biogenidec.com/PRESS_RELEASE_DETAILS.aspx?ID=5981&ReqId=1621631, accessed on October 28, 2011, 3 pages	

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Examiner Signature		Date Considered	

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
LUKASHEV *et al.*
Appl. No.: To be assigned
(*Continuation of Appl. No. 12/526,296; § 371(c) Date: January 13, 2011*)
Filed: Herewith
For: **Treatment for Multiple Sclerosis (As Amended)**

Confirmation No.: *To be assigned*
Art Unit: *To be assigned*

Examiner: *To be assigned*
Atty. Docket: 2159.3210002/JMC/MRG/U-S

Third Supplemental Information Disclosure Statement

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Listed on accompanying IDS Form PTO/SB/08b equivalent are documents that may be considered material to the patentability of this application as defined in 37 C.F.R. §1.56, and in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.97 and 1.98. The numbering on this Third Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Second Supplemental Information Disclosure Statement filed concurrently herewith in connection with the above-captioned application.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed publication

dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

Applicants have checked the appropriate boxes below.

☐ 1. Statement under 37 C.F.R. 1.704(d). Each item of information contained in this Information Disclosure Statement was first cited in a communication from a foreign patent office in a counterpart application and this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty days prior to the filing of this information disclosure statement.

☒ 2. Filing under 37 C.F.R. § 1.97(b). This Information Disclosure Statement is being filed within three months of the date of filing of a national application other than a continued prosecution application (CPA), OR within three months of the date of entry of the national stage as set forth in 37 C.F.R. § 1.491 in an international application, OR before the mailing date of a first Office Action on the merits OR

before the mailing of a first Office Action after the filing of a request for continued examination under 37 C.F.R. § 1.114. No statement or fee is required.

☐ 3. Filing under 37 C.F.R. § 1.97(c). This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection, or Notice of Allowance, or an action that otherwise closes prosecution in the application.

☐ a. Statement under 37 C.F.R. § 1.97(e)(1). I hereby state that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. Statement under 37 C.F.R. § 1.97(e)(2). I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ c. Attached is our PTO-2038 Credit Card Payment Form in the amount of $180.00 in payment of the fee under 37 C.F.R. § 1.17(p).

☐ 4. Filing under 37 C.F.R. § 1.97(d) This Information Disclosure Statement is being filed more than three months after the U.S. filing date and after the mailing date of a Final Rejection or Notice of Allowance, but on or before payment of the Issue Fee. Enclosed find our PTO-2038 Credit Card Payment Form in the amount of $180.00 in payment of the fee under 37 C.F.R. § 1.17(p); in addition:

☐ a. Statement under 37 C.F.R. § 1.97(e)(1). I hereby state that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. Statement under 37 C.F.R. § 1.97(e)(2). I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ 5. The document(s) was/were cited in a search report by a foreign patent office in a counterpart foreign application. Submission of an English language version of the search report that indicates the degree of relevance found by the foreign office is provided in satisfaction of the requirement for a concise explanation of relevance. 1138 OG 37, 38 and MPEP 609.04(a)(III).

☐ 6. A concise explanation of the relevance of the non-English language document(s) appears below in accordance with 37 C.F.R. § 1.98(a)(3).

☒ 7. Copies of documents **NPL328-NPL336** are submitted.

☐ 8. Copies of the _____ documents were cited by or submitted to the Office in an IDS that complies with 37 C.F.R. § 1.98(a)-(c) in Application No._____, filed _____, which is relied upon for an earlier filing date under 35 U.S.C. § 120. Thus, copies of these documents are not attached. 37 C.F.R. § 1.98(d).

☐ 9. It is expected that the examiner will review the prosecution and cited art in the parent application no(s). _____ in accordance with MPEP 2001.06(b), and indicate in the next communication from the office that the art cited in the earlier prosecution history has been reviewed in connection with the present application.

☒ 10. In accordance with the Federal Circuit decision in *Dayco Prods., Inc. v. Total Containment, Inc.* 329 F.3d 1358 (Fed. Cir. 2003), Applicants submit herewith

Office Actions from the co-pending U.S. Patent Application No. 12/526,296, § 371(c) Date January 13, 2011, as documents **NPL334** and **NPL335**.

The identification of these Office Actions is not to be construed as a waiver of secrecy as to those applications now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination.

It is respectfully requested that the Examiner initial and return a copy of the enclosed IDS Forms, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Marsha A. Rose

Marsha A. Rose
Attorney for Applicants
Registration No. 58,403

Date: 2/13/2012

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FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 7

Complete if Known	
Application Number	*To be assigned*
Filing Date	Herewith
First Named Inventor	Matvey E. LUKASHEV
Art Unit	*To be assigned*
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U.S. PATENT DOCUMENTS

Examiner initials*	Cite No.[1]	Document Number: Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	US1	4,515,974	05-07-1985	Zecher *et al.*	
	US2	4,746,668	05-24-1988	Sato *et al.*	
	US3	4,851,439	07-25-1989	Speiser *et al.*	
	US4	4,959,389	09-25-1990	Speiser *et al.*	
	US5	5,149,695	09-22-1992	Speiser *et al.*	
	US6	5,214,196	05-25-1993	Blank	
	US7	5,242,905	09-07-1993	Blank	
	US8	5,359,128	10-25-1994	Blank	
	US9	5,424,332	06-13-1995	Speiser *et al.*	
	US10	5,451,667	09-19-1995	Speiser *et al.*	
	US11	6,277,882 B1	08-21-2001	Joshi *et al.*	
	US12	6,355,676 B1	03-12-2002	Joshi *et al.*	
	US13	6,359,003 B1	03-19-2002	Joshi *et al.*	
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	US15	6,509,376 B1	01-21-2003	Joshi *et al.*	
	US16	6,858,750 B2	02-22-2005	Joshi *et al.*	
	US17	7,157,423 B2	01-02-2007	Joshi *et al.*	
	US18	7,320,999 B2	01-22-2008	Joshi *et al.*	
	US19	7,432,240 B2	10-07-2008	Joshi *et al.*	
	US20	7,612,110 B2	11-03-2009	Joshi *et al.*	

FOREIGN PATENT DOCUMENTS

Examiner initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	FP1	JP 54-80439 A	06-27-1979	Ogawa Hiroe		
	FP2	EP 0 188 749 A2	07-30-1986	Speiser *et al.*		
	FP3	WO 89/01930 A1	03-09-1989	Dexter Biotechnics		
	FP4	EP 0 312 697 A2	04-26-1989	Speiser *et al.*		
	FP5	DE 38 34 794 A1	04-19-1990	Schielein, F.		
	FP6	EP 0 518 388 A2	12-16-1992	Speiser *et al.*		
	FP7	JP 6-345644 A	12-20-1994	Unitika Ltd.		
	FP8	WO 94/28883 A1	12-22-1994	Brown, Raymond		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or notcitation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 7

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	US21	7,619,001 B2	11-17-2009	Joshi *et al.*	
	US22	7,790,916 B2	09-07-2010	Joshi *et al.*	
	US23	7,803,840 B2	09-28-2010	Joshi *et al.*	
	US24	7,915,310 B2	03-29-2011	Joshi *et al.*	
	US25	2004/0054001 A1	03-18-2004	Joshi *et al.*	
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	US27	2010/0130607 A1	05-27-2010	Gold	
	US28	5,538,968	07-23-1996	Chiesi *et al.*	
	US29	5,548,059	08-20-1996	Bayley *et al.*	
	US30	5,972,363	10-26-1999	Clikeman *et al.*	
	US31	6,812,248 B2	11-02-2004	Zhang *et al.*	
	US32	7,056,950 B2	06-06-2006	Rath	
	US33	7,279,331 B2	10-09-2007	Black *et al.*	
	US34	7,364,900 B2	04-29-2008	Black *et al.*	
	US35	7,417,045 B2	08-26-2008	Anilkumar *et al.*	
	US36	7,638,119 B2	12-29-2009	Johnson *et al.*	
	US37	7,871,977 B2	01-18-2011	Rischer *et al.*	
	US38	2003/0176365 A1	09-18-2003	Blass	
	US39	2005/0245612 A1	11-03-2005	Blass	
	US40	2008/0089861 A1	04-17-2008	Went *et al.*	

FOREIGN PATENT DOCUMENTS

Examiner initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	FP9	JP 8-99906 A	04-16-1996	Chugai Pharmaceutical Co., Ltd.		
	FP10	WO 97/09984 A1	03-20-1997	Takeda Chemical Industries, Ltd.		
	FP11	WO 97/13504 A1	04-17-1997	Medgene Limited		
	FP12	CA 2,248,955 A1	05-20-1997	Fumapharm AG		
	FP13	JP 9-221428 A	08-26-1997	Fujisawa Pharmaceutical Co.		
	FP14	WO 97/44054 A2	11-27-1997	University of Alberta		
	FP15	WO 97/48405 A1	12-24-1997	Belyaev, Jury Evgenievich		
	FP16	WO 98/04290 A2	02-05-1998	Perrine *et al.*		

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Art Unit	*To be assigned*
Examiner Name	*To be assigned*
Attorney Docket Number	2159.3210002/JMC/MRG/U-S

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	FP18	EP 0 852 233 A1	07-08-1998	Nippon Shinyaku Company, Limited		
	FP19	DE 197 21 099 A1	11-26-1998	Fumapharm AG		
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	FP21	WO 01/59072 A1	08-16-2001	Philadelphia Health and Education Corporation; University of Medicine and Dentistry of New Jersey		
	FP22	WO 02/02190 A2	01-10-2002	Johns Hopkins School of Medicine		
	FP23	RU 2 189 813 C1	09-27-2002	Rossijskij NII Gematologii Transfuziologii		
	FP24	WO 03/032969 A2	04-24-2003	National Research Council of Canada		

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	FP26	WO 2006/037342 A2	04-13-2006	Aditech Pharma AB		
	FP27	WO 2006/050730 A1	05-18-2006	Aditech Pharma AB		
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	FP29	WO 2007/006307 A2	01-18-2007	Aditech Pharma AB		
	FP30	WO 2007/042035 A2	04-19-2007	Aditech Pharma AB		
	FP31	WO 2008/096271 A2	08-14-2008	Gold, Ralf		
	FP32	WO 2008/097596 A2	08-14-2008	Biogen Idec MA Inc.		

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	FP33	WO 95/25102 A1	09-21-1995	Novo Nordisk A/S		
	FP34	WO 96/01122 A1	01-18-1996	Dana-Farber Cancer Institute		
	FP35	GB 2 291 422 A	01-24-1996	Fujisawa Pharmaceutical Co., Ltd		
	FP36	WO 96/08970 A1	03-28-1996	The Trustees of the University of Pennsylvania; Apollon, Inc.		
	FP37	CN 1125141 A	06-26-1996	Zhongmei Huadong Pharmaceutica		
	FP38	EP 0 793 966 A1	09-10-1997	Hanmi Pharmaceutical Co., Ltd.		
	FP39	WO 02/38142 A2	05-16-2002	Massachusetts Institute of Technology		
	FP40	WO 02/064129 A2	08-22-2002	Rath, Matthias		

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Sheet 6 of 7

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	FP42	WO 2005/023241 A1	03-17-2005	Fumapharm AG		
	FP43	WO 2006/088836 A2	08-24-2006	Schering Corporation; Pharmacopeia Drug Discovery, Inc.		
	FP44	WO 2006/088837 A2	08-24-2006	Schering Corporation; Pharmacopeia Drug Discovery, Inc.		
	FP45	WO 2006/088840 A1	08-24-2006	Schering Corporation; Pharmacopeia Drug Discovery, Inc.		
	FP46	WO 2006/088919 A2	08-24-2006	Schering Corporation; Pharmacopeia Drug Discovery, Inc.		
	FP47	WO 2006/088920 A1	08-24-2006	Schering Corporation; Pharmacopeia Drug Discovery, Inc.		
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	FP49	WO 2006/091428 A2	08-31-2006	Schering Corporation; Pharmacopeia Drug Discovery, Inc.		
	FP50	WO 2007/042034 A1	04-19-2007	Aditech Pharma AB		

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NON PATENT LITERATURE DOCUMENTS			
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	NPL1	Thomson Innovation Patent Record, DWPI Accession No. 1979-58797B, English language Abstract of Japanese Patent Publication No. 54-80439 A, (1979)	Abs.
	NPL2	English language Abstract of German Patent Publication No. DE 38 34 794 A1, European Patent Office, Espacenet database — Worldwide (2001)	Abs.
	NPL3	English language Abstract of Japanese Patent Publication No. JP 6-345644 A, European Patent Office, Espacenet database — Worldwide (2001)	Abs.
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	NPL5	English language Abstract of Japanese Patent Publication No. JP 9-221428 A, European Patent Office, Espacenet database — Worldwide (2001)	Abs.
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	NPL8	English language Abstract of WIPO Patent Publication No. WO 2005/027899 A1, European Patent Office, Espacenet database — Worldwide (2005)	Abs.
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	NPL21	DE HAAN, P., "The Risk of Sensibilization and Contact Urticaria upon Topical Application of Fumaric Acid Derivatives," *Dermatology 188*:126-130, Karger AG, Switzerland (1994)	
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	NPL24	DETHLEFSEN, L.A., "Toxic Effects of Acute Glutathione Depletion by Buthionine Sulfoximine and Dimethylfumarate on Murine Mammary Carcinoma Cells," *Radiation Res. 114*:215-224, Academic Press, Inc., United States (1988)	
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	NPL31	FLIEGNER, L. and SPIEGEL, P., "Osteomalazie als offenbar seltene Nebenwirkung der oralen Fumarsäuretherapie," *Hautarzt 43*:554-560, Springer-Verlag, Germany (1992) (Abstract Only in English)	Abs.
	NPL32	FURLAN, R., *et al.*, "Interferon-β treatment in multiple sclerosis patients decreases the number of circulating T cells producing interferon-γ and interleukin-4," *J. Neuroimmunol. 111*:86-92, Elsevier Science B.V., Netherlands (2000)	
	NPL33	GALLI, G., *et al.*, "Macrophage-derived chemokine production by activated human T cells *in vitro* and *in vivo*: preferential association with the production of type 2 cytokines," *Eur. J. Immunol. 30*:204-210, WILEY-VCH Verlag GmbH, Germany (2000)	
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	NPL35	GENAIN, C.P., *et al.*, "Late Complications of Immune Deviation Therapy in a Nonhuman Primate," *Science 274:*2054-2057, American Association for the Advancement of Science, United States (1996)	
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	NPL37	GHORESCHI, K., *et al.*, "Fumarates induce a DC2 phenotype in dendritic cells that establishes protective Th2 responses," *Arch. Dermatol. Forschung 296*:420, Springer Verlag, Germany (2005) (Abstract Only)	Abs.
	NPL38	GHORESCHI, K., *et al.*, "Fumaric acid ester an antipsoriatic drug abolishes the capacity of T cells to induce Th1-mediated autoimmune disease," *Arch. Dermatol. Res. 294*:28, Springer Verlag, Germany (2002) (Abstract Only)	Abs.
	NPL39	GIELEN, A.W., *et al.*, "Expression of T cell immunoglobulin- and mucin-domain-containing molecules-1 and -3 (TIM-1 and -3) in the rat nervous and immune systems," *J. Neuroimmunol. 164*:93-104, Elsevier B.V., Netherlands (2005)	
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	NPL41	GIOVANNONI, G. and MILLER, D.H., "Multiple sclerosis and its treatment," *J. R. Coll. Physicians Lond. 33(4):*315-322, Royal College of Physicians, England (1999)	
	NPL42	GUGGENMOS, J., *et al.*, "Antibody Cross-Reactivity between Myelin Oligodendrocyte Glycoprotein and the Milk Protein Butyrophilin in Multiple Sclerosis," *J. Immunol. 172*:661-668, The American Association of Immunologists, Inc., United States (2004)	
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	NPL44	HINTZEN, R.Q. and POLMAN, C.H., "Th-cell modulation in multiple sclerosis," *Immunol. Today 18(10):507-508*, Elsevier/North-Holland Biomedical Press, England (1997)	
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	NPL49	ISSAZADEH, S., *et al.*, "Cytokine production in the central nervous system of Lewis rats with experimental autoimmune encephalomyelitis: dynamics of mRNA expression for interleukin-10, interleukin-12, cytolysin, tumor necrosis factor α and tumor necrosis factor β," *J. Neuroimmunol. 61*:205-212, Elsevier Science B.V, Netherlands (1995)	
	NPL50	ISSAZADEH, S., *et al.*, "Interferon γ, Interleukin 4 and Transforming Growth Factor β in Experimental Autoimmune Encephalomyelitis in Lewis Rats: Dynamics of Cellular mRNA Expression in the Central Nervous System and Lymphoid Cells," *J. Neurosci. Res. 40*:579-590, Wiley-Liss, Inc., United States (1995)	

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	NPL51	ISSAZADEH, S., *et al.*, "Cytokines in relapsing experimental autoimmune encephalomyelitis in DA rats: persistent mRNA expression of proinflammatory cytokines and absent expression of interleukin-10 and transforming growth factor-β," *J. Neuroimmunol. 69*:103-115, Elsevier Science B.V., Netherlands (1996)	
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	NPL54	KHADEMI , M., *et al.*, "Induction of systemic TNFα in Natalizumab-treated multiple sclerosis," *Eur. J. Neurol. 15*:309-312, European Federation of Neurological Sciences, England (2008)	
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	NPL61	KRAKOWSKI, M. and OWENS, T., "Interferon-γ confers resistance to experimental allergic encephalomyelitis," *Eur. J. Immunol. 26*:1641-1646, VCH Verlagsgesellschaft mbH, Germany (1996)	
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	NPL71	LINK, J., *et al.*, "Optic neuritis is associated with myelin basic protein and proteolipid protein reactive cells producing interferon-γ, interleukin-4 and transforming growth factor-*β*," *J. Neuroimmunol. 49*:9-18, Elsevier Science B.V., Netherlands (1994)	
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	NPL81	MÄÄTTÄ, J.A., *et al.*, "Neutrophils secreting tumor necrosis factor alpha infiltrate the central nervous system of BALB/c mice with experimental autoimmune encephalomyelitis," *J. Neuroimmunol. 90*:162-175, Elsevier Science B.V., Netherlands (1998)	
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	NPL91	LINK, H., *et al.,* "Virus-reactive and autoreactive T cells are accumulated in cerebrospinal fluid in multiple sclerosis," *J. Neuroimmunol. 38*:63-74, Elsevier Science Publishers B.V., Netherlands (1992)	
	NPL92	LITJENS, N.H.R., *et al.,* "Monomethylfumarate affects polarization of monocyte-derived dendritic cells resulting in down-regulated Th1 lymphocyte responses," *Eur. J. Immunol. 34*:565-575, WILEY-VCH Verlag GmbH & Co. KGaA, Germany (2004)	
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	NPL101	MUSTAFA, M.I., *et al.,* "T cell immunity and interferon-γ secretion during experimental allergic encephalomyelitis in Lewis rats," *J. Neuroimmunol. 31*:165-177, Elsevier Science Publishers B.V., Netherlands (1991)	
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	NPL104	MUSTAFA, M., *et al.,* "Protective Influences on Experimental Autoimmune Encephalomyelitis by MHC Class I and Class II Alleles," *J. Immunol. 153*:3337-3344, The American Association of Immunologists, United States (1994)	
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	NPL107	NIBBERING, P.H., *et al.,* "Effects of Monomethylfumarate on Human Granulocytes," *J. Invest. Dermatol. 101*:37-42, The Society for Investigative Dermatology, Inc., United States (1993)	
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	NPL111	OLSSON, T., *et al.,* "Autoreactive T Lymphocytes in Multiple Sclerosis Determined by Antigen-induced Secretion of Interferon-γ," *J. Clin. Invest. 86*:981-985, The American Society for Clinical Investigation, Inc., United States (1990)	
	NPL112	OLSSON, T., "Cytokines in neuroinflammatory disease: role of myelin autoreactive T cell production of interferon-gamma," *J. Neuroimmunol. 40*:211-218, Elsevier Science Publishers B.V., Netherlands (1992)	
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	NPL120	PANITCH, H.S., *et al.,* "Exacerbations Of Multiple Sclerosis In Patients Treated With Gamma Interferon," *Lancet 329*:893-895, Lancet Publishing Group, England (1987)	

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	NPL121	PEREIRA, M.A., *et al.,* "Use of azoxymethane-induced foci of aberrant crypts in rat colon to identify potential cancer chemopreventive agents," *Carcinogenesis 15(5)*:1049-1054, Oxford University Press, England (1994)	
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	NPL129	ROHOWSKY-KOCHAN, C., *et al.,* "Impaired interleukin-12 production in multiple sclerosis patients," *Mult. Scler. 5*:327-334, Stockton Press, England (1999)	
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	NPL131	ROMAGNANI, S., "The Th1/Th2 paradigm," *Immunol. Today 18(6)*:263-266, Elsevier Science Ltd., England (1997)	
	NPL132	ROOK, G.A.W., *et al.,* "Bacterial vaccines for the treatment of multiple sclerosis and other autoimmune diseases," *Immunol. Today 21(10)*:503-508, Elsevier Science Ltd., England (2000)	
	NPL133	SAMOILOVA, E.B., *et al.,* "Experimental Autoimmune Encephalomyelitis in Intercellular Adhesion Molecule-1-Deficient Mice," *Cell. Immunol. 190*:83-89, Academic Press, United States (1998)	
	NPL134	SEBÖK, B., *et al.,* "Antiproliferative and cytotoxic profiles of antipsoriatic fumaric acid derivatives in keratinocyte cultures," *Eur. J. Pharmacol. 270*:79-87, Elsevier Science B.V., Netherlands (1994)	
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	NPL138	SMELTZ, R.B. and SWANBORG, R.H., "Concordance and Contradiction Concerning Cytokines and Chemokines in Experimental Demyelinating Disease," *J. Neurosci. Res. 51*:147-153, Wiley-Liss, Inc., United States (1998)	
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	NPL140	SPENCER, S.R., *et al.,* "Induction of Glutathione Transferases and NAD(P)H:Quinone Reductase by Fumaric Acid Derivatives in Rodent Cells and Tissues," *Cancer Res. 50*:7871-7875, American Association for Cancer Research, United States (1990)	

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	NPL141	SU, J.Y.C., *et al.*, "Reduction of H_2O_2-evoked, intracellular calcium increases in the rat N18-RE-105 neuronal cell line by pretreatment with an electrophilic antioxidant inducer," *Neurosci. Lett. 273*:109-112, Elsevier Science Ireland Ltd., Ireland (1999)	
	NPL142	SUN, J.-B., *et al.*, "Treatment of experimental autoimmune encephalomyelitis by feeding myelin basic protein conjugated to cholera toxin B subunit," *Proc. Natl. Acad. Sci. USA 93*:7196-7201, National Academy of Sciences, United States (1996)	
	NPL143	THIO, H.B., *et al.*, "Fumaric acid derivatives evoke a transient increase in intracellular free calcium concentration and inhibit the proliferation of human keratinocytes," *Brit. J. Dermatol. 131*:856-861, Blackwell Scientific Publications, England (1994)	
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	NPL145	WALLSTRÖM, E., *et al.*, "Memantine abrogates neurological deficits, but not CNS inflammation, in Lewis rat experimental autoimmune encephalomyelitis," *J. Neurol. Sci. 137*:89-96, Elsevier Science B.V., Netherlands (1996)	
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	NPL151	ZIPP, F., "No Evidence for Generation of Th-2-like MBP-Specific T-Cell Lines by Blockade of the Costimulatory Molecule B7-1," *Scand. J. Immunol. 52*:510-514, Blackwell Science Ltd., England (2000)	
	NPL152	ALEXANDER, A. and WONG, S., "Graft Versus Host Disease - Pathophysiology & Management," *Jacksonville Medicine: Bone Marrow Transplantation 51(11)*:1-7, Duval County Medical Society Foundation for the Duval, Clay, Nassau, St. Johns & Putnam Medical Societies, United States (2000)	
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	NPL154	BROCHET, B., "[Non-specific immunosuppression and multiple sclerosis]," *Rev. Neurol. (Paris) 154(8-9)*:629-634, Masson, France (1998) (Abstract Only)	Abs.
	NPL155	CALABRESE, V., *et al.*, "Acetylcarnitine Induces Heme Oxygenase in Rat Astrocytes and Protects Against Oxidative Stress: Involvement of the Transcription Factor Nrf2," *J. Neurosci. Res. 79*:509-521, Wiley-Liss, Inc., United States (2005)	
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	NPL161	GILGUN-SHERKI, Y., *et al.*, "The role of oxidative stress in the pathogensis of multiple sclerosis: The need for effective antioxidant therapy," *J. Neurol. 251*:261-268, Springer-Verlag, Germany (2004)	
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	NPL163	GUTZMER, R., *et al.*, "Erfolgreiche Therapie einer Haut- und Lungensarkoidose mit Fumarsäureestern," *Hautarzt 55*:553-557, Springer-Verlag, Germany (2004)	
	NPL164	GUTZMER, R., *et al.*, "[Successful treatment of skin and lung sarcoidosis with fumaric acid ester].," *Hautarzt 55*:553-557, Springer-Verlag, Germany (2004) (Abstract Only)	Abs.
	NPL165	HAGEDORN, M., *et al.*, "Therapie der rezidivierenden benignen Aphthosis mit Fumarsäureestern," *Akt. Dermatol. 31*:383-387, Georg Thieme Verlag KG, Germany (2005) (Abstract Only in English)	Abs.
	NPL166	KENSLER, T.W., *et al.*, "Cell Survival Responses to Environmental Stresses Via the Keap1-Nrf2-ARE Pathway," *Annu. Rev. Pharmocol. Toxicol. 47*:6.1-6.28, Annual Reviews, United States (2007; Epub August 2006)	
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	NPL171	LAHTI, A., *et al.*, "Acetylsalicylic acid inhibits non-immunologic contact urticaria," *Contact Dermatitis 16*:133-135, Munksgaard International Publishers Ltd., Denmark (1987)	
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	NPL174	LIANG, Q., *et al.*, "Noninvasive, Repetitive, Quantitative Measurement of Gene Expression from a Bicistronic Message by Positron Emission Tomography, Following Gene Transfer with Adenovirus," *Mol. Ther. 6(1)*:73-82, The American Society of Gene Therapy, United States (2002)	
	NPL175	LUKER, G.D., *et al.*, "Noninvasive Bioluminescence Imaging of Herpes Simplex Virus Type 1 Infection and Therapy in Living Mice," *J. Virol. 76(23)*:12149-12161, American Society for Microbiology, United States (2002)	
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	NPL181	O'GARRA, A., *et al.*, "CD4$^+$ T-cell subsets in autoimmunity," *Curr. Opin. Immunol. 9*:872-883, Current Biology Ltd., England (1997)	
	NPL182	OLSSON, T., *et al.*, "Chapter 22: MHC and Non-MHC Genetics of Experimental Autoimmune Encephalomyelitis," in *From Basic Immunology to Immune-Mediated Demyelination*, Martino, G. and Adorini, L., eds., p. 246-264, Springer-Verlag, Italy (1999)	
	NPL183	OLSSON, T., "Critical Influences of the Cytokine Orchestration on the Outcome of Myelin Antigen-Specific T-Cell Autoimmunity in Experimental Autoimmune Encephalomyelitis and Multiple Sclerosis," *Immunol. Rev. 144*:245-268, Munksgaard, Denmark (1995)	
	NPL184	PASHENKOV, M., *et al.*, "Recruitment of dendritic cells to the cerebrospinal fluid in bacterial neuroinfections," *J. Neuroimmunol. 122*:106-116, Elsevier Science B.V., Netherlands (2002)	
	NPL185	PERMANA, P.A., *et al.*, "Macrophage-secreted factors induce adipocyte inflammation and insulin resistance," *Biochem. Biophys. Res. Commun. 341*:507-514, Elsevier Inc., United States (Epub January 2006)	
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	NPL187	ROODNAT, J.I., *et al.*, "Akute Niereninsuffizienz bei der Behandlung der Psoriasis mit Fumasäure-Estern," *Schweiz. med. Wschr. 119*:826-830, Basel, B. Schwabe & Co., Switzerland (1989) (Abstract Only in English)	Abs.
	NPL188	RUDGE, P., "Cyclosporine and multiple sclerosis: The cons," *Neurology 38(7)(Suppl 2)*:29-30, Lippincott Williams & Wilkins, United States (1988)	
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	NPL191	SCHILLING, F. and SCHOPF, R.E., "Adultes Debré-de Toni-Fanconi-Syndrom mit Osteomalazie, erworben durch Langzeittherapie einer Psoriasis mit Fumarsäureester - zugleich ein Beitrag zur malazischen Osteoarthropathie," *Akt. Rheumatol. 24(6)*:174-179, Georg Thieme Verlag, Germany (1999) (Abstract Only in English)	Abs.
	NPL192	SCHILLING, S., *et al.*, "Fumaric acid esters are effective in chronic experimental autoimmune encephalomyelitis and suppress macrophage infiltration," *Clin. Exp. Immunol. 145*:101-107, British Society for Immunology, England (2006)	
	NPL193	SCHWINGHAMMER, T.L. and BLOOM, E.J., "Pharmacologic prophylaxis of acute graft-versus-host disease after allogeneic marrow transplantation," *Clinical Pharm. 12*:736-761, American Society of Hospital Pharmacists, Inc., United States (1993)	
	NPL194	SHIH, A.Y., *et al.*, "A Small-Molecule-Inducible Nrf2-Mediated Antioxidant Response Provides Effective Prophylaxis against Cerebral Ischemia *In Vivo*," *J. Neurosci. 25(44)*:10321-10335, Society for Neuroscience, United States (2005)	
	NPL195	SUMMERS, S.A., "Ceramides in insulin resistance and lipotoxicity," *Prog. Lipid Res. 45*:42-72, Elsevier Ltd., England (January 2006; Epub December 2005)	
	NPL196	THIMMULAPPA, R.K., *et al.*, "Nrf2 is a critical regulator of the innate immune response and survival during experimental sepsis," *J. Clin. Invest. 116(4)*:984-995, American Society for Clinical Investigation, United States (April 2006)	
	NPL197	VAN HORSSEN, J., *et al.*, "NAD(P)H:quinone oxidoreductase 1 expression in multiple sclerosis lesions," *Free Radic. Biol. Med. 41*:311-317, Elsevier Inc., United States (Epub April 2006)	
	NPL198	VAN LOENEN, A.C., *et al.*, "Fumaarzuurtherapie: van fictie tot werkelijkheid?" *Pharm. Weekbl. 124*:894-900, D B Centens Witgeversmij, Netherlands (1989) (Abstract Only in English)	Abs.
	NPL199	VANDERMEEREN, M., *et al.*, "Dimethylfumarate Is an Inhibitor of Cytokine-Induced E-Selection, VCAM-1, and ICAM-1 Expression in Human Endothelial Cells," *Biochem. Biophys. Res. Comm. 234*:19-23, Academic Press, United States (1997)	
	NPL200	VANDERMEEREN, M., *et al.*, "Dimethylfumarate is an Inhibitor of Cytokine-Induced Nuclear Translocation of NF-κB1, But Not RelA in Normal Human Dermal Fibroblast Cells," *J. Inves. Dermatol. 116*:124-130, The Society for Investigative Dermatology, Inc., United States (2001)	

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	NPL201	WAKABAYASHI, N., *et al.*, "*Keap1*-null mutation leads to postnatal lethality due to constitutive Nrf2 activation," *Nat. Genet. 35(3)*:238-245, Nature Publishing Group, United States (2003)	
	NPL202	WANSCHER, B. and SØRENSEN, P.S., "Nye behandlingsmuligheder for dissemineret sklerose?" *Ugeskr Læger 156(43)*:6353-6358, Den Alm Danske Laegerforening, Denmark (1994) (Abstract Only in English)	Abs.
	NPL203	WERDENBERG, D., *et al.*, "Presystemic Metabolism and Intestinal Absorption of Antipsoriatic Fumaric Acid Esters," *Biopharm. Drug Dispos. 24(6)*:259-273, John Wiley & Sons, Ltd., England (2003)	
	NPL204	WERDENBERG, D., *Stability, Permeability and Pharmacokinetics of Perorally Administered Fumarates*, Doctoral Dissertation submitted to the Swiss Federal Institute of Technology Zurich, pp. 86, 87, 90, 125 (2003)	
	NPL205	ZHU, K. and MROWIETZ, U., "Inhibition of Dendritic Cell Differentiation by Fumaric Acid Esters," *J. Invest. Dermatol. 116*:203-208, The Society for Investigative Dermatology, Inc., United States (2001)	
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	NPL207	"Oral Compound BG-12 Achieves Primary Endpoint in Phase II Study of Relapsing-Remitting Multiple Sclerosis; Treatment with BG-12 Led to Statistically Significant Reductions in MRI Measures," Biogen Idec, accessed at http://phx.corporate-ir.net/staging/phoenix.zhtml?c=148682&p=irol-newsArticle_print&ID=861749&highlight, published online May 30, 2006, 2 pages	
	NPL208	"Phase II Study of Oral Compound BG-12 Meets Primary Endpoint in Multiple Sclerosis," Biogen Idec, accessed at http://phx.corporate-ir.net/staging/phoenix.zhtml?c=148682&p=irol-newsArticle_print&ID=801882&highlight, published online January 9, 2006, 1 page	
	NPL209	"Polyarthritis," Wikipedia.org, accessed at www.en.wikipedia.org/wiki/Polyarthritis, accessed on September 3, 2008, 4 pages	
	NPL210	*Immunmodulation durch Fumaderm. Das richtungsweisende Konzept*, Charite-Berlin Hautklinik Symposium, November 1-3, 1996, p. 1-27	

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	NPL211	Partial English language translation, 4 pages, of *Immunmodulation durch Fumaderm. Das richtungsweisende Konzept*, Charite-Berlin Hautklinik Symposium, November 1-3, 1996, p. 1-27	
	NPL212	ANDO, D.G., *et al.,* "Encephalitogenic T Cells in the B10.PL Model of Experimental Allergic Encephalomyelitis (EAE) Are of the Th-1 Lymphokine Subtype," *Cell. Immunol. 124*:132-143, Academic Press, Inc., United States (1989)	
	NPL213	BAKER, D., *et al.,* "Induction of chronic relapsing experimental allergic encephalomyelitis in Biozzi mice," *J. Neuroimmunol. 28(3)*:261-270, Elsevier Science Publishers B.V. (Biomedical Division), Netherlands, (1990)	
	NPL214	BAXTER, A.G., *et al.,* "High And Low Diabetes Incidence Nonobese Diabetic (NOD) Mice: Origins And Characterisation," *Autoimmunity 9*:61-67, Harwood Academic Publishers GmbH, England (1991)	
	NPL215	BAYARD, W., *et al.,* "Perorale Langzeitbehandlung der Psoriasis mit Fumarsäurederivaten" *Hautarzt 38*:279-285, Springer-Verlag, Germany (1987) (Abstract Only in English)	Abs.
	NPL216	BEN-NUN, A., *et al.,* "The rapid isolation of clonable antigen-specific T lymphocyte lines capable of mediating autoimmune encephalomyelitis," *Eur. J. Immunol. 11*:195-199, Verlag Chemie, GmbH, Germany (1981)	
	NPL217	BUTTER, C., *et al.,* "Mononuclear cell trafficking and plasma protein extravasation into the CNS during chronic relapsing experimental allergic encephalomyelitis in Biozzi AB/H mice," *J. Neurol. Sci. 104*:9-12, Elsevier Science Publishers B.V., Netherlands (1991)	
	NPL218	DINKOVA-KOSTOVA, A.T., *et al.,* "Potency of Michael reaction acceptors as inducers of enzymes that protect against carcinogenesis depends on their reactivity with sulfhydryl groups," *Proc. Natl. Acad. Sci. USA 98(6)*:3404-3409, National Academy of Sciences, United States (2001)	
	NPL219	*Encyclopedia of Molecular Biology and Molecular Medicine*, Meyers, R.A., ed., p. 343, VCH Verlagsgesellschaft mbH, Germany (1996)	
	NPL220	ERCOLINI, A.M. and MILLER, S.D., "Mechanisms of Immunopathology in Murine Models of Central Nervous System Demyelinating Disease," *J. Immunol. 176(6)*:3293-3298, The American Association of Immunologists, Inc., United States (March 2006)	

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	NPL221	EUGSTER, H.-P., *et al.,* "Severity of symptoms and demyelination in MOG-induced EAE depends on TNFR1," *Eur. J. Immunol. 29*:626-632, WILEY-VCH Verlag GmbH, Germany (1999)	
	NPL222	FREIREICH, E.J., *et al.,* "Quantitative Comparison Of Toxicity Of Anticancer Agents In Mouse, Rat, Hamster, Dog, Monkey, And Man," *Cancer Chemother. Reports 50(4)*:219-244, National Cancer Institute, United States (1966)	
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	NPL225	HABIG, W.H., *et al.,* "Glutathione S-Transferases: The First Enzymatic Step in Mercapturic Acid Formation," *J. Biol. Chem. 249(22)*:7130-7139, The American Society for Biological Chemists, Inc., United States (1974)	
	NPL226	HARRIS, J.O., *et al.,* "Serial Gadolinium-enhanced Magnetic Resonance Imaging Scans in Patients with Early, Relapsing-Remitting Multiple Sclerosis: Implications for Clinical Trials and Natural History," *Ann. Neurol. 29*:548-555, American Neurological Association, United States (1991)	
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	NPL228	HEMMINKI, A., *et al.,* "*In Vivo* Molecular Chemotherapy and Noninvasive Imaging With an Infectivity-Enhanced Adenovirus," *J. Natl. Cancer Inst. 94(10)*:741-749, Oxford University Press, United States (2002)	
	NPL229	JI, H., *et al.,* "Different modes of pathogenesis in T-cell-dependent autoimmunity: clues from two TCR transgenic systems," *Immunol. Rev. 169*:139-146, Munksgaard International Publishers, Denmark (1999)	
	NPL230	KAPPOS, L., *et al.,* "Efficacy of a novel oral single-agent Fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase II study," oral presentation on May 30, 2006, at the 16th Meeting of the European Neurological Society, May 27-31, 2006, Lausanne, Switzerland	

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	NPL231	KAPPOS, L., *et al.*, "Efficacy of a novel oral single-agent fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase 2 study," Abstract O108, Proceedings of the 16th Meeting of the European Neurological Society, May 27-31, 2006, Lausanne, Switzerland (Abstract Only)	Abs.
	NPL232	KAPPOS, L., *et al.*, "The Efficacy of BG00012 in Patients With Relapsing-Remitting Multiple Sclerosis: Subgroup Analyses From the Phase 2b Study," poster from the 60th Annual Meeting of the American Academy of Neurology, April 12-19, 2008, Chicago, IL, United States	
	NPL233	KERMODE, A.G., *et al.*, "Breakdown Of The Blood-Brain Barrier Precedes Symptoms And Other MRI Signs Of New Lesions In Multiple Sclerosis," *Brain 113*:1477-1489, Oxford University Press, England (1990)	
	NPL234	"Klinische Studie mit Fumaderm® als magensaftresistente Mikrotabletten," Report, 11 pages	
	NPL235	KURODA, K. and AKAO, M., "Antitumor And Anti-Intoxication Activities Of Fumaric Acid In Cultured Cells," *Gann. 72(5)*:777-782, Japanese Cancer Association and the Japanese Foundation for Cancer Research, Japan (1981)	
	NPL236	Biosis Database, Accession No. PREV197662032843, English language abstract for KURODA, K., *et al.*, "Inhibitory Effect Of Capsella-Bursa-Pastoris Extract On Growth Of Ehrlich Solid Tumor In Mice," *Cancer Res. 36(6)*:1900-1903, American Association for Cancer Research, United States (1976) (Abstract Only)	Abs.
	NPL237	LINKER, R.A., *et al.*, "CNTF is a major protective factor in demyelinating CNS disease: A neurotrophic cytokine as modulator in neuroinflammation," *Nature Medicine 8(6)*:620-624, Nature America Inc., United States (2002)	
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	NPL240	*The Merck Manual of Diagnosis and Therapy*, 15th Edition, Berkow, R. and Fletcher, A.J., eds., p. 327, Merck Sharp & Dohme Research Lab, United States (1987)	

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	NPL241	NIEBOER, C., *et al.,* "Treatment of psoriasis with fumaric acid derivates," *Proceedings of the 239th Meeting of the Netherlands Society for Dermatology and Venereology Amsterdam, 14 February 1987, Br. J. Dermatol. 117(6)*:791-92, Blackwell Scientific Publications, England (1987) (Abstract Only)	Abs.
	NPL242	NIOI, P. and HAYES, J.D., "Contribution of NAD(P)H:quinone oxidoreductase 1 to protection against carcinogenesis, and regulation of its gene by the Nrf2 basic-region leucine zipper and the arylhydrocarbon receptor basic helix-loop-helix transcription factors," *Mutat. Res. 555*:149-171, Elsevier B.V., Netherlands (2004)	
	NPL243	OLSSON, T., "15: Future prospects of cytokines in the pathogenesis and management of multiple sclerosis," in Frontiers in Multiple Sclerosis, *Volume 2*, p. 139-150, Siva, A., *et al.*, eds., Martin Dunitz Ltd., England (1999)	
	NPL244	OLSSON, T., "Chapter 6: Cytokines in Multiple Sclerosis and Its Experimental Models," in *Neuroscience Intelligence Unit 5: T-Cell Autoimmunity and Multiple Sclerosis*, Londei, M., ed., p. 91-112, R.G. Landes Company, United States (1999)	
	NPL245	Biosis Database, Accession No. PREV199497368291, English language abstract for PEARL, J.M., *et al.,* "Fumarate-enriched blood cardioplegia results in complete functional recovery of immature myocardium," *Ann. Thorac. Surg. 57(6)*:1636-1641, Elsevier, Netherlands (1994) (Abstract Only)	Abs.
	NPL246	PEETERS, A.J., *et al.,* "Fumaric Acid Therapy for Psoriatic Arthritis. A Randomized, Double-blind, Placebo-controlled Study," *Br. J. Rheumatol.* XXXI(7):502-504, British Association for Rheumatology and Rehabilitation, England (1992)	
	NPL247	PEETERS, A.J., *et al.,* "Gunstig effect van fumaarzuurtherapie bij arthritis psoriatica: een dubbelblind, placebo-gecontroleerd onderzoek," *Ned. Tijdschr. Geneeskd. 136(49)*:2428-2431, Bohn Stafleu van Loghum, Netherlands (1992) (Abstract Only in English)	Abs.
	NPL248	PERRELLA, O., *et al.,* "Interleukin-10 and IFN-α in multiple sclerosis: is there a balance?" *J. Neurovirol. 3(Suppl 1)*:P17, Stockton Press, United States (1997) (Abstract Only)	Abs.
	NPL249	POLMAN, C.H., *et al.,* "Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald Criteria," *Ann. Neurol. 58(6)*:840-846, Wiley-Liss, Inc., United States (2005)	
	NPL250	PROCHASKA, H.J. and SANTAMARIA, A.B., "Direct Measurement of NAD(P)H:Quinone Reductase from Cells Cultured in Microtiter Wells: A Screening Assay for Anticarcinogenic Enzyme Inducers," *Anal. Biochem. 169*:328-336, Academic Press, Inc., United States (1988)	

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	NPL251	ROITT, I.M., *et al.,* eds., "23.Autoimmunity and Autoimmune Disease," in *Immunology*, p. 23.1-23.12, Gower Medical Publishing, United States (1985)	
	NPL252	ROSTAMI-YAZDI, M., *et al.,* "Detection of Metabolites of Fumaric Acid Esters in Human Urine: Implications for Their Mode of Action," *J. Invest. Dermatol. 129*:231-234, Nature Publishing Group, United States (2008)	
	NPL253	RUSHMORE, T.H., *et al.,* "The Antioxidant Responsive Element: Activation By Oxidative Stress And Identification of the DNA Consensus Sequence Required For Functional Activity," *J. Biol. Chem. 266(18)*:11632-11639, The American Society for Biochemistry and Molecular Biology, Inc., United States (1991)	
	NPL254	Biosis Database, Accession No. PREV199699044855, English language abstract for SCHMIDT, K.N, *et al.,* "Anti-psoriatic drug anthralin activates transcription factor NF-kappa-B in murine keratinocytes," *J. Immunol. 156(11)*:4514-4519, American Association of Immunologists, United States (1996) (Abstract Only)	Abs.
	NPL255	SHI, N., *et al.,* "Brain-specific expression of an exogenous gene after i.v. administration," *Proc. Natl. Acad. Sci. USA 98(22)*:12754-12759, National Academy of Sciences, United States (2001)	
	NPL256	SOBEL, R.A., *et al.* "The Immunopathology Of Experimental Allergic Encephalomyelitis. I. Quantitative Analysis of Inflammatory Cells *In Situ*," *J. Immunol. 132(5)*:2393-2401, American Association of Immunologists, United States (1984)	
	NPL257	STANGEL, M., *et al.,* "Fumarat in der Behandlung der Multiplen Sklerose: Mögliche Wirkmechanismen und Studien," *Der Nervenarzt 79*:212-217, Springer Medizin Verlag, Germany (2008) (Abstract Only in English)	Abs.
	NPL258	STÜHLINGER, W., *et al.*, "Nephrotoxische Wirkung einer Therapie mit Fumarsäureestern bei Psoriasis," *Dtsch. Med. Wschr. 115*:1712-1715, Georg Thieme Verlag Stuttgart, Germany (1990) (Abstract Only in English)	Abs.
	NPL259	TRAUGOTT, U., "Detailed Analysis of Early Immunopathologic Events during Lesion Formation in Acute Experimental Autoimmune Encephalomyelitis," *Cell. Immunol. 119*:114-129, Academic Press, Inc., United States (1989)	
	NPL260	TUNG, C.-H., *et al.,* "*In Vivo* Imaging of Proteolytic Enzyme Activity Using a Novel Molecular Reporter," *Cancer Res. 60*:4953-4958, American Association for Cancer Research, Inc., United States (2000)	

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	NPL261	TUOHY, V.K., *et al.,* "A Synthetic Peptide From Myelin Proteolipid Protein Induces Experimental Allergic Encephalomyelitis," *J. Immunol. 141(4)*:1126-1130, The American Association of Immunologists, United States (1988)	
	NPL262	ÚNER, A.H., *et al.,* "Characteristics of Auto Anti-idiotypic Antibodies Reactive with Antibodies Expressing the Pathogenic Idiotype, $Id^{LN}F_1$, in the (NZB x SWR)F_1 Model for Lupus Nephritis and its Parental Strains," *J. Autoimmun. 11*:233-240, Academic Press, England (1998)	
	NPL263	VAN MUISWINKEL, F.L., *et al.,* "Expression of NAD(P)H:quinone oxidoreductase in the normal and Parkinsonian substantia nigra," *Neurobiol. Aging 25*:1253-1262, Elsevier Inc., United States (2004)	
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	NPL266	*The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 10th Edition, p. 396, WINDHOLZ, M., *et al.,* eds., Merck & Co., Inc., United States (1983)	
	NPL267	ZAMVIL, S., *et al.,* "T-cell clones specific for myelin basic protein induce chronic relapsing paralysis and demyelination" *Nature 317*:355-358, Nature Publishing Group, England (1985)	
	NPL268	ZAMVIL, S.S. and STEINMAN, L., "The T Lymphocyte In Experimental Allergic Encephalomyelitis," *Ann. Rev. Immunol. 8*:579-621, Annual Reviews Inc., United States (1990)	
	NPL269	Office Action mailed April 26, 2000, in U.S. Application No. 09/194,862, Joshi, R.K., *et al.,* § 371(c) date July 8, 1999 (now U.S. Patent No. 6,436,992 B1)	
	NPL270	Office Action mailed October 31, 2000, in U.S. Application No. 09/402,103, Joshi, R.K., *et al.,* § 371(c) date September 27, 1999 (now U.S. Patent No. 6,277,882 B1)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO				Complete if Known	
FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*				Application Number	*To be assigned*
				Filing Date	Herewith
				First Named Inventor	Matvey E. LUKASHEV
				Art Unit	*To be assigned*
				Examiner Name	*To be assigned*
Sheet	28	of	30	Attorney Docket Number	2159.3210002/JMC/MRG/U-S

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume number, publisher, city and/or country where published	T[2]
	NPL271	Office Action mailed May 21, 2001, in U.S. Application No. 09/743,978, Joshi, R.K., *et al.*, § 371(c) date January 17, 2001 (now U.S. Pat. No. 6,355,676 B1)	
	NPL272	Office Action mailed December 7, 2001, in U.S. Application No. 09/831,620, Joshi, R.K., *et al.*, § 371(c) date May 10, 2001 (now U.S. Pat. No. 6,509,376 B1)	
	NPL273	Office Action mailed March 4, 2002, in U.S. Application No. 09/831,620, Joshi, R.K., *et al.*, § 371(c) date May 10, 2001 (now U.S. Patent No. 6,509,376 B1)	
	NPL274	Office Action mailed August 12, 2003, in U.S. Application No. 10/148,858, Joshi, R.K., *et al.*, § 371(c) date May 28, 2002 (now U.S. Patent No. 6,858,750 B2)	
	NPL275	Office Action mailed March 23, 2004, in U.S. Application No. 10/148,858, Joshi, R.K., *et al.*, § 371(c) date May 28, 2002 (now U.S. Patent No. 6,858,750 B2)	
	NPL276	Office Action mailed March 22, 2004, in U.S. Application No. 10/197,077, Joshi, R.K., *et al.*, filed July 17, 2002 (now U.S. Patent No. 7,320,999 B2)	
	NPL277	Office Action mailed November 28, 2005, in U.S. Application No. 10/197,077, Joshi, R.K., *et al.*, filed July 17, 2002 (now U.S. Patent No. 7,320,999 B2)	
	NPL278	Office Action mailed June 21, 2006, in U.S. Application No. 10/197,077, Joshi, R.K., *et al.*, filed July 17, 2002 (now U.S. Patent No. 7,320,999 B2)	
	NPL279	Office Action mailed May 15, 2007, in U.S. Application No. 10/197,077, Joshi, R.K., *et al.*, filed July 17, 2002 (now U.S. Patent No. 7,320,999 B2)	
	NPL280	Office Action mailed December 3, 2007, in U.S. Application No. 11/765,563, Joshi, R.K., *et al.*, filed June 20, 2007 (now U.S. Patent No. 7,612,110 B2)	

Examiner Signature		Date Considered	

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO				Complete if Known	
FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT *(Use as many sheets as necessary)*				Application Number	*To be assigned*
				Filing Date	Herewith
				First Named Inventor	Matvey E. LUKASHEV
				Art Unit	*To be assigned*
				Examiner Name	*To be assigned*
Sheet	29	of	30	Attorney Docket Number	2159.3210002/JMC/MRG/U-S

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume number, publisher, city and/or country where published	T[2]
	NPL281	Office Action mailed September 9, 2008, in U.S. Application No. 11/765,563, Joshi, R.K., *et al.,* filed June 20, 2007 (now U.S. Patent No. 7,612,110 B2)	
	NPL282	Office Action mailed March 12, 2009, in U.S. Application No. 11/765,563, Joshi, R.K., *et al.,* filed June 20, 2007 (now U.S. Patent No. 7,612,110 B2)	
	NPL283	Office Action mailed December 14, 2007, in U.S. Application No. 11/765,578, Joshi, R.K., *et al.,* filed June 20, 2007 (now U.S. Patent No. 7,619,001 B2)	
	NPL284	Office Action mailed July 25, 2008, in U.S. Application No. 11/765,578, Joshi, R.K., *et al.,* filed June 20, 2007 (now U.S. Patent No. 7,619,001 B2)	
	NPL285	Office Action mailed September 15, 2008, in U.S. Application No. 11/765,578, Joshi, R.K., *et al.,* filed June 20, 2007 (now U.S. Patent No. 7,619,001 B2)	
	NPL286	Office Action mailed March 30, 2009, in U.S. Application No. 11/765,578, Joshi, R.K., *et al.,* filed June 20, 2007 (now U.S. Patent No. 7,619,001 B2)	
	NPL287	Office Action mailed October 2, 2009, in U.S. Application No. 12/405,661, Joshi, R.K., *et al.,* filed March 17, 2009 (now U.S. Patent No. 7,803,840 B2)	
	NPL288	Office Action notification date January 19, 2010, in U.S. Application No. 12/405,661, Joshi, R.K., *et al.,* filed March 17, 2009 (now U.S. Patent No. 7,803,840 B2)	
	NPL289	Office Action notification date May 20, 2010, in U.S. Application No. 12/405,661, Joshi, R.K., *et al.,* filed March 17, 2009 (now U.S. Patent No. 7,803,840 B2)	
	NPL290	Office Action notification date March 23, 2010, in U.S. Application No. 12/405,665, Joshi, R.K., *et al.,* filed March 17, 2009 (now U.S. Patent No. 7,915,310 B2)	

Examiner Signature		Date Considered	

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Substitute for form 1449/PTO

FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 30 of 30

Complete if Known	
Application Number	*To be assigned*
Filing Date	Herewith
First Named Inventor	Matvey E. LUKASHEV
Art Unit	*To be assigned*
Examiner Name	*To be assigned*
Attorney Docket Number	2159.3210002/JMC/MRG/U-S

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume number, publisher, city and/or country where published	T[2]
	NPL291	Office Action notification date September 9, 2010, in U.S. Application No. 12/405,665, Joshi, R.K., *et al.*, filed March 17, 2009 (now U.S. Patent No. 7,915,310 B2)	
	NPL292	English language Abstract of Chinese Patent Publication No. CN 1125141 A, European Patent Office, Espacenet database — Worldwide (Abstract Only)	Abs.
	NPL293	WALLACE, D.C., "Mitochondrial Diseases in Man and Mouse," *Science 283*:1482-1488, American Association for the Advancement of Science, United States (1999)	

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Examiner Signature		Date Considered	

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: LUKASHEV *et al.* Appl. No.: To be assigned (*Continuation of Appl. No. 12/526,296; § 371(c) Date: January 13, 2011*) Filed: Herewith For: **Treatment for Multiple Sclerosis (As Amended)**	Confirmation No.: To be assigned Art Unit: To be assigned Examiner: To be assigned Atty. Docket: 2159.3210002/JMC/MRG/U-S

Second Supplemental Information Disclosure Statement

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Listed on accompanying IDS Forms PTO/SB/08a equivalent and/or PTO/SB/08b equivalent are documents that may be considered material to the patentability of this application as defined in 37 C.F.R. §1.56, and in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.97 and 1.98. The numbering on this Second Supplemental Information Disclosure Statement is a continuation of the numbering in the First Supplemental Information Disclosure Statement filed concurrently herewith in connection with the above-captioned application.

Applicants bring to the Examiner's attention document NPL294, which is a Memorandum of Meeting Minutes for a meeting held on August 30, 2006 ("memorandum"), attended by U.S. Food and Drug Administration (FDA) and Biogen Idec MA Inc. (assignee of the current application) representatives. The memorandum (page 3, bottom line to page 4, line 2) contains a reference to a BG00012 (dimethyl fumarate) dose of 240 mg b.i.d. (240 mg twice daily) corresponding to a 480 mg/day

dose. Prior to the meeting of August 30, 2006, Matvey E. Lukashev and Gilmore O'Neill, employees of Biogen Idec MA Inc., conceived of the subject matter presently claimed in this application. A declaration executed by Matvey E. Lukashev and Gilmore O'Neill is filed separately herewith.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

Applicants have checked the appropriate boxes below.

☐ 1. Statement under 37 C.F.R. 1.704(d). Each item of information contained in this Information Disclosure Statement was first cited in a communication from a foreign patent office in a counterpart application and this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty days prior to the filing of this information disclosure statement.

☒ 2. Filing under 37 C.F.R. § 1.97(b). This Information Disclosure Statement is being filed within three months of the date of filing of a national application other than a continued prosecution application (CPA), OR within three months of the date of entry of the national stage as set forth in 37 C.F.R. § 1.491 in an international application, OR before the mailing date of a first Office Action on the merits OR before the mailing of a first Office Action after the filing of a request for continued examination under 37 C.F.R. § 1.114. No statement or fee is required.

☐ 3. Filing under 37 C.F.R. § 1.97(c). This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection, or Notice of Allowance, or an action that otherwise closes prosecution in the application.

☐ a. Statement under 37 C.F.R. § 1.97(e)(1). I hereby state that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than

three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. Statement under 37 C.F.R. § 1.97(e)(2). I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ c. Attached is our PTO-2038 Credit Card Payment Form in the amount of $180.00 in payment of the fee under 37 C.F.R. § 1.17(p).

☐ 4. Filing under 37 C.F.R. § 1.97(d) This Information Disclosure Statement is being filed more than three months after the U.S. filing date and after the mailing date of a Final Rejection or Notice of Allowance, but on or before payment of the Issue Fee. Enclosed find our PTO-2038 Credit Card Payment Form in the amount of $180.00 in payment of the fee under 37 C.F.R. § 1.17(p); in addition:

☐ a. Statement under 37 C.F.R. § 1.97(e)(1). I hereby state that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than

three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. Statement under 37 C.F.R. § 1.97(e)(2). I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ 5. The document(s) was/were cited in a search report by a foreign patent office in a counterpart foreign application. Submission of an English language version of the search report that indicates the degree of relevance found by the foreign office is provided in satisfaction of the requirement for a concise explanation of relevance. 1138 OG 37, 38 and MPEP 609.04(a)(III).

☒ 6. A concise explanation of the relevance of the non-English language documents appears below in accordance with 37 C.F.R. § 1.98(a)(3).

Document **FP51**, **DE 25 30 372 A1**, is in the German language. An English language translation of document FP51 is cited as document **NPL311** and submitted herewith.

Document **FP52, DE 26 21 214 A1**, is in the German language. An English language translation of document FP52 is cited as document **NPL312** and submitted herewith.

Document **FP53, DE 28 40 498 B1**, is in the German language. An English language translation of document FP53 is cited as document **NPL313** and submitted herewith.

Document **NPL295, Altmeyer and Nüchel (1996)**, is in the German language. An English language translation of document NPL295 is cited as document **NPL296** and submitted herewith.

Document **NPL297, Altmeyer and Nüchel (1997)**, is in the German language. An English language translation of document NPL297 is cited as document **NPL298** and submitted herewith.

Document **NPL304, Mrowietz**, is in the German language. An English language translation of document NPL304 is cited as document **NPL305** and submitted herewith.

Document **NPL309, Sadjak *et al.***, is in the German language. An English language translation of document NPL309 is cited as document **NPL310** and submitted herewith.

☐ 7. Copies of the documents are submitted.

☒ 8. Copies of documents FP51-FP53 and NPL294-NPL327 were cited by or submitted to the Office in an IDS that complies with 37 C.F.R. § 1.98(a)-(c) in Application No. 12/526,296, with a § 371(c) date of January 13, 2011, which is relied upon for an earlier filing date under 35 U.S.C. § 120. Thus, copies of these documents are not attached. 37 C.F.R. § 1.98(d).

☒ 9. It is expected that the examiner will review the prosecution and cited art in the parent application no. 12/526,296 in accordance with MPEP 2001.06(b), and indicate in the next communication from the office that the art cited in the earlier prosecution history has been reviewed in connection with the present application.

☐ 10. In accordance with the Federal Circuit decision in *Dayco Prods., Inc. v. Total Containment, Inc.* 329 F.3d 1358 (Fed. Cir. 2003), Applicants submit herewith Office Actions from the co-pending U.S. Patent Application No. _____, filed _____, as documents _____ to _____.

The identification of these Office Actions is not to be construed as a waiver of secrecy as to those applications now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination.

It is respectfully requested that the Examiner initial and return a copy of the enclosed IDS Forms, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Marsha A. Rose

Marsha A. Rose
Attorney for Applicants
Registration No. 58,403

Date: 2/13/2012

1100 New York Avenue, N.W.
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(202) 371-2600

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Amendments to the Specification

Please amend the title as follows:

Treatment for Multiple Sclerosis ~~NRF2 screening assays and related methods and compositions~~

Please amend paragraph [0128], beginning on page 33, line 21, as follows:

[0128] Immunohistochemistry was performed using the Dakoautostainer as follows. Endogenous peroxidase was quenched by a 10 minute incubation in 3% H_2O_2 / Methanol. The rabbit anti Nrf2 antibody C-20 (sc-722, Santa Cruz Biotechnology) was added at a 1:250 dilution in Dako Diluent with Background Reducing Components (Dako # S3022) C-20 antibody was detected using the Envision anti rabbit labeled polymer-HRP (Dako #K4003) and DAB (Vector Labs #SK-4100) was used as the chromogenic substrate. Morphometric analysis of Nrf2 immunostaining was performed using ImageJ software from NIH ~~(http://rsb.info.ih.gov/ij/)~~.

On page 1, below the title of the invention, please add the following new paragraph:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application No. 12/526,296, § 371(c) Date January 13, 2011, now pending, which is the U.S. National Phase of International Application No. PCT/US2008/001602, filed February 7, 2008, which claims the benefit of U.S. Provisional Application 60/888,921, filed February 8, 2007.